TB ToolKit

Michigan Department of Community Health
Laboratory Testing for Tuberculosis

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Guidelines for Submission of Specimens for Mycobacterial Examination to Michigan Department of Community Health Bureau of Laboratories

Specimen Submission Guidelines

The accuracy and clinical usefulness of laboratory analysis is limited by the quality and appropriateness of the specimen. The techniques used for the collection and submission of the specimens can influence the outcome of testing results.

Appropriate specimens are submitted by using collection units supplied by the Laboratory Support Unit of the Michigan Department of Community Health, Bureau of Laboratories. The Laboratory Support Unit is responsible for assembling the various units that are distributed to health departments, licensed physician's offices and licensed health care facilities. Order units by completing the Requisition for Clinical Specimen Containers (DCH-0568). The correct collection unit is listed as unit number 12. Orders may be submitted by mail, fax (517-335-9039) or by phone (517-335-9867).

Please ship specimens to the following address:

Michigan Department of Community Health
Bureau of Laboratories
3350 North Martin Luther King Jr. Blvd.
Building 44 Room 155
P.O. Box 30035
Lansing, MI 48909

NOTE: All packages containing clinical specimens and/or etiologic agents must conform to current regulations for the transporting of specimens of this type. These regulations are subject to change. Current regulations may be found at the following sites:

Federal Postal Regulations	www.cdc.gov/od/ohs/biosfty/shipregs.htm
United Postal Service	www.ups.com
Federal Express	www.fedex.com/us
DHL	www.dhl.com

The shipper is responsible for being sure that their package is in compliance with current regulations!

Specimen Rejection Policy

All specimens are subject to rejection if they:

- Are received with either specimen container unlabeled or incomplete test requisition form, or the specimen label not matching the test requisition form.
- Are leaking and can easily be replaced by re-collection. In the event that a specimen is received leaking, every attempt will be made to salvage leaking or improperly submitted samples of cerebrospinal fluid or samples attained through surgical means providing that the safety of the laboratory worker is not compromised.
- Are submitted in an inappropriate manner, i.e., are not shipped according to International Aviation Transportation Authority (IATA) regulations or other applicable standards.

Important Information to be Aware of:

- If the submitter of any specimen has not provided all required information on the test requisition, the form will be returned. The testing will not be reported until the completed test requisition is received. If the delay in testing will compromise the test results, the submitter will be contacted by telephone or fax to clarify the test requisition.

Reporting Results:

MDCH Bureau of Laboratories makes every effort to process, test, and report out specimens as quickly as possible. New positive results are communicated to the submitter by phone the same day as the results are reported.

For additional information and to download the Requisition for Clinical Specimen Containers (DCH-0568) form and test requisitions (Microbiology/Virology Test Requisitions Forms DCH-0583), visit the MDCH Laboratory web site at www.Michigan.gov/mdchlab.

Guidelines for Submission of Specimens for Mycobacterial Examination to Michigan Department of Community Health Bureau of Laboratories

Instructions for Submission of Specimens

NOTE: **Specimens will not be tested if not properly labeled, test requisition is not completed or the specimen label does not match the test requisition.**

MATERIALS NEEDED:

- Tuberculosis and Fungal Diagnosis Specimen container
- Microbiology/Virology Test Requisition form (DCH-0583)

SPUTUM

1. An early morning sample is desired. The specimen should be coughed up from deep within the chest—it should **not** be saliva from the mouth.
2. After coughing, patient should hold the sterile tube up to the mouth and expel the sputum into the tube. Fill the tube about one-half full, if possible. **Do not get sputum on the outside of the tube.**

OTHER TYPES OF SPECIMENS

Consult the Michigan Department of Community Health, Division of Infectious Diseases at 517-335-8067.

INSTRUCTIONS FOR SPECIMEN SUBMISSION:

1. Screw cap on the tube as tightly and evenly as possible to prevent from leaking. Using parafilm or vinyl tape (**not** scotch or masking tape), tape the cap on the tube to secure the cap and prevent from leaking.
2. Label the tube with the same name/unique identifier used on the test requisition.
3. Record the name/unique identifier on tube and test requisition for your records. You will use it to link the specimen to the patient.
4. Place the properly labeled tube, **wrapped in absorbent material such as paper towel or tissue and enclosed in the plastic bag provided,** into aluminum screw-capped can and tighten the cap securely.
5. Wrap **completed** test requisition around the **outside** of aluminum screw-capped can.
6. Place aluminum can with completed test requisition into screw-capped cardboard mailing container and secure cap with tape.

7. Complete and apply the return address, Biological Substance label to cardboard container and ship immediately by the most convenient means available (i.e., courier, U.S. First Class, Priority or Express mail etc.) to:
   Michigan Department of Community Health
   Bureau of Laboratories
   3350 North Martin Luther King Jr. Blvd.
   Building 44 Room 155
   P.O. Box 30035
   Lansing, MI 48909

CLINICAL SPECIMEN SHIPPING UNITS REQUISITION

Fax/Mail/E-mail Orders to: Michigan Department of Community Health – Laboratory Support Unit
927 Terminal Road
Lansing MI 48906

FAX 517-335-9039 **PHONE** 517-335–9867 **WEB** http://www.michigan.gov/mdchlab

Send To (No PO Boxes):	Date:
	Phone:
	Attention:

Unit Number	Type of Laboratory Service	Circle Number of Complete Tests Desired
One	**Enteric Bacterial Infections**	25 50 Other_____
Two	**Chlamydia & Gonorrhea - Amplified Test – Swabs**	50 100 Other_____
Two - U	**Chlamydia & Gonorrhea - Amplified Test -Urine Specimens**	50 100 Other_____
Three	**Viral Load Testing for HIV - 1** For submission from HIV-1 positive patients enrolled in MDCH approved programs **only**.	1 2 Other_____
Four	**Oral Fluid Specimen Test System for HIV-1** Mailing Components **only**.	10 50 100 200
Five	**Enteric Viral Infections (e.g., Norovirus)** **Contact laboratory at 517-335-8067**	**Special Request Only**
Six	**Parasitic Infections**	20 40 Other_____
Seven	**Blood Lead Sampling** Please Specify Sample Type ☐ **Capillary** ☐ **Filter Paper** ☐ **Venous**	100 Other_____
Seven "A"	**Environmental Lead Sampling** Indicate quantity of test requisitions desired (DCH-0558 – Revised 04/04) >>>>>	1 5 10 50 Other_____
Eight	**Bacterial, Fungal and Viral Serology** (For HIV Serology – Order Unit 49)	25 50 100 Other_____
Ten	**Syphilis by Darkfield Fluorescent** exam for *Treponema pallidum*.	1 2 Other_____
Twelve	**Tuberculosis and Fungal Diagnosis Specimens** For submission of clinical specimens for microscopy and culture.	25 50 100 Other_____
Thirteen	**CD4/CD8 & Viral Load Testing for HIV-1** For submission from HIV-1 positive patients enrolled in MDCH approved programs.	1 2 Other_____
Fourteen	**PBB, PCB, Pesticide Testing** For submission of serum & breast milk specimens for analysis. **Contact laboratory at 517-335-9490**	**Special Request Only**
Fifteen	***Bordetella pertussis*** – Culture, Isolation, & PCR	1 2 Other_____
Seventeen	**Mercury Analysis** – Urine, Blood, Other. **Contact laboratory at 517-335-9490**	**Special Request Only**
Nineteen	**HIV Genotyping -** For submission from HIV-1 positive patients enrolled in MDCH approved programs.	1 2 Other_____
Twenty	**Vaccinia/Variola/Pox Virus** Contact laboratory at 517-335-8067	**Special Request Only**
Twenty-Two	**Chemical Terrorism Specimen Packaging Unit -** Shipping Materials/Blanks (Contact laboratory at 517-335-9490)	**Special Request Only**
Twenty-Three	**Chemical Terrorism Unit –** Training Manual/Evidence Tape/Blanks (Contact laboratory at 517-335-9490)	**Special Request Only**
Forty-Two A	**Bacterial and Fungal Cultures** For submission of Infectious Substances – Category "A" **Dangerous Goods Form Required**	1 5 Other_____
Forty-Two B	**Bacterial and Fungal Cultures** For submission of Infectious Substances – Category "B" A.K.A. - Biological Substance	1 5 Other_____
Forty-Four	**Chlamydia Culture and Isolation -** For submission of specimens for diagnosis of genital, neonatal infections, pneumonia.	1 2 Other_____ (One Month Expiration - Order Accordingly)
Forty-Five	**Viral Disease Examination and Culture** For submission of miscellaneous specimens for Viral Isolation	1 2 Other_____ (One Month Expiration - Order Accordingly)
Forty-Six	**Food Borne Illness -** For submission of food, stool and vomitus**.**	**Available to Health Officers Only**
Forty-Seven	**Rabies Examinations** - For submission of animal heads for detection of rabies. ☐ **Check here for 3 gallon pails**	1 2 Other_____
Forty-Nine	**HIV Serology -** For submission of serum for HIV Antibody testing to; ☐ Detroit City HD ☐ Kent County HD	50 100 Other_____
Fifty	**HIV Serology -** For submission of dried **Blood Spots** for HIV Antibody testing.	50 100 Other_____
Fifty-One	**HIV Direct Detection - Special Request Only** Contact laboratory at 517-335-8067.	Special Request Only

Microbiology/Virology Test Requisition

Bureau of Laboratories Michigan Department of Community Health

PO Box 30035 3350 North Martin Luther King Jr. Blvd. Lansing Michigan 48909

Laboratory Records: 517-335-8059 Fax: 517-335-9871 Technical Information 517-335-8067 Web: HTTP://www.Michigan.gov/mdchlab

Date Received at MDCH	MDCH Sample #

AGENCY - SUBMITTER INFORMATION	ENTER EPIC CODE IF KNOWN >>>>>>>>>>>>
Return Results to:	Phone (24/7)
	FAX
CONTACT PERSON/ REFERRING PHYSICIAN/ PROVIDER NAME	NATIONAL PROVIDER IDENTIFIER:

PATIENT INFORMATION - NAME (LAST, FIRST, MIDDLE INITIAL OR UNIQUE IDENTIFIER) Must Match Specimen Label Exactly

SUBMITTER'S PATIENT # - IF APPLICABLE

PATIENT'S **CITY**-RESIDENCE | **ZIP** CODE | **GENDER** ☐ Female ☐ Male

RACE BLACK WHITE MULTIRACIAL AMERICAN INDIAN, ESKIMO, OR ALEUT ASIAN/PACIFIC ISLANDER UNKNOWN

ANCESTRY ☐ HISPANIC ☐ NON-HISPANIC ARAB DESCENT ☐ UNKNOWN | **MEDICAID #**

DATE OF BIRTH M M D D Y Y Y Y | **ONSET DATE** M M D D Y Y Y Y

SUBMITTER'S SPECIMEN # - IF APPLICABLE

SPECIMEN INFORMATION - INDICATE TEST REQUESTED - SEE REVERSE IF NOT LISTED BELOW

0001 ☐ AFB Slide/Culture-Clinical Specimen
0005 ☐ AFB Identification - Cultural Isolate
0102 ☐ Fungal Identification - Cultural Isolate
0200 ☐ Aerobic Culture Complete # 5 on Reverse
0501 ☐ Parasitology – Stool
0601 ☐ *Salmonella/Shigella* Serotyping-Human
0551 ☐ Enteric Examination

0673 ☐ *C. trachomatis* (Non-culture)[1]
2030 ☐ HIV- Oral Mucosal Transudate
2100 ☐ Syphilis (USR Test)
2107 ☐ Syphilis TP-PA (Must have prior MDCH approval)[2]
2210 ☐ Herpes Simplex Virus - Culture
2500 ☐ Rubella IgG
2515 ☐ Fungal Serology Comp. Fix.

2600 ☐ Measles IgG
2610 ☐ Mumps IgG
2620 ☐ Varicella Zoster IgG
2740 ☐ HBsAg Complete # 1 on Reverse
2745 ☐ Hepatitis C Screen
2760 ☐ HBS – ANTI (Anti-HBs)
2810 ☐ Rabies AB Serology Complete # 3

☐ Other-Specify Test Code/Name: _____ ☐ Other-Specify Test Code/Name: _____

DATE COLLECTED	M M D D Y Y Y Y	TIME COLLECTED	☐ A.M. ☐ P.M.

INDICATE SPECIMEN SOURCE BELOW

☐ Bronchial ☐ Gastric ☐ Plasma ☐ Sputum ☐ Urine ☐ Whole Blood
☐ Cervix ☐ Nasopharyngeal ☐ Serum ☐ Throat ☐ Food - Specify: _____
☐ CSF ☐ Oral Mucosal Transudate ☐ Stool ☐ Urethra ☐ Other - Specify: _____

SERUM STATUS - If Applicable ☐ Acute ☐ Convalescent | [2]MDCH Prior Approval Given By:_____

INDICATE TEST REASON BELOW

☐ Diagnosis ☐ Surveillance ☐ Suspected Outbreak – Specify: _____
☐ Other – Specify: _____

STD* ☐ Symptoms ☐ Prenatal Visit ☐ Infected Partner ☐ Partner Risk ☐ History of STD (< 3years) ☐ Age recommended for Testing
☐ "Plan First!" Client ☐ IUD Insertion

OUTBREAK IDENTIFIER (Foodborne ONLY - If Applicable)	ORGANISM SUSPECTED (If Applicable)

1	IF REQUESTING EXAMINATION FOR: HEPATITIS B TEST CODE 2740 COMPLETE ALL THAT APPLY																		
☐ Pregnancy (HBsAg)	☐ Exposure to someone with Hepatitis B	INFECTED PERSON'S DATE OF BIRTH	M	M	D	D	Y	Y	Y	Y									
INFECTED PERSON'S NAME																			
IF AN INFANT, MOTHER'S NAME																			
☐ Other (Specify):																☐ Court Order	☐ At Risk		

2	IF REQUESTING EXAMINATION FOR: SYPHILIS - DFA TEST CODE 2105 COMPLETE THIS SECTION			
Duration of Lesion			☐ Days ☐ Months ☐ Years	Specify Site:

3	IF REQUESTING EXAMINATION FOR: RABIES ANTIBODY SEROLOGY TEST CODE 2810 COMPLETE THIS SECTION								
Date of Last Rabies Vaccination	M	M	D	D	Y	Y	Y	Y	

4	IF REQUESTING EXAMINATION FOR: LYME BORRELIOSIS TEST CODE 2111 COMPLETE THIS SECTION										
ONSET DATE	M	M	D	D	Y	Y	Y	Y	EARLY DISEASE	☐ Valid Early Disease	☐ Erythema migrans (5 cm at least in diameter)
LATE DISEASE	☐ Neurologic ☐ Cardiologic ☐ Rheumatologic								State/County of Exposure		

5	IF REQUESTING EXAMINATION FOR: AEROBIC/ANAEROBIC CULTURE TEST CODES 0200/0300 COMPLETE ALL THAT APPLY

☐ Aerobe ☐ Anaerobe ☐ Microaerophile Gram ☐ Positive ☐ Negative ☐ Variable ☐ Rod ☐ Coccus ☐ Diplococcus

Bacterial Growth Char.: MacConkey ☐Pos ☐Neg Oxidase ☐Pos ☐Neg Catalase ☐Pos ☐Neg Dextrose ☐Oxidation ☐Fermentation

☐ Other: _____

2270	ADENOVIRUS BY CULTURE
0004	AFB SUSCEPTIBILITY - Cultural Isolate
0300	ANAEROBIC CULTURE – ID Complete # 5
2771	ARBOVIRUS ENCEP. PANEL (IgM) §
0709	AUTOCLAVE TEST STRIPS
2145	*BRUCELLA* SEROLOGY
2200	*CHLAMYDIA TRACHOMATIS* – Culture
2230	CYTOMEGALOVIRUS CULTURE
2580	CYTOMEGALOVIRUS IgG
2400	ENTEROVIRUS BY CULTURE
0603	*E. COLI* (SLT) TOXIN & SEROLOGY
0701	FOODBORNE ILLNESS - Stool or Food
2516	FUNGAL IMMUNODIFFUSION
0103	FUNGAL SLIDE & CULTURE Clinical Specimens
2155	*FRANCISELLA* SEROLOGY
2860	HANTAVIRUS
2800	HEPATITIS A VIRUS (IgM)
2590	HERPES SIMPLEX VIRUS IgG
2952	HCV - PCR
0400	*LEGIONELLA* CULTURE
2110	*LEGIONELLA* - DFA
0402	*LEGIONELLA* - HA
0708	LYME DISEASE CULTURE (Human)
0718	LYME DISEASE CULT. (Non-Human)
2111	LYME DISEASE - EIA Complete # 4 Above
2113	LYME DISEASE-IFA (Tick or Culture)
0801	*NEISSERIA GONORRHOEAE* - Isolation
0851	*NEISSERIA* - REFERRED CULTURE
0502	PARASITOLOGY - BLOOD
0503	PARASITOLOGY - WORM
0750	*PERTUSSIS* PCR
2105	SYPHILIS DFA **Complete # 2 Above**
2103	SYPHILIS VDRL - CSF Only
2121	TETANUS TOXIN EIA
2130	*TOXOPLASMA GONDII* - IgG
2140	*TOXOPLASMA GONDII* – IgM
2220	VARICELLA ZOSTER – CULTURE
2350	VIRAL RESPIRATORY PANEL – CULT.

§ May – October Includes Eastern Equine, California, St. Louis and West Nile.

[2]The Following Tests Must Have **Prior** MDCH Approval

2961	BACTERIAL TYPING – PFGE
0702	BOTULISM TOXIN
2973	ENTEROVIRUS - PCR
2954	HEPATITIS A VIRUS – PCR
2950	HIV – PCR
2250	MUMPS - CULTURE
2983	MUMPS - PCR
2820	MEASLES IgM
4309	NOVAL INFLUENZA A - PCR
2951	NOROVIRUS – PCR
0450	*PERTUSSIS* CULTURE
2830	RUBELLA IgM
0602	*SALMONELLA* SEROTYPING (Non-Human)
2102	SYPHILIS FTA - ABS DS
2109	SYPHILIS IgM WESTERN BLOT
0705	TOXIC SHOCK TESTING

***Sexually Transmitted Diseases – Definitions**

Symptoms:	Patient requesting examination due to symptoms, or, symptoms discovered on examination.
Infected Partner:	Patient has known exposure to STD (self-reported or documented).
Partner Risk:	Patient has multiple sex partners.
History of STD:	Patient has been diagnosed with a sexually transmitted disease within last 3 years.
Prenatal Visit:	Patient examination is part of prenatal visit.
Age recommended:	Recommended age criteria for screening female patients is ≤ 24 for family planning clinics, adolescent and juvenile detention sites, and all ages for STD clinics.
"Plan First!" Clients:	A "Plan First!" client seeking family planning services will receive screening and teaching. As a Title X Standards & Guideline requirement, *Chlamydia trachomatis* and *Neisseria gonorrhoeae* screening must be offered to "Plan First!" clients < 24 years of age, prior to provision of a contraceptive method, if risk factors are reported.
IUD Insertion:	Title X mandates that clients who are provided with Intrauterine Device (IUD) insertion must be tested for *N. gonorrhea* and *Chlamydia trachomatis* for diagnostic purposes and/or for maintenance of health status.

[1]All tests positive for *Chlamydia* will automatically be tested for *N. gonorrhoeae.*

Mycobacterial Slide and Culture Isolation

ANALYTES TESTED: *Mycobacterium tuberculosis* and *Mycobacterium* species.

TEST CODE: 0001

USE OF TEST:

To determine the presence of *Mycobacterium tuberculosis* and other *Mycobacterium* spp. in clinical specimens obtained from human patients: with clinical illness suggestive of Tuberculosis or other mycobacterial disease.

SPECIMEN COLLECTION AND SUBMISSION GUIDELINES:

Test Request Form DCH-0583 (DCH-0583 fillable)
Specimen Submission Guidelines
Transport Temperature: Ambient (Do not allow to freeze)

SPECIMEN TYPE:

Specimen Required:

Human clinical specimens, including sputum, urine, cerebrospinal fluid, tissues(not dry), bone marrow, blood, gastric contents (must be neutralized to pH 7.0 and less than 72 hours from time of collection) and other body fluids
Minimum Acceptable Volume: Minimum quantity of 5 ml of liquid specimen (1.0 ml of cerebrospinal fluid) or tissue 0.5 cm^3 to 2.0 cm^3 in size. Tissue biopsies (not dry) are accepted.

Container: Sterile, 50 ml, screw cap, polypropylene tube.
Shipping Unit: Unit 12 (IATA Category B).

SPECIMEN REJECTION CRITERIA:

Critical Data Needed For Testing:

Patient name or unique identifier
Specimen source
Date of specimen collection
Submitter name and address

Specimens will be rejected if they:

- are of insufficient quantity
- are of insufficient quality

- are received with either the specimen container not labeled or test request form does not contain critical data or does not agree with the information on the specimen.
- are not shipped according to IATA shipping regulations.
- are leaking and can easily be recollected. Every attempt will be made to salvage leaking or improperly submitted samples of cerebrospinal fluid, biopsy tissues, aspirates and other specimens attained by surgical means providing that the safety of the laboratory worker is not compromised.
- are submitted in improper transport medium (i.e. transport medium that is expired or a type which could compromise recovery of acid-fast organisms.

TEST PERFORMED:

Methodology: Fluorescent acid-fast microscopic examination and MGIT rapid broth/LJ-7H11S solid medium slant culture examination. Both tests are performed on all specimens.

Turn Around Time:

1. AFB microscopic examination - same day as received.
2. AFB culture isolation - 1 to 6 weeks.

Where/When Performed: Lansing/Monday through Friday.

RESULT INTERPRETATION:

Slide:

1. Positive AFB slide report means that acid fast bacilli (AFB) are detected in the clinical specimen indicates possible mycobacterial disease.
2. Negative microscopic examination for AFB does not exclude the presence of AFB in the specimen, since AFB are detected in less that 60% of AFB culture positive specimens.

Culture:

1. Positive AFB slide report: “Acid-fast bacilli found” indicates that acid fast bacilli (AFB) were detected in the clinical specimen which suggests possible mycobacterial disease.
2. Negative AFB culture report: "Mycobacteria not found" indicates that *Mycobacterium* spp. did not grow after 6 weeks of incubation , so viable AFB were not present.

FEES: N/A

NOTES:

1. Prior consultation with the laboratory is required before fecal specimens will be examined for *Mycobacterium* spp.
2. Although all cerebrospinal fluids will be examined upon request, optimal results will be obtained from larger volumes (3 ml or greater).
3. Occasionally, other microorganisms such as fungi and *Nocardia* spp. survive the decontamination process. If these microorganisms are grown from specimens which are normally considered sterile, the organisms may be identified if requested by the submitter.
4. Neutralized gastric contents (pH 7.0) must be received at MDCH within 72 hours of the time of collection of the specimen. Specimens which are not neutralized or which are greater than 72 hours old upon receipt will not be tested. It is best to collect gastric specimens early in the work week to assure that testing is not delayed by extended delivery time due to the weekend.
5. Failure to observe acid-fast bacilli (AFB) on microscopic examination or to grow AFB from culture examination does not rule out mycobacterial disease

ALIASES:

Mycobacterial Exam
Genetic Amplification Probe Direct Specimen Test for *M. tuberculosis* complex

ANALYTES TESTED: *Mycobacterium tuberculosis* complex

TEST CODE: 0006

USE OF TEST:

To determine the presence of *Mycobacterium tuberculosis* complex (Mtbc) by amplification of Mtbc specific genetic material (mRNA) from acid fast, smear positive respiratory clinical specimens. This is performed directly on the processed clinical specimen.

SPECIMEN COLLECTION AND SUBMISSION GUIDELINES:

Test Request Form DCH-0583 (DCH-0583 fillable)
Specimen Submission Guidelines
Transport Temperature: Ambient (Do not allow to freeze)

SPECIMEN TYPE:

Specimen Required:

Acceptable specimen types include: sputum (induced or expectorated), bronchial specimens (broncho-alveolar lavage or bronchial aspirate), or tracheal aspirates from patients not receiving antimicrobial therapy for tuberculosis. Genetic amplification testing will not be repeated on a specimen from a patient previously diagnosed with Mtbc. Specimens containing blood will not be tested. Processed spun sediments prepared by other TB laboratories from specimens listed above will be accepted for testing only by prior arrangement and notification. Non-pulmonary or AFB smear negative specimens will not be tested.

Minimum Acceptable Volume: Minimum quantity of 0.5 ml of processed spun sediment.
Container: Sealed, screw cap tube.
Shipping Unit: Unit 12 (IATA Category B).

SPECIMEN REJECTION CRITERIA:

Critical Data Needed For Testing:

MICHIGAN DEPARTMENT OF COMMUNITY HEALTH
BUREAU OF LABORATORIES
Mycobacterial Exam
Genetic Amplification Probe Direct Specimen Test for *M. tuberculosis* complex
Rev. February 2009

Patient name or unique identifier
Specimen source
Date of specimen collection
Submitter name, address and phone number

Specimens of any type will be subject to rejection if they:

- are of insufficient quantity
- are of insufficient quality
- are from a non-pulmonary source
- are tissue
- are bloody
- are received broken or leaking
- are from a patient previously diagnosed with Mtbc.
- are processed spun sediments referred by another laboratory without prior arrangement with the MDCH TB laboratory (517-335-9636) and prior notification, i.e. Faxing a completed "MDCH notification FAX submission sheet".
- are received with either the specimen container not labeled or test request form does not contain critical data or does not agree with the information on the specimen.
- are not shipped according to IATA shipping regulations.
- are received in a time frame which is detrimental to the intended use of the test.

TEST PERFORMED:

Methodology: Gen Probe (MTD)Direct Amplified Genetic Probe for *M.tuberculosis* complex (RNA PCR assay)
Turn Around Time: Specimens received Monday through Thursday - 24 hrs.
Specimens received Fridays - 72 hrs.
Where/When Performed: Lansing/Monday through Friday.

RESULT INTERPRETATION:

1. Positive – mRNA specific for *Mycobacterium tuberculosis* complex indicates that *M. tuberculosis*, *M. bovis*, *M. bovis* BCG, *M. africanum*, or *M. microti* has been detected in the clinical specimen, i.e. positive for Mtbc.
2. Negative – mRNA specific for *Mycobacterium tuberculosis* complex has not been detected, i.e. negative for Mtbc.
3. Inconclusive – MTD test results cannot reliably indicate either that *Mycobacterium complex* is present or absent due to presence of inhibitory substances in the specimen.

Reference Range: N/A

FEES: N/A

NOTES:

Blood in the specimen may cause equivocal results
Positive test results are not quantitative
The MTD assay is not a test of cure or viability of the Mtbc
Use of the MTD test is not validated for testing non-pulmonary specimens, tissues or other body fluids
The MTD test is not validated for testing AFB smear negative specimens
MTD product literature recommends that specimen be tested within 72 hours for reliable results

ALIASES:

PCR for Mtbc
Direct Genetic Probe for Mtbc
Nuclear Amplification Test for Mtbc

Mycobacterium spp. Referred Culture Identification

ANALYTES TESTED: Pure culture isolates of acid-fast bacilli

TEST CODE: 0005

USE OF TEST: To speciate pure culture isolates of acid-fast bacilli referred for species identification.

SPECIMEN COLLECTION AND SUBMISSION GUIDELINES:

Test Request Form DCH-0583 (DCH-0583 fillable)
Specimen Submission Guidelines
Transport: Ambient Temperature (do not allow to freeze)

SPECIMEN TYPE:

Specimen Required: Acid fast bacterial growth on egg based or synthetic agar slants in screw-cap tubes or from AFB positive bottles from rapid broth AFB detection systems.

Minimum Acceptable Volume: Detectable AFB growth
Container: Sealed screw cap solid medium slants or broth medium tubes/vials'
Shipping Unit: Unit 42 (IATA Category A)

SPECIMEN REJECTION CRITERIA:

Critical Data Needed For Testing:

Patient name or unique identifier
Specimen source
Date of specimen collection
Submitter name and address

Specimens of any type will be subject to rejection if they:

- are of insufficient quantity.
- are of insufficient quality.
- are of excessive age for the type of examination requested.
- are received with either the specimen container not labeled or test request form does not contain critical data or does not agree with the information on the specimen.

- are not shipped according to IATA shipping regulations.
- are broken or leaking and can easily be replaced.
- are mixed or overgrown with non-mycobacterial organisms.
- are submitted in petri.

TEST PERFORMED:

Methodology: Genetic Probes, HPLC and phenotypic biochemical testing
Turn Around Time:

Mycobacterium tuberculosis complex: 24-48 hours.
Mycobacterium avium complex, kansasii, xenopi and gordonae : 24-48 hours
Mycobacterium spp. other than above: 2-21 days

Where/When Performed: Lansing/Monday through Friday.

RESULT INTERPRETATION:

Speciation can confirm a previously identified mycobacterium or provide an identification if not already known. However, unless the isolate is *Mycobacterium tuberculosis*, its significance and relationship to the patient's pathologic process cannot be determined in the laboratory. Mycobacteria other than tuberculosis (MOTT) will be identified by rapid means, if possible. However, isolates that cannot be identified by rapid methods will be reported as MOTT. Further species identification of these isolates using other identification methods is available by request.

NOTES:

1. Please contact the Microbiology Laboratory with any questions concerning the submission of cultures for mycobacteriology testing.

2. Susceptibility testing is only available for *M. tuberculosis* complex.
3. The reporting of cultures submitted for identification but which are <u>not</u> pure isolates will be delayed and may not be attempted.
4. An identification of mycobacteria other than tuberculosis (MOTT) does not determine clinical significance or that a disease process exists due to MOTT.

ALIASES:

AFB Identification
Mycobacterial Identification

Mycobacterial Susceptibility Testing (*Mycobacterium tuberculosis* only)

ANALYTES TESTED: *Mycobacterium tuberculosis* culture isolates
TEST CODE: 0004

USE OF TEST:

For determining the susceptibility of *Mycobacterium tuberculosis* to anti-tuberculosis antibiotics commonly used to treat tuberculosis.

SPECIMEN COLLECTION AND SUBMISSION GUIDELINES:

Test Request Form DCH-0583 (DCH-0583 fillable)
Specimen Submission Guidelines
Transport Temperature: Ambient (do not allow to freeze)

SPECIMEN TYPE:

Specimen Required: Pure, viable cultures of *Mycobacterium tuberculosis* submitted on solid culture medium or liquid broth

Minimum Acceptable Volume: Visible growth
Container: Sealed screw cap solid medium slants or broth medium tubes/vials.
Shipping Unit: Unit 42 (IATA Category A)

SPECIMEN REJECTION CRITERIA:

Critical Data Needed For Testing:
Patient name or unique identifier
Specimen source
Date of specimen collection
Submitter name and address

Specimens of any type will be subject to rejection if they:

- are of insufficient quantity.
- are of insufficient quality.
- are of excessive age for the type of examination requested.

- are received with either the specimen container not labeled or test request form does not contain critical data or does not agree with the information on the specimen.
- are not shipped according to IATA shipping regulations.
- are broken or leaking and can easily be replaced.
- are mixed or overgrown with non-mycobacterial organisms.
- are submitted on petri plates.

TEST PERFORMED:

Methodology:

Bactec 460 Rapid Broth Susceptibility Method
Proportion Plate Method on Middlebrook 7H10 solid medium

Turn Around Time:

Bactec Rapid Broth Method: 7-14 days
Proportion Plate 7H10 Method: 4-21 days.

Where/When Performed: Lansing/Monday through Friday.

RESULT INTERPRETATION:

Results of susceptibility testing of *Mycobacterium tuberculosis* anti-mycobacterial antibiotics is expressed as “Susceptible” or “Resistant”.

These primary antituberculosis drugs will be routinely tested:

Isoniazid
Ethambutol
Rifampin
Pyrazinamide

These secondary antibiotics will be tested and reported when resistance is found to any one of the primary antibiotics and also when requested.

Streptomycin
Kanamycin
Ethionamide
Capreomycin
Cycloserine
Ciprofloxacin
Ofloxacin
Amikacin
PAS (p-aminosalicylic acid)

Reference Range: N/A

FEES: N/A

NOTES:

1. Contact the Microbiology Laboratory (517-335-9636) with questions concerning submission of cultures for susceptibility testing.
2. Susceptibility testing of *Mycobacterium tuberculosis* is performed and reported on the first *Mycobacterium tuberculosis* isolate received from a new patient, i.e. patient with no prior history of tuberculosis. Testing will be repeated at 90 day intervals if isolates of *Mycobacterium tuberculosis* continue be produced from a TB patient.
3. MDCH does not perform susceptibility testing on isolates of mycobacteria other than tuberculosis.

ALIASES:

AFB LAB TESTING

SPECIMEN

1. **REQUIRES THREE SPECIMENS ON THREE SUCCESSIVE DAYS.**
2. **BEST RESULTS COME FROM MATERIAL EXPECTORATED BY PATIENT SOON AFTER AWAKENING IN THE MORNING.**
3. **SPECIMEN SHOULD BE DELIVERED TO THE LAB ASAP.**

AFB SLIDE EXAMINATION (1 DAY)

1. **LEAST SENSITIVE OF ALL AFB TESTS**
2. **REQUIRES 100,000 AFB/ML FOR SLIDE TO BE POSITIVE**
3. **IF POSITIVE THE PATIENT CAN INFECT OTHERS.**
4. **POSITIVE SLIDE – CANNOT DETERMINE WHETHER TB OR MOTT**
5. **REPORT – WITHIN 24 HOURS OF RECEIVING SPECIMEN AT LAB.**

DIRECT PCR TB PROBE TEST (1-2 DAYS)

1. **VERY SENSITIVE AND VERY SPECIFIC**
2. **REQUIRES ONLY ONE AFB TO BE POSITIVE**
3. **PERFORMED ONLY ON NON-BLOODY PULMONARY SPECIMENS.**
4. **PERFORMED ON ONE OF THE NEW PATIENT'S FIRST SLIDE POSITIVE SPECIMENS (NOT AFTER TREATMENT IS STARTED)**
5. **POSITIVE (RELIABLE) - *Mycobacterium tuberculosis* complex (NOT MOTT)**
6. **REPORT – WITHIN 24 HOURS OF THE SLIDE POSITIVE REPORT**
7. **TEST NOT OFFERRED BY MOST LABS.**

AFB CULTURE (7-10 DAYS)

1. **MORE SENSITIVE THAN SLIDE**
2. **ONLY REQUIRES 10 AFB/ML OF SPECIMEN**
3. **CULTURE MAY BE AFB POSITIVE EVEN THOUGH THE SLIDE WAS REPORTED AFB NEGATIVE.**
4. **RAPID BROTH TESTING – POSITIVE WITHIN IN 1-2 WEEKS**
5. **AFB POSITIVE CULTURES ARE EXPECTED TO BE REPORTED IN LESS THAN 21 DAYS OF RECEIPT OF SPECIMEN IN THE LAB.**
6. **NEGATIVE CULTURE REQUIRES 6 WEEKS TO REPORT.**

AFB IDENTIFICATION (10-12 DAYS)

1. **PERFORMED AS SOON AS CULTURE BECOMES POSITIVE**
2. **RAPID PRELIMINARY IDENTIFICATION –MAY BE EXECTED TO BE REPORTED WITHIN 1-3 DAYS OF POSITIVE CULTURE REPORT.**
3. **PRELIMINARY IDENTIFICATION IS BASED UPON HPLC OR GENETIC PROBE.**
4. **GENETIC PROBE (NON-PCR) – REPORTS *M.tuberculosis* complex or MOTT ID**
5. **HPLC – REPORTS MOST *Mycobacterium* species**

SUSCEPTIBILITY (21 DAYS)

1. **PERFORMED ON GROWTH FROM CULTURE**
2. **PRIMARY ANTIBIOTIC SUSCEPTIBILITY REPORT MAY BE EXPECTED ONE WEEK FROM *M.tuberculosis* complex ID REPORT.**
3. **PYRAZINAMIDE SUSCEPTIBILITY REPORT MAY BE EXPECTED ONE WEEK AFTER PRIMARY DRUG REPORT.**
4. **SECONDARY AND TERTIARY ANTIBIOTICS MAY BE REQUESTED AND ARE REPORTED APPROXIMATELY THREE WEEKS AFTER INITIATED.**

Flow Diagram for TB Specimens

SPECIMEN

DIGESTION / DECONTAMINATION

Media Inoculation
(Medium Slants & Broth)

Culture Examination

AFB Positive Growth

Genetic Probe/HPLC
(AFB Identification)

Indirect Susceptibility

Smear Preparation & Staining
(AO & ZN)

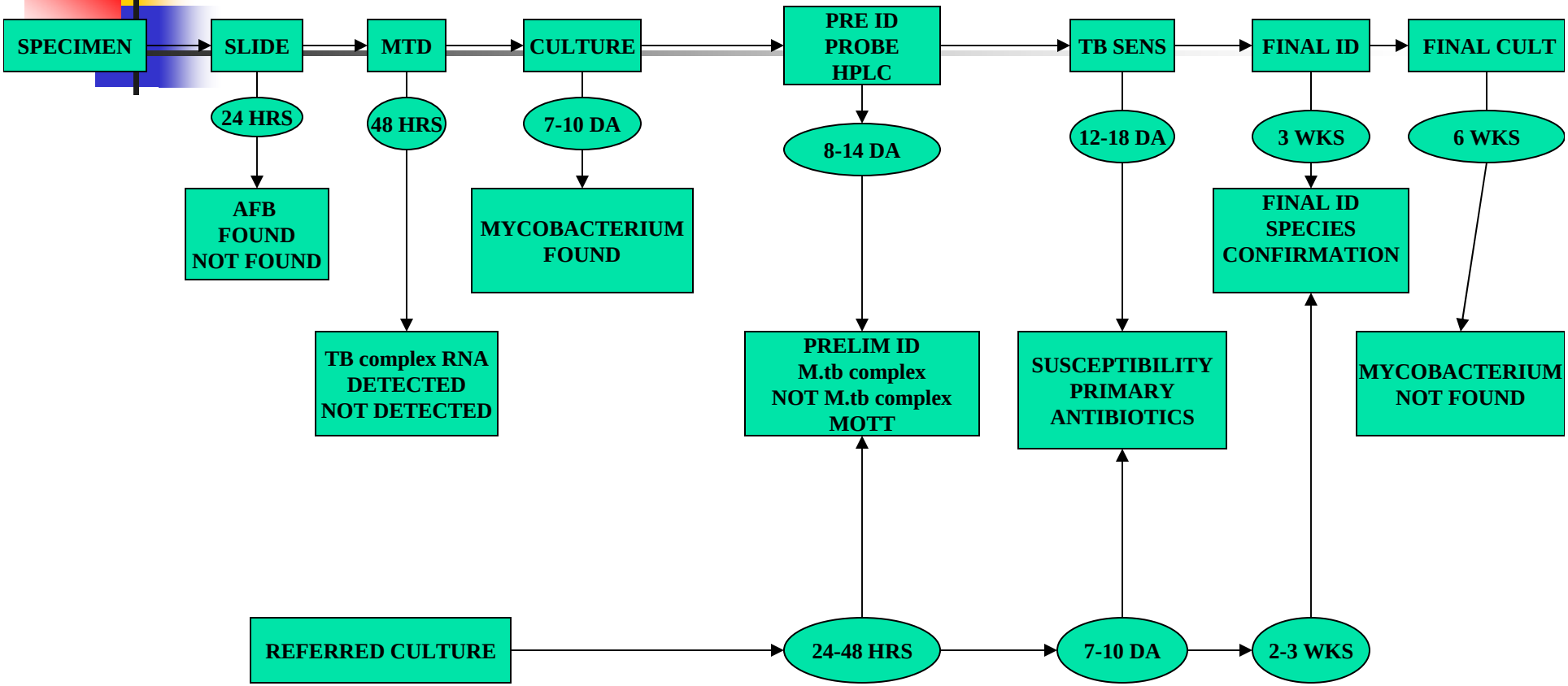
AFB Slide Examination

AFB Positive Slide (New)

Direct Amplified Probe (MTD)
(AFB Identification)

Direct Susceptibility

AFB TEST TIME-LINE



MDCH LAB REPORTS

"AFB SLIDE EXAMINATION REPORT"

(24 hours after specimen is received at the laboratory)

1. "Acid fast bacilli not found"

Acid fast bacilli are not present in high enough numbers to be seen on the microscopic slide examination. Report does not eliminate the posibility that TB bacillus is present. Patient is not considered infectious and does not need to be isolated from others.

2. "Acid fast bacilli found"

Acid fast bacilli were found and in very high numbers, high enough to consider patient to be very infectious. Patient may be infected with TB bacillus. Isolate patient from others.

3. "Few Acid fast bacilli found"

Acid fast bacilli were found in high enough numbers to be considered infectious. Patient may be infected with TB bacillus. Isolate patient from others.

NOTE:

a) **LEAST SENSITIVE OF ALL AFB TESTS**
b) **REQUIRES 100,000 AFB/ML FOR SLIDE TO BE POSITIVE**
c) **POSITIVE PATIENT CAN INFECT OTHERS.**
d) **POSITIVE SLIDE – CANNOT DETERMINE WHETHER TB OR MOTT**
e) **REPORTED WITHIN 24 HOURS OF RECEIVING SPECIMEN AT LAB.**

"AMPLIFIED TB PROBE (PCR) REPORT"

(24 hours after receiving a positive AFB slide report)

1. Mycobacterium tuberculosis complex rRNA "DETECTED"

Genetic material (RNA) has been found, which indicates that TB bacillus is present in the patient. TB RNA may be present as a result of active infection with *M.tuberculosis* or *M.bovis*. However, TB RNA may also be present following successful therapy which has rendered the TB bacillus to be non-viable or inactive. (Report on RVCT)

2. Mycobacterium tuberculosis complex rRNA "NOT DETECTED"

TB RNA is "NOT" present in the patient's specimen. So, the AFB found on the positive AFB slide examination is due to another mycobacterial species and is not normally considered to be communicable or infectious to others.

NOTE:

a) **VERY SENSITIVE AND VERY SPECIFIC**
b) **REQUIRES ONLY ONE AFB TO BE POSITIVE**
c) **PERFORMED ONLY ON NON-BLOODY PULMONARY SPECIMENS.**
d) **PERFORMED ON ONE OF THE NEW PATIENT'S FIRST SLIDE POSITIVE SPECIMENS (NOT AFTER TREATMENT IS STARTED)**
e) **POSITIVE (RELIABLE) - *Mycobacterium tuberculosis* complex (NOT MOTT)**
f) **REPORT – WITHIN 24 HOURS OF THE SLIDE POSITIVE REPORT**
g) **TEST NOT OFFERED BY MOST LABS.**

"CULTURE ISOLATION REPORT"

(AFB positive reports may require less than 6 weeks/AFB negative culture reports require at least 6 weeks)

1. "ACID FAST BACILLI FOUND ON CULTURE/IDENTIFICATION REPORT WILL FOLLOW"

Acid fast bacilli have been found on culture media which may be due to growth of a mycobacterial species including the possibility of the TB bacillus, *M.tuberculosis*. A rapid identification test will be performed within 24 hours to determine whether the bacterium found is *M.tuberculosis* or not. (A preliminary mycobacterial identification report may be expected within 24 -48 hours)

2. " MYCOBACTERIUM NOT FOUND"

No mycobacterial growth has been found, including *M.tuberculosis*, after 6 weeks of incubation of culture media.

NOTE:

a) **MORE SENSITIVE THAN SLIDE**
b) **ONLY REQUIRES 10 AFB/ML OF SPECIMEN**
c) **CULTURE MAY BE AFB POSITIVE EVEN THOUGH THE SLIDE WAS REPORTED AFB NEGATIVE.**
d) **RAPID BROTH TESTING – POSITIVE WITHIN 1-2 WEEKS**
e) **AFB POSITIVE CULTURES ARE EXPECTED TO BE REPORTED IN LESS THAN 21 DAYS OF RECEIPT OF SPECIMEN IN THE LAB.**
f) **NEGATIVE CULTURE REQUIRES 6 WEEKS TO REPORT.**

"AFB IDENTIFICATION REPORT"

Preliminary Identification:

(24-48 hours after culture medium has produced AFB growth, growth is referred for preliminary mycobacterial identification testing)

1. "PRELIMINARY REPORT (PROBE/HPLC) Mycobacterium tuberculosis complex ADDITIONAL REPORT WILL FOLLOW"

The culture isolate referred for identification has been identified as *M.tuberculosis* complex. (Report on RVCT). Expect to receive another report confirming and clarifying this report.

2. "PRELIMINARY REPORT (PROBE/HPLC) Mycobacterium sp. Other than M.tuberculosis ADDITIONAL REPORT WILL FOLLOW"

The culture isolate referred for identification has been determined be a *Mycobacterium species* other than *M.tuberculosis* complex (MOTT). (No RVCT report is necessary) Expect another report clarifying the specific mycobacterial species.

Final Identification:

(2-3 weeks after the preliminary ID)

1. "FINAL REPORT Mycobacterium tuberculosis"

M. tuberculosis has been confirmed by testing subsequent to genetic probe or HPLC testing. (RVCT should have already been submitted)

2. "FINAL REPORT Mycobacterium spp."

A Mycobacterium species other than *M.tuberculosis* , such as *M.gordonae*, *M.avium* complex, or *M.fortuitum* complex, has been confirmed by testing subsequent to genetic probe or HPLC testing. (RVCT is not required)

NOTE:

a) **PERFORMED AS SOON AS CULTURE BECOMES POSITIVE**
b) **RAPID PRELIMINARY IDENTIFICATION –MAY BE EXECTED TO BE REPORTED WITHIN 1-3 DAYS OF POSITIVE CULTURE REPORT.**
c) **PRELIMINARY IDENTIFICATION IS BASED UPON HPLC OR GENETIC PROBE.**
d) **GENETIC PROBE – REPORTS *M.tuberculosis* complex or MOTT ID**
e) **HPLC – REPORTS MOST *Mycobacterium* species.**

"TB SUSCEPTIBILITY REPORT"

(Primary antibiotics reported 7 days after preliminary ID report / secondary antibiotics 3 weeks later)

1. "SUSCEPTIBILITY REPORT

Mycobacterium tuberculosis

Antibiotic		Interpretation
Isoniazid	0.2 mcg/ml	RESISTANT
Isoniazid	1.0 mcg/ml	SUSCEPTIBLE
Ciprofloxacin	2.0 mcg/ml	SUSCEPTIBLE
Streptomycin	2.0 mcg/ml	SUSCEPTIBLE
Streptomycin	10.0 mcg/ml	SUSCEPTIBLE
Ethambutol	5.0 mcg/ml	SUSCEPTIBLE
Rifampin	1.0 mcg/ml	RESISTANT
Kanamycin	6.0 mcg/ml	SUSCEPTIBLE
Ethionamide	5.0 mcg/ml	SUSCEPTIBLE
Cycloserine	30.0 mcg/ml	SUSCEPTIBLE
Capreomycin	10.0 mcg/ml	SUSCEPTIBLE
Pyrazinamide	100.0 mcg/ml	SUSCEPTIBLE
Ethambutol	10.0 mcg/ml	SUSCEPTIBLE
Amikacin	6.0 mcg/ml	SUSCEPTIBLE
Ofloxacin	2.0 mcg/ml	SUSCEPTIBLE
P-aminosalicylic acid	2.0	SUSCEPTIBLE
P-aminosalicylic acid	10.0	SUSCEPTIBLE

NOTE:

a) **PERFORMED ON GROWTH FROM CULTURE**

b) **PRIMARY ANTIBIOTIC SUSCEPTIBILITY REPORT MAY BE EXPECTED ONE WEEK FROM *M.tuberculosis* complex ID REPORT**

c) **PYRAZINAMIDE SUSCEPTIBILITY REPORT MAY BE EXPECTED ONE WEEK AFTER PRIMARY DRUG REPORT**

d) **SECONDARY AND TERTIARY ANTIBIOTICS MAY BE REQUESTED AND ARE REPORTED APPROXIMATELY THREE WEEKS AFTER INITIATED.**

"TB GENOTYPING (DNA FINGERPRINTING)"

(Results are reported to MDCH TB epidemiology within 7 days after *M.tuberculosis* complex identifiction)

Genotyping results:

1. **Are not needed if local TB control program staff has already identified an epi-link between patients as a result of contact investigations.**
2. **Are only used when contact investigation has failed to determine epidemiological links.**
3. **May associate a case with a cluster of cases of the same genotype.**
4. **Are sent by Michigan's TB genotyping laboratory to MDCH epidemiology staff for analysis.**
5. **Are communicated to local health departments when relatedness to another case is suggested.**

NOTE:

a) **Contact investigation preceeds genotyping.**
b) **Same genotype suggests relatedness but does not confirm relatedness.**
c) **Cases with the same genotype may be related.**
d) **Cases with the same genotype may not be related at all.**
e) **Genotyping may be needed by the laboratory to determine whether a new positive case is due to cross contamination or lab error.**

GLOSSARY OF TB LABORATORY TERMS

Acid-fast bacilli (AFB): Bacteria that retain certain dyes after being washed in an acid solution. Most acid-fast organisms are mycobacterium. *Nocardia* spp. and *Rhodococcus* spp. may also be weakly acid-fast. When AFB are seen on a stained smear of sputum or other clinical specimen, a diagnosis of TB should be suspected; however, the diagnosis of TB is not confirmed until an identification of *M. tuberculosis* complex has been reported, either by an amplified genetic TB probe testing, i.e. MTD/PCR performed directly on the specimen or by HPLC or non amplified genetic TB Probe testing performed on bacterial growth detected on culture medium.

Amplified Genetic Probe (Gen Probe's MTD test): A laboratory procedure used to test directly a patient's pulmonary specimen without waiting for growth from culture. This test procedure amplifies genetic material, DNA or RNA, which has been extracted from AFB which are found in the specimen. It uses a polimerase chain reaction (PCR) to provid enough genetic material for rapid and precise genetic probe identification of *M.tuberculosis and M. bovis*. The identification test can be performed directly on the patient's specimen and can be completed within 2 hours.

BACTEC®: Is a commonly used rapid broth culture method for early growth of acid fast bacilli. It provides rapid growth (in 7-14 days) and rapid drug-susceptibility testing (in 5-6 days). When BACTEC® is used in conjunction with rapid identification methods, *M. tuberculosis* complex can be identified within 10-14 days of specimen collection.

Culture: (noun) Bacterial growth on microbiological media. To "culture" (verb) refers to the process of growing bacteria in the laboratory so that organisms can be tested for identification, antibiotic susceptibility and genotyping. To culture can also mean to inoculate a patient's specimen to microbiological culture media in an attempt to grow bacteria, (i.e. a "culture" (noun) of bacteria).

DNA Probe: A laboratory procedure used for testing bacterial growth from culture which provides rapid and precise identification of AFB (e.g. *M tuberculosis and M. bovis*). The identification test can be completed within 2 hours after AFB growth has been detected in culture media.

Droplet nuclei: Microscopic liquid particles produced when a person coughs, sneezes, shouts, or sings. The droplets produced by an infectious TB patient can carry tubercle bacilli and may remain suspended in the air for prolonged periods of time being suspended in normal air currents in the room.

Drug resistance, acquired: A resistance to one or more anti-TB drugs that develops while a patient is receiving therapy and which usually results from the

patient's nonadherence to therapy or the prescription of an inadequate regimen by a health care provider.

Drug resistance, primary: A resistance to one or more anti-TB drugs that exists before a patient is treated with the drug(s). Primary resistance occurs in persons exposed to an infected case which has been diagnosed with a drug-resistant strain of *M. tuberculosis*.

Drug susceptibility pattern: The anti-TB drugs to which the tubercle bacilli cultured from a TB patient are susceptible or resistant based on drug susceptibility tests.

Drug susceptibility tests: Laboratory tests that determine whether the tubercle bacilli cultured from a patient are susceptible or resistant to various anti-TB drugs.

EMB: Ethambutol – a primary anti-TB drug used to treat tuberculosis caused by *M.tuberculosis* or *M.bovis*.

Exposed (to TB): Having come in contact with a case of active tuberculosis, who is considered to be infectious, i.e. AFB slide positive and producing sputum or coughing.

Fluorochrome stain: A technique for staining a clinical specimen with fluorescent dyes to perform a microscopic examination (smear) for mycobacteria. This technique is preferable to other staining techniques because the mycobacteria can be seen easily and the slides can be read quickly.

Genetic Probe: A laboratory procedure used for testing bacterial growth for DNA or RNA unique to a cultured bacterial isolate, which can be used to provide rapid and precise identification of AFB (e.g. *M tuberculosis and M. bovis*). The identification test can be completed within 2 hours after AFB growth has been detected.

High Performance Liquid Chromatography (HPLC): Detects differences in the spectrum of mycolic acids in the cell wall harvested for culture growth, equally rapid as a nucleic acid probe, and can identify most pathogenic mycobacteria species.

INH: Isoniazid – a primary anti-TB drug used to treat tuberculosis caused by *M.tuberculosis* or *M.bovis*.

Infected with TB: to have inhaled droplet nuclei containing the tubercle bacillus.

Infectious: An active case of tuberculosis with AFB which can be seen by microscopic examination of the person's pulmonary secretions (sputum).

MOTT: Mycobacterium other than *Mycbacterium tuberculosis* (TB).

Mycobacterium Tuberculosis direct test (MTD): Amplified genetic probe test performed for the detection of *M. tuberculosis* in both smear positive and smear negative clinical specimens.

Multidrug-resistant tuberculosis (MDR-TB): Active TB caused by *M. tuberculosis* organisms that are resistant to more than one anti-TB drug.

***M tuberculosis* complex**: A group of closely related mycobacterial species that can cause active TB (e.g., *M tuberculosis*, *M. bovis*, *M. africanum* and *M.microti*); most TB in the United States is caused by *M. tuberculosis*.

Nucleic acid probes: A rapid method of species identification. Once a culture is grown nucleic acid probes can identify species in 2-4 hours.

PZA: Pyrazinamide – a primary anti-TB drug used to treat tuberculosis caused by *M.tuberculosis* or *M.bovis*.

PAN Sensitive: TB case whose TB infection has been determined to be susceptible to "Primary anti-tuberculosis drugs", i.e. INH, EMB, RA, Strep and PZA.

QuantiFERON ® - TB Gold test (QFT-G): Whole blood test for use as an aid in diagnosing Mycobacterium tuberculosis infection, including latent tuberculosis infection and tuberculosis disease. This test was approved by the U.S. Food and Drug Administration in 2005.

Resistance: The ability of some strains of bacteria, including *M. tuberculosis*, to grow and multiply in the presence of certain drugs that ordinarily kill them; such strains are referred to as drug-resistant strains.

RA: Rifampin– a primary anti-TB drug used to treat tuberculosis caused by *M.tuberculosis* or *M.bovis*.

SIRE: the antimycobacterial drugs, Streptomycin, Isoniazid, Rifampin and Ethambutol, which are four primary antibiotics to test the susceptibility of *M.tuberculosis* and *Mycobacterium bovis.*

Smear (AFB smear): A laboratory technique for visualizing mycobacteria. The specimen is applied (smeared) onto a microscope slide, fixed and stained, then examined using a microscope. Smear results should be available within 24 hours. If mycobacteria (AFB) are observed on an AFB smear, it is usually an indication that the patient is infectious. However, a positive result does not

confirm the diagnosis of TB because organisms other than *M. tuberculosis* (MOTT) may also be seen on the smear as AFB.

Specimen: Any body fluid, secretion, or tissue sent to the laboratory for the purpose of laboratory testing, such as for AFB smear and to culture for *M.tuberculosis*.

Sputum: Phlegm coughed up from deep within the lungs. If a patient has pulmonary disease, an examination of the sputum by smear and culture can be helpful in evaluating the organism responsible for the infection.

Sputum smear, positive: when AFB are visible on the sputum smear viewed using a microscope. Persons with a sputum found to be smear positive for AFB are considered more infectious than those with smear-negative sputum.

TAT: Turn around time

Tubercle bacilli: *M.tuberculosis* bacilli.

Virulence: The degree of pathogenicity of a microorganism as indicated by the severity of the disease produced and its ability to invade the tissues of a host, *M. tuberculosis* is a virulent organism.

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Federal Shipping Regulations www.cdc.gov/od/ohs/biosfty/shipregs.htm

MDCH Bureau of Laboratorie's guidelines and forms www.michigan.gov/mdchlab

Centers for Disease Control and Prevention (CDC) www.cdc.gov

CDC Guidelines for use of Quantiferon test www.cdc.gov/mmwr/

American Lung Association of Michigan www.alam.org

MI-ACET www.michigantb.org

MDSS: Suspect/Active Tuberculosis Case Reporting Guide

MDCH TB Program- January 2011

For more information:

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Introduction:

The Michigan Disease Surveillance System (MDSS) TB Case Report Form is designed to collect information on suspects and cases of active tuberculosis (TB) disease diagnosed in Michigan. The MDCH TB Program began collecting suspect and active TB case report data through the MDSS TB Case Report Form in January, 2008. The data collected in this form is very similar to the data that has historically been collected on the Report of Verified Case of Tuberculosis (RVCT) which is the currently used case report form. There are some additional variables that have been added to the November 2010 release of MDSS TB Form. The newest MDSS form reflects the newest required data elements from the CDC.

Local patient identifying information, though collected by state and local health departments, is not transmitted to the CDC. The surveillance information transmitted to the CDC is used for statistical and analytic reports in which no individual can be identified, and for special investigations of the natural history and epidemiology of TB. Thus, consistency and accuracy of data collection is important so that Michigan is properly represented in the national TB picture. The following instructions are designed to explain the reporting process that will be used in the new MDSS TB Form.

The MDSS TB Suspect/Case Report Form Sections:

1) Report of Suspect/Verified Case of Tuberculosis Section (Pages 1-5): Investigation Information, Patient Information, Demographics, Referral Information, Clinical Information, Laboratory Information, Epidemiologic Information, and Treatment Information are collected in this five-page section.

2) Follow-Up Report 1 – Initial Drug Susceptibility Report Section, **State Use Only**, (Page 6): Susceptibility results from the MDCH Lab are collected in this section.

3) Follow-Up Report 2 – Case Completion Report Section (Pages 7-8): Treatment outcomes are collected in this section.

4) Contact Information Section (Page 9): General Information about contacts to active TB cases is collected on this form.

5) Other Information Section (Page 10): Comments or Additional Information is collected in this section.

Process for Reporting Suspect and Active Cases of Tuberculosis:

1) A suspect /active case of TB can be reported to the Local Health Department (LHD) by a laboratory or health care practitioner (HCP). Similar to other reports in the MDSS, lab reports from the MDCH lab will be submitted electronically into the MDSS. Also, like other reportable conditions, HCPs may enter initial information about a suspect/active case of TB into the MDSS; therefore LHD staff need to be aware of new reports of TB cases in the MDSS that require investigation.

2) If entering the case manually, LHD reports a suspect/active case to MDCH TB Program by entering the case into the MDSS under the reportable condition: "Tuberculosis" as soon as a specimen has been submitted to a lab and/or the patient has been started on TB treatment. It is important at this step to leave the Investigation Status as "New".

3) If an electronic lab report is submitted and MDCH staff knows the case will be counted, a RVCT number and count date will be added and the status will be changed to "Active".

4) LHD will then complete the Report of Suspect/Verified Case of Tuberculosis section, pages 1-5, the fields "Submitted By", "Date", "Health Department", "Phone Number" and "Ext." on page 11 and change the Investigation Status to "Review" to indicate the case is ready for review by MDCH TB Program. It is important at this step to leave the Investigation Status as "Review" as this is the signal for the MDCH TB Program to review the case for counting. For any data that are unknown, please mark "unknown" or "pending" as appropriate.

5) When drug susceptibility information is available, MDCH TB Program will enter the information into Follow-Up 1 Report, page 6, of the MDSS.

   The case will then be marked by MDCH as "Completed" to send updated notification to CDC.

6) Once the case has been submitted, the investigation status will be changed to "Completed-follow up" for the duration of therapy. This allows MDCH and LHD to edit the RVCT form; these edits will be sent to CDC on a weekly basis.

7) LHD staff are responsible for case management of the TB patient. The follow-up 2 form of the RVCT should be completed upon therapy completion and not before. The investigation status should remain as "Completed- follow up" until completed.

8) After the Follow-Up 2 information has been added to the MDSS, change the investigation status to "Review". MDCH will review all of the entered information and once all necessary information is collected, MDCH will mark the case "Completed" for final notification to CDC.

General Instructions for Form Completion:

The instructions in this guide are not a substitute for guidelines about TB diagnosis, treatment, or control. Any contradictions between the implied content of these instructions and the policies and practices of local health departments or other local health providers should be discussed, according to the context, with the state TB program.

All data items on the forms should be completed according to these instructions. Please direct all questions for clarification, or assistance with unusual circumstances to the state TB Epidemiologist.

The sections and variables that are marked "State Use Only" should be left blank. All other questions should only be left blank or marked pending if the information requested is pending.

Mark the one best choice from among the values listed unless the field is marked "select all that apply". For example, the Site of Disease field allows more than one selection. If the answer to an item is not among the choices given on the form, please note it in the Comments section of the form.

If a valid value cannot be determined for a data item, mark the field "unknown" or if there is not an "unknown" option, please write "unknown" in the text field or leave the numeric field blank. This will let the MDCH TB Program know that the person who completed the form attempted to collect this information, but was unable to do so. All of the data collected on the TB Case Reporting forms are a standard part of suspect TB case work-up. All data items left blank or marked "unknown" without explanation will be verified with you by state TB Program staff.

Patient history, without medical documentation, should not be accepted for any of the clinical, treatment, or laboratory information requested on the Tuberculosis Case Reports. The information required by the forms can however, be obtained from any documented medical records such as those found in hospitals, clinics, directly observed therapy records, pharmacy and prescription records.

Detailed Instructions for Completing Each Section:

I. REPORT OF SUSPECT/VERIFIED CASE OF TB (RVCT) SECTION:

i. Investigation Information:

1. Investigation ID **(Automatic)** – This number is automatically generated by MDSS and cannot be changed.

2. State TB Case Number **(State Use Only)** – This number is assigned by MDCH as the official identification number for the case. If there is communication needed between the state and CDC, this is the number that is used in order to protect confidentiality of the patient.

3. Part of an outbreak **(State Use Only)** – This field designates whether a TB case is involved in a genotype cluster and will be marked as such when genotyping information is available from MDCH Lab.

4. Outbreak Name **(State Use Only) –** If the TB case is involved in a genotype cluster (indicated in the previous field), this field designates the name of the genotype cluster. This number allows for matching cases based on their genotypes.

5. Referral Date **(Automatic) –** This date is automatically generated by MDSS and cannot be changed.

6. Investigation Status – This field defaults to "New".

   New – This option indicates that a case is new and ready for investigation by the LHD.

   Active – This option is used for cases that will be counted but do not have the RVCT form completed.

   Review – This option indicates that the TB Report Form is ready for review by MDCH TB Program.

   Completed (*State Use Only*) – This option is only used by MDCH TB Program. It is important that only MDCH marks investigation status as "Completed" since this triggers the MDSS to transmit the data to CDC.

   Completed – Follow up – This option is used after the case has been "Completed" and sent to the CDC. This will be the status that allows changes to be made while the case is still undergoing treatment. Once the treatment is complete, the status will be changed back to "completed".

   Superceded – This option is used in the deduplication process. This should no longer be used.

   Cancelled – This option should only be used if there was no investigation for some reason.

Otherwise, if there is an investigation and a case was ruled out, the "Case Status" field should be marked "not a case" and the investigation status field should be marked "completed."

7. Case Status:

   Confirmed – This option indicates that a TB case meets one of the CDC TB Case Definitions (See Appendix A).

   Confirmed- Non Resident – This option indicates that the case has been counted in another State or country but is being managed by a local health department in Michigan. This is used to measure the burden of tuberculosis disease. If this status is chosen, a "Linking State Case Number" should be entered.

   Not a Case – This option is marked if a suspect case is initially reported but subsequently does not match one of the CDC TB Case Definitions.

   Probable – This option is a standard field in MDSS for all conditions/diseases. However, due to the unique nature of the CDC TB Case Definitions a TB case is considered either suspect or confirmed. Therefore, this option should not be selected.

   Suspect – This option is marked when a suspect TB case is reported to or discovered by the LHD. A suspect case is one in which there is clinical or laboratory evidence supporting submission of a specimen to a laboratory and/or starting the patient on TB treatment.

8. Patient Status:

   Inpatient – This option indicates that the patient is hospitalized at the time of diagnosis or discovery.

   Outpatient – This option indicates that the patient is not hospitalized at the time of diagnosis or discovery.

   Died – This indicates that the patient is dead at the time of diagnosis or discovery.

9. Patient Status Date **(Automatic)** – This date is automatically generated by MDSS and is the date at which the patient status is identified. This date can be changed by the user if needed.

10. Diagnosis Date – This is the date at which the diagnosis of TB was made by a Health Care Practitioner. In general, the diagnosis date should precede or be the same as the date when treatment was initiated. If treatment was not initiated at the time of case-reporting or the date of treatment initiation is unknown, use the following guidelines to enter a diagnosis date. For patients diagnosed clinically (no specimens collected, no results available or negative results but patient is clinically suggestive of tuberculosis disease), enter the date treatment was initiated. For patients with laboratory results suggestive of tuberculosis (e.g. AFB-positive sputum smear or preliminary identification of M.

11. Onset Date – This is the date at onset of TB signs or symptoms.

ii. Patient Information:

1. Patient ID **(Automatic)** – This number is automatically generated by MDSS and cannot be changed.

2. First – This is the patient's first or given name.

3. Last – This is the patient's last or surname.

4. Middle – This is the patient's middle name/initial.

5. Patient Address of Residence **(Can only be modified through address history tab)**

   This should represent the home address or community which the patient considers their home, whether permanent or temporary in nature. Coordination among neighboring LHDs may be necessary to determine proper jurisdiction for a given case. For example, cases diagnosed in an acute care hospital are not recorded at the address of the hospital, but rather at the patient's regular home address. However, those diagnosed in a long term care or correctional facility are usually recorded at the address of that facility.

   Immigrants, migrants, U.S. military personnel, and other transitory individuals should be reported as residents of the community in which they reside at the time of diagnosis. Homeless persons or others without any fixed residence should also be reported in the community in which they are living at the time of diagnosis (e.g., the address of the shelter in which the patient spent the night).

   Street Address – This is the patient's street address at the time of diagnosis.

   Within City Limits
   Yes – The patient lives within the city limits
   No – The patient does not live within the city limits

   City – This is the patient's city of residence at the time of diagnosis.

   County – This is the patient's county of residence at the time of diagnosis.

   State – This is the patient's state of residence at the time of diagnosis.

   Zip – This is the patient's zip code at time of residence.

6. Home Phone – This is the patient's current home telephone number. This number should be updated as it changes.

Ext. – This is the extension number to the patient's current home phone number.

7. Other Phone – This is any other telephone number that is used to reach the patient.

   Ext. – This is the extension number to the patient's other phone number.

8. Parent/Guardian (required if under 18, leave blank if unknown)

   First – This is the parent/guardian's first name.

   Last – This is the parent/guardian's last name.

   Middle – This is the parent/guardian's middle name/initial.

iii. Demographics:

1. Sex – Female or Male. Mark the appropriate box for the biological sex of the patient.

2. Date of Birth – Indicate the month, day, and year of the birth of the patient in the format mm/dd/yyyy. Partial dates are not acceptable.

3. Age **(Automatic)** – This number is automatically generated by MDSS and cannot be changed. This is the age at onset.

4. Age Units **(Automatic) –** This number is automatically generated by MDSS and cannot be changed. This is the age unit at onset.

5. Race – Select one based on the patient's self identity. Indicate the race that the patient considers himself or herself to be.

   Caucasian – Persons who have origins in any of the original peoples of Europe, the Middle East or North Africa.

   African American – Persons who have origins in any of the black racial groups of Africa.

   American Indian/Alaska Native – Persons who have origins in any of the original peoples of North and South America (including Central America), and who maintain tribal affiliation or community attachment.

   Hawaiian/Pacific Islander – Persons who have origins in any of the original peoples of Hawaii or other Pacific Islands. Specify, in the space provided, the Pacific Island or ethnic group to which the person associates. These include: Carolinian, Chamarro, Chuukese, Fijian, Guamanian, Kiribati, Kosraean, Mariana Islander, Marshallese, Melanesian, Micronesian, Native Hawaiian, New Hebrides, Palauan,

Papua New Guinean, Pohnpeian, Polynesian, Saipanese, Samoan, Solomon Islander, Tahitian, Tokelauan, Tongan, and Yapese.

Asian – Persons who have origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent. Specify, in the space provided, the Asian country or ethnic group to which the person associates. These include: Asian Indian, Bangladeshi, Bhutanese, Burmese, Cambodian, Chinese, Filipino, Hmong, Indonesian, Iwo Jiman, Japanese, Korean, Laotion, Madagascar, Malaysian, Maldivian, Nepalese, Okinawan, Pakistani, Singaporean, Sri Lankan, Thai, and Vietnamese.

6. Hispanic Ethnicity – Select one based on the patient's self identity. Indicate whether or not the person considers themselves to be Hispanic or Latino.

   Hispanic/Latino – The patient considers himself/herself to be of Spanish, Hispanic or Latino origin. Persons who are from many of the countries of Central or South America, Mexico, Puerto Rico, Cuba, or Dominican Republic are likely to consider themselves to be Hispanic or Latino.

   Non-Hispanic/Latino – The patient does not consider himself/herself to be Hispanic or Latino.

7. Arab Ethnicity – Select one based on the patient's self identity. Indicate whether or not the person considers themselves to be Arab.

   Arab- The patient considers himself/herself to be of Arab origin. Persons who are from many countries of the Middle East, Iraq, Iran, Syria, Lebanon, are likely to consider themselves to be Arab.

   Non-Arab – The patient does not consider himself/herself to be Arab.

8. Worksites/School – This is the name of the workplace or school the patent attends at the time of signs or symptoms onset.

9. Occupation/Grade – This is the patient's occupation or grade in school at the time of sign or symptom onset.

iv. Additional Surveillance Information

1. Count Status – This field is only used by the MDCH TB program. It is used by the CDC to determine whether or not to count as a case.

   Count as a TB case – The case will be counted in the State as a case of TB.

   Verified Case: Counted by another U.S. area – The TB case is being managed in the State but has been counted in another U.S. area. U.S. areas include all 50 states, US

territories, US Islands Areas and U.S. outlying areas (e.g., Puerto Rico, American Samoa, Federated States of Micronesia, Guam, Republic of the Marshall Islands, Commonwealth of the Northern Mariana Islands, Republic of Palau, and the U.S. Virgin Islands).

Verified case: TB treatment in other country – The TB case is being managed in the State but was counted by another country

2. Linking State Case Number – Each case can have up to 2 RVCT State Case Numbers associated with to it. Under the Reason, explain the purpose of the link by entering one of the codes.

   Epi Link – The State Case number entered is an epidemiologically linked case, source case, or contact with another case. If you have identified the source case for the TB case for which you are completing the RVCT and the RVCT State Case Number of the source case is available, enter the RVCT State Case Number of the source case here. Another example of an epidemiologically linked case is transmission from one family member to another.

   Recurrence/Previous diagnosis of TB – If you are completing a "recurrence" RVCT for a diagnosis of TB disease in the same patient that recurred *within* 12 months after the completion of therapy, you must enter the RVCT State Case Number of the original TB case here. A previous diagnosis of TB can have occurred any time in the past. A patient is considered to have a previous diagnosis of TB if: 1. TB disease was verified in the past **or** 2. The patient completed therapy (even if the case-to-case interval is within 12 months) **or** 3. The patient was lost to supervision for more than 12 months and now has verified disease again.

   Transfer – If you are managing a TB case counted by another area (out of state); enter the RVCT State Case Number of the case from the transferring jurisdiction here. Transfer cases are linked when the patient is in therapy and transfers from another reporting area that is not in Michigan. The patient could have moved or appeared at a health department in another are after being lost to follow up.

v. Referral Information:

1. Person Providing Referral – This is the person that initially reported the case to the LHD.

   First – This is the first name of the person reporting the case to the LHD.

   Last – This is the last name of the person reporting the case to the LHD.

   Phone – This is the telephone number for the person reporting the case to the LHD.

   Ext. – This is the extension to the telephone number of the person reporting the case to the LHD.

   Email – This is the email address for the person reporting the case to the LHD.

2. Primary Physician – This is the physician who is the TB patient's primary care giver during the duration of his or her TB treatment. If TB treatment is being given by the physician at a LHD TB clinic, please use the name of this physician.

First – This is the first name of the primary care physician.

Last – This is the last name of the primary care physician.

Phone – This is the telephone number where the primary care physician can best be contacted.

Ext. – This is the extension to the telephone number where the primary physician can best be contacted.

Email – This is the email address where the primary physician can best be contacted.

Street Address – This is the primary physician's office street address.

City – This is the city where the primary physician's office is located.

County – This is the county where the primary physician's office is located.

State – This is the state where the primary physician's office is located.

Zip – This is the zip code where the primary physician's office is located.

vi. Clinical Information:

1. Primary Reason Evaluated for TB Disease – This is the primary reason why the TB patient was evaluated for TB disease (select one choice only).

TB Symptoms – This option is marked when a patient is evaluated for TB disease due to signs and symptoms consistent with TB (e.g., prolonged or persistent cough, fever, lymphadenopathy, night sweats, and weight loss). For example, if a TB patient seeks medical care due to TB symptoms, then "TB Symptoms" should be the primary reason why the patient was evaluated for TB disease.

Abnormal Chest Radiograph – This option is marked when a patient has an incidental chest radiograph consistent with TB disease. The reason for taking the chest radiograph should **not** have been to rule out TB disease. For example, if a patient had a chest radiograph as part of preoperative testing, where there was no suspicion of TB disease and an abnormal result suggesting TB was observed thus leading to TB diagnosis, the option "Abnormal Chest Radiograph" should be selected.

Contact Investigation – This option is marked when a patient is diagnosed with TB as a result of being evaluated during a contact investigation.

Immigration Medical Exam – This option is marked when a patient is diagnosed with TB as a result of a medical examination which is part of the immigration application process. An immigration medical exam may be performed overseas or in the US depending on the situation. If TB is diagnosed in either setting due to the immigration medical exam, the option "Immigration Medical Exam" should be selected.

Targeted Testing – This option should be selected when a patient is evaluated for TB because of a positive TST that was given during targeted testing, or because the patient was considered at high risk for TB (e.g., persons from areas of the world with high rates of TB). The option "Targeted Testing" should **not** be selected if another more appropriate option exists such as contact investigation or immigration medical exam.

Health Care Worker – This option should be selected when a patient is evaluated for TB disease due to a positive TST which was administered because the patient was a health care worker. Health care worker refers to all paid and unpaid persons working in healthcare settings who have the potential to be exposed to Mycobacterium tuberculosis.

Employment/administrative Testing – This option should be selected if the patient was evaluated for TB disease due to a routine employment physical examination, employment tuberculin skin testing requirement, or primary or secondary school program for routine tuberculin skin testing. This category reflects an administrative requirement (e.g., a tuberculin skin testing program applied to all 5th graders in a school or to all job applicants) rather than targeted testing of a select group of individuals considered at high risk. If skin testing was performed because the individual was considered to be part of a known high risk group, select "Targeted testing" or other more appropriate category such as "Health care worker." If employment was health care related, check "Health care worker" rather than "Employment/administrative testing."

Incidental Lab Result – This option should be selected if a specimen is collected and has an incidental result that is smear positive for acid fast bacilli (AFB) or culture positive for *Mycobacterium tuberculosis* (e.g., when the specimen was tested for AFB or cultured for TB without suspicion of TB disease or when TB disease was not considered a possible diagnosis, such as during a bronchoscopy or autopsy, organ donation, hospitalization or analysis for a disease other than *M. tuberculosis*.

2. Verification Criteria **(State Use Only)**: This is the variable that is used by CDC when MDCH submits the case.

3. Date Counted (State Use Only): This date is the month, day, and year that the MDCH verifies the case as TB and includes it in the official TB case count.

4. Previous Diagnosis of Tuberculosis: This field designates whether a TB case has ever been

Yes – Select "Yes" if the patient has had a previous diagnosis of TB disease. A previous diagnosis of latent TB infection (i.e., LTBI) should **not** be entered. A patient is considered to have had a previous diagnosis of TB disease if s/he had verified disease in the past, had completed therapy or was lost to supervision for more than 12 consecutive months, and now has verified disease again. Often, TB disease is confused with latent TB infection (LTBI) and LTBI should not be coded as previous TB disease. Therefore, documentation of the previous episode of TB disease is important. Written documentation of the previous episode of TB diseases is ideal. However, if the TB disease episode occurred years ago, or in another location (e.g., country) obtaining written documentation can be difficult. Therefore, when written documentation is not available, reliable verbal documentation of a previous episode of TB disease is acceptable (e.g., medications taken, length of medication, sputum smear examination results).

If "Yes" is selected, please provide the year of previous TB disease diagnosis.

No – Select "No" if the patient has never been diagnosed with TB disease in the past.

5. Site of TB Disease: This field designates the *primary* location of the TB disease in the patient.

6. Other Sites of TB Disease (1): This field designates a secondary location of TB disease in the patient. Select one from the dropdown menu if appropriate.

7. Other Sites of TB Disease (2): This field designates a secondary location of TB disease in the patient. Select one from the dropdown menu if appropriate.

8. Other Sites of TB Disease (3): This field designates a secondary location of TB disease in the patient. Select one from the dropdown menu if appropriate.

9. Status at Diagnosis of TB: This field designates the whether the patient was alive or dead at the time of TB disease diagnosis.

   Alive – Select "Alive" if the patient was living at the time of TB disease diagnosis. Patients whose TB was suspected and who were started on at least two anti-tuberculosis drugs prior to the day of death should be classified as alive at the time of TB diagnosis even though the TB case may not be verified and counted until after death.

   Dead – Select "Dead" if the patient was deceased at the time the investigation of possible TB disease was initiated. Patients who were only on one antituberculosis drug prior to the day of death because TB disease was not suspected, and who were then diagnosed with TB disease after death are classified as dead at the time of TB diagnosis. For example, if a person who was taking isoniazid as preventive therapy for latent TB infection dies, and is found after death to have had TB disease, this person should be classified as "Dead" at TB diagnosis.

If "Dead" was selected, please indicate if TB was a cause of death: This field designates whether TB was listed as a primary or other cause of death in the patient's death certificate. If available, please send written documentation of the cause of death (i.e. copy of death certificate).

If "Dead" was selected, please provide the date of death.

vii. Laboratory Information:

1. Sputum Smear: This field indicates the result of an AFB smear of a sputum specimen. For the purposes of this question, please only include smears that were done on spontaneous or induced sputum samples. *Do not* include specimens that were collected by any other means such as microscopic examination of pulmonary secretions obtained by tracheal suction, bronchoscopy procedures (e.g., bronchial washing, scrapings, biopsies), or gastric aspiration (see Smear/Pathology/Cytology of Tissue and Other Body Fluids – Question 3 below)

   Positive – Select "Positive" if any of the examinations are positive for acid-fast organisms (i.e., AFB).

   Negative – Select "Negative" if the results of all examinations (or the only examination) were negative.

   Not Done – Select "Not Done" if it is known that no sputum smears were performed.

2. Sputum Smear Collection Date: If the sputum smear was "positive" or "negative", indicate the date (mm/dd/yyyy) the sputum specimen was collected. If several examinations were done and one or more sputum specimens were "positive" for acid-fast organisms, enter the date the *first* positive sputum was collected. If several sputum specimens were done and all were "negative" for acid-fast organisms, enter the date the *first* negative specimen was collected.

3. Sputum Culture: This field indicates the result of a sputum culture. For the purposes of this question, please only include smears that were done on spontaneous or induced sputum samples. *Do not* include specimens that were collected by any other means such as microscopic examination of pulmonary secretions obtained by tracheal suction, bronchoscopy procedures (e.g., bronchial washing, scrapings, biopsies), or gastric aspiration (see Culture of Tissue and Other Body Fluids – Question 7 below).

   Positive – Select "Positive" if a sputum culture result was positive for *M. tuberculosis* (*Mycobacterium tuberculosis*) complex. If several sputum cultures were done, check "Positive" if any one is positive for *M. tuberculosis* complex.

   Negative – Select "Negative" if the results of all sputum cultures (or the only sputum culture) were negative for *M. tuberculosis* complex.

Not Done – Select "Not Done" if it is known that no cultures were performed.

4. Sputum Culture Collection Date: If the sputum culture was "positive" or "negative", indicate the date (mm/dd/yyyy) the sputum specimen was collected. If several sputum cultures were done and one or more were "positive" for *M. tuberculosis* complex, enter the date the *first* positive specimen was collected. If several sputum cultures were done and all were "negative" for *M. Tuberculosis* complex, enter the date the *first* negative specimen was collected.

5. Sputum Culture Report Date: This is the date that the sputum culture report is released or made available.

6. Smear/Pathology/Cytology of Tissue and Other Body Fluids: This field indicates the result of a smear, pathology examination or cytology examination of specimen of tissue or body fluids. For the purposes of this question, tissue or body fluids *do not* include sputum.

   Positive – Select "Positive" if any tissue or body fluid other than sputum (e.g., tracheal aspirate, bronchial washing, urine, bone marrow, lymph node, cerebral spinal fluid, lung, pleura) collected from procedures (e.g., bronchoscopy, biopsy, gastric aspiration, pleural fluid aspiration) was either: positive for acid-fast organisms (i.e., AFB) during a smear examination, **OR** showed granulomas, granulomatous inflammation, or other pathologic or histologic findings consistent with TB disease during a pathologic/cytologic examination (e.g., such findings would be listed on the pathology or cytology report).

   Negative – Select "Negative" if the results of all examinations (or the only examination) were negative.

   Not Done – Select "Not Done" if such examinations (e.g., smear, pathology/cytology) of tissue or body fluids are known not to have been done.

7. Smear/Pathology/Cytology collection date: If the smear/pathology/cytology was "positive" or "negative", indicate the date (mm/dd/yyyy) the specimen was collected. If several examinations were done and all were "negative", enter the date the first negative specimen was collected.
   a. If the smear/pathology/cytology was "positive" – Enter the anatomic code that corresponds to the location in the body from which the specimen was collected.
   b. Type of exam – If smear/pathology/cytology was performed, please indicated the type of exam that was done. Select "smear" if a smear was done to examine for AFB. Select "pathology/cytology" if a pathologic/cytologic examination was done. This information is usually found on the laboratory report.

8. Culture of Tissue and Other Body Fluids: This field indicates the result of a culture of tissue or body fluids. For the purposes of this question, tissue or body fluids *do not* include sputum.

   Positive – Select "Positive" if any tissue or body fluid, other than sputum (e.g., tracheal

aspirate, bronchial washing, urine, bone marrow, lymph node, cerebral spinal fluid, lung, pleura) collected from procedures (e.g., bronchoscopy, biopsy, gastric aspiration, pleural fluid aspiration) was positive for *M. tuberculosis* complex.

Negative – Select "Negative" if all tissue or fluid cultures, other than sputum cultures, were negative for *M. tuberculosis* complex.

Not Done – Select **"**Not done" if tissue or body fluid cultures are known not to have been done.

9. Culture of Tissue and Other Body Fluids Collection Date: If the culture of tissue and other body fluids was "positive" or "negative", indicate the date (mm/dd/yyyy) the specimen was collected. If several cultures were done and one or more cultures were "positive for *M. tuberculosis* complex, enter the date the first positive culture specimen was collected. If several cultured were done and all were "negative", enter the date the first negative culture specimen was collected.
    a. If culture positive, enter anatomic code—if the culture of tissue and other body fluids was "positive" please enter the anatomic code that corresponds to the location in the body from which the specimen was collected.

10. Nucleic Acid Amplification Test (NAA) Result: This field indicates the result of a nucleic acid amplification test.

    Positive – Select "Positive" if the NAA test was positive for *M. tuberculosis* complex. If several NAA tests were done and one or more were "Positive", enter the results for the first positive NAA test.

    Negative – Select "Negative" if all NAA test were negative for *M. tuberculosis* complex.

    Not Done – Select "Not Done" if an NAA test was not performed.

    Indeterminate – Select "Indeterminate" if the NAA test yielded indeterminate results (e.g., inconclusive, inhibitory).

11. Nucleic Acid Amplification Test Result Collection Date: If the NAA test result was "positive" or "negative" please enter the date on which the specimen was collected.
    a. If nucleic acid amplification test is positive, indicate if specimen type for the NAA test was sputum. If not sputum, enter anatomic code that corresponds to the location in the body from which the specimen was collected.

12. Nucleic Acid Amplification Report Date: This is the date the test results of the NAA test are reported or released.

13. NAA reporting lab type: For positive NAA tests, name the type of laboratory where the test was performed.

14. Initial Chest Radiograph: This field indicates the result of the initial chest radiograph taken during the diagnostic evaluation for TB.

    Normal – Select "Normal" if the initial chest radiograph(s) showed no abnormalities consistent with TB and was normal.

    Abnormal – Select "Abnormal" if the initial chest radiograph(s) showed any abnormalities (e.g., hilar adenopathy, infiltrate(s), cavity, scarring) associated with TB.

    Not Done – Select "Not Done" if an initial chest radiograph is known not to have been done.

    For Abnormal Initial Chest Radiograph: Evidence of Cavity – If the initial chest radiograph(s) was abnormal, please indicate whether any of the initial chest radiograph(s) obtained showed evidence of one or more cavities by selecting "Yes", "No", or "Unknown".

    For Abnormal Initial Chest Radiograph: Evidence of miliary TB – If the initial chest radiograph(s) was abnormal, please indicate whether any of the initial chest radiograph(s) obtained showed evidence of "miliary" disease (e.g., "miliary" TB or "miliary or "bilateral micronodular" pattern) by selecting "Yes", "No", or "Unknown".

15. Initial Chest CT Scan or Other Chest Imaging Study: This field indicates the result of an initial chest CT scan or other chest imaging study taken during diagnostic evaluation for TB.

    Normal – Select "Normal" if the initial chest CT scan or other chest imaging study showed no abnormalities consistent with TB and was normal.

    Abnormal – Select "Abnormal" if the initial chest CT scan or other chest imaging study showed any abnormalities (e.g., hilar adenopathy, infiltrate(s), cavity, scarring) associated with TB.

    Not done – Select "Not Done" if an initial chest CT scan or other chest imaging study is known not to have been done.

    For Abnormal Chest Scan: Evidence of Cavity - If the initial chest CT scan or other chest imaging study was abnormal, please indicate whether any of the initial chest CT scan or other chest imaging study obtained showed evidence of one or more cavities by selecting "Yes", "No", or "Unknown".

    For Abnormal Chest CT Scan: Evidence of miliary TB – If the initial chest CT scan or other chest imaging study was abnormal, please indicate whether any of the initial chest CT scan or other chest imaging study obtained showed evidence of "miliary" disease (e.g., "miliary" TB or "miliary or "bilateral micronodular" pattern) by selecting "Yes", "No", or "Unknown".

16. Tuberculin (Mantoux) Skin Test at Diagnosis: This field indicates the result of the Tuberculin Skin Test (TST) performed during the diagnostic TB disease evaluation.

Positive – Select "Positive" if the patient meets the criteria for a positive TST as defined by current guidelines.

Negative – Select "Negative" if the TST did not meet current criteria for a positive TST as defined by current guidelines.

Not Done – Select "Not Done" if the TST is known to not have been done.

TST Placement Date – If the TST was "Positive" or "Negative" please indicate the date the initial TST was placed on the patient.

TST Read Date – If the TST was "Positive" or "Negative" please indicate the date the TST was read (measured).

Millimeters (mm) of induration – If the TST was "Positive" or "Negative" please indicate the measurement of the induration in millimeters. If the available skin test result indicates only that the result was "Positive" or "Negative," but does not give the millimeters of induration, code the millimeters of induration as "99".

17. Previously Positive TST: This field indicates whether the TB patient had a positive TST result in the past.

Date of Previously Positive TST – If the TB patient has had a positive TST result in the past, please indicate the date the prior TB test was given.

18. Interferon Gamma Release Assay for Mycobacterium tuberculosis at Diagnosis: This field indicates the result of an Interferon Gamma Release Assay (IGRA, QuantiFERON or T-Spot) that was performed during the diagnostic evaluation for TB disease.

Positive – Select "Positive" if any IGRA test result suggested *M. tuberculosis* infection is likely.

Negative – Select "Negative" if all IGRA test results suggested *M. tuberculosis* infection is unlikely.

Indeterminate – Select "Indeterminate" if the IGRA test results were not reported as positive or negative.

Not Done – Select "Not Done" if IGRA testing is known to not have been performed.

Interferon Gamma Release Assay: Type of Test – If any IGRA for *M. tuberculosis* was performed please indicate the type of test that was administered, "QuantiFERON-TB Test" or "T-Spot.TB Test".

Interferon Gamma Release Assay Collection Date – If any interferon gamma release assay

for *M. tuberculosis* was performed please indicate the date the blood sample was collected. If more than one test was conducted, and one or more test results were "Positive," enter the date the first positive IGRA blood sample wasvcollected. If one or more IGRA tests were done and all the results were negative, enter the date the first negative IGRA blood sample was collected. If all test results were indeterminate, enter the date the first indeterminate result was reported.

viii. Epidemiologic Information:

1. Country of Birth: The U.S. Census Bureau defines a "U.S.-Born" person to be someone born in 1 of the 50 states or the District of Columbia, or someone born outside the United States to at least one parent who was a U.S. citizen. In order to be consistent with the U.S. Census Bureau and to be able to apply census bureau population data to calculate TB rates, CDC and the State of Michigan use the same definition. U.S. Territories, U.S. Island Areas, and U.S. Outlying Areas (e.g., American Samoa, Federated States of Micronesia, Guam, Republic of the Marshall Islands, Commonwealth of the Northern Mariana Islands, Republic of Palau, Puerto Rico, U.S. Virgin Islands) should be considered as distinct areas and their specific names should be entered in this field. Choose the appropriate country from the drop-down menu.

   Month-Year Arrived in the US – If the patient was born outside the United States please enter the month and year in which they arrived in the U.S.

2. Immigration Status: This field designates the immigration status of a patient that was born outside of the United States. The criteria regarding the birthplace of the patient is slightly different in this field as compared to the previous Country of Birth field. If a TB patient was born in one of the 50 United States, born abroad of a U.S. citizen parent (e.g., born on a military installation), or born in one of the U.S. Territories, U.S. Island Areas, or U.S. Outlying Areas (e.g., American Samoa, Federated States of Micronesia, Guam, Republic of the Marshall Islands, Commonwealth of the Northern Mariana Islands, Republic of Palau, Puerto Rico, U.S. Virgin Islands) then a visa would not be issued and "Not Applicable/U.S.-born" should be checked. Of note, people born in Puerto Rico, U.S. Virgin Islands and Guam are U.S. citizens. If the patient does not fit into the category "Not Applicable/U.S.-born" then one of the following options should be selected:

   Immigrant Visa – Select "Immigrant Visa" for foreign-born TB patients who first entered the U.S. with permanent resident status (e.g., immigrants).

   Student Visa "F", "M", "J" – Select "Student Visa" for foreign-born TB patients who first entered the U.S on a student visa. This is a non-immigrant visa and is obtained by an alien coming temporarily to the U.S. to pursue a full course of study in an approved institution.

   Asylee or Parolee – Select "Asylee or Parolee" for foreign-born patients who first entered the U.S seeking asylum or who are parolees. An asylee is a person already in the U.S. who is unable or unwilling to return to his or her country of nationality because of persecution or a well-founded fear of persecution. A parolee is an alien, appearing to be inadmissible to the

inspecting officer, allowed to enter the U.S. under urgent humanitarian reasons or when that alien's entry is determined to be for significant public benefit.

Tourist Visa "B" – Check "Tourist Visa" for foreign-born TB patients who first entered the U.S temporarily for business or pleasure. This is a non-immigrant visa.

Employment Visa "H", "E", "L", "J" – Select "Employment Visa" for foreign-born patients who first entered the U.S with a non-immigrant employment visa (an alien coming to the U.S. to work for a temporary period of time). There are many different non-immigrant employment visas depending upon type of work. (Note: Some persons entering the U.S. for work are immigrants; they should be checked as "immigrants").

"V" Visa or "K" Visa – Select "V" Visa or "K" Visa for foreign-born TB patients who first entered the U.S with a "V" visa or "K" visa. A "V" visa is a non-immigrant category that allows a spouse or child of a U.S. lawful permanent resident to live and work in the U.S. A "K" visa is a non-immigrant category that allows a fiancé of a U.S. citizen to temporarily enter the U.S. for a specific purpose (i.e., marriage).

Refugee – Select "Refugee" for foreign-born patients who first entered the U.S as refugees. A refugee is a person outside the U.S. who is unable or unwilling to return to that country because of persecution or a well-founded fear of persecution.

Other Immigration Status – Select "Other Immigration Status" for foreign-born TB patients who first entered the U.S with other immigration status, which is not Immigrant, Refugee, Asylee, Parolee, Student, Tourist, Employment, "V" visa, or "K" visa status, and is not "Unknown." This includes foreign-born persons who were not required to obtain a visa (e.g., foreign-born visitors from specific countries such as Canada that are part of the U.S. visa waiver program and are not required to obtain visas if visiting the U.S. for short periods of time (e.g., ≤90 days)), or those who entered the U.S. with no official immigration status at entry (e.g., "undocumented" status). If possible, please specify the reason for selecting this option.

Unknown – Select "Unknown" for jurisdictions with directives or policies forbidding asking a TB patient their immigration status; foreign-born TB patients who do not know their immigration status at first entry to the U.S; those who may have had a visa at entry to the U.S., but the type of visa is unknown; and those who refuse to respond.

3. Pediatric Patients (<15 years old): This section is designed to better capture important information about pediatric TB patients (<15 years old), this variable will request information on country of birth for primary guardian(s) of the pediatric case and whether the pediatric TB patient lived outside the U.S. for an uninterrupted period of more than 2 months. Please fill out this section for all pediatric TB patients (<15 years old).

   A. Patient Lived outside US for >2 months – This field indicates whether the pediatric patient has lived outside of the US for an uninterrupted period of >2 months. If the pediatric patient lived outside the U.S. in more than one country for an uninterrupted

most recent
countries. For this question, "lived" is defined as the place where a person lives or sleeps most of the time or the place the person considers to be their usual home during the stated time period. Although it may be difficult to determine the exact amount of time that a person lived outside the U.S. for an uninterrupted period, indicate "Yes" and the country code(s) if time period is believed to be >= 8 weeks.

Yes – Select "Yes" if the pediatric TB patient lived outside the U.S. for an uninterrupted period of more than 2 months and enter the countries. If the patient lived in more than one country, enter up to three countries in which the patient lived for more than 2 uninterrupted months most recently.

No – Select "No" if the pediatric TB patient did not live outside the U.S. for an uninterrupted period of more than 2 months.

Unknown – Select "Unknown" if it is unknown whether the pediatric TB patient lived outside the U.S. for an uninterrupted period of more than 2 months.

If yes, enter country (1) – If the pediatric TB patient lived outside the U.S. for an uninterrupted period of more than 2 months and specify the country in the drop-down menu.

If yes, enter country (2) – If the pediatric TB patient lived outside the U.S., in more than one country, for an uninterrupted period of more than 2 months select the second most recent country from the drop-down menu.

If yes, enter country (3) – If the pediatric TB patient lived outside the U.S. in more than one country for an uninterrupted period of more than 2 months select the third most recent country from the drop-down menu.

B. Country of Birth for Primary Guardian(s) – Please enter the country of birth for the primary guardian(s) (e.g., mother, father, foster parent, grandparent) of the pediatric TB patient and enter the appropriate countries for up to two parents or primary guardians. If the guardian was born in one of the 50 United States or born abroad of a U.S. citizen parent (e.g., born on a military installation), select "United States" as the country of birth. U.S. Territories, U.S. Island Areas, and U.S. Outlying Areas (e.g., American Samoa, Federated States of Micronesia, Guam, Republic of the Marshall Islands, Commonwealth of the Northern Mariana Islands, Republic of Palau, Puerto Rico, U.S. Virgin Islands) should be considered distinct areas and their specific names should be selected.

Country of Birth for Primary Guardian 1 – Please indicate the country of birth of the first primary guardian.

Country of Birth for Primary Guardian 2 – Please indicate the country of birth of the second primary guardian.

4. HIV Information: CDC recommends that **ALL** TB cases receive HIV counseling, testing, and referral at the time of TB diagnostic evaluation or TB diagnosis. Refer to the CDC public health surveillance definition for HIV infection.

HIV Status – Please indicate the HIV status of the TB patient at the time of diagnosis.

Negative – Select "Negative" if the patient has had a documented negative HIV test at the time of TB diagnostic evaluation or at TB diagnosis. Undocumented patient history that an HIV test result was negative is not acceptable. Such patients should be offered the opportunity to be tested for HIV. In addition, if a patient has had a negative test in the past, regardless of when the HIV test was performed, the patient should be offered HIV counseling and testing at the time of TB diagnostic evaluation or TB diagnosis. If the patient had received HIV counseling and testing a short period before the TB diagnostic evaluation or TB diagnosis (e.g., a few months) and the documented results were negative for HIV infection, and the patient has absolutely no risk for HIV, then these HIV test results may be used for this question. The length of time prior to TB diagnosis for which a negative HIV test result may be accepted should be based on clinical judgment of patient risk, not to exceed one year.

Positive – Select "Positive" if the patient is tested for HIV and the laboratory result is interpreted as positive according to published criteria OR the patient has a documented medical history of a previous positive HIV test, or a documented previous diagnosis of HIV infection or AIDS.

Indeterminate – Select "Indeterminate" if the patient has had a documented indeterminate HIV test at the time of TB diagnostic evaluation or TB diagnosis. Undocumented patient history is not acceptable.

Refused – Select "Refused" if the patient was offered the test at the time of the TB diagnostic evaluation or TB diagnosis, but declined to be tested.

Not Offered – Select "Not Offered" if the patient was not offered the test at the time of the TB diagnostic evaluation or TB diagnosis.

Test Done, Results Unknown – Select "Test Done, Results Unknown" if the patient had a HIV test at the time of the TB diagnostic evaluation or TB diagnosis and the results are not known to the TB program.

Unknown – Select "Unknown" if it is not known if the patient has had an HIV test, was ever offered a test, or was referred for HIV counseling and testing (e.g., anonymous testing center, private testing center), but it is unknown whether the HIV counseling and testing was done.

If Positive, State HIV/AIDS Patient Number (If AIDS reported 1993 or later) – If the HIV status is positive, please enter the State HIV/AIDS patient number.

If Positive, City/County HIV/AIDS Patient Number (If AIDS reported 1993 or later) – If the

HIV status is positive, please enter the State HIV/AIDS patient number.

5. Homeless Within Past Year: This field indicates whether the TB patient was homeless within the 12 months prior to the time when the TB diagnostic evaluation was performed. A homeless person may be defined as an individual who lacks a fixed, regular, and adequate nighttime residence; or an individual who has a primary nighttime residence that is a supervised publicly or privately operated shelter designed to provide temporary living accommodations, including welfare hotels, congregate shelters, and transitional housing for the mentally ill; or an institution that provides a temporary residence for individuals intended to be institutionalized; or a public or private place not designated for, or ordinarily used as, a regular sleeping accommodation for human beings. A homeless person may also be defined as a person who has no home (e.g., is not paying rent, does not own a home, and is not steadily living with relatives or friends). Another definition is a person who lacks customary and regular access to a conventional dwelling or residence. Included as homeless are persons who live on streets or in nonresidential buildings. Also included are residents of homeless shelters, shelters for battered women, welfare hotels, and single room occupancy (SRO) hotels. In the rural setting, where there are usually few shelters, a homeless person often will live on the street or with relatives in substandard housing. Being homeless does not refer to a person who is imprisoned or in a correctional facility.

   No – Select "No" if the patient was not homeless during the 12 months prior to the time when the TB diagnostic evaluation was performed.

   Yes – Select "Yes" if the patient was homeless at any time during the 12 months prior to the time when the TB diagnostic evaluation was performed.

   Unknown – Select "Unknown" if it is not known whether the patient was homeless during the 12 months prior to the time when the TB diagnostic evaluation was performed.

6. Resident of Correctional Facility at Time of Diagnosis: This question indicates whether the TB patient was an inmate in a correctional facility at the time TB diagnostic evaluation was performed.

   No – Select "No" if the TB patient was not an inmate in a correctional facility at the time of the TB diagnostic evaluation.

   Yes – Select "Yes" if the TB patient was an inmate in a correctional facility at the time of the TB diagnostic evaluation.

   Unknown – Select "Unknown" if it is unknown whether the patient was an inmate in a correctional facility at the time of TB diagnostic evaluation.

   If yes, specify type of correctional facility at time of diagnosis – If the TB patient was an inmate in a correctional facility at the time of TB diagnostic evaluation, please indicate the type of correctional facility. If the TB patient was an inmate of more than one facility when

the diagnostic evaluation was performed, select the facility where the majority of the TB diagnostic evaluation was performed.

Federal Prison – Select "Federal Prison" if the TB patient was an inmate in a confinement facility administered by a federal agency. For the purpose of this question, privately operated federal correctional facilities are included in "federal prison."

State Prison – Select "State Prison" if the TB patient was an inmate in a confinement facility administered by a state agency. For the purpose of this question, privately operated state correctional facilities are included in "state prison."

Local Jail – Select "Local Jail" if the TB patient was an inmate in a confinement facility usually administered by a local law enforcement agency, intended for adults but sometimes also containing juveniles, which holds persons detained pending adjudication and/or persons committed after adjudication for sentences of usually a year or less. Temporary holding facilities, or lockups, that do not hold persons after being formally charged in court are excluded. Both city and county jails are included in this category. Federal and state prisoners who are boarded at local jails should be reported as residents of the local jail. For the purpose of this question, privately operated local correctional facilities are included in "local jail."

Juvenile Correctional Facility – Select "Juvenile Correctional Facility" it the TB patient is a resident of a public or private residential facility, including juvenile detention centers, reception and diagnostic centers, ranches, camps, farms, boot camps, residential treatment centers, and halfway houses or group homes. The juveniles served by these facilities include those charged or adjudicated as delinquents; non-delinquent/non-criminal offender (e.g., runaways, truants, incorrigibles, curfew violators); and those committed or detained for treatment of abuse, dependency, neglect, or other reasons. Juveniles who are boarded at federal or state prisons or local jails should be reported as residents of the sites at which they are boarded.

ICE (Former INS) Detention – Select "ICE (Former INS) Detention" if the TB patient was in the custody of Immigration and Customs Enforcement (ICE) at the time of TB diagnostic evaluation. Persons in ICE custody can be housed in stand alone ICE Detention Centers or other correctional facilities (e.g., federal or state prison, local jail) when a stand-alone ICE Detention Center is not available.

Other Correctional Facility – Select "Other Correctional Facility" if the TB patient was an inmate in a correctional facility at the time of TB diagnostic evaluation that was not listed above. Example of other correctional facilities are Indian reservation facilities (e.g., tribal jails), military stockades and jails, federal Park Police facilities, police lockups (temporary-holding facilities for persons who have not been formally charged in court), or other correctional facilities that are not included in the other choices and is not "Unknown." Please specify the type or name of the facility in space provided.

Unknown – Select "Unknown" if it is not known whether the TB patient was an inmate in a

correctional facility at the time of TB diagnostic evaluation.

7. Resident of Long-Term Care Facility at Time of Diagnosis: This field indicates whether the TB patient was living in a long-term care facility at the time of TB diagnostic evaluation.

   No – Select "No" if the TB patient was not living in a long-term care facility at the time of TB diagnostic evaluation.

   Yes – Select "Yes" if the TB patient was living in a long term care facility at the time of diagnosis.

   Unknown – Select "Unknown" if it is not known whether the TB patient was living in a long-term care facility at the time of TB diagnostic evaluation.

   If yes, specify type of long-term care facility at time of diagnosis – If the TB patient was living in a long-term care facility at the time of TB diagnostic evaluation, please indicate the type of long-term care facility.

   Nursing Home – Select "Nursing Home" if the TB patient was living in a facility at the time of TB diagnostic evaluation having 3 beds or more *and* is certified as a skilled nursing facility, or certified as an immediate care facility, or is licensed as a nursing home, or is identified as a nursing care unit of a retirement center, or is determined to provide nursing or medical care and/or supervision over medications that may be self-administered.

   Hospital-Based Facility – Select "Hospital-Based Facility" if the TB patient was living in a nursing home at the time of TB diagnostic evaluation that is a distinct unit of hospital, with 3 or more beds, that is either physically attached or if not attached, managed by a hospital. Facilities may be certified by Medicare or Medicaid, or licensed by the State.

   Residential Facility – Select "Residential Facility" if the TB patient was living in a facility at the time of TB diagnostic evaluation with 3 or more beds and meets both of the following criteria: 1) was not classified as a nursing home or hospital-based facility as described above, and 2) provides personal care or supervision to its residents, not nursing care services, in addition to room and board (e.g., help with bathing, dressing, eating, walking, shopping). Included under residential facilities are assisted living facilities, homes for mentally retarded or developmentally disabled persons, board and care homes (e.g., residential care homes, group homes, homes for the aged, family care homes, adult foster care homes, personal care homes, adult congregate living facilities, residential community care facilities, domiciliary care homes).

   Mental Health Residential Facility – Select "Mental Health Residential Facility" if the TB patient was living in mental health residential facility at the time of TB diagnostic evaluation that provides 24-hour care in a hospital or residential treatment or supportive setting. This includes state and local mental hospitals, private psychiatric hospitals, non-federal general hospitals with separate psychiatric services, VA medical centers, multi-service mental health organizations with residential treatment programs, and residential treatment centers for

emotionally disturbed children. Excluded are other federal psychiatric facilities and Indian reservation facilities, for these select "Other Long-Term Care Facility" below instead.

Alcohol or Drug Treatment Facility – Select "Alcohol or Drug Treatment Facility" if the TB patient was living in a long-term rehabilitation/residential facility at the time of TB diagnostic evaluation that is designated for treatment of 30 days or longer. This category does not include all ambulatory or outpatient facilities, hospital inpatient detoxification units, etc.

Other Long-Term Care Facility – Select "Other Long-Term Care Facility" if the TB patient was living in a facility at the time of TB diagnostic evaluation that was not mentioned above that are designated for treatment of 30 days or longer and is not "Unknown." Please specify the type or name of the facility in space provided.

Unknown – Select "Unknown" if it is not known whether the TB patient was living in a long-term care facility at the time of TB diagnostic evaluation.

8. Injecting Drug Use Within Past Year: This field indicates whether the TB patient was using injectable drugs within 12 months of the date of TB diagnosis. Injection drug use involves the use of hypodermic needles and syringes for injection of drugs not prescribed by a health care provider. Route of administration may be intravenous, subcutaneous or intramuscular. Drugs injected may include heroin, cocaine, amphetamines, PCP, LSD, barbiturates, steroids, etc. Injection drug use within the past year should be sought as an indicator of recent activity (e.g. when did the patient last inject drugs). Medical documentation or other indices of a history of enrollment in a drug treatment program (e.g. methadone treatment, narcotics anonymous, etc.), medical or laboratory documentation of injecting drug use (e.g. urine toxicology), or physical evidence (e.g. needle tracks) may be useful in answering this question. Since the patient interview for injection drug use is often negative initially, it may be necessary to inquire at multiple visits.

No – Select "No" if the TB patient has not used injectable drugs in the past 12 months.

Yes – Select "Yes" if it is known the TB patient used injectable drugs within 12 months of the date of TB diagnosis.

Unknown – Select "Unknown" if it is unknown whether the TB patient has used injectable drugs in the past 12 months.

9. Non-Injecting Drug Use Within Past Year: This field indicates whether the TB patient has used non-injection drugs within 12 months of the date of TB diagnosis. Non-injection drug use involves the use of licensed, prescription, or illegal drugs that were not injected and were not prescribed by a health care provider. The drug(s) may be ingested, inhaled or smoked. Non-injection drugs may include heroin, cocaine, amphetamines, Valium, PCP, LSD, barbiturates, marijuana, nitrates, inhalants, steroids, etc. Use of non-injection drugs within the past year should be sought as an indicator of recent activity (e.g. when

No – Select "No" if the TB patient has not used non-injection drugs in the past 12 months.

Yes – Select "Yes" if it is known the TB patient was using non-injection drugs within 12 months of the date of TB diagnosis.

Unknown – Select "Unknown" if it is unknown whether the TB patient has used non-injection drugs in the past 12 months.

10. Excess Alcohol Use Within Past Year: This field indicates whether the TB patient excessively consumed alcohol within 12 months of the date of TB diagnosis. Reliable indicators of excess alcohol use include: participation in Alcoholics Anonymous or alcohol treatment programs described by the patient, the patient's family or acquaintances; a health care provider report of chronic, high intake of alcohol with behavior associated with alcohol abuse; repeated visits to health care facilities during which alcohol intoxication was observed; reported alcohol use coupled with the existence of organic, alcohol-associated disease (e.g. cirrhosis, pancreatitis); or a diagnosis of alcoholism on available medical records. Use of excess alcohol within the past year should be sought as an indicator of recent activity (e.g. when did the patient last have a drink). Since the patient interview for excess alcohol use is often negative initially, it may be necessary to inquire at multiple visits.

No – Select "No" if the TB patient was not excessively consuming alcohol within the past 12 months.

Yes – Select "Yes" if it is known the TB patient was excessively consuming alcohol within the past 12 months

Unknown – Select "Unknown" if it is unknown whether the TB patient was excessively consuming alcohol within the past 12 months.

11. Occupation Within Past 24 Months: This field designates the TB patient's occupation(s) within 2 years of the date of TB diagnosis.

Employed – Select "Employed" if the TB patient was working in the 24 months prior to TB diagnosis.

Unemployed – Select "Unemployed" if the TB patient was not employed during 24 months prior to the diagnostic TB evaluation. This should not include persons who are ineligible for employment such as infants, children, students, housewives, retirees, and persons receiving

permanent disability benefits or persons who were institutionalized - such individuals should be included in the "Other" option and indicated as such (i.e., Retired, Child, Student etc). "Unemployed" should be checked if the person was unemployed for the majority of the prior 24 month period; shorter time frames, such as 1 week of unemployment in the past 12 months such not be coded as "Unemployed."

Unknown – Select "Unknown" if it is not known whether the patient was employed in the 24 months prior to TB diagnosis.

Other – Select "Other" if the patient had special circumstances for which they were not employed such as infants, children, students, homemakers (e.g., housewife, househusband), persons receiving permanent disability benefits or persons who were institutionalized, retirees etc. If "Other" is selected, please specify the reason in the text field.

If Employed - If the TB patient was employed within the past 24 months, please indicate the type/setting of the employment. If the patient performed one of the occupations listed or was employed in more than one setting, select all that apply. For example, if a patient is a physician who works in both a hospital and a prison medical clinic, mark both "Health Care Worker" and "Correctional Employee".

12. Additional TB Risk Factors: This field indicates the additional TB risk factors that the TB patient may have (*select all that apply*). Documentation of additional TB risk factors from the medical records or a reliable source (e.g., health care provider) is preferred. Undocumented (e.g. verbal reporting from the patient or non-health care provide) reporting is not acceptable. Please note that other specific TB risk factors (e.g., occupation, HIV) are collected elsewhere in the MDSS TB Form.

Contact of Infectious TB Patient – Select "Contact of Infectious TB Patient" if the TB patient for whom the MDSS TB form is being completed, is a known contact of an infectious TB patient. If this infectious TB patient is known to have had multi-drug resistant TB, and the TB patient for whom the MDSS TB form is being completed was not a contact of any other infectious TB patient, select the option "Contact of MDR-TB Patient" and do not check "Contact of infectious TB patient." The association between the TB patients may have been found through investigation (e.g., a formal contact investigation) or identified as an incidental finding. For the purpose of this question, the contact should be recent and should not have occurred more than 2 years ago.

Contact of MDR-TB Patient – Select "Contact of MDR-TB Patient" if the TB patient for whom the MDSS TB form is being completed is a contact of a multi-drug resistant (MDR) TB patient, regardless of whether the MDR-TB case was infectious or not. Multi-drug resistant TB is defined as resistance to at least isoniazid and rifampin. If this MDR-TB patient was the only known contact for the patient for whom you are completing the MDSS TB form, check "Contact of MDR-TB patient" and do not check "Contact of infectious TB patient." The association between the TB patients may have been found through investigation (e.g., a formal contact investigation) or identified as an incidental finding. For the purpose of this question, the contact should be recent and should not have occurred more than 2 years ago. This question is being

asked because clinical management of the TB patient may be affected if the TB patient is a contact of a documented MDR-TB patient.

Contact of XDR-TB Patient – Select "Contact of XDR-TB Patient" if the TB patient for which the MDSS TB form is being completed is a contact of a extensively drug resistant (XDR) TB patient, regardless of whether the XDR-TB case was infectious or not. Extensively drug resistant TB is defined as resistance to isoniazid and rifampin, plus resistance to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin). If this XDR-TB patient was the only known contact for the patient for whom you are completing the MDSS TB form, check "Contact of XDR-TB patient" and do not check "Contact of infectious TB patient." The association between the TB patients may have been found through investigation (e.g., a formal contact investigation) or identified as an incidental finding. For the purpose of this question, the contact should be recent and should not have occurred more than 2 years ago. This question is being asked because clinical management of the TB patient may be affected if the TB patient is a contact of a documented XDR-TB patient.

Missed Contact – Select "Missed Contact" if, after having been diagnosed with TB disease, the TB patient for whom the MDSS TB form is being completed was found to have been a contact of a known TB patient. For the purpose of this question, the contact should be recent and should not have occurred more than 2 years ago. DO NOT include TB patients identified as having TB disease during a contact investigation or as a result of a contact investigation in this choice, because these patients are not "missed contacts" since they were identified during a contact investigation, despite having TB disease. This "risk factor" is trying to capture those TB patients that could be identified as a preventable case of TB.

Incomplete LTBI Treatment – Select "Incomplete LTBI Treatment" if the TB patient was previously identified as having latent TB infection (LTBI) and was not treated completely for LTBI. This "risk factor" is trying to capture those TB patients that could be identified as a preventable case of TB.

Diabetes Mellitus – Select "Diabetes Mellitus" if the TB patient has diabetes mellitus (Type I or Type II) at the time of TB diagnosis.

End-Stage Renal Disease – Select "End-Stage Renal Disease" (i.e., ESRD), if the TB patient has end-stage renal disease or chronic renal failure at the time of TB diagnosis.

Post-organ Transplantation – Select "Post-organ transplantation" if the TB patient has a history of solid organ transplantation (e.g., renal, cardiac).

TNF-α Antagonist Therapy – Select "TNF-α Antagonist Therapy", if the TB patient had recently received or has been receiving tumor necrosis factor-alpha (TNF-α) antagonist therapy at the time of TB diagnosis. The Food and Drug Administration (FDA) has approved TNF-α antagonist therapy for treatment of rheumatoid arthritis and other selected autoimmune diseases. The FDA has also recently determined that TB disease is a potential adverse reaction from treatment with TNF-α antagonists. The three currently FDA approved TNF-α antagonists are infliximab (Remicade®), etanercept (Enbrel®), and adalimumab (Humira®).

Immunosupression (not HIV/AIDS) – Select "Immunosupression (not HIV/AIDS)", if the TB patient has immunosuppression due to either a medical condition or medication, such as hematological or reticuloendothelial malignancies [e.g., leukemia, Hodgkin's lymphoma, carcinoma of the head or neck], or immunosuppressive therapy, such as prolonged use of high dose adrenocorticosteriods (e.g., prednisone). If the TB patient has diabetes mellitus or end-stage renal disease, select either "Diabetes Mellitus" and/or "End-Stage Renal Disease" for this question, and do not check "immunosuppression" unless the patient has another immunosuppressive condition. If the patient is infected with HIV, complete the "HIV Status" Question, and do not check "immunosuppression" for this question, unless the patient has another immunosuppressive condition.

Other – Select "Other", if the TB patient has a TB risk factor not included in the above choices [e.g., undernutrition (e.g., intestinal bypass surgery for obesity, gastrectomy, jejunoileal bypass, chronic malabsorption syndromes), silicosis, travel to a TB endemic country]. If "Other" is selected, please indicate specific risk factor in the test field.

Unknown – Select "Unknown", if no TB risk factors could be identified.

ix. Treatment Information:

1. Date Therapy Started: This field designates the date when the TB patient began therapy for TB or suspected TB. This may be (in order of preference) the date the patient first ingested medication, the date medication was first dispensed to patient, or the date medication was first prescribed to patient by health care provider. This date must be documented by medical or pharmacy records.

2. Directly Observed Therapy (DOT): This field indicates whether the TB patient is receiving Directly Observed Therapy (DOT) defined as supervised therapy in which a health care provider (e.g. nurse, outreach worker, etc.) has direct visual observation of a patient's ingestion of medication. This is the recognized standard of care for TB in the United States. Performing pill counts or dropping the filled prescription off to the patient and not observing the patient ingest the medication is not acceptable and does **not** constitute DOT.

   Yes – Select "Yes" if the patient is receiving DOT.

   No – Select "No" if the patient is not receiving DOT.

   Unknown – Select "Unknown" if it is not known whether the patient is receiving DOT.

   If Yes, DOT Start Date – If the TB patient is receiving DOT, please indicate the date at which the DOT was started.

3. Initial Drug Regimen: This table designates the treatment initially prescribed for the treatment of TB disease. Mark "Yes" for each drug that is known to be part of the initial

II. FOLLOW-UP REPORT 1: INITIAL DRUG SUCEPTIBILITY REPORT SECTION (STATE USE ONLY)

i. Drug Susceptibility Report Done:
ii. Specimen Collection Date:
iii. Was Drug Susceptibility Testing Completed:
iv. If Yes, Enter Specimen Type:
v. If not Sputum, enter Anatomic Code:
vi. Susceptibility Results:

III. FOLLOW-UP REPORT 2: CASE COMPLETION REPORT

1. Case Completion Report Completed: This field indicates whether the Case Completion (Follow-Up 2) report has been completed.

   Yes – Select "Yes" if all relevant fields on this page have been completed.

   No – Select "No" if all relevant fields have not been completed.

2. Sputum Culture Conversion Documented: This field indicates whether a sputum specimen had culture conversion from culture positive to culture negative during the course of treatment.

   No – Select "No" if the patient had an initially positive sputum culture and no subsequent negative sputum culture (e.g. all follow-up sputum cultures were positive, patient could not produce sputum after therapy started, or no follow-up sputum cultures were obtained). If a sputum specimen was not collected, select "No" for this variable.

   Yes – Select "Yes" if the patient had an initially positive sputum culture followed by one or more consistently negative sputum cultures.

   Unknown – Select "Unknown" if it is not known whether a sputum culture conversion was documented.

   If Yes, Date Specimen Collected on First Consistently Negative Culture – Indicate the month, day and year the first culture positive sputum specimen was collected. This information is available on the laboratory report form. Partial dates are not acceptable.

   If No, Reason for Not Documenting Sputum Culture Conversion – If sputum culture conversion was not documented, please indicate the reason.

Clinically Improved: No follow-up sputum despite induction – Select "Clinically Improved: No follow-up sputum despite induction" if repeat sputum collection was attempted, including induced sputum collection, but patient was not able to produce sputum due to clinical improvement.

No follow-up sputum collection – Select "No follow-up sputum collection" if induction was not attempted (e.g., if the health care provider did not order a repeat specimen, or if there were no facilities or equipment for induction).

No initial sputum result or none collected – Select "No initial sputum result or none collected" if a sputum sample was not collected or a positive culture result was not obtained at the time of diagnosis.

Died – Select "Died" if the patient died before having an opportunity to submit a follow-up sputum specimen.

Patient Lost – Select "Patient Lost" if the patient was lost to follow-up before having an opportunity to submit a follow-up sputum specimen.

Patient Refused – Select "Patient Refused" if the patient refused to provide a sputum specimen for a repeat culture.

Other – Select "Other" if there was another reason not included in the above choices, such as treatment failure or the patient moved outside the U.S. If "Other" is selected, please indicate the reason there was no sputum culture conversion documented in the text field.

Unknown – Select "Unknown" if the reason for not obtaining a repeat sputum culture to document sputum culture conversion is unknown.

3. US-Mexico Binational Status: This field indicates whether the TB patient held US Mexico Binational status. For the purposes of this question, a TB patient with US-Mexico Binational status is one for which optimal case management requires communication or collaboration with TB control programs or health-care providers on the opposite side of the border. For example, a TB control program in the United States would transfer clinical or laboratory data, refer a patient for treatment completion, or share information for contact investigation with a Mexican TB control program OR the case-patient is a contact of a Binational TB case-patient or is the TB source case-patient for contacts on the opposite side of the U.S.-Mexico border.

If a Binational TB case, reason why – If the TB patient is a Binational case, please indicate the reason.

Diagnostic/Clinical/Treatment Information Exchange – Select "Diagnostic/Clinical/ Treatment Information Exchange" if the TB patient's case management involved exchange of information regarding the diagnosis, clinical management and/or treatment between entities in the US and in Mexico.

Contacts – Select "Contacts" if the TB patient is a contact of a Binational TB case-patient or is the TB source case-patient for contacts on the opposite side of the U.S.-Mexico border.

Laboratory/Radiologic Testing – Select "Laboratory/Radiologic Testing" if the TB patient's care involved either laboratory or radiologic testing, performed in Mexico, which was used in the TB patient's diagnosis.

4. Did the patient move during TB therapy: This field indicates whether the patient moved anytime during TB therapy. Communication between TB control programs to ensure continuity of care and submission of follow-up reports regarding a patient who is moving from one area to another should be conducted in the most efficient manner possible and the responsibility for submitting follow-up reporting generally remains with the reporting area that initially reported the case to MDCH and counted it.

No – Select "No" if a patient did not move during TB therapy or moved within the same local health department jurisdiction.

Yes – Select "Yes" if the patient moved to an area where a new local health jurisdiction had to provide and/or coordinate TB care.

Unknown – Select "Unknown" if it is not known whether the TB patient moved during treatment.

If Yes, moved to where – For a patients who moved to a new local health jurisdiction during treatment, indicate where the TB patient moved (select all that apply):

In-state, out of jurisdiction – Select "In-state, out of jurisdiction", if the patient moved within the current state, but moved out of the local heath jurisdiction, such as to a different health department or county.

Out of state – Select "Out of state", if the patient moved to another state during their TB treatment. If the patient moved to one of the U.S. Territories, U.S. Island Areas, and U.S. Outlying Areas (e.g., American Samoa, Federated States of Micronesia, Guam, Republic of the Marshall Islands, Commonwealth of the Northern Mariana Islands, Republic of Palau, Puerto Rico, U.S. Virgin Islands): for the purpose of this question, you should select "Out of state".

Out of the U.S. – Select "Out of the U.S." if the patient moved from your jurisdiction to another country. If the patient moved to one of the U.S. Territories, U.S. Island Areas, and U.S. Outlying Areas (e.g., American Samoa, Federated States of Micronesia, Guam, Republic of the Marshall Islands, Commonwealth of the Northern Mariana Islands, Republic of Palau, Puerto Rico, U.S. Virgin Islands), you should select "Out of state".

If transnational referral was made to another TB program or physician outside the U.S., please indicate in the comments section. Transnational referral includes participation in

programs such as TBNet or CureTB, communication with Immigrations and Customs Enforcement to ensure case management after deportation, or individual efforts by programs to complete a case management transfer and obtain information from TB programs and physicians outside the U.S. for case completion.

If moved in state, out of jurisdiction, enter county #1 – If "In-state, out of jurisdiction" was marked above, please select the jurisdiction to which the patient moved from the dropdown menu. There are two spaces to indicate jurisdictions to which the patient moved. If the patient moved more than once, enter the address of the first move here.

If moved in state, out of jurisdiction, enter county #2 – See above. If the patient moved more than once, enter the address of the second move here.

If moved out of state, enter state #1 – If "Out of state" was marked above, please select the state to which the patient moved from the dropdown menu. There are two spaces to indicate states to which the patient moved. If the patient moved more than once, enter the address of the first move here.

If moved out of state, enter state #2 – See above. If the patient moved more than once, enter the address of the second move here.

If moved out of the US, enter country #1 – If "Out of the U.S." was marked above, please select the country to which the patient moved from the dropdown menu. There are two spaces to indicate countries to which the patient moved. If the patient moved more than once, enter the address of the first move here.

If moved out of the US, enter country #2 – See above. If the patient moved more than once, enter the address of the second move here.

5. Date Therapy Stopped: Enter the date (month, day, and year) that the patient stopped taking therapy for TB disease or suspected TB disease. This may be (in order of preference) the date the patient last ingested medication, the date medication dispensed to patient would have run out if the patient had taken all the medication, or the date medication prescribed to patient would have run out if the patient had taken all the medication from the date of the prescription. The time period represented by the interval between "Date Therapy Started" (From the RVCT section of the MDSS TB form) and "Date Therapy Stopped" is meant to encompass the entire period (including interruptions in therapy) that the patient was receiving medication to treat TB disease or suspected TB. Treatment with anti-tuberculosis medications for disease caused by a mycobacterium other than M. tuberculosis complex should not be included.

6. Reason Therapy Stopped or Never Started: Provide the primary reason that therapy was ended and not resumed. This item should be completed when the case is closed to supervision.

   <u>Completed Therapy</u> – Select "Completed Therapy" if the patient successfully

completed the prescribed course of therapy.

Lost – Select "Lost" if the patient was lost to follow-up and could not be located to complete treatment.

Uncooperative or Refused – Select "Uncooperative or Refused" if the patient was uncooperative or refused to complete treatment. If the patient later restarts, the Completion form should be updated as appropriate.

Adverse Treatment Effect – Select "Adverse Treatment Effect" if therapy was permanently stopped due to an adverse treatment event with anti-tuberculosis medications (e.g., life threatening drug reaction).

Not TB – Select "Not TB" if a patient started on treatment presumptively was subsequently determined not to suffer from M. tuberculosis complex. This may be due to identification of a mycobacteria other than tuberculosis (atypical organism or MOTT), or due to another diagnosis that is more appropriate for the patient's circumstances.

Died – Select "Died" if the patient died before therapy was completed. If "Died" is selected please attempt to obtain documentation of death (e.g., death certificate) as this will help ascertain whether the patient's cause of death was related to TB.

Other – Select "Other" if therapy is discontinued for a reason not listed above. Please specify the reason treatment was stopped in the space provided.

Unknown – Select "Unknown" if the reason that therapy stopped is not known.

If Died, enter cause of death – If the patient was alive at diagnosis but died before TB therapy was completed, indicate the cause of death. Information under "If Died" may be filled out for cases whose reason for stopping therapy was death, who stopped therapy due to adverse treatment event then died, or patients who were lost but later determined to have died from another source such as death indices. Ideally, written documentation of the cause of death (e.g., death certificate, autopsy report, medical records) is recommended; however, a reliable verbal source (e.g., a health care provider) will be accepted.

Related to TB disease – Select "Related to TB disease" if the patient's cause of death was related or due to TB disease. If TB is listed on the death certificate as either the immediate cause, an underlying cause, or other significant condition contributing to death, check "Related to TB disease" for whether TB was a cause of death.

Related to TB therapy – Select "Related to TB therapy" if TB therapy (e.g., adverse treatment event) was related to the cause of death.

Unrelated to TB disease – Select "Unrelated to TB disease" if TB disease or therapy did not have anything to do with the cause of death or if TB was not listed as either the immediate cause, an underlying cause, or other significant condition contributing to death.

Unknown – Select "Unknown", if the patient's cause of death is unknown.

7. Reason Therapy Extending >12 months: This variable will help assess the reason(s) attributed to why antituberculosis therapy extended for more than 12 months. "Date Therapy Started" (RVCT Section) and "Date Therapy Stopped" (Follow-up 2 Section) should be used to calculate the length of antituberculosis therapy and determine if it was more than 12 months. Sources for the reasons why therapy was extended include patient medical records, patient interview, and health care provider interview.

Rifampin resistance (only) – Select "Rifampin resistance (only)" if the patient had TB that was resistant only to Rifampin, which would require a treatment protocol lasting more than 12 months per recommended TB treatment guidelines.

Other Drug Resistance (non-Rifampin) – Select "Other Drug Resistance (non-Rifampin)" if the patient had TB that was resistant to anti-tuberculosis drugs other than or in addition to Rifampin, which would require a treatment protocol lasting more than 12 months per recommended TB treatment guidelines. Please specify the type of drug resistance in the space provided.

Adverse drug reaction – Select "Adverse drug reaction", if the patient had a significant adverse drug reaction or adverse treatment event due to antituberculosis medications that prolonged therapy (e.g., life threatening reactions, reactions requiring permanent change in antituberculosis medications).

Non-adherence – Select "Non-adherence", if there were barriers to adherence to anti-tuberculosis therapy for the patient (e.g., patient did not adhere to therapy causing treatment interruption) or if the patient was non-compliant resulting in extension of therapy beyond 12 months.

Failure – Select "Failure", if the patient has a positive sputum culture at or beyond month 4 of treatment. All treatment failure isolates should be compared to the initial isolate using DNA fingerprinting.

Clinically indicated - other reasons – Select "Clinically indicated – other reasons", if the patient had clinically-indicated reasons other than those listed above for extending therapy more than 12 months (e.g., central nervous system (CNS) TB, including tuberculosis meningitis, severe liver disease).

Other – Select "Other" if the reason for stopping therapy does not include any of the choices listed above (e.g., health care provider choice) and is not "Unknown." Additional space is provided at the bottom of the form to write comments regarding "Other" reasons. Please specify the reason treatment was extended >12 months in the space provided.

Unknown – Select "Unknown", if the reason for therapy being extended is not known.

8. Type of Health Care Provider: This field indicates the type of health care provider the TB patient had during their TB treatment.

Local/State Health Department (HD) – Select "Local/State Health Department (HD)" if the primary responsibility for clinical outpatient decision making (*excluding* diagnostic work-up, contact investigations, anti-TB medications, and DOT) is the local or state health department (e.g., TB program, health clinic).

Public non-Local/State HD – Select "Public non-Local/State HD" if the primary responsibility for clinical outpatient decision making (*excluding* diagnostic work-up, contact investigations, anti-TB medications, and DOT) is a Public non- Local/State HD.

IHS, Tribal HD, or Tribal Corporation – Select "IHS, Tribal HD or Tribal Corporation" if the primary responsibility for clinical outpatient decision making (*excluding* diagnostic work-up, contact investigations, anti-TB medications, and DOT) is the Indian Health Service (IHS) or an American Indian or Alaska Native Tribal Health Department or Tribal Healthcare Corporation.

Private – Select "Private" if the primary responsibility for clinical outpatient decision making (*excluding* diagnostic work-up, contact investigations, anti-TB medications, and DOT) is a private provider [e.g., private physician or health care provider, private Health Maintenance Organization (HMO), or private managed care provider]. This category also includes the private provider that has the primary responsibility for clinical outpatient decision making for a TB patient, even though the TB control program or local/state health department may be periodically contacting the private provider for the purpose of completing the RVCT and to ensure proper TB case management.

Institutional – Select "Institutional" if the primary responsibility for clinical outpatient decision making (*excluding* diagnostic work-up, contact investigations, anti-TB medications, and DOT) is an institution such as a correctional facility or a long-term care facility (e.g., nursing home, assisted living facility).

No Outpatient Care – Select "No Outpatient Care" if the patient did not receive any outpatient TB care. Such situations could include TB diagnosed at autopsy, patients who died prior to receiving outpatient TB care, and patients that received all of their TB care as an inpatient in a hospital or similar acute care facility.

Other – Select "Other" if the primary responsibility for clinical outpatient decision making (*excluding* diagnostic work-up, contact investigations, anti-TB medications, and DOT) is a provider that is not included in any of the other categories and is not "Unknown" (e.g., city/county/state owned hospitals that are not part of the health department providing outpatient care, private hospital providing outpatient care, Veterans Administration, federal program, military facility, or community-based organization (CBO).

Unknown – Select "Unknown" if the type of health care provider is unknown. If "Unknown" is checked, no other choice for type of health care provider should be checked.

9. Directly Observed Therapy: This field indicates whether the TB patient received Directly Observed Therapy (DOT) defined as supervised therapy in which a health care provider (e.g. nurse, outreach worker, etc.) has direct visual observation of a patient's ingestion of medication. This is the recognized standard of care for TB in the United States. Performing pill counts or dropping the filled prescription off to the patient and not observing the patient ingest the medication is not acceptable and does **not** constitute DOT.

Number of DOT weeks – Please indicate the total number of calendar weeks (Sunday through Saturday) that the patient received the following minimum amounts of medication under supervision at either type of site. If the patient was both DOT and Self-administered, *only* count those weeks that were supervised, thus the number of weeks recorded here will be less than the total weeks of therapy given.

Minimum doses by DOT to count week: 1) For patients on a daily DOT regimen, count the week only if *five or more* of the week's doses were supervised. 2) For patients on a twice-weekly DOT regimen, count the week only if *both* the week's doses were supervised. 3) For patients on a thrice-weekly DOT regimen, count the week only if *all three* of the week's doses were supervised.

Number of self-administered weeks – Please indicate the total number of calendar weeks (Sunday through Saturday) that the patient did not receive DOT and took his or her medication without supervision.

Number of unknown weeks – Please indicate the total number of calendar weeks (Sunday through Saturday) for which it is not known how the patient's TB medication was administered.

10. Was Follow-up Drug Susceptibility Testing Done: This variable will help assess the frequency of acquired drug resistance. Provide information on drug susceptibility testing performed on any TB isolate more than 30 days after the initial susceptibility testing.

No – Select "No" if no follow-up drug susceptibility testing was done.

Yes – Select "Yes" if the patient had follow-up drug susceptibility testing performed after the initial testing

Unknown – Select "Unknown" if it is unknown whether the patient had Follow-up drug susceptibility performed after the initial testing.

If Yes, Enter Date Final Isolate Collected for Which Drug Susceptibility Was Done – Please indicate the date of collection for the isolate from which final susceptibility was done.

If Yes, enter specimen type – Please indicate the type of specimen on which the follow-up

drug susceptibility testing was performed.

Sputum – Select "Sputum" if follow-up drug susceptibility testing was performed on a sputum sample.

Other – Select "Other" if follow-up drug susceptibility testing was performed on a sample other than sputum.

If not Sputum, enter Anatomic Code – If the specimen for follow-up drug susceptibility was something other than sputum, please select the anatomic code from the drop down menu.

11. Isolate submitted for genotyping: **(State Use Only)**. This Field indicates whether a specimen was submitted for genotyping.

    Genotype Accession Number for current episode – **(State Use Only)**. This field indicates the number that is used to identify a patient's genotype result and is used as an identifier at MDCH and CDC.

12. Final Susceptibility Results: This table is used to record results for the final isolate for which drug susceptibility testing is performed. For each drug listed, please indicate the result of susceptibility testing by selecting "Resistant", "Susceptible", "Not Done", or "Unknown" as appropriate. "Not Done" indicates that susceptibility testing was not done for that specific drug. If there is another drug for which susceptibility is performed that is not listed, please indicate which drug was tested in the comments field at the end of the MDSS TB form and select the result of the testing from the dropdown menu next to "Other" in the table.

IV. Contact Information – This section is used to collect information on the contacts of active TB patients that are identified in contact investigations.

1. Name of Contact: Please indicate the last and first name of the contact in this field.

2. Birth date: Please indicate the date of birth for the contact in this field (mm/dd/yyyy).

3. Contact Level: Please indicate the level of interaction that each contact had with the patient by selecting from the dropdown menu. This should correspond to the concentric circle approach to contact investigation. The contact level choices are Close (1st Circle), Casual (2nd Circle), and Remote (3rd Circle).

4. Prior Positive PPD: This field indicates whether the contact had had a prior positive tuberculin skin test. Please select the appropriate response (Yes, No, Unknown) from the dropdown menu.

5. Initial PPD Date: This field indicates the date the initial TST was placed (mm/dd/yyyy).

6. Initial PPD Result: This field indicates the result of the initial TST. Please indicate the

7. Final PPD Date: This field indicates the date the final TST was placed (mm/dd/yyyy). This test is usually placed 8-10 weeks after the contact's initial exposure to TB.

8. Final PPD Result: This field indicates the result of the final TST. Please indicate the measurement of induration in millimeters (mm).

9. X-Ray Date: This field indicates the date of X-Ray for the contact to the TB patient. This X-Ray would be done if a patient has a positive PPD or other risk factors.

10. X-Ray Result: This field indicates the result of an X-Ray if it was taken. Please type the result of the X-Ray in the space provided.

V. Other Information:

1. Local 1: This field should be used as needed for local health department notes.

2. Local 2: This field should be used as needed for local health department notes.

3. Name of Person Interviewed: If a proxy is interviewed for the patient please indicate the name of the person interviewed. A proxy is someone who is close enough to the patient to provide reliable information regarding the patient's life (e.g., spouse, parent, son or daughter, close friend) if for some reason the patient cannot provide the needed information.

   Relationship to Patient – If a proxy is interviewed, indicate the proxy's relationship to the patient.

   Date of interview – If a proxy is interviewed; indicate the date the interview was performed.

4. Submitted by: Indicate the name of the local person submitting the MDSS TB form.

5. Date: Indicate the date the MDSS TB form is submitted. This date should be the date that the investigation status is marked "Active" which is when MDCH TB Program will review the information to consider the patient for case counting.

6. Health Department: Indicate the local health department that is submitting the MDSS TB form.

7. Phone Number: Indicate the phone number for the person submitting the MDSS TB form.

   Ext – Indicate the extension number for the telephone number of the person submitting the MDSS TB form.

8. Comments or Additional Information: This section is for any comments or additional information that is pertinent about the TB patient or investigation. If a case is considered to be clinical or provider-diagnosed, a brief description of the case should be entered here. If a field elsewhere on the MDSS TB form asks for additional information to be written in the "comments section" this is the field where it should be written.

TB Elimination

Recommendations for Human Immunodeficiency Virus (HIV) Screening in Tuberculosis (TB) Clinics

What are the recommendations for human immunodeficiency virus (HIV) screening in tuberculosis (TB) clinics?

In revised recommendations from 2006, CDC recommends HIV screening for all TB patients after the patient is notified that testing will be performed, unless the patient declines (i.e., opt-out screening). Routine HIV testing is also recommended for TB suspects and contacts to TB patients. Persons at high risk for HIV infection should be screened for HIV at least annually. Separate written consent and prevention counseling for HIV testing should no longer be required.

How do the new 2006 recommendations for HIV screening differ from previous ones?

These recommendations address health care settings only and do not replace previous recommendations for HIV testing in non-clinical, outreach, or field settings. They aim to eliminate missed opportunities for HIV screening and reduce significant barriers to HIV testing in health care settings by:

- Using opt-out HIV screening.
- Screening persons at high risk for HIV annually.
- Eliminating the need for separate written consent for HIV testing.
- Eliminating the need for prevention counseling as part of HIV testing.

What is opt-out screening?

Opt-out screening is defined as performing HIV testing after notifying the patient that the test will be performed and that although the patient may decline or defer testing, it is strongly recommended. Assent is inferred unless the patient declines testing.

Why does CDC recommend that TB clinics screen their patients for HIV infection?

HIV infection is the most important known risk factor for progression from latent TB infection to TB disease. Progression to TB disease is often rapid among HIV-infected persons and can be deadly. In addition, TB outbreaks can rapidly expand in HIV-infected patient groups.

Targeted testing based on provider assessment of patient risk behaviors fails to identify a substantial number of persons who are HIV-infected. This is because many individuals may not perceive themselves to be at risk for HIV or do not disclose their risks. Routine HIV testing reduces the stigma associated with testing. When HIV is diagnosed early, appropriately timed interventions can lead to improved health outcomes, including slower progression and reduced mortality. Identifying TB patients, suspects, and contacts who are HIV-infected allows for optimal TB screening of these groups and opportunities to prevent TB in those without disease.

Who should be tested for HIV in TB clinics?

All patients should be tested for HIV. This includes TB suspects, patients, and contacts.

Can rapid HIV tests be used to screen TB patients and their contacts?

Yes. Rapid HIV tests, using fingerprick or oral specimens, can be used. Results are available in about 20 minutes. Although the rapid HIV test kits cost about $10 more per test than standard lab assays, they have been shown to be cost-effective and to increase patients' acceptance of HIV testing. Another option is to collect oral swab specimens and use standard lab assays.

What education and training resources on HIV counseling and testing are available?

Resources for education and training on HIV counseling and testing are available from CDC-funded HIV/AIDS programs in each state health department and from the National Network of STD/HIV Prevention Training Centers . Additionally, the Health Resources and Services Administration (HRSA) has regional AIDS Education and Training Centers (AETCs) and other local performance sites that can provide training in HIV counseling and testing to TB staff.

Also available is a Contact Investigation and Management Protocol to facilitate HIV counseling, testing,and referral during TB contact investigations. The protocol was developed by the New York City Bureau of TB Control, in collaboration with the New York City Department of Health HIV Training Institute, with funding from CDC.

Additional Information

CDC. Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings. *MMWR* 2006; 55 (No. RR-14).
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5514a1.htm

CDC. HIV Testing in Health Care Settings.
http://www.cdc.gov/hiv/topics/testing/healthcare/index.htm

CDC. Rapid HIV Testing.
http://www.cdc.gov/hiv/topics/testing/rapid/index.htm

Resources

National Network of STD/HIV Prevention Training Centers.
http://depts.washington.edu/nnptc

AIDS Education and Training Centers (AETCs).
http://www.aidsetc.org/aidsetc?page=ab-00-00

New York City Bureau of Tuberculosis Control. Contact Investigation and Management Protocol.
http://www.nyc.gov/html/doh/html/tb/tb-controllers.shtml

TB Education & Training Resources

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(Printable Version)

[Tuberculosis: The Connection between TB and HIV (the AIDS Virus)]

Abstract

This brochure explains TB and its connection with HIV/AIDS. It discusses TB transmission and describes the symptoms of TB and pulmonary TB

Available From

Asian Pacific Health Care Venture Inc
1530 Hillhurst Ave Ste 200
Los Angeles, CA 90027
Main Phone: (323) 644-3880
http://aphcv.apanet.org

Publication Date

2002

Author

Asian Pacific Health Care Venture Inc

Format

Brochure/Pamphlet

Physical Description

1 folded sheet (6 p.): mono, ill.

Language

Chinese

Country of Origin

United States

Audiences

Asians/Pacific Islanders, **Foreign-born/Immigrant**, Persons With **HIV**/AIDS, Persons With LTBI, Persons With TB

Document URL

PDF:
http://www.findtbresources.org/scandocs/AD31165.pdf

Topic

General TB Information, **HIV**/AIDS Co-infection

Notes

This brochure is available in English, Korean, Spanish, and Vietnamese.

To order this material, contact the Organization in the Available From field.
To view this material online, click the link in the Document URL field.

Disclaimer: The information on the TB Education and Training Resources Web Site is made available as a public service. Neither the Centers for Disease Control and Prevention nor the National Prevention Information Network endorses the organizations, Web sites, and materials presented. It is the responsibility of the user to evaluate this information prior to use based on individual, community, and organizational needs and standards.

Tuberculosis y VIH (Virus del SIDA)
(Tuberculosis Facts: TB and HIV (The AIDS Virus))

Abstract
This fact sheet provides information about the connection between **HIV**/AIDS and TB, TB transmission, and the difference between latent TB infection and active TB disease.

Available From
North Carolina Department of Health and Human Services
Communicable Disease Control Branch
TB Control Program
1902 Mail Service Center
Raleigh, NC 27699-1902
Main Phone: (919) 733-7286
http://www.epi.state.nc.us/epi/tb/

Publication Date
November 2001

Author
North Carolina Department of Health and Human Services

Format
Fact Sheet

Physical Description
1 p.: mono., ill.

Language
Spanish

Country of Origin
United States

Audiences
Foreign-born/Immigrant, Hispanics, Persons With **HIV**/AIDS, Persons With TB

Document URL
PDF:
http://www.findtbresources.org/scandocs/AD30040.pdf

Topic
General TB Information, **HIV**/AIDS Co-infection, Treatment- Latent TB Infection, Treatment- TB Disease

Notes
This fact sheet is also available in English.

To order this material, contact the Organization in the Available From field.
To view this material online, click the link in the Document URL field.

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endorses the organizations, Web sites, and materials presented. It is the responsibility of the user to evaluate this information prior to use based on individual, community, and organizational needs and standards.

[The Connection between TB and HIV]

Abstract

This pamphlet discusses TB transmission and describes the differences between treating TB in persons with and without HIV/AIDS.

Available From

New York City Department of Health and Mental Hygiene
Bureau of Tuberculosis Control
125 Worth St
New York, NY 10013
Main Phone: (212) 442-9968
http://www.nyc.gov/html/doh/html/tb/tb.shtml

Publication Date

1999

Author

New York City Department of Health and Mental Hygiene

Format

Brochure/Pamphlet

Physical Description

1 folded sheet (6 p.): col.

Language

Chinese

Country of Origin

United States

Audiences

Asians/Pacific Islanders, **Foreign-born/Immigrant**, General Public, Persons With HIV/AIDS, Persons With TB

Topic

HIV/AIDS Co-infection, Treatment, Treatment-TB Disease

To order this material, contact the Organization in the Available From field.

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Lo Que No Sabe de Tuberculosis Puede Ser su Muerte
(What You Don't Know about Tuberculosis Could Kill You)

Abstract

This videotape discusses TB, the TB skin test, and the symptoms of active TB. It identifies populations at risk for TB, methods of transmission, and explains the differences between active TB disease and latent TB infection.

Available From

Texas Department of Health
Tuberculosis Elimination Division
1100 W 49th Street
Austin, TX 78756-3199
Main Phone: (512) 458-7447
http://www.tdh.state.tx.us/tb/default.htm

Publication Date

1996

Author

Texas Department of Health

Format

Videotape

Physical Description

1 videotape (7 mins.): sd., col.; 1/2 in. (VHS).

Language

Spanish

Country of Origin

United States

Audiences

Foreign-born/Immigrant, General Public, Hispanics, Inmates

Topic

Corrections, Diagnosis, Diagnosis- Skin Test, **HIV**/AIDS Co-infection, Treatment- Adverse Reactions, Treatment- Latent TB Infection, Treatment- Patient Adherence, Treatment- TB Disease

Notes

This videotape is available in English.

To order this material, contact the Organization in the Available From field.

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HIV and TB: Tuberculosis (Qaaxo)

(HIV and TB (Tuberculosis))

Abstract

This pamphlet discusses TB and its relationship to **HIV**/AIDS.

Available From

Canadian Public Health Association
1565 Carling Ave Ste 400
Ottawa, ON Canada K1Z 8R1

Format

Brochure/Pamphlet

Physical Description

Main Phone: (613) 725-3434
Toll Free Number: (877) 999-7740
http://www.clearinghouse.cpha.ca

Publication Date
1995

Author
Canadian AIDS Society

1 folded sheet (8 p.): col., ill.

Language
Somali

Country of Origin
Canada

Audiences
Foreign-born/Immigrant, Persons With **HIV**/AIDS, Persons With LTBI, Persons With TB

Document URL
PDF:
http://www.findtbresources.org/scandocs/AD23258.pdf

Topic
Diagnosis- Screening, Diagnosis- Skin Test, **HIV**/AIDS Co-infection, Pregnant Women, Treatment, Treatment- Latent TB Infection, Treatment- Medication Information, Treatment- TB Disease

Notes
This pamphlet is available in English, French, Spanish, Tamil, and Vietnamese.

To order this material, contact the Organization in the Available From field.
To view this material online, click the link in the Document URL field.

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VIH ea TB (Tuberculose)
(HIV and TB (Tuberculosis))

Abstract
This pamphlet discusses TB and its relationship to persons with **HIV**/AIDS; specifically, how latent TB infection (LTBI) and active TB disease affect a person with HIV/AIDS.

Available From
Canadian Public Health Association
1565 Carling Ave Ste 400
Ottawa, ON Canada K1Z 8R1
Main Phone: (613) 725-3434

Format
Brochure/Pamphlet

Physical Description

Toll Free Number: (877) 999-7740
http://www.clearinghouse.cpha.ca

Publication Date
1994

Author
Canadian AIDS Society

1 folded sheet (8 p.): col., ill.

Language
Portuguese

Country of Origin
Canada

Audiences
Foreign-born/Immigrant, Persons With **HIV**/AIDS, Persons With LTBI, Persons With TB

Document URL
PDF:
http://www.findtbresources.org/scandocs/AD31469.pdf

Topic
Diagnosis, Diagnosis- Screening, Diagnosis- Skin Test, **HIV**/AIDS Co-infection, Pregnant Women, Treatment, Treatment- Latent TB Infection, Treatment- Medication Information, Treatment- TB Disease

Notes
This pamphlet is also available in Cree, English, French, Ojibway, Somali, Spanish, Tamil, and Vietnamese.

To order this material, contact the Organization in the Available From field.
To view this material online, click the link in the Document URL field.

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Conozca La Tuberculosis : Manual Para el Paciente con Notas de los Riesgos por La Infeccion del VIH (Virus de la Inmunodeficiencia Humana)
(Understanding Tuberculosis Today : A Handbook for Patients with Notes on the Effect of HIV Infection)

Abstract
This pamphlet provides general information about TB and examines how TB affects various groups, including children and persons with **HIV**/AIDS. It also provides case studies of persons

with TB that show the benefits of patient adherence to medical therapies.

Available From

Arkansas Department of Health
Tuberculosis Program
4815 W Markham St Slot 45
Little Rock, AR 72205-3867
Main Phone: (501) 661-2152
http://www.healthyarkansas.com

Publication Date

February 1992

Author

Stead, W. W.
Arkansas Department of Health

Edition

8th

Format

Brochure/Pamphlet

Physical Description

32 p.: col., ill.; appendix, refs.

Language

Spanish

Country of Origin

United States

Audiences

Foreign-born/Immigrant, Hispanics, Persons With **HIV**/AIDS, Persons With TB

Topic

Children, Diagnosis, General TB Information, **HIV**/AIDS Co-infection, Treatment, Treatment- Adverse Reactions, Treatment- Latent TB Infection, Treatment- Medication Information, Treatment- Patient Adherence, Treatment- TB Disease

Notes

This pamphlet is available in English.

To order this material, contact the Organization in the Available From field.

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'O ka Pilina Mawaena o AIDS a me TB he Mea Nui Paha no 'oe...E Heluhelu Mai i Keia Palapala!

(The Link between AIDS and TB Could Be Important to You...Read This!)

Abstract

This pamphlet discusses the difference between **HIV**/AIDS and TB, the transmission of HIV and

TB, the meaning of a positive skin test for TB and a positive antibody test for HIV, and reasons why individuals should be tested for both.

Available From

Hawaii State Department of Health
Tuberculosis Control Program
Lanakila Health Center
1700 Lanakila Ave
Honolulu, HI 96817
Main Phone: (808) 832-5731
http://www.hawaii.gov/doh/resource/comm_dis/tb/

Publication Date

September 1988

Author

Hawaii State Department of Health

Format

Brochure/Pamphlet

Physical Description

1 folded sheet (6 p.): mono., ill.

Language

Hawaiian

Country of Origin

United States

Audiences

Asians/Pacific Islanders, **Foreign-born/Immigrant**, Persons With **HIV**/AIDS, Persons With TB

Document URL

PDF:
http://www.findtbresources.org/scandocs/AD23685.pdf

Topic

Diagnosis, Diagnosis- Laboratory Procedures, Diagnosis- Screening, Diagnosis- Skin Test, General TB Information, **HIV**/AIDS Co-infection

Notes

This pamphlet is available in Cambodian, Chinese, Ilocano, Japanese, Korean, Lao, Samoan, Tagalog, Thai, Tongan, Vietnamese, and Visayan.

To order this material, contact the Organization in the Available From field.
To view this material online, click the link in the Document URL field.

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[The Link between AIDS and TB Could Be Important to You...Read This!]

Abstract

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Available From

Hawaii State Department of Health
Tuberculosis Control Program
Lanakila Health Center
1700 Lanakila Ave
Honolulu, HI 96817
Main Phone: (808) 832-5731
http://www.hawaii.gov/doh/resource/comm_dis/tb/

Publication Date

June 1988

Author

Hawaii State Department of Health

Format

Brochure/Pamphlet

Physical Description

1 folded sheet (6 p.): mono., ill.

Language

Japanese

Country of Origin

United States

Audiences

Asians/Pacific Islanders, **Foreign-born/Immigrant**, Persons With **HIV**/AIDS, Persons With TB

Document URL

PDF:
http://www.findtbresources.org/scandocs/AD23678.pdf

Topic

Diagnosis, Diagnosis- Laboratory Procedures, Diagnosis- Screening, Diagnosis- Skin Test, General TB Information, **HIV**/AIDS Co-infection

Notes

This pamphlet is available in Cambodian, Chinese, Hawaiian, Ilocano, Korean, Lao, Samoan, Tagalog, Thai, Tongan, Vietnamese, and Visayan.

To order this material, contact the Organization in the Available From field.
To view this material online, click the link in the Document URL field.

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[The Link between AIDS and TB Could Be Important to You...Read This!]

Abstract
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Available From
Hawaii State Department of Health
Tuberculosis Control Program
Lanakila Health Center
1700 Lanakila Ave
Honolulu, HI 96817
Main Phone: (808) 832-5731
http://www.hawaii.gov/doh/resource/comm_dis/tb/

Publication Date
June 1988

Author
Hawaii State Department of Health

Format
Brochure/Pamphlet

Physical Description
1 folded sheet (6 p.): mono., ill.

Language
Chinese

Country of Origin
United States

Audiences
Asians/Pacific Islanders, **Foreign-born/Immigrant**, General Public, Persons With **HIV**/AIDS, Persons With TB

Document URL
PDF:
http://www.findtbresources.org/scandocs/AD23679.pdf

Topic
General TB Information, **HIV**/AIDS Co-infection

Notes
This pamphlet is available in Cambodian, Hawaiian, Ilocano, Japanese, Korean, Lao, Samoan, Tagalog, Thai, Tongan, Vietnamese, and Visayan.

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Abstract

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Available From

Hawaii State Department of Health
Tuberculosis Control Program
Lanakila Health Center
1700 Lanakila Ave
Honolulu, HI 96817
Main Phone: (808) 832-5731
http://www.hawaii.gov/doh/resource/comm_dis/tb/

Publication Date

June 1988

Author

Hawaii State Department of Health

Format

Brochure/Pamphlet

Physical Description

1 folded sheet (6 p.): mono., ill.

Language

Lao

Country of Origin

United States

Audiences

Asians/Pacific Islanders, **Foreign-born/Immigrant**, Persons With **HIV**/AIDS, Persons With TB

Document URL

PDF:
http://www.findtbresources.org/scandocs/AD23675.pdf

Topic

Diagnosis, Diagnosis- Laboratory Procedures, Diagnosis- Screening, Diagnosis- Skin Test, General TB Information, **HIV**/AIDS Co-infection

Notes

This pamphlet is available in Cambodian, Chinese, Hawaiian, Ilocano, Japanese, Korean, Samoan, Tagalog, Thai, Tongan, Vietnamese, and Visayan.

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[The Link between AIDS and TB Could Be Important to You...Read This!]

Abstract
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Available From
Hawaii State Department of Health
Tuberculosis Control Program
Lanakila Health Center
1700 Lanakila Ave
Honolulu, HI 96817
Main Phone: (808) 832-5731
http://www.hawaii.gov/doh/resource/comm_dis/tb/

Publication Date
June 1988

Author
Hawaii State Department of Health

Format
Brochure/Pamphlet

Physical Description
1 folded sheet (6 p.): mono., ill.

Language
Korean

Country of Origin
United States

Audiences
Asians/Pacific Islanders, **Foreign-born/Immigrant**, Persons With **HIV**/AIDS, Persons With TB

Document URL
PDF:
http://www.findtbresources.org/scandocs/AD23676.pdf

Topic
Diagnosis, Diagnosis- Laboratory Procedures, Diagnosis- Screening, Diagnosis- Skin Test, General TB Information, **HIV**/AIDS Co-infection

Notes
This pamphlet is available in Cambodian, Chinese, Hawaiian, Ilocano, Japanese, Lao, Samoan, Tagalog, Thai, Tongan, Vietnamese, and Visayan.

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[The Link between AIDS and TB Could Be Important to You...Read This!]

Abstract

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Available From

Hawaii State Department of Health
Tuberculosis Control Program
Lanakila Health Center
1700 Lanakila Ave
Honolulu, HI 96817
Main Phone: (808) 832-5731
http://www.hawaii.gov/doh/resource/comm_dis/tb/

Publication Date

June 1988

Author

Hawaii State Department of Health

Format

Brochure/Pamphlet

Physical Description

1 folded sheet (6 p.): mono., ill.

Language

Thai

Country of Origin

United States

Audiences

Asians/Pacific Islanders, **Foreign-born/Immigrant**, Persons With **HIV**/AIDS, Persons With TB

Document URL

PDF:
http://www.findtbresources.org/scandocs/AD23677.pdf

Topic

Diagnosis, Diagnosis- Laboratory Procedures, Diagnosis- Screening, Diagnosis- Skin Test, General TB Information, **HIV**/AIDS Co-infection

Notes

This pamphlet is available in Cambodian, Chinese, Hawaiian, Ilocano, Japanese, Korean, Lao, Samoan, Tagalog, Tongan, Vietnamese, and Visayan.

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[The Link between AIDS and TB Could Be Important to You...Read This!]

Abstract

This pamphlet discusses the difference between **HIV**/AIDS and TB, the transmission of HIV and TB, the meaning of a positive skin test for TB and a positive antibody test for AIDS, and reasons why individuals should be tested for both.

Available From

Hawaii State Department of Health
Tuberculosis Control Program
Lanakila Health Center
1700 Lanakila Ave
Honolulu, HI 96817
Main Phone: (808) 832-5731
http://www.hawaii.gov/doh/resource/comm_dis/tb/

Publication Date

June 1988

Author

Hawaii State Department of Health

Format

Brochure/Pamphlet

Physical Description

1 folded sheet (6 p.): mono., ill.

Language

Cambodian

Country of Origin

United States

Audiences

Asians/Pacific Islanders, **Foreign-born/Immigrant**, Persons With **HIV**/AIDS, Persons With TB

Document URL

PDF:
http://www.findtbresources.org/scandocs/AD23672.pdf

Topic

Diagnosis, Diagnosis- Skin Test, **HIV**/AIDS Co-infection

Notes

This pamphlet is available in Chinese, Hawaiian, Ilocano, Japanese, Korean, Lao, Samoan, Tagalog, Thai, Tongan, Vietnamese, and Visayan.

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And Ugnayan sa Pagitan ng 'AIDS' at Tisis Mahalaga Para sa Iyo...Basahin mo Ito!

(The Link between AIDS and TB Could Be Important to You...Read This!)

Abstract

This pamphlet discusses the difference between **HIV**/AIDS and TB, the transmission of HIV and TB, the meaning of a positive skin test for TB and a positive antibody test for HIV, and reasons why individuals should be tested for both.

Available From

Hawaii State Department of Health
Tuberculosis Control Program
Lanakila Health Center
1700 Lanakila Ave
Honolulu, HI 96817
Main Phone: (808) 832-5731
http://www.hawaii.gov/doh/resource/comm_dis/tb/

Publication Date

May 1988

Author

Hawaii State Department of Health

Format

Brochure/Pamphlet

Physical Description

1 folded sheet (6 p.): mono., ill.

Language

Tagalog

Country of Origin

United States

Audiences

Asians/Pacific Islanders, **Foreign-born/Immigrant**, Persons With **HIV**/AIDS, Persons With TB

Document URL

PDF:
http://www.findtbresources.org/scandocs/AD23698.pdf

Topic

Diagnosis, Diagnosis- Laboratory Procedures, Diagnosis- Screening, Diagnosis- Skin Test, General TB Information, **HIV**/AIDS Co-infection

Notes

This pamphlet is available in Cambodian, Chinese, Hawaiian, Ilocano, Japanese, Korean, Lao, Samoan, Thai, Tongan, Vietnamese, and Visayan.

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Ang Kalabutan sa AIDS ug TB Mahinundganon Alang Kanimo...Basaha Kini!
(The Link between AIDS and TB Could Be Important to You...Read This!)

Abstract
This pamphlet discusses the difference between **HIV**/AIDS and TB, the transmission of HIV and TB, the meaning of a positive skin test for TB and a positive antibody test for HIV, and reasons why individuals should be tested for both.

Available From
Hawaii State Department of Health
Tuberculosis Control Program
Lanakila Health Center
1700 Lanakila Ave
Honolulu, HI 96817
Main Phone: (808) 832-5731
http://www.hawaii.gov/doh/resource/comm_dis/tb/

Publication Date
June 1988

Author
Hawaii State Department of Health

Format
Brochure/Pamphlet

Physical Description
1 folded sheet (6 p.): mono., ill.

Language
Visayan

Country of Origin
United States

Audiences
Asians/Pacific Islanders, **Foreign-born/Immigrant**, Persons With **HIV**/AIDS, Persons With TB

Document URL
PDF:
http://www.findtbresources.org/scandocs/AD23680.pdf

Topic
Diagnosis, Diagnosis- Laboratory Procedures, Diagnosis- Screening, Diagnosis- Skin Test, General TB Information, **HIV**/AIDS Co-infection

Notes
This pamphlet is available in Cambodian, Chinese, Hawaiian, Ilocano, Japanese, Korean, Lao, Samoan, Tagalog, Thai, Tongan, and Vietnamese.

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Koe Fekau'aki 'ae 'Eitisi (AIDS) Moe TB Mahalo Na'a Mahu'inga pe 'Aonga 'Eni Kiate Koe...Lau 'Eni!
(The Link between AIDS and TB Could Be Important to You...Read This!)

Abstract
This pamphlet discusses the difference between **HIV**/AIDS and TB, the transmission of HIV and TB, the meaning of a positive skin test for TB and a positive antibody test for HIV, and reasons why individuals should be tested for both.

Available From
Hawaii State Department of Health
Tuberculosis Control Program
Lanakila Health Center
1700 Lanakila Ave
Honolulu, HI 96817
Main Phone: (808) 832-5731
http://www.hawaii.gov/doh/resource/comm_dis/tb/

Publication Date
May 1988

Author
Hawaii State Department of Health

Format
Brochure/Pamphlet

Physical Description
1 folded sheet (6 p.): mono., ill.

Language
Tongan

Country of Origin
United States

Audiences
Asians/Pacific Islanders, **Foreign-born/Immigrant**, Persons With **HIV**/AIDS, Persons With TB

Document URL
PDF:
http://www.findtbresources.org/scandocs/AD23683.pdf

Topic
Diagnosis, Diagnosis- Laboratory Procedures, Diagnosis- Screening, Diagnosis- Skin Test, General TB Information, **HIV**/AIDS Co-infection

Notes
This pamphlet is available in Cambodian, Chinese, Hawaiian, Ilocano, Japanese, Korean, Lao, Samoan, Tagalog, Thai, Vietnamese, and Visayan.

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Moi Lien Quan Giua Benh AIDS va Benh LAO co The he Trong Cho Ban...Ban Hay Doc Tai Lieu Nay!
(The Link between AIDS and TB Could Be Important to You...Read This!)

Abstract
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Available From
Hawaii State Department of Health
Tuberculosis Control Program
Lanakila Health Center
1700 Lanakila Ave
Honolulu, HI 96817
Main Phone: (808) 832-5731
http://www.hawaii.gov/doh/resource/comm_dis/tb/

Publication Date
June 1988

Author
Hawaii State Department of Health

Format
Brochure/Pamphlet

Physical Description
1 folded sheet (6 p.): mono., ill.

Language
Vietnamese

Country of Origin
United States

Audiences
Asians/Pacific Islanders, **Foreign-born/Immigrant**, Persons With **HIV**/AIDS, Persons With TB

Document URL
PDF:
http://www.findtbresources.org/scandocs/AD23681.pdf

Topic
Diagnosis, Diagnosis- Laboratory Procedures, Diagnosis- Screening, Diagnosis- Skin Test, General TB Information, **HIV**/AIDS Co-infection

Notes
This pamphlet is available in Cambodian, Chinese, Hawaiian, Ilocano, Japanese, Korean, Lao,

Samoan, Tagalog, Thai, Tongan, and Visayan.

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O le Feso'otaiga i le va o le AIDS ma le TB e Ono Taua ia te oe...Faitau Mea ia!

(The Link between AIDS and TB Could Be Important to You...Read This!)

Abstract

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1700 Lanakila Ave
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Main Phone: (808) 832-5731
http://www.hawaii.gov/doh/resource/comm_dis/tb/

Publication Date

June 1988

Author

Hawaii State Department of Health

Format

Brochure/Pamphlet

Physical Description

1 folded sheet (6 p.): mono., ill.

Language

Samoan

Country of Origin

United States

Audiences

Asians/Pacific Islanders, **Foreign-born/Immigrant**, Persons With **HIV**/AIDS, Persons With TB

Document URL

PDF:
http://www.findtbresources.org/scandocs/AD23682.pdf

Topic

Diagnosis, Diagnosis- Laboratory Procedures, Diagnosis- Screening, Diagnosis- Skin Test, General TB Information, **HIV**/AIDS Co-infection

Notes

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Ti Singgalut Iti Baet ti AIDS Ken Sarut Mabalin a Nasken Kenka...Basaem Daytoy!

(The Link between AIDS and TB Could Be Important to You...Read This!)

Abstract

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1700 Lanakila Ave
Honolulu, HI 96817
Main Phone: (808) 832-5731
http://www.hawaii.gov/doh/resource/comm_dis/tb/

Publication Date

May 1988

Author

Hawaii State Department of Health

Format

Brochure/Pamphlet

Physical Description

1 folded sheet (6 p.): mono., ill.

Language

Ilocano

Country of Origin

United States

Audiences

Asians/Pacific Islanders, **Foreign-born/Immigrant**, Persons With **HIV**/AIDS, Persons With TB

Document URL

PDF:
http://www.findtbresources.org/scandocs/AD23684.pdf

Topic

Diagnosis, Diagnosis- Laboratory Procedures,

Diagnosis- Screening, Diagnosis- Skin Test, General TB Information, **HIV**/AIDS Co-infection

Notes

This pamphlet is available in Cambodian, Chinese, Hawaiian, Japanese, Korean, Lao, Samoan, Tagalog, Thai, Tongan, Vietnamese, and Visayan.

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Tuberculosis Facts – Testing for TB

What is TB?

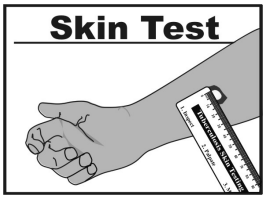
"TB" is short for a disease called tuberculosis. TB is spread through the air from one person to another. TB germs are passed through the air when someone who is sick with **TB disease** of the lungs or throat coughs, speaks, laughs, sings, or sneezes. Anyone near the sick person can breathe TB germs into their lungs.

TB germs can live in your body without making you sick. This is called **latent TB infection**. This means you have only inactive (sleeping) TB germs in your body. The inactive germs cannot be passed on to anyone else. However, if these germs wake up or become active in your body and multiply, you will get sick with **TB disease**.

When TB germs are active (multiplying in your body), this is called **TB disease**. These germs usually attack the lungs. They can also attack other parts of the body, such as, the kidneys, brain, or spine. **TB disease** will make you sick. People with **TB disease** may spread the germs to people they spend time with every day.

How do I know if I have been infected with TB?

If you have been around someone who has **TB disease**, you should go to your doctor or your local health department for tests.



There are two tests that can be used to help detect TB. Usually a skin test is done. A small needle is used to put some testing material, called tuberculin, under the skin. In 2-3 days, you return to the health care worker who will check to see if there is a reaction to the test. In some cases, another test called QuantiFERON-TB Gold (QFT-G) is given. It is a blood test that measures how a person's system reacts to the germs that cause TB.

To tell if someone has **TB disease**, other tests such as chest x-ray and a sample of sputum (phlegm that is coughed up from deep in the lungs) may be needed.

Note: If you have ever had a "positive" reaction to a TB skin test or if you have been treated with TB drugs in the past, tell your health care worker.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
Division of Tuberculosis Elimination
www.cdc.gov/tb
October 2007

Do I Need a TB Skin Test?

Tuberculosis (TB) Skin testing is recommended only for people who: have symptoms of TB or are at higher risk for becoming infected with TB germs or are at higher risk of becoming sick if they have the TB infection.

Should I be tested?

You may need the TB test if you:

- have any signs of TB (cough, tiredness, night sweats, fever, weight loss, coughing up blood)
- have close contact with someone who has TB disease
- are a health care worker
- live or work in a prison, jail, mental institution, or a nursing home
- have lived or traveled in a country where a lot of people have TB
- use needles to inject drugs
- have certain medical conditions such as
  - cancer
  - severe kidney disease
  - diabetes
  - silicosis
  - HIV infection
  - are on steroid medication
  - are severely underweight

A health care worker will ask you questions to find out if you should be tested for TB.
Please tell the health care worker if you have had a positive reaction to a TB test in the past or been on medication for TB disease or to prevent TB disease.

What if my employer or school requires a TB Test?

If the health care worker determines that you do not need to be tested, you will be given a letter for your employer, school, or who ever sent you for the test. The letter will state that you have had a negative TB screening assessment and a skin test was not needed.

Not Everyone Needs a TB Skin Test

If you have questions, contact your public health department or your doctor.

Text - Virginia Department of Health Division of TB Control
www.vdh.virginia.gov/epi/tb November 8, 2002
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A **Healthy Roads Media** project
www.healthyroadsmedia.org

Funded by the National Library of Medicine under contract N01-LM-1-3513
from the Greater Midwest Region of the National Network of Libraries of Medicine.

STOP TB Infection Before It Makes You Sick!

What is TB?
"TB" is the short name for the disease called tuberculosis. TB can attack any part of the body, but it most often attacks the lungs.

How do I get TB infection?
When a person with TB disease in the lungs or throat coughs, speaks, laughs or sneezes, tiny TB germs spray into the air. Anyone nearby can breathe the TB germs into their lungs. You cannot get TB from shaking hands, sharing glasses and dishes, or from toilet seats. TB germs can live in your body without making you sick. Your body fights the TB germs to keep you healthy. This is **TB infection**. Sometimes, your body cannot fight the TB germs. If these TB germs make you sick, this is called **TB disease**. If you get TB disease, you need medical help. You can get well with the right treatment. You can die if you don't get treatment.

How do I know if I have TB infection?
A skin test is one way to tell if you have TB infection. This test is done on the arm. Your health care provider will explain the test to you. If a small bump appears on your arm at the test site, your test may be "positive". If a health care worker decides that your test is positive, you have TB infection. You may have a "negative" test. BUT, if you were around a person with active TB disease, you may need to have the test again.

My skin test was positive. What do I do now?
The first step will be to have a chest x-ray to make sure you do not have TB disease. If your x-ray does not show TB disease, you may still need medicine to keep your TB germs from making you sick. Your health care provider may give you one or more medicines to treat the infection. It is very important that you take your medicines. **It takes a long time to kill the TB germs.**

What do I need to know about my medicines? You may have to take your medicines for 4 to 9 months. Your health care provider will tell you how to take your medicines. Ask your health care provider about side effects of your medicines. If you have questions, contact your public health department or your doctor.

Protect yourself, your family and friends from TB.
Finish your TB treatment!

Text - Virginia Department of Health Division of TB Control
www.vdh.virginia.gov/epi/tb November 8, 2002
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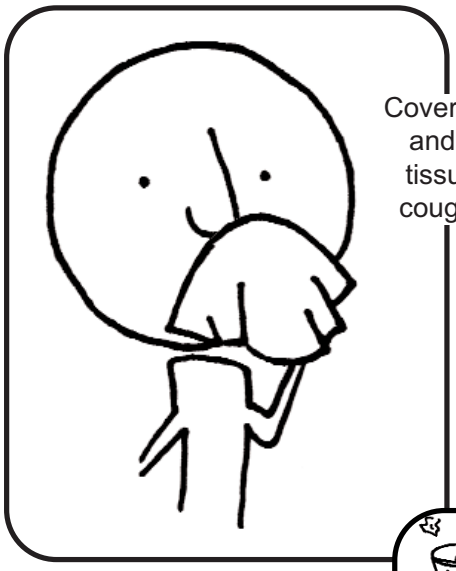
A **Healthy Roads Media** project
www.healthyroadsmedia.org

Funded by the National Library of Medicine under contract N01-LM-1-3513
from the Greater Midwest Region of the National Network of Libraries of Medicine.

Stop the spread of germs that make you and others sick!

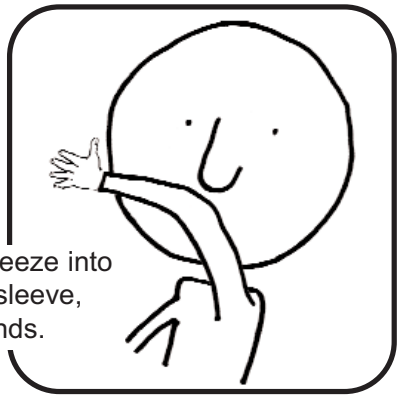
Cover your Cough



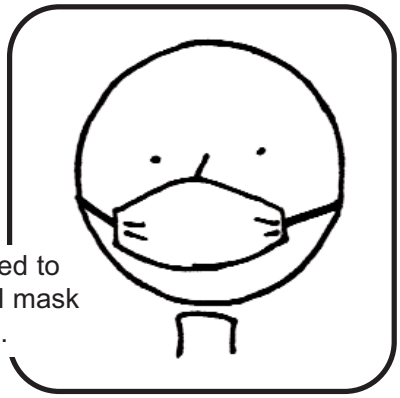
Cover your mouth and nose with a tissue when you cough or sneeze

or

cough or sneeze into your upper sleeve, not your hands.



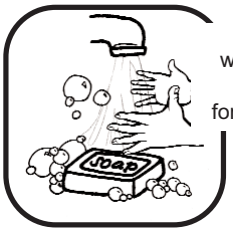
Put your used tissue in the waste basket.



You may be asked to put on a surgical mask to protect others.

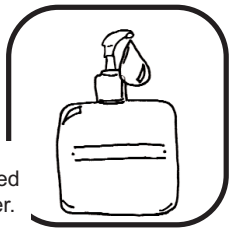
Clean your Hands

after coughing or sneezing.



Wash hands with soap and warm water for 20 seconds *or*

clean with alcohol-based hand cleaner.



CDC SAFER · HEALTHIER · PEOPLE

MINNESOTA MDH DEPARTMENT OF HEALTH

Minnesota Department of Health
717 SE Delaware Street
Minneapolis, MN 55414
612-676-5414 or 1-877-676-5414
www.health.state.mn.us

Minnesota Antibiotic Resistance Collaborative

APIC ASSOCIATION FOR PROFESSIONALS IN INFECTION CONTROL AND EPIDEMIOLOGY, INC

BCG Vaccine

Introduction

BCG, or bacille Calmette-Guérin, is a vaccine for tuberculosis (TB) disease. BCG is used in many countries with a high prevalence of TB to prevent childhood tuberculous meningitis and miliary disease. However, BCG is not generally recommended for use in the United States because of the low risk of infection with *Mycobacterium tuberculosis*, the variable effectiveness of the vaccine against adult pulmonary TB, and the vaccine's potential interference with tuberculin skin test reactivity. The BCG vaccine should be considered only for very select persons who meet specific criteria and in consultation with a TB expert.

Recommendations

Children. BCG vaccination should only be considered for children who have a negative tuberculin skin test and who are continually exposed, and cannot be separated from, adults who

- Are untreated or ineffectively treated for TB disease (if the child cannot be given long-term treatment for infection); or
- Have TB caused by strains resistant to isoniazid and rifampin.

Health Care Workers. BCG vaccination of health care workers should be considered on an individual basis in settings in which

- A high percentage of TB patients are infected with *M. tuberculosis* strains resistant to both isoniazid and rifampin;
- There is ongoing transmission of such drug-resistant *M. tuberculosis* strains to health care workers and subsequent infection is likely; or
- Comprehensive TB infection-control precautions have been implemented but have not been successful.

Health care workers considered for BCG vaccination should be counseled regarding the risks and benefits associated with both BCG vaccination and treatment of latent TB infection (LTBI).

Contraindications

Immunosuppressed Persons. BCG vaccination should not be given to persons who are immunosuppressed (e.g., persons who are HIV-infected) or who are likely to become immunocompromised (e.g., persons who are candidates for organ transplant).

Pregnant Women. BCG vaccination should not be given during pregnancy. Even though no harmful effects of BCG vaccination on the fetus have been observed, further studies are needed to prove its safety.

Testing for TB in BCG-Vaccinated Persons

Many foreign-born persons have been BCG-vaccinated. BCG vaccination may cause a positive reaction to the tuberculin skin test (TST), which may complicate decisions about prescribing treatment. Despite this potential for BCG to interfere with test results, the TST and the QuantiFERON®-TB Gold test (QFT-G) are not contraindicated for persons who have been vaccinated with BCG. The presence or size of a TST reaction in these persons does not predict whether BCG will provide any protection against TB disease. Furthermore, the size of a TST reaction in a BCG-vaccinated person is not a factor in determining whether the reaction is caused by LTBI or the prior BCG vaccination.

Treatment for LTBI in BCG-Vaccinated Persons

Treatment of LTBI substantially reduces the risk that TB infection will progress to disease. Careful assessment to rule out the possibility of TB disease is necessary before treatment for LTBI is started. Evaluation of TST reactions in persons vaccinated with BCG should be interpreted using the same criteria for those not BCG-vaccinated. Persons in the following high-risk groups should be given treatment for LTBI if their reaction to the TST is ≥5 mm of induration:

- HIV-infected persons
- Recent contacts to a TB case
- Persons with fibrotic changes on chest radiograph consistent with old TB
- Patients with organ transplants
- Persons who are immunosuppressed for other reasons (e.g., taking the equivalent of >15 mg/day of prednisone for 1 month or longer, taking TNF-alpha antagonists)

In addition, persons in the following high-risk groups should be considered for treatment of LTBI if their reaction to the TST is ≥10 mm of induration:

- Recent arrivals (< 5 years) from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, hospitals, and other health care facilities)
- Mycobacteriology laboratory personnel
- Persons with clinical conditions that place them at high-risk for developing TB disease (e.g., diabetes)
- Children < 4 years of age, or children and adolescents exposed to adults in high-risk categories

Persons with no known risk factors for TB may be considered for treatment of LTBI if their reaction to the tuberculin test is ≥15 mm of induration. However, targeted skin testing programs should only be conducted among high-risk groups. All testing activities should be accompanied by a plan for follow-up care for persons with TB infection or disease.

Additional Information

CDC. Development of new vaccines for tuberculosis: recommendations of the Advisory Council for the Elimination of Tuberculosis (ACET). *MMWR* 1998; 47 (No. RR-13). www.cdc.gov/mmwr/preview/mmwrhtml/00054407.htm

CDC. The role of BCG vaccine in the prevention and control of tuberculosis in the United States: a joint statement by ACET and the Advisory Committee on Immunization Practices. *MMWR* 1996;45 (No. RR-4). www.cdc.gov/mmwr/preview/mmwrhtml/00041047.htm

World Health Organization. Issues Relating to the Use of BCG in Immunization Programmes-A Discussion Document (1999). www.who.int/vaccines-documents/DocsPDF99/www9943.pdf

TB Elimination

Tuberculosis Information for International Travelers

What is tuberculosis (TB)?

Tuberculosis (TB) is a disease caused by germs that are spread from person to person through the air. TB usually affects the lungs, but it can also affect other parts of the body, such as the brain, the kidneys, or the spine. In most cases, TB is treatable and curable; however, persons with TB can die if they do not get proper treatment.

What is multidrug-resistant tuberculosis (MDR TB)?

Multidrug-resistant TB (MDR TB) is TB that is resistant to at least two of the best anti-TB drugs, isoniazid and rifampin. These drugs are considered first-line drugs and are used to treat all persons with TB disease.

What is extensively drug resistant tuberculosis (XDR TB)?

Extensively drug resistant TB (XDR TB) is a rare type of MDR TB. XDR TB is defined as TB which is resistant to isoniazid and rifampin, plus resistant to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).

Because XDR TB is resistant to first-line and second-line drugs, patients are left with treatment options that are much less effective.

XDR TB is of special concern for persons with HIV infection or other conditions that can weaken the immune system. These persons are more likely to develop TB disease once they are infected, and also have a higher risk of death once they develop TB.

How is TB spread?

Drug-susceptible TB and MDR TB are spread the same way. TB germs are put into the air when a person with TB disease of the lungs or throat coughs, sneezes, speaks, or sings. These germs can float in the air for several hours, depending on the environment. Persons who breathe in the air containing these TB germs can become infected.

TB is not spread by

- shaking someone's hand
- sharing food or drink
- touching bed linens or toilet seats
- sharing toothbrushes
- kissing
- smoking or sharing cigarettes

How does drug resistance happen?

Resistance to anti-TB drugs can occur when these drugs are misused or mismanaged. Examples include when patients do not complete their full course of treatment; when health-care providers prescribe the wrong treatment, the wrong dose, or length of time for taking the drugs; when the supply of drugs is not always available; or when the drugs are of poor quality.

Are international travelers at risk for getting MDR or XDR TB while traveling?

Although MDR and XDR TB are occurring globally, they are still rare. HIV-infected travelers are at greatest risk if they come in contact with a person with MDR or XDR TB. All travelers should avoid high risk settings where there are no infection control measures in place.

Are international travelers at risk for getting MDR or XDR TB while traveling? (continued)

Documented places where transmission has occurred include crowded hospitals, prisons, homeless shelters, and other settings where susceptible persons come in contact with persons with TB disease.

Air travel itself carries a relatively low risk of infection with TB of any kind.

What is the risk of acquiring TB on an airplane?

The risk of acquiring any type of TB depends on several factors, such as extent of disease in the patient with TB, duration of exposure, and ventilation. Most important, there must be someone with infectious TB disease on the same flight to present any risk. If someone on the flight does have TB disease, persons on flights lasting 8 hours or longer are at greater risk than persons on shorter flights.

How can TB be prevented?

Travelers should avoid close contact or prolonged time with known TB patients in crowded, enclosed environments (for example, clinics, hospitals, prisons, or homeless shelters).

Travelers who will be working in clinics, hospitals, or other health care settings where TB patients are likely to be encountered should consult infection control or occupational health experts. They should ask about administrative and environmental procedures for preventing exposure to TB. Once those procedures are implemented, additional measures could include using personal respiratory protective devices.

Is there a vaccine to prevent TB?

There is a vaccine for TB disease called Bacille Calmette-Guérin (BCG) . It is used in some countries to prevent severe forms of TB in children. However, BCG is not generally recommended in the United States because it has limited effectiveness for preventing TB overall.

What should I do before traveling internationally?

Travelers who anticipate possible prolonged exposure to persons with TB (for example, those who expect to come in contact routinely with clinic, hospital, prison, or homeless shelter populations) should have a tuberculin skin test (TST) before leaving the United States. If the test reaction is negative, they should have a repeat test 8 to10 weeks after returning to the United States. Additionally, annual testing may be recommended for those who anticipate repeated or prolonged exposure or an extended stay over a period of years. Because persons with HIV infection are more likely to have an impaired response to the TST, travelers who are HIV positive should tell their physicians about their HIV infection status.

What should I do if I think I have been exposed to someone with TB disease?

If you think you have been exposed to someone with TB disease, you should contact your doctor or local health department about getting a TB skin test or the QuantiFERON®-TB Gold test (QFT-G), a blood test. And tell the doctor or nurse ***when*** you spent ***time*** with this person.

What are the symptoms of TB disease?

The general symptoms of TB disease include feelings of sickness or weakness, weight loss, fever, and night sweats. The symptoms of TB disease of the lungs may also include coughing, chest pain, and coughing up blood. Symptoms of TB disease in other parts of the body depend on the area affected. If you have these symptoms, you should contact your doctor or local health department.

Where can I find other health information about my travel destination?

CDC's Travelers' Health website (www.cdc.gov/travel/destinat.htm) lists health information for travelers by destination.

CDC issues travel notices when there is a health threat to travelers. These notices describe levels of risk for the traveler and recommended preventive measures to take at each level of risk. Travel notices are organized by disease and by travel destination.

Additional Information

CDC. Questions and Answers About TB (2005). http://www.cdc.gov/nchstp/tb/faqs/qa.htm

CDC. Tuberculosis: General Information (2006). http://www.cdc.gov/nchstp/tb/pubs/tbfactsheets/250010.htm

CDC. Tuberculin Skin Testing (2006). http://www.cdc.gov/nchstp/tb/pubs/tbfactsheets/250140.htm

CDC. BCG Vaccine (2006). http://www.cdc.gov/nchstp/tb/pubs/tbfactsheets/250120.htm

CDC. Health Information for International Travel – The "Yellow Book": Chapter 4 – Prevention of Specific Infectious Diseases: Tuberculosis (2005-2006). http://www.cdc.gov/travel/yb/index.htm

WHO. Tuberculosis and Air Travel: Guidelines for Prevention and Control (2006). http://whqlibdoc.who.int/hq/2006/WHO_HTM_TB_2006.363_eng.pdf

IMPORTANT FACTS ABOUT INH

Please contact your medical provider or local health department if you develop the following symptoms:

- Clumsiness or unsteadiness
- Dark urine
- Loss of appetite
- Nausea or vomiting
- Numbness, tingling, burning or pain in hands or feet
- Unusual tiredness or weakness
- Yellow eyes or skin
- Blurred vision or loss of vision with or without pain
- Convulsions
- Fever
- Sore throat
- Joint pain
- Mental depression
- Mood or mental changes
- Skin rash
- Unusual bruising or bleeding

PROPER USE OF INH

- If you are taking INH by mouth and it upsets your stomach, take it with food. Antacids may also help. However, do not take aluminum containing antacids within 1 hour of taking INH.
- It is important that you do not miss a dose. It is also very important to take pyridoxine every day along with INH. Do not miss any dose.
- If you miss a dose of the medicines, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule.
- INH should be stored away from heat and direct light.
- Keep the oral form of this medication from freezing.
- Do not store the tablet form of this medicine in the bathroom, near the kitchen sink, or in other damp places. Heat or moisture may cause the medicine to break down. Keep away from children.Certain foods, such as cheese (swiss or cheshire) or fish (tuna, skipjack or sardinella) may cause reaction in some people (redness or itching of skin, hot feeling, fast or pounding heart beat, headache, light headedness, sweating, chills or clammy feeling).

APPOINTMENTS			
DATE	TIME	NURSE	COMMENTS

DIRECTIONS FOR PICKING UP MEDICATIONS

1. Call local health department during business hours.
   8:30 – 12:00 Noon & 1:00-4:30 P.M. Monday through Friday
   (See back for telephone numbers)

2. Do not run out of medication before calling the health department. Please call your nurse 3-5 days before needing your next medication refill.

3. If your nurse is not available, please ask to speak with another nurse, especially if you are experiencing side effects from the medicine.

4. Please obtain requested labs one week prior to your refill appointment.

5. Please notify your nurse one week in advance if you are planning extended travel out of state for more than one month.

6. If you are moving to another area, please notify your nurse 1-2 weeks prior to your relocation.

7. Your nurse will contact another local health department near your residence, allowing you to continue uninterrupted treatment.

CENTRAL MICHIGAN DISTRICT HEALTH DEPARTMENT
OFFICE SITES

Office Hours
8:30 – 12:00 Noon & 1:00 – 4:30 P.M. Monday through Friday

Administrative Office
2012 E. Preston
Mt. Pleasant, MI 48858
(989) 773-5921

Branch Office Locations

Arenac
3727 Deep River Road
Standish, MI 48658
(989) 846-6541

Clare
225 W. Main Street
Harrison, MI 48625
(989) 539-6731

Gladwin
103 N. Bowery
Gladwin, MI 48624
(989) 426-9431

Isabella
2012 E. Preston
Mt. Pleasant, MI 48858
(989) 773-5921

Osceola
4329 220th Avenue
Reed City, MI 49677
(231) 832-5532

Roscommon
1015 Short Drive
Prudenville, MI 48651
(989) 366-9166

Nsg.Appt Info 8/30/07

Central Michigan District Health Department

Promoting Healthy Families, Healthy Communities

APPOINTMENT

INFORMATION

Nurse:_____

Phone Number_____

TUBERCULOSIS (TB) SCREENING AND TESTING

Background: TB is a communicable disease caused by *Mycobacterium tuberculosis*, or the tubercle bacillus. It is spread primarily by tiny airborne particles (droplet nuclei) expelled by a person who has infectious TB. If another person inhales air containing these droplet nuclei, transmission may occur. Although the majority of TB cases are pulmonary, TB can occur in almost any anatomical site. TB can cause disability and/or death if not detected and treated appropriately.

Targeted High-Risk Groups for TB Screening:

- Close contacts of persons with active TB
- Foreign- born persons from areas where TB is common
- Residents and workers in high-risk congregate settings
- Health care workers who serve high-risk clients
- Medically under-served, low-income populations
- Persons with certain medical conditions, such as HIV infection, diabetes, cancer, etc.
- Children exposed to adults in high-risk categories
- Persons who inject illicit drugs
- High-risk racial or ethnic minority populations defined locally as having an increased prevalence of TB

Signs and Symptoms of TB:

Pulmonary symptoms

- Productive, prolonged cough (≥ 3 weeks)
- Chest pain
- Hemoptysis

Systemic symptoms

- Fever
- Chills
- Night sweats
- Loss of appetite
- Weight loss
- Becomes easily fatigued

Other symptoms may occur depending on the part of the body affected.

Standard TB Skin Testing Method: Mantoux (intradermal). Multiple puncture tests such as "Tine" are not recommended. Health care workers trained to perform the Mantoux intradermal test should administer TB skin tests.

PPD testing has no effect on the response to MMR vaccination. If tuberculin skin testing is needed at the same time as administration of measles-containing vaccine, PPD and vaccine can be administered at the same visit. If measles-containing vaccine has been administered recently, PPD screening should be delayed at least 4 weeks after vaccination.

Reading TB Skin Test Results:
A trained health care worker should read the reaction to the Mantoux test 48 to 72 hours after the injection. Patients should never be allowed to read their own tuberculin skin test results. If a patient fails to show up for the scheduled reading, a positive reaction may still be measurable up to 1 week after testing. However, if a patient who fails to return within 72 hours has a negative test, tuberculin testing should be repeated.

Classifying the Tuberculin Reaction
Interpretation of a positive tuberculin skin test (TST) has been somewhat controversial in Michigan. Many providers are currently using the 10mm cut off as a determinate of a positive TST in individuals without risk factors. The Michigan Department of Community Health TB Program along with the Michigan Advisory Committee for the Elimination of TB (MIACET) have recently issued recommendations based on the Centers for Disease Control and Prevention (CDC) recommendations which are as follows:

≥ 5mm is classified as positive in:

- HIV-positive persons
- Recent contacts of a TB case
- Persons with fibrotic changes on chest x-ray consistent with old healed TB
- Patients with organ transplants and other immunosuppressed patients

≥10 mm is classified as positive in:

- Recent arrivals from high-prevalence countries
- Injection drug users
- Residents and employees of high risk congregate settings
- Mycobacteriology laboratory personnel
- Persons with clinical conditions that place them at high risk
- Children < 4 years of age, or children and adolescents exposed to adults in high-risk categories

≥15 mm is classified as positive in persons with no known risk factors for TB

Skin Test Sensitivity:

It may take 2-10 weeks to develop a positive reaction after infection

Active TB Disease versus Latent TB Infection:
Persons who are infected with tuberculosis, but who do not have TB disease cannot spread the infection to other people. TB infection in a person who does not have TB disease is not considered a case of TB and is often referred to as having latent TB infection (LTBI).
In some people, the TB bacilli overcome the defenses of the immune system and begin to multiply, resulting in the progression from TB infection to TB disease. This process may occur soon after or many years after infection. In the United States, unless they are treated, approximately 5% of persons who have been infected with tuberculosis will develop TB disease in the first year or two after infection and another 5% will develop disease sometime later in life.

Reporting Requirements:
Any suspected or confirmed case of TB disease should be reported by their physician within 24 hours of diagnosis to the local health department. Laboratories are also required to report. Individuals with positive TB skin tests who are not infectious (latent TB infection) are not required to be reported.

Laboratory Services Available from Michigan Department of Community Health (these tests are available at no cost):
- sputum smears and/or culture
- drug susceptibilities are performed on all TB specimens
- direct amplification testing

Reminders:
- Persons with a history of a positive reaction to TB skin testing should not be re-tested. Persons with positive TB skin test results should have a chest x-ray as part of the initial evaluation of their tuberculosis skin test, if negative, repeat chest x-rays are not needed unless symptoms develop that could be attributed to TB. Persons with a history of positive TB skin testing who develop signs and symptoms suggestive of TB should undergo a medical evaluation including a chest x-ray.
- Pregnant women should be targeted for tuberculin skin testing only if they have a specific risk factor for latent TB infection or for progression of LTBI to disease.
- Tuberculin skin testing is not contraindicated for BCG vaccinated persons.

Resources Available from your Local Health Department:
- TB medication for county residents
- Medical assessment and treatment
- Consultation/advice
- TB skin test training may be available

Recommendations for TB Screening of Health Care Workers
- New employees with a history of negative skin tests:
  - Complete two-step testing
- New employee with a history of a positive TB skin test:
  - Complete a TB health questionnaire
  - Obtain a chest x-ray if a current (within 6 months) one is not available

- The employer shall offer tuberculin skin tests (TST) or blood assay *M. tuberculosis* (BAMT) annually to employees/health-care workers in settings where risk assessment has determined that employees/heath-care workers will or will possibly be exposed to persons with TB disease or to clinical specimens that might contain *M. tuberculosis*.
- Established employee working in a facility with potential ongoing transmission, offer test every eight to ten weeks until the cause of transmission has been corrected and no additional evidence of ongoing transmission is apparent.
- Established employee with a history of positive test, complete annual health questionnaire (no annual chest x-ray)
- Employee with known exposure to TB, test immediately and again in eight to ten weeks.

Additional Resources:
- MDCH TB Control Program (517) 335-8165 or www.michigan.gov/tb
- www.michigantb.org
- www.cdc.gov/nchstp/tb/

Tuberculin Skin Testing

What is It?

The **Mantoux tuberculin skin test** (TST) is the standard method of determining whether a person is infected with *Mycobacterium tuberculosis*. Reliable administration and reading of the TST requires standardization of procedures, training, supervision, and practice.

How is the TST Administered?

The TST is performed by injecting 0.1 ml of tuberculin purified protein derivative (PPD) into the inner surface of the forearm. The injection should be made with a tuberculin syringe, with the needle bevel facing upward. The TST is an intradermal injection. When placed correctly, the injection should produce a pale elevation of the skin (a wheal) 6 to 10 mm in diameter.

How is the TST Read?

The skin test reaction should be read between 48 and 72 hours after administration. A patient who does not return within 72 hours will need to be rescheduled for another skin test.

The reaction should be measured in millimeters of the induration (palpable, raised, hardened area or swelling). The reader should not measure erythema (redness). The diameter of the indurated area should be measured across the forearm (perpendicular to the long axis).

How Are TST Reactions Interpreted?

Skin test interpretation depends on two factors:

- Measurement in millimeters of the induration
- Person's risk of being infected with TB and of progression to disease if infected

Classification of the Tuberculin Skin Test Reaction

An induration of **5 or more millimeters** is considered positive in	An induration of **10 or more millimeters** is considered positive in	An induration of **15 or more millimeters** is considered positive in
– HIV-infected persons – A recent contact of a person with TB disease – Persons with fibrotic changes on chest radiograph consistent with prior TB – Patients with organ transplants – Persons who are immunosuppressed for other reasons (e.g., taking the equivalent of >15 mg/day of prednisone for 1 month or longer, taking TNF-alpha antagonists)	– Recent immigrants (< 5 years) from high-prevalence countries – Injection drug users – Residents and employees of high-risk congregate settings – Mycobacteriology laboratory personnel – Persons with clinical conditions that place them at high risk – Children < 4 years of age – Infants, children, and adolescents exposed to adults in high-risk categories	any person, including persons with no known risk factors for TB. However, targeted skin testing programs should only be conducted among high-risk groups.

What Are False-Positive Reactions?

Some persons may react to the TST even though they are not infected with *M. tuberculosis*. The causes of these false-positive reactions may include, but are not limited to, the following:

- Infection with nontuberculosis mycobacteria
- Previous BCG vaccination
- Incorrect method of TST administration
- Incorrect interpretation of reaction
- Incorrect bottle of antigen used

What Are False-Negative Reactions?

Some persons may not react to the TST even though they are infected with *M. tuberculosis*. The reasons for these false-negative reactions may include, but are not limited to, the following:

- Cutaneous anergy (*anergy* is the inability to react to skin tests because of a weakened immune system)
- Recent TB infection (within 8-10 weeks of exposure)
- Very old TB infection (many years)
- Very young age (less than 6 months old)
- Recent live-virus vaccination (e.g., measles and smallpox)
- Overwhelming TB disease
- Some viral illnesses (e.g., measles and chicken pox)
- Incorrect method of TST administration
- Incorrect interpretation of reaction

Who Can Receive a TST?

Most persons can receive a TST. TST is contraindicated only for persons who have had a severe reaction (e.g., necrosis, blistering, anaphylactic shock, or ulcerations) to a previous TST. It is not contraindicated for any other persons, including infants, children, pregnant women, persons who are HIV-infected, or persons who have been vaccinated with BCG.

How Often Can TSTs Be Repeated?

In general, there is no risk associated with repeated tuberculin skin test placements. If a person does not return within 48-72 hours for a tuberculin skin test reading, a second test can be placed as soon as possible. There is no contraindication to repeating the TST, unless a previous TST was associated with a severe reaction.

What is a Boosted Reaction?

In some persons who are infected with *M. tuberculosis*, the ability to react to tuberculin may wane over time. When given a TST years after infection, these persons may have a false-negative reaction. However, the TST may stimulate the immune system, causing a positive, or boosted reaction to subsequent tests. Giving a second TST after an initial negative TST reaction is called two-step testing.

Why is Two-Step Testing Conducted?

Two-step testing is useful for the initial skin testing of adults who are going to be retested periodically, such as health care workers or nursing home residents. This two-step approach can reduce the likelihood that a boosted reaction to a subsequent TST will be misinterpreted as a recent infection.

Can TSTs Be Given To Persons Receiving Vaccinations?

Vaccination with live viruses may interfere with TST reactions. For persons scheduled to receive a TST, testing should be done as follows:

- Either on the same day as vaccination with live-virus vaccines or 4-6 weeks after the administration of the live-virus vaccine
- At least one month after smallpox vaccination

Additional Information

American Thoracic Society and CDC. Diagnostic standards and classification of tuberculosis in adults and children. *Am J Respir Crit Care Med* 2000; 161. www.thoracic.org/adobe/statements/tbadult1-20.pdf

CDC. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. *MMWR* 2005; 54 (No. RR-17). www.cdc.gov/mmwr/pdf/rr/rr5417.pdf

CDC. Mantoux Tuberculin Skin Test: Training Materials Kit (2003).

CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000; 49 (No. RR-6). www.cdc.gov/MMWR/PDF/rr/rr4906.pdf

THE MANTOUX TUBERCULIN SKIN TEST

A GUIDE FOR PROVIDERS

NYC Health
nyc.gov/health

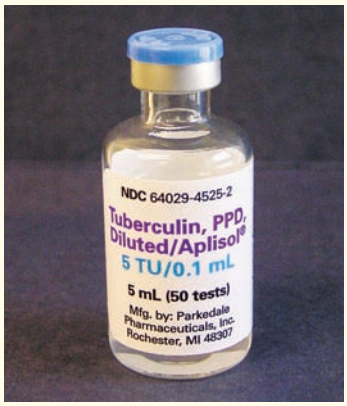
Talk to your patient about:

- **Taking care of the injection site**
- **Returning in 48-72 hours to have test read**
- **Who to contact with questions or problems**

ADMINISTER THE TEST

Prepare the Materials

1. **Wash** hands and put on gloves.
2. **Explain** to patient why test is being done and how it will be performed.
3. **Check** expiration/opening date on PPD vial.
4. **Place** patient's arm on flat surface, exposing palm side surface of forearm.
5. **Locate** injection site (2-4 inches below elbow; no scars, bumps, veins).
6. **Clean** injection site with alcohol swab.
7. **Wipe** top of vial with new alcohol swab.
8. **Place** vial on flat surface and insert syringe into vial.
9. **Invert** vial, keeping needle tip below fluid level.
10. **Pull** back plunger, drawing in slightly more than 0.1 ml PPD solution.
11. **Remove** syringe from vial and tap lightly to dispel air bubbles.
12. **Hold** syringe point up and expel air/excess fluid, leaving exactly 0.1 ml PPD solution in syringe.



Keep the PPD Vial Cool

- Always store in refrigerator
- Place in cooling container when in use

Inject the PPD Solution

1. **Stretch** skin of injection site with the thumb of your non-dominant hand.
2. **Insert** needle intradermally, bevel up, at a 5-15 degree angle.
3. **Inject** the PPD solution slowly (you should feel firm resistance).
4. **Remove** needle (DO NOT RECAP) and discard immediately in sharps container.
5. **Ensure** 6-10 mm diameter wheal (measure using TST ruler).

If wheal < 6 mm, repeat test 2 inches from site, or on opposite arm. If wheal is still < 6 mm, talk to supervisor.

Carefully inject the PPD solution

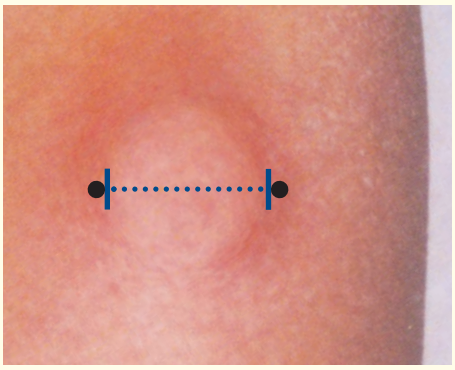
Educate Your Patient

1. **Educate** patient on possible reactions and care of the TST site.
2. **Document** each test on the patient card.
3. **Schedule** patient for an appointment to read the test in 48-72 hours.

READ THE RESULTS

Measure the Induration

1. **Inspect** visually for reaction at injection site.
2. **Palpate** for hard, dense, and raised formation (induration).
3. **Mark** opposite edges of induration with dots, using a black water mark pen.
4. **Measure** induration (not redness) **transversely**, from one marked edge to the other, using a TST ruler.
5. **Interpret** positive/negative results based on size of induration and risk factors (see chart below).
6. **Explain** meaning of positive/negative results and necessary follow-up.
7. **Give** patient literature and copy of TST results.
8. **Document** results in your medical records.



Measure induration with a TST ruler

Interpret the Test Results

The following measurements of induration are classified as positive, based on individual risk factors:

INDURATION DIAMETER	INDIVIDUAL RISK FACTORS
≥5 mm	**Positive test result for:** ▪ Persons with HIV infection ▪ Recent contacts of persons with active TB disease ▪ Persons with evidence of old, healed TB lesions on chest X-rays ▪ Persons with organ transplants and other immunosuppressed persons, including those receiving prolonged corticosteroid therapy (the equivalent of >15 mg/d of prednisone for one month or more) and TNF-α blockers
≥10 mm	**Positive test result for:** ▪ Persons who have immigrated within the past 5 years from areas with high TB rates* ▪ Injection drug users ▪ Persons who live or work in institutional settings where exposure to TB may be likely, such as hospitals, prisons, homeless shelters, SROs, and nursing homes ▪ Mycobacteriology laboratory personnel ▪ Persons with clinical conditions associated with increased risk of progression to active TB, including: silicosis; chronic renal failure; diabetes; more than 10% below ideal weight or BMI < 18.5; gastrectomy/jejunoileal bypass; some hematologic disorders (such as leukemia and lymphomas); and certain cancers (such as carcinoma of the head, neck, or lung, leukemias, and lymphomas) ▪ Children < 5 years, and children or adolescents exposed to adults in high-risk categories ▪ Persons with prolonged stay in areas with high TB rates*
≥15 mm	**Positive test result for:** ▪ Persons at low risk for active TB disease for whom testing is not generally indicated

* Countries with high rates of TB include China, Dominican Republic, Ecuador, Haiti, Honduras, India, Mexico, Pakistan, Peru, Philippines, South Korea, and all of Africa.

For detailed information on the testing and treatment of latent TB infection in children and adults see: www.nyc.gov/html/doh/downloads/pdf/chi/chi25-4.pdf

ALWAYS WASH HANDS AND CHANGE GLOVES AFTER EACH PATIENT

DIS5911001 - 5.06

NYC Health
nyc.gov/health
THE NEW YORK CITY DEPARTMENT of HEALTH and MENTAL HYGIENE
Michael R. Bloomberg, Mayor
Thomas R. Frieden, MD, MPH, Commissioner

For more information, providers can call (212) 788-4162

QuantiFERON®-TB Gold Test

What is it?

The QuantiFERON®-TB Gold test (QFT-G) is a whole-blood test for use as an aid in diagnosing *Mycobacterium tuberculosis* infection, including latent tuberculosis infection (LTBI) and tuberculosis (TB) disease. This test was approved by the U.S. Food and Drug Administration (FDA) in 2005.

How does it work?

Blood samples are mixed with antigens (substances that can produce an immune response) and controls. For QFT-G, the antigens include mixtures of synthetic peptides representing two *M. tuberculosis* proteins, ESAT-6 and CFP-10. After incubation of the blood with antigens for 16 to 24 hours, the amount of interferon-gamma (IFN-gamma) is measured.

If the patient is infected with *M. tuberculosis*, their white blood cells will release IFN-gamma in response to contact with the TB antigens. The QFT-G results are based on the amount of IFN-gamma that is released in response to the antigens.

Clinical evaluation and additional tests (such as a chest radiograph, sputum smear, and culture) are needed to confirm the diagnosis of LTBI or TB disease.

What are the advantages?

- Requires a single patient visit to draw a blood sample.
- Results can be available within 24 hours.
- Does not boost responses measured by subsequent tests, which can happen with tuberculin skin tests (TST).
- Is not subject to reader bias that can occur with TST.
- Is not affected by prior BCG (bacille Calmette-Guérin) vaccination.

What are the disadvantages and limitations?

- Blood samples must be processed within 12 hours after collection while white blood cells are still viable.
- There are limited data on the use of QFT-G in children younger than 17 years of age, among persons recently exposed to *M. tuberculosis*, and in immunocompromised persons (e.g., impaired immune function caused by HIV infection or acquired immunodeficiency syndrome [AIDS], current treatment with immunosuppressive drugs, selected hematological disorders, specific malignancies, diabetes, silicosis, and chronic renal failure).
- Errors in collecting or transporting blood specimens or in running and interpreting the assay can decrease the accuracy of QFT-G.
- Limited data on the use of QFT-G to determine who is at risk for developing TB disease.

When should you use the test?

QFT-G can be used in all circumstances in which the tuberculin skin test (TST) is currently used, including contact investigations, evaluation of recent immigrants who have had BCG vaccination, and TB screening of health care workers and others undergoing serial evaluation for *M. tuberculosis*. However, caution should be used when testing certain populations because of limited data in the use of QFT-G.

Before the QFT-G is conducted, arrangements should be made with a qualified laboratory and courier service, if needed, to ensure prompt and proper processing of blood.

What are the steps in administering the test?

- Confirm arrangements for testing in a qualified laboratory and arrange for delivery of the blood sample in time for the laboratory to initiate testing within 12 hours of blood collection.
- Draw a sample of whole blood from patient into a tube with heparin anti-clotting agent, according to manufacturer's instructions.
- Schedule an appointment for the patient to receive test results and, if then needed, medical evaluation and possible treatment for TB disease or LTBI.

How do you interpret test results?

Interpretation of QFT-G results is based on IFN-gamma concentrations in test samples. Each QFT-G result and its interpretation should be considered in conjunction with other epidemiological, historical, physical, and diagnostic findings.

A positive result suggests that *M. tuberculosis* infection is likely; a negative result suggests that infection is unlikely; and indeterminate result suggests QFT-G results cannot be interpreted as a result of low mitogen response or high background response.

A diagnosis of LTBI requires that TB disease be excluded by medical evaluation, which should include checking for signs and symptoms suggestive of TB disease, a chest radiograph, and, when indicated, examination of sputum or other clinical samples for the presence of *M. tuberculosis*.

Additional Information

Centers for Disease Control and Prevention. Guidelines for the investigation of contacts of persons with infectious tuberculosis and Guidelines for using the QuantiFERON®-TB Gold test for detecting *Mycobacterium tuberculosis* infection, United States. MMWR 2005; 54 (No. RR-15).
http://www.cdc.gov/mmwr/pdf/rr/rr5415.pdf

Centers for Disease Control and Prevention. Guidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in Health-Care Settings, 2005. *MMWR* 2005; 54 (No.RR-17).
http://www.cdc.gov/mmwr/pdf/rr/rr5417.pdf

Get-QFT (Locator site for QuantiFERON®-TB Gold)
http://www.quantiferon.com*

* This link is provided solely as a service to our users. It does not constitute an endorsement of the QFT-Gold testing institutions included on the website by CDC or the Federal Government, and none should be inferred. CDC is not responsible for the content found at this link.

The Difference Between Latent TB Infection and Active TB Disease

What Is TB?

Tuberculosis (TB) is a disease caused by a germ called *Mycobacterium tuberculosis* that is spread from person to person through the air. TB usually affects the lungs, but it can also affect other parts of the body, such as the brain, the kidneys, or the spine. When a person with infectious TB coughs or sneezes, droplet nuclei containing *M. tuberculosis* are expelled into the air. If another person inhales air containing these droplet nuclei, he or she may become infected. However, not everyone infected with TB bacteria becomes sick. As a result, two TB-related conditions exist: latent TB infection and active TB disease.

What Is Latent TB Infection?

Persons with latent TB infection do not feel sick and do not have any symptoms, but usually have a positive reaction to the tuberculin skin test or QuantiFERON®-TB Gold test. They are infected with *M. tuberculosis*, but do not have active TB disease. **Persons with latent TB infection are not infectious and cannot spread TB infection to others.**

Overall, about 5 to 10% of infected persons will develop active TB disease at some time in their lives. About half of those people who develop active TB will do so within the first two years of infection. For persons whose immune systems are weak, especially those with HIV infection, the risk of developing active TB disease is considerable higher than for persons with normal immune systems.

Of special concern are persons infected by someone with extensively drug-resistant TB (XDR TB) who later develop active TB disease; these persons will have XDR TB, not regular TB disease.

A person with latent TB infection (LTBI)
Usually has a skin test or blood test result indicating TB infection
Has a normal chest x-ray and a negative sputum test
Has TB bacteria in his/her body that are alive, but inactive
Does not feel sick
Cannot spread TB bacteria to others
Needs treatment for latent TB infection to prevent TB disease; however, if exposed and infected by a person with multidrug-resistant TB (MDR TB) or extensively drug-resistant TB (XDR TB), preventive treatment may not be an option

What Is Active TB Disease?

In some people, TB bacteria overcome the defenses of the immune system and begin to multiply, resulting in the progression from latent TB infection to active TB disease. Some people develop active TB disease soon after infection, while others develop active TB disease later when their immune system becomes weak.

The general symptoms of active TB disease include

- Unexplained weight loss
- Loss of appetite
- Night sweats
- Fever
- Fatigue
- Chills

The symptoms of TB of the lungs include

- Coughing for 3 weeks or longer
- Hemoptysis (coughing up blood)
- Chest pain

What Is Active TB Disease? (cont.)

Other symptoms depend on the part of the body that is affected.

Persons with active TB disease are considered infectious and may spread TB bacteria to others. If TB disease is suspected, persons should be referred for a complete medical evaluation. If it is determined that a person has active TB disease, therapy is given to treat it. TB disease is a serious condition and can lead to death if not treated.

A person with active TB disease
Usually has a skin test or blood test result indicating TB infection
May have an abnormal chest x-ray, or positive sputum smear or culture
Has active TB bacteria in his/her body
Usually feels sick and may have symptoms such as coughing, fever, and weight loss
May spread TB bacteria to others
Needs treatment to treat active TB disease

Additional Information

American Thoracic Society (ATS) and CDC. Diagnostic standards and classification of tuberculosis in adults and children. *Am J Respir Crit Care Med* 2000; 161. www.thoracic.org/adobe/statements/tbadult1-20.pdf

ATS, CDC, and Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; 52 (No. RR-11). www.cdc.gov/MMWR/PDF/rr/rr5211.pdf

CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000; 49 (No. RR-6). www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm

CDC. Multidrug-Resistant Tuberculosis (MDR TB). http://www.cdc.gov/tb/pubs/tbfactsheets/mdrtb.htm

CDC. Extensively Drug-Resistant Tuberculosis (XDR TB). http://www.cdc.gov/tb/pubs/tbfactsheets/xdrtb.htm

TREATMENT OF LATENT TUBERCULOSIS INFECTION (LTBI)

WITH REVISED GUIDELINES FOR RIF-PZA

CHARLES P. FELTON NATIONAL TUBERCULOSIS CENTER AT HARLEM HOSPITAL
Samuel L. Kountz Pavilion • 15 West 136th Street • Sixth Floor • New York, NY 10037 • phone (212) 939-8254 • fax (212) 939-8259 • http://harlemtbcenter.org

WHO TO TEST

Target tuberculin skin testing (TST) at persons at high risk for TB:

- **Persons at risk for recent *M.tb* infection**
- **Persons at risk for progression to active TB**

Treat LTBI—it benefits the individual and the community.

Adherence is the key to successful prevention.

WHO TO TREAT

CATEGORY OF PERSON TESTED	TST <5 mm	TST ≥5 mm	TST ≥10 mm	TST ≥15 mm
Child <5 years and **recent contact***	TREAT	TREAT	TREAT	TREAT
HIV-infected and **recent contact***	TREAT	TREAT	TREAT	TREAT
Immunosuppressed and **recent contact***	TREAT	TREAT	TREAT	TREAT
HIV-infected	Do Not Treat	TREAT	TREAT	TREAT
Immunosuppressed persons	Do Not Treat	TREAT	TREAT	TREAT
Recent contact of TB case	Do Not Treat	TREAT	TREAT	TREAT
Fibrotic changes on chest X-ray	Do Not Treat	TREAT	TREAT	TREAT
Recent arrival from endemic country	Do Not Treat	Do Not Treat	TREAT	TREAT
Injection drug user	Do Not Treat	Do Not Treat	TREAT	TREAT
Resident/Employee institutional setting§	Do Not Treat	Do Not Treat	TREAT	TREAT
Mycobacteria lab personnel	Do Not Treat	Do Not Treat	TREAT	TREAT
High-risk clinical conditions‡	Do Not Treat	Do Not Treat	TREAT	TREAT
Child <4 years	Do Not Treat	Do Not Treat	TREAT	TREAT
Persons <18 exposed to high-risk adults	Do Not Treat	Do Not Treat	TREAT	TREAT
No risk factors (TST discouraged)	Do Not Treat	Do Not Treat	Do Not Treat	Consider Treating

* Contacts should receive a tuberculin skin test (TST) immediately. Even if TST is 00mm, these groups should be treated and TST placed again 12 weeks after last exposure to TB case. Treatment can be discontinued in a healthy child if second TST is negative.

§ **TST Conversion:** An increase in reaction size of ≥10 mm within 2 years should be considered a TST conversion indicative of recent infection with *M.tb.*

‡ Silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (e.g. leukemias and lymphomas), other specific malignancies (e.g. carcinoma of the head and neck or lung), weight loss of ≥10% of ideal body weight, gastrectomy, jejunoileal bypass.

Pregnancy: Treat during pregnancy if either HIV-infected or recent *M.tb* infection.

HOW TO TREAT

Drug	Interval and Duration	Adult Dosage (max)	Criteria for Completion	Comments
INH	Daily for 9 mos.	5 mg/kg (300 mg)	270 doses within 12 mos.	**Preferred regimen for all persons.** INH may be administered concurrently with NRTIs, protease inhibitors, or NNRTIs. **DOT must be used with twice-weekly dosing.**
	Twice-weekly for 9 mos.	15mg/kg (900 mg)	76 doses within 12 mos.	
INH	Daily for 6 mos.	5 mg/kg (300 mg)	180 doses within 9 mos.	Not indicated for persons with HIV infection or fibrotic lesions, or for children. **DOT must be used with twice-weekly dosing.**
	Twice-weekly for 6 mos.	15mg/kg (900 mg)	52 doses within 9 mos.	
RIF*	Daily for 4 mos.	RIF 10 mg/kg (600 mg)	120 doses within 6 mos.	For contacts of patients with INH-resistant, RIF-susceptible TB.
RIF* plus PZA	Daily for 2 mos.	RIF 10 mg/kg (600 mg) PZA 15-20 mg/kg (2.0 g)	60 doses within 3 mos.	**Generally should not be offered** for treatment of LTBI for HIV-infected or HIV-negative persons. Consider use when completion of longer treatment courses is unlikely and when patients can be monitored closely. Consult TB/LTBI expert. Inform patients of potential hepatotoxicity and advise against use of potentially hepatotoxic agents, e.g. acetaminophen. Dispense no more than a 2-week supply. **DOT must be used with twice-weekly dosing.**
	Twice-weekly for 2-3 mos	RIF 10 mg/kg (600 mg) PZA 50 mg/kg (4.0g)	16-26 doses within 3-4 mos.	

Abbreviations: INH = isoniazid, RIF = rifampin, PZA = pyrazinamide, NRTIs = nucleoside reverse transcriptase inhibitors, NNRTIs = non-nucleoside reverse transcriptase inhibitors, DOT = directly observed therapy, mos. = months
Pregnancy: INH regimens preferred for pregnant women. PZA should be avoided during first trimester.
MDR-TB exposure: For persons who are likely to be infected with INH and RIF (multidrug) resistant-TB and at high risk of reactivation, PZA and ethambutol or PZA and a quinolone for 6-12 months are recommended. (Consult expert.)
* **HIV co-infection**: Protease inhibitors or NNRTIs should not be administered concurrently with RIF; an alternative is rifabutin 300 mg daily. Rifabutin should not be used with hard-gel saquinavir or delavirdine. Dose adjustment of rifabutin may be required: to 150 mg twice-weekly with ritonavir or lopinavir/ritonavir, to 150 mg daily or 300 mg twice-weekly with other protease inhibitors, or to 450-600 mg daily or 600 mg twice-weekly with efavirenz.

HOW TO MONITOR

For all patients:

- Initial clinical evaluation, including radiologic studies to rule out active TB
- Consider possible rifamycin-associated drug interactions, eg. oral contraceptives, antiretrovirals, methadone, oral hypoglycemics, and anticoagulants
- Provider conversant in patient's language should educate patients about side effects associated with LTBI treatment and advise to stop treatment and promptly seek medical evaluation if these occur
- Follow-up evaluations at least monthly if receiving INH or RIF alone; at 2, 4, 6, and 8 weeks if receiving RIF and PZA
- Include careful questioning about side effects and a brief physical examination checking for evidence of hepatitis or other side effects
- Inform persons considering treatment with RIF-PZA of potential hepatotoxicity and ask about history of liver disease or adverse effects from INH or other drugs
- If side effects occur, evaluate promptly and change treatment as indicated
- Routine monthly monitoring of liver function tests (LFTs) not generally indicated, except in the following circumstances:
  - Abnormal LFT at baseline
  - HIV infection
  - Pregnancy or immediate postpartum
  - Chronic liver disease
  - Regular alcohol use
  - RIF-PZA regimen

Medication should be withheld and patients evaluated if:

- Transaminase levels >3 times upper limit of normal in presence of symptoms
- Transaminase levels >5 times upper limit of normal in asymptomatic patient
- In patients on RIF-PZA: transaminase levels > normal if symptomatic, or if bilirubin > normal even if asymptomatic.

A joint project of Harlem Hospital, Columbia University, Health & Hospitals Corporation, and New York City Department of Health and Mental Hygiene; funded by The Centers for Disease Control and Prevention.
January 2005

TREATMENT OF LATENT TUBERCULOSIS INFECTION (LTBI) IN PREGNANCY AND POSTPARTUM

WITH REVISED GUIDELINES FOR RIF-PZA

CHARLES P. FELTON NATIONAL TUBERCULOSIS CENTER AT HARLEM HOSPITAL
Samuel L. Kountz Pavilion • 15 West 136th Street • Sixth Floor • New York, NY 10037 • phone (212) 939-8254 • fax (212) 939-8259 • http://harlemtbcenter.org

WHO TO TEST

Target tuberculin skin testing (TST) for pregnant women only if at risk for TB:

- **Women at risk for recent *M.tb* infection**
- **Women at risk for progression to active TB**

Treat LTBI—it benefits the individual and the community.

Adherence is the key to successful prevention.

WHO TO TREAT

CATEGORY OF WOMAN TESTED	TST <5 mm	TST ≥5 mm	TST ≥10 mm	TST ≥15 mm
HIV-infected and **recent contact***	TREAT NOW	TREAT NOW	TREAT NOW	TREAT NOW
Immunosuppressed and **recent contact***	TREAT NOW	TREAT NOW	TREAT NOW	TREAT NOW
HIV-infected*	Do Not Treat	TREAT NOW	TREAT NOW	TREAT NOW
Recent contact of TB case*	Do Not Treat	TREAT NOW	TREAT NOW	TREAT NOW
Resident/Employee institutional setting*§	Do Not Treat	Do Not Treat	TREAT NOW	TREAT NOW
Mycobacteria lab personnel*§	Do Not Treat	Do Not Treat	TREAT NOW	TREAT NOW
MAY DELAY TREATMENT UNTIL POSTPARTUM				
Immunosuppressed persons	Do Not Treat	TREAT	TREAT	TREAT
Fibrotic changes on chest X-ray	Do Not Treat	TREAT	TREAT	TREAT
Recent arrival from endemic country	Do Not Treat	Do Not Treat	TREAT	TREAT
Injection drug user	Do Not Treat	Do Not Treat	TREAT	TREAT
High-risk clinical conditions‡	Do Not Treat	Do Not Treat	TREAT	TREAT
Persons <18 exposed to high-risk adults	Do Not Treat	Do Not Treat	TREAT	TREAT
No risk factors (TST discouraged)	Do Not Treat	Do Not Treat	Do Not Treat	Consider Treating

* Pregnant women with recent TB infection and/or HIV co-infection should be treated during pregnancy, even during first trimester. Contacts should receive a tuberculin skin test (TST) immediately and TST repeated 12 weeks after last exposure to TB case. Even if initial TST is 00 mm, an HIV-infected contact should continue treatment irrespective of results of TST at 12 weeks.

§ **TST Conversion:** An increase in reaction size of ≥10 mm within 2 years should be considered a TST conversion indicative of recent infection with *M.tb.*

‡ Silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (e.g. leukemias and lymphomas), other specific malignancies (e.g. carcinoma of the head and neck or lung), weight loss of ≥10% of ideal body weight, gastrectomy, jejunoileal bypass.

HOW TO TREAT

Drug	Interval and Duration	Adult Dosage (max)	Criteria for Completion	Comments
INH*	Daily for 9 mos.	5 mg/kg (300 mg)	270 doses within 12 mos.	**Preferred regimen for all persons.** INH may be administered concurrently with NRTIs, protease inhibitors, or NNRTIs.
	Twice-weekly for 9 mos.	15mg/kg (900 mg)	76 doses within 12 mos.	**DOT must be used with twice-weekly dosing.**
INH*	Daily for 6 mos.	5 mg/kg (300 mg)	180 doses within 9 mos..	Not indicated for persons with HIV infection or fibrotic lesions.
	Twice-weekly for 6 mos.	15mg/kg (900 mg)	52 doses within 9 mos.	**DOT must be used with twice-weekly dosing.**
RIF‡	Daily for 4 mos.	RIF 10 mg/kg (600 mg)	120 doses within 6 mos.	For contacts of patients with INH-resistant, RIF-susceptible TB.
RIF plus PZA‡	Daily for 2 mos.	RIF 10 mg/kg (600 mg) PZA 15-20 mg/kg (2.0 g)	60 doses within 3 mos.	**Generally should not be offered** for treatment of LTBI for HIV-infected or HIV-negative persons. Consider use when completion of longer treatment courses is unlikely and when patients can be monitored closely. Consult TB/LTBI expert. Inform patients of potential hepatotoxicity and advise against use of potentially hepatotoxic agents, e.g. acetaminophen. Dispense no more than a 2-week supply.
	Twice-weekly for 2-3 mos.	RIF 10 mg/kg (600 mg) PZA 50 mg/kg (4.0g)	16-26 doses within 3-4 mos.	**DOT must be used with twice-weekly dosing.**

Abbreviations: INH = isoniazid, RIF = rifampin, PZA = pyrazinamide, NRTIs = nucleoside reverse transcriptase inhibitors, NNRTIs = non-nucleoside reverse transcriptase inhibitors, DOT = directly observed therapy, mos. = months

*** All pregnant and breast-feeding women taking INH should receive pyridoxine (B_6) supplementation.**

‡ **HIV co-infection**: Protease inhibitors or NNRTIs should not be administered concurrently with RIF; an alternative is rifabutin 300 mg daily. Rifabutin should not be used with hard-gel saquinavir or delavirdine. Dose adjustment of rifabutin may be required: to 150 mg twice-weekly with ritonavir or lopinavir/ritonavir, to 150 mg daily or 300 mg twice-weekly with other protease inhibitors, or to 450-600 mg daily or 600 mg twice-weekly with efavirenz.

MDR-TB exposure: For persons who are likely to be infected with INH and RIF (multidrug) resistant-TB and at high risk of reactivation, PZA and ethambutol or PZA and a quinolone for 6-12 months are recommended. (Consult expert.) Avoid PZA during first trimester.

HOW TO MONITOR

For all patients:

- Initial clinical evaluation, including radiologic studies to rule out active TB
- Consider possible rifamycin-associated drug interactions, eg. oral contraceptives, antiretrovirals, methadone, oral hypoglycemics, and anticoagulants
- Provider conversant in patient's language should educate patients about side effects associated with LTBI treatment and advise to stop treatment and promptly seek medical evaluation if these occur
- Follow-up evaluations at least monthly if receiving INH or RIF alone; at 2, 4, 6, and 8 weeks if receiving RIF and PZA
- Include careful questioning about side effects and a brief physical examination checking for evidence of hepatitis or other side effects
- Inform persons considering treatment with RIF-PZA of potential hepatotoxicity and ask about history of liver disease or adverse effects from INH or other drugs
- If side effects occur, evaluate promptly and change treatment as indicated
- Routine baseline and monthly monitoring of liver function tests (LFTs) is indicated during treatment of LTBI in pregnancy and early postpartum.

Medication should be withheld and patients evaluated if:

- Transaminase levels >3 times upper limit of normal in presence of symptoms
- Transaminase levels >5 times upper limit of normal in asymptomatic patient
- In patients on RIF-PZA: transaminase levels > normal if symptomatic, or if bilirubin > normal even if asymptomatic.

A joint project of Harlem Hospital, Columbia University, Health & Hospitals Corporation, and New York City Department of Health and Mental Hygiene; funded by The Centers for Disease Control and Prevention.
January 2005

TREATMENT INFORMATION

- Tuberculosis treatment should always be undertaken in consultation with a physician who is **well versed and experienced** in its management.
- All patients should be initially started on a 4-drug regimen of Isoniazid **(INH)**, Rifampin **(RIF)**, Pyrazinamide **(PZA)**, and Ethambutol **(EMB)**. Following the initial 8-week phase of treatment, the continuation phase should consist of **INH** and **RIF** in pansensitive cases.
- Directly Observed Therapy (DOT) is the international standard of care for all patients with TB disease and is essential for management of cases of multidrug-resistant TB (MDR-TB).
- Patients with TB should have monthly monitoring of sputum for AFB smear and culture, until negative.
- For all patients, drug susceptibility testing should be done on the initial *M. tuberculosis* isolates. Susceptibility testing should be repeated for patients who are not responding to therapy or who have positive cultures after 3 months of therapy.
- Treatment regimens for pulmonary TB are also effective for treating extrapulmonary TB.
- All new and suspected cases of active TB should be reported to state and/or local health departments.
- A single drug should never be added to a failing treatment regimen. Treatment of suspected drug-resistant TB should always include 2-3 new drugs.
- Based on medication history and drug susceptibility results, treatment for MDR-TB (i.e., resistance to at least INH and RIF) must be daily, individualized, and prolonged. **It is vital to seek expert consultation**.
- Treatment of tuberculosis benefits both the community as a whole and the individual patient; thus, any public health program or private provider must not only prescribe an appropriate regimen, but **also ensure adherence until treatment completion**.

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Treatment of Tuberculosis: Standard Therapy for Active Disease in Adults and Adolescents 2007

Based on the 2002 Official Joint Statement of the American Thoracic Society, Centers for Disease Control and Prevention, & Infectious Diseases Society of America, published in the Morbidity & Mortality Weekly Report, June 20, 2003. This card is not intended as a complete reference for treatment of TB.

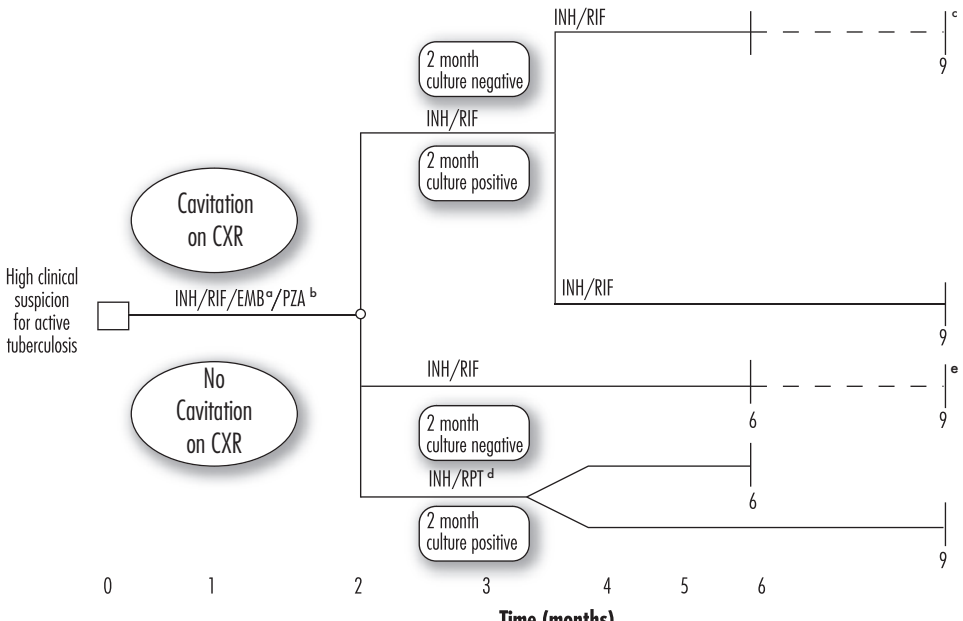
ANTI-TB DRUGS: FIRST-LINE MEDICATIONS – STANDARD THERAPY FOR ACTIVE DISEASE IN ADULTS

Treatment regimens that include four different first-line antituberculosis medications are recommended for the initial treatment of TB in adults. The initial regimen should include **INH**, **RIF**, **PZA**, and **EMB** unless there are contraindications to any of the drugs or if the patient is pregnant.[a] Rifampin should generally not be used in patients who are receiving protease inhibitors or nonnucleoside reverse transcriptase inhibitors. **All antituberculosis medications should be given concurrently, as a single dose**, in order to prevent development of resistant organisms and to enhance adherence, as well as achieve optimum serum blood levels. This card is not intended as a complete reference for treatment of tuberculosis.

DRUG	DOSAGES GIVEN IN MG/KG; [MAXIMUM DOSE]				Adverse Reactions	Monitoring	Comments
	Daily	Once Weekly[d]	2x Weekly[d]	3x Weekly[d]			
Isoniazid **INH:**[c] PO	5 [300 mg]	15 [900 mg]	15 [900 mg]	15 [900 mg]	Hepatic enzyme elevation, hepatitis, rash, peripheral neuropathy, mild CNS effects, drug interactions	In patients with preexisting liver disease or who develop abnormal liver function that does not require discontinuation of the drug; LFTs should be measured monthly & when symptoms occur.	Hepatitis risk increases with age, alcohol use, & concurrent use of other hepatotoxic drugs. Supplementation with pyridoxine in patients with nutritional deficiency, medical conditions associated with peripheral neuropathy (i.e., diabetes, chronic renal failure/dialysis, HIV) and during pregnancy is recommended.
Rifampin **RIF:**[c] PO	10 [600 mg]		10 [600 mg]	10 [600 mg]	GI intolerance, drug interactions, hepatitis, bleeding problems, flulike symptoms, orange discoloration of bodily fluids	Drug interactions should be noted.[b]	Significant interactions with methadone, oral contraceptives, & other drugs.[b] Educate patients about normal discoloration of bodily fluids.
Rifapentine **RPT:** PO		10-15 [600-900 mg] (continuation phase)			Hematologic toxicity, GI symptoms, polyathralgias, hepatotoxicity, pseudojaundice, flulike symptoms, orange discoloration of bodily fluids	Although drug interactions are less problematic than with RIF, they still require monitoring.	Used once weekly with INH, in the continuation phase only for HIV-seronegative patients with non-cavitary, drug susceptible pulmonary TB who have negative sputum smears at 2 months.
Rifabutin* **RBT:** PO	5 [300 mg]		5 [300 mg]	5 [300 mg]	Cutaneous reactions, GI reactions, flulike symptoms, hepatotoxity, severe immunologic reactions, orange discoloration of bodily fluids, drug interactions due to induction of hepatic microsomal enzymes, uveitis	Although drug interactions are less problematic than with RIF, they still require monitoring.	Used a substitute for RIF if patient demonstrates RIF intolerance or is taking drugs that have unacceptable interactions with RIF.
DRUG	**Patient's Weight**	**Daily**	**2x weekly**	**3x weekly**			
Pyrazinamide **PZA:**[c] PO	40-55 kg	18.2-25.0 [1g]	36.4-50.0 [2 g]	27.3-37.5 [1.5 g]	Hepatitis, GI intolerance, rash, joint aches, hyperuricemia, gout (rare)	LFTs in patients with underling liver disease or in conjunction with RIF for treatment of LTBI; baseline uric acid.	Little information about safety of use in pregnancy. Reduce dose in patients with renal insufficiency.
	56-75 kg	20.0-26.8 [1.5 g]	40.0-53.6 [3 g]	33.3-44.6 [2.5 g]			
	76-90 kg	22.2-26.3 [2 g]	44.4-52.6 [4 g]	33.3-39.5 [3 g]			
Ethambutol **EMB:** PO	40-55 kg	14.5-20.0 [.8 g]	36.4-50.0 [2 g]	21.8-30.0 [1.2 g]	Optic neuritis	Baseline visual acuity tests and questioning each month.	Adjust dosing when creatinine clearance is <70 ml/minute.
	56-75 kg	16.0-21.4 [1.2 g]	37.3-50.0 [2.8 g]	26.7-35.7 [2 g]			
	76-90 kg	17.8-21.1 [1.6 g]	44.4-52.6 [4 g]	26.7-31.6 [2.4 g]			

*[a]During pregnancy, initial regimen should include INH, RIF, EMB. A minimum of 9 months of therapy should be given. [b]See Morbidity & Mortality Weekly Report 52(RR-11), p. 47. [c]Fixed-dose combinations of INH+RIF+PZA (Rifater®) and INH + RIF (Rifamate®) are preferred when DOT is not used. [d]All intermittent regimens must be directly observed. *Not yet approved by the U.S. Food and Drug Administration for use in the treatment of tuberculosis.*

TREATMENT OF TUBERCULOSIS



[a]EMB may be discontinued when results of drug susceptibility testing indicate no drug resistance. [b]PZA may be discontinued after 2 months (56 doses). [c]With cavitation on initial CXR and 2-month culture being negative, therapy may be extended to 9 months at clinician's discretion. [d]RPT should not be used in HIV-infected patients with tuberculosis, in patients with extrapulmonary tuberculosis, or in patients with positive AFB smears at 2 months. [e]At clinician's discretion, therapy may be extended to 9 months if 2-month culture is positive.

DRUG REGIMENS FOR CULTURE-POSITIVE PULMONARY TUBERCULOSIS CAUSED BY DRUG-SUSCEPTIBLE ORGANISMS IN ADULTS: Consult the ATS/CDC/IDSA "Treatment of Tuberculosis" statement for more specific detail on the regimens listed below as well as alternative regimens not listed here.

MOST Preferred

	Initial Phase	Continuation Phase		
	Interval & Doses *(minimal duration)*		**Interval & Doses[a,b]** *(minimum duration)*	**Range of Total Doses** *(minimum duration)*
4 - Drug Combination		**2 - Drug Combination**		
INH RIF PZA EMB	7 days/wk for 56 doses (8 wks) or 5 days/wk for 40 doses (8 wks)	INH/RIF	7 days/wk for 126 doses (18 wks) or 5 days/wk for 90 doses (18 wks)	182-130 (26 wks)
		INH/RIF[c]	2x /wk for 36 doses (18 wks)	92-76 (26 wks)
		INH/RPT[d]	1x /wk for 18 doses (18 wks)	74-58 (26 wks)
INH RIF PZA EMB	7 days/wk for 14 doses (2 wks) then 2x/wk for 12 doses (6 wks) or 5 days/wk for 10 doses (2 wks) then 2x weekly for 12 doses (6 wks)	INH/RIF[c]	2x /wk for 36 doses (18 wks)	62-58 (26 wks)
		INH/RPT[d]	1x /wk for 18 doses (18 wks)	44-40 (26 wks)
INH RIF PZA EMB	3x weekly for 24 doses (8 wks)	INH/RIF	3x /wk for 54 doses (18 wks)	78 (26 wks)

[a] When DOT is used, drugs may be given 5 days/week & the necessary number of doses adjusted accordingly.
[b] Patients with cavitation on initial chest radiograph & positive cultures at completion of 2 months of therapy should recieve a 7-month (31 week; either 217 doses [daily] or 62 doses [2x/week]) continuation phase.
[c] Not recommended for HIV-infected patients with CD4+ cell counts <100 cells/µl.
[d] Should only be used in HIV-negative patients who have negative sputum smears upon completion of 2 months of therapy & who do not have cavitation on initial chest radiograph. During this regimen, if 2-month specimen is culture positive, treatment should be extended an extra 3 months.

TREATMENT INFORMATION

This card is intended as a convenient, but not a complete reference for health care providers managing the care of HIV-infected patients with drug susceptible TB. As HIV and TB treatment guidelines change frequently, consult http://www.cdc.gov/tb and http://aidsinfo.nih.gov for up-to-date information in addition to the references listed below.

- TB treatment regimens should be directly observed to assure patient adherence, and therapy should be prolonged if there is a delay in clinical or bacteriological response. The continuation phase should be extended from 4 to 7 months (9 months of total treatment) if the 2-month treatment culture is positive and if cavitation is seen in the chest x-ray after 4 months of treatment.
- Although the principles of TB treatment are similar for children and adults, there are unique considerations in the treatment of HIV and TB co-infected children. Children should be treated without delay. However, consultation with a specialist experienced in managing co-infected children is advised because indications for antiretroviral therapy, dosing of medications, and optimal length of TB therapy in children can vary.
- To prevent acquired rifamycin resistance in persons with advanced HIV infection ($CD4^+$ T-cell counts <100/mm^3) and TB, use more frequent therapy (3x weekly or daily) with RIF or RBT-based therapies.
- Rifapentine, a long-acting rifamycin, is not recommended for the treatment of TB in HIV-infected persons because of its association with acquired rifamycin resistance.

For complete treatment information, consult the following references:

— CDC. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: principles of therapy and revised recommendations. *MMWR* 1998; 47.

— CDC. Updated guidelines for the use of rifabutin or rifampin for the treatment and prevention of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. *MMWR* 2000; 49:185-9.

— CDC. Updated guidelines for the use of rifamycins for the treatment of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. *MMWR* 2004; 53:37.

— CDC. Treatment of tuberculosis. *MMWR* 2003; 52 (RR-11).

— American Academy of Pediatrics, Committee on Infectious Diseases. Tuberculosis. In L.K. Pickering (Ed.), 2006 *Red Book: Report of the Committee on Infectious Diseases*. 27th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2006:678-704.

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Treatment of Tuberculosis (TB) in Adult and Adolescent Patients Co-infected with the Human Immunodeficiency Virus (HIV) 2007

Highly active antiretroviral therapy (HAART) is frequently recommended for TB and HIV co-infected patients. The management of these patients is complex and should be undertaken by experienced health care providers. Drug interactions make TB treatment in HIV-infected patients taking nonnucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI) more difficult. Rifamycins induce cytochrome P450 (CYP450) hepatic enzymes that accelerate the metabolism of PIs and NNRTIs and may significantly reduce the serum levels of these drugs. If a rifamycin is excluded from the TB treatment regimen, this may result in delayed sputum conversion, prolong the duration of therapy, and possibly result in a poorer outcome. Rifabutin has been shown to be an effective substitute for rifampin, and because of its lesser effect on CYP450 induction is used *preferably* in the treatment for patients on PIs and NNRTIs. No dose adjustments are needed while using rifamycins and nucleoside/nucleotide reverse transcriptase inhibitors (NRTI/NtRTI) nor for fusion inhibitors.

RECOMMENDATIONS FOR CO-ADMINISTRATION OF RIFAMYCINS AND NNRTIs AND PIs

Rifabutin (RBT)-Based Regimen

Nonnucleoside reverse transcriptase inhibitors

RBT	NNRTI[1]
450-600 mg/day or 600 mg 3x/week	Efavirenz (standard dose)
300 mg/day or 300 mg 3x/week	Nevirapine (standard dose)

Protease Inhibitors

RBT	Single PI
150 mg/day or 300 mg 3x/week	Amprenavir/fos-amprenavir (usual dose)
150 mg/day or 300 mg 3x/week	Indinavir 1000 mg TID
150 mg/day or 300 mg 3x/week	Nelfinavir 1250 mg BID
150 mg alternate days or 3x/week	Atazanavir (usual dose)
150 mg alternate days or 3x/week	Ritonavir (usual dose)
RBT	**Dual PI**
150 mg alternate days or 3x/week	Lopinavir/ritonavir (usual dose)
150 mg alternate days or 3x/week	Ritonavir (any dose) booster with saquinavir, indinavir, amprenavir, fos-amprenavir, atazanavir, or tipranavir
150 mg alternate days	Ritonavir + darunavir (usual dose)

Do not use delavirdine and unboosted saquinavir with RBT

[1]These recommendations apply to regimens that do not include PIs, which can substantially increase RBT levels.

Rifampin (RIF)-Based Regimen

Nonnucleoside reverse transcriptase inhibitors

RIF	NNRTI
600 mg/day	Efavirenz 800 mg/day (max)[2]

Do not use nevirapine and delavirdine with RIF.

Protease Inhibitors

Do not use amprenavir, atazanvir, fos-amprenavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, or boosted/unboosted saquinavir with RIF.

[2]If efavirenz 800 mg cannot be tolerated, reduce to 600 mg.

ANTI-TB TREATMENT REGIMENS (TB-DRUG SENSITIVE) FOR PATIENTS RECEVING HAART

Initiation of HAART for co-infected patients is based on HIV RNA levels (viral load), $CD4^+$ T-cell counts, and a history of certain HIV-associated clinical conditions. Clinicians and patients need to also consider other existing medical issues (e.g., drug interactions and toxicities, ability to adhere to two complex treatment regimens, and laboratory abnormalities). A staggered initiation of anti-TB treatment and HAART for patients not currently on HAART might promote greater adherence to both treatment regimens and reduce any associated drug toxicity. This strategy might include starting HAART at the end of the 2-month induction phase of TB therapy or after TB therapy is completed. For some patients, switching from a RIF-based regimen to a RBT-based regimen will be necessary if HAART is initiated before the completion of anti-TB treatment. However, the potent effect of RIF as a CYP450 inducer continues up to at least 2 weeks following the discontinuation of RIF. Thus, clinicians need to plan for a 2-week "washout" period between the last dose of RIF and first doses of PIs and/or NNRTIs. Alternatively, if HAART will be initiated during anti-TB treatment, the induction phase should include RBT instead of RIF.

Induction Phase		**Continuation Phase**		
Drugs Daily mg/kg [maximum dosage]	**Duration**	**Drugs Daily** mg/kg [maximum dosage]	**Drugs 3x weekly** mg/kg [maximum dosage]	**Duration**
Isoniazid (INH): 5 [300][1]	2 months (8 weeks)	INH: 5 [300]	INH: 15 [900]	4 months (18 weeks)
Rifampin (RIF): 10 [600][2]		RIF: 10 [600]	RIF: 10 [600]	
OR		OR		
Rifabutin (RBT): 5 [300][2,3]				
Pyrazinamide (PZA):– – –[4] [2 g]		INH: 5 [300]	INH: 15 [900]	
Ethambutol (EMB):– – –[4] [1.6 g]		RBT: 5 [300]	RBT: 5 [300]	

[1]Pyridoxine (vitamin B6) 50 mg/day should be given to all HIV-infected patients taking INH.
[2]Rifamycins have significant interactions with methadone, oral contraceptives, and other drugs. See *MMWR* 2003; 52 (RR-11), p. 47.
[3]RBT dosage is based on weight and class of co-administered HIV drugs (i.e., NNRTI and/or PI) in the HAART regimen. Maximum RBT dosage varies when administered with efavirenz.
[4]See weight-based dosing charts in *MMWR* 2003; 52 (RR-11), p. 6.

TREATMENT INFORMATION

The treatment of TB in children should be undertaken in consultation with a physician experienced in its management, especially for patients with CNS, miliary, or multidrug-resistant (MDR) TB and with HIV-infection.

- TB in infants and children is commonly primary disease, which presents with intrathoracic adenopathy, middle and lower lung infiltrates, or pleural effusion. However, older children and adolescents may manifest an adult-type or reactivation pattern TB with upper lobe infiltrates, cavitation, and sputum production.
- Children with active TB are often found to be smear and culture negative when clinical specimens (e.g., sputum, gastric aspirates, etc.) are examined; *these children should be treated as having active disease not culture-negative TB*. In such instances, when an isolate from a pediatric case is not available, drug susceptibility results from the adult source case can be used to guide therapy.
- Drug-susceptible pulmonary disease is treated for 6 months: the initial (2-month) phase employs 3 drugs (INH, RIF, PZA) and the continuation (4-month) phase consists of INH and RIF. A fourth drug (usually EMB or an aminoglycoside) is added to the initial regimen only if there are risk factors for drug resistance in the child or source case and is continued until drug susceptibility studies are known. Treat isolated hilar adenopathy with 6 months of INH and RIF alone; however, where drug resistance is a consideration, add PZA for the initial 2 months.
- Extrapulmonary disease is treated the same as pulmonary disease except for CNS or miliary TB which is treated for 9-12 months. After expert consultation, this may involve adding a 4th drug (EMB, an aminoglycoside, or ethionamide) and steroids (indicated for CNS TB and considered for severe miliary, endobronchial, and pericardial disease and pleural effusion). For skeletal TB, orthopedic intervention and prolonged therapy may be indicated.
- Based on medication history and drug susceptibility results, treatment for MDR TB (resistance to at least INH and RIF) must be individualized and prolonged. Use of second-line drugs is required in cases of MDR TB and is beyond the scope of this drug card.
- The clinical manifestations and radiographic appearance of TB disease in children with HIV tend to be similar to those in immunocompetent children, but manifestations in these children can be more severe and unusual and can include extrapulmonary involvement. Optimal therapy has not been established; therapy should include at least 3 first-line drugs (INH, RIF, PZA) initially and be continued for at least 9 months.
- Treatment of tuberculosis benefits both the community as a whole and the individual patient; thus, **all public health programs and private providers not only must prescribe an appropriate regimen but also ensure adherence until treatment completion.**
- All new and suspected cases of TB should be reported to your state and local health departments so that source case or contact investigations can be conducted and case management provided.

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Treatment of Tuberculosis: Standard Therapy for Active Disease in Children 2007

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ANTI-TB DRUGS: FIRST-LINE MEDICATIONS
STANDARD THERAPY FOR ACTIVE DISEASE IN CHILDREN

Regimen — Regimens should include 3 different first-line anti-tuberculosis medications for the initial treatment of tuberculosis (TB) in children and adolescents. All patients should be started on **INH, RIF, and PZA** unless there are contraindications, or if there is evidence of resistance to any of the drugs in the patient or source case.

Administration and Monitoring — Directly Observed Therapy (DOT) is the international standard of care for all patients with TB disease. All anti-TB medications should be given concurrently, as a single dose, in order to prevent development of resistant organisms and to enhance adherence, as well as to achieve optimum serum blood levels. Adjust weight-based dosages as weight changes. Liver function tests are only recommended for children with severe disease. Monthly medical examination is standard for all cases.

DRUG	Dosage Forms	Daily mg/kg [Max Dose]	Twice Weekly[a] mg/kg [Max Dose]	Adverse Reactions	Comments
Isoniazid **INH:** PO	Scored tablets 100 mg, 300 mg Syrup 10 mg/mL	10-15 [300 mg]	20-30 [900 mg]	Mild hepatic enzyme elevation, hepatitis, peripheral neuropathy, hypersensitivity	When treated with INH, breastfed infants, pregnant adolescents, and symptomatic HIV-infected or malnourished patients and patients on milk and/or meat-deficient diets, should receive pyridoxine (B6) supplementation.
Rifampin **RIF:** PO	Capsules 150 mg, 300 mg	10-20 [600 mg]	10-20 [600 mg]	Hepatitis, influenza-like reaction, orange discoloration of secretions	RIF decreases serum levels of many drugs. Significant interactions can result when patients are treated with protease inhibitors or non-nucleoside reverse transcriptase inhibitors. Oral contraceptives may also be ineffective.[b] Educate patients about discoloration of bodily fluids.
Pyrazinamide **PZA:** PO	Scored tablets 500 mg	20-40 [2 g]	50 [2 g]	Hepatitis, hyperuricemia	Little known information about safety of PZA use during pregnancy. In pregnancy, use INH+RIF+EMB for 9 months.
Ethambutol **EMB:** PO	Tablets 100 mg, 400 mg	15-25 [2.5 g]	50 [2.5 g]	Optic neuritis, decreased red-green color discrimination, gastrointestinal disturbance, hypersensitivity	If drug resistance is a concern, EMB may be added to the initial regimen. Conduct baseline and monthly monitoring for visual acuity and red-green color discrimination; however, in young children, monitoring for visual acuity may not be possible. In such cases, weigh risk vs. benefit.

[a]*All intermittent regimens must be directly observed.* [b]*See MMWR 2003; 52(RR-11), p. 47.*

TREATMENT INFORMATION

- Tuberculosis treatment should always be undertaken in consultation with a physician who is **well versed and experienced** in its management.
- All patients should be initially started on a 4-drug regimen of Isoniazid **(INH)**, Rifampin **(RIF)**, Pyrazinamide **(PZA)**, and Ethambutol **(EMB)**. Following the initial 8-week phase of treatment, the continuation phase should consist of **INH** and **RIF** in pansensitive cases.
- Directly Observed Therapy (DOT) is the international standard of care for all patients with TB disease and is essential for management of cases of multidrug-resistant TB (MDR-TB).
- Patients with TB should have monthly monitoring of sputum for AFB smear and culture, until negative.
- For all patients, drug susceptibility testing should be done on the initial *M. tuberculosis* isolates. Susceptibility testing should be repeated for patients who are not responding to therapy or who have positive cultures after 3 months of therapy.
- Treatment regimens for pulmonary TB are also effective for treating extrapulmonary TB.
- All new and suspected cases of active TB should be reported to state and/or local health departments.
- A single drug should never be added to a failing treatment regimen. Treatment of suspected drug-resistant TB should always include 2-3 new drugs.
- Based on medication history and drug susceptibility results, treatment for MDR-TB (i.e., resistance to at least INH and RIF) must be daily, individualized, and prolonged. **It is vital to seek expert consultation**.
- Treatment of tuberculosis benefits both the community as a whole and the individual patient; thus, any public health program or private provider must not only prescribe an appropriate regimen, but **also ensure adherence until treatment completion**.

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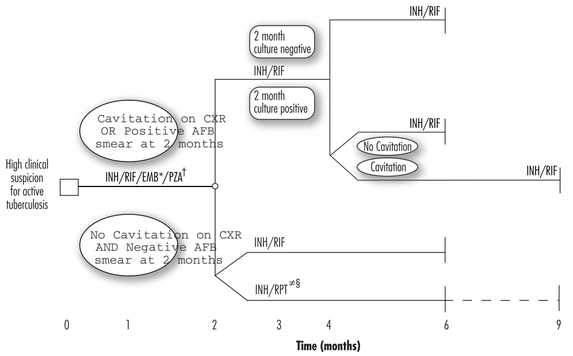
ANTI-TB DRUGS: FIRST-LINE MEDICATIONS – STANDARD THERAPY FOR ACTIVE DISEASE IN ADULTS

Treatment regimens that include four different first-line antituberculosis medications are recommended for the initial treatment of tuberculosis (TB) in adults. All patients should initially be started on a four-drug regimen of **INH**, **RIF**, **PZA** and **EMB** unless there are contraindications to any of the drugs or if the patient is pregnant.[a] Rifampin should generally not be used in patients who are receiving protease inhibitors or nonnucleoside reverse transcriptase inhibitors. Rifampin also decreases serum levels of many drugs.[b] **All antituberculosis medications should be given concurrently, as a single dose**, in order to prevent development of resistant organisms and to enhance adherence, as well as achieve optimum serum blood levels. Adjust weight-based dosages as weight changes. This card is not intended as a complete reference for treatment of tuberculosis.

DRUG	DOSAGES GIVEN IN MG/KG; [MAXIMUM DOSE]				Adverse Reactions	Monitoring	Comments
	Daily	Once Weekly[d]	2x Weekly[d]	3x Weekly[d]			
Isoniazid **INH:**[c] PO	5 [300 mg]	15 [900 mg]	15 [900 mg]	15 [900 mg]	Hepatic enzyme elevation, hepatitis, rash, peripheral neuropathy, mild CNS effects, drug interactions	In patients with preexisting liver disease or who develop abnormal liver function that does not require discontinuation of the drug, LFTs should be measured monthly & when symptoms occur.	Hepatitis risk increases with age, alcohol use, & concurrent use of other hepatotoxic drugs. Supplementation with pyridoxine in patients with nutritional deficiency, medical conditions associated with peripheral neuropathy (i.e., diabetes, chronic renal failure/dialysis, HIV) and during pregnancy is recommended.
Rifampin **RIF:**[c] PO	10 [600 mg]		10 [600 mg]	10 [600 mg]	GI intolerance, drug interactions, hepatitis, bleeding problems, flulike symptoms, orange discoloration of bodily fluids	Drug interactions should be noted.[b]	Significant interactions with methadone, oral contraceptives, & other drugs.[b,c] Educate patients about normal discoloration of bodily fluids.
Rifapentine **RPT:** PO		10 [600 mg] (continuation phase)			Hematologic toxicity, uretis, GI symptoms, polyarthralgias, hepatotoxicity, pseudojaundice, flulike symptoms, orange discoloration of bodily fluids	Although drug interactions are less problematic than with RIF, they still require monitoring.	Used once weekly with INH, in the continuation phase only for HIV-seronegative patients with non-cavitary, drug susceptible pulmonary TB who have negative sputum smears at 2 months.
Rifabutin* **RBT:** PO	5 [300 mg]	5 [300 mg]	5 [300 mg]		Cutaneous reactions, GI reactions, flulike symptoms, hepatotoxity, severe immunologic reactions, orange discoloration of bodily fluids, drug interactions due to induction of hepatic microsomal enzymes	Although drug interactions are less problematic than with RIF, they still require monitoring.	Used a substitute for RIF if patient demonstrates RIF intolerance or is taking drugs that have unacceptable interactions with RIF.
Pyrazinamide **PZA:**[c] PO	20-25 [2.0 g]		50-70 [4.0 g]	50-70 [3.0 g]	Hepatitis, GI intolerance, rash, joint aches, hyperuricemia, gout (rare)	LFTs in patients with underling liver disease or in conjunction with RIF for treatment of LTBI; baseline uric acid.	Little information about safety of use in pregnancy. Reduce dose in patients with renal insufficiency.
Ethambutol **EMB:** PO	15-25 [1.6 g]		50 [4.0 g]	25-30 [2.4 g]	Optic neuritis	Baseline visual acuity tests and questioning each month.	Adjust dosing when creatinine clearance is <70 ml/minute.

*[a]During pregnancy, initial regimen should include INH, RIF, EMB. A minimum of 9 months of therapy should be given. [b]See Morbidity & Mortality Weekly Report 52(RR-11), p. 47. [c]Fixed-dose combinations of INH+RIF+PZA (Rifater®) and INH + RIF (Rifamate®) are preferred when DOT is not used. [d]All intermittent regimens must be directly observed. *Not yet approved by the U.S. Food and Drug Administration for use in the treatment of tuberculosis.*

Treatment of Tuberculosis



*EMB may be discontinued when results of drug susceptibility testing indicate no drug resistance. †PZA may be discontinued after 2 months (56 doses). # RPT should not be used in HIV-infected patients with tuberculosis or in patients with extrapulmonary tuberculosis. §Therapy should be extended to 9 months if 2-month culture is positive.

DRUG REGIMENS FOR CULTURE-POSITIVE PULMONARY TUBERCULOSIS CAUSED BY DRUG-SUSCEPTIBLE ORGANISMS IN ADULTS

Consult the ATS/CDC/IDSA "Treatment of Tuberculosis" statement for more specific detail on the regimens listed below as well as alternative regimens not listed here.

MOST Preferred

	Initial Phase	Continuation Phase		
	Interval & Doses *(minimal duration)*		**Interval & Doses** *(minimum duration)*	**Range of Total Doses** *(minimum duration)*
4 - Drug Combination		**2 - Drug Combination**		
INH RIF PZA EMB	7 days/wk for 56 doses (8 wks) or 5 days/wk for 40 doses (8 wks)	INH/RIF	7 days/wk for 126 doses (18 wks) or 5 days/wk for 90 doses (18 wks)	182-130 (26 wks)
		INH/RIF	2x /wk for 36 doses (18 wks)	92-76 (26 wks)
		INH/RPT	1x /wk for 18 doses (18 wks)	74-58 (26 wks)
INH RIF PZA EMB	7 days/wk for 14 doses (2 wks) then 2x/wk for 12 doses (6 wks) or 5 days/wk for 10 doses (2 wks) then 2x weekly for 12 doses (6 wks)	INH/RIF	2x /wk for 36 doses (18 wks)	62-58 (26 wks)
		INH/RPT	1x /wk for 18 doses (18 wks)	44-40 (26 wks)
INH RIF PZA EMB	3x weekly for 24 doses (8 wks)	INH/RIF	3x /wk for 54 doses (18 wks)	78 (26 wks)

ANTI-TB DRUGS: SECOND-LINE MEDICATIONS: Since toxicities are greater when using second-line drugs, the following medication should **only** be used for patients with drug resistance or drug intolerance **in consultation with a physician experienced in the management of drug resistant TB. Never add a single drug to a failing regimen**.

All patients with drug-resistant TB should be placed on directly observed therapy (DOT). Second-line drugs are not intended for intermittent use and should be given on a daily basis. Exercise extreme caution when using these drugs during pregnancy due to known and unknown risk to the fetus. The following drugs are listed alphabetically.

DRUG	Daily Dose [Max]	Adverse Reactions	Monitoring	Comments
Amikacin/kanamycin (AM/KM):* IM/IV	15 mg/kg [1 g] [b]	Renal toxicity, vestibular dysfunction, hearing loss, electrolyte abnormalities, dizziness	Baseline and monthly auditory and renal function.	Avoid or reduce dose in adults over 59 (10 mg/kg with a maximum dose of 750 mg). Should not be used concurrently with other aminoglycosides or Capreomycin.
Capreomycin (CM): IM/IV	15 mg/kg [1 g] [b]	Auditory, vestibular, and renal toxicity, electrolyte abnormalities	Baseline and monthly auditory and renal function as well as serum K+ and Mg++ levels.	Avoid or reduce dose in adults over 59 (10 mg/kg daily with maximum dose of 750 mg). Decrease dose in renal insufficiency. Should not be used with aminoglycosides.
Cycloserine (CS): PO	10-15 mg/kg [1 g]; 500-750 mg divided BID	CNS effects, peripheral neuritis, psychosis, seizures, depression, headaches, rash, drug interactions	Neuropsychiatric status assessed monthly.	Use cautiously in patients with renal insufficiency. Pyridoxine may decrease CNS effects. Avoid sunlight. Consider dosing at mealtime. Although recommended, it is unusual for patients to tolerate this dosage. Serum concentration measurements are useful in determining the optimal dose.
Ethionamide (ETA): PO	15-20 mg/kg [1 g]; 500-750 mg or divided BID	GI intolerance, hepatotoxicity, neurotoxicity, endocrine effects, metallic taste, hypersensitivity	Baseline LFTs recommended in all patients. For patients with preexisting liver disease or who develop abnormal liver function that does not require discontinuation of the drug, LFTs should be measured monthly & when symptoms occur.	Reduce dosage in patients with creatinine clearance of >30ml/min; start with low dosage and increase as tolerated. To reduce GI upset, give in divided dose. May cause hypothyroid condition, especially if used with PAS.
Gatifloxacin (GAT):* PO/IV	400 mg	GI intolerance, headache, dizziness, rash, vaginitis, drug interactions, hypersensitivity reaction		Cross resistance with Ciprofloxacin and Ofloxacin. [a] Should not be administered within 2 hours of taking antacid/medications containing divalent cations.
Levofloxacin (LEV):* PO/IV	500-750 mg	GI intolerance, headache, dizziness, rash, vaginitis, drug interactions, hypersensitivity reaction		Cross resistance with Ciprofloxacin and Ofloxacin. [a] Should not be administered within 2 hours of taking antacid/medications containing divalent cations.
Moxifloxacin (MOX):* PO/IV	400 mg	GI intolerance, headache, dizziness, rash, vaginitis, drug interactions, hypersensitivity reaction		Cross resistance with Ciprofloxacin and Ofloxacin. [a] Should not be administered within 2 hours of taking antacid/medications containing divalent cations.
p-Aminosalicylic acid (PAS): PO	150 mg/kg divided BID [12 g]	GI intolerance, hypersensitivity, hepatotoxicity, malabsorption syndrome, coagulopathy	Baseline hepatic enzymes and thyroid function.	May cause hypothyroid condition if used with ETA. Monitor cardiac patients for sodium load. Doubling of prothrombin time lessened with use of SM.
Streptomycin (SM): IM	15 mg/kg [1 g] [b]	Ototoxicity (hearing loss or vestibular dysfunction), neurotoxicity, renal toxicity	Baseline hearing & serum creatinine measurement. Monthly renal function assessment and questioning regarding auditory or vestibular symptoms.	Avoid or reduce dose in adults over 59 (10mg/kg daily with a maximum dose of 750 mg). Decrease dose in renal insufficiency.

*Ciprofloxacin, Clarithromycin, Clofazamine, & Ofloxacin are no longer 2nd line drugs, but can be used as alternatives to the listed options in cases of drug resistance/intolerance. [b] Usual dose is 750-1000 mg IV/IM; given as a single dose 5-7 days/week & reduced to 2-3 days/week after the first 2-4 months or after culture conversion, depending on efficacy of drug regimen. *Not yet approved by the U.S. Food and Drug Administration for use in the treatment of tuberculosis.

Diagnosis of Tuberculosis Disease

When Should You Suspect Tuberculosis (TB)?

TB is a disease caused by *Mycobacterium tuberculosis*. TB disease should be suspected in persons who have the following symptoms:

- Unexplained weight loss
- Loss of appetite
- Night sweats
- Fever
- Fatigue

If TB disease is in the lungs (pulmonary), symptoms may include:

- Coughing for ≥ 3 weeks
- Hemoptysis (coughing up blood)
- Chest pain

If TB disease is in other parts of the body (extrapulmonary), symptoms will depend on the area affected.

How Do You Evaluate Persons Suspected of Having TB Disease?

A complete medical evaluation for TB includes the following:

1. Medical History

Clinicians should ask about the patient's history of TB exposure, infection, or disease. It is also important to consider demographic factors (e.g., country of origin, age, ethnic or racial group, occupation) that may increase the patient's risk for exposure to TB or to drug-resistant TB. Also, clinicians should determine whether the patient has medical conditions, especially HIV infection, that increase the risk of latent TB infection progressing to TB disease.

2. Physical Examination

A physical exam can provide valuable information about the patient's overall condition and other factors that may affect how TB is treated, such as HIV infection or other illnesses.

3. Mantoux Tuberculin Skin Test and/or QuantiFERON®-TB Gold Test

The Mantoux tuberculin skin test (TST) and the QuantiFERON®-TB Gold test (QFT-G) are used to test for *M. tuberculosis* infection. Additional tests are required to confirm TB disease. The Mantoux tuberculin skin test is performed by injecting a small amount of fluid called tuberculin into the skin in the lower part of the arm. The test is read within 48 to 72 hours by a trained health care worker, who looks for a reaction (induration) on the arm.

The QFT-G is a blood test. It measures the patient's immune system reaction to *M. tuberculosis*. Once the blood samples are taken, they must be processed within 12 hours. Interpretation of QFT-G results is influenced by the patient's estimated risk for TB infection.

4. Chest Radiograph

A posterior-anterior chest radiograph is used to detect chest abnormalities. Lesions may appear anywhere in the lungs and may differ in size, shape, density, and cavitation. These abnormalities may suggest TB, but cannot be used to definitively diagnose TB. However, a chest radiograph may be used to rule out the possibility of pulmonary TB in a person who has had a positive reaction to a TST or QFT-G and no symptoms of disease.

5. Diagnostic Microbiology

The presence of acid-fast-bacilli (AFB) on a **sputum smear** or other specimen often indicates TB disease. Acid-fast microscopy is easy and quick, but it *does not confirm a diagnosis of TB because some acid-fast-bacilli are not M. tuberculosis.* Therefore, a **culture** is done on all initial samples to confirm the diagnosis. (However, a positive culture is not always necessary to begin or continue treatment for TB.) A positive culture for *M. tuberculosis* confirms the diagnosis of TB disease. Culture examinations should be completed on all specimens, regardless of AFB smear results. Laboratories should report positive results on smears and cultures within 24 hours by telephone or fax to the primary health care provider and to the state or local TB control program, as required by law.

6. Drug Resistance

For all patients, the initial *M. tuberculosis* isolate should be tested for drug resistance. It is crucial to identify drug resistance as early as possible to ensure effective treatment. Drug susceptibility patterns should be repeated for patients who do not respond adequately to treatment or who have positive culture results despite 3 months of therapy. Susceptibility results from laboratories should be promptly reported to the primary health care provider and the state or local TB control program.

Additional Information

American Thoracic Society (ATS) and CDC. Diagnostic standards and classification of tuberculosis in adults and children. *Am J Respir Crit Care Med* 2000;161.
www.thoracic.org/adobe/statements/tbadult1-20.pdf

ATS, CDC, and Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003;52 (No. RR-11).
www.cdc.gov/mmwr/PDF/rr/rr5211.pdf
Errata - www.cdc.gov/mmwr/preview/mmwrhtml/mm5351a5.htm

Centers for Disease Control and Prevention. Guidelines for the investigation of contacts of persons with infectious tuberculosis and Guidelines for using the QuantiFERON®-TB Gold test for detecting *Mycobacterium tuberculosis* infection, United States. *MMWR* 2005; 54 (No. RR-15).
www.cdc.gov/mmwr/pdf/rr/rr5415.pdf

<Your facility name>
TUBERCULOSIS DISEASE ASSESSMENT

DEMOGRAPHIC INFORMATION		
Name:	Date:	
Address:	DOB:	Age:
Length at this address:	Race:	
Previous address:	Length at address:	
Phone Number:	Alternate Phone Number:	
Contact Person:	Country of Birth:	
Local Health Jurisdiction at time of diagnosis:		

MEDICAL HISTORY	
Medical Provider:	Phone Number:
Address:	
Previous Medical Provider:	

Health Assessment			
Height:	Weight:	BP:	Date of H/V Exam:
Contact to confirmed TB case? Yes No		Type/Length of Exposure:	
PPD Converter? Yes No	Date		

Current Symptoms & Onset Date								
Yes	No		Yes	No		Yes	No	
		Cough			Diarrhea			Peripheral Neuropathy
		Hemoptysis			Abdominal Pain			Fever
		Fatigue			Rash/Itching			Chest Pain
		Night Sweats			Anorexia			Enlarged Lymph Nodes
		Weight Loss			Joint Pain			Hoarseness/Laryngitis
		Other:						

Current Health Problems					
Yes	No		Yes	No	
		Greater than 10% less than ideal weight			Substance Abuse
		Heart Problems			Sensory Problems (eye, ear)
		Liver Problems			Cancer
		History of Hepatitis			Crohn's Disease
		Diabetes			Gastrectomy/ Intestinal Bypass
		Rheumatoid Arthritis			Auto-Immune Disorder
		Dialysis/Renal Failure			Organ recipient
		Renal Problems			Prior TB Treatment (incomplete)
		Silicosis			High Risk Employment
		Mental Illness			Other:
		Pregnancy			

Lab Information				
Date of last Chest X-ray :			Location:	
Date of last TB skin test:		Results:		Where given:
TB Skin Test History:				
Date of last sputum specimen:			Lab:	
Lab location of TB culture:			Probe date / result:	
Contact name:			Facility:	
Address:			Phone Number:	
Lab location of TB sensitivity:				
Contact name:			Facility:	
Address:			Phone Number:	
Specimen sent to MDCH?:	Yes	No	Date:	
Liver enzymes completed>:	Yes	No	Date:	Results:
Date of last HIV test:			Results:	
Genotyping Cluster ID:				
LHD County / Contacts / Epi link:				

SOCIAL / CULTURAL

Psychosocial: (Check those that apply)

Yes	No		Yes	No	
		Alcohol Use			Dysfunctional Family
		IV Drug User			Language Barrier
		Non- IV Drug User			Cultural Barrier
		Behavioral/Mental Health Problems			Foreign Born/Country/VISA status
		Learning Disability			Transportation
		Forgetfulness			Long Work Hours
		Cannot Read			Uninsured
		Low Reading Comprehension			Inadequate finances
		Denial			Non-Compliant
		Anger			Transportation problems
		Fear			No sick leave time at job
		Support System			In need of Incentive & Enablers funds
		Homeless			Other barriers to treatment
		Migrant			

Living in a Congregate Center:

Yes	No		
		Resident of longterm care facility	Name of Facility
		History of incarceration Date	Contact Person
		Where	Address
		Group Home	Phone Number
		Center for Disabled	Fax Number
		Hospital	
		Assisted Living	
		Other	

ENVIRONMENTAL		
Sleeping Area Room Size:		
Where does client spend most of waking hours?	Sleeping hours?	
Number of Household Contacts:	Other close contacts:	
Work or primary environment outside of the home:		
Name of worksite/group:		
Contact Person:	Title:	
Address:		
Phone Number:	Fax Number:	
Type of work:	Job responsibilities:	
Type of building:	Primary work area:	
Square footage:	Ceiling Height:	Ventilation:
Do windows open?	Fans:	Air Conditioning:
Lunch area / Break room		
Coworkers - Frequency & duration of exposure:		
Number of co-workers with closest contact to index case:		
Travel Mode: Car Bus Other		

CONTACTS	
Client's infectivity period dates:	
Description of client's daily routine:	
List the frequency & duration client spent at these locations/activities:	
Home:	Health Care Settings:
School:	Extracurricular Activities (meetings, parties, holidays):
Church:	Church Activities:
Hobbies:	Volunteer Activities:
Leisure:	Homeless Shelter (type, size, ventilation):
Recent travel within 3 months of symptom onset (travel history):	

List of Contacts

(Contacts should include the following: household contacts (HHC), school classmates (SC), co-workers (CW), friends (F) social contacts (SC), girl or boyfriends (GF/BF), sexual partners (SP), car poolers (CP)).

NAME	TYPE	DURATION	FREQUENCY

REFERRALS		
Yes	No	
		Department of Human Services (DHS)
		Local Health Department Programs (WIC, MIHP, Family Planning, Other)
		Food Pantry
		Medical Provider
		Mental Health
		Substance Abuse
		HIV Testing
		Homeless Shelter
		Directly Observed Therapy (DOT) Providerr
		Other
		American Lung Association of Michigan
		TB Net
		State-at-Large Program

TUBERCULOSIS CLASSIFICATION		
Class	**Type**	**Description**
3	TB disease Clinically active	*Mycobacterium tuberculosis* complex cultured (if this has been done) Clinical, bacteriologic, or radiographic evidence of current disease
4	TB disease Not Clinically active	History of episode(s) of TB **Or** Abnormal but stable radiographic findings Positive reaction to the TST or IGRA Negative bacteriologic studies (if done) **And** No clinical or radiographic evidence of current disease
5	TB suspect	Diagnosis Pending

Special Instructions:	Isolation: _____	Instructed to Wear Mask: _____
Identified Special Educational Needs:		
Comments:		
Directly Observed Therapy (DOT) Plan:		

Signature - Nurse Case Manager

Date

STATE OF MICHIGAN

IN THE CIRCUIT COURT FOR THE COUNTY OF _____

IN RE: _____

_____

Attorney's Name (P#)
Address
Phone Number

_____

AFFIDAVIT OF _____ M.D. (or D.O.)

STATE OF MICHIGAN)
) ss
COUNTY OF _____)

_____, M.D. or D.O., having been first duly sworn, deposes and says:

1. I am a physician licensed to practice medicine in the State of Michigan.

2. Respondent, _____, is presently a patient at _____ Hospital, _____ (hospital address), Room _____ (room number of Respondent), in _____, Michigan.

3. Respondent is a _____ (age) year old male/female, and has been diagnosed as suffering from active pulmonary tuberculosis.

4. Respondent has never completed the treatment regimen necessary for the disease.

5. Respondent is presently active and contagious.

6. Respondent's infectious condition requires immediate medical treatment.

7. In my opinion, Respondent is unable or unwilling, absent a Court order, to complete the treatment regimen necessary for his affliction and to conduct himself in a manner that will not expose others to the risk of infection.

8. Given that Respondent is afflicted with actively infectious pulmonary tuberculosis, and is unable or unwilling to submit to the treatment necessary for his affliction, it is my opinion that if Respondent were released from hospitalization, he/she would pose an immediate health danger to the public at large.

_____
Full Name, M.D. or D.O.

Dated: _____

Subscribed and sworn to before me
this _____ day of _____, 2007.

_____
Notary Public, _____ County Michigan
My Commission expires: _____
Acting in the County of _____

MODEL ORDER FOR CONTACT EVALUATION

<Date>

<Patient Name>
<Address>

Re: Health Officer's Order for Contact Evaluation

Dear Patient,

This letter is a follow up to the letter sent to you on <date>, informing you of the need to obtain a medical evaluation because of your exposure to a case of pulmonary tuberculosis. Public health regulations in the state of Michigan MCL 333.5201 et. seq require that a person identified as a high-priority contact to someone with active or suspected active tuberculosis must submit to a complete medical evaluation, which may include a tuberculin skin test (TST) and chest x-ray, if necessary. Despite repeated telephone calls and visits to your home on the following days <dates/times>, and letters mailed to your home on <dates>, you have not yet had this evaluation. On <date> a warning notice was sent to you by certified mail, advising you that you must submit to medical evaluation or risk having legal actions brought against you.

Be advised that this evaluation is mandatory. This letter is to inform you that since you have not responded to any of the above efforts or the warning notice issued on <date>, pursuant to <citation giving authority for health order>, I am **ordering** you to report to the <local health department, phone #> **within 7 (seven) days** of receipt of this letter to make arrangements for this mandatory medical evaluation. If you fail to comply with this health officer's order, a court order will be sought for your confinement to a designated facility until the evaluation is completed <citation giving authority for confinement pending testing>.

Your cooperation in this matter is deeply appreciated.

Sincerely,

<name of health officer or medical director>

MODEL WARNING FOR CONTACT EVALUATION

<Date>

Patient Name
Address

Re: Warning Notice for Contact Evaluation

Dear Patient,

This letter is to inform you that you have been exposed to someone with pulmonary tuberculosis (TB). Public health regulations in the state of Michigan MCL 333.5201 et. seq require that a person identified as a high-priority contact to someone with active or suspected active tuberculosis must submit to a complete medical evaluation, which may include a tuberculin skin test (TST) and chest x-ray, if necessary. To date, despite repeated telephone calls and visits to your home on the following days <dates/times>, and letters mailed to your home on <dates>, you have not yet had this evaluation.

Be advised that this evaluation is mandatory. This letter is to inform you that the <local health department> is able to give you this evaluation at no cost. It is extremely important that you contact the <local health department> at <phone #> within 7 days of receiving this letter to arrange for the evaluation or discuss other means of getting the evaluation. Please be assured that the <local health department> staff is prepared to assist you if necessary to ensure you receive this evaluation.

If you do not respond to this warning and do not get this evaluation, you will be subject to legal actions ordering you to get the evaluation.

Your cooperation in this matter is deeply appreciated.

Sincerely,

<name of health officer or medical director>

STATE OF MICHIGAN

IN THE CIRCUIT COURT FOR THE COUNTY OF _____

IN RE: _____

_____

Attorney's Name (P#)
Address
Phone Number

_____

PETITION FOR EX PARTE ORDER OF COMMITMENT FOR MEDICAL TREATMENT AND OF TEMPORARY DETENTION PENDING HEARING

The _____ Health Department, by the undersigned attorney, pursuant to MCL 333.5205, petitions this Court for entry of an Ex Parte Order of Commitment for Medical Treatment and of Temporary Detention pending Hearing for the above-named individual and in support of its Petition states:

1. Respondent is a _____ (age) year old male/female with a date of birth of _____, 19__.

2. On information and belief, Respondent is a resident of the City of _____, County of _____ and the State of Michigan.

3. Respondent currently suffers from pulmonary tuberculosis, a hazardous communicable disease.

4. Respondent's tuberculosis requires immediate medical treatment.

5. Respondent was diagnosed with tuberculosis when he/she was hospitalized from _____, 2007 to _____, 2007 at _____ Hospital. Respondent left _____ Hospital against medical advice, was admitted to _____ Hospital on _____, 2007, and was transferred to _____ Hospital on _____, 2007.

6. Respondent has a history of _____ (mental or other disability) and drug abuse (mostly alcohol).

7. Respondent is belligerent and has been uncooperative with the staff of all three (3) Institutions where he/she has been hospitalized.

8. Respondent has a history of being hospitalized a number of times at the _____ (mental or other disability) Hospital in _____ (City or County) when it was open.

9. Respondent is currently homeless.

10. If Respondent were allowed to leave his treatment facility in his present condition, he/she would pose an immediate health hazard to the public.

11. Respondent is unable or unwilling to conduct himself/herself in a manner that would not expose others to the risk of infection.

12. Respondent is unable or unwilling to voluntarily submit to the care necessary for his/her disease.

13. Respondent has failed or refused to comply with a warning notice hand-delivered to him/her on _____, 2007, pursuant to MCL 333.5203.

WHEREFORE, Petitioner, _____ Health Department, asks this Honorable Court:

1. To set a hearing on the allegations set forth in this petition pursuant to MCL 333.5205(2)(d) to be held as soon as possible but not later than fourteen (14) days after the date of the filing of this petition pursuant to MCL 333.5205(5).

2. To enter an *ex parte* order for the temporary detention of Respondent until the date of the hearing pursuant to MCL 333.5207(5).

3. To enter an order committing Respondent for treatment of tuberculosis pending a hearing on this petition.

Respectfully submitted,

_____
Attorney for Health Department

Dated: _____

STATE OF MICHIGAN

IN THE CIRCUIT COURT FOR THE COUNTY OF _____

IN RE: _____

_____

Attorney's Name (P#)
Address
Phone Number

_____

AFFIDAVIT OF _____ M.D. (or D.O.)

STATE OF MICHIGAN)
) ss
COUNTY OF _____)

_____, M.D. or D.O., having been first duly sworn, deposes and says:

1. I am a physician licensed to practice medicine in the State of Michigan.

2. Respondent, _____, is presently a patient at _____ Hospital, _____ (hospital address), Room _____ (room number of Respondent), in _____, Michigan.

3. Respondent is a _____ (age) year old male/female, and has been diagnosed as suffering from active pulmonary tuberculosis.

4. Respondent has never completed the treatment regimen necessary for the disease.

5. Respondent is presently active and contagious.

6. Respondent's infectious condition requires immediate medical treatment.

7. In my opinion, Respondent is unable or unwilling, absent a Court order, to complete the treatment regimen necessary for his affliction and to conduct himself in a manner that will not expose others to the risk of infection.

8. Given that Respondent is afflicted with actively infectious pulmonary tuberculosis, and is unable or unwilling to submit to the treatment necessary for his affliction, it is my opinion that if Respondent were released from hospitalization, he/she would pose an immediate health danger to the public at large.

_____
Full Name, M.D. or D.O.

Dated: _____

Subscribed and sworn to before me
this _____ day of _____, 2007.

_____
Notary Public, _____ County Michigan
My Commission expires: _____
Acting in the County of _____

STATE OF MICHIGAN

IN THE CIRCUIT COURT FOR THE COUNTY OF _____

IN RE: _____

_____

Attorney's Name (P#)
Address
Phone Number

_____

EX PARTE ORDER OF COMMITMENT FOR MEDICAL TREATMENT AND OF TEMPORARY DETENTION PENDING HEARING

At a session of said Court held in the Courthouse,
City of _____, County of _____,
Michigan on _____.

PRESENT: HONORABLE _____

The _____ Health Department, having filed a petition for *Ex Parte* Order of Commitment for Medical Treatment and of Temporary Detention Pending Hearing; it appearing to the Court from the petition, and affidavit filed in support of the petition, that Respondent suffers from actively infectious tuberculosis and would, if released from hospitalization, pose an immediate danger to the health of others; and the Court being otherwise fully advised in this matter:

IT IS HEREBY ORDERED that the petition for commitment shall be brought on for hearing on _____ at _____, in the _____ noon before the Honorable _____, Judge of the Circuit Court, _____ (Address of Courthouse), _____ (city), Michigan and that Petitioner shall cause Respondent to be

personally served with a copy of the Petition for Commitment and a true copy of this Order, at least three (3) days prior to that hearing pursuant to MCL 333.5205(5);

IT IS FURTHER ORDERED that Respondent _____, as hereby is, temporarily detained at _____ Hospital for the continued treatment of tuberculosis until the date of the hearing pursuant to MCL 333.5207(5);

IT IS FURTHER ORDERED that Respondent shall comply with the regulations of the facility to which he/she is committed;

IT IS FURTHER ORDERED that during the period in which Respondent is detained for treatment, the treatment facility, its agents and employees, are authorized to provide related and/or ancillary care and/or treatment to him/she, including, but not limited to, feeding, bathing, testing, and examinations;

IT IS FURTHER ORDERED that the _____ Health Department may for reasonable cause change the facility to which Respondent is detained for treatment;

IT IS FURTHER ORDERED that during the period of detention, local and/or state police authorities are authorized and directed to return Respondent to the treatment facility to which he/she is detained, or to another facility providing suitable tubercular care;

IT IS FURTHER ORDERED that during the period of detention, local and/or state police authorities, the treatment facility, its agents and employees, and/or the _____ Health Department, its agents and employees, may contract with public or private ambulance services for the necessary transportation of Respondent;

IT IS FURTHER ORDERED that the following is appointed as counsel for respondent:

_____.

_____
Circuit Court Judge

MODEL (*EX PARTE)* PETITION FOR TEMPORARY QUARANTINE/ISOLATION AND MEDICAL EXAMINATION PENDING HEARING

STATE OF MICHIGAN

IN THE CIRCUIT COURT FOR THE COUNTY OF _____

IN RE: _____

Attorney's Name (P#)
Address
Phone Number

(*EX PARTE)* PETITION FOR TEMPORARY QUARANTINE/ISOLATION AND MEDICAL EXAMINATION PENDING HEARING

The City/County of _____, through its Health Department, by the undersigned attorney, pursuant to MCL 333.5205 and/or 333.5207, petitions this Court for entry of an *Ex Parte* Order for a Temporary Quarantine and Medical Examination of _____ person (s) pending a hearing for the above-named individual or group and in support of its Petition states:

1. Respondent is a _____ year old male/female.
2. On information and belief, Respondent is a resident of _____ City/County, and the State Of Michigan.
3. Respondent currently suffers from active tuberculosis.
4. Respondent's tuberculosis requires immediate medical treatment.
5. Respondent was diagnosed with tuberculosis on ____(Date and Location).
6. Respondent has a medical history of _____(mental health disability or some other health disease or disability)_____.
7. Respondent is uncooperative, belligerent, etc.

8. Respondent is unable and unwilling to conduct himself in a manner that would not expose others to the risk of tuberculosis infection.

9. Respondent is unable or unwilling to voluntarily submit to the care necessary for his tuberculosis which may include temporary isolation/quarantine in his home or other place or due to his/her homelessness is unable to isolate/quarantine himself/herself.

10. Respondent has failed or refused to comply with either a verbal or written warning notice (hand) delivered to him/her on ____(Date)____, pursuant to MCL 333.5203.

11. This Court has jurisdiction over this matter pursuant to MCL 333.5201 *et seq*.

12. In support of this petition, the Affidavit of _____(M.D. or D.O.)____, is attached.

WHEREFORE Petitioner, the City/County of _____ through its Health Department, respectfully asks this Honorable Court to issue and Order for the following:

1. to set a hearing on the allegations set forth in this petition pursuant to MCL 333.5205 (2) (d) to be held as soon as possible, but not later than fourteen (14) days after the date of the filling of this petition pursuant to MCL 333.5205 (5).
2. to enter and *ex parte* Order for the temporary isolation/quarantine of Respondent until the date of the hearing pursuant to MCL 333.5207 (5).
3. to enter an Order committing Respondent for treatment of his/her tuberculosis pending a hearing on this petition.

Respectfully submitted,

_____Attorney_____

Date:

MODEL ORDER FOR TUBERCULOSIS TREATMENT NONADHERENCE

<Date>

<Patient Name & address>

Subject: Order for Tuberculosis Treatment/Evaluation Adherence

Dear <Patient's name>:

I have been informed by <name of physician / clinic director / medical director> that you have been diagnosed with <active pulmonary tuberculosis / latent tuberculosis infection> and are being treated for this condition by <private physician name / local health department clinic>. <Private physician name / local health department clinic> has also informed me that your treatment may include directly-observed therapy (DOT) <#> days per week until <date>, or until your treatment is completed, as well as periodic medical examinations as directed by <private physician name / local health department>.

Since <date> you have not followed this treatment plan, and have refused all efforts from <staff member(s)> to help you follow this treatment plan. Efforts to help you follow your treatment plan included visits and telephone calls to your home by staff members of <private clinic / local health department> on the following days: <list dates / times of visits or calls>, as well as reminders of clinic appointments mailed to your home on <list dates>. You have been offered various incentives and other helpful means to ensure your cooperation with this treatment plan. You have also been educated about the seriousness of your <latent tuberculosis infection / active pulmonary tuberculosis>, as well as the consequences to yourself and others who may be exposed to your disease, if you do not follow your treatment plan.

Public health regulations MCL 333.5203 require that you follow the treatment plan as recommended by your local health department. However, you have not responded to any of <local health department's> efforts to assist you in complying with your treatment plan. You also failed to respond to a warning notice sent to you on <date>. Pursuant to <citation>, this letter serves as an **order** that you must <report to/call> the <local health department/clinic> at <address, phone #> **within 7 (seven) days** of receiving this letter, to make arrangements to follow your treatment plan. If you fail to follow this health order, or you fail to comply with your treatment plan again at any point in the future, a court order will be sought for your confinement to a designated treatment facility until such time as you complete a full course of anti-tuberculosis treatment, or you are released from commitment by order of a physician <citation>.

Sincerely,

<name of health officer or medical director>

WARNING NOTICE

<Date>

Mr. Huber T. Tuber
1313 Mockingbird Lane
Wayne County, MI 48218

Personal Delivery
Registered Mail

Dear Mr. Tuber,

On <date> you had a <posituve sputum smear, CXR, CT scan> at <hospital name>. Because of abnormal <posituve sputum smear, CXR, CT scan> results, you are suspected of having active tuberculosis (TB).

The Michigan Public Health Code requires that <local health department> act immediately to confirm whether you have active TB, and to ensure that if you have active TB, you complete an appropriate course of treatment.

This is a **warning notice** pursuant to the Public Health Code, Michigan Compiled Laws Section 333.5203 et seq. **You are required to cooperate** with the <local health department> to prevent the spread of tuberculosis.

You must cooperate, as follows:

1. **You must report to the TB clinic on <date & time>.** The TB Clinic is located at <address> and the phone number is <#>. The <name> County <TB Control Program/Health Department> is solely responsible for medical management of your TB treatment. A required treatment plan will be reviewed with you, and given to you in writing at that time.

2. You must be available at <address> or an approved Direct Observation Therapy (DOT) location for **every** scheduled Direct Observation Therapy visit by the <name> county public health nurse. You **must** take all TB medications in the presence of the <name> county public health nurse.

3. You must report to the <name> County TB clinic, or other designated location, for **all** scheduled physician visits, testing, and/or and other medical evaluation related to TB.

4. You must name and give contact information for all persons with whom you have spent time during your contagious period.
5. You must continue TB treatment, until you are no longer considered to be contagious **and** you complete a full course of treatment, **or** you have been determined not to have active TB by <health department staff/physician>. If you have any questions regarding compliance with your TB treatment, contact <health department staff, #>.

6. If you fail to comply with this warning notice or your treatment plan, the Public Health Department **will** seek court intervention in this matter from the <name> County Probate Court. This may include commitment to an appropriate facility for treatment.

If court intervention is sought, you will have the right to a notice, a hearing, and other rights provided under Michigan law. These rights shall be available to you before the court issues an order, unless there is an emergency. In the case of an emergency, the County may act first without a notice or hearing, although a court hearing will follow. We trust that this will not be necessary.

Sincerely,

<name>
<Health Officer>

<LOCAL HEALTH DEPARTMENT>
RECIPIENT ACKNOWLEDGEMENT OF WARNING NOTICE

The contents of the attached **WARNING NOTICE have** been explained to me.
I understand that I must comply with the conditions in the **NOTICE.**

_____ _____
Client Signature Date

_____ _____
Witness Date

_____
Refusal

The client refused to sign the above acknowledgement of the **WARNING NOTICE.**

_____ _____
Witness Date

MODEL WARNING FOR TUBERCULOSIS TREATMENT NONADHERENCE

<Date>

<Patient Name & address>

Subject: Warning Notice for Tuberculosis Treatment/Evaluation Nonadherence

Dear <Patient's name>:

I have been informed by <name of physician / clinic director / medical director> that you have been diagnosed with <active pulmonary tuberculosis / latent tuberculosis infection> and are being treated for this condition by <private physician name / local health department clinic>. <Private physician name / local health department clinic> has also informed me that your treatment may include directly-observed therapy (DOT) <#> days per week until <date>, or until your treatment is completed, as well as periodic medical examinations as directed by <private physician name / local health department>.

Since <date> you have not followed this treatment plan, and have refused many efforts from <staff member(s)> to help you follow this treatment plan. Efforts to help you follow your treatment plan included visits and telephone calls to your home by staff members of <private clinic / local health department> on the following days: <list dates / times of visits or calls>, as well as reminders of clinic appointments mailed to your home on <list dates>. You have been offered various incentives and other helpful means to ensure your cooperation with this treatment plan. You have also been educated about the seriousness of your <latent tuberculosis infection / active pulmonary tuberculosis>, as well as the consequences to yourself and others who may be exposed to your disease, if you do not follow your treatment plan.

Public health regulations MCL 333.5203 require that you follow the treatment plan as recommended by your local health department. This letter serves as a **warning** that if you continue to fail in following your treatment plan, you will be subject to further legal action that will include a written **order** to follow your treatment plan. If you still fail to follow your treatment plan, a court order will be sought for your commitment to a designated treatment facility until such time as you complete a full course of anti-tuberculosis treatment, or you are released from commitment by order of a physician MCL 333.5205.

In order to avoid further legal action against you, please call the <name of local health department> at <tel #>, within 7 days of receiving this letter to make arrangements to continue your treatment plan. Please be assured that the staff of <name of local health department> will help you in any reasonable way to ensure your adherence to treatment and the fastest recovery possible.

Sincerely,

<name of health officer or medical director>

***MODEL* (EX PARTE) STRICT OR MODIFIED ISOLATION ORDER**

STATE OF MICHIGAN

IN THE CIRCUIT COURT FOR THE COUNTY OF _____

IN RE: _____

(EX PARTE) ISOLATION ORDER

At a session of the said
Court held in the Courthouse,
City/County of _____,
Michigan on _____.
PRESENT: HONORABLE _____

Pursuant to MCL 333.5205 of the Michigan Public Health Code, the City/County of _____, through its Health Department, having filed an *Ex Parte* petition seeking an Order for a Temporary Isolation and Medical Examination of _____ person (s) pending a hearing for the above-named individual (s) showing that Respondent(s) suffers from active, infectious tuberculosis and would, if released from isolation, pose an immediate danger to the health of others; and the Court being otherwise fully advised in this matter states the following:

IT IS HEREBY ORDERED that the following person(s):

_____
(Name of person subject to isolation.)

hereinafter referred to as the patient,

1) Shall be isolated under the conditions specified in this order until ____(Date)_____, or until this order is rescinded, whichever occurs first.

Violation of or failure to comply with this order may result in civil detention, and is a misdemeanor punishable by imprisonment, fine, or both.

2) This order is issued because the patient has been diagnosed as a case or suspected case of _____.

3) The patient shall be isolated at the following location:

_____.
(Street address where patient is to be isolated.)

4) If the patient is hospitalized, appropriate infection control practices shall be implemented by the hospital. The patient shall not be moved from isolation or to a new isolation location without approval of the local health officer.

5) If the patient is not hospitalized, a copy of the notice attached to this order shall be prominently posted at the entrance(s) to the room(s) where the patient is confined, and the conditions of isolation shall be as follows (only checked items and written instructions shall apply):

___ The patient shall have a bed in a separate room.

___ All persons, except those caring for the patient, shall be excluded from the sick room.

___ The persons caring for the patient shall wear N95 masks during all contact with the patient.

6) The patient or the patient's authorized lawful representative may contact the following representative of the local health department to seek clarification of any part of this order:_____. If the patient or his/her authorized lawful representative believe that the patient is not a case or suspected case as described in paragraph 2 of this order, or objects to the appropriateness of the conditions of isolation contained in this order, the patient or his/her lawful authorized

representative may seek judicial relief from this order and request a formal hearing pursuant to MCL 333.5205 and/or 333.5207.

IT IS SO ORDERED.

_____

CIRCUIT COURT JUDGE

Attachment A
Additional Instructions for
Cases Involving Airborne or Droplet Transmission

___ The patient shall wear a N95 or surgical mask when in the same room as any person not subject to isolation. The patient shall cover his/her nose and mouth with a disposable tissue when coughing or sneezing.

___ Persons caring for the patient shall wear N95 or surgical masks when in the same room as the patient.

Notice

Isolation Order in Effect

Entry restricted to caregivers and health department personnel.

All persons entering shall comply with infection control procedures set forth in the isolation order.

By order of the _____
(Name of county or city)
health department.

MIOSHA

General Industry Safety and Health Division
Michigan Occupational Safety and Health Administration
Department of Labor and Economic Growth

DIVISION INSTRUCTION

DOCUMENT IDENTIFIER: GISHD-COM-05-2R2	DATE: May 22, 2007

SUBJECT: Enforcement Policy and Procedures for Evaluating Occupational Exposure to Tuberculosis (TB)

ABSTRACT

I. **Purpose:** This instruction establishes policies and procedures to ensure uniform enforcement of occupational health regulations when conducting an inspection related to occupational exposures to tuberculosis (TB).

II. **References:**

A. Appendix A: TB Inspection Checklist.

B. Centers for Disease Control (CDC) and Prevention Morbidity and Mortality Weekly Report (MMWR): Guidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in Health-Care Settings, December 30, 2005 / Vol. 54 / No. RR-17.

C. Centers for Disease Control (CDC) and Prevention Morbidity and Mortality Weekly Report (MMWR): Guidelines for Using the QuantiFERON-TB GOLD Test for Detecting *Mycobacterium tuberculosis* Infection, United States, December 16, 2005 / Vol. 54 / No. RR-15; 49.

D. Centers for Disease Control (CDC) and Prevention Morbidity and Mortality Weekly Report (MMWR): Prevention and Control of Tuberculosis in Correctional and Detention Facilities: Recommendation from CDC, July 7, 2006 / Vol. 55 / No. RR-9.

E. Collective Bargaining Agreements: Michigan State Employees Association (MSEA), and Michigan Public Employees (MPE).

F. Department of Health and Human Services, Public Health Service, 42 CFR Part 84; Final Rule.

G. Michigan Occupational Safety and Health Administration (MIOSHA) Field Operations Manual (FOM) most recent version.

H. Michigan Occupational Safety and Health Administration (MIOSHA) Press Release February 2, 2005: MIOSHA Delays Requirement for Annual Fit-testing for Occupational Exposure to Tuberculosis (TB).

I. Occupational Health Standards, Parts 11, 451, 470 and 474.

III. **Scope:** This instruction applies to the General Industry Safety and Health Division (GISHD).

IV. **Distribution:** MIOSHA Staff. General: MIOSHA Web Site accessible.

V. **Cancellations:** This Instruction replaces MIOSHA Division Instruction, Occupational Exposure to Tuberculosis, GISHD-COM-05-2R1 dated July 11, 2005.

VI. **Contact:** John Brennan, Division Director

VII. **Originator:** _____
John Brennan, Division Director

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I. Purpose. This instruction establishes policies and procedures to ensure uniform enforcement of occupational health regulations when conducting an inspection related to occupational exposures to TB. This instruction provides guidelines for GISHD compliance officers to follow when conducting inspections at and preparing citations for worksites where there is potential employee exposure to TB.

II. Scope. This instruction applies to compliance inspections conducted by GISHD.

III. References.

A. Appendix A: TB Inspection Checklist.

B. Centers for Disease Control (CDC) and Prevention Morbidity and Mortality Weekly Report (MMWR): Guidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in Health-Care Settings, December 30, 2005 / Vol. 54 / No. RR-17.

C. Centers for Disease Control (CDC) and Prevention Morbidity and Mortality Weekly Report (MMWR): Guidelines for Using the QuantiFERON-TB GOLD Test for Detecting *Mycobacterium tuberculosis* Infection, United States, December 16, 2005 / Vol. 54 / No. RR-15; 49.

D. Centers for Disease Control (CDC) and Prevention Morbidity and Mortality Weekly Report (MMWR): Prevention and Control of Tuberculosis in Correctional and Detention Facilities: Recommendation from CDC, July 7, 2006 / Vol. 55 / No. RR-9.

E. Collective Bargaining Agreements: Michigan State Employees Association (MSEA), and Michigan Public Employees (MPE).

F. Department of Health and Human Services, Public Health Service, 42 CFR Part 84; Final Rule.

G. Michigan Occupational Safety and Health Administration (MIOSHA) Field Operations Manual (FOM) most recent version.

H. Michigan Occupational Safety and Health Administration (MIOSHA) Press Release February 2, 2005: MIOSHA Delays Requirement for Annual Fit-testing for Occupational Exposure to Tuberculosis (TB).

I. Occupational Health Standards, Parts 11, 451, 470 and 474.

IV. Cancellation. This instruction replaces MIOSHA Division Instruction, Occupational Exposure to Tuberculosis, GISHD-COM-05-2R1 dated July 11, 2005.

V. Originator. This instruction was authorized by John Brennan, Division Director, GISHD.

VI. Definitions. For a complete list of definitions applicable to TB, refer to the list of definitions in the 2005 CDC Guidelines. A copy of these guidelines along with their appendices may be viewed at the CDC website using the following link: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5417a1.htm.

VII. Background.

A. The TB bacillus [*Mycobacterium (M.) tuberculosis*] is carried through the air in tiny infectious droplet nuclei of 1 to 5 microns in diameter. These droplets may be generated when a person with pulmonary and laryngeal TB disease coughs, speaks, sings, sneezes, or spits. *M. tuberculosis* is generally transmitted only through the air, not by surface contact. Normal air currents can keep them airborne for prolonged periods and spread them throughout a room or building. When inhaled by susceptible persons, the mycobacteria in these droplets may become established in the lungs and, in some cases, spread throughout the body. Usually within 2-12 weeks after initial infection with M. *tuberculosis*, the immune response limits further multiplication of the tubercle bacilli and immunologic test result for M. *tuberculosis* infection may become positive. This condition is referred to as latent TB infection (LTBI). Persons with LTBI are usually asymptomatic and are not infectious. After an interval of months, years, or even decades, the initial infection may then progress to clinical illness (i.e. tuberculosis disease).

B. After being present in many countries for decades, cases of TB dropped rapidly in the 1940s and 1950s when the first effective antibiotic therapies for TB were introduced. In 1985 the decline ended and the number of active TB cases in the US (as well as Michigan) began to rise again. According to the CDC, between 1985 and 1992, cases of TB in the US increased by 20 percent. Multi-drug resistant TB posed a particularly high hazard and the highest death rate. Due to greatly improved public health control measures, data reported to the CDC, for the years 1993 through 2001, indicated that the number of diagnosed TB cases had dropped in each of those years. However, an estimated 10 to15 million people in the United States (US) are still infected with *M. tuberculosis* without displaying symptoms (latent TB) and about one in ten of these will develop active (infectious) TB within their lifetimes. In addition, although much research is being done to find a cure, multi-drug resistant TB in particular remains a difficult disease to treat.

C. The prevalence of TB disease is not distributed evenly throughout all segments of the US population. The populations in the US who are still at greatest risk include:

1. People with human immunodeficiency virus (HIV) / acquired immunodeficiency syndrome (AIDS).

2. Foreign-born nationals from countries that still have a high rate of infection.

3. Homeless individuals or people living in high poverty areas.

4. Drug addicts, alcoholics, or prisoners who are incarcerated.

5. Residents in long-term care facilities such as nursing homes.

6. Medical care providers or other health care workers in facilities housing or treating high-risk populations.

D. In health care settings where services are provided to persons who have suspected or confirmed infectious TB disease, health-care workers who come in close contact with infectious TB persons are at greater risk of becoming infected with TB than the general population. Certain high-risk medical or laboratory procedures that are cough inducing or aerosol generating can further increase the risk of infection for health care workers.

VIII. Scope of Inspections.

A. Inspections for occupational exposure to TB shall be conducted in response to employee complaints, referrals, related fatality/catastrophes, or as part of all industrial hygiene compliance inspections conducted in workplaces where the CDC has identified workers as having a greater risk and/or incidence of TB infection than in the general population. The degree of an employee's risk of occupational exposure to TB will vary based on a number of factors discussed in detail in the 2005 CDC Guidelines.

In response to employee complaints about occupational exposure to TB, the Federal Occupational Safety and Health Administration (OSHA) has conducted inspections, and issued citations where appropriate. State Plan States such as MIOSHA, are expected to implement enforcement policies and procedures (that are at least as effective as OSHA) for inspections concerning occupational exposure to TB in settings listed in paragraph E below. Current MIOSHA compliance activities are based on the 2005 CDC Guidelines.

B. Enforcement activities for occupational exposure to TB apply to settings (as listed in paragraph E below) where employees (paid and unpaid including part-time, temporary, contract, and full-time) have the potential for occupational exposure to *M. tuberculosis* through sharing of air space with persons with infectious TB disease, or contact with clinical specimens that might contain TB.

C. In the 2005 CDC Guidelines, health-care settings or health-care-associated settings are defined as places where health care is delivered. The term “health-care setting” includes inpatient settings, outpatient settings, TB clinics, settings in

correctional facilities in which health care is delivered, settings in which home-based health-care and emergency medical services are provided, and laboratories handling clinical specimens that might contain *M. tuberculosis*.

D. Various setting types might be present in a single facility. Healthcare settings include inpatient settings, outpatient settings, and nontraditional facility-based settings.

1. Inpatient settings include:

   a) Patient rooms

   b) Emergency departments (ED)

   c) Intensive care units (ICU)

   d) Surgical suites

   e) Laboratories and laboratory procedure areas

   f) Bronchoscopy suites

   g) Sputum induction or inhalation therapy rooms

   h) Autopsy suites

   i) Embalming rooms

2. Outpatient settings include:

   a) TB treatment facilities

   b) Medical offices

   c) Ambulatory-care settings

   d) Dialysis units

   e) Dental-care settings

3. Nontraditional facility-based settings include:

   a) Emergency medical service (EMS)

   b) Correctional facilities (e.g., prisons, jails, and detention centers) including the medical departments

   c) Home-based health-care and outreach settings

d) Long-term-care settings (e.g., hospice, long term facilities for the elderly)

e) Homeless shelters

f) Law enforcement settings

g) Drug treatment centers

E. Employees Covered:

1. The following employees/health-care workers (paid and unpaid including part-time, temporary, contract, and full-time personnel including transport staff) are covered under the MIOSHA enforcement requirements for occupational exposure to TB, and must be included in their respective employer's TB screening program:

a) Employees who have potential occupational exposure to *M. tuberculosis* through sharing air space with persons with suspected or confirmed infectious TB disease.

b) Employees whose duties involve contact with suspected or confirmed infectious TB patients.

c) Employees who enter airborne infection isolation (AII) rooms whether or not occupied by a TB patient.

d) Employees who participate in aerosol-generating or aerosol-producing procedures (e.g. bronchoscopy, sputum induction, and administration of aerosolized medications.

e) Employees who participate in suspected or confirmed *M. tuberculosis* specimen processing.

f) Employees who install, maintain, or replace environmental controls equipment including heating, ventilation, and air conditioning (HVAC) equipment in areas where persons with TB disease are encountered.

2. Dental health care personnel are covered by this directive if they perform dental treatment on suspected or confirmed active TB patients.

3. Emergency Medical Services (EMS) personnel are covered under this directive if they perform high hazard procedures on known or suspected TB individuals, or if they transport suspected or confirmed infectious TB individuals in an enclosed vehicle.

4. Law enforcement officers and correctional facility staff (custodial and medical) are also covered under this directive if they work in close proximity with known or suspected TB detainees in jails or temporary holding cells.

5. For homeless shelters and drug treatment centers:

   a) If a homeless shelter or a drug treatment center has elected not to treat TB patients in-house, the facility must establish protocols that provide for rapid early identification, followed by immediate transfer of suspected or confirmed TB individuals to a hospital for treatment. The affected employees must also be provided with the required TB training, two-step baseline tuberculin skin tests, and post-exposure medical evaluation, at the minimum.

   b) If a homeless shelter and drug treatment center has elected to treat TB patients in-house, the facility must comply with the full provisions of this directive which requires a comprehensive TB infection program including maintenance of airborne infection isolation rooms, providing complete TB screening program, and complying with the respiratory protection requirements.

IX. Employer Responsibilities.

A. Although there is no specific MIOSHA standard for TB, an employer's obligation to protect its employees from the hazard of TB are those set forth in the Michigan Occupational Safety and Health Act (Act 154 of the Public Acts of 1974, as amended). Rule 408.1011, Section 11(a) of Act 154 requires all employers to furnish to each employee, employment and a place of employment which is free from recognized hazards that are causing, or are likely to cause, death or serious physical harm to the employee.

B. Recommendations for preventing the transmission of TB in health care settings have been established in the 2005 CDC Guidelines. Under these guidelines, the control of TB is to be accomplished through early identification, isolation and treatment of persons with infectious TB; through implementation of TB infection control program and procedures to reduce the risk of health-care-associated (nosocomial) exposures; through education and training of employees; through the use of administrative and/or environmental/engineering controls; and through the use of respiratory protection. MIOSHA believes that these guidelines reflect an appropriate, widely recognized and accepted standard practice to be followed by employers in carrying out their responsibilities under Act 154. A copy of these guidelines can be accessed at the CDC website: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5417a1.htm.

X. Protection of Employees/Health Care Workers Against Occupational Exposure to TB

A. The employer shall develop and implement a TB exposure control program. The program must be reviewed and updated annually. Some portions of the program do not have to be in writing but the program must include the following elements:

1. The TB infection control policy.

2. The respiratory protection program.

3. Employee training.

4. TB screening.

5. Medical surveillance.

6. Use and maintenance of engineering controls.

7. Administrative controls.

8. Examples of administrative controls include:

a) Assigning responsibility for TB infection control in the setting.

b) Conducting a TB risk assessment of the setting.

c) Developing and instituting a written TB infection control plan to ensure prompt detection, airborne precautions, and treatment of persons who have suspected or confirmed TB disease.

d) Ensuring the timely availability of recommended laboratory processing, testing, and reporting of results to the ordering physician and infection control team.

e) Implementing effective work practices for the management of patients with suspected or confirmed TB disease.

f) Ensuring proper cleaning and sterilization or disinfection of potentially contaminated equipment (usually endoscopes).

g) Training and educating employees regarding TB, with specific focus on prevention, transmission, and symptoms.

h) Screening and evaluating employees who are at risk for TB disease or who might be exposed to *M. tuberculosis* (i.e., TB screening program).

i) Applying epidemiologic-based prevention principles, including the use of setting-related infection control data.

j) Using appropriate signage advising respiratory hygiene and cough etiquette.

k) Coordinating efforts with the local or state health department.

9. Examples of environmental/engineering controls include:

a) Primary environmental controls consist of controlling the source of infection by using local exhaust ventilation (e.g., hoods, tents, or booths) and diluting and removing contaminated air by using general ventilation.

b) Secondary environmental controls consist of controlling the airflow to prevent contamination of air in areas adjacent to the source (airborne infection isolation rooms), and cleaning the air by using high efficiency particulate air (HEPA) filtration or ultraviolet germicidal irradiation (UVGI) lamp.

10. The requirements for respiratory protection are outlined in section I below.

B. The employer shall conduct initial and annual risk assessment for the potential of employee exposure to *M. tuberculosis* in each setting, regardless of whether or not patients with suspected or confirmed TB disease are expected to be encountered in the setting. Risk assessments shall be conducted for the entire setting, and for individual units within the setting to identify specific job duties that pose high risk of employee exposure to *M. tuberculosis*. The TB risk assessments will be used to determine the risk classifications of the entire setting and the respective functional units/settings within the overall setting. The risk assessments will also be used to determine the types of controls needed for a setting (See Appendix B of the 2005 CDC Guidelines for a sample TB Risk Assessment Worksheet).

C. A risk classification shall be determined for the entire setting and for functional settings located within the setting. In certain settings (e.g., health-care organizations that encompass multiple sites or types of services), specific areas defined by geography, functional units, patient population, job type, or location within the setting might have different risk classifications. The risk classification shall be used to determine the provision of a TB screening program for employees, and the frequency of screening.

D. For the purpose of TB screening, the three TB screening risk classifications are:

1. Low risk classification applies to settings in which persons with TB disease are not expected to be encountered, and, therefore exposure to *M. tuberculosis* is unlikely. This classification also applies to employees or health-care workers who will never be exposed to persons with TB disease

or to clinical specimens that might contain *M. tuberculosis. Examples include:*

a) Inpatient settings with less than 200 beds, and less than three suspected or confirmed TB patients in the preceding year.

b) Inpatient settings with more than 200 beds, and less than six suspected or confirmed TB patients in the preceding year.

c) Outpatient, outreach, home-based, and non-traditional health-care settings with less than three suspected or confirmed TB patients in the preceding year.

d) TB treatment settings in which persons who will be treated have been demonstrated to have latent TB infection (LTBI) and not infectious TB disease; settings in which a system is in place to promptly detect persons who show signs or symptoms or with signs or symptoms of TB disease, and transfer them to an appropriate setting for treatment; and settings in which no cough-inducing or aerosol-generating procedures are performed.

e) Laboratories in which clinical specimens that might contain *M. tuberculosis* are not manipulated.

2. Medium risk classification applies to settings in which the risk assessment has determined that employees/health care workers will or will possibly be exposed to persons with TB disease or to clinical specimens that might contain *M. tuberculosis*. *Examples include:*

a) Inpatient settings with less than 200 beds, and had three or more suspected or confirmed TB patients in the preceding year.

b) Inpatient settings with more than 200 beds, and had six or more suspected or confirmed TB patients in the preceding year.

c) Outpatient, outreach, home-based, and non-traditional health-care settings that had three or more suspected or confirmed TB patients in the preceding year.

d) TB treatment settings in which persons with TB disease are encountered; and settings in which the criteria for low risk classification are not otherwise met.

e) Laboratories in which clinical specimens that might contain *M. tuberculosis* are manipulated.

f) Potential ongoing transmission classification applies to any setting (or group of employees/health care workers) where evidence suggestive of person-to-person (e.g., patient-to-patient, patient-to-employee, employee-to-patient, or employee-to-employee) transmission of *M. tuberculosis* has occurred in the setting during the preceding year. Evidence of person-to-person transmission of *M. tuberculosis* includes clusters of tuberculin skin test (TST) or blood assay for *M. tuberculosis* (BAMT) conversions, employee/health care worker with confirmed TB disease, increased rates of TST or BAMT conversions, unrecognized TB disease in patients or employees/health care workers, or recognition of an identical strain of *M. tuberculosis* in patients or employee/health care workers with TB disease identified by deoxyribonucleic acid (DNA) fingerprinting. Potential ongoing transmission shall be used only as a temporary classification, shall be investigated immediately by the employer, and appropriate corrective actions taken to resolve the ongoing transmission. After it has been determined that the ongoing transmission has ceased, the setting shall be reclassified as medium risk classification for at least one year before returning to a lower risk classification if necessary.

3. If uncertainty exists regarding whether to classify a setting as low risk or medium risk, the setting shall be classified as medium risk.

E. The employer shall establish and implement a protocol for the early identification of patients/individuals who have suspected or confirmed infectious TB disease (Refer to the 2005 CDC Guidelines for information on how to develop and implement early identification protocol).

F. Medical Surveillance and Frequency of TB Screening for Employees:

1. The employer shall develop and implement an employer-paid medical surveillance program that includes TB screening program.

2. Baseline TB Screening: The employer, in covered workplaces, shall offer baseline TB screening to all current employees and new employees who have potential exposure to *M. tuberculosis* using two-step tuberculin skin tests (TST) or a single blood assay for *M. tuberculosis* (BAMT). Baseline TB screening shall be offered within 10 days of hire, and prior to occupational exposure. TB screening, as well as post-exposure follow-up and treatment evaluations shall be offered at no cost to the employees, and at times and locations convenient to the employees. Administering, reading, and interpreting of the tuberculin skin tests shall be performed by a qualified individual as described in the CDC Guidelines.

3. The employer shall ensure that an employee who declines to accept tuberculin skin tests or blood assay *M. tuberculosis* signs a waiver statement with all of the following provisions.

   a) Understanding of the risk associated with TB.

   b) Acknowledgement of opportunity to accept TB skin testing at no cost to him/her.

   c) Affirmation that she/he is declining TB skin testing.

   d) Future availability of TB skin testing at no cost if desired and if still in at-risk status.

4. Periodic TB Screening (Frequency): Periodic TB screening shall be administered using the following frequency and schedule:

   a) The employer shall offer tuberculin skin tests (TST) or blood assay *M. tuberculosis* (BAMT) annually to employees/health-care workers in settings where risk assessment has determined that employees/heath-care workers will or will possibly be exposed to persons with TB disease or to clinical specimens that might contain *M. tuberculosis*.

   b) For low risk settings or employees/health care workers: Annual TB screening is not required after baseline screening for employees/health care workers whose duties do not include contact with suspect or confirmed TB patients or laboratory/clinical specimens that might contain *M. tuberculosis.*

   c) For medium risk settings or employees/health care workers: In addition to baseline TB screening, the employer shall offer tuberculin skin tests (TST) or blood assay *M. tuberculosis* (BAMT) annually to employees/health care workers who have negative baseline test results.

   d) In the event of a potential ongoing transmission, the employer shall offer affected employees TB testing to be performed every 8-10 weeks until the cause(s) of the transmission have been corrected, and no additional evidence of ongoing transmission is apparent.

5. A "tuberculin skin test" (TST) means the administering of intradermal injection (Mantoux method) of tuberculin by designated, trained personnel.

6. A worker with documented positive tuberculin skin test result, or a worker who has received treatment for TB disease, or who has received

preventive therapy for latent TB infection, is exempt from TB screening. Instead of participating in annual TB testing, such workers shall receive chest radiograph (chest x-ray) to exclude TB disease; must complete a medical questionnaire annually for the purpose of identifying any symptoms suggestive of TB disease; and must periodically be provided with information about the signs and symptoms of TB and the need for immediate medical evaluation by a physician or a trained health care professional to determine if the worker is experiencing symptoms of TB disease. Treatment for LTBI should be considered in accordance with CDC guidelines.

7. Reassessment following exposure or change in health: Workers who experience exposure to individuals who have suspected or confirmed infectious TB disease, and for whom infection control precautions have not been taken, shall be managed in accordance with 2005 CDC Guidelines and as outlined in subsection (7) below. Employees who develop symptoms of TB disease shall be immediately evaluated according to the 2005 CDC Guidelines.

8. Case management of infected employees: A covered employer must implement an evaluation and case management program (at no cost to employees) of infected workers as follows:

   a) Conversion to a positive TB test shall be followed-up promptly by appropriate medical, laboratory, and radiographic evaluations to determine whether the employee has infectious TB disease.

   b) An employee who exhibits signs or symptoms of active TB (e.g., weight loss, night sweats, bloody sputum, anorexia, or fever) shall be evaluated promptly for TB disease. The employee should not be allowed to return to work until a diagnosis of infectious TB disease has been excluded, or until the employee is on therapy and has been determined by a physician to be noninfectious.

   c) The employer shall make reasonable accommodation (e.g., alternative job assignments or voluntary transfer) for employees who are known to be HIV-infected or otherwise severely immunosuppressed, and who work in settings where they may be exposed to *M. tuberculosis*. Such employees shall be referred to employee health professionals who can individually counsel the employees regarding their risk for TB disease. Upon the request of the immunocompromised employee, the employer shall offer, but not compel, a work setting in which the employee would have the lowest possible risk for occupational exposure to *M. tuberculosis*. Evaluation of these situations should also include consideration of

the provisions of the Americans with Disabilities Act of 1990 and other applicable federal, state, and local laws.

d) Emergency Medical Service (EMS) personnel should be included in the follow-up contact investigations of patients with infectious TB disease. The Ryan White Comprehensive AIDS Resource Emergency Act of 1990 (Public law 101-381) mandates notification of EMS personnel after they have been exposed to a patient with suspected or confirmed infectious TB disease (Title 42 U.S. Code 1994) (http://hab.hrsa.gov/data2/adap/introduction.htm).

G. Worker Education and Training: The employer shall provide for all employees who have actual or potential exposure to *M. tuberculosis* or patients with infectious TB, training and information to ensure employee knowledge of issues listed (1) through (5) of this subsection below. Training on TB should be repeated as needed.

1. Mode of TB transmission.

2. Recognizing signs and symptoms of TB disease.

3. TB Screening.

4. Post exposure medical surveillance protocols and therapy.

5. Site specific infection control protocols including the purpose and proper use of control methods such as airborne infection isolation (AII) rooms, ventilation, respiratory protection, etc.

H. Environmental/Engineering Controls: The use of an engineering control method must be based on its ability to abate the hazard.

1. Individuals with suspected or confirmed infectious TB disease must be placed in AII rooms. High hazard procedures on individuals with suspected or confirmed infectious TB disease must be performed in AII treatment or isolation rooms, booths, and/or hoods. AII refers to a negative pressure room or an area that exhausts room air directly outside or through HEPA filters if recirculation is unavoidable.

2. Facilities that intend to transfer suspected or known TB individuals to another facility for treatment and therapy do not need to establish AFB isolations rooms. Other measures (such as administration controls, respiratory protection, and training, etc.) shall however, be used to protect employees from exposure to TB.

3. Isolation and treatment rooms in use by individuals with suspected or confirmed infectious TB disease shall be kept under negative pressure to

induce airflow into the room from all surrounding areas (e.g. corridors, ceiling plenums, plumbing chases, etc.) See the CDC Guidelines for a description of engineering controls as well as methods for testing the effectiveness of these controls.

4. The employer must assure that AII rooms are maintained under negative pressure. At a minimum, the employer must use non-irritant smoke trails or some other indicator to demonstrate that the direction of the airflow is from the corridor into the isolation or treatment room with the door closed. Such demonstration must be conducted at least monthly for rooms that are not being used for TB patients but could potentially be used for such patients. The 2005 CDC Guidelines recommend daily negative pressure checks when a TB isolation room is undergoing changes to the ventilation system, or while the room is being used for TB isolation. If an anteroom exists, direction of the airflow must be demonstrated at the inner door between the isolation/treatment room and the anteroom.

5. Air exhausted from AII or treatment rooms must be safely exhausted directly outside, and not re-circulated into the general ventilation system.

6. In circumstances where air recirculation is unavoidable, HEPA filters must be installed in the duct system from the room to the general ventilation system. For these HEPA filters, a regularly scheduled monitoring program should be implemented to demonstrate as-installed effectiveness. The monitoring program should include:

   a) A recognized field-test method.

   b) Acceptance criteria.

   c) Testing frequency.

7. The air handling system shall be appropriately marked with a TB warning sign in locations where maintenance personnel would have access into the ducts, fans, or filters for maintenance or repair activities.

8. In order to avoid leakage, all potentially contaminated air which is ducted through the facility from TB isolation and treatment rooms, must be kept under negative pressure until it is discharged safely outdoors (i.e. away from occupied areas and air intakes), or decontaminated by a recognized process (e.g. HEPA filter) before being re-circulated back into the isolation/treatment room or into the general ventilation system. HEPA filters must be properly installed and maintained. UV radiation as a sole means of decontamination shall NOT be used. The 2005 CDC Guidelines allow the use of UV radiation in waiting rooms, emergency rooms,

corridors, ventilation ducts, and the like where patients with undiagnosed TB could potentially contaminate the air.

9. The opening and closing of doors in an occupied TB AII or treatment room which is not equipped with an anteroom compromises the ability to maintain negative pressure in the room. For these rooms, the employer must utilize a combination of controls and practices to minimize spillage of contaminated air into the corridor or surrounding areas. Recognized controls and practices include, but are not limited to: minimizing entry to the room; adjusting the hydraulic closer to slow the door movement and reduce displacement effects; adjusting doors to swing into the room where fire codes permit; avoiding placement of room exhaust intake near the door; and using telephones or intercom to communicate with the patients, etc.

10. If high-hazard procedures are performed in AII or treatment rooms without benefit of source control ventilation or local exhaust ventilation (e.g. hood, booth, tent, etc.), and droplets are released into the environment (e.g. through coughing), then a purge time interval must be imposed during which personnel must use a respirator when entering the room. Nonessential personnel and individuals must be restricted from entering the room during the purge time interval.

11. Interim or supplemental ventilation units equipped with HEPA filters as described in the 2005 CDC Guidelines are acceptable.

I. Respiratory Protection, Part 451, 29 CFR 1910.134.

1. 29 CFR 1910.134 (a)(2) of the Respiratory Protection Standard requires that respirators be provided by the employer when such equipment is necessary to protect the health of the employee. The employer shall provide respirators, which are applicable and suitable for the purpose intended. The employer shall be responsible for the establishment and maintenance of a respiratory protection program which shall include the requirements outlined in paragraph (c) of the respiratory protection standard. Work settings [described in VIII (E)] where use of a TB respirator is necessary or required, shall comply with all applicable provisions of Part 451.

2. Requirements for a Minimally Acceptable Respirator Program.

a) The National Institute for Occupational Safety and Health (NIOSH) has determined that the minimal acceptable respirators for protection against TB infections are: the N-95 air purifying, particulate respirator certified under 42 CFR Part 84, Subpart K. HEPA, N-99 or N-100 respirators are also acceptable.

b) Affected employees must wear appropriate respirators as indicated above in the following circumstances:

(1) When employees enter rooms occupied by individuals who have suspected or confirmed infectious TB.

(2) When employees enter an AII room after discharge of TB patients, and before the air in the room has been properly purged.

(3) When employees are present during the performance of high hazard procedures on individuals who have suspected or confirmed infectious TB. Examples of high hazard procedures include: aerosolized medication treatment, bronchoscopy, sputum induction, endotracheal intubations and suction procedures, and autopsies.

(4) When emergency medical response personnel or other transport, in a closed vehicle, an individual with suspected or confirmed infectious TB.

c) When use of respiratory protection (including disposable respirators) is required, a written respiratory protection program must be developed and implemented in accordance with Part 451, 1910.134(c).

d) If a facility chooses to use disposable respirators as part of their respiratory protection program, their reuse by the same health care worker is permitted as long as the respirator maintains its structural and functional integrity, and the filter material is not physically damaged or soiled. The facility must address the circumstances in which a disposable respirator will be considered to be contaminated and not available for reuse.

3. Selection of Respirators

a) Respiratory protective devices used in health-care settings for protection against *M. tuberculosis* shall meet the following criteria:

(1) Certified by National Institute for Occupational Safety and Health (NIOSH) as a non-powered particulate filter respirator (N-, R-, or P-95, 99, or 100), including disposable respirators, or powered air-purifying respirators (PAPR) with high efficiency filters.

(2) Ability to adequately fit respirator wearers (e.g., a fit factor of >100 for disposable and half-mask respirators) who are included in a respiratory protection program.

(3) Ability to fit the different facial sizes and characteristics of employees. (This criterion can usually be met by making respirators available in different sizes and models.)

b) The fit of filtering face piece respirators varies because of different facial types and respirator characteristics. Assistance with selection of respirators should be obtained through consultation with respirator fit-testing experts, CDC, occupational health and infection control professional organizations, peer-reviewed research, respirator manufacturers, and advanced respirator training courses.

c) The ability to be qualitatively or quantitatively fit tested in a reliable way to obtain a face-seal leakage of $\leq$10%.

d) The ability to be checked for face piece fit, in accordance with MIOSHA standards and good industrial hygiene practice, by the workers each time they put on their respirators.

J. Employee Medical Records and Trade Secrets, R. 325.3451 through R 325.3476-Access to Employee Medical and Exposure Records:

1. A record concerning employee exposure to TB is an employee exposure record within the meaning of the above rules.

2. A record of TB skin test results, as well as records of employee medical evaluation and treatment, is considered employee medical records within the meaning of these rules. Where known, the worker's exposure record should contain a notation of the type of TB to which the employee was exposed (e.g. multi-drug resistant TB).

K. Accident Prevention Signs and Tags, Part 476, Rule 4501:

1. In accordance with Part 476, Rule 4501 (4) (b), a warning sign shall be posted outside the airborne infection isolation (AII) or treatment room. The warning sign must contain a signal word (i.e. "STOP," "HALT," "NO ADMITTANCE") or a biological hazard symbol, as well as a major message (e.g. "special respiratory isolations," “respiratory isolations," or “airborne infection isolation”). A description of the necessary precautions to be taken (e.g. "respirators must be donned before entering") or a message referring people to the nursing station for pre-entry instruction into AII rooms must also be posted outside the room.

2. The employer shall affix biological hazard tags on air handling component (e.g. fans, ducts, filters) to identify TB hazards to employees who work on the air handling systems that transport TB contaminated air. (See 2005 CDC Guidelines for additional information).

L. Recording and Reporting of Occupational Injuries and Illnesses, Part 11, R 408.22101 – R 408.22141.

1. TB Infection (positive TB screening results) and TB disease are both recordable on the MIOSHA 300 log for the designated high-risk workplaces described in Section VIII (E). A positive skin test for TB, even on baseline testing (except pre-employment screening), is recordable on the MIOSHA 300 log because there is a presumption of work-relatedness in these settings, unless there is clear documentation that an outside exposure had occurred.

2. If an employee's TB infection, which has been entered on the MIOSHA 300 log, progresses to TB disease during the five-year maintenance period, the original entry for the infection shall be updated to reflect the new information. Because it is clinically difficult to determine if TB disease resulted from an earlier exposure indicated by the earlier skin test conversion, or from subsequent exposures, only one case should be entered to avoid double counting.

3. If a setting provides a TB screening within two weeks of employment and the test is positive, it does not have to be recorded on the MIOSHA 300 forms. However, the initial test must be performed prior to any potential workplace exposure within the initial two weeks of employment.

4. In accordance with Part 56 of Public Act 368 of 1978, the employer or representing physician is required to submit reports of known or suspected occupation TB infection or disease to MIOSHA.

XI. Scheduling of Inspections.

A. The MIOSHA TB specialist shall conduct all TB fatalities, catastrophes or programmed inspections. TB related complaints and referrals should be investigated by industrial hygienists (IH) in the appropriate health district offices with the approval of the health supervisor and in consultation with the MIOSHA TB specialist.

B. Complaints specifically alleging an existing TB hazard at any of the workplaces listed in Section VIII (E) will always require an evaluation of TB hazards at that site.

C. Complaints, referrals or limited scope inspections at any of the facilities defined in Section VIII (E) may be expanded to include an evaluation of TB hazards at the worksite. However the scope of an inspection shall NOT be expanded to include a TB investigation if the facility has NOT had a documented TB case within the previous six (6) months preceding the date of the inspection.

D. If one of the facilities listed in Sections IX (B) has had a documented case of active TB within the previous six (6) months, the scope of the inspection SHALL be expanded to address TB related issues. The assigned IH must consult with the MIOSHA TB specialist during the investigation and when writing citations related to TB exposures.

E. All TB investigations must include a review of the employer's plans to protect employees from TB exposure.

1. Employee interviews and worksite observations shall be used to verify the employer's conformance with the employer's plans for employee TB protection.

2. Some portions of the plan/program do not have to be in writing but all plans should include the following elements.

a) TB exposure control plan

b) The respiratory protection program.

c) Employee training.

d) TB screening.

e) Medical surveillance.

f) Use/maintenance of engineering controls.

g) Administrative controls.

F. The appropriate health supervisor must review all case files that include a TB investigation and related citations. The health supervisor should consult with the TB specialist whenever reviewing a case file that includes a TB investigation. In addition, the appropriate Safety and Health Manager as well as the GISHD Director must review all case files that include citations related to TB. Some files may also need to be reviewed by additional agency or department administrators.

XII. Procedures for Inspections That Will or May Include a TB Investigation.

A. Normal inspection procedures as described in the MIOSHA FOM shall be followed along with additional steps described in subsections (B) through (G) below.

B. When entering a hospital or other setting listed in Section VIII (E) the IH shall present credentials and explain the nature/scope of the investigation to the Administrator, Medical Director, or other person in charge of the facility.

C. In addition, the IH shall request the participation, during the opening conference, of the infection control director (if there is one) and/or any other employee who is responsible for administering or implementing portions of the employer's occupational health control program. These may include the training director, facilities engineer, head of nursing, etc.

D. During the opening conference the IH shall first establish whether or not the facility has had an active TB case within the six (6) months preceding the opening conference date. If no active TB case was reported at the worksite within the previous six (6) months, complaints or referrals will NOT be expanded to include TB. If an active TB case was reported at the worksite within the previous six (6) months, complaints and referrals will be expanded at that time to include an evaluation/review of the employer's TB Exposure Control Program.

E. Although employers are not required to maintain all elements of a general TB Exposure Control Program in writing, the IH should ask if the employer has developed a complete written program. If the employer has a written plan, the plan should be reviewed to assist in determining a facility's implementation of its own established policies. The IH shall also verify implementation of the employer's program through employee interviews and if feasible, direct observations. Professional judgment shall be used to identify which areas of a facility (e.g., emergency rooms, respiratory therapy areas, bronchoscopy suites, morgue, etc.) should be evaluated during the walk-through phase of the investigation. If a deficiency is found in the implementation of the TB Exposure Control Program (in accordance with this instruction) a citation shall be proposed for the deficiency.

F. If the facility has not developed an overall written TB Exposure Control Program, or if the written program is found inadequate in any respect, the IH shall stress the need and importance of developing and implementing protocols to ensure the early identification, diagnostic evaluation and effective treatment of employees as well as patients that might have infectious TB, in order to prevent transmission of TB from patients to employees. As long as all required elements are developed and implemented, the lack of an overall written program will not result in a citation being issued. However, citations will be issued for failure to have portions of the overall program in writing, if a specific standard requires that a

particular program element must be written as well as implemented; i.e. Part 451, Respiratory Protection requires that a respiratory protection program must be written as well as implemented.

G. IHs who perform smoke-trail visualization tests to evaluate the effectiveness of the ventilation provided in a TB AII room should follow appropriate protocol prior to performing the test. The IH must be prepared to present to the employer a material safety data sheet (MSDS) for the smoke that is released during a smoke-visualization test. Evaluation of the ventilation may include other safe methods that determine the adequacy or effectiveness of the ventilation, but may not include actual entry into a room that would potentially expose an IH to TB.

XIII. Protective Measures for IH Performing TB Inspections.

A. Health supervisors shall ensure that IHs performing TB related investigations are familiar with the CDC Guidelines and terminology and are adequately trained on health care work settings. Consultation with the TB Specialist should be done prior to beginning a TB investigation.

B. All IHs in GISHD shall be offered the baseline two-step tuberculin skin test (TST) or a single blood assay for *M. tuberculosis* (BAMT) prior to conducting a TB investigation. All compliance officers in GISHD shall be offered a chance to participate in annual TB screening unless the officer has tested positive on a previous test.

C. Compliance IHs shall avoid contact with an individual who has infectious TB. If an IH is inadvertently exposed to an individual who has infectious TB, a follow-up examination in accordance with the 2005 CDC Guidelines must be provided.

D. A professional licensed health care provider shall perform all TB skin tests, medical surveillance, and post-exposure follow-up medical evaluations.

E. IHs shall NOT enter AII rooms occupied by TB patients in order to evaluate employer compliance with MIOSHA regulations.

F. IHs shall never intentionally engage in any activities that involve potential exposure to TB. The existence of hazards related to TB exposures and the adequacy of work practices shall be established through employee interviews, a review of the employer's written and/or implemented policies and procedures, as well as personal observation of work practices, in a manner that prevents exposure; i.e. through an observation window.

G. If an AII room is occupied by a patient with confirmed or suspect TB disease or the room has not been adequately purged when a smoke-trail test is performed, the IH must assume that the isolation room is not safe for entry.

XIV. Recording in IMIS.

A. A MIOSHA TB-related investigation is any occupational health inspection conducted for the purpose of investigating the occurrence or alleged occurrence of employee exposure to TB, or any health related inspection that results in a TB-related citation.

B. When a TB investigation is conducted, a MIOSHA-1-GISHD (Inspection Report) must be completed by the IH as done in any inspection. However, the code "N 2 TB" must also be entered in Item 42, Optional Information.

XV. Citation Policy.

A. Relevant chapters of the FOM must be followed when preparing and issuing citation for hazards related to TB.

B. The rules and standards listed below may be cited when TB hazards or violations are found in the target workplaces. Employers must comply with the provisions of these requirements in particular, whenever an employee may be occupationally exposed to TB.

C. Act 154 of 1974, as amended, R 408.1011, Section 11(a) (General Duty Clause).

D. Part 451, Respiratory Protection, 1910.134.

E. Part 476, Rule 4501, Accident Prevention Signs and Tags.

F. Part 470, Employee Medical Records and Trade Secrets, R 325.3451 through R 325.3476.

G. Part 11, Recording and Reporting Occupational Injuries and Illnesses, R 408.22101 through R 408.22142.

XVI. Violations and Citation Guidelines.

A. All elements of subsections B through G below, in this section, must be addressed by employers at high risk settings described in Section VIII (E) to ensure adequate protection of employees from occupational TB hazards. Violations of these MIOSHA rules and requirements will frequently be classified as serious.

B. Guidelines for Citing Violations of the General Duty Clause: [L 408.1011(a) of Act 154, Public Act of 1974 as amended].

1. Section 11(a) of Act 154 provides: "An employer shall furnish to each employee, employment and a place of employment which is free from recognized hazards that are causing, or are likely to cause, death or serious physical harm to the employees."

2. Section 11(a) citations must meet the requirements outlined in the MIOSHA FOM and shall be issued only where there is a hazard which cannot be cited under, and abated by compliance with, a specific MIOSHA standard.

3. Occupational exposure to TB is a serious and recognized hazard and feasible methods do exist to prevent, eliminate, or reduce employee exposure to TB.

4. Industry recognition, for the purposes of citing section 11(a) for TB issues, means the employer's recognition of the hazard of employees being infected with TB through exposures detailed below in subsections (a) and (b) of this section. The high-risk workplaces listed in Section VIII (E) generally acknowledge the determination of the TB hazards and exposure controls as described by CDC, which is the nationally recognized authority on TB. The employer's TB Exposure Control Program or a generic infection control program can constitute further evidence of knowledge and hazard recognition.

5. The presence of a hazard, not simply the absence of a particular means of abatement, is the basis for the general duty clause citation. All applicable abatement methods identified for correcting the same hazard shall be issued under a single Section 11(a) citation.

6. If a citation for a violation of the General Duty Clause is justified, violations/deficiencies related to the requirements of early identification protocols, TB skin testing, post exposure medical evaluation, case management of infected employees, employee TB education and training, and environmental/engineering controls, shall be cited under section 11(a) of Act 154.

7. Citations for violations of Section 11(a) shall be issued only to employers whose employees work in the types of settings described in Section VIII (E) and whose employees have one or both of the following exposures.

   a) Potential exposure to the exhaled air from an individual with suspect or confirmed pulmonary TB disease.

   b) Exposure, without protection, to a high hazard procedure performed on an individual with suspected or confirmed infectious TB disease, and which has the potential to generate infectious airborne droplet nuclei. Examples of high hazard procedures include: aerosolized medication treatment, bronchoscopy, sputum induction, endotracheal intubation and suctioning procedures, emergency dental endoscopic procedures, and autopsies.

c) Exposure within the context of this directive means the condition of being subjected to air potentially contaminated with airborne droplet nuclei of *M. tuberculosis*.

d) A suspect TB case is one in which the setting has identified an individual as having symptoms consistent with TB. The CDC has identified the symptoms to be: productive cough, coughing-up blood, and weight loss, loss of appetite, lethargy/weakness, night sweats, or fever. Each covered setting may establish its own criteria for early identification of suspect individuals.

8. The following language may be used in writing a general duty citation:

a) "MCL 408.1011(a), Act 154, Public Act of 1974, as amended: On [specify date of violation] the employer failed to furnish each employee, employment and a place of employment which was free from recognized hazards that were causing, or were likely to cause, death or serious physical harm to the employees. Workers [specify job classifications] who were working in [specify department, ward, unit or location], were exposed to the hazard of being infected with *M. tuberculosis* through unprotected contact with [specify group such as patients, inmates, clients, etc.] who was/were infectious or suspected to be infectious with *M. tuberculosis*. [Describe your observations or list the deficiencies determined.]"

b) "Abatement Requirement: Ensure that employees are protected from occupational TB exposure and infection. Feasible abatement methods for reducing this hazard, as recommended by the Centers for Disease Control and Prevention, include, but are not limited to: [list abatement methods]."

C. Guidelines for Citing Violations of Part 451, 29 CFR 1910.134, Respiratory Protection Standard.

Violations of respiratory protection for TB shall be cited under Part 451, and shall follow the policies and guidelines established in the most recent MIOSHA Directive or administrative policies.

D. Guidelines for Citing Violations of Employee Medical Records and Trade Secrets Standards, R. 325.3451 through R 325.3476.

During all TB investigations, these records shall be handled in compliance with the requirements of the Employee Medical Records and Trade Secrets Standard.

E. Guidelines for Citing Violations of Part 476, Rule 4501 (4)(b): If a citation is warranted under Part 476, Rule 4501 (4)(b), the following language may be used in the violation statement:

"SIGNS AND TAGS, PART 476, Rule 4501(4)(b): Appropriate hazard warning signs were not used to signify the actual or potential presence of a biohazard and to identify equipments, containers, rooms, materials, experimental animals, or combinations thereof, which contained, or were contaminated with viable hazardous agents. The warning signs posted outside respiratory isolation or treatment rooms [indicate room numbers, building wing, department, unit, etc.] did not contain a signal work or a biological hazard symbol, in conjunction with a major message and the necessary precautions to be taken before entry into the isolation or treatment room."

F. Guidelines for Citing Violations of TB Recordkeeping: Recording and Reporting of Occupational Injuries and Illnesses, Part 11, R 408.22101 – R 408.22141

TB recordkeeping violations shall be cited in accordance with MIOSHA FOM.

Appendix A is a blank copy of the MIOSHA TB Inspection Checklist. This checklist must be filled out and included in the case file of all TB inspections.

APPENDIX A

Michigan Department of Labor & Economic Growth
Michigan Occupational Safety and Health Administration
(MIOSHA)

TB INSPECTION CHECKLIST

SECTION A – GENERAL INFORMATION

ESTABLISHMENT NAME: _____

WORKSITE ADDRESS: _____

_____

_____

INSPECTION NO.: _____

DATE OF INSPECTION: _____

IH NAME: _____ DISTRICT: _____

1) Establishment is: (circle whichever applies)
   a) Health care setting
   b) Correctional institution
   c) Long-term care facility for the elderly
   d) Homeless shelter
   e) Drug treatment center
   f) Emergency medical service
   g) Police department
   h) Dental office
   i) Doctors office
   j) Local public health clinic
   k) Other (describe) _____

2) Has establishment had any suspected or confirmed TB cases within the past six (6) months? Y N

3) Is this inspection due to a TB complaint, a TB referral, or programmed inspection? Y N

4) Do affected workers in the establishment have "exposure" to any of the following:

   a) Exhaled air (with or without the use of appropriate protection) from individuals with suspected or confirmed pulmonary TB, or laboratory specimens that might contain *M. tuberculosis*? Y N

   b) High hazard procedures such as aerosolized medication treatment, bronchoscopy, sputum induction, endotracheal intubation and suction procedures, emergency dental, endoscopic procedures, autopsies, pulmonary function testing, etc. (with or without appropriate protection) or handling of laboratory specimens that might contain *M. tuberculosis*? Y N

NOTE: If "YES" to question #2, #3, or #4 continue. If "NO" to question #2, #3, or #4 STOP and discontinue TB investigation.

5) Does establishment have a TB infection control program? Y N

6) Is the infection control program in writing? Y N

7) Does establishment have a designated infection control coordinator? Y N

   If yes, Name and Title of Infection Control Coordinator:

   _____

8) Has establishment performed TB risk assessment for the work units or settings within the establishment? Y N

9) Based on the TB risk assessment, what is the risk classification for the overall establishment/setting? (See definitions below and check whichever applies.)

a) Low Risk: [ ]

In patient settings with <200 beds, and <3 suspected/confirmed TB patients in previous year; or equal to/greater than 200 beds, and <6 suspected or confirmed TB patients; or settings in which persons with TB disease are not expected to be encountered, and, therefore, exposure to *M. tuberculosis* is unlikely. This classification also applies to employees or health-care workers who will never be exposed to persons with TB disease or to clinical specimens that might contain *M. tuberculosis.*

b) Medium Risk: [ ]

In patient settings with <200 beds, and more than or equal to 3 suspected/confirmed TB patients in previous year; or equal to or greater than 200 beds, and more than or equal to 6 suspected or confirmed TB patients; or settings in which persons with TB disease are expected to be encountered, and, therefore, exposure to *M. tuberculosis* is likely. This classification also applies to employees or health-care workers who will be exposed to persons with TB disease or to clinical specimens that might contain *M. tuberculosis.*

c) Potentially Ongoing Transmission: [ ]

Any setting (or group of employees/health care workers) where there is evidence suggestive of person-to-person (e.g., patient-to-patient, patient-to-employee, employee-to-patient, or employee-to-employee) transmission of *M. tuberculosis* has occurred in the setting during the preceding year. Evidence of person-to-person transmission of *M. tuberculosis* includes clusters of tuberculin skin test (TST) or blood assay for *M. tuberculosis* (BAMT) conversions, employee/health-care worker with confirmed TB disease, increased rates of TST or BAMT conversions, unrecognized TB disease in patients or employees/health-care workers, or recognition of an identical strain of *M. tuberculosis* in patients or employee/health-care workers with TB disease identified by deoxyribonucleic acid (DNA) fingerprinting. Potential ongoing transmission classification shall be used only as a temporary classification.

10) Based on the TB risk assessment, does any unit or settings within the establishment have a Medium Risk classification? Y N

If Yes, indicate the work unit, department, or setting: _____

11) Based on the TB risk assessment, does any unit or settings within the establishment have a Potentially Ongoing Transmission classification? Y N

Yes, indicate the work unit, department, or setting: _____

SECTION B – ITEMS COVERED UNDER GENERAL DUTY CLAUSE – 408.1011(a)

Note: If establishment has never had an active TB case, and there is no evidence of employee conversion based on TB skin test or blood assay TB test result, general duty citation shall not be issued since there is no evidence of TB hazard present. Recommendations should, however, be made to institute and implement TB exposure control program.

For each item below circle (AV) if the (N) response applies, and there is a violation of the corresponding item. (AV = Alleged Violation)

Early Identification Protocol

Employee Medical Surveillance and TB Screening

Does the establishment have/implement an Early Identification Protocol to identify Patients/individuals who may have suspected or confirmed TB disease? Y N AV

If yes, describe: _____
_____
_____
_____

1) For establishments who have employees with potential exposure to *M. tuberculosis*, does the employer offer two-step baseline tuberculin skin test (TST) or a single blood assay for *M. tuberculosis* (BAMT) to all current potentially exposed employees and all new employees within 10 days of hire, and prior to occupational exposure. Y N AV

2) Is TB screening offered at no cost to the employee? Y N AV

3) Is TB screening offered at times and locations convenient to the workers? Y N AV

4) Is TB screening administered, read, and interpreted by a qualified individual? Y N AV

5) Does each employee who declines to accept tuberculin skin test or blood assay *M. tuberculosis* sign a waiver statement? Y N AV

6) Does the waiver statement contain the following provisions:

   a) Understanding of the risk associated with TB. Y N AV

   b) Acknowledgement of opportunity to accept TB skin testing at no cost to him/her. Y N AV

   c) Affirmation that she/he is declining TB skin testing. Y N AV

d) Future availability of TB skin testing at no cost if desired and if still in at-risk status. Y N AV

TB Screening - Low Risk Settings

Does the employer offer two-step baseline tuberculin skin test (TST) or a single blood assay *M. tuberculosis* (BAMT) to all current potentially exposed employees and all new employees prior to exposure? Y N AV NA

Note: Annual TB screening is not required for low risk settings.

TB Screening - Medium Risk Settings

1) Does the employer offer two-step baseline tuberculin (TST) or a single blood assay *M. tuberculosis* (BAMT) to all current potentially exposed employees and all new employees prior to exposure? Y N AV NA

2) Does the employer offer annual tuberculin skin test (TST) or blood assay for *M. tuberculosis* (BAMT) to all current potentially exposed employees? Y N AV NA

TB Screening - Settings with Potentially Ongoing Transmission

1) Does the employer offer two-step baseline initial baseline tuberculin skin test (TST) or a single blood assay *M. tuberculosis* (BAMT) to all current potentially exposed employees and all new employees prior to exposure? Y N AV NA

2) In the event of a potential ongoing transmission, does/did the employer offer affected employees with tuberculin skin test (TST) or blood assay for *M. tuberculosis* (BAMT) performed every 8 - 10 weeks until the cause(s) of the transmission have been corrected, and no additional evidence of ongoing transmission is apparent. Y N AV NA

NOTE: A worker with documented positive tuberculin skin test result, or a worker who has received treatment for TB disease, or who has received preventive therapy for latent TB infection, is exempt from TB screening. Instead of participating in annual TB testing, such workers shall receive chest radiograph (chest x-ray) to exclude TB disease; must complete a medical questionnaire annually for the purpose of identifying any symptoms suggestive of TB disease; and must periodically be provided with information about the signs and symptoms of TB and the need for immediate medical evaluation by a physician or a trained health care professional to determine if the worker is experiencing symptoms of TB disease. Treatment for LTBI should be considered in accordance with CDC guidelines.

Post-Exposure Evaluation/Reassessment

Check here [ ] and skip this subsection if there has <u>not</u> been a documented employee exposure incident. Otherwise, complete this section.

1) Does the employer reassess employees who experience incidental exposure (with or without appropriate protection) to individuals with suspected or confirmed infectious TB?	Y	N	AV	NA
2) Does the employer implement immediate follow-up evaluations (physical, laboratory, and radiographic) of employees who convert to positive TB skin test in order to determine whether the employee has infectious TB disease?	Y	N	AV	NA
3) Does the employer re-evaluate and manage employees who develop symptoms of TB disease?	Y	N	AV	NA
4) Does the employer institute work restrictions for infectious TB employees?	Y	N	AV	NA

<u>Worker Education and Training</u>

1) Have all current workers been provided training and information on TB related hazards?	Y	N	AV	
2) Does the facility have a provision to train new employees?	Y	N	AV	
3) Does the training cover the following topics:				
a) Mode of transmission?	Y	N	AV	
b) Signs and symptoms of TB disease?	Y	N	AV	
c) Medical surveillance and therapy?	Y	N	AV	
d) Site-specific protocols for TB exposure control (e.g.: signs, general precautions, etc.)?	Y	N	AV	
e) Purpose and proper use of engineering controls (i.e. AFB isolation rooms, exhaust ventilation, etc., if applicable)?	Y	N	AV	NA
f) Purpose and proper use of respiratory protection?	Y	N	AV	
g) Recognizing and reporting to a designated person, patients or clients with symptoms suggestive of infectious TB?	Y	N	AV	
h) Post-exposure protocols to be followed in the event of an exposure incident?	Y	N	AV	

<u>Engineering/Environmental Controls</u>

Check here [ ] and skip this subsection if the facility transfers TB patients to another facility for treatment, and does not use isolation rooms for TB patients. Otherwise, complete this section.

1) Are individuals with suspected or confirmed infectious TB disease placed in airborne infection isolation (AII) rooms?	Y	N	AV	NA
2) Are high hazard procedures on individuals with suspected or confirmed infectious TB performed in AII rooms, booths or hoods?	Y	N	AV	NA
3) Are the isolation/treatment rooms (when in use by individuals with suspected or confirmed infectious TB disease) kept under negative pressure from all surrounding areas?	Y	N	AV	NA
4) Are the isolation/treatment rooms equipped with local exhaust or source control ventilation (e.g. hood, booth tent, etc.) and used during high hazard procedures (e.g. cough-induced procedures)?	Y	N	AV	NA
5) If the response to (d) above is NO, is there a time interval imposed during which personnel must use a respirator when entering the room?	Y	N	AV	NA
6) Is air from AII rooms exhausted directly outside, and not re-circulated into the general ventilation system?	Y	N	AV	NA
7) If air exhausted from the AII rooms is re-circulated into the general ventilation system:				
a) Is the air decontaminated (e.g.: with the use of HEPA filters installed in the duct system) before being re-circulated back into the isolation/treatment rooms or the general ventilation system?	Y	N	AV	NA
b) Are the HEPA filters checked and monitored on a regular schedule (daily for occupied, and monthly for unoccupied TB isolation rooms) to ensure continuous effectiveness?	Y	N	AV	NA
c) Is the air handling system (duct work, fans, filters, etc.) appropriately marked with TB warning in areas where maintenance personnel would have access into the equipment?	Y	N	AV	NA
8) If AII isolation/treatment rooms are also used to treat non-TB patients, are the rooms purged and decontaminated between discharge of a TB patient and admittance of a non-TB patient? If yes, describe method and time interval: _____ _____ _____	Y	N	AV	NA

SECTION C – RESPIRATORY PROTECTION [Part 451, 1910.134]

1) Do employees wear respirators in the following circumstances:

a) When they enter rooms housing individuals with suspected or confirmed infectious TB?	Y	N	AV	NA
b) When present during performance of high hazard procedures on individuals who have suspected or confirmed infectious TB?	Y	N	AV	NA
c) While transporting individuals with suspected or confirmed infectious TB during emergency medical response?	Y	N	AV	NA
d) When working in close contact with individuals with suspected or confirmed infectious TB?	Y	N	AV	NA

Note: If questions a, b, c, or d above DO NOT apply, skip the rest of the Respiratory Protection section. Otherwise, complete the rest of this section.

2) What type(s) of respirator(s) do the workers wear?

_____ Non-powered particulate respirators NIOSH-approved as N95, R95, P95, N99, N100, or P100: (NIOSH certification #_____).

_____ Powered air-purifying respirators (PAPRs) with high efficiency filters (HEPA): (NIOSH certification # _____).

_____ Other (describe): _____

3) Are the respirators maintained in their originally approved structural and functional form, as well as in sanitary condition?	Y	N	AV
4) Does the facility have a complete written respiratory protection program?	Y	N	AV
5) Has each affected worker been provided respiratory training?	Y	N	AV
6) Has each affected worker been provided initial fit testing?	Y	N	AV
7) Has each affected worker been provided annual fit testing?	Y	N	AV
8) Has each affected worker been provided medical evaluation?	Y	N	AV
9) Do the workers reuse disposable respirators?	Y	N	
10) Does the facility have stipulated time and use limits after which disposable respirators can no longer be reused?	Y	N	AV

SECTION D – ACCIDENT PREVENTION SIGNS AND TAGS [Part 4501]

Check here [ ] and skip this section if facility does not use AII rooms for TB patients. Otherwise, complete this section.

1) Is there an appropriate warning sign posted outside each AII isolation or treatment room? Y N AV NA

2) Are there biological hazard tags/symbols on air handling equipment, (e.g. fans, ducts, filters) that are used to transport TB contaminated air? Y N AV NA

SECTION E – ACCESS TO EMPLOYEE MEDICAL AND EXPOSURE RECORDS

[Part 470, R 325.3451 Thru R 325.3476]

1) Does the facility maintain employee medical and exposure records concerning employee exposure to TB in accordance with R 325.3451 thru R 325.3476? Y N AV

2) Do employees and their designated representatives have access to the exposure and medical records? Y N AV

SECTION F – RECORDING AND REPORTING OF OCCUPATIONAL INJURIES & ILLNESSES – MIOSHA 300 Log [Part 11, R 408.22101 Thru R 408.22142]

Note: MIOSHA 300 log for the previous five (5) years must be reviewed during all TB related inspections.

Skin test conversions on pre-employment TB skin tests, or initial baseline TB skin tests performed within two weeks of hire and before work assignment to area of potential exposure to TB are not attributed to exposure in the workplace, and are not required to be recorded on the MIOSHA 300 log.

The attending physician or the employer is required to file an Occupational Disease Report for each employee who develops occupational TB disease.

1) Has facility had incidents of employee positive TB skin test conversion? Y N

2) Did the conversions occur on initial baseline TB skin testing? **(If yes, does not have to be recorded on I & I log as a conversion).** Y N

3) Did the conversions occur on pre-employment skin testing? **(If yes, does not have to be recorded on I & I log as a conversion).** Y N

4) Did the conversions occur on skin testing performed within two weeks of employment? **(If yes, does not have to be recorded on I & I log as a conversion).** Y N

5) Did the conversions occur before work assignment to area of potential exposure to TB? **(If yes, does not have to be recorded on I & I log as a conversion).**	Y	N	
6) If response to 2, 3, 4, or 5 above is "No", were all the conversions recorded in the Injury & Illness Log (MIOSHA 300)?	Y	N	AV
7) Are the entries recorded in Column M (3) of the Illnesses Section?	Y	N	AV
8) Did the facility update its I & I log entries when there was a progression of employees TB infection to actual TB disease?	Y	N	AV

Comments: _____
_____
_____
_____

LHD Contact List

R1 R2N R2S R3 R5 R6 R7 R8

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*** Region 1 continued on next page**

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*** Region 5 continued on next page**

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Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection

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Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection

This Official Statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This Statement was endorsed by the Council of the Infectious Diseases Society of America (IDSA), September 1999, and the sections of this Statement as it relates to infants and children were endorsed by the American Academy of Pediatrics (AAP), August 1999.

EXECUTIVE SUMMARY

This statement provides new recommendations for targeted tuberculin testing and treatment regimens for persons with latent tuberculosis infection (LTBI) and updates previously published guidelines (*1,2*). This statement is issued in recognition of the importance of these activities as an essential component of the TB Elimination Strategy promoted by the U.S. Public Health Service Advisory Council on the Elimination of Tuberculosis, and reports the deliberations of expert consultants convened by the American Thoracic Society (ATS) and Centers for Disease Control and Prevention (CDC).

Isoniazid for 6–12 mo has been the mainstay of treatment for LTBI in the United States for more than 30 yr. However, the application of isoniazid for LTBI has been limited because of poor adherence, due to the relatively long duration of treatment required, and because of concerns about toxicity. Therefore, there has been interest in the development of shorter, rifampin-based regimens as alternatives to isoniazid for the treatment of LTBI. During the past decade, a series of studies of "short-course" treatment of LTBI in persons with human immunodeficiency virus (HIV) infection has been undertaken. The results of these trials have recently become available, and the in-depth analyses of these and prior studies of isoniazid form the scientific basis of the treatment guidelines presented in this report. In addition, many changes to previous recommendations regarding testing for and treatment of LTBI are presented (Table 1).

Targeted Tuberculin Testing

Targeted tuberculin testing for LTBI is a strategic component of tuberculosis (TB) control that identifies persons at high risk for developing TB who would benefit by treatment of LTBI, if detected. Persons with increased risk for developing TB include those who have had recent infection with *Mycobacterium tuberculosis* and those who have clinical conditions that are associated with an increased risk for progression of LTBI to active TB (*see* Tables 2 and 3). Following that principle, targeted tuberculin testing programs should be conducted only among groups at high risk and discouraged in those at low risk. Infected persons who are considered to be at high risk for developing active TB should be offered treatment of LTBI irrespective of age.

Based on the sensitivity and specificity of the purified protein derivative (PPD) tuberculin skin test and the prevalence of TB in different groups, three cut-points have been recommended for defining a positive tuberculin reaction: ≥5 mm, ≥10 mm, and

≥15 mm of induration (*see* Table 7). For persons who are at highest risk for developing active TB if they are infected with *M. tuberculosis* (i.e., persons with HIV infection, who are receiving immunosuppressive therapy, who have had recent close contact with persons with infectious TB, or who have abnormal chest radiographs consistent with prior TB), ≥5 mm of induration is considered positive. For other persons with an increased probability of recent infection or with other clinical conditions that increase the risk for progression to active TB, ≥10 mm of induration is considered positive. These include recent immigrants (i.e., within the last 5 yr) from high prevalence countries; injection drug users; residents and employees of high-risk congregate settings (including health care workers with exposure to TB); mycobacteriology laboratory personnel; persons with clinical conditions such as silicosis, diabetes mellitus, chronic renal failure, leukemias and lymphomas, carcinoma of the head or neck and lung, weight loss of ≥10% ideal body weight, gastrectomy, and jejunoileal bypass; and children younger than 4 yr of age or infants, children, and adolescents exposed to adults in high-risk categories. For persons at low risk for TB, for whom tuberculin testing is not generally indicated, ≥15 mm of induration is considered positive.

Treatment of Latent Tuberculosis Infection

In this report, treatment recommendations use an adaptation of the rating system from recent U.S. Public Health Service documents (*3*) that grades the strength of the recommendation (A, B, or C) and the quality of evidence supporting the recommendation (I, II, or III). Four regimens are recommended for the treatment of adults with LTBI. (*See* Tables 8 and 10 for detailed recommendations, dosages, and contraindications.)

Drugs	Duration (mo)	Interval	Rating* (Evidence)†	
			HIV⁻	HIV⁺
Isoniazid	9	Daily	A (II)	A (II)
		Twice weekly	B (II)	B (II)
Isoniazid	6	Daily	B (I)	C (I)
		Twice weekly	B (II)	C (I)
Rifampin–pyrazinamide	2	Daily	B (II)	A (I)
	2–3	Twice weekly	C (II)	C (I)
Rifampin	4	Daily	B (II)	B (III)

* A = preferred; B = acceptable alternative; C = offer when A and B cannot be given.

† I = randomized clinical trial data; II = data from clinical trials that are not randomized or were conducted in other populations; III = expert opinion.

The isoniazid daily regimen for 9 mo is recommended because prospective, randomized trials in HIV-negative persons indicate that 12 mo of treatment is more effective than 6 mo of treatment. However, in subgroup analyses of several trials the maximal beneficial effect of isoniazid is likely achieved by 9 mo, and minimal additional benefit is gained by extending therapy to 12 mo. When compared with placebo, both 6-mo and 12-mo regimens are effective in HIV-positive patients; however, these regimens have not been compared with each other in randomized trials.

Although a 9-mo regimen of isoniazid is the preferred regimen for the treatment of LTBI, a 6-mo regimen also provides substantial protection and has been shown to be superior to placebo in both HIV-negative and HIV-positive persons. In some situations,

treatment for 6 mo rather than 9 mo may provide a more favorable outcome from a cost-effectiveness standpoint. Thus, based on local conditions, health departments or providers may conclude that a 6-mo rather than a 9-mo course of isoniazid is preferred.

Table 1. Changes from prior recommendations on tuberculin testing and treatment of latent tuberculosis infection (LTBI)

Tuberculin testing

- Emphasis on targeted tuberculin testing among persons at high risk for recent LTBI or with clinical conditions that increase the risk for tuberculosis (TB), regardless of age; testing is discouraged among persons at lower risk
- For patients with organ transplants and other immunosuppressed patients (e.g., persons receiving the equivalent of ≥15 mg/d prednisone for 1 mo or more), 5 mm of induration rather than 10 mm of induration rather than 10 mm of induration as a cut-off level for tuberculin positivity
- A tuberculin skin test conversion is defined as an increase of ≥10 mm of induration within a 2-yr period, regardless of age

Treatment of latent tuberculosis infection

- For human imunodeficiency virus (HIV)-negative persons, isoniazid given for 9 mo is preferred over 6-mo regimens
- For HIV-positive persons and those with fibrotic lesions on chest X-ray consistent with previous TB, isoniazid should be given for 9 mo instead of 12 mo
- For HIV-negative and HIV-positive persons, rifampin and pyrazinamide should be given for 2 mo
- For HIV-negative and HIV-positive persons, rifampin should be given for 4 mo

Clinical and laboratory monitoring

- Routine baseline and follow-up laboratory monitoring can be eliminated in most persons with LTBI, except for those with HIV infection, pregnant women (or those in the immediate postpartum period), and persons with chronic liver disease or those who use alcohol regularly
- Emphasis on clinical monitoring for signs and symptoms of possible adverse effects, with prompt evaluation and changes in treatment, as indicated

Both the 9-mo and 6-mo isoniazid regimens may be given intermittently (i.e., twice weekly). When isoniazid is given intermittently, it should be administered only as directly observed therapy (DOT).

The 2-mo daily regimen of rifampin and pyrazinamide is recommended on the basis of a prospective randomized trial of treatment of LTBI in HIV-infected persons that showed the 2-mo regimen to be similar in safety and efficacy to a 12-mo regimen of isoniazid. Twice-weekly treatment with rifampin and pyrazinamide for 2 or 3 mo may be considered when alternative regimens cannot be given. This intermittent regimen should always be administered as DOT. Some experts recommend that the 2-mo regimen of daily rifampin and pyrazinamide also be given by DOT, which can consist of five observed and two self-administered doses each week. In situations in which rifampin cannot be used (e.g., HIV-infected persons receiving protease inhibitors), rifabutin may be substituted.

Rifampin given daily for 4 mo is recommended on the basis of the efficacy of a similar regimen in a) a prospective randomized trial of tuberculin-positive persons with silicosis and b) a nonrandomized trial in persons exposed to individuals with isoniazid-resistant TB. This option may be especially useful for patients who cannot tolerate isoniazid or pyrazinamide.

Before beginning treatment of LTBI, active TB should be ruled out by history, physical examination, chest radiography, and, when indicated, bacteriologic studies.

Special considerations for treatment of LTBI apply to the following populations:

- When isoniazid is chosen for treatment of LTBI in persons with HIV infection or those with radiographic evidence of prior TB, 9 mo rather that 6 mo is recommended.
- For pregnant, HIV-negative women, isoniazid given daily or twice weekly for 9 or 6 mo is recommended. For women at risk for progression of LTBI to disease, especially those who are infected with HIV or who have likely been infected recently, initiation of therapy should not be delayed on the basis of pregnancy alone, even during the first trimester. For women whose risk for active TB is lower, some experts recommend waiting until after delivery to start treatment.
- For children and adolescents, isoniazid given either daily or twice weekly for 9 mo is the recommended regimen.
- For contacts of patients with isoniazid-resistant, rifampin-susceptible TB, rifampin and pyrazinamide given daily for 2 mo is recommended, and for patients with intolerance to pyrazinamide, rifampin given daily for 4 mo is recommended.
- For persons who are likely to be infected with isoniazid- and rifampin-resistant (multidrug) TB and who are at high risk for developing TB, pyrazinamide and ethambutol or pyrazinamide and a quinolone (i.e., levofloxacin or ofloxacin) for 6–12 mo are recommended. Immunocompetent contacts may be observed or treated for at least 6 mo, and immunocompromised contacts (e.g., HIV-infected persons) should be treated for 12 mo.

Clinical and Laboratory Monitoring

Once patients have been identified and then tested for LTBI, they should receive an initial clinical evaluation. They should also receive follow-up evaluations at least monthly (if receiving isoniazid alone or rifampin alone) and at 2, 4, and 8 wk (if receiving rifampin and pyrazinamide). This evaluation should include questioning about side effects and a brief physical assessment checking for signs of hepatitis. Patients should be educated about the side effects associated with treatment of LTBI and advised to stop treatment and promptly seek medical evaluation when they occur.

Baseline laboratory testing is not routinely indicated for all patients at the start of treatment for LTBI (*see* Table 8). Patients whose initial evaluation suggests a liver disorder should have baseline hepatic measurements of serum aspartate aminotransferase (serum glutamic oxaloacetic transaminase) (AST [SGOT]) or alanine aminotransferase (serum glutamic pyruvic transaminase) (ALT [SGPT]) and bilirubin. Baseline testing is also indicated for patients with HIV infection, pregnant women, and women in the

immediate postpartum period (i.e., within 3 mo of delivery), persons with a history of chronic liver disease (e.g., hepatitis B or C, alcoholic hepatitis, or cirrhosis), persons who use alcohol regularly, and persons at risk for chronic liver disease. Baseline testing is not routinely indicated in older persons. However, such testing may be considered on an individual basis, particularly for patients who are taking other medications for chronic medical conditions. Active hepatitis and end-stage liver disease are relative contraindications to the use of isoniazid or pyrazinamide for treatment of LTBI.

Routine laboratory monitoring during treatment of LTBI is indicated for persons whose baseline liver function tests are abnormal and other persons at risk for hepatic disease. Laboratory testing may also be indicated for the evaluation of possible adverse effects that occur during the course of treatment (e.g., liver function studies for patients with symptoms compatible with hepatotoxicity or a uric acid measurement to evaluate complaints of joint pain). Some experts recommend that isoniazid should be withheld if transaminase levels exceed three times the upper limit of normal if associated with symptoms and five times the upper limit of normal if the patient is asymptomatic.

INTRODUCTION

History of Treatment of Latent Tuberculosis Infection and Relevance to Tuberculosis Control

For more than three decades, treatment of persons with latent *Mycobacterium tuberculosis* infection (LTBI) to prevent the development of active disease has been an essential component of tuberculosis (TB) control in the United States (4). In the United States and other countries with a low incidence of TB, most new, active cases have occurred among persons who were once infected, contained this infection, and then later developed active TB (5). The identification and treatment of infected persons at highest risk for developing disease benefit both infected persons and susceptible persons in their communities. Until recently, isoniazid was the only drug proven effective and thus recommended for treatment of LTBI.

Shortly after isoniazid was found to be effective for the treatment of TB, clinical trials were begun to assess the ability of the drug to prevent progression of primary disease in children. When it was found that this intervention was highly effective, larger trials were begun to evaluate the drug for treatment of infected contacts of TB patients and of other persons at high risk (e.g., those with radiographic evidence of prior, untreated TB) (*6*). In 1965, isoniazid treatment of LTBI was first recommended for general use by the American Thoracic Society (ATS) (*7*). This initial statement recommended isoniazid for persons with evidence of previously untreated TB and persons with recent tuberculin skin test conversions, including all children younger than 3 yr of age with a positive tuberculin skin test. In 1967, ATS and PHS broadened the recommendations to include all persons who had had a purified protein derivative (PPD) tuberculin skin-test reaction of ≥10 mm. The recommendations stated that chemoprophylaxis is mandatory for a) persons with inactive cases of TB who were not previously treated and their contacts, b) persons with tuberculin skin test conversions, c) persons with specified medical conditions, and d) all persons younger than 20 yr of age who had had positive

tuberculin skin tests (*8*). With widespread use of such an inexpensive drug that had "virtually no side effects," it was believed that "chemoprophylaxis [could] reduce future morbidity from TB in high risk groups by some 50 to 75 percent" (*8*).

However, despite this belief, the goal of reducing TB morbidity by such a substantial percentage through the administration of isoniazid was never reached. In 1970, among several thousand persons who began isoniazid treatment as a result of an outbreak of TB on Capitol Hill in the District of Columbia, 19 persons developed clinical signs of liver disease and two persons died of hepatic failure attributed to isoniazid (*9*). The recognition that isoniazid was associated with potentially fatal hepatitis led to the development of guidelines regarding pretreatment screening and monitoring to minimize the risk for severe complications (*10*). In 1974, following a study to quantify the risk for isoniazid-related hepatitis (*11*), guidelines for treatment of LTBI were updated. The revised guidelines excluded low-risk persons aged older than 35 yr of age as candidates for treatment (*12*).

Subsequent controversy over the appropriate age cut-off for these low-risk, tuberculin-positive persons ensued, with one group concluding that the risks of treatment of LTBI outweighed the benefits for young adults (*13*). This controversy and resulting confusion led to a decrease in the use of isoniazid for treating persons with LTBI—even persons at high risk for whom treatment was indicated (*14*). In 1983, the guidelines were further revised to recommend routine clinical and laboratory monitoring for persons aged older than 35 yr of age and other persons at risk for hepatotoxicity (*15*). Recent studies have suggested that since the advent of routine monitoring, the risk for severe hepatotoxicity has been substantially reduced (*16*).

Because widespread use and the potential impact of isoniazid treatment of LTBI became limited by actual and perceived toxicity and patient nonadherence because of the relatively long period of treatment required, alternatives to isoniazid were suggested (*17*). The introduction of rifampin, which appeared to be a better sterilizing agent than isoniazid, suggested the possibility that rifampin-based regimens might be safer, more effective, and shorter. The occurrence of the human immunodeficiency virus (HIV) epidemic and the need to evaluate the efficacy of treatment for LTBI in persons coinfected with HIV and *M. tuberculosis* led to a series of studies of short-course treatment of LTBI in HIV-infected persons (*18*). The results of these studies have recently become available and have contributed substantially to guidelines on treatment of LTBI in persons with HIV infection (*3*).

Relationship of Tuberculin Testing to Treatment of Latent Tuberculosis Infection

As the rate of active TB in the United States has decreased, identification and treatment of persons with latent infection who are at high risk for active TB have become essential components of the TB elimination strategy promoted by the PHS Advisory Council on the Elimination of Tuberculosis (*19*). Because testing persons for infection and provision of treatment are interrelated, these recommendations include sections on program activities aimed at identifying high-risk infected persons and tuberculin skin testing, as well as recommendations on the use of new, short-course treatment regimens.

Change in Nomenclature

Identification of persons with LTBI has previously been accomplished by widespread tuberculin skin testing of individuals or groups at variable risk for TB. In many situations, this screening was done with limited consideration of the risk for TB in the population(s) being tested. To focus on groups at the highest risk for TB, the term "targeted tuberculin testing" is used in these guidelines to encourage directed program activities.

Although the terms "preventive therapy" and "chemoprophylaxis" have been used for decades, they have also been confusing. "Preventive therapy" has referred to the use of a simple regimen (usually isoniazid) to prevent the development of active TB disease in persons known or likely to be infected with *M. tuberculosis*, but it rarely results in true primary prevention (i.e., prevention of infection in persons exposed to persons with infectious TB). To describe the intended intervention more accurately, this report uses the terminology "treatment of LTBI" rather than "preventive therapy" or "chemoprophylaxis." This change in nomenclature will hopefully promote greater understanding of the concept for both patients and providers, resulting in more widespread implementation of this essential TB control strategy.

SCIENTIFIC RATIONALE

Targeted Tuberculin Testing

Groups at Risk and Risk Factors for Infection with M. tuberculosis

Targeted tuberculin testing for LTBI identifies persons at high risk for TB who would benefit by treatment of LTBI, if detected. Persons at high risk for TB (i.e., risk substantially greater than that of the general U.S. population) have either been infected recently with *M. tuberculosis* or have clinical conditions that are associated with an increased risk of progression of LTBI to active TB (Tables 2 and 3). Screening of low-risk persons and testing for administrative purposes (e.g., certification of school teachers) should be replaced by targeted testing.

Persons or groups with presumed recent M. tuberculosis *infection*. Persons infected with *M. tuberculosis* are at greatest risk for developing disease shortly after infection has occurred (Table 2). In two controlled trials examining the efficacy of treatment of LTBI among contacts of persons with active TB and among patients in mental hospitals, the tuberculin skin tests of 1472 participants in the placebo groups of the trials converted from negative to positive. Among persons whose tests converted, 19 developed disease in the first year of follow-up (12.9 cases per 1000 person-years) compared with 17 persons in the subsequent 7 yr of follow-up (1.6 cases per 1,000 person-years) (*6*). In a study of TB vaccines given to British schoolchildren, 2550 unvaccinated participants' tuberculin skin tests converted. Of these, 121 (4.7%) developed clinical TB within 15 yr of entry into the study: 54% developed disease during the first year after infection and 82% developed disease within 2 yr of infection (*20*).

In designing and planning targeted testing programs, several groups of persons can be identified as being at increased risk for being recently infected with *M. tuberculosis*. A high prevalence of either LTBI or active TB has been documented among close

contacts of persons with infectious pulmonary TB (*21*); both of these characteristics are likely attributable to recent contact with infectious persons. Likewise, persons whose tuberculin skin tests convert from negative to positive within a period of 2 yr are presumed to have been infected recently.

Table 2. Incidence of active tuberculosis (TB) in persons with a positive tuberculin test, by selected risk factors

Risk factor	TB cases/1,000 person-years
Recent TB infection	
Infection <1 yr past	12.9 (*6*)*
Infection 1–7 yr past	1.6
Human immunodeficiency virus (HIV) infection	35.0–162 (*28*)
Injection drug use	
HIV seropositive	76.0 (*31*)
HIV seronegative or unknown	10.0 (*31*)
Silicosis	68 (*36*)
Radiographic findings consistent with prior TB	2.0–13.6 (*32–34*)
Weight deviation from standard	
Underweight by ≥15%	2.6 (*35*)
Underweight by 10–14%	2.0
Underweight by 5–9%	2.2
Weight within 5% of standard	1.1
Overweight by ≥5%	0.7

* Numbers in parentheses are reference numbers.

Persons who have immigrated from areas of the world with high rates of TB have incidence rates that approach those of their countries of origin for the first several years after arrival in the United States (*22*). This high rate likely results from infection with *M. tuberculosis* in the native country before immigration and progression to disease soon after arrival in the United States. This hypothesis is supported by a) DNA fingerprinting studies with restriction fragment length polymorphism (RFLP) interpreted to correlate with low rates of recent transmission of TB among foreign-born case patients in the United States (*23*) and b) other data indicating that with time, the incidence of TB in foreign-born persons declines to approach that of the U.S. population (*24*).

Children, especially those younger than 5 yr of age, who have a positive tuberculin skin test are likely to be in the early stage of LTBI and are at high risk for progression to active disease, with the potential for disseminated TB (*25*). The risk for developing active TB is also increased in adolescents and young adults (*25*).

Recent U.S. studies (including RFLP studies) have helped characterize certain epidemiologically defined groups of persons with high rates of TB transmission and increased risk for being recently infected (e.g., homeless persons, those with HIV infection, and injection drug users) (*23,26*). In addition, persons who reside or work in institutional settings (e.g., hospitals, homeless shelters, correctional facilities, nursing homes, and residential homes for patients with AIDS [*27*]) with persons at risk for TB may have an ongoing risk for acquiring TB infection. However, the risk for transmission varies greatly, and the likelihood that a specific institution is a site of transmission of *M. tuberculosis* can be determined only by local epidemiological data.

Clinical conditions associated with progression to active tuberculosis. HIV infection contributes most to an increased risk for progression of LTBI to active TB. Rates of

progression to TB among HIV-infected persons have ranged from 35 to 162 per 1000 person-years of observation (Table 2) (*28*). In a prospective cohort study of persons with HIV infection in the United States, the annual risk of active-TB among persons with a positive tuberculin test was 45 cases per 1000 person-years (*29*). Injection drug users also have an increased risk for progressing to active TB (10 cases per 1000 person-years) (*30*), and this risk is even greater for injection drug users coinfected with HIV and TB (76 cases per 1000 person-years) (*31*). These higher rates may reflect increased transmission, more recent infection in this population, and the increased risk associated with injection drug use and HIV infection.

The risk for active TB is also increased in a) persons with pulmonary fibrotic lesions seen on chest radiographs (presumed to be from prior, untreated TB) and b) underweight persons. Persons with fibrotic lesions on chest radiographs consistent with prior, healed TB have a risk for progression to active TB of 2.0–13.6 per 1000 person-years of observation (*32–34*). A study of 23,541 U.S. Naval recruits with tuberculin reactions ≥10 mm demonstrated that recruits who were ≥15% underweight from the standard weight for their height had a risk of progression to disease that was twofold that of persons who were within 5% of the standard weight for their height and more than threefold that of persons who were overweight (*35*).

Studies indicate that several other clinical conditions increase the risk for active TB, although participants in these studies were not stratified by tuberculin-test status (Table 3).

Table 3. Relative risk* for developing active tuberculosis (TB), by selected clinical conditions

Clinical condition	Relative risk
Silicosis	30 (*37,38*)†
Diabetes mellitus	2.0–4.1 (*42–44*)
Chronic renal failure/hemodialysis	10.0–25.3 (*39–41*)
Gastrectomy	2–5 (*45–47*)
Jejunoileal bypass	27–63 (*48–49*)
Solid organ transplantation	
Renal	37 (*50*)
Cardiac	20–74 (*51,52*)
Carcinoma of head or neck	16 (*53*)

* Relative to control population; independent of tuberculin-test status.
† Numbers in parentheses are reference numbers.

Tuberculin-positive persons with silicosis have an approximately 30-fold greater risk for developing TB (*36–38*). Persons with chronic renal failure who are on hemodialysis also have an increased risk: 10–25 times greater than the general population (*39–41*). Persons with diabetes mellitus have a risk for developing active TB that is twofold to fourfold greater than persons without diabetes mellitus, and this risk is likely greater in persons with insulin-dependent or poorly controlled diabetes (*42–44*). Other clinical conditions that have been associated with active TB include gastrectomy with attendant weight loss and malabsorption (*45–47*), jejunoileal bypass (*48,49*), renal (*50*) and cardiac (*51,52*) transplantation, carcinoma of the head or neck (*53*), and other neoplasms (e.g., lung cancer, lymphoma, and leukemia [*54*]).

Persons receiving prolonged therapy with corticosteroids and other immunosuppressive agents may be at risk for reactivation of TB, but the exact risk is unknown (*1*).

Because prednisone (or its equivalent) given >15 mg/d for 2–4 wk suppresses tuberculin reactivity (*55,56*), and because lower doses or those given intermittently are not associated with TB, this dose is likely the lower limit that could predispose persons to develop TB (*57*). Reactivation of TB is more likely to occur in persons receiving higher doses of corticosteroids for prolonged periods of time, especially in populations at high risk for TB, but specific thresholds of dose and duration that could increase the risk for TB are unknown (*58*). Persons who use alcohol may be at increased risk for acquiring or developing TB, but given the many other potential risk factors that commonly occur among such persons, alcohol use has been difficult to identify as a separate risk factor for TB (*2,42,59,60*).

Operational Considerations

In *A Strategic Plan for the Elimination of Tuberculosis in The United States*, published by CDC in 1989 (*61*), the responsibility for detection and treatment of LTBI in high-risk groups was assigned directly to public health agencies. At that time, the administration of skin tests, interpretation of test results, and intensive follow-up required to ensure adherence with and to prevent side effects of isoniazid treatment were believed to be beyond the scope of most private health care providers.

However, in 1995, CDC published recommendations on targeted testing and treatment of LTBI that emphasized the importance of health departments in assisting local providers in the development, implementation, and evaluation of TB screening programs appropriate for their communities (*2*). This recommendation was based on the recognition that changes in the organization, delivery, and financing of health care in the United States have led to most routine tuberculin testing being done outside of the public health system (*62*). For example, populations that previously received clinical services, including diagnosis of LTBI, at public health clinics are now increasingly being enrolled as members of managed care organizations.

Because health departments might lack access to high-risk populations and the resources necessary to undertake targeted testing programs, the participation of other health care providers is essential to ensure the successful implementation of community efforts to prevent TB in high-risk groups. Community sites where persons at high risk may be accessed and where targeted testing programs have been evaluated include neighborhood health centers (*63*), jails (*64*), homeless shelters (*65*), inner-city sites (*66*), methadone (*67*) and syringe/needle-exchange programs (*68*), and other community-based social service organizations (*69*).

Diagnosis of Latent Tuberculosis Infection

Tuberculin Skin Testing

The tuberculin skin test is the only proven method for identifying infection with *M. tuberculosis* in persons who do not have TB disease. Although the available tuberculin skin-test antigens are <100% sensitive and specific for detection of infection with *M. tuberculosis*, no better diagnostic methods have yet been devised. Proper use of the tuberculin skin test requires knowledge of the antigen used (tuberculin), the immunologic basis for the reaction to this antigen, the technique(s) of administering and reading the test, and the results of epidemiologic and clinical experience with the test. Detailed information on these topics is provided in the ATS/CDC Statement *Diagnostic Standards and Classification of Tuberculosis in Adults and Children* (*70*).

Immunologic basis for the tuberculin reaction. Infection with *M. tuberculosis* produces a delayed-type hypersensitivity reaction to certain antigenic components (tuberculins) that are contained in extract of culture filtrate of the organism. Purified protein derivative (PPD) tuberculin, which is used for most skin testing, is isolated from culture filtrate by protein precipitation.

The reaction to intracutaneously injected tuberculin is a delayed-type (cellular) hypersensitivity (DTH) reaction, and infection by *M. tuberculosis* usually results in a DTH response to PPD tuberculin that is detectable 2–12 wk after infection (*71*). However, a DTH reaction to PPD tuberculin may also indicate infection with various nontuberculous mycobacteria or vaccination with Bacille Calmette-Guérin (BCG), a live attenuated mycobacterial strain derived from *Mycobacterium bovis*. Delayed hypersensitivity reactions to tuberculin usually begin 5–6 h after injection, reach a maximum at 48–72 h, and subside over a period of a few days, although positive reactions often persist for up to 1 wk (*72*).

Sensitivity and specificity of skin-test reactions. Knowledge of tuberculin-test sensitivity and specificity, as well as positive predictive value, is required to interpret skin-test reactions properly. For persons with LTBI and normal immune responsiveness, test sensitivity approaches 100% (*73*). However, false-positive tuberculin tests occur in persons who have been infected with nontuberculous mycobacteria and in persons who have received BCG vaccine. These false-positive reactions result in a lower specificity and a low positive predictive value in persons who have a low probability of LTBI. The general U.S. population currently has an estimated *M. tuberculosis* infection rate of 5–10%, and children entering school in many areas of the country have a 0.1–1% prevalence of infection. Even if the test has a specificity approaching 99%, testing of persons in such low-prevalence groups would result in most positive tests being false-positive tests (*71*). However, the specificity of the test is also dependent on the criterion used to define a "positive" test. The specificity can be improved by progressively increasing the reaction size that separates positive from negative reactors (at the expense of decreasing test sensitivity) (*73*).

Previous BCG vaccination. Intracutaneous inoculation with BCG is currently used in many parts of the world as a vaccine against tuberculosis. Tuberculin reactivity caused by BCG vaccination generally wanes with the passage of time but can be boosted by the tuberculin skin test. Periodic skin testing may prolong reactivity to tuberculin in vaccinated persons (*74*). No reliable method has been developed to distinguish tuberculin reactions caused by vaccination with BCG from those caused by natural mycobacterial infections, although reactions of ≥20 mm of induration are not likely caused by BCG (*75*).

HIV infection and anergy testing. HIV-infected persons may have a compromised ability to react to tuberculin skin tests because of cutaneous anergy associated with progressive HIV immunosuppression (*76*). However, the usefulness of anergy testing in selecting tuberculin-negative, HIV-infected persons who might benefit from treatment of LTBI has not been demonstrated (*77*).

Chest Radiographs

In persons with LTBI, the chest radiograph is usually normal, although it may show abnormalities suggestive of prior TB. Previous, healed TB can produce various radiographic findings that usually differ from those associated with active TB. Dense pulmonary nodules, with or without visible calcification, may be seen in the hilar area or

upper lobes. Smaller nodules, with or without fibrotic scars, are often seen in the upper lobes, and upper-lobe volume loss often accompanies these scars. Nodules and fibrotic lesions of previous, healed TB have well-demarcated, sharp margins and are often described as "hard." Bronchiectasis of the upper lobes is a nonspecific finding that sometimes occurs from previous pulmonary TB. Pleural scarring may be caused by prior TB but is more commonly caused by trauma or other infections. Nodules and fibrotic scars may contain slowly multiplying tubercle bacilli with substantial potential for future progression to active TB (*32*). Conversely, calcified nodular lesions (calcified granulomas) and apical or basal pleural thickening pose a lower risk for future progression to active TB.

Sputum Examinations

The presumptive diagnosis of active pulmonary TB is often made on the basis of microscopic examination of a stained sputum smear for acid-fast bacilli (AFB). Confirmation of the diagnosis usually requires identification of *M. tuberculosis* in culture. In asymptomatic persons with normal chest radiographs, AFB are rarely seen on sputum smear examination, and tubercle bacilli are not found in cultures of respiratory specimens. However, some HIV-infected persons with sputum culture-positive TB have been described as having normal chest radiographs.

Treatment of Latent Tuberculosis Infection

Isoniazid

Experimental studies. Before clinical trials of isoniazid for the treatment of LTBI were begun in the United States, its efficacy was demonstrated in guinea pigs. In a study conducted by PHS, guinea pigs receiving varying doses of isoniazid were challenged with virulent tubercle bacilli (*78*). Those animals receiving a daily dosage of at least 5 mg/kg were protected (i.e., survival was comparable to control animals who were not challenged with the bacillus). On the basis of these studies, the dose of 5 mg/kg was chosen for clinical studies in humans.

Clinical trials in HIV-negative persons. Many randomized, controlled clinical trials of isoniazid for the treatment of LTBI were conducted in the 1950s and 1960s (*6*). These trials were conducted in seven countries, both industrialized and developing, and involved more than 100,000 participants at risk for TB, including children with primary TB, contacts of active case patients, persons who had had tuberculin skin reactions, institutionalized patients with mental disease, and persons with inactive TB. Most studies compared 12 mo of isoniazid with placebo. The outcomes measured in these studies included progression of primary TB, tuberculin conversion in uninfected contacts, prevention of TB in infected persons, and recurrence of disease. The effectiveness of treatment, as measured by the decrease in TB among all persons participating in these trials, varied from 25 to 92%. However, when analysis was restricted to persons who were compliant with the medication, the protective efficacy was approximately 90%. Substantial protection was conferred even if pill taking was irregular but sustained, suggesting the possibility that intermittent treatment may be efficacious.

Only one trial, conducted by the International Union Against Tuberculosis (IUAT) (*32*), was designed to evaluate various durations of isoniazid. In this trial, a placebo

regimen was compared with isoniazid regimens lasting for 3, 6, and 12 mo among persons with fibrotic pulmonary lesions consistent with inactive TB. The 5-yr incidence rates of tuberculosis were 1.43% for placebo compared with 1.13, 0.50, and 0.36% for the 3-, 6-, and 12-mo regimens, respectively (Table 4). The rates indicated a 65% effectiveness for the 6-mo isoniazid regimen and 75% effectiveness for the 12-mo regimen; persons who received 6 mo of isoniazid had a 40% higher risk for TB compared with those who received 12 mo of therapy.

Table 4. Efficacy of various durations of isoniazid preventive therapy for persons with fibrotic lesions, by length of treatment—International Union Against Tuberculosis (IUAT) Trial, 1969–1977

	5-yr Tuberculosis incidence* (% reduction)			
Group	**Placebo**	**12 wk**	**24 wk**	**52 wk**
All participants (n = 27,830)†	14.3	11.3 (21)	5.0 (65)	3.6 (75)
Adherent participants‡ (n = 21,635)§	15	9.4 (31)	4.7 (69)	1.1 (93)
Fibrotic lesions <2 cm^2 (n = 18,663)†	11.6	9.2 (20)	4.0 (66)	4.2 (64)¶
Fibrotic lesions >2 cm^2 (n = 8,428)§	21.3	16.2 (24)	7.0 (67)	2.4 (89)

* Per 1000 person-years.

† Comparing placebo to 24 and 52 wk, $p < 0.05$; differences between placebo and 12 wk and between 24 and 52 wk not significant.

‡ Collected pill calendars for "almost all" of the months assigned for their regimen and had taken at least 80% of the pills from the calendar by the time of the next monthly visit.

§ For all interregimen comparisons ($p < 0.05$).

¶ Persons who developed tuberculosis on 52-wk regimen and had small fibrotic lesions were less likely to have collected pill calendars (47%) than all other groups (≥80%) ($p < 0.001$).

Source: International Union Against Tuberculosis Committee on Prophylaxis. Efficacy of vaious durations of isoniazid thereapy for tuberculosis: five years of follow-up in the IUAT trial. *Bull. WHO* 1982;60:555-64.

The difference in the two regimens is magnified when study subjects who received "almost all" of the monthly drug allotments for their scheduled duration of therapy and who were believed to have taken ≥80% of the medication each month were compared. In this subgroup, which constituted 78% of the entire study population, the resulting 5-yr incidence rates were 1.5% for persons receiving placebo compared with 1.0, 0.5, and 0.1% for the 3-, 6-, and 12-mo regimens, respectively. In this analysis, isoniazid taken for 6 mo was 69% efficacious and for 12 mo was 93% efficacious; participants on the 6-mo regimen had a fourfold higher risk for TB than those on the 12-mo regimen. Although the incidence of TB was similar for persons with small lesions (<2 cm^2) assigned the 6-mo and 12-mo regimens, such persons were less adherent to treatment. The 12-mo regimen provided a substantial reduction in risk compared with the 6-mo regimen among compliant persons with small lesions (Table 4).

Additional information on the efficacy and effectiveness of different lengths of therapy with isoniazid for the treatment of LTBI has been derived from a randomized study of household contacts conducted by PHS (21). Among persons believed to have taken ≥80% of their assigned medication during the months they took isoniazid, those who took medication for at least 10 mo experienced a 68% reduction in TB (Table 5). In

Table 5. Tuberculosis morbidity rates per 1,000 household contacts, by percentage of pills taken and duration of therapy during participation in U.S. Public Health Service Trial

Percentage of pills taken	Duration of therapy (mo)	Placebo			Isoniazid			Percentage change
		Population*	Case-patients†	Rate‡	Population*	Case-patients†	Rate‡	
≥80%	10–12	5094	127	24.9	4802	38	7.9	–68.3
≥80%	1–9	752	14	18.6	767	12	15.6	–16.1
60–79%	≥10	953	25	26.2	804	9	11.2	–57.3
40–59%	≥10	368	7	19.0	438	4	9.1	–52.1

*Excludes contacts who were tuberculin negative both at admission and at 12 mo.

† Excludes case patients who stopped taking pills because they developed active disease (29 placebo, five isoniazid).

‡ Rate for 10 yr of observation.

Source: Adapted from Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis: a general review. Adv. Tuberc Res 1970;17:28–106.

contrast, among persons who took ≥80% of the medication for <10 mo, only a 16% reduction in the TB rate occurred. The same data can be further examined to determine whether reduction in the rate of TB was affected more by duration of therapy or the amount of medication. The effectiveness of isoniazid decreased slightly for less compliant patients who took 40–79% of the prescribed medication during the 10-mo period (52–57% reduction compared to 68% reduction), suggesting that even an intermittent treatment regimen would be effective if taken for at least 10 mo (Table 5).

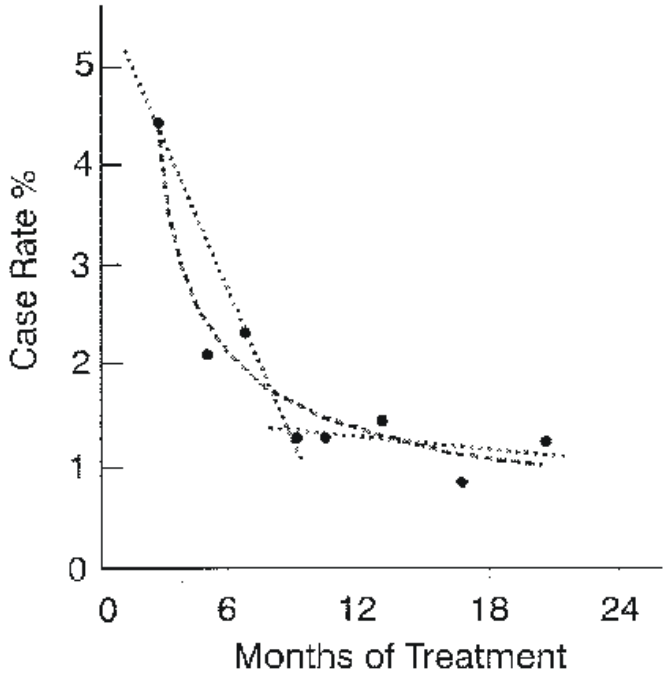
In a community-based study conducted in Bethel, Alaska (*79*), persons who took <25% of the prescribed annual dose had a threefold higher risk for TB than those who took ≥50% of the annual dose. However, a more recent analysis of study data indicated that the efficacy decreased significantly if <9 mo of isoniazid was taken (Figure 1) (*80*).

Effectiveness data from the IUAT study, published data on isoniazid-associated hepatitis, and cost information obtained from a survey of U.S. TB programs were used to assess the cost effectiveness of various durations of isoniazid (*81*). The cost per case of TB prevented with the 6-mo regimen was determined to be half of the cost as either the 3-mo or 12-mo regimens. This cost-effectiveness analysis was largely responsible for the widespread adoption of the 6-mo regimen of isoniazid for the treatment of LTBI in HIV-seronegative persons with normal chest radiographs (*82*). However, the protection conferred by taking at least 9 mo of isoniazid is greater than that conferred by taking 6 mo; it is not likely that further protection is conferred by extending the duration of treatment from 9 to 12 mo (*80*).

Clinical trials in HIV-positive persons. Seven randomized, controlled trials have evaluated different regimens for the treatment of LTBI infection in persons with HIV infection (Table 6). Five of these studies evaluated isoniazid regimens using comparison groups that either received a placebo or were not actively treated.

In the first study, conducted in Haiti during 1986–1992, 12 mo of daily isoniazid resulted in a substantial reduction in TB (83%) among tuberculin-positive persons (*83*). Protection was constant over the 4 yr of follow-up after treatment. Two other studies, which evaluated 6 mo of isoniazid taken daily by tuberculin-positive persons, had differing results: the drug provided a significant level of protection in Uganda (68%) (*84*) but did not provide a significant level of protection in Kenya (40%) (*85*). A fourth study evaluated a 6-mo, twice-weekly regimen of isoniazid in both tuberculin-positive

Figure 1*



*Tuberculosis case rates (%) in the Bethel Isoniazid Studies population according to the number of months isoniazid was taken in the combined programs. Dots represent observed values; thin line, the calculated curve (y=a+b/x); and dotted lines the calculated values based on the first four and the last five observations (y=a+bx). Source: Comstock, G.W. 1999. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? Int. J. Tuberc. Lung Dis. 3:847–850. Reprinted by permission of the International Union Against Tuberculosis and Lung Disease.

and -negative persons in Zambia (*86*). The overall level of protection was minimal but significant (38%). Although the level of protection among tuberculin-positive persons was higher (70%), it was not significant because of the limited number of persons in this group.

The Uganda study also evaluated the 6-mo regimen of daily isoniazid in anergic persons, as did the fifth study conducted in the United States (*87*). In both studies, the level of protection against TB was low, and neither study demonstrated a significant level of protection.

Additional evaluations of isoniazid were conducted in tuberculin-negative persons who were not assessed for anergy (*83,85,86*). The level of protection provided by isoniazid among this population was not significant in any of the studies. Thus, for HIV-infected persons, treatment should be targeted at tuberculin-positive persons. A recently published metaanalysis of these trials supports this conclusion (*88*).

Safety and tolerability. In 1965, when isoniazid was first recommended in the United States for treatment of LTBI, it was not thought to cause severe toxicity. In the PHS studies conducted among TB contacts, the percentage of persons stopping treatment because of suspected drug reactions was low and approximately equivalent for the placebo and isoniazid groups (*21*). The occurrence of hepatitis was rare and was not assumed to be caused by isoniazid. However, studies conducted in the late 1960s

Table 6. Prospective, randomized clinical trials of preventive therapy of tuberculosis (TB) in persons infected with human immunodeficiency virus (HIV)

Study (reference no.)	Study subjects' purified protein derivative (PPD) status* (n)	Drug regimen (mo)	No. TB Cases (%)	TB rate/100 person-years	Relative risk of TB (95% confidence interval)
Pape (*83*)	PPD$^+$ (25)	Placebo, daily (12)	6 (24)	10.0	1
Haiti 1986–1992	PPD$^+$ (38)	Isoniazid 300 mg, daily (12)	2 (5)	1.7	0.17 (0.03–0.83)
	PPD$^-$ (35)	Placebo, daily (12)	5 (14)	5.7	1
	PPD$^-$ (20)	Isoniazid 300 mg, daily (12)	2 (10)	3.2	0.56 (0.11–2.5)
Whalen (*84*)	PPD$^+$ (464)	Placebo, daily (6)	21 (5)	3.41	1
Uganda 1993–1997	PPD$^+$ (536)	Isoniazid 300 mg, daily (6)	7 (1)	1.08	0.32 (0.14–0.76)
	PPD$^+$ (556)	Isoniazid 300 mg/Rifampin 600 mg, daily (3)	9 (2)	1.32	0.41 (0.19–0.89)
	PPD$^+$ (462)	Isoniazid 300 mg/Rifampin 600 mg/ Pyrazinamide 2000 mg, daily (3)	10 (2)	1.73	0.43 (0.20–0.92)
	Anergic (323)	Placebo, daily (6)	10 (3)	3.06	1
	Anergic (395)	Isoniazid 300 mg, daily (6)	9 (2)	2.53	0.75 (0.30–1.89)
Hawken (*85*)	PPD$^{+/-}$ (342)	Placebo, daily (6)	23 (7)	3.86	1
Kenya 1992–1996	PPD$^{+/-}$ (342)	Isoniazid 300 mg, daily (6)	25 (7)	4.29	0.92 (0.49–1.71)
	PPD$^+$ (67)	Placebo, daily (6)		8.03	1
	PPD$^+$ (69)	Isoniazid 300 mg, daily (6)		5.59	0.60 (0.23–1.60)
	PPD$^-$ (235)	Placebo, daily (6)		2.73	1
	PPD$^-$ (224)	Isoniazid 300 mg, daily (6)		3.28	1.23 (0.55–2.76)
Mwinga (*86*)	PPD$^{+/-}$ (350)†	Placebo (isoniazid), twice weekly (6)	44 (13)	8.06	1
Zambia 1992–1996	PPD$^{+/-}$ (352)†	Isoniazid 900 mg, twice weekly (6)	27 (8)	4.94	0.62 (0.38–0.99)
	PPD$^{+/-}$ (351)†	Rifampin 600 mg/pyrazinamide 3500 mg twice weekly (3)	25 (7)	4.65	0.58 (0.35–0.95)
Gordin (*87*)	Anergic (257)	Placebo, daily (6)	6 (2)	0.9	1
United States 1991–1996	Anergic (260)	Isoniazid 300 mg, daily (6)	3 (1)	0.4	0.48 (0.12–1.91)
Halsey (*110*)	PPD$^+$ (370)	Isoniazid, 600–800 mg, twice weekly (6)	14 (4)	1.7	1
Haiti 1990–1994	PPD$^+$ (380)	Rifampin 450–600 mg/pyrazinamide 1500–2500 mg, twice weekly (2)	19 (5)	1.8	1.1
Gordin (*111*)	PPD$^+$ (792)	Isoniazid 300 mg, daily (12)	26 (3)	1.1	1
United States, Mexico, Haiti, Brazil 1991–1997	PPD$^+$ (791)	Rifampin 600 mg/pyrazinamide 20 mg/kg, daily (2)	19 (2)	0.8	0.67 (0.36–1.24)

*PPD$^+$ = PPD ≥5 mm; PPD$^-$ = PPD <5 mm.

† Percentage tuberculin-positive; 27% in placebo, 23% in isoniazid, and 22% in rifampin/pyrazinamide.

SOURCE: Adapted from Cohn DL, El-Sadr WM. Treatment of latent tuberculosis infection. *In*: Reichman LB, Hershfield E, eds. Tuberculosis: a comprehensive international approach, 2nd ed. New York: Marcel Dekker, 2000;471–502.

suggested that isoniazid did cause hepatitis and indicated that asymptomatic increase in hepatic transaminases occurred among persons receiving the drug (*89*). It was not until the 1970s, when several persons receiving isoniazid for LTBI died from hepatitis, that the likelihood of isoniazid hepatitis was understood (*9*).

The largest and most comprehensive study of isoniazid hepatitis was conducted by PHS during 1971–1972 (*11*). In this survey, nearly 14,000 persons who received isoniazid were monitored for the development of hepatitis. The overall rate of probable isoniazid hepatitis was 1%, but it was age related, with no cases occurring among persons younger than 20 yr of age and the highest rate (2.3%) occurring among persons older than 50 yr of age. An association of hepatitis also was found with alcohol consumption, with rates being fourfold higher among persons consuming alcohol daily than among those who did not drink alcohol. Rates among males and females were

equivalent and were lower among black males and higher among Asian males compared with rates among white males. Hepatitis rates were lower among participants in the IUAT trial, although the same positive association with age was observed (*32*). In the PHS surveillance study, eight deaths from hepatitis occurred among the participants, seven of which were among persons living in Baltimore. Several years after completion of the study, a review of death certificates showed a marked increase in deaths from cirrhosis during 1972 in Baltimore and surrounding counties, suggesting that another cofactor may have been associated with the cluster of deaths observed in the study (*90*).

A comprehensive analysis of deaths from isoniazid-associated hepatitis in the United States found that women may be at increased risk of death (*91*). Other reports have suggested that the risk for isoniazid-associated hepatitis may be increased by the administration of the drug to pregnant women in the third trimester and the immediate postpartum period (*92*) or by the concomitant administration of acetaminophen (*93*). Although experimental evidence suggests that acetaminophen hepatotoxicity is potentiated by isoniazid (*94*), a more detailed study of deaths from isoniazid-associated hepatitis did not implicate acetaminophen as a factor (*95*).

Isoniazid-related deaths continue to be reported. However, the likelihood of this occurrence can be greatly reduced by careful monthly monitoring and stopping of medication if symptoms occur (*96*). In a recent study, seven of eight patients receiving a liver transplant following the development of fulminant, isoniazid-related hepatitis continued to take the drug for a least 10 d after onset of symptoms of hepatotoxicity (*97*).

Following the PHS surveillance study, guidelines on the use of isoniazid for the treatment of LTBI were revised to recommend that low-risk persons older than 35 year of age with reactive tuberculin skin tests not be treated, that no more than 1 mo drug supply be issued at a time, and that monthly questioning and education about signs and symptoms of hepatitis should be routine (*12*). The guidelines were further revised to recommend baseline and periodic liver-function tests for persons at risk for hepatotoxicity, including persons aged 35 yr of age or older (*15*).

More recently, a survey found that many public health TB clinics now use clinical, rather than biochemical, monitoring for hepatotoxicity during treatment of LTBI (*98*). Clinical monitoring is based on educating patients about the symptoms of hepatotoxicity and instructing them to stop treatment immediately if such symptoms occur and to report to the clinician for evaluation. After using clinical monitoring exclusively, one public health TB clinic reported only 11 cases of clinical hepatotoxicity (one of which required hospitalization) and no deaths among more than 11,000 persons with LTBI during isoniazid treatment over a 7-yr period (*99*). Based on this emerging experience with clinical monitoring, some authorities have called for the establishment of new recommendations for drug toxicity monitoring "that are congruent with established therapeutic/toxicity relationships" (*98*).

Recent studies of isoniazid treatment of LTBI in HIV-infected persons have demonstrated that the medication was well tolerated and not associated with substantial increases in hepatic side effects. In a recent meta-analysis of placebo-controlled trials, adverse drug reactions were slightly but not significantly more common among persons receiving isoniazid (*88*).

Despite the high efficacy and relative safety of isoniazid treatment for LTBI, its use has been frequently debated; much literature has been published regarding whether and when to prescribe isoniazid (*13,100–102*). However, because the arguments

embodied in that literature emerged more than two decades ago, in a different environmental context with different risks and contingencies, its appropriateness to current circumstances is uncertain.

Although the likelihood that a patient treated with isoniazid would develop hepatitis was low, it presented a valid argument against the use of isoniazid among persons who had no increased risk for developing active TB. Most of the arguments concerning the use of this drug, which appeared from the 1970s through the early 1980s, focused on persons at low risk for reacting to tuberculin, primarily those 35 yr of age or older who were likely at higher risk for isoniazid-associated hepatitis than younger patients.

Because the debate over whether to prescribe or withhold isoniazid for persons older than 35 yr of age at low risk for reacting to tuberculin involved a trade-off between risk for developing active TB versus risk for developing isoniazid-induced hepatitis, decision analysis was used by most investigators (*103*). Despite many analyses, the decision to treat persons at low risk for reacting to tuberculin at any age continued to be controversial. Although various analyses supported both sides of the debate, none of the calculated benefits of isoniazid was substantial.

Short-course Regimens

Experimental studies in animals. Because of high rates of nonadherence with the long duration of isoniazid (i.e., 6–12 mo) and the rare occurrence of fatal isoniazid hepatitis, short-course, rifampin-containing treatment regimens have recently been evaluated. The studies evaluating rifampin were based on data from several studies in mouse models of chronic TB. One study compared isoniazid with regimens of rifampin alone; rifampin and pyrazinamide; and isoniazid, rifampin, and pyrazinamide (*104*). The rifampin-only regimen sterilized lung and spleen tissues within 4 mo, and the combination of rifampin and pyrazinamide sterilized tissues within 2 mo. The isoniazid, rifampin, and pyrazinamide regimen was of intermediate efficacy, taking longer than the rifampin and pyrazinamide regimen to sterilize tissues. The isoniazid regimen had not sterilized tissues by the end of 6 mo.

The apparent superiority of the rifampin–pyrazinamide regimen over the regimen containing the same two drugs plus isoniazid might be explained by impaired absorption of rifampin when given simultaneously with other drugs in mice (*105*). Support for this hypothesis came from a study using a Cornell mouse model (*106*) that compared 6-wk regimens of rifampin, rifampin–isoniazid, rifampin–pyrazinamide, and rifampin–pyrazinamide–isoniazid, with delayed administration of rifampin when given with other drugs. The efficacy of all three regimens was similar, with trend toward a lower colony count in spleens of animals given more drugs, and lower colony counts in the lungs of mice given rifampin–isoniazid. Experimental studies have also suggested that rifabutin alone, taken daily, and rifabutin–isoniazid, taken twice weekly, may effectively treat LTBI in 3 mo (*107*).

Clinical trials in HIV-negative persons. The only randomized clinical trial to evaluate rifampin-containing regimens among HIV-seronegative persons was conducted in tuberculin-positive persons with silicosis in Hong Kong (*36*). In this study, daily regimens of 6 mo of isoniazid, 3 mo of rifampin, or 3 mo of isoniazid and rifampin were compared with a 6-mo placebo control. Analyzing only those patients who were assumed to be compliant yielded an estimate of efficacy in preventing TB of 63% for the 3-mo rifampin regimen, 48% for the 6-mo isoniazid regimen, and 41% for the 3-mo isoniazid–rifampin regimen. All of these differences were significantly different from the placebo regimen

but were not statistically different from each other. The annual incidence rate was about 7% per year in the placebo group and about 4% per year in the three active-treatment regimens combined.

The largest programmatic experience using rifampin-based treatment of LTBI comes from Blackburn, England, where children at increased risk of TB have been treated with daily rifampin–isoniazid since 1981 (*108*). During 1981–1996, the treatment duration was shortened from 9 to 3 mo, and the proportion of pediatric TB case patients as a percentage of all reported cases decreased from 25 to 4%. Although not a controlled clinical trial, these data suggest that this intervention has been highly effective in reducing the rate of childhood TB in this city. Thus, this regimen is currently recommended for the treatment of both adults and children with LTBI in the United Kingdom (*109*).

Clinical trials in HIV-positive persons. Most clinical trials of rifampin-based treatment of LTBI have been conducted among HIV-infected persons (Table 6); two were placebo controlled. The Uganda study also evaluated regimens of isoniazid–rifampin and isoniazid–rifampin–pyrazinamide taken daily for 3 mo in tuberculin-positive persons (*84*). The isoniazid–rifampin regimen provided 59% protection, and the three-drug regimen with pyrazinamide provided 57% protection—levels similar to those provided by 6 mo of isoniazid alone. The Zambia study also evaluated a self-administered regimen of rifampin and pyrazinamide taken twice weekly for 3 mo (*86*). The level of protection was 42%, similar to that conferred by the 6-mo, twice-weekly isoniazid regimen. Among tuberculin-positive persons, the level of protection conferred by rifampin and pyrazinamide was 70%, comparable with that conferred by 6 mo of isoniazid taken twice weekly, but not statistically significant.

In two trials, rifampin and pyrazinamide regimens have been compared with regimens of isoniazid alone in tuberculin-positive persons. A second study conducted in Haiti during 1990–1994 compared twice-weekly regimens of 6 mo of isoniazid and 2 mo of rifampin and pyrazinamide, with half of the doses directly observed (*110*). Protection at 12 mo was similar in the two groups, and, compared with the rate of TB observed among patients who received placebo in the earlier Haiti trial, the twice-weekly regimens were estimated to have reduced the risk for TB by approximately 80%. A multinational study comparing a 12-mo regimen of isoniazid taken daily with a 2-mo regimen of rifampin and pyrazinamide taken daily was conducted in the United States, Haiti, Brazil, and Mexico (*111*). A total of 1583 patients were enrolled and followed for an average of 3 yr. The annual risk of culture-confirmed TB was 0.8% for patients assigned the 2-mo regimen and 1.1% for patients assigned the 12-mo isoniazid regimen, a difference that was not significant.

In conclusion, as evidenced by the large multinational study, a 2-mo regimen of rifampin and pyrazinamide taken daily provides protection against TB equivalent to a 12-mo regimen of isoniazid taken daily. The data supporting the use of a twice-weekly rifampin and pyrazinamide treatment regimen are less conclusive. The only study that has evaluated a rifampin-alone regimen, the Hong Kong study in persons with silicosis, suggests that daily rifampin for 3 mo provides similar protection to that conferred from 6 mo of isoniazid (*36*). In the Uganda study, 3-mo regimens of a) isoniazid and rifampin and b) isoniazid, rifampin, and pyrazinamide provided protection equivalent to that of 6 mo of isoniazid (*84*).

All of the studies of treatment of LTBI in HIV-infected persons included death and/or progression of HIV disease as endpoints. In the earlier Haiti study, isoniazid likely conferred protection against progression of HIV disease among tuberculin-positive

subjects (*83*). In the multinational study, persons receiving the 2-mo regimen had lower mortality rates and less progression of HIV disease, although these differences were not statistically significant (*111*). In none of the other studies was active treatment protective against death or HIV progression.

Safety and tolerability. Before the conduct of the studies in HIV-infected persons, a pilot study to assess the safety and tolerability of short-course regimens was conducted in 402 HIV-seronegative adults in North America (*112,113*). Participants were randomized to receive either 2 mo of rifampin and pyrazinamide, 4 mo of rifampin only, or 6 mo of isoniazid. The rifampin–pyrazinamide regimen was associated with a higher number of AST elevations of >100 IU (17 compared with only one in the rifampin group and five in the isoniazid group) and more frequent adverse reactions resulting in drug discontinuation (15 compared with none in the rifampin group and two in the isoniazid group). The rates of adverse reactions and abnormal AST elevations were higher than those reported in studies involving HIV-positive populations and those described in a clinical trial of isoniazid, rifampin, and pyrazinamide for the treatment of active TB in HIV-seronegative persons (*114*).

Two smaller pilot studies of rifampin and pyrazinamide treatment of LTBI using identical protocols were conducted in adults in Poland (*115*) and children in Germany (*116*). The results of the study in Poland were similar to those in the study in North America; the children in Germany tolerated the regimens well and did not experience changes in hepatic function.

In the Hong Kong study of patients with silicosis, no significant differences were noted in the occurrence of severe adverse reactions in the three drug regimens studied (*36*). However, patients receiving isoniazid had a higher incidence of abnormal liver function tests during treatment.

In the clinical trials involving HIV-infected persons, a trend of increased adverse reactions occurred among persons taking a daily regimen that included pyrazinamide. The Uganda study reported that persons taking the three-drug, pyrazinamide-containing regimen had higher rates of paresthesias, arthralgias, and significant increases in serum AST (*84*). The multinational study reported minimal increases in the number of persons receiving the 2-mo rifampin and pyrazinamide regimen who had the drugs permanently discontinued, most commonly because of nausea and vomiting and narcotic withdrawal (*111*). However, abnormal liver function tests were more common among patients taking isoniazid.

In the Haiti study conducted during 1990–1994 and the Zambia study, regimens of twice-weekly rifampin and pyrazinamide were well tolerated. In the Haiti study, no severe adverse reactions were observed; rates of abnormal liver function were low (1–3%) and did not differ by regimen (*110*). In the Zambia study, 3% of persons given isoniazid stopped treatment because of an adverse reaction compared with 4% of those given rifampin and pyrazinamide (*86*). Biochemical hepatitis was more frequent in the isoniazid group, whereas rash was more common in persons receiving rifampin and pyrazinamide.

Adherence

Testing for and treating LTBI requires several steps, including administering the test, reading the test, medically evaluating infected persons, initiating treatment, and completing therapy. Because persons with LTBI are not clinically ill and may not be

motivated to undergo treatment, nonadherence occurs commonly in all steps of the treatment process.

The health care system can compromise patient adherence to testing and treatment of LTBI (*117*). A lengthy referral process may discourage patients from being evaluated for a positive tuberculin test or initiating treatment for LTBI. Long waiting times in the clinic may also discourage patients from attending follow-up visits. Other factors that may affect adherence with testing and treatment include the clinic's hours of operation, distance of the clinic from the patient's home, the cleanliness of the clinic, and the attitude of clinic staff.

Since the advent of effective chemotherapy for active TB, adherence to treatment regimens has been recognized as a substantial problem for TB control—especially for treatment of LTBI. Recent data reported to CDC indicate that only 60% of patients who start treatment for LTBI complete at least 6 mo of treatment (CDC, TB Program Management Reports); adherence is influenced by the length of therapy, complexity of the regimen, and side effects of the medications. Adherence to treatment decreases with time, whereas the efficacy of the regimen increases with the length of therapy (*32*). Patients may be more adherent to the 2-mo regimen of rifampin and pyrazinamide because of the shorter length of therapy; however, this regimen also involves taking multiple medications, and patients may not tolerate this regimen as well as isoniazid, thus potentially resulting in nonadherence.

The Haiti study of rifampin and pyrazinamide taken twice weekly and the multinational study both reported better adherence with the shorter, 2-mo regimens. In the Haiti study, 74% of persons assigned to the 2-mo rifampin and pyrazinamide regimen were believed to have taken ≥80% of the prescribed medication compared with 55% of persons taking isoniazid for 6 mo (*110*). Nonadherence was similar during the first 2 mo of therapy for both groups. The multinational study reported an 80% completion rate for persons assigned to the 2-mo rifampin and pyrazinamide regimen compared with 69% for the 12-mo isoniazid regimen (*111*). In the pilot study of HIV-seronegative persons, during the first 2 mo of therapy about 60% of those assigned to the rifampin and pyrazinamide regimen were judged to be nonadherent, compared with about 20% of those assigned to the 6-mo isoniazid regimen (*113*). However, overall completion rates were lower for the isoniazid regimen because of continued nonadherence during the last 4 mo of therapy.

Determinants of adherence to treatment of TB and LTBI are not well understood (*118*). For example, demographic factors are not reliable predictors of adherence. However, culturally influenced beliefs and attitudes may result in misinformation about TB and may adversely affect adherence (*119*). The main strategies that have been employed to promote adherence with treatment of LTBI are patient education (*120*), the use of lay health workers from the patient's social and/or cultural group (*118,121*), incentives (e.g., cash payments) (*122*), and directly observed therapy (DOT) (*64*).

The intervention most likely to improve adherence for treatment of LTBI has been DOT, which requires direct observation of the patient ingesting each dose of medication and usually includes the provision of comprehensive services that attempt to meet the patient's basic needs and the use of incentives and enablers (*123–125*). Although randomized trials have yet to be reported, available information suggests that DOT leads to higher rates of completion than self-supervised therapy, and, under certain circumstances, is more cost effective (*67*).

RECOMMENDATIONS

Implementation of Targeted Tuberculin Testing

Decision to Tuberculin Test Is Decision to Treat

Targeted tuberculin testing programs should be designed for one purpose: to identify persons at high risk for TB who would benefit by treatment of LTBI. Following that principle, targeted tuberculin testing programs should be conducted among groups at risk for recent infection with *M. tuberculosis* and those who, regardless of duration of infection, are at increased risk for progression to active TB (Table 7). With the exception of initial testing of persons at low risk whose future activity will place them at increased risk of exposure (e.g., employment in a setting where TB transmission may occur), screening of low-risk persons is discouraged because it diverts resources from activities of higher priority. In addition, a substantial proportion of tuberculin-test-positive persons from low-risk populations may have false-positive skin tests (*73*).

Testing is also discouraged unless a plan has been developed to complete a course of treatment in persons found to have LTBI. Such planning should include arrangements for medical evaluation (e.g., chest radiographs) of persons with positive skin tests and for the medical supervision of the course of treatment.

Identification and Access to High-risk Groups

A flexible approach to identifying high-risk groups is recommended, and state and local public health agencies are encouraged to analyze their TB case reports and data obtained from tuberculin skin testing to identify high-risk groups based on local trends in the epidemiology of TB. Thus designing and conducting skin-test-screening surveys to determine whether population groups are at high risk for TB may be desirable. Populations at risk can be accessed at HIV treatment facilities, drug treatment centers, homeless shelters, community health centers and schools serving foreign-born persons, and selected community-based organizations. Mandated skin-testing programs (e.g., those that formerly were conducted among teachers and foodhandlers) should be discouraged unless the targeted groups contain substantial proportions of persons at high risk (*126*).

Role of the Health Department

In this community-based approach to targeted testing and treatment of LTBI, the health department TB program should be instrumental in planning and coordination, setting performance standards, and overseeing quality of service. The health department is responsible for assessing the community's TB problem, identifying high-risk groups based on the local epidemiology of TB, and ascertaining the sites of most convenient access to those groups. In addition, the health department should assume responsibility for organizing the community-based approach, recruiting health professionals, educating such professionals about TB, and motivating them to institute targeted testing and treatment programs. The health department should also serve as advisor, consultant, and facilitator to community providers and institutions that conduct testing and treatment programs. The health department should assist in identifying potential funding sources and ensure linkages with essential clinical and

consultation sources. It should provide in-service training on tuberculin skin testing and treatment, written protocols for activities including patient tracking and skin testing, and patient and provider educational material translated into appropriate languages. The health department may also need to provide chest radiography and subsidize the supply of antituberculosis drugs. Finally, the health department should be responsible for providing or facilitating the ongoing evaluation of community-based targeted testing and treatment programs, including development and monitoring of program indicators (e.g., rates of skin tests administered that are read, proportion of tests read that are positive, and initiation and completion rates of treatment). The health department should also routinely collect and review these data to determine yield and relative effectiveness of targeted testing and treatment of LTBI in the community.

To achieve a high rate of acceptance of testing and completion of treatment in a community-based program, barriers to success should be anticipated, identified, and managed. The concept of taking drugs to treat a latent infection that is not causing current health problems is unfamiliar to most persons, and education of the patient is essential (*120*). Other known barriers include culturally derived health beliefs that differ from those of Western medicine, inability to communicate with medical providers in one's primary language, inability to afford the costs of medical evaluation and treatment, and lack of access to medical care (*118*). Patients should not be expected to pay directly for public health interventions (e.g., testing, evaluation, and treatment of LTBI). The more convenient this process of testing and treatment, the more likely patients will adhere to therapy—especially as targeted testing and treatment of LTBI are extended beyond the province of public health TB clinics to sites where primary health care is delivered.

Diagnosis of Latent Tuberculosis Infection

Tuberculin Skin Testing

Administering and reading tests. The tuberculin test, like all medical tests, is subject to variability, but many of the inherent variations in administering and reading tests can be avoided by careful attention to details. The preferred skin test for *M. tuberculosis* infection is the intradermal, or Mantoux, method. It is administered by injecting 0.1 ml of 5 tuberculin units (TU) PPD intradermally into the dorsal or volar surface of the forearm. Tests should be read 48–72 h after test administration, and the transverse diameter of induration should be recorded in millimeters. Multiple puncture tests (i.e., Tine and Heaf) and PPD strengths of 1 TU and 250 TU are not sufficiently accurate and should not be used.

Interpreting skin-test reactions. Based on the sensitivity and specificity of the tuberculin skin test and the prevalence of TB in different groups, three cut-off levels have been recommended for defining a positive tuberculin reaction: ≥5 mm, ≥10 mm, and ≥15 mm of induration (Table 7). For persons who are at highest risk for developing TB disease if they become infected with *M. tuberculosis*, a cut-off level of ≥5 mm is recommended. Persons who are immunosuppressed because of disease (e.g., HIV infection) or drugs (e.g., systemic corticosteroids) have a high likelihood of developing TB disease if they are infected with *M. tuberculosis*. Likewise, persons who have had recent close contact with an infectious TB case patient and those with abnormal chest

Table 7. Criteria for tuberculin positivity, by risk group

Reaction ≥5 mm of induration	Reaction ≥10 mm of induration	Reaction ≥15 mm of induration
Human immunodeficiency virus (HIV)-positive persons	Recent immigrants (i.e., within the last 5 yr) from high prevalence countries	Persons with no risk factors for TB
Recent contacts of tuberculosis (TB) case patients	Injection drug users	
Fibrotic changes on chest radiograph consistent with prior TB	Residents and employees† of the following high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other health care facilities, residential facilities for patients with acquired immunodeficiency syndrome (AIDS), and homeless shelters	
Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of ≥15 mg/d of prednisone for 1 mo or more)*	Mycobacteriology laboratory personnel	
	Persons with the following clinical conditions that place them at high risk: silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (e.g., leukemias and lymphomas), other specific malignancies (e.g., carcinoma of the head or neck and lung), weight loss of ≥10% of ideal body weight, gastrectomy, and jejunoileal bypass	
	Children younger than 4 yr of age or infants, children, and adolescents exposed to adults at high-risk	

*Risk of TB in patients treated with corticosteroids increases with higher dose and longer duration.

† For persons who are otherwise at low risk and are tested at the start of employment, a reaction of ≥15 mm induration is considered positive.

SOURCE: Adapted from Centers for Disease Control and Prevention. Screening for tuberculosis and tuberculosis infection in high-risk populations: recommendations of the Advisory Council for the Elimination of Tuberculosis. MMWR 1995;44(No. RR-11):19–34.

radiographs consistent with prior TB are at high risk for TB. Thus, to ensure that persons at highest risk are evaluated and appropriately treated, the sensitivity provided by a ≥5 mm cut-off for a positive test is appropriate.

A reaction of ≥10 mm of induration should be considered positive for those persons with an increased probability of recent infection or with other clinical conditions that increase the risk for TB (e.g., recent immigrants from high-prevalence countries and injection drug users) (Table 7). In addition to those groups listed, high-prevalence populations identified by analysis of local epidemiologic data should be targeted for testing.

Routine tuberculin testing is not recommended for populations at low risk for LTBI. However, if these persons are tested (e.g., at entry into a work site where risk for exposure to TB is anticipated and a longitudinal tuberculin testing program is in place), a higher cut-off of ≥15 mm is recommended.

Skin-test conversion. For persons with negative tuberculin skin-test reactions who undergo repeat skin testing (e.g., health care workers), an increase in reaction size of ≥10 mm within a period of 2 yr should be considered a skin-test conversion indicative of recent infection with *M. tuberculosis*.

Previous vaccination with BCG. Tuberculin skin testing is not contraindicated for persons who have been vaccinated with BCG, and the skin-test results of such persons can be used as described to support or exclude the diagnosis of *M. tuberculosis* infection. However, no method can reliably distinguish tuberculin reactions caused by vaccination with BCG from those caused by natural mycobacterial infections. Therefore, a positive reaction to tuberculin in BCG-vaccinated persons indicates infection with *M. tuberculosis* when the person tested is at increased risk for recent infection or has medical conditions that increase the risk for disease (Table 7).

Anergy testing in persons infected with HIV. Anergy testing is not recommended for routine use in persons who are infected with HIV or otherwise immunocompromised (*77*). However, it may assist in guiding individual treatment decisions in selected situations.

Chest Radiographs

A chest radiograph is indicated for all persons being considered for treatment of LTBI to exclude active pulmonary TB. Children younger than 5 yr of age should have both posterior–anterior and lateral radiographs. All other persons should receive posterior–anterior radiographs; additional radiographs should be performed at the physician's discretion. Because of the risk for progressive and/or congenital TB, pregnant women who have a positive tuberculin skin test or who have negative skin-test results but who are recent contacts of persons with infectious TB disease should have chest radiographs (with appropriate shielding) as soon as feasible, even during the first trimester of pregnancy.

If chest radiographs are normal and no symptoms consistent with active TB are present, tuberculin-positive persons may be candidates for treatment of LTBI. If radiographic or clinical findings are consistent with pulmonary or extrapulmonary TB, further studies (e.g., medical evaluation, bacteriologic examinations, and a comparison of the current and old chest radiographs) should be done to determine if treatment for active TB is indicated.

Sputum Examinations

Sputum examination is not indicated for most persons being considered for treatment of LTBI. However, persons with chest radiographic findings suggestive of prior, healed TB infections should have three consecutive sputum samples, obtained on different days, submitted for AFB smear and culture. Most persons with radiographs that show only calcified pulmonary nodules do not require bacteriologic examination. HIV-infected persons with respiratory symptoms who are being considered for treatment of LTBI should also have sputum specimens submitted for mycobacterial examination, even if the chest radiograph is normal. If the results of sputum smears and cultures are negative and respiratory symptoms can be explained by another etiology, the person is a candidate for treatment of LTBI. If bacteriologic results are negative but the activity or etiology of a radiographic abnormality is questionable, further evaluation with bronchoscopy or needle aspiration biopsy should be undertaken. Single drug treatment of LTBI should not be started until active TB has been excluded. In such situations, multidrug therapy can be started and continued pending results of sputum cultures. A repeat chest film should be obtained to exclude active TB, as indicated by improvement in the abnormality even in the presence of negative cultures.

Treatment of Latent Tuberculosis Infection

Individual Drugs

Isoniazid. Isoniazid is the most widely used of the antituberculosis agents—it is bactericidal, relatively nontoxic, easily administered, and inexpensive. Isoniazid is highly active against *M. tuberculosis* (most strains being inhibited *in vitro* by concentrations of 0.05–0.20 µg/ml). Absorption from the gastrointestinal tract is nearly complete, with peak serum concentrations of 2–5 µg/ml occurring 0.5–2.0 h after administration of a 300-mg dose. The drug penetrates well into all body fluids and cavities, producing concentrations similar to those found in serum. Hepatitis is the most severe toxic effect of isoniazid, and alcohol consumption may increase toxicity (Table 8). Peripheral neuropathy, caused by interference with metabolism of pyridoxine, is associated with isoniazid administration but is uncommon at a dose of 5 mg/kg. In persons with conditions in which neuropathy is common (e.g., diabetes, uremia, alcoholism, malnutrition, and HIV infection), pyridoxine should be given with isoniazid. Pregnant women and persons with seizure disorders should also take both pyridoxine and isoniazid. Mild central nervous system effects are common with isoniazid and may necessitate adjustments in the timing of administration of the drug to enhance compliance. The interaction of isoniazid and phenytoin increases the serum concentration of both drugs. When these drugs are given concomitantly, the serum level of phenytoin should be monitored. No known interactions exist between isoniazid and the antiretroviral medications used for the treatment of HIV infection.

Rifampin. Rifampin is a rifamycin derivative that is bactericidal for *M. tuberculosis*. Most strains of *M. tuberculosis* are inhibited in vitro by concentrations of 0.5 µg/ml. It is quickly absorbed from the gastrointestinal tract, with peak serum concentrations of 7–14 µg/ml occurring 1.5–3.0 h after ingestion. Although approximately 75% of the drug is protein bound, it penetrates well into tissues and cells. Penetration through noninflamed meninges is poor, but therapeutic concentrations are achieved in cerebrospinal fluid when the meninges are inflamed. The most common adverse reaction to rifampin is gastrointestinal upset. Other reactions include skin eruptions, hepatitis, and, rarely, thrombocytopenia (Table 8). The frequency of these reactions is low. Because rifampin induces hepatic microsomal enzymes, it may accelerate clearance of drugs metabolized by the liver (e.g., methadone, coumadin derivatives, glucocorticoids, hormonal contraceptives, oral hypoglycemic agents, digitalis, anticonvulsants, dapsone, ketoconazole, and cyclosporin). By accelerating the metabolism of estrogen, rifampin may interfere with the effectiveness of oral contraceptives. In persons with HIV infection who are taking HIV protease inhibitors, rifampin is usually contraindicated because drug interactions between rifampin and these agents can lead to increased rifampin levels and decreased protease-inhibitor levels, resulting in increased risk for rifampin toxicity and decreased protease-inhibitor efficacy. Rifampin is also contraindicated or should be used with caution in HIV-infected patients who are taking non-nucleoside reverse transcriptase inhibitors (NNRTIs). Intermittent administration of doses of rifampin >10 mg/kg may be associated with thrombocytopenia, an influenza-like syndrome, hemolytic anemia, and acute renal failure. However, these reactions are uncommon at the recommended dose of 10 mg/kg/d. Rifampin is excreted in urine, tears, sweat, and other body fluids and colors them orange. Patients should be advised of discoloration of body fluids and of possible permanent discoloration of soft contact lenses.

Pyrazinamide. Pyrazinamide is bactericidal for *M. tuberculosis* in an acid environment. The drug is active against organisms in macrophages, presumably because of the acid environment within the cell. At a pH of 5.5, the minimal inhibitory concentration of pyrazinamide for *M. tuberculosis* is 20 µg/ml. Absorption from the gastrointestinal tract is nearly complete, with peak serum concentrations of 30–50 µg/ml occurring approximately 2 h after ingestion with doses of 20–25 mg/kg. The most common side effect of pyrazinamide is gastrointestinal upset (Table 8). The most severe adverse reaction is liver injury. No substantial increase in hepatotoxicity results from adding 15–30 mg/kg of pyrazinamide to a regimen of rifampin during 2 mo of therapy for active TB (*114*). Hyperuricemia also occurs, but acute gout is uncommon (*127*). No known interactions exist between pyrazinamide and antiretroviral medications.

Rifabutin. Rifabutin is another rifamycin that is highly active against *M. tuberculosis*. Its mechanism of action is the same as that of rifampin, so that most rifampin-resistant strains are also resistant to rifabutin. Most strains of *M. tuberculosis* are inhibited by concentrations of 0.1 µg/ml. A dose of 300 mg results in peak serum concentrations of 5 µg/ml after 2–3 h. The major advantage of rifabutin is the longer serum half-life and reduced hepatic induction of microsomal metabolism compared with that of rifampin. Rifabutin is extensively metabolized in the liver (and to a lesser extent in the intestinal wall); only 8% of a dose is excreted unchanged in the urine. Doses of up to 300 mg daily are usually well tolerated. Side effects attributed to rifabutin include rash, gastrointestinal intolerance, neutropenia, myalgias, and dysguesia. Hepatotoxicity is rare, but rifabutin can cause drug-induced hepatitis. Rates of side effects increase when rifabutin is administered with a CYP-3A4 inhibitor (e.g., clarithromycin); side effects that have been noted under these circumstances include uveitis (*128*) and abnormal skin pigmentation (*129*). Similar to rifampin, rifabutin can also decrease concentrations and clinical efficacy of methadone, coumadin derivatives, glucocorticoids, hormonal contraceptives, oral hypoglycemic agents, digitalis, anticonvulsants, dapsone, ketoconazole, and cyclosporin, as well as itraconazole, ß-blockers, and theophylline. Doses of these medications may have to be increased when administered with rifabutin. When administered with rifabutin, protease inhibitors, used for the treatment of HIV infection, may lead to increased levels of rifabutin and decreased levels of the protease inhibitor; however, these effects are generally less than those that occur with rifampin and can be accommodated by dose adjustments (Table 8). NNRTIs, used for the treatment of HIV infection, may also necessitate rifabutin dose adjustment.

Treatment Regimens

Treatment of LTBI is an essential part of the strategy to eliminate TB in the United States. Persons with LTBI who are included among those at increased risk for TB should be offered treatment. The choice of the specific treatment regimen is based on many considerations as detailed in the following sections.

U.S. Public Health Service Rating System. To help clinicians make informed treatment decisions based on the most current research results, evidence-based ratings are assigned to the drug treatment recommendations (general recommendations have no rating) (Table 9). The ratings system is similar to that used in previous PHS documents (*3*) and includes a letter and a Roman numeral: the letter indicates the strength of the recommendation, and the Roman numeral indicates the quality of the evidence supporting the recommendation. Thus, clinicians can use the ratings to differentiate

Table 8. Medications to treat latent tuberculosis infection: doses, toxicities, and monitoring requirements

Drug	Oral dose (mg/kg) (maximum dose)				Adverse reactions	Monitoring	Comments
	Daily		Twice weekly*				
	Adults	Children	Adults	Children			
Isoniazid	5 (300 mg)	10–20 (300 mg)	15 (900 mg)	20–40 (900 mg)	Rash Hepatic enzyme elevation Hepatitis Peripheral neuropathy Mild central nervous system effects Drug interactions resulting in increased phenytoin (Dilantin) or Disulfiram (Antabuse) levels	Clinical monitoring monthly Liver function tests† at baseline in selected cases‡ and repeat measurements if: Baseline results are abnormal Patient is pregnant, in the immediate postpartum period, or at high risk for adverse reactions Patient has symptoms of adverse reactions	Hepatitis risk increases with age and alcohol consumption Pyridoxine (vitamin B_6, 10–25 mg/d) might prevent peripheral neurophathy and central nervous system effects
Rifampin	10 (600 mg)	10–20 (600 mg)	10 (600 mg)	—	Rash Hepatitis Fever Thrombocytopenia Flu-like symptoms Orange-colored body fluids (secretions, urine, tears)	Clinical monitoring at weeks 2, 4, and 8 when pyrazinamide given Complete blood count, platelets, and liver function tests† at baseline in selected cases‡ and repeat measurements if Baseline results are abnormal Patient has symptoms of adverse reactions	Rifampin is contraindicated or should be used with caution in human immunodeficiency virus (HIV)-infected patients taking protease inhibitors (PIs) or nonnucleoside reverse transcriptase inhibitors (NNRTIs) Decreases levels of many drugs (e.g., methadone, coumadin derivatives, glucocorticoids, hormonal contraceptives, estrogens, oral hypoglycemic agents, digitalis, anticonvulsants, dapsone, ketoconazole, and cyclosporin) Might permanently discolor soft contact lenses

Table 8. *(Continued)* Medications to treat latent tuberculosis infection: doses, toxicities, and monitoring requirements

Drug	Oral dose (mg/kg) (maximum dose)				Adverse reactions	Monitoring	Comments
	Daily		Twice weekly*				
	Adults	Children	Adults	Children			
Rifabutin	5 (300 mg)[§]	—	5 (300 mg)[§]	—	Rash Hepatitis Fever Thrombocytopenia Orange-colored body fluids (secretions, urine, tears) With increased levels of rifabutin Severe arthralgias Uveitis Leukopenia	Clinical monitoring at Weeks 2, 4, and 8 when pyrazinamide given Complete blood count, platelets, and liver function tests[†] at baseline in selected cases[‡] and repeat measurements if Baseline results are abnormal Patient has symptoms of adverse reactions Use adjusted daily dose of rifabutin and monitor for decreased antiretroviral activity and for rifabutin toxicity if rifabutin taken concurrently with PIs or NNRTIs[§]	Rifabutin is contraindicated for HIV-infected patients taking hard-gel saquinavir or delavirdine; caution is also advised if rifabutin is adminis tered with soft-gel saquinavir Reduces levels of many drugs (e.g., PIs, NNTRIs, methadone, dapsone, ketoconazole, coumadin derivatives, hormonal contraceptive, digitalis, sulfonylureas, diazepam, ß-blockers, anticonvulsants, and theophylline) Might permanently discolor contact lenses
Pyrazinamide	15–20 (2.0 g)		50 (4.0 g)	—	Gastrointestinal upset Hepatitis Rash Arthralgias Gout (rare)	Clinical monitoring at Weeks 2, 4, and 8 Liver function tests[†] at baseline in selected cases[‡] and repeat measurements if Baseline results are abnormal Patient has symptoms of adverse reactions	Treat hyperuricemia only if patient has symptoms Might make glucose control more difficult in persons with diabetes Should be avoided in pregnancy but can be given after first trimester

* All intermittent dosing should be administered by directly observed therapy.

† AST or ALT and serum bilirubin.

‡ HIV infection, history of liver disease, alcoholism, and pregnancy.

§ If nelfinavir, indinavir, amprenavir, or ritonavir is administered with rifabutin, blood concentrations of these protease inhibitors decrease. Thus, the dose of rifabutin is reduced from 300 mg to 150 mg/d when used with nelfinavir, indinavir, or amprenavir; and to 150 mg (two or three times a week) when used with ritonavir. If efavirenz is administered with rifabutin, blood concentrations of rifabutin decrease. Thus, when rifabutin is used concurrently with efavirenz, the daily dose of rifabutin should be increased from 300 mg to 450 mg or 600 mg. Pharmacokinetic studies suggest that rifabutin might be given at usual doses with nevirapine. It is not currently known whether dose adjustment of rifabutin is required when used concurrently with soft-gel saquinavir. For patients receiving multiple PIs or a PI in combination with an NNRTI, drug interactions with rifabutin are likely more complex; in such situations, the use of rifabutin is not recommended until additional data are available.

Table 9. Adapted Public Health Service rating system for the strength of treatment recommendations and quality of evidence

Strength of the recommendation
A. Preferred; should generally be offered
B. Alternative; acceptable to offer
C. Offer when preferred or alternative regimens cannot be given
D. Should generally not be offered
E. Should never be offered
Quality of evidence supporting the recommendation
I. At least one randomized trial with clinical endpoints
II. Clinical trials that either are not randomized or were conducted in other populations
III. Expert opinion

between recommendations based on data from clinical trials and those based on the opinions of experts familiar with the relevant clinical practice and scientific rationale for such practice (when clinical trial data are not available).

Recommended regimens. Four regimens are recommended for the treatment of adults with LTBI (Table 10). The antituberculosis medications used in these regimens have varying doses, toxicities, and monitoring requirements (Table 8). All patients being given twice-weekly treatment should receive DOT, because nonadherence to intermittent dosing results in a larger proportion of the total doses missed than does daily dosing. DOT should be used whenever feasible, especially with 2-mo regimens and in certain settings (e.g., some institutional settings, community outreach programs, and for some persons living in households with patients who are receiving home-based DOT for active TB).

Isoniazid for 9 mo. The isoniazid daily regimen for 9 mo receives an A recommendation. Prospective, randomized trials of up to 12 mo of therapy in HIV-uninfected persons suggest that the maximal beneficial effect of isoniazid is achieved by 9 mo; minimal additional benefit is gained by extending treatment to 12 mo. Thus, this updated recommendation represents a shortening of the previous recommendation of isoniazid daily for 12 mo for HIV-infected persons and a lengthening of the previously recommended 6 mo for HIV-uninfected persons (*1*). Both 12-mo and 6-mo regimens of isoniazid have substantially reduced rates of TB in HIV-infected persons compared with placebo (*88*), but the 6-mo regimen has not been directly compared with the 12-mo regimen in HIV-infected persons. Thus, the recommendation for 9 mo of isoniazid in HIV-infected persons is based on extrapolation of available data. Intermittent dosing of 9 mo of isoniazid for treatment of LTBI has not been studied comparatively. However, analogous with the continuation phase of treatment for active TB (where twice-weekly dosing is equivalent to daily dosing), twice-weekly dosing of isoniazid is also acceptable for treatment of LTBI, but is recommended at the B level as an acceptable alternative regimen.

Isoniazid for 6 mo. Although a 9-mo regimen of isoniazid is the preferred treatment of LTBI for an individual patient, a 6-mo regimen also provides substantial protection and has been demonstrated to be superior to placebo in both HIV-infected and HIV-uninfected persons (*32,84*). From a societal perspective, treatment for 6 mo rather than 9 mo may provide a more cost-effective outcome (*81*). Thus, based on individual situations, health departments or other providers may prefer to concentrate efforts in

Table 10. Recommended drug regimens for treatment of latent tuberculosis (TB) infection in adults

Drug	Interval and duration	Comments	Rating* (Evidence)† HIV⁻	HIV⁺
Isoniazid	Daily for 9 mo[‡,§]	In human immunodeficiency virus (HIV)-infected patients, isoniazid may be administered concurrently with nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors, or non-nucleoside reverse transcriptase inhibitors (NNRTIs)	A (II)	A (II)
	Twice weekly for 9 mo[‡,§]	Directly observed therapy (DOT) must be used with twice-weekly dosing	B (II)	B (II)
Isoniazid	Daily for 6 mo[§]	Not indicated for HIV-infected persons, those with fibrotic lesions on chest radiographs, or children	B (I)	C (I)
	Twice weekly for 6 mo[§]	DOT must be used with twice-weekly dosing	B (II)	C (I)
Rifampin plus pyrazinamide	Daily for 2 mo	May also be offered to persons who are contacts of pyrazinamide patients with isoniazid-resistant, rifampin-susceptible TB	B (II)	A (I)
		In HIV-infected patients, protease inhibitors or NNRTIs should generally not be administered concurrently with rifampin; rifabutin can be used as an alternative for patients treated with indinavir, nelfinavir, amprenivir, ritonavir, or efavirenz, and possibly with nevirapine or soft-gel saquinavir[¶]		
	Twice weekly for 2–3 mo	DOT must be used with twice-weekly dosing	C (II)	C (I)
Rifampin	Daily for 4 mo	For persons who cannot tolerate pyrazinamide	B (II)	B (III)
		For persons who are contacts of patients with isoniazid-resistant, rifampin-susceptible TB who cannot tolerate pyrazinamide		

* Strength of recommendation: A=preferred; B=acceptable alternative; C=offer when A and B cannot be given.

† Quality of evidence: I=randomized clinical trial data; II=data from clinical trials that are not randomized or were conducted in other populations; III=expert opinion.

‡ Recommended regimen for children younger than 18 yr of age.

§ Recommended regimens for pregnant women. Some experts would use rifampin and pyrazinamide for 2 mo as an alternative regimen in HIV-infected pregnant women, although pyrazinamide should be avoided during the first trimester.

¶ Rifabutin should not be used with hard-gel saquinavir or delavirdine. When used with other protease inhibitors or NNRTIs, dose adjustment of rifabutin may be required (see Table 8).

ensuring the implementation of a 6-mo rather than a 9-mo course of isoniazid. Isoniazid for 6 mo, taken either daily or twice weekly, is recommended at the B level for HIV-negative persons and at the C level for HIV-positive persons. The shorter regimen is not recommended for children or persons with radiographic evidence of prior tuberculosis.

Rifampin and pyrazinamide for 2 mo. The 2-mo daily regimen of rifampin and pyrazinamide is recommended on the basis of a prospective randomized trial of treatment of LTBI in HIV-infected persons that demonstrated the 2-mo regimen to be similar in safety and efficacy to a 12-mo regimen of isoniazid (*111*). Although this regimen has not been evaluated in HIV-uninfected persons with LTBI, the efficacy is not expected to differ significantly. However, the toxicities may be increased (*113*); therefore, the recommendation is made at the A level for HIV-infected persons and at the B level for HIV-uninfected persons until further data are available. Two randomized, prospective trials of intermittent dosing of rifampin and pyrazinamide for 2 and 3 mo, respectively, have been reported in HIV-infected persons (*86, 110*); in neither case was the sample size adequate to conclude with certainty that efficacy was equivalent to daily dosing. Moreover, both studies compared the twice-weekly rifampin and pyrazinamide regimen to the 6-mo isoniazid regimen. Therefore, rifampin and pyrazinamide given twice weekly for 2–3 mo may be considered when alternative regimens cannot be given. This recommendation is made at the C level.

Rifampin for 4 mo. Rifampin given daily for 3 mo has resulted in better protection than placebo in treatment of LTBI in HIV-uninfected persons with silicosis in a randomized prospective trial (*36*). However, because the patients receiving rifampin had a high rate of active TB (4%), experts have concluded that a 4–mo regimen would be more prudent when using rifampin alone. This 4-mo rifampin regimen is recommended at the B level for both HIV-infected and HIV-uninfected persons. This option may be useful for patients who cannot tolerate isoniazid or pyrazinamide.

Choice of regimen. Because more than one regimen can be used to treat LTBI, health care providers should discuss options with the patient, and, when possible, help patients make the decision, unless medical indications dictate a specific regimen. Discussion should include the length and complexity of the regimens, possible adverse effects, and potential drug interactions.

Completion of treatment. Completion of therapy is based on total number of doses administered—not on duration of therapy alone. The 9-mo regimen of daily isoniazid should consist of 270 doses, at minimum, administered within 12 mo, allowing for minor interruptions in therapy. The 6-mo regimen of isoniazid should consist of at least 180 doses administered within 9 mo. Twice-weekly isoniazid regimens should consist of at least 76 doses administered within 12 mo for the 9-mo regimen and 52 doses within 9 mo for the 6-mo regimen. The daily regimen of rifampin (or rifabutin) and pyrazinamide should consist of at least 60 doses to be administered within 3 mo. The regimen of daily rifampin alone should consist of at least 120 doses administered within 6 mo.

Ideally, patients should receive medication on a regular dosing schedule until completion of the indicated course. However, in practice some doses may be missed, requiring the course to be lengthened. When reinstituting therapy for patients who have interrupted treatment, clinicians might need to continue the regimen originally prescribed (as long as needed to complete the recommended duration of the particular

regimen) or renew the entire regimen if interruptions were frequent or prolonged enough to preclude completion of treatment as recommended. In either situation, when therapy is restored after an interruption of more than 2 mo, a medical examination to rule out active TB disease is indicated.

Special considerations.

Treatment of HIV-infected persons. Recommendations for HIV-infected adults largely parallel those for HIV-uninfected adults, although the quality of evidence and strengths of the recommendations vary (Table 10). However, when isoniazid is chosen for treatment of LTBI in persons with HIV infection, 9 mo is recommended rather that 6 mo. In addition, rifampin is generally contraindicated or should be used with caution in persons who are taking protease inhibitors (PIs) or NNRTIs (*169*). Experts have recommended that for HIV-infected persons who are candidates for treatment of LTBI and need PI or NNRTI therapy, rifabutin can be substituted for rifampin in some circumstances; rifabutin can safely be used with indinavir, nelfinavir, amprenavir, ritonavir, and efavirenz, but not with hard-gel saquinavir, or delavirdine. Caution is advised if rifabutin is administered with soft-gel saquinavir, because data regarding use of rifabutin with soft-gel saquinavir or nevirapine are limited.

No specific data have been generated for treatment of LTBI with rifabutin-containing regimens, but such a recommendation is supported by analogy with treatment for active TB (where rifabutin can be substituted for rifampin with no loss of efficacy) and by experimental studies in mice (*107,130*). Rifabutin can be administered at one half the usual daily dose (i.e., reduced from 300 mg to 150 mg/d) with indinavir, nelfinavir, or amprenavir or at one-fourth the usual dose (i.e., 150 mg every other day or three times a week) with ritonavir. The daily rifabutin dose is 450 mg or 600 mg when used with efavirenz; pharmacokinetic studies suggest that rifabutin might be given at usual doses with nevirapine. For patients receiving multiple PIs or a PI in combination with an NNRTI, drug interactions with rifabutin are likely more complex; in such situations, the use of rifabutin is not recommended until additional data are available. The substitution of rifapentine for rifampin is not recommended because rifapentine's safety and effectiveness have not been established for patients infected with HIV (*131*). Furthermore, the drug interactions between rifapentine and HIV protease inhibitors have not been studied in detail, although one study has indicated that rifapentine causes substantial reduction in the serum level of indinavir when the drugs are given together (*132*).

In tuberculin-negative, HIV-infected persons, treatment of LTBI has not been effective (*3*). However, most tuberculin-negative HIV-infected contacts of patients with active TB should receive treatment for presumptive LTBI—even when repeat testing after contact has ended is not indicative of LTBI. Furthermore, some experts recommend treatment of possible LTBI for HIV-infected residents of institutions that pose an ongoing high risk for exposure to *M. tuberculosis* (e.g., prisons, jails, and homeless shelters).

Persons with fibrotic lesions/suspected disease. For patients who have a chest radiograph demonstrating old fibrotic lesions thought to represent previous infection with TB and a positive tuberculin skin test (≥5 mm) without evidence of active disease and no history of treatment for TB, three acceptable regimens can be used for treatment. These regimens include 9 mo of isoniazid, 2 mo of rifampin plus pyrazinamide, or 4 mo of rifampin (with or without isoniazid), providing that infection with drug-resistant organisms is judged to be unlikely. Patients who begin multidrug therapy for

suspected pulmonary TB but are subsequently determined not to have active disease (i.e., AFB cultures are negative and chest radiographs are stable) should complete treatment with at least 2 mo of a regimen containing rifampin and pyrazinamide if the tuberculin skin test is positive and other causes of the radiographic abnormalities have been excluded.

Persons with evidence suggestive of healed, primary TB (i.e., calcified solitary pulmonary nodules, calcified hilar lymph nodes, and apical pleural capping) are not at increased risk for TB. Their risk for TB and need for treatment of LTBI should be determined by consideration of other risk factors and the size of the tuberculin reaction (Table 7).

Pregnancy and lactation. Pregnancy has minimal influence on the pathogenesis of TB or the likelihood of LTBI progressing to disease (*133, 134*). Although one study demonstrated a decrease in lymphocyte reactivity to tuberculin during pregnancy (*135*), other studies have not demonstrated an effect of pregnancy on cutaneous delayed hypersensitivity to tuberculin (*136, 137*). The current classification scheme for interpreting the Mantoux tuberculin skin test is likely valid in pregnancy, although it has not been verified in this group of women. There is no evidence that the tuberculin skin test has adverse effects on the pregnant mother or fetus (*138*).

Pregnant women should be targeted for tuberculin skin testing only if they have a specific risk factor for LTBI or for progression of LTBI to disease. Although the need for treatment of active TB during pregnancy is unquestioned, the treatment of LTBI in pregnant women is more controversial. Some experts prefer to delay treatment until after delivery because pregnancy itself does not increase the risk of progression to disease, and two studies suggest that women in pregnancy and the early postpartum period may be vulnerable to isoniazid hepatotoxicity (*91, 92*). However, because conditions that promote hematogenous spread of organisms to the placenta (e.g., recent infection and HIV infection) or progression of LTBI to disease can endanger both the mother and baby (*139*), many experts agree that pregnant women with these conditions and LTBI should be treated during pregnancy and have careful clinical and laboratory monitoring for hepatitis. The possible risk for isoniazid hepatotoxicity must be weighed against the risk for developing active TB and the consequences to both the mother and her child should active disease develop.

Extensive use of isoniazid during pregnancy has indicated that although it readily crosses the placental barrier, the drug is not teratogenic even when given during the first 4 mo of gestation (*140*). Regarding rifampin, one study revealed that 3% of 446 fetuses exposed *in utero* to rifampin had abnormalities (i.e., limb reductions, central nervous system abnormalities, and hypoprothrombinemia) compared with 2% for ethambutol and 1% for both isoniazid and controls (*138*). Hemorrhagic disease of the newborn has been described following the use of rifampin in the mother (*141*). However, extensive experience with the use of rifampin to treat TB in pregnant women suggests it is safe in most circumstances. Although pyrazinamide has been used to treat TB in pregnant women, no published data exist concerning the effects of the drug on the fetus. Thus, although pyrazinamide may be considered after the first trimester in women with HIV infection (*142*), it should otherwise be avoided.

The preferred regimen for treatment of LTBI in pregnant women is isoniazid, administered either daily or twice weekly. Although rifampin is probably safe, no efficacy data support its use. For women at high risk for progression of LTBI to disease, especially

those who are infected with HIV or who have been infected recently, initiation of therapy should not be delayed on the basis of pregnancy alone, even during the first trimester. For these women, careful clinical and/or laboratory monitoring for hepatitis should be undertaken. Pregnant women taking isoniazid should receive pyridoxine supplementation.

Toxic effects of antituberculosis drugs delivered in breast milk have not been reported. One study concluded that a breastfeeding infant would develop serum levels of no more than 20% of the usual therapeutic levels of isoniazid for infants and <11% of other antituberculosis drugs (*143*). Breastfeeding is not contraindicated when the mother is being treated for LTBI. However, infants whose breastfeeding mothers are taking isoniazid should receive supplemental pyridoxine. The amount of isoniazid provided by breast milk is inadequate for treatment of the infant.

Children and adolescents. Several fundamental aspects of the natural history and treatment of LTBI in children must be considered when making recommendations about therapy. Infants and young children (i.e., those younger than 5 yr of age) with LTBI have been infected recently, and are at high risk for progression to disease. Data suggest that untreated infants with LTBI have up to a 40% likelihood of developing TB (*144*). The risk for progression decreases gradually through childhood. Infants and young children are more likely than older children and adults to develop life-threatening forms of TB, especially meningeal and disseminated disease. Children with LTBI have more years at risk to develop TB than adults. Isoniazid therapy for LTBI appears to be more effective for children than adults, with several large clinical trials demonstrating risk reduction of 70–90% (*145,146*). The risk for isoniazid-related hepatitis is minimal in infants, children, and adolescents, who generally tolerate the drug better than adults (*147,148*). Isoniazid therapy is widely accepted for use in children. Because of differences in pathogenesis of TB infection and disease in children compared with adults, information from clinical trials involving adults cannot be applied directly to children without confirmatory pediatric trials. The only published efficacy trials of treatment of LTBI in children have studied isoniazid alone.

The only recommended regimen for treatment of LTBI in HIV-uninfected children is a 9-mo course of isoniazid as self-administered daily therapy or by DOT twice weekly. Routine monitoring of serum liver enzyme concentrations is not necessary but should be considered in children at risk for hepatic disease. When children taking antituberculosis therapy develop hepatitis, a search for causes other than isoniazid or other drugs should be undertaken and the therapy discontinued. Routine administration of pyridoxine is not recommended for children taking isoniazid, but should be given to (*1*) breastfeeding infants, (*2*) children and adolescents with diets likely to be deficient in pyridoxine, and (*3*) children who experience paresthesias while taking isoniazid.

Isoniazid given twice weekly has been used extensively to treat LTBI in children, especially schoolchildren and close contacts of case patients (*125*). On the basis of clinical experience, this method of administration is safe, but its effectiveness has not been established definitively. DOT should be considered when it is unlikely that the child and family will be adherent to daily self-administration.

In the United States, rifampin alone has been used for the treatment of LTBI in infants, children, and adolescents when isoniazid could not be tolerated or the child has had contact with a case patient infected with an isoniazid-resistant but rifamycin-susceptible organism (*149*). However, no controlled clinical trials have been conducted.

A 3-mo regimen of rifampin and isoniazid has been used in England, with programmatic data suggesting that the regimen is effective (*108*). No reports have been published concerning the efficacy of rifampin and pyrazinamide therapy in children with LTBI, although a randomized study involving a limited number of children indicated that this regimen was well tolerated (*116*).

No studies have been published regarding the efficacy of any form of treatment for LTBI in HIV-infected children. The American Academy of Pediatrics currently recommends a 9-mo course of isoniazid (*150*). Most experts recommend that routine monitoring of serum liver enzyme concentrations be performed and pyridoxine given when HIV-infected children are treated with isoniazid. The optimal length of rifampin therapy in children with LTBI is not known; however, the American Academy of Pediatrics recommends 6 mo of treatment (*150*).

Contacts of patients with tuberculosis.

- Contacts of patients with drug-susceptible tuberculosis. Persons who are contacts of patients with drug-susceptible TB and who have positive tuberculin skin-test reactions (≥5 mm) should be treated with one of the recommended regimens—regardless of age (Table 10). In addition, some tuberculin-negative contacts should be considered for treatment. Because of susceptibility to severe disease, children younger than 5 yr of age with negative skin tests should be treated and another skin test performed 8–12 wk after contact has ended. If the repeat skin test is positive, treatment should continue for the recommended period of time; if the repeat skin test is negative, the treatment should be stopped. Immunosuppressed persons, including those with HIV infection, who are contacts of persons with active TB should also receive treatment, even if repeat skin testing does not indicate LTBI.
- Contacts of patients with isoniazid-resistant tuberculosis. No definitive data exist concerning treatment of contacts who have been exposed to patients with probable or confirmed isoniazid-resistant TB. A decision analysis and Delphi methodology have been used to recommend either rifampin alone or in combination with isoniazid or ethambutol when the risk of isoniazid-resistant infection is >50% (*151*). An expert panel has recommended use of rifampin for vulnerable contacts (e.g., those with HIV infection) of patients with isoniazid-resistant TB (*152*).

In an outbreak of isoniazid- and streptomycin-resistant TB among homeless persons, six (9%) of 71 persons with skin tests that converted who received no preventive therapy developed TB, compared with three (8%) of 38 who received isoniazid, and zero of 98 persons who received rifampin or isoniazid and rifampin (*153*). Similarly, of 157 high school students who took rifampin after being exposed to a patient with isoniazid-resistant, active TB, none developed TB during the second year of the study (*149*). However, one episode of rifampin prophylaxis failure was reported among contacts of a case patient with isoniazid-resistant TB in a community outbreak (*154*).

For contacts of patients with isoniazid-resistant, rifampin-susceptible TB, a 2-mo regimen of rifampin and pyrazinamide is recommended. For patients with intolerance to pyrazinamide, a 4-mo regimen of rifampin alone is recommended. In situations in which rifampin cannot be used, rifabutin can be substituted.

- Contacts of patients with multidrug-resistant tuberculosis. The occurrence of outbreaks of multidrug-resistant TB (MDR TB) (i.e., TB caused by strains of *M. tuberculosis* resistant to at least isoniazid and rifampin) and the rise in resistance rates worldwide have focused attention on options for treatment of persons exposed to and presumed

to be infected by such organisms (*155*). As with exposure to isoniazid-resistant TB, this problem has not been evaluated in prospective studies. A Delphi technique among 31 experts failed to achieve consensus on the management of such persons (*156*).

Persons infected with isoniazid- and rifampin-resistant organisms are unlikely to benefit from treatment with regimens containing these agents. Therefore, use of a regimen containing other agents active against *M. tuberculosis* should be considered. When possible, selection of drugs for such a regimen should be guided by *in vitro* susceptibility test results from the isolate to which the patient was exposed and is presumed infected.

For persons who are likely to be infected with MDR TB and at high risk of developing TB, pyrazinamide and ethambutol or pyrazinamide and a fluoroquinolone (i.e., levofloxacin or ofloxacin) for 6–12 mo are recommended, if the organisms from the index case-patient are known to be susceptible to these agents (*157*). Immunocompetent contacts may be observed without treatment or treated for at least 6 mo; immunocompromised contacts (e.g., HIV-infected persons) should be treated for 12 mo. Side effects of pyrazinamide and fluoroquinolones include gastrointestinal symptoms and hepatic transaminase elevations (158). All persons with suspected MDR TB infection should be followed for at least 2 yr, irrespective of treatment. Expert consultation should be sought for the treatment of persons exposed to patients with MDR TB.

No studies have been published regarding treatment of LTBI in children following exposure to multidrug-resistant TB. Ethambutol at 15 mg/kg is safe in children (*159*). The combination of pyrazinamide and ethambutol for 9–12 mo is recommended if the isolate is susceptible to both drugs. Long-term use of fluoroquinolones in children should be avoided. Deleterious effects on growing cartilage have been observed in animals treated with fluoroquinolones (*160*), although no defects in bone growth occurred among a limited number of children with cystic fibrosis treated with ciprofloxacin or ofloxacin (*161*). When pyrazinamide and ethambutol cannot be used, many experts recommend using a combination of two other drugs to which the infecting organism is likely susceptible (*162, 163*).

Low-risk tuberculin test reactors. When treatment of LTBI is being considered for persons who are at low risk for developing TB, the decision should be based on factors such as likelihood of drug toxicity if treatment is given and likelihood of TB transmission to vulnerable contacts (e.g., infants and HIV-infected persons) if treatment were not given and the patient were to develop active TB. Included in this decision are the patient's preferences and values. When the assessed risk of drug toxicity exceeds the anticipated benefits of therapy, treatment for LTBI is not usually appropriate.

BCG-vaccinated persons. A history of BCG vaccination, with or without a BCG scar, should not influence the decision regarding whether to treat LTBI. The criteria previously described should be applied without modification (164).

Directly observed therapy and measures to increase adherence. Any regimen that is given intermittently (i.e., twice weekly) should be given only under direct observation. Some experts recommend that the 2-mo regimen of daily rifampin and pyrazinamide also be given by DOT, which, for ease of administration, may consist of five observed and two self-administered doses each week.

Patients with the highest priority for DOT are those at the highest risk of progression from latent to active TB, including persons with HIV infection and young children who are contacts of infectious patients with pulmonary TB. DOT may be conveniently and

effectively used for the treatment of household contacts of patients receiving DOT for active TB and for treatment observed by staff members in certain facilities (e.g., schools and homeless shelters).

If it is not possible to provide DOT to enhance adherence with treatment of LTBI, the prescribed regimen should be incorporated into patients' daily routines. Medical providers can encourage adherence to treatment by establishing rapport with patients. Providers should explain in simple, clear language what LTBI is, the health threat it presents, and how it is eradicated. Patients should be encouraged to ask questions. Patient education should ideally be conducted in the patient's primary language, or through a medical interpreter, if necessary. Each visit between patient and medical provider during therapy is an opportunity to reinforce the patient's understanding of LTBI and its treatment.

In addition to education about potential drug toxicity, patients should be told about common side effects and counseled on drug management. (For example, medications should be taken with food when gastrointestinal symptoms have occurred after medication was taken on an empty stomach, and salicylic acid can be used for symptomatic treatment of arthralgia caused by pyrazinamide.)

Most interventions to improve adherence require substantial financial resources. Providing flexible clinic hours, reducing waiting times for patients, spending time with patients to counsel and educate, and directly observing patients ingesting medications increase operating expenses. Even the least intensive approaches to improve adherence increase program costs. The costs of these approaches to improving patient adherence underscore the need to target tuberculin testing and treatment of LTBI to those groups with an increased risk for recent infection or those persons at high risk for progression to active TB, if infected. In addition, programs should invest in approaches to increase adherence, especially for those persons who are at greatest risk for progressing to disease. Better success in motivating patients to accept and to complete treatment is necessary to achieve the full potential of this intervention to protect persons from TB and to reduce the incidence of the disease in the community.

Pretreatment Evaluation and Monitoring of Treatment

Pretreatment evaluation. The pretreatment evaluation of persons who are targeted for treatment of LTBI provides an opportunity for health care providers to a) establish rapport with patients, b) discuss the details of the patients' risk for TB, c) emphasize the benefits of treatment and the importance of adherence to the drug regimen, d) review possible adverse effects of the regimen, including interactions with other drugs, and e) establish an optimal follow-up plan. The evaluation should include an interview conducted in the patients' primary language with assistance of qualified medical interpreters, if necessary.

The patient history should document risk factors for TB, prior treatment for TB or LTBI, and preexisting medical conditions that constitute a contraindication to treatment or are associated with an increased risk for adverse effects of treatment. A detailed history of current and previous drug therapy should be obtained, with particular attention to previous adverse reactions to drugs contemplated for treatment of LTBI, and to current use of drugs which may interact with the drugs used for treatment. Women receiving rifampin and oral contraceptives are at increased risk for becoming pregnant and should be advised to consider an additional form of contraception. Practitioners should consider using a standardized history form to ensure that all elements

of the pretest evaluation are thoroughly covered for each patient.

Baseline laboratory testing is not routinely indicated for all patients at the start of treatment for LTBI (Table 8). Patients whose initial evaluation suggests a liver disorder should have baseline hepatic measurements of serum AST (SGOT) or ALT (SGPT) and bilirubin. Baseline testing is also indicated for patients infected with HIV, pregnant women and those in the immediate postpartum period (i.e., within 3 mo of delivery), persons with a history of liver disease (e.g., hepatitis B or C, alcoholic hepatitis or cirrhosis), persons who use alcohol regularly, and others who are at risk for chronic liver disease. Baseline testing is no longer routinely indicated in persons older than 35 yr of age. However, such testing may be considered on an individual basis, particularly for patients who are taking other medications for chronic medical conditions. Active hepatitis and end-stage liver disease are relative contraindications to the use of isoniazid or pyrazinamide for treatment of LTBI.

Monitoring of treatment. Clinical monitoring is indicated for all patients; this involves education of patients about the symptoms and signs that can result as adverse effects of the drug(s) being prescribed and the need for prompt cessation of treatment and clinical evaluation should symptoms occur. These include any of the following: unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paresthesias of the hands and feet, persistent fatigue, weakness or fever lasting 3 or more days, abdominal tenderness (especially right upper quadrant discomfort), easy bruising or bleeding, and arthralgia (Table 8). Clinical monitoring begins at the first visit and should be repeated at each monthly visit. At monthly visits, patients should be instructed to interrupt therapy and contact their providers immediately upon the onset of such symptoms or any unexplained illness occurring during treatment.

Patients being treated for LTBI should receive a clinical evaluation, including a brief physical assessment checking for signs of hepatitis, at least monthly if receiving isoniazid alone or rifampin alone and at 2, 4, and 8 wk if receiving both rifampin and pyrazinamide (Table 8). These evaluations represent opportunities to review the indications for treatment, adherence with therapy since the last visit, symptoms of adverse drug effects and drug interactions, and plans to continue treatment. As with the baseline evaluation, a standardized questionnaire may facilitate those interviews.

Routine laboratory monitoring during treatment of LTBI is indicated for patients whose baseline liver function tests are abnormal and for other persons at risk for hepatic disease (Table 8). In addition, laboratory testing (e.g., liver function studies for patients with symptoms compatible with hepatotoxicity or a uric acid measurement to evaluate patients who develop acute arthritis) should be used to evaluate possible adverse effects that occur during the course of treatment. Some experts recommend that isoniazid be withheld if a patient's transaminase level exceeds 3 times the upper limit of normal if associated with symptoms and five times the upper limit of normal if the patient is asymptomatic.

Reporting of serious adverse events. Practitioners and other health professionals should report serious adverse events associated with the treatment of LTBI to the U.S. Food and Drug Administration's MedWatch program. Serious adverse events include those associated with hospitalization, permanent disability, or death. Reporting may be by mail, telephone (1-800-FDA-1088), fax (1-800-FDA-0178), or the Internet site (www.fda.gov/medwatch).

PRIORITIES FOR FUTURE RESEARCH

Diagnosis

The only widely available method to detect LTBI is the tuberculin skin test. However, the specificity of the test is decreased by cross reactions from BCG vaccination and sensitization by nontuberculous mycobacteria. When used in populations in which the risk for TB is low, the test's positive predictive value is poor. In addition, the requirement that the person tested return for the test to be read 48–72 h after test administration creates operational problems. Thus, more specific and sensitive tests are needed to diagnose LTBI and to identify persons at greatest risk for progressing to active disease. Especially useful would be tests that distinguish skin-test reactions caused by TB infection from those caused by BCG vaccination or infection with nontuberculous mycobacteria, tests that correlate with the presence of living organisms, and tests that accurately identify LTBI in immunodeficient persons.

Operational Research

Acceptability, Tolerability, and Effectiveness of Daily Rifampin and Pyrazinamide

More data are needed regarding the acceptability, tolerability, and effectiveness of the 2-mo regimen of daily rifampin and pyrazinamide in HIV-negative persons. Data are especially needed from older adults and children.

Intermittent Rifampin-containing Regimens

No studies of rifampin alone taken twice weekly for the treatment of LTBI have been conducted. Data from two studies in HIV-infected persons that included intermittent (i.e., twice weekly) rifampin and pyrazinamide administration suggested that these regimens were effective (*86,110*). Before additional trials of intermittent rifampin regimens are undertaken, animal model data are needed to compare these regimens with regimens using other longer-acting rifamycin derivatives (*see* Efficacy Studies of New Drugs).

Isoniazid Taken Twice Weekly

It is unlikely that a formal efficacy study of intermittent isoniazid for the treatment of LTBI will be undertaken, unless it is included as a control arm for studies of newer regimens. However, several TB-control programs have had considerable experience using this regimen. Data from these programs should be examined, especially as they relate to acceptability and completion of treatment. The analysis of aggregate data available in TB programs may also be useful in estimating the effectiveness of this regimen.

Studies in Children and Pregnant Women

Studies are needed to provide information regarding the use of newer regimens for the treatment of LTBI in children and pregnant women. The safety of pyrazinamide for pregnant women and their fetuses should be determined. More information is needed

regarding hepatotoxicity of isoniazid in pregnant and postpartum women. Studies are needed to establish the safety and effectiveness of rifampin alone and rifampin plus pyrazinamide for treatment of LTBI in infants, children, and adolescents. The best target populations for these studies would be HIV-infected children in places in which TB is prevalent and household contacts of TB case patients. In addition, the effectiveness of twice-weekly regimens for treatment of LTBI in children should be confirmed. Data concerning the safety and effectiveness of alternative therapies for MDR LTBI in children are needed. Finally, epidemiologic research to determine the best tools to identify children at high risk for LTBI should be undertaken.

Reporting and Monitoring in New Settings

These recommendations call for the establishment of LTBI treatment programs in new community settings (e.g., managed care organizations and neighborhood clinics). Consequently, operational research will be needed to evaluate the implementation of these programs in settings other than health departments. These studies should assess the knowledge base of treating clinicians and identify the obstacles to be overcome for the successful implementation of community-based LTBI treatment programs.

Combination Rifampin and Pyrazinamide Preparations

If field and programmatic data establish the effectiveness and acceptability of the rifampin and pyrazinamide regimen for the treatment of LTBI, the availability of a combination product would facilitate its administration. However, the argument concerning the usefulness of combination products in preventing the emergence of drug resistance in patients with active TB is not as compelling for persons being treated for LTBI. Nonetheless, methods to facilitate provision of this treatment and increase adherence (e.g., blister packs containing medication for 2 wk of treatment for several different body weights) would be useful.

Efficacy Studies of New Drugs

No novel compounds currently can be considered candidates for the treatment of LTBI. However, several rifamycin derivatives with half-lives substantially greater than rifampin are of interest because of the possibility of widely spaced, intermittent administration. In experimental studies involving mice, the combination of rifapentine and isoniazid given once weekly for 3 mo was as active as rifampin and pyrazinamide given daily for 2 mo (*165*). Rifalazil, which has an even longer half-life, is more active than rifapentine and perhaps could be dosed less frequently without compromising efficacy (*166*). The class of nitroimidazole compounds is also of interest because of their potential activity against dormant tubercle bacilli (*167*). Unfortunately, no animal models of LTBI exist that optimize the preclinical evaluation of new drugs.

Studies of Immunomodulators and Vaccines

Recent studies have indicated that immunotherapy with specific cytokines and immunomodulators may be beneficial to response to TB treatment. However, their application in the treatment of LTBI is uncertain. Some epidemiologic studies have suggested that high levels of certain cytokines (e.g., interferon gamma) may protect against the development of active TB. If further studies support this finding,

interventions that stimulate production of protective cytokines may have a role in the treatment of LTBI. The development of a postinfection vaccine to be administered to persons with LTBI has been given high priority (*168*).

Decision/Cost-Effectiveness Analyses

Focus on Testing for and Treatment of Latent TB Infection in High-risk and Diverse Populations

Future decision and cost-effectiveness analyses should be expanded to include targeted testing. Instead of beginning at the "treat-don't-treat" point, new models might be most useful if they begin with the decision of whether to test. These studies should focus on groups at high risk and specific subgroups characterized by varied risks and benefits of treatment. Using this conceptual framework will help place decision modeling more clearly into a "real world" context, incorporating the linked contingencies that exist.

Comparison of Strategies Using Both Shorter and Longer Treatment Regimens

Future decision and cost-effectiveness analyses should compare the shorter course regimens to the longer, 9-mo regimen of daily isoniazid. These analyses will benefit from investigations of the toxicities and efficacies of shorter regimens. In addition, although adherence presumably will be better with shorter treatment regimens, the rifampin and pyrazinamide regimen may be less well-tolerated in some groups of patients, thus resulting in low adherence. Decision and cost-effectiveness analyses should explore a range of toxicities in the models until investigations better establish these risks. By investigating the effect of a range of toxicities and adherence on the decision outcome, studies can help identify priority areas for research. Updated analyses on the use of alternate regimens for the treatment of drug-resistant LTBI are also needed.

Use of Multiple Analytic Perspectives

When two different perspectives are relevant for a decision, both perspectives should be modeled and analyzed. For example, when the benefits to an individual person with LTBI are different from the benefits to the public, both perspectives must be made explicit in decision models. When decision analysis is inadequate to deal with public health issues (e.g., reduction in contagion), additional models are needed to augment views of the benefits and costs of following each viable course of action.

Policies designed to target and treat populations at high risk for TB are motivated by the need to benefit the individual patient as well as the health of the public by averting active disease in persons most likely to develop it. As policies are instituted that identify high-risk groups for testing and treatment, the social and ethical ramifications of these policies must be considered. The individual persons who comprise many of the high-risk groups targeted for testing and treatment often represent disenfranchised segments of urban populations (e.g., persons who are homeless, incarcerated, and medically underserved, and residents in long-term care facilities). Ideally, the outcomes and utilities that are used in these decision models will incorporate the values and preferences of these patients and the outcomes important to the general public.

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3. Indicate whether you are registering for CME, CEU, or CNE credit.
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GOALS and OBJECTIVES

This *MMWR* provides recommendations regarding targeted tuberculin testing and treatment of latent tuberculosis infection (LTBI) that were developed by the American Thoracic Society and the Division of Tuberculosis Elimination, CDC. The goal of this report is to guide clinical practice and policy development associated with targeted testing and the treatment of latent tuberculosis infection. Upon completion of this educational activity, the reader should be able to 1) describe the purpose of targeted tuberculin testing; 2) describe the classification of the tuberculin reaction; 3) describe the regimens for treatment of latent TB infection for HIV-positive and HIV-negative persons; and 4) describe how patients should be monitored during treatment of LTBI.

To receive continuing education credit, please answer all of the following questions.

1. Which of the following statements is TRUE?

A. All pregnant women should be targeted for tuberculin skin testing.

B. Tuberculin skin testing is not recommended for recent close contacts to an infectious TB case-patient.

C. Routine tuberculin skin testing is not recommended for populations at low risk for LTBI.

D. Tuberculin skin testing is contraindicated for persons who have been vaccinated with BCG.

2. Which of the following statements is FALSE?

A. Baseline laboratory testing is indicated for all patients at the start of treatment for LTBI.

B. Patients whose initial evaluation suggests a liver disorder should have baseline hepatic measurements.

C. Baseline laboratory testing is indicated for patients with HIV infection, pregnant women, and those in the immediate postpartum period.

D. Baseline testing is no longer routinely indicated in persons aged >35.

3. In which groups is an induration size of 5 millimeters NOT considered a positive reaction?

A Recent contacts of a TB case-patient.

B. HIV-positive persons.

C. Patients with organ transplants and other immunosuppressed patients.

D. Children < 4 years, or children and adolescents exposed to adults in high-risk categories.

E. All of the above.

4. Which of the following groups should be given high priority for the treatment of LTBI?

A. Patients with end-stage renal disease/hemodialysis.

B. HIV-positive persons.

C. Recent contacts of a TB case-patient.

D. Persons with fibrotic changes on chest radiograph consistent with prior TB.

E. All of the above.

5. Which of the following regimens is an alternative to isoniazid for treatment of LTBI in HIV-positive persons?

A. Streptomycin and ethambutol.

B. Rifampin and pyrazinamide.

C. Ethambutol and pyrazinamide.

D. Rifampin and ethambutol.

6. Which of the following treatment regimens for LTBI is an alternative to isoniazid for HIV-positive persons who are receiving protease inhibitors or nonnucleoside reverse transcriptase inhibitors?

A. Streptomycin and ethambutol.

B. Rifampin and pyrazinamide.

C. Ethambutol and pyrazinamide.

D. Rifabutin and pyrazinamide.

7. How often should patients be evaluated for adverse reactions to TB medications during treatment of LTBI?

A. At least monthly if receiving isoniazid alone.

B. At least monthly if receiving rifampin alone.

C. At 2, 4, and 8 weeks if receiving both rifampin and pyrazinamide.

D. All of the above.

8. Which of the following statements is TRUE?

A. A 9-month regimen of isoniazid is the preferred treatment of LTBI in HIV-negative persons.

B. A 3-month regimen of daily rifampin may be useful for patients who cannot tolerate isoniazid or pyrazinamide.

C. A 2-month regimen of rifampin and pyrazinamide is the preferred treatment of LTBI for HIV-positive persons.

D. All of the above.

9. Which of the following is the preferred regimen for the treatment of LTBI in pregnant women?

A. Isoniazid administered daily or twice weekly.

B. Rifampin administered daily or twice weekly.

C. Rifampin and pyrazinamide administered daily.

D. Ethambutol administered daily.

10. A tuberculin skin test reaction of 10 millimeters of induration is considered positive in which group?

A. Persons with no risk factors for TB.

B. Recent contacts of TB case-patients.

C. HIV-positive persons.

D. Recent immigrants from high prevalence countries.

E. All of the above.

11. Indicate your work setting.

A. State/local health department.
B. Other public health setting.
C. Hospital clinic/private practice.
D. Managed care organization.
E. Academic institution.
F. Other.

12. Which best describes your professional activities?

A. Physician.
B. Nurse.
C. Health educator.
D. TB control staff.
E. Other.

13. I plan to use these recommendations as the basis for . . . (Indicate all that apply.)

A. health education materials.
B. insurance reimbursement policies.
C. local practice guidelines.
D. public policy.
E. other.

14. Each month, approximately how many TB patients do you treat?

A. None
B. 1-5.
C. 6-20.
D. 21-50.
E. 50-100.
F. >100.

15. How much time did you spend reading this report and completing the exam?

A. More than 2 ½ hours but fewer than 3 hours.
B. 3 to 3 ½ hours.
C. More than 3 ½ hours but fewer than 4 hours.
D. 4 hours or more.

16. After reading this report, I am confident I can describe the purpose of targeted tuberculin testing.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

17. After reading this report, I am confident I can describe the classification of the tuberculin reaction.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

18. After reading this report, I am confident I can describe the regimens for treatment of latent TB infection for HIV-positive and HIV-negative persons.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

19. After reading this report, I am confident I can describe how patients should be monitored during treatment of LTBI.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

20. The objectives are relevant to the goal(s) of this report.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

21. The tables and figures are useful.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

22. Overall, the presentation of the report enhanced my ability to understand the material.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

23. These recommendations will affect my practice.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

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B. Advertisement (e.g., flyer, publication cover, newsletter, and journal).
C. Co-worker/supervisor.
D. Conference presentation.
E. MMWR subscriber.
F. Other.

Correct answers for questions 1–10.

1. C; 2. A; 3. D; 4. E; 5. B; 6. D; 7. D; 8. D; 9. A; 10. D.

MMWR Response Form for Continuing Education Credit
June 9, 2000/Vol. 49/No. RR-6

Targeted Tuberculosis Testing and Treatment of Latent Tuberculosis Infection

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5. [ ] A [ ] B [ ] C [ ] D
6. [ ] A [ ] B [ ] C [ ] D
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11. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F
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23. [ ] A [ ] B [ ] C [ ] D [ ] E
24. [ ] A [ ] B [ ] C [ ] D [ ] E

Signature ***Date I Completed Exam***

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MMWR™

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Recommendations and Reports June 20, 2003 / Vol. 52 / No. RR-11

Treatment of Tuberculosis

American Thoracic Society, CDC, and Infectious Diseases Society of America

INSIDE: Continuing Education Examination

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

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The following drugs, which are suggested for use in selected cases, are not approved by the Food and Drug Administration for treatment of tuberculosis: rifabutin, amikacin, kanamycin, moxifloxacin, gatifloxacin, and levofloxacin.

Michael Iseman, M.D., has indicated that he has a financial relationship with Ortho-McNeil, which manufactures Levaquin®. The remaining preparers have signed a conflict of interest disclosure form that verifies no conflict of interest.

Treatment of Tuberculosis

American Thoracic Society, CDC, and Infectious Diseases Society of America

Purpose

The recommendations in this document are intended to guide the treatment of tuberculosis in settings where mycobacterial cultures, drug susceptibility testing, radiographic facilities, and second-line drugs are routinely available. In areas where these resources are not available, the recommendations provided by the World Health Organization, the International Union against Tuberculosis, or national tuberculosis control programs should be followed.

What's New In This Document

- The responsibility for successful treatment is clearly assigned to the public health program or private provider, not to the patient.
- It is strongly recommended that the initial treatment strategy utilize patient-centered case management with an adherence plan that emphasizes direct observation of therapy.
- Recommended treatment regimens are rated according to the strength of the evidence supporting their use. Where possible, other interventions are also rated.
- Emphasis is placed on the importance of obtaining sputum cultures at the time of completion of the initial phase of treatment in order to identify patients at increased risk of relapse.
- Extended treatment is recommended for patients with drug-susceptible pulmonary tuberculosis who have cavitation noted on the initial chest film and who have positive sputum cultures at the time 2 months of treatment is completed.
- The roles of rifabutin, rifapentine, and the fluoroquinolones are discussed and a regimen with rifapentine in a once-a-week continuation phase for selected patients is described.
- Practical aspects of therapy, including drug administration, use of fixed-dose combination preparations, monitoring and management of adverse effects, and drug interactions are discussed.
- Treatment completion is defined by number of doses ingested, as well as the duration of treatment administration.
- Special treatment situations, including human immunodeficiency virus infection, tuberculosis in children, extrapulmonary tuberculosis, culture-negative tuberculosis, pregnancy and breastfeeding, hepatic disease and renal disease are discussed in detail.
- The management of tuberculosis caused by drug-resistant organisms is updated.
- These recommendations are compared with those of the WHO and the IUATLD and the DOTS strategy is described.
- The current status of research to improve treatment is reviewed.

This Official Joint Statement of the American Thoracic Society, CDC, and the Infectious Diseases Society of America was approved by the ATS Board of Directors, by CDC, and by the Council of the IDSA in October 2002. This report appeared in the *American Journal of Respiratory and Critical Care Medicine* (2003;167:603–62) and is being reprinted as a courtesy to the American Thoracic Society, the Infectious Diseases Society of America, and the *MMWR* readership.

Summary

Responsibility for Successful Treatment

The overall goals for treatment of tuberculosis are 1) to cure the individual patient, and 2) to minimize the transmission of *Mycobacterium tuberculosis* to other persons. Thus, successful treatment of tuberculosis has benefits both for the individual patient and the community in which the patient resides. For this reason the prescribing physician, be he/she in the public or private sector, is carrying out a public health function with responsibility not only for prescribing an appropriate regimen but also for successful completion of therapy. Prescribing physician responsibility for treatment completion is a fundamental principle in tuberculosis control. However, given a clear understanding of roles and responsibilities, oversight of treatment may be shared between a public health program and a private physician.

Organization and Supervision of Treatment

Treatment of patients with tuberculosis is most successful within a comprehensive framework that addresses both clinical and social issues of relevance to the patient. It is essential that treatment be tailored and supervision be based on each patient's clinical and social circumstances (patient-centered care). Patients may be managed in the private sector, by public health departments, or jointly, but in all cases the health department is ultimately responsible for ensuring that adequate, appropriate diagnostic and treatment services are available, and for monitoring the results of therapy.

It is strongly recommended that patient-centered care be the initial management strategy, regardless of the source of supervision. This strategy should always include an adherence plan that emphasizes directly observed therapy (DOT), in which patients are observed to ingest each dose of antituberculosis medications, to maximize the likelihood of completion of therapy. Programs utilizing DOT as the central element in a comprehensive, patient-centered approach to case management (enhanced DOT) have higher rates of treatment completion than less intensive strategies. Each patient's management plan should be individualized to incorporate measures that facilitate adherence to the drug regimen. Such measures may include, for example, social service support, treatment incentives and enablers, housing assistance, referral for treatment of substance abuse, and coordination of tuberculosis services with those of other providers.

Recommended Treatment Regimens

The recommended treatment regimens are, in large part, based on evidence from clinical trials and are rated on the basis of a system developed by the United States Public Health Service (USPHS) and the Infectious Diseases Society of America (IDSA). The rating system includes a letter (A, B, C, D, or E) that indicates the strength of the recommendation and a roman numeral (I, II, or III) that indicates the quality of evidence supporting the recommendation (Table 1).

There are four recommended regimens for treating patients with tuberculosis caused by drug-susceptible organisms. Although these regimens are broadly applicable, there are modifications that should be made under specified circumstances, described subsequently. Each regimen has an initial phase of 2 months followed by a choice of several options for the continuation phase of either 4 or 7 months. The recommended regimens together with the number of doses specified by the regimen are described in Table 2. The initial phases are denoted by a number (1, 2, 3, or 4) and the continuation phases that relate to the initial phase are denoted by the number plus a letter designation (a, b, or c). Drug doses are shown in Tables 3, 4, and 5.

TABLE 1. Infectious Diseases Society of America/United States Public Health Service rating system for the strength of treatment recommendations based on quality of evidence*

Strength of the recommendation
A. Preferred; should generally be offered
B. Alternative; acceptable to offer
C. Offer when preferred or alternative regimens cannot be given
D. Should generally not be offered
E. Should never be offered
Quality of evidence supporting the recommendation
I. At least one properly randomized trial with clinical end points
II. Clinical trials that either are not randomized or were conducted in other populations
III. Expert opinion

* Reprinted by permission from Gross PA, Barrett TL, Dellinger EP, Krause PJ, Martone WJ, McGowan JE Jr, Sweet RL, Wenzel RP. Clin Infect Dis 1994;18:421.

The general approach to treatment is summarized in Figure 1. Because of the relatively high proportion of adult patients with tuberculosis caused by organisms that are resistant to isoniazid, four drugs are necessary in the initial phase for the 6-month regimen to be maximally effective. Thus, in most circumstances, the treatment regimen for all adults with previously untreated tuberculosis should consist of a 2-month initial phase of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) (Table 2, Regimens 1–3). If (when) drug susceptibility test results are known and the organisms are fully susceptible, EMB need not be included. For children whose visual acuity cannot be monitored, EMB is usually not recommended except when there is an increased likelihood of the disease being caused by INH-resistant organisms (Table 6) or when the child has "adult-type" (upper lobe infiltration, cavity formation) tuberculosis. If PZA cannot be included in the initial phase of treatment, or if the isolate is resistant to PZA alone (an unusual circumstance), the initial phase should consist of INH, RIF, and EMB given daily for 2 months (Regimen 4). Examples of circumstances in which PZA may be withheld include severe liver disease, gout, and, perhaps, pregnancy. EMB should be included in the initial phase of Regimen 4 until drug susceptibility is determined.

The initial phase may be given daily throughout (Regimens 1 and 4), daily for 2 weeks and then twice weekly for 6 weeks (Regimen 2), or three times weekly throughout (Regimen 3). For patients receiving daily therapy, EMB can be discontinued as soon as the results of drug susceptibility studies demonstrate that the isolate is susceptible to INH and RIF. When the patient is receiving less than daily drug administration, expert opinion suggests that EMB can be discontinued safely in less than 2 months (i.e., when susceptibility test results are known), but there is no evidence to support this approach.

Although clinical trials have shown that the efficacy of streptomycin (SM) is approximately equal to that of EMB in the initial phase of treatment, the increasing frequency of resistance to SM globally has made the drug less useful. Thus, SM is not recommended as being interchangeable with EMB unless the organism is known to be susceptible to the drug or the patient is from a population in which SM resistance is unlikely.

The continuation phase (Table 2) of treatment is given for either 4 or 7 months. The 4-month continuation phase should be used in the large majority of patients. The 7-month

TABLE 2. Drug regimens for culture-positive pulmonary tuberculosis caused by drug-susceptible organisms

Initial phase			Continuation phase			Range of total doses (minimal duration)	Rating* (evidence)†	
Regimen	Drugs	Interval and doses‡ (minimal duration)	Regimen	Drugs	Interval and doses‡§ (minimal duration)		HIV−	HIV+
1	INH RIF PZA EMB	Seven days per week for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)¶	1a	INH/RIF	Seven days per week for 126 doses (18 wk) or 5 d/wk for 90 doses (18 wk)¶	182–130 (26 wk)	A (I)	A (II)
			1b	INH/RIF	Twice weekly for 36 doses (18 wk)	92–76 (26 wk)	A (I)	A (II)#
			1c**	INH/RPT	Once weekly for 18 doses (18 wk)	74–58 (26 wk)	B (I)	E (I)
2	INH RIF PZA EMB	Seven days per week for 14 doses (2 wk), then twice weekly for 12 doses (6 wk) or 5 d/wk for 10 doses (2 wk),¶ then twice weekly for 12 doses (6 wk)	2a	INH/RIF	Twice weekly for 36 doses (18 wk)	62–58 (26 wk)	A (II)	B (II)#
			2b**	INH/RPT	Once weekly for 18 doses (18 wk)	44–40 (26 wk)	B (I)	E (I)
3	INH RIF PZA EMB	Three times weekly for 24 doses (8 wk)	3a	INH/RIF	Three times weekly for 54 doses (18 wk)	78 (26 wk)	B (I)	B (II)
4	INH RIF EMB	Seven days per week for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)¶	4a	INH/RIF	Seven days per week for 217 doses (31 wk) or 5 d/wk for 155 doses (31 wk)¶	273–195 (39 wk)	C (I)	C (II)
			4b	INH/RIF	Twice weekly for 62 doses (31 wk)	118–102 (39 wk)	C (I)	C (II)

Definition of abbreviations: EMB = Ethambutol; INH = isoniazid; PZA = pyrazinamide; RIF = rifampin; RPT = rifapentine.

* Definitions of evidence ratings: A = preferred; B = acceptable alternative; C = offer when A and B cannot be given; E = should never be given.

† Definition of evidence ratings: I = randomized clinical trial; II = data from clinical trials that were not randomized or were conducted in other populations; III = expert opinion.

‡ When DOT is used, drugs may be given 5 days/week and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be an effective practice.

§ Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31 week; either 217 doses [daily] or 62 doses [twice weekly]) continuation phase.

¶ Five-day-a-week administration is always given by DOT. Rating for 5 day/week regimens is AIII.

\# Not recommended for HIV-infected patients with $CD4^+$ cell counts <100 cells/µl.

** Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on initial chest radiograph (see text). For patients started on this regimen and found to have a positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

continuation phase is recommended only for three groups: patients with cavitary pulmonary tuberculosis caused by drug-susceptible organisms and whose sputum culture obtained at the time of completion of 2 months of treatment is positive; patients whose initial phase of treatment did not include PZA; and patients being treated with once weekly INH and rifapentine and whose sputum culture obtained at the time of completion of the initial phase is positive. The continuation phase may be given daily (Regimens 1a and 4a), two times weekly by DOT (Regimens 1b, 2a, and 4b), or three times weekly by DOT (Regimen 3a). For human immunodeficiency virus (HIV)-seronegative patients with noncavitary pulmonary tuberculosis (as determined by standard chest radiography), and negative sputum smears at completion of 2 months of treatment, the continuation phase may consist of rifapentine and INH given once weekly for 4 months by DOT (Regimens 1c and 2b) (Figure 1). If the culture at completion of the initial phase of treatment is positive, the once weekly INH and rifapentine continuation phase should be extended to 7 months. All of the 6-month regimens, except the INH–rifapentine once weekly continuation phase for persons with HIV infection (Rating EI), are rated as AI or AII, or BI or BII, in both HIV-infected and uninfected patients. The once-weekly continuation phase is contraindicated (Rating EI) in patients with HIV infection because of an unacceptable rate of failure/relapse, often with rifamycin-resistant organisms. For the same reason twice weekly treatment, either as part of the initial phase (Regimen 2) or continuation phase (Regimens 1b and 2a), is not recommended for HIV-infected patients with $CD4^+$ cell counts <100 cells/µl. These patients should receive either daily (initial phase) or three times weekly (continuation phase) treatment. Regimen 4 (and 4a/4b), a 9-month regimen, is rated CI for patients without HIV infection and CII for those with HIV infection.

Deciding To Initiate Treatment

The decision to initiate combination antituberculosis chemotherapy should be based on epidemiologic information; clinical, pathological, and radiographic findings; and the results of microscopic examination of acid-fast bacilli (AFB)–stained sputum (smears) (as well as other appropriately collected diagnostic specimens) and cultures for mycobacteria. A purified protein derivative (PPD)-tuberculin skin test may be done at the time of initial evaluation, but a negative PPD-tuberculin skin test does not exclude the diagnosis of active tuberculosis. However, a positive PPD-tuberculin skin test

Please note: An erratum has been published for this issue. To view the erratum, please click here.

TABLE 3. Doses* of antituberculosis drugs for adults and children†

Drug	Preparation	Adults/children	Doses: Daily	11×/wk	2×/wk	3×/wk
First-line drugs						
Isoniazid	Tablets (50 mg, 100 mg, 300 mg); elixir (50 mg/5 ml); aqueous solution (100 mg/ml) for intravenous or intramuscular injection	Adults (max.)	5 mg/kg (300 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)
		Children (max.)	10–15 mg/kg (300 mg)	—	20–30 mg/kg (900 mg)	—
Rifampin	Capsule (150 mg, 300 mg); powder may be suspended for oral administration; aqueous solution for intravenous injection	Adults‡ (max.)	10 mg/kg (600 mg)	—	10 mg/kg (600 mg)	10 mg/kg (600 mg)
		Children (max.)	10–20 mg/kg (600 mg)	—	10–20 mg/kg (600 mg)	—
Rifabutin	Capsule (150 mg)	Adults‡ (max.)	5 mg/kg (300 mg)	—	5 mg/kg (300 mg)	5 mg/kg (300 mg)
		Children	Appropriate dosing for children is unknown	Appropriate dosing for children is unknown	Appropriate dosing for children is unknown	Appropriate dosing for children is unknown
Rifapentine	Tablet (150 mg, film coated)	Adults	—	10 mg/kg (continuation phase) (600 mg)	—	—
		Children	The drug is not approved for use in children	The drug is not approved for use in children	The drug is not approved for use in children	The drug is not approved for use in children
Pyrazinamide	Tablet (500 mg, scored)	Adults	See Table 4	—	See Table 4	See Table 4
		Children (max.)	15–30 mg/kg (2.0 g)	—	50 mg/kg (2 g)	—
Ethambutol	Tablet (100 mg, 400 mg)	Adults	See Table 5	—	See Table 5	See Table 5
		Children§ (max.)	15–20 mg/kg daily (1.0 g)	—	50 mg/kg (2.5 g)	—
Second-line drugs						
Cycloserine	Capsule (250 mg)	Adults (max.)	10–15 mg/kg/d (1.0 g in two doses), usually 500–750 mg/d in two doses¶	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
		Children (max.)	10–15 mg/kg/d (1.0 g/d)	—	—	—
Ethionamide	Tablet (250 mg)	Adults# (max.)	15–20 mg/kg/d (1.0 g/d), usually 500–750 mg/d in a single daily dose or two divided doses#	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
		Children (max.)	15–20 mg/kg/d (1.0 g/d)	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
Streptomycin	Aqueous solution (1-g vials) for intravenous or intramuscular administration	Adults (max.)	**	**	**	**
		Children (max.)	20–40 mg/kg/d (1 g)	—	20 mg/kg	—
Amikacin/ kanamycin	Aqueous solution (500-mg and 1-g vials) for intravenous or intramuscular administration	Adults (max.)	**	**	**	**
		Children (max.)	15–30 mg/kg/d (1 g) intravenous or intramuscular as a single daily dose	—	15–30 mg/kg	—
Capreomycin	Aqueous solution (1-g vials) for intravenous or intramuscular administration	Adults (max.)	**	**	**	**
		Children (max.)	15–30 mg/kg/d (1 g) as a single daily dose	—	15–30 mg/kg	—
p-Aminosalicylic acid (PAS)	Granules (4-g packets) can be mixed with food; tablets (500 mg) are still available in some countries, but not in the United States; a solution for intravenous administration is available in Europe	Adults	8–12 g/d in two or three doses	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
		Children	200–300 mg/kg/d in two to four divided doses (10 g)	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
Levofloxacin	Tablets (250 mg, 500 mg, 750 mg); aqueous solution (500-mg vials) for intravenous injection	Adults	500–1,000 mg daily	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
		Children	††	††	††	††

Please note: An erratum has been published for this issue. To view the erratum, please click here.

TABLE 3. (*Continued*) Doses* of antituberculosis drugs for adults and children†

Drug	Preparation	Adults/children	Doses			
			Daily	11×/wk	2×/wk	3×/wk
Moxifloxacin	Tablets (400 mg); aqueous solution (400 mg/250 ml) for intravenous injection	Adults	400 mg daily	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
		Children	‡‡	‡‡	‡‡	‡‡
Gatifloxacin	Tablets (400 mg); aqueous solution (200 mg/20 ml; 400 mg/40 ml) for intravenous injection	Adults	400 mg daily	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
		Children	§§	§§	§§	§§

* Dose per weight is based on ideal body weight. Children weighing more than 40 kg should be dosed as adults.
† For purposes of this document adult dosing begins at age 15 years.
‡ Dose may need to be adjusted when there is concomitant use of protease inhibitors or nonnucleoside reverse transcriptase inhibitors.
§ The drug can likely be used safely in older children but should be used with caution in children less than 5 years of age, in whom visual acuity cannot be monitored. In younger children EMB at the dose of 15 mg/kg per day can be used if there is suspected or proven resistance to INH or RIF.
¶ It should be noted that, although this is the dose recommended generally, most clinicians with experience using cycloserine indicate that it is unusual for patients to be able to tolerate this amount. Serum concentration measurements are often useful in determining the optimal dose for a given patient.
\# The single daily dose can be given at bedtime or with the main meal.
** Dose: 15 mg/kg per day (1 g), and 10 mg/kg in persons more than 59 years of age (750 mg). Usual dose: 750–1,000 mg administered intramuscularly or intravenously, given as a single dose 5–7 days/week and reduced to two or three times per week after the first 2–4 months or after culture conversion, depending on the efficacy of the other drugs in the regimen.
†† The long-term (more than several weeks) use of levofloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. However, most experts agree that the drug should be considered for children with tuberculosis caused by organisms resistant to both INH and RIF. The optimal dose is not known.
‡‡ The long-term (more than several weeks) use of moxifloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. The optimal dose is not known.
§§ The long-term (more than several weeks) use of gatifloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. The optimal dose is not known.

TABLE 4. Suggested pyrazinamide doses, using whole tablets, for adults weighing 40–90 kilograms

	Weight (kg)*		
	40–55	56–75	76–90
Daily, mg (mg/kg)	1,000 (18.2–25.0)	1,500 (20.0–26.8)	2,000† (22.2–26.3)
Thrice weekly, mg (mg/kg)	1,500 (27.3–37.5)	2,500 (33.3–44.6)	3,000† (33.3–39.5)
Twice weekly, mg (mg/kg)	2,000 (36.4–50.0)	3,000 (40.0–53.6)	4,000† (44.4–52.6)

* Based on estimated lean body weight.
† Maximum dose regardless of weight.

TABLE 5. Suggested ethambutol doses, using whole tablets, for adults weighing 40–90 kilograms

	Weight (kg)*		
	40–55	56–75	76–90
Daily, mg (mg/kg)	800 (14.5–20.0)	1,200 (16.0–21.4)	1,600† (17.8–21.1)
Thrice weekly, mg (mg/kg)	1,200 (21.8–30.0)	2,000 (26.7–35.7)	2,400† (26.7–31.6)
Twice weekly, mg (mg/kg)	2,000 (36.4–50.0)	2,800 (37.3–50.0)	4,000† (44.4–52.6)

* Based on estimated lean body weight.
† Maximum dose regardless of weight.

supports the diagnosis of culture-negative pulmonary tuberculosis, as well as latent tuberculosis infection in persons with stable abnormal chest radiographs consistent with inactive tuberculosis (see below).

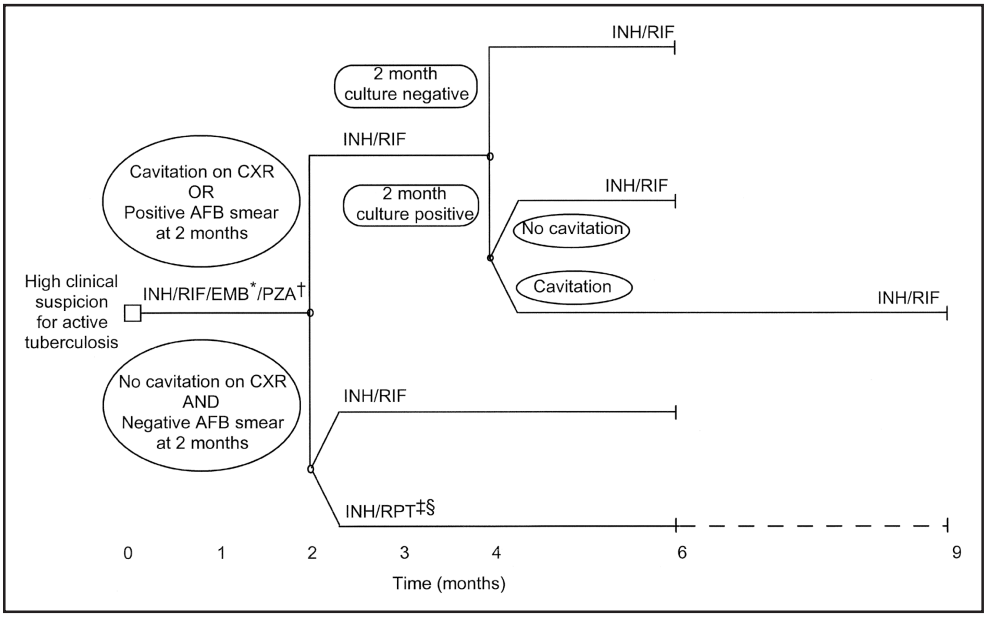
If the suspicion of tuberculosis is high or the patient is seriously ill with a disorder, either pulmonary or extrapulmonary, that is thought possibly to be tuberculosis, combination chemotherapy using one of the recommended regimens should be initiated promptly, often before AFB smear results are known and usually before mycobacterial culture results have been obtained. A positive AFB smear provides strong inferential evidence for the diagnosis of tuberculosis. If the diagnosis is confirmed by isolation of *M. tuberculosis* or a positive nucleic

TABLE 6. Epidemiological circumstances in which an exposed person is at increased risk of infection with drug-resistant *Mycobacterium tuberculosis**

- Exposure to a person who has known drug-resistant tuberculosis
- Exposure to a person with active tuberculosis who has had prior treatment for tuberculosis (treatment failure or relapse) and whose susceptibility test results are not known
- Exposure to persons with active tuberculosis from areas in which there is a high prevalence of drug resistance
- Exposure to persons who continue to have positive sputum smears after 2 months of combination chemotherapy
- Travel in an area of high prevalence of drug resistance

* This information is to be used in deciding whether or not to add a fourth drug (usually EMB) for children with active tuberculosis, not to infer the empiric need for a second-line treatment regimen.

FIGURE 1. Treatment algorithm for tuberculosis.



Patients in whom tuberculosis is proved or strongly suspected should have treatment initiated with isoniazid, rifampin, pyrazinamide, and ethambutol for the initial 2 months. A repeat smear and culture should be performed when 2 months of treatment has been completed. If cavities were seen on the initial chest radiograph or the acid-fast smear is positive at completion of 2 months of treatment, the continuation phase of treatment should consist of isoniazid and rifampin daily or twice weekly for 4 months to complete a total of 6 months of treatment. If cavitation was present on the initial chest radiograph and the culture at the time of completion of 2 months of therapy is positive, the continuation phase should be lengthened to 7 months (total of 9 months of treatment). If the patient has HIV infection and the $CD4^+$ cell count is <100/µl, the continuation phase should consist of daily or three times weekly isoniazid and rifampin. In HIV-uninfected patients having no cavitation on chest radiograph and negative acid-fast smears at completion of 2 months of treatment, the continuation phase may consist of either once weekly isoniazid and rifapentine, or daily or twice weekly isoniazid and rifampin, to complete a total of 6 months (bottom). Patients receiving isoniazid and rifapentine, and whose 2-month cultures are positive, should have treatment extended by an additional 3 months (total of 9 months).

* EMB may be discontinued when results of drug susceptibility testing indicate no drug resistance.

† PZA may be discontinued after it has been taken for 2 months (56 doses).

‡ RPT should not be used in HIV-infected patients with tuberculosis or in patients with extrapulmonary tuberculosis.

§ Therapy should be extended to 9 months if 2-month culture is positive.

CXR = chest radiograph; EMB = ethambutol; INH = isoniazid; PZA = pyrazinamide; RIF = rifampin; RPT = rifapentine.

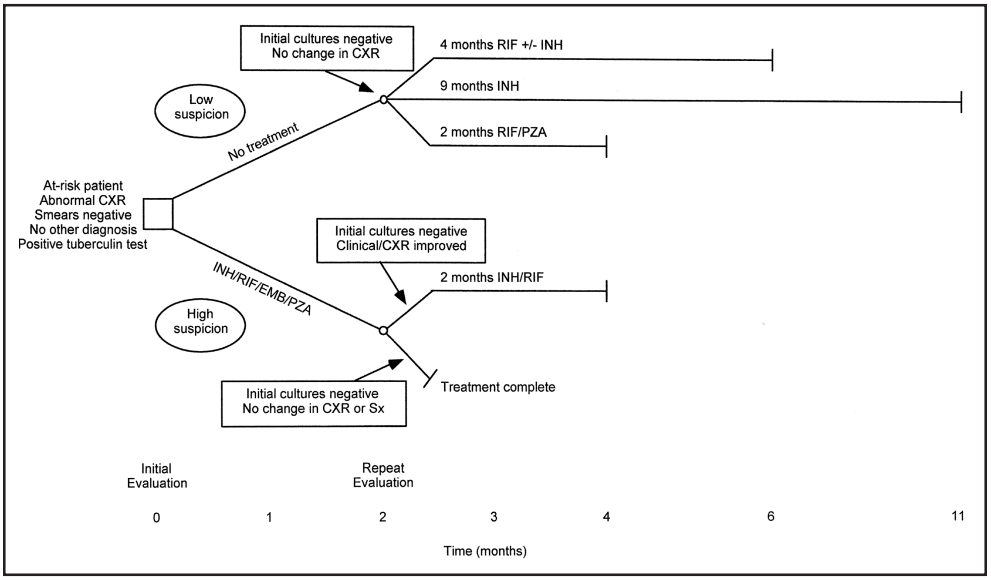
acid amplification test, treatment can be continued to complete a standard course of therapy (Figure 1). When the initial AFB smears and cultures are negative, a diagnosis other than tuberculosis should be considered and appropriate evaluations undertaken. If no other diagnosis is established and the PPD-tuberculin skin test is positive (in this circumstance a reaction of 5 mm or greater induration is considered positive), empirical combination chemotherapy should be initiated. If there is a clinical or radiographic response within 2 months of initiation of therapy and no other diagnosis has been established, a diagnosis of culture-negative pulmonary tuberculosis can be made and treatment continued with an additional 2 months of INH and RIF to complete a total of 4 months of treatment, an adequate regimen for culture-negative pulmonary tuberculosis (Figure 2). If there is no clinical or radiographic response by 2 months, treatment can be stopped and other diagnoses including inactive tuberculosis considered.

If AFB smears are negative and suspicion for active tuberculosis is low, treatment can be deferred until the results of mycobacterial cultures are known and a comparison chest radiograph is available (usually within 2 months) (Figure 2). In low-suspicion patients not initially being treated, if cultures are negative, the PPD-tuberculin skin test is positive (5 mm or greater induration), and the chest radiograph is unchanged after 2 months, one of the three regimens recommended for the treatment of latent tuberculosis infection could be used. These include (*1*) INH for a total of 9 months, (*2*) RIF with or without INH for a total of 4 months, or (*3*) RIF and PZA for a total of 2 months. Because of reports of an increased rate of hepatotoxicity with the RIF–PZA regimen, it should be reserved for patients who are not likely to complete a longer course of treatment, can be monitored closely, and do not have contraindications to the use of this egimen.

Baseline and Follow-Up Evaluations

Patients suspected of having tuberculosis should have appropriate specimens collected for microscopic examination and mycobacterial culture. When the lung is the site of disease, three sputum specimens should be obtained. Sputum induction with hypertonic saline may be necessary to obtain specimens and bronchoscopy (both performed under appropriate infection control measures) may be considered for patients who are unable to produce sputum, depending on the clinical circumstances. Susceptibility testing for INH, RIF, and EMB should be performed on a positive initial culture, regardless of the source of the specimen. Second-line drug susceptibility testing should be done only in reference laboratories and be limited to specimens from patients who have had prior therapy, who are contacts of patients with drug-resistant tuberculosis, who have demonstrated resistance to

FIGURE 2. Treatment algorithm for active, culture-negative pulmonary tuberculosis and inactive tuberculosis



The decision to begin treatment for a patient with sputum smears that are negative depends on the degree of suspicion that the patient has tuberculosis. The considerations in choosing among the treatment options are discussed in text. If the clinical suspicion is high (bottom), then multidrug therapy should be initiated before acid-fast smear and culture results are known. If the diagnosis is confirmed by a positive culture, treatment can be continued to complete a standard course of therapy (see Figure 1). If initial cultures remain negative and treatment has consisted of multiple drugs for 2 months, then there are two options depending on repeat evaluation at 2 months (bottom): 1) if the patient demonstrates symptomatic or radiographic improvement without another apparent diagnosis, then a diagnosis of culture-negative tuberculosis can be inferred. Treatment should be continued with isoniazid and rifampin alone for an additional 2 months; 2) if the patient demonstrates neither symptomatic nor radiographic improvement, then prior tuberculosis is unlikely and treatment is complete once treatment including at least 2 months of rifampin and pyrazinamide has been administered. In low-suspicion patients not initially receiving treatment (top), if cultures remain negative, the patient has no symptoms, and the chest radiograph is unchanged at 2–3 months, there are three treatment options: these are 1) isoniazid for 9 months, 2) rifampin with or without isoniazid for 4 months, or 3) rifampin and pyrazinamide for 2 months. CXR = chest X-ray; EMB = ethambutol; INH = isoniazid; PZA = pyrazinamide; RIF = rifampin; Sx = signs/symptoms. (It should be noted that the RIF/PZA 2-month regimen should be used only for patients who are not likely to complete a longer course of treatment and can be monitored closely.)

rifampin or to other first-line drugs, or who have positive cultures after more than 3 months of treatment.

It is recommended that all patients with tuberculosis have counseling and testing for HIV infection, at least by the time treatment is initiated, if not earlier. For patients with HIV infection, a $CD4^+$ lymphocyte count should be obtained. Patients with risk factors for hepatitis B or C viruses (e.g., injection drug use, foreign birth in Asia or Africa, HIV infection) should have serologic tests for these viruses. For all adult patients baseline measurements of serum amino transferases (aspartate aminotransferase [AST], alanine aminotransferase [ALT]), bilirubin, alkaline phosphatase, and serum creatinine and a platelet count should be obtained. Testing of visual acuity and red-green color discrimination should be obtained when EMB is to be used.

During treatment of patients with pulmonary tuberculosis, a sputum specimen for microscopic examination and culture should be obtained at a minimum of monthly intervals until two consecutive specimens are negative on culture. More frequent AFB smears may be useful to assess the early response to treatment and to provide an indication of infectiousness. For patients with extrapulmonary tuberculosis the frequency and kinds of evaluations will depend on the site involved. In addition, it is critical that patients have clinical evaluations at least monthly to identify possible adverse effects of the antituberculosis medications and to assess adherence. Generally, patients do not require follow-up after completion of therapy but should be instructed to seek care promptly if signs or symptoms recur.

Routine measurements of hepatic and renal function and platelet count are not necessary during treatment unless patients have baseline abnormalities or are at increased risk of hepatotoxicity (e.g., hepatitis B or C virus infection, alcohol abuse). At each monthly visit patients taking EMB should be questioned regarding possible visual disturbances including blurred vision or scotomata; monthly testing of visual acuity and color discrimination is recommended for patients taking doses that on a milligram per kilogram basis are greater than those listed in Table 5 and for patients receiving the drug for longer than 2 months.

Identification and Management of Patients at Increased Risk of Treatment Failure and Relapse

The presence of cavitation on the initial chest radiograph combined with having a positive sputum culture at the time the initial phase of treatment is completed has been shown in clinical trials to identify patients at high risk for adverse outcomes (treatment failure, usually defined by positive cultures after 4 months of treatment, or relapse, defined by recurrent tuberculosis at any time after completion of treatment and apparent cure). For this reason it is particularly important to conduct a microbiological evaluation 2 months after initiation of treatment (Figure 1). Approximately 80% of patients

with pulmonary tuberculosis caused by drug-susceptible organisms who are started on standard four-drug therapy will have negative sputum cultures at this time. Patients with positive cultures after 2 months of treatment should undergo careful evaluation to determine the cause. For patients who have positive cultures after 2 months of treatment and have not been receiving DOT, the most common reason is nonadherence to the regimen. Other possibilities, especially for patients receiving DOT, include extensive cavitary disease at the time of diagnosis, drug resistance, malabsorption of drugs, laboratory error, and biological variation in response.

In USPHS Study 22, nearly 21% of patients in the control arm of the study (a continuation phase of twice weekly INH and RIF) who had both cavitation on the initial chest radiograph and a positive culture at the 2-month juncture relapsed. Patients who had only one of these factors (either cavitation or a positive 2-month culture) had relapse rates of 5–6% compared with 2% for patients who had neither risk factor. In view of this evidence, it is recommended that, for patients who have cavitation on the initial chest radiograph and whose 2-month culture is positive, the minimum duration of treatment should be 9 months (a total of 84–273 doses depending on whether the drugs are given daily or intermittently) (Figure 1 and Table 2). The recommendation to lengthen the continuation phase of treatment is based on expert opinion and on the results of a study of the optimal treatment duration for patients with silicotuberculosis showing that extending treatment from 6 to 8 months greatly reduced the rate of relapse (Rating AIII). The recommendation is also supported by the results of a trial in which the once weekly INH–rifapentine continuation phase was extended to 7 months for patients at high risk of relapse. The rate of relapse was reduced significantly compared with historical control subjects from another trial in which the continuation phase was 4 months.

For patients who have either cavitation on the initial film or a positive culture after completing the initial phase of treatment (i.e., at 2 months), the rates of relapse were 5–6%. In this group decisions to prolong the continuation phase should be made on an individual basis.

Completion of Treatment

A full course of therapy (completion of treatment) is determined more accurately by the total number of doses taken, not solely by the duration of therapy. For example, the "6-month" daily regimen (given 7 days/week; see below) should consist of at least 182 doses of INH and RIF, and 56 doses of PZA. Thus, 6 months is the minimum duration of treatment and accurately indicates the amount of time the drugs are given only if there are no interruptions in drug administration. In some cases, either because of drug toxicity or nonadherence to the treatment regimen, the specified number of doses cannot be administered within the targeted period. In such cases the goal is to deliver the specified number of doses within a recommended maximum time. For example, for a 6-month daily regimen the 182 doses should be administered within 9 months of beginning treatment. If treatment is not completed within this period, the patient should be assessed to determine the appropriate action to take—continuing treatment for a longer duration or restarting treatment from the beginning, either of which may require more restrictive measures to be used to ensure completion.

Clinical experience suggests that patients being managed by DOT administered 5 days/week have a rate of successful therapy equivalent to those being given drugs 7 days/week. Thus, "daily therapy" may be interpreted to mean DOT given 5 days/week and the required number of doses adjusted accordingly. For example, for the 6-month "daily" regimen given 5 days/week the planned total number of doses is 130. (Direct observation of treatment given 5 days/week has been used in a number of clinical trials, including USPHS Study 22, but has not been evaluated in a controlled trial; thus, this modification should be rated AIII.) As an option, patients might be given the medications to take without DOT on weekends.

Interruptions in treatment may have a significant effect on the duration of therapy. Reinstitution of treatment must take into account the bacillary load of the patient, the point in time when the interruption occurred, and the duration of the interruption. In general, the earlier in treatment and the longer the duration of the interruption, the more serious the effect and the greater the need to restart therapy from the beginning.

Practical Aspects of Patient Management During Treatment

The first-line antituberculosis medications should be administered together; split dosing should be avoided. Fixed-dose combination preparations may be administered more easily than single drug tablets and may decrease the risk of acquired drug resistance and medication errors. Fixed-dose combinations may be used when DOT is given daily and are especially useful when DOT is not possible, but they are not formulated for use with intermittent dosing. It should be noted that for patients weighing more than 90 kg the dose of PZA in the three-drug combination is insufficient and additional PZA tablets are necessary. There are two combination formulations approved for use in the United States: INH and RIF (Rifamate®) and INH, RIF, and PZA (Rifater®).

Providers treating patients with tuberculosis must be especially vigilant for drug interactions. Given the frequency of

comorbid conditions, it is quite common for patients with tuberculosis to be taking a variety of other medications, the effects of which may be altered by the antituberculosis medications, especially the rifamycins. These interactions are described in Section 7, Drug Interactions.

Adverse effects, especially gastrointestinal upset, are relatively common in the first few weeks of antituberculosis therapy; however, first-line antituberculosis drugs, particularly RIF, must not be discontinued because of minor side effects. Although ingestion with food delays or moderately decreases the absorption of antituberculosis drugs, the effects of food are of little clinical significance. Thus, if patients have epigastric distress or nausea with the first-line drugs, dosing with meals or changing the hour of dosing is recommended. Administration with food is preferable to splitting a dose or changing to a second-line drug.

Drug-induced hepatitis, the most serious common adverse effect, is defined as a serum AST level more than three times the upper limit of normal in the presence of symptoms, or more than five times the upper limit of normal in the absence of symptoms. If hepatitis occurs INH, RIF, and PZA, all potential causes of hepatic injury, should be stopped immediately. Serologic testing for hepatitis viruses A, B, and C (if not done at baseline) should be performed and the patient questioned carefully regarding exposure to other possible hepatotoxins, especially alcohol. Two or more antituberculosis medications without hepatotoxicity, such as EMB, SM, amikacin/kanamycin, capreomycin, or a fluoroquinolone (levofloxacin, moxifloxacin, or gatifloxacin), may be used until the cause of the hepatitis is identified. Once the AST level decreases to less than two times the upper limit of normal and symptoms have significantly improved, the first-line medications should be restarted in sequential fashion. Close monitoring, with repeat measurements of serum AST and bilirubin and symptom review, is essential in managing these patients.

Treatment in Special Situations

HIV infection

Recommendations for the treatment of tuberculosis in HIV-infected adults are, with a few exceptions, the same as those for HIV-uninfected adults (Table 2). The INH–rifapentine once weekly continuation phase (Regimens 1c and 2b) is contraindicated in HIV-infected patients because of an unacceptably high rate of relapse, frequently with organisms that have acquired resistance to rifamycins. The development of acquired rifampin resistance has also been noted among HIV-infected patients with advanced immunosuppression treated with twice weekly rifampin- or rifabutin-based regimens. Consequently, patients with $CD4^+$ cell counts <100/µl should receive daily or three times weekly treatment (Regimen 1/1a or Regimen 3/3a). DOT and other adherence-promoting strategies are especially important for patients with HIV-related tuberculosis.

Management of HIV-related tuberculosis is complex and requires expertise in the management of both HIV disease and tuberculosis. Because HIV-infected patients are often taking numerous medications, some of which interact with antituberculosis medications, it is strongly encouraged that experts in the treatment of HIV-related tuberculosis be consulted. A particular concern is the interaction of rifamycins with antiretroviral agents and other antiinfective drugs. Rifampin can be used for the treatment of tuberculosis with certain combinations of antiretroviral agents. Rifabutin, which has fewer problematic drug interactions, may also be used in place of rifampin and appears to be equally effective although the doses of rifabutin and antiretroviral agents may require adjustment. As new antiretroviral agents and more pharmacokinetic data become available, these recommendations are likely to be modified.

On occasion, patients with HIV-related tuberculosis may experience a temporary exacerbation of symptoms, signs, or radiographic manifestations of tuberculosis while receiving antituberculosis treatment. This clinical or radiographic worsening (paradoxical reaction) occurs in HIV-infected patients with active tuberculosis and is thought to be the result of immune reconstitution as a consequence of effective antiretroviral therapy. Symptoms and signs may include high fevers, lymphadenopathy, expanding central nervous system lesions, and worsening of chest radiographic findings. The diagnosis of a paradoxical reaction should be made only after a thorough evaluation has excluded other etiologies, particularly tuberculosis treatment failure. Nonsteroidal antiinflammatory agents may be useful for symptomatic relief. For severe paradoxical reactions, prednisone (1–2 mg/kg per day for 1–2 weeks, then in gradually decreasing doses) may be used, although there are no data from controlled trials to support this approach (Rating CIII).

Children

Because of the high risk of disseminated tuberculosis in infants and children younger than 4 years of age, treatment should be started as soon as the diagnosis of tuberculosis is suspected. In general, the regimens recommended for adults are also the regimens of choice for infants, children, and adolescents with tuberculosis, with the exception that ethambutol is not used routinely in children. Because there is a lower bacillary burden in childhood-type tuberculosis there is less concern with the development of acquired drug resistance. However, children and adolescents may develop "adult-type"

tuberculosis with upper lobe infiltration, cavitation, and sputum production. In such situations an initial phase of four drugs should be given until susceptibility is proven. When clinical or epidemiologic circumstances (Table 6) suggest an increased probability of INH resistance, EMB can be used safely at a dose of 15–20 mg/kg per day, even in children too young for routine eye testing. Streptomycin, kanamycin, or amikacin also can be used as the fourth drug, when necessary.

Most studies of treatment in children have used 6 months of INH and RIF supplemented during the first 2 months with PZA. This three-drug combination has a success rate of greater than 95% and an adverse drug reaction rate of less than 2%. Most treatment studies of intermittent dosing in children have used daily drug administration for the first 2 weeks to 2 months. DOT should always be used in treating children.

Because it is difficult to isolate *M. tuberculosis* from a child with pulmonary tuberculosis, it is frequently necessary to rely on the results of drug susceptibility tests of the organisms isolated from the presumed source case to guide the choice of drugs for the child. In cases of suspected drug-resistant tuberculosis in a child or when a source case isolate is not available, specimens for microbiological evaluation should be obtained via early morning gastric aspiration, bronchoalveolar lavage, or biopsy.

In general, extrapulmonary tuberculosis in children can be treated with the same regimens as pulmonary disease. Exceptions are disseminated tuberculosis and tuberculous meningitis, for which there are inadequate data to support 6-month therapy; thus 9–12 months of treatment is recommended.

The optimal treatment of pulmonary tuberculosis in children and adolescents with HIV infection is unknown. The American Academy of Pediatrics recommends that initial therapy should always include at least three drugs, and the total duration of therapy should be at least 9 months, although there are no data to support this recommendation.

Extrapulmonary tuberculosis

The basic principles that underlie the treatment of pulmonary tuberculosis also apply to extrapulmonary forms of the disease. Although relatively few studies have examined treatment of extrapulmonary tuberculosis, increasing evidence suggests that 6- to 9-month regimens that include INH and RIF are effective. Thus, a 6-month course of therapy is recommended for treating tuberculosis involving any site with the exception of the meninges, for which a 9- 12-month regimen is recommended. Prolongation of therapy also should be considered for patients with tuberculosis in any site that is slow to respond. The addition of corticosteroids is recommended for patients with tuberculous pericarditis and tuberculous meningitis.

Culture-negative pulmonary tuberculosis and radiographic evidence of prior pulmonary tuberculosis

Failure to isolate *M. tuberculosis* from persons suspected of having pulmonary tuberculosis on the basis of clinical features and chest radiographic examination does not exclude a diagnosis of active tuberculosis. Alternative diagnoses should be considered carefully and further appropriate diagnostic studies undertaken in persons with apparent culture-negative tuberculosis. The general approach to management is shown in Figure 2. A diagnosis of tuberculosis can be strongly inferred by the clinical and radiographic response to antituberculosis treatment. Careful reevaluation should be performed after 2 months of therapy to determine whether there has been a response attributable to antituberculosis treatment. If either clinical or radiographic improvement is noted and no other etiology is identified, treatment should be continued for active tuberculosis. Treatment regimens in this circumstance include one of the standard 6-month chemotherapy regimens or INH, RIF, PZA, and EMB for 2 months followed by INH and RIF for an additional 2 months (4 months total). However, HIV-infected patients with culture-negative pulmonary tuberculosis should be treated for a minimum of 6 months.

Persons with a positive tuberculin skin test who have radiographic evidence of prior tuberculosis (e.g., upper lobe fibronodular infiltrations) but who have not received adequate therapy are at increased risk for the subsequent development of tuberculosis. Unless previous radiographs are available showing that the abnormality is stable, it is recommended that sputum examination (using sputum induction if necessary) be performed to assess the possibility of active tuberculosis being present. Also, if the patient has symptoms of tuberculosis related to an extrapulmonary site, an appropriate evaluation should be undertaken. Once active tuberculosis has been excluded (i.e., by negative cultures and a stable chest radiograph), the treatment regimens are those used for latent tuberculosis infection: INH for 9 months, RIF (with or without INH) for 4 months, or RIF and PZA for 2 months (for patients who are unlikely to complete a longer course and who can be monitored closely) (Figure 2).

Renal insufficiency and end-stage renal disease

Specific dosing guidelines for patients with renal insufficiency and end-stage renal disease are provided in Table 15. For patients undergoing hemodialysis, administration of all drugs after dialysis is preferred to facilitate DOT and to avoid premature removal of drugs such as PZA and cycloserine. To avoid toxicity it is important to monitor serum drug

concentrations in persons with renal failure who are taking cycloserine or EMB. There is little information concerning the effects of peritoneal dialysis on clearance of antituberculosis drugs.

Liver disease

INH, RIF, and PZA all can cause hepatitis that may result in additional liver damage in patients with preexisting liver disease. However, because of the effectiveness of these drugs (particularly INH and RIF), they should be used if at all possible, even in the presence of preexisting liver disease. If serum AST is more than three times normal before the initiation of treatment (and the abnormalities are not thought to be caused by tuberculosis), several treatment options exist. One option is to treat with RIF, EMB, and PZA for 6 months, avoiding INH. A second option is to treat with INH and RIF for 9 months, supplemented by EMB until INH and RIF susceptibility are demonstrated, thereby avoiding PZA. For patients with severe liver disease a regimen with only one hepatotoxic agent, generally RIF plus EMB, could be given for 12 months, preferably with another agent, such as a fluoroquinolone, for the first 2 months; however, there are no data to support this recommendation.

In all patients with preexisting liver disease, frequent clinical and laboratory monitoring should be performed to detect drug-induced hepatic injury.

Pregnancy and breastfeeding

Because of the risk of tuberculosis to the fetus, treatment of tuberculosis in pregnant women should be initiated whenever the probability of maternal disease is moderate to high. The initial treatment regimen should consist of INH, RIF, and EMB. Although all of these drugs cross the placenta, they do not appear to have teratogenic effects. Streptomycin is the only antituberculosis drug documented to have harmful effects on the human fetus (congenital deafness) and should not be used. Although detailed teratogenicity data are not available, PZA can probably be used safely during pregnancy and is recommended by the World Health Organization (WHO) and the International Union against Tuberculosis and Lung Disease (IUATLD). If PZA is not included in the initial treatment regimen, the minimum duration of therapy is 9 months.

Breastfeeding should not be discouraged for women being treated with the first-line antituberculosis agents because the small concentrations of these drugs in breast milk do not produce toxicity in the nursing newborn. Conversely, drugs in breast milk should not be considered to serve as effective treatment for tuberculosis or for latent tuberculosis infection in a nursing infant. Pyridoxine supplementation (25 mg/day) is recommended for all women taking INH who are either pregnant or breastfeeding. The amount of pyridoxine in multivitamins is variable but generally less than the needed amount.

Management of Relapse, Treatment Failure, and Drug Resistance

Relapse refers to the circumstance in which a patient becomes and remains culture negative while receiving therapy but, at some point after completion of therapy, either becomes culture positive again or has clinical or radiographic deterioration that is consistent with active tuberculosis. In the latter situation rigorous efforts should be made to establish a diagnosis and to obtain microbiological confirmation of the relapse to enable testing for drug resistance. Most relapses occur within the first 6–12 months after completion of therapy. In nearly all patients with tuberculosis caused by drug-susceptible organisms and who were treated with rifamycin-containing regimens using DOT, relapses occur with susceptible organisms. However, in patients who received self-administered therapy or a nonrifamycin regimen and who have a relapse, the risk of acquired drug resistance is substantial. In addition, if initial drug susceptibility testing was not performed and the patient fails or relapses with a rifamycin-containing regimen given by DOT, there is a high likelihood that the organisms were resistant from the outset.

The selection of empirical treatment for patients with relapse should be based on the prior treatment scheme and severity of disease. For patients with tuberculosis that was caused by drug-susceptible organisms and who were treated under DOT, initiation of the standard four-drug regimen is appropriate until the results of drug susceptibility tests are available. However, for patients who have life-threatening forms of tuberculosis, at least three additional agents to which the organisms are likely to be susceptible should be included.

For patients with relapse who did not receive DOT, who were not treated with a rifamycin-based regimen, or who are known or presumed to have had irregular treatment, it is prudent to infer that drug resistance is present and to begin an expanded regimen with INH, RIF, and PZA plus an additional two or three agents based on the probability of in vitro susceptibility. Usual agents to be employed would include a fluoroquinolone (levofloxacin, moxifloxacin, or gatifloxacin), an injectable agent such as SM (if not used previously and susceptibility to SM had been established), amikacin, kanamycin, or capreomycin, with or without an additional oral drug.

Treatment failure is defined as continued or recurrently positive cultures during the course of antituberculosis therapy. After 3 months of multidrug therapy for pulmonary tuberculosis caused by drug-susceptible organisms, 90–95% of patients will have negative cultures and show clinical improvement. Thus,

patients with positive cultures after 3 months of what should be effective treatment must be evaluated carefully to identify the cause of the delayed conversion. Patients whose sputum cultures remain positive after 4 months of treatment should be deemed treatment failures.

Possible reasons for treatment failure in patients receiving appropriate regimens include nonadherence to the drug regimen (the most common reason), drug resistance, malabsorption of drugs, laboratory error, and extreme biological variation in response. If treatment failure occurs, early consultation with a specialty center is strongly advised. If failure is likely due to drug resistance and the patient is not seriously ill, an empirical retreatment regimen could be started or administration of an altered regimen could be deferred until results of drug susceptibility testing from a recent isolate are available. If the patient is seriously ill or sputum AFB smears are positive, an empirical regimen should be started immediately and continued until susceptibility tests are available. For patients who have treatment failure, *M. tuberculosis* isolates should be sent promptly to a reference laboratory for drug susceptibility testing to both first- and second-line agents.

A fundamental principle in managing patients with treatment failure is never to add a single drug to a failing regimen; so doing leads to acquired resistance to the new drug. Instead, at least two, and preferably three, new drugs to which susceptibility could logically be inferred should be added to lessen the probability of further acquired resistance. Empirical retreatment regimens might include a fluoroquinolone, an injectable agent such as SM (if not used previously and the patient is not from an area of the world having high rates of SM resistance), amikacin, kanamycin, or capreomycin, and an additional oral agent such as *p*-aminosalicylic acid (PAS), cycloserine, or ethionamide. Once drug-susceptibility test results are available, the regimen should be adjusted according to the results.

Patients having tuberculosis caused by strains of *M. tuberculosis* resistant to at least INH and RIF (multidrug-resistant [MDR]) are at high risk for treatment failure and further acquired drug resistance. Such patients should be referred to or consultation obtained from specialized treatment centers as identified by the local or state health departments or CDC. Although patients with strains resistant to RIF alone have a better prognosis than patients with MDR strains, they are also at increased risk for treatment failure and additional resistance and should be managed in consultation with an expert.

Definitive randomized or controlled studies have not been performed to establish optimum regimens for treating patients with the various patterns of drug-resistant tuberculosis; thus, treatment recommendations are based on expert opinion, guided by a set of general principles specified in Section 9, Management of Relapse, Treatment Failure, and Drug Resistance. Table 16 contains treatment regimens suggested for use in patients with various patterns of drug-resistant tuberculosis (all are rated AIII).

The role of resectional surgery in the management of patients with extensive pulmonary MDR tuberculosis has not been established in randomized studies and results have been mixed. Surgery should be performed by surgeons with experience in these situations and only after the patient has received several months of intensive chemotherapy. Expert opinion suggests that chemotherapy should be continued for 1–2 years postoperatively to prevent relapse.

Treatment of Tuberculosis in Low-Income Countries: Recommendations of the WHO and Guidelines from the IUATLD

To place the current guidelines in an international context it is necessary to have an understanding of the approaches to treatment of tuberculosis in high-incidence, low-income countries. It is important to recognize that the American Thoracic Society/CDC/Infectious Diseases Society of America (ATS/CDC/IDSA) recommendations cannot be assumed to be applicable under all epidemiologic and economic circumstances. The incidence of tuberculosis and the resources with which to confront the disease to an important extent determine the approaches used. Given the increasing proportion of patients in low-incidence countries who were born in high-incidence countries, it is also important for persons managing these cases to be familiar with the approaches used in the countries of origin.

The major international recommendations and guidelines for treating tuberculosis are those of the WHO and of the IUATLD. The WHO document was developed by an expert committee whereas the IUATLD document is a distillation of IUATLD practice, validated in the field.

The WHO and IUATLD documents target, in general, countries in which mycobacterial culture, drug susceptibility testing, radiographic facilities, and second-line drugs are not widely available as a routine. A number of differences exist between these new ATS/CDC/IDSA recommendations, and the current tuberculosis treatment recommendations of the WHO and guidelines of the IUATLD. Both international sets of recommendations are built around a national case management strategy called "DOTS," the acronym for "directly observed therapy, short course," in which direct observation of therapy (DOT) is only one of five key elements. The five components of DOTS are 1) government commitment to sustained tuberculosis control activities, 2) case detection by

sputum smear microscopy among symptomatic patients self-reporting to health services, 3) a standardized treatment regimen of 6–8 months for at least all confirmed sputum smear–positive cases, with DOT for at least the initial 2 months, 4) a regular, uninterrupted supply of all essential antituberculosis drugs, and 5) a standardized recording and reporting system that enables assessment of treatment results for each patient and of the tuberculosis control program overall.

A number of other differences exist as well:

- The WHO and the IUATLD recommend diagnosis and classification of tuberculosis cases and assessment of response based on sputum AFB smears. Culture and susceptibility testing for new patients is not recommended because of cost, limited applicability, and lack of facilities.
- Chest radiography is recommended by both the WHO and IUATLD only for patients with negative sputum smears and is not recommended at all for follow-up.
- Both 6- and 8-month treatment regimens are recommended by the WHO. The IUATLD recommends an 8-month regimen with thioacetazone in the continuation phase for HIV-negative patients. For patients suspected of having or known to have HIV infection, ethambutol is substituted for thioacetazone
- The WHO and the IUATLD recommend a standardized 8-month regimen for patients who have relapsed, had interrupted treatment, or have failed treatment. Patients who have failed supervised retreatment are considered "chronic" cases and are highly likely to have tuberculosis caused by MDR organisms. Susceptibility testing and a tailored regimen using second-line drugs based on the test results are recommended by the WHO, if testing and second-line drugs are available. The IUATLD recommendations do not address the issue.
- Neither baseline nor follow-up biochemical testing is recommended by the WHO and the IUATLD. It is recommended that patients be taught to recognize the symptoms associated with drug toxicity and to report them promptly.

A Research Agenda for Tuberculosis Treatment

New antituberculosis drugs are needed for three main reasons: 1) to shorten or otherwise simplify treatment of tuberculosis caused by drug-susceptible organisms, 2) to improve treatment of drug-resistant tuberculosis, and 3) to provide more efficient and effective treatment of latent tuberculosis infection. No truly novel compounds that are likely to have a significant impact on tuberculosis treatment are close to clinical trials. However, further work to optimize the effectiveness of once-a-week rifapentine regimens using higher doses of the drug and using rifapentine in combination with moxifloxacin is warranted, on the basis of experimental data.

New categories of drugs that have shown promise for use in treating tuberculosis include the nitroimidazopyrans and the oxazolidinones. Experimental data also suggest that a drug to inhibit an enzyme, isocitrate lyase, thought to be necessary for maintaining the latent state, might be useful for treatment of latent tuberculosis infection.

A number of other interventions that might lead to improved treatment outcome have been suggested, although none has undergone rigorous clinical testing. These include various drug delivery systems, cytokine inhibitors, administration of "protective" cytokines such as interferon-γ and interleukin-2, and nutritional supplements, especially vitamin A and zinc.

Research is also needed to identify factors that are predictive of a greater or lesser risk of relapse to determine optimal length of treatment. Identification of such factors would enable more efficient targeting of resources to supervise treatment. In addition, identification of behavioral factors that identify patients at greater or lesser likelihood of being adherent to therapy would also enable more efficient use of DOT.

1. Introduction and Background

Since 1971 the American Thoracic Society (ATS) and CDC have regularly collaborated to develop joint guidelines for the diagnosis, treatment, prevention, and control of tuberculosis (*1*). These documents have been intended to guide both public health programs and health care providers in all aspects of the clinical and public health management of tuberculosis in low-incidence countries, with a particular focus on the United States. The most recent version of guidelines for the treatment of tuberculosis was published in 1994 (*2*).

The current document differs from its predecessor in a number of important areas that are summarized above. The process by which this revision of the recommendations for treatment was developed was modified substantially from the previous versions. For the first time the Infectious Diseases Society of America (IDSA) has become a cosponsor of the statement, together with the ATS and CDC. The IDSA has had representation on prior statement committees but has not previously been a cosponsor of the document. Practice guidelines that serve to complement the current statement have been developed by the IDSA (*3*). In addition to the IDSA, representatives of the American Academy of Pediatrics (AAP), the (United States) National Tuberculosis Controllers Association (NTCA), the Canadian Thoracic Society (CTS), the IUATLD, and the WHO participated in the revision. By virtue of their different perspectives these committee members served to provide broader input and to help ensure that the guidelines are

Provider Responsibility

Treatment of tuberculosis benefits both the community as a whole and the individual patient; thus, any public health program or private provider (or both in a defined arrangement by which management is shared) undertaking to treat a patient with tuberculosis is assuming a public health function that includes not only prescribing an appropriate regimen but also ensuring adherence to the regimen until treatment is completed.

placed in an appropriate context. It should be emphasized that the current guidelines are intended for areas in which mycobacterial cultures, drug susceptibility tests, radiographic facilities, and second-line drugs are available, either immediately or by referral, on a routine basis.

For this revision of the recommendations essentially all clinical trials of antituberculosis treatment in the English language literature were reviewed and the strength of the evidence they presented was rated according to the IDSA/USPHS rating scale (*4*).

This revision of the recommendations for treatment of tuberculosis presents a significant philosophic departure from previous versions. In this document the responsibility for successful treatment of tuberculosis is placed primarily on the provider or program initiating therapy rather than on the patient. It is well established that appropriate treatment of tuberculosis rapidly renders the patient noninfectious, prevents drug resistance, minimizes the risk of disability or death from tuberculosis, and nearly eliminates the possibility of relapse. For these reasons, antituberculosis chemotherapy is both a personal and a public health measure that cannot be equated with the treatment of, for example, hypertension or diabetes mellitus, wherein the benefits largely accrue to the patient. Provider responsibility is a central concept in treating patients with tuberculosis, no matter what the source of their care. All reasonable attempts should be made to accommodate the patient so that a successful outcome is achieved. However, interventions such as detention may be necessary for patients who are persistently nonadherent.

The recommendations in this statement are not applicable under all epidemiologic circumstances or across all levels of resources that are available to tuberculosis control programs worldwide. Although the basic principles of therapy described in this document apply regardless of conditions, the diagnostic approach, methods of patient supervision, and monitoring for response and for adverse drug effects, and in some instances the regimens recommended, are quite different in high-incidence, low-income areas compared with low-incidence, high-income areas of the world. A summary of the important differences between the recommendations in this document and those of the IUATLD and the WHO is found in Section 10,Treatment of Tuberculosis in Low-Income Countries: Recommendations of the WHO and the IUTLD.

In the United States there has been a call for the elimination of tuberculosis, and a committee constituted by the Institute of Medicine (IOM) issued a set of recommendations for reaching this goal (*5*). The IOM committee had two main recommendations related to treatment of tuberculosis; first, that all U.S jurisdictions have health regulations that mandate completion of therapy (treatment until the patient is cured); and second, that all treatment be administered in the context of patient-centered programs that are based on individual patient characteristics and needs. The IOM recommendations emphasize the importance of the structure and organization of treatment services, as well as the drugs that are used, to treat patients effectively. This philosophy is the core of the DOTS strategy (described in Section 10 Treatment of Tuberculosis in Low-Income Countries: Recommendations oof the WHO and the IUTLD), developed by the IUATLD and implemented globally by the WHO. Thus, although there are superficial differences in the approach to tuberculosis treatment between high- and low-incidence countries, the fundamental concern, regardless of where treatment is given, is ensuring patient adherence to the drug regimen and successful completion of therapy (*6*).

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2. Organization and Supervision of Treatment

Successful treatment of tuberculosis depends on more than the science of chemotherapy. To have the highest likelihood of success, chemotherapy must be provided within a clinical and social framework based on an individual patient's circumstances. Optimal organization of treatment programs requires an effective network of primary and referral services and cooperation between clinicians and public health officials, between health care facilities and community outreach programs, and between the private and public sectors of medical care. This section describes the approaches to organization of treatment that serve to ensure that treatment has a high likelihood of being successful.

As noted previously, antituberculosis chemotherapy is both a personal health measure intended to cure the sick patient and a basic public health strategy intended to reduce the transmission of *Mycobacterium tuberculosis*. Typically, tuberculosis treatment is provided by public health departments, often working in collaboration with other providers and organizations including private physicians, community health centers, migrant health centers, correctional facilities, hospitals, hospices, long-term care facilities, and homeless shelters. Private providers and public health departments may cosupervise patients, assuring that the patient completes therapy in a setting that is not only mutually agreeable but also enables access to tuberculosis expertise and resources that might otherwise not be available. In managed care settings delivery of tuberculosis treatment may require a more structured public/private partnership, often defined by a contract, to assure completion of therapy. Regardless of the means by which treatment is provided, the ultimate legal authority for assuring that patients complete therapy rests with the public health system.

2.1. Role of the Health Department

The responsibility of the health department in the control of tuberculosis is to ensure that all persons who are suspected of having tuberculosis are identified and evaluated promptly and that an appropriate course of treatment is prescribed and completed successfully (*1,2*). A critical component of the evaluation scheme is access to proficient microbiological laboratory services, for which the health department is responsible.

The responsibilities of the health department may be accomplished indirectly by epidemiologic surveillance and monitoring of treatment decisions and outcome, applying generally agreed-on standards and guidelines, or more directly by provision of diagnostic and treatment services, as well as by conducting epidemiologic investigations. Given the diverse sociodemographic characteristics of patients with tuberculosis and the many mechanisms by which health care is delivered, the means by which the goals of the health department are accomplished may be quite varied.

In dealing with individual patients, approaches that focus on each person's needs and characteristics should be used to determine a tailored treatment plan that is designed to ensure completion of therapy (*3*). Such treatment plans are developed with the patient as an active participant together with the physician and/or nurse, outreach workers, social worker (when needed), and others as appropriate. Given that one-half the current incident cases of tuberculosis in the United States were born outside the United States (similar circumstances prevail in most other low-incidence countries), translation of materials into the patient's primary language is often necessary to ensure his/her participation in developing the treatment plan. Ideally, a specific case manager is assigned individual responsibility for assuring that the patient completes therapy. The treatment plan is reviewed periodically and revised as needed. These reviews may be accomplished in meetings between the patient and the assigned provider, as well as more formally through case and cohort evaluations. The treatment plan is based on the principle of using the least restrictive measures that are likely to achieve success. The full spectrum of measures that may be employed ranges from, at an absolute minimum, monthly monitoring of the patient in the outpatient setting to legally mandated hospitalization (*4*). Directly observed therapy (DOT) is the preferred initial means to assure adherence. For nonadherent patients more restrictive measures are implemented in a stepwise fashion. Any approach must be balanced, ensuring that the needs and rights of the patient, as well as those of the public, are met. Care plans for patients being managed in the private sector should be developed jointly by the health department and the private provider, and must address identified and anticipated barriers to adherence.

2.2. Promoting Adherence

Louis Pasteur once said, "The microbe is nothing...the terrain everything" (*5*). Assuming appropriate drugs are prescribed, the terrain (the circumstances surrounding each patient that may affect his or her ability to complete treatment)

What's DOT?

Direct observation of therapy (DOT) involves providing the antituberculosis drugs directly to the patient and watching as he/she swallows the medications. It is the preferred core management strategy for all patients with tuberculosis.

becomes the most important consideration in completion of tuberculosis treatment. Many factors may be part of this terrain. Factors that interfere with adherence to the treatment regimen include cultural and linguistic barriers to cooperation, lifestyle differences, homelessness, substance abuse, and a large number of other conditions and circumstances that, for the patient, are priorities that compete with taking treatment for tuberculosis (*6*). Barriers may be patient related, such as conflicting health beliefs, alcohol or drug dependence, or mental illness, or they may be system related, such as lack of transportation, inconvenient clinic hours, and lack of interpreters (*7*). Effective tuberculosis case management identifies and characterizes the terrain and determines an appropriate care plan based on each of the identified factors. Additional advantages of the patient-centered approach are that, by increasing communication with the patient, it provides opportunities for further education concerning tuberculosis and enables elicitation of additional information concerning contacts.

To maximize completion of therapy, patient-centered programs identify and utilize a broad range of approaches based on the needs and circumstances of individual patients. Among these approaches, DOT is the preferred initial strategy and deserves special emphasis. Although DOT itself has not been subjected to controlled trials in low-incidence areas (and, thus, is rated AII), observational studies and a meta-analysis in the United States strongly suggest that DOT, coupled with individualized case management, leads to the best treatment results (*8–10*). To date there have been three published studies of DOT in high-incidence areas, two of which (*11*,*12*) showed no benefit and one (*13*) in which there was a significant advantage for DOT. What is clear from these studies is that DOT cannot be limited merely to passive observation of medication ingestion; there must be aggressive interventions when patients miss doses. Using DOT in this manner can only improve results.

DOT can be provided daily or intermittently in the office, clinic, or in the "field" (patient's home, place of employment, school, street corner, bar, or any other site that is mutually agreeable) by appropriately trained personnel. DOT should be used for all patients residing in institutional settings such as hospitals, nursing homes, or correctional facilities, or in other settings, such as methadone treatment sites, that are conducive to observation of therapy (*14*). However, even in such supervised settings careful attention must be paid to ensuring that ingestion of the medication is, in fact, observed. It is essential that all patients being treated with regimens that use intermittent drug administration have all doses administered under DOT because of the potentially serious consequences of missed doses. DOT also enables early identification of nonadherence, adverse drug reactions, and clinical worsening of tuberculosis. DOT provides a close connection to the health care system for a group of patients at high risk of other adverse health events and, thus, should facilitate identification and management of other conditions.

The use of DOT does not guarantee ingestion of all doses of every medication (*15*). Patients may miss appointments, may not actually swallow the pills, or may deliberately regurgitate the medications. Consequently, all patients, including those who are being treated by DOT, should continue to be monitored for signs of treatment failure. DOT is only one aspect of a comprehensive patient-centered program that, in addition, includes incentives and enablers described subsequently (*16–20*). Patients who are more likely to present a transmission risk to others or are more likely to have problems with adherence (Table 7) should be prioritized for DOT when resources are limited. When DOT is not being used, fixed-dose combination preparations (see Section 6.2, Fixed-Dose Combination Preparations) containing INH and RIF or INH, RIF, and PZA reduce the risk of the patient taking only one drug and may help prevent the development of drug resistance. Combination formulations are easier to administer and also may reduce medication errors.

Depending on the identified obstacles to completion of therapy, the treatment plan may also include enablers and incentives such as those listed in Table 8. Studies have examined the use of a patient-centered approach that utilizes DOT in addition to other adherence-promoting tools (*9*,*21*,*22*). These studies demonstrate, as shown in Figure 3, that "enhanced DOT" (DOT together with incentives and enablers) produces the highest treatment completion rates (in excess of 90% across a range of geographic and socioeconomic settings), and reinforces the importance of patient-related factors in designing and implementing case management (*9*,*23*).

TABLE 7. Priority situations for the use of directly observed therapy

1. Patients with the following conditions/circumstances:
   - Pulmonary tuberculosis with positive sputum smears
   - Treatment failure
   - Drug resistance
   - Relapse
   - HIV infection
   - Previous treatment for either active tuberculosis or latent tuberculosis infection
   - Current or prior substance abuse
   - Psychiatric illnesses
   - Memory impairment
   - Previous nonadherence to therapy
2. Children and adolescents

TABLE 8. Possible components of a multifaceted, patient-centered treatment strategy

Enablers: Interventions to assist the patient in completing therapy*
- Transportation vouchers
- Child care
- Convenient clinic hours and locations
- Clinic personnel who speak the languages of the populations served
- Reminder systems and follow-up of missed appointments
- Social service assistance (referrals for substance abuse treatment and counseling, housing, and other services)†
- Outreach workers (bilingual/bicultural as needed; can provide many services related to maintaining patient adherence, including provision of DOT, follow-up on missed appointments, monthly monitoring, transportation, sputum collection, social service assistance, and educational reinforcement)
- Integration of care for tuberculosis with care for other conditions

Incentives: Interventions to motivate the patient, tailored to individual patient wishes and needs and, thus, meaningful to the patient*
- Food stamps or snacks and meals
- Restaurant coupons
- Assistance in finding or provision of housing‡
- Clothing or other personal products
- Books
- Stipends
- Patient contract

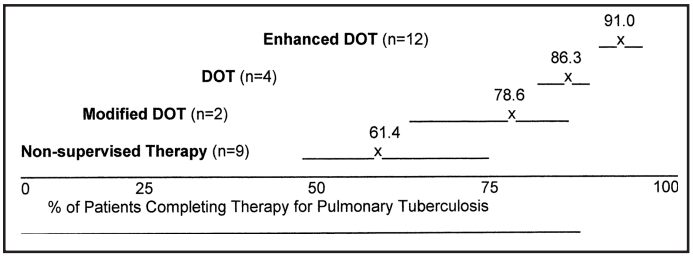
Definition of abbreviation: DOT = Directly observed therapy.

* **Source:** Burman WJ, Cohn DL, Rietmeijer CA, Judson FN, Sbabaro JA, Reves RR. Noncompliance with directly observed therapy for tuberculosis: epidemiology and effect on the outcome of treatment. Chest 1997;111:1168–1173.

† **Source:** Bayer R, Stayton C, Devarieux M, Healton C, Landsman S, Tsai W. Directly observed therapy and treatment completion in the United States; is universal supervised therapy necessary? Am J Public Health 1998;88:1052–1058.

‡ **Source:** Volmink J, Matchaba P, Gainer P. Directly observed therapy and treatment adherence. Lancet 2000;355:1345–1350.

FIGURE 3. Range and median of treatment completion rates by treatment strategy for pulmonary tuberculosis reported in 27 studies



DOT = Directly observed therapy; n = number of studies; Modified DOT = DOT given only for a portion of the treatment period, often while the patient was hospitalized; Enhanced DOT = individualized incentives and enablers were provided in addition to DOT.

Source: Chaulk CP, Kazdanjian VA. Directly observed therapy for treatment completion of tuberculosis: consensus statement of the Public Health Tuberculosis Guidelines Panel. JAMA 1998;279:943–948. Reprinted with permission.

Intensive educational efforts should be initiated as soon as the patient is suspected of having tuberculosis. The instruction should be at an educational level appropriate for the patient and should include information about tuberculosis, expected outcomes of treatment, the benefits and possible adverse effects of the drug regimen, methods of supervision, assessment of response, and a discussion of infectiousness and infection control. The medication regimen must be explained in clear, understandable language and the verbal explanation followed with written instructions. An interpreter is necessary when the patient and health care provider do not speak the same language. Materials should be appropriate for the culture, language, age, and reading level of the patient. Relevant information should be reinforced at each visit.

The patient's clinical progress and the treatment plan must be reviewed at least monthly to evaluate the response to therapy and to identify adherence problems. Use of a record system (Figure 4) either manual or computer-based, that quantifies the dosage and frequency of medication administered, indicates AFB smear and culture status, and notes symptom improvement as well as any adverse effects of treatment serves to facilitate the regular reviews and also provides data for cohort analyses. In addition, adherence monitoring by direct methods, such as the detection of drugs or drug metabolites in the patient's urine, or indirect methods, such as pill counts or a medication monitor, should be a part of routine management, especially if the patient is not being given DOT.

Tracking patients is also a critical concern for those charged with assuring completion of treatment. It has been shown that patients who move from one jurisdiction to another before completion of therapy are much more likely to default than patients who do not move (*24*). Factors that have been shown to be associated with moving/defaulting include diagnosis of tuberculosis in a state correctional facility, drug and alcohol

Tracking Tuberculosis

Inter- and intrastate notifications constitute the key patient-tracking systems for patients moving within the United States. International notifications can also be made, although specific tracking programs vary by country. Currently there are two formal patient-tracking systems in operation for patients moving across the United States–Mexico border: *TB Net*, operated by the Migrant Clinician Network based in Austin, Texas (http://www.migrantclinician.org; telephone, 512-327-2017) and *Cure TB*, managed by the San Diego County, California, Division of Tuberculosis Control (http://www.curetb.org; telephone, 619-692-5719).

FIGURE 4. Example of flow chart for patient monitoring

Name: Last: _____, First: _____ **DRUG O'GRAM**

Year: _____

DRUG	Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
	Smear (- / +)															
	Culture (- / +)															
	Sensitivities (√ = done)															
RIFATER	X--X = drug															
RIFAMATE	S = sensitive															
ISONIAZID	R = resistant															
RIFAMPIN																
PYRAZINAMIDE																
ETHAMBUTOL																
STREPTOMYCIN																
KANAMYCIN																
CYCLOSERINE																
ETHIONAMIDE																
PAS																
LEVOFLOXACIN																
CAPREOMYCIN																
RIFABUTIN																
AMIKACIN																
OTHER _____																
OTHER _____																

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abuse, and homelessness. Communication and coordination of services among different sources of care and different health departments are especially important for patients in these groups as well as for migrant workers and other patients with no permanent home. Such communication may also be necessary across national boundaries, especially the United States–Mexico border, and there are systems in place to facilitate such communication and tracking.

Some patients, for example those with tuberculosis caused by drug-resistant organisms, or who have comorbid conditions, such as HIV infection, alcoholism, or other significant underlying disorders, may need to be hospitalized in a facility where tuberculosis expertise is available and where there are appropriate infection control measures in place. Hospitalization may be necessary for nonadherent patients for whom less restrictive measures have failed (*25–27*). Public health laws exist in most states that allow the use of detainment under these circumstances, at least for patients who remain infectious (*28*). Court-ordered DOT has been used successfully in some states as a less costly alternative. The use of these interventions depends on the existence of appropriate laws, cooperative courts, and law enforcement officials, and the availability of appropriate facilities. Health departments must be consulted to initiate legal action when it is necessary.

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Legal Action For Tuberculosis in New York City: 1993–1999

- Regulatory orders were issued for less than 4% of 8,000 patients.
- Detainment was based on tuberculosis status, not on sociodemographic factors.
- Legal orders varied:
  - DOT—150 patients
  - Detainment—139 patients
  - Examination for tuberculosis ordered—12 patients
  - Completion of treatment ordered—3 patients
- Less restrictive, court-ordered DOT was often as effective as detainment: 96% (excluding those who died or moved) completed treatment; 2% continued treatment for multidrug-resistant tuberculosis (from Gasner and coworkers [*27*])

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3. Drugs in Current Use

Currently, there are 10 drugs approved by the United States Food and Drug Administration (FDA) for treating tuberculosis (Table 9). In addition, the fluoroquinolones, although not approved by the FDA for tuberculosis, are used relatively commonly to treat tuberculosis caused by drug-resistant organisms or for patients who are intolerant of some of the first-line drugs. Rifabutin, approved for use in preventing *Mycobacterium avium* complex disease in patients with HIV infection but not approved for tuberculosis, is useful for treating tuberculosis in patients concurrently taking drugs that have

TABLE 9. Antituberculosis drugs currently in use in the United States

First-line drugs	Second-line drugs
Isoniazid	Cycloserine
Rifampin	Ethionamide
Rifapentine	Levofloxacin*
Rifabutin*	Moxifloxacin*
Ethambutol	Gatifloxacin*
Pyrazinamide	*p*-Aminosalicylic acid
	Streptomycin
	Amikacin/kanamycin*
	Capreomycin

* Not approved by the Food and Drug Administration for use in the treatment of tuberculosis.

unacceptable interactions with other rifamycins. Amikacin and kanamycin, nearly identical aminoglycoside drugs used in treating patients with tuberculosis caused by drug-resistant organisms, are not approved by the FDA for tuberculosis.

Of the approved drugs isoniazid (INH), rifampin (RIF), ethambutol (EMB), and pyrazinamide (PZA) are considered first-line antituberculosis agents and form the core of initial treatment regimens. Rifabutin and rifapentine may also be considered first-line agents under the specific situations described below. Streptomycin (SM) was formerly considered to be a first-line agent and, in some instances, is still used in initial treatment; however, an increasing prevalence of resistance to SM in many parts of the world has decreased its overall usefulness. The remaining drugs are reserved for special situations such as drug intolerance or resistance.

The drug preparations available currently and the recommended doses are shown in Tables 3, 4, and 5.

3.1. First-Line Drugs

3.1.1. Isoniazid

Role in treatment regimen. Isoniazid (INH) is a first-line agent for treatment of all forms of tuberculosis caused by organisms known or presumed to be susceptible to the drug. It has profound early bactericidal activity against rapidly dividing cells (*1,2*).

Dose. See Table 3.

Adults (maximum): 5 mg/kg (300 mg) daily; 15 mg/kg (900 mg) once, twice, or three times weekly.

Children (maximum): 10–15 mg/kg (300 mg) daily; 20–30 mg/kg (900 mg) twice weekly (*3*).

Preparations. Tablets (50 mg, 100 mg, 300 mg); syrup (50 mg/5 ml); aqueous solution (100 mg/ml) for intravenous or intramuscular injection.

Adverse effects.

Asymptomatic elevation of aminotransferases: Aminotransferase elevations up to five times the upper limit of normal occur in 10–20% of persons receiving INH alone for treatment of latent tuberculosis infection (*4*). The enzyme levels usually return to normal even with continued administration of the drug.

Clinical hepatitis: (see Table 10.) Data indicate that the incidence of clinical hepatitis is lower than was previously thought. Hepatitis occurred in only 0.1–0.15% of 11,141 persons receiving INH alone as treatment for latent tuberculosis infection in an urban tuberculosis control program (*5*). Prior studies suggested a higher rate, and a meta-analysis of six studies estimated the rate of clinical hepatitis in patients given INH alone to be 0.6% (*6–8*). In the meta-analysis the rate of clinical hepatitis was 1.6% when INH was given with other agents, not including RIF. The risk was higher when the drug was combined with RIF, an average of 2.7% in 19 reports (*8*). For INH alone the risk increases with increasing age; it is uncommon in persons less than 20 years of age but is nearly 2% in persons aged 50–64 years (*6*). The risk also may be increased in persons with underlying liver disease, in those with a history of heavy alcohol consumption, and, data suggest, in the postpartum period, particularly among Hispanic women (*9*).

TABLE 10. Clinical hepatitis in persons taking isoniazid and rifampin*

Drug	Number of studies	Patients	Clinical Hepatitis (%)
INH	6	38,257	0.6
INH plus other drugs but *not* RIF	10	2,053	1.6
INH plus RIF	19	6,155	2.7
RIF plus other drugs but *not* INH	5	1,264	1.1

Definition of abbreviations: INH = Isoniazid; RIF = rifampin.

* **Source:** Steele MA, Burk RF, Des Prez RM. Toxic hepatitis with isoniazid and rifampin: a meta-analysis. Chest 1991;99:465–471. Reprinted with permission.

Fatal hepatitis: A large survey estimated the rate of fatal hepatitis to be 0.023%, but more recent studies suggest the rate is substantially lower (*10,11*). The risk may be increased in women. Death has been associated with continued administration of INH despite onset of symptoms of hepatitis (*12*).

Peripheral neurotoxicity (*13,14*)*:* This adverse effect is dose related and is uncommon (less than 0.2%) at conventional doses (*15–17*). The risk is increased in persons with other conditions that may be associated with neuropathy such as nutritional deficiency, diabetes, HIV infection, renal failure, and alcoholism, as well as for pregnant and breastfeeding women. Pyridoxine supplementation (25 mg/day) is recommended for patients with these conditions to help prevent this neuropathy (*18*).

Central nervous system effects: Effects such as dysarthria, irritability, seizures, dysphoria, and inability to concentrate have been reported but have not been quantified.

Lupus-like syndrome (*19*)*:* Approximately 20% of patients receiving INH develop anti-nuclear antibodies. Less than 1% develop clinical lupus erythematosis, necessitating drug discontinuation.

Hypersensitivity reactions: Reactions, such as fever, rash, Stevens-Johnson syndrome, hemolytic anemia, vasculitis, and neutropenia are rare.

Monoamine (histamine/tyramine) poisoning: This has been reported to occur after ingestion of foods and beverages with high monoamine content but is rare (*20–22*). If flushing occurs, patients should be instructed to avoid foods and drinks, such as certain cheeses and wine, having high concentrations of monoamines.

Diarrhea: Use of the commercial liquid preparation of INH, because it contains sorbitol, is associated with diarrhea.

Use in pregnancy. INH is considered safe in pregnancy, but the risk of hepatitis may be increased in the peripartum period (*9,23*). Pyridoxine supplementation (25 mg/day) is recommended if INH is administered during pregnancy (*18*). It should be noted that multivitamin preparations have variable amounts of pyridoxine but generally less than 25 mg/day and, thus, do not provide adequate supplementation.

CNS penetration. Penetration is excellent. Cerebrospinal fluid (CSF) concentrations are similar to concentrations achieved in serum (*24*).

Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) INH can be used safely without dose adjustment in patients with renal insufficiency (*25*) and with end-stage renal isease who require chronic hemodialysis (*26*).

Use in hepatic disease. (See Section 8.8: Hepatic Disease.) The risk of drug accumulation and drug-induced hepatitis may be increased in the presence of hepatic disease; however, INH may be used in patients *with* stable hepatic disease. Laboratory and clinical monitoring should be more frequent in such situations.

Monitoring. Routine monitoring is not necessary. However, for patients who have preexisting liver disease or who develop abnormal liver function that does not require discontinuation of the drug, liver function tests should be measured monthly and when symptoms occur. Serum concentrations of phenytoin and carbamazepine may be increased in persons taking INH. However, in combination therapy with RIF the effects of INH on serum concentrations of the anticonvulsants are limited by the decrease caused by RIF. Thus, it is important to measure serum concentrations of these drugs in patients receiving INH with or without RIF and adjust the dose if necessary.

3.1.2. Rifampin

Role in treatment regimen. Rifampin (RIF) is a first-line agent for treatment of all forms of tuberculosis caused by organisms with known or presumed sensitivity to the drug. It has activity against organisms that are dividing rapidly (early bactericidal activity) (*1*) and against semidormant bacterial populations, thus accounting for its sterilizing activity (*27*). Rifampin is an essential component of all short-course regimens.

Dose. See Table 3.

Adults (maximum): 10 mg/kg (600 mg) once daily, twice weekly, or three times weekly.

Children (maximum): 10–20 mg/kg (600 mg) once daily or twice weekly.

Rifabutin and Rifapentine

The newer rifamycins, rifabutin and rifapentine, should be considered first-line drugs in special situations: rifabutin for patients who are receiving medications, especially antiretroviral drugs, that have unacceptable interactions with rifampin or who have experienced intolerance to rifampin; and rifapentine, together with INH, in a once-a-week continuation phase for certain selected patients who meet specified criteria.

Preparations. Capsules (150 mg, 300 mg); contents of capsule may also be mixed in an appropriate diluent to prepare an oral suspension; aqueous solution for parenteral administration.

Adverse effects (*28*).

Cutaneous reactions (*29*)*:* Pruritis with or without rash may occur in as many as 6% of patients but is generally self-limited *(30*). This reaction may not represent true hypersensitivity and continued treatment with the drug may be possible. More severe, true hypersensitivity reactions are uncommon, occurring in 0.07–0.3% of patients (*17,31,32*).

Gastrointestinal reactions (nausea, anorexia, abdominal pain): The incidence is variable, but symptoms are rarely severe enough to necessitate discontinuation of the drug (*28–30*).

Flulike syndrome: This may occur in 0.4–0.7% of patients receiving 600 mg twice weekly but not with daily administration of the same dose (*31–34*). Symptoms are more likely to occur with intermittent administration of a higher dose (*29,35*).

Hepatotoxicity: Transient asymptomatic hyperbilirubinemia may occur in as many as 0.6% of patients receiving the drug. More severe clinical hepatitis that, typically, has a cholestatic pattern may also occur (*8,36*). Hepatitis is more common when the drug is given in combination with INH (2.7%) than when given alone (nearly 0%) or in combination with drugs other than INH (1.1%) (*8*).

Severe immunologic reactions: In addition to cutaneous reactions and flulike syndrome, other reactions thought to be immune mediated include the following: thrombocytopenia, hemolytic anemia, acute renal failure, and thrombotic thrombocytopenic purpura. These reactions are rare, each occurring in less than 0.1% of patients (*31,32,37*).

Orange discoloration of bodily fluids (sputum, urine, sweat, tears): This is a universal effect of the drug. Patients should be warned of this effect at the time treatment is begun. Soft contact lenses and clothing may be permanently stained.

Drug interactions due to induction of hepatic microsomal enzymes: There are a number of drug interactions (described in Section 7, Drug Interactions, and Table 12) with potentially serious consequences. Of particular concern are reductions, often to ineffective levels, in serum concentrations of common drugs, such as oral contraceptives, methadone, and warfarin. In addition there are important bidirectional interactions between rifamycins and antiretroviral agents. Because information regarding rifamycin drug interactions is evolving rapidly, readers are advised to consult the CDC web site www.cdc.gov/nchstp/tb/ to obtain the most up-to-date information.

Use in pregnancy. RIF is considered safe in pregnancy (*38*).

CNS penetration. Concentrations in the CSF may be only 10–20% of serum levels, but this is sufficient for clinical efficacy. Penetration may be improved in the setting of meningitis (*39*).

Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) RIF can be used safely without dose adjustment in patients with renal insufficiency and end-stage renal disease (*26,40*).

Use in hepatic disease. (see Section 8.8: Hepatic Disease.) Clearance of the drug may be impaired in the presence of liver disease, causing increased serum levels (*40*). However, because of the critical importance of rifampin in all short-course regimens, it generally should be included, but the frequency of clinical and laboratory monitoring should be increased.

Monitoring. No routine monitoring tests are required. However, rifampin causes many drug interactions described in Section 7, Drug Interactions, that may necessitate regular measurements of the serum concentrations of the drugs in question.

3.1.3. Rifabutin

Role in treatment regimen. Rifabutin is used as a substitute for RIF in the treatment of all forms of tuberculosis caused by organisms that are known or presumed to be susceptible to this agent. The drug is generally reserved for patients who are receiving any medication having unacceptable interactions with rifampin (*41*) or have experienced intolerance to rifampin.

Dose. See Table 3.

Adults (maximum): 5 mg/kg (300 mg) daily, twice, or three times weekly. The dose may need to be adjusted when there is concomitant use of protease inhibitors or nonnucleoside reverse transcriptase inhibitors. When rifabutin is used with efavirenz the dose of rifabutin should be increased to 450–600 mg either daily or intermittently. Because information regarding rifamycin drug interactions is evolving rapidly readers are advised to consult the CDC web site, http://www.cdc.gov/nchstp/tb/, to obtain the most up-to-date information.

Children (maximum): Appropriate dosing for children is unknown.

Preparations: Capsules (150 mg) for oral administration.

Adverse effects.

Hematologic toxicity: In a placebo-controlled, double-blind trial involving patients with advanced acquired immunodeficiency syndrome (AIDS) (CD4+ cell counts <200 cells/µl), neutropenia occurred in 25% compared with 20% in patients receiving placebo ($p = 0.03$). Neutropenia severe enough to necessitate discontinuation of the drug occurred in 2% of patients receiving the drug (product insert B; Adria Laboratories, Columbus, OH). The effect is dose related, occurring more frequently with daily than with intermittent administration of the same dose (*42*). In several studies of patients with and without HIV infection, neither neutropenia nor thrombocytopenia was associated with rifabutin (*43–47*).

Uveitis: This is a rare (less than 0.01%) complication when the drug is given alone at a standard (300 mg daily) dose. The occurrence is higher (8%) with higher doses or when rifabutin is used in combination with macrolide antimicrobial agents that reduce its clearance (*48*). Uveitis may also occur with other drugs that reduce clearance such as protease inhibitors and azole antifungal agents.

Gastrointestinal symptoms: These symptoms occurred in 3% of patients with advanced HIV infection given 300 mg/day (package insert). In subsequent studies no increased incidence of gastrointestinal symptoms was noted among patients taking rifabutin (*43,44,46–48*).

Polyarthralgias: This symptom occurred in 1–2% of persons receiving a standard 300-mg dose (package insert). It is more common at higher doses (*48*). Polyarthralgias have not been noted in more recent studies involving both HIV-infected and uninfected patients (*43,44,46,47*).

Hepatotoxity: Asymptomatic elevation of liver enzymes has been reported at a frequency similar to that of RIF (*48*). Clinical hepatitis occurs in less than 1% of patients receiving the drug.

Pseudojaundice (skin discoloration with normal bilirubin): This is usually self-limited and resolves with discontinuation of the drug (*49*).

Rash: Although initially reported to occur in as many as 4% of patients with advanced HIV infection, subsequent studies suggest that rash is only rarely (less than 0.1%) associated with rifabutin (*46*).

Flulike syndrome: Flulike syndrome is rare (less than 0.1%) in patients taking rifabutin.

Orange discoloration of bodily fluids (sputum, urine, sweat, tears): This is a universal effect of the drug. Patients should be warned of this effect at the time treatment is begun. Soft contact lenses and clothing may be permanently stained.

Use in pregnancy. There are insufficient data to recommend the use of rifabutin in pregnant women; thus, the drug should be used with caution in pregnancy.

CNS penetration. The drug penetrates inflamed meninges (*50*).

Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) Rifabutin may be used without dosage adjustment in patients with renal insufficiency and end-stage renal disease (*50*).

Use in hepatic disease. (See Section 8.8: Hepatic Disease.) The drug should be used with increased clinical and laboratory monitoring in patients with underlying liver disease. Dose reduction may be necessary in patients with severe liver dysfunction (*50*).

Monitoring. Monitoring is similar to that recommended for rifampin. Although drug interactions are less problematic with rifabutin, they still occur and close monitoring is required.

3.1.4. Rifapentine

Role in treatment regimen. Rifapentine may be used once weekly with INH in the continuation phase of treatment for HIV-seronegative patients with noncavitary, drug-susceptible pulmonary tuberculosis who have negative sputum smears at completion of the initial phase of treatment (*51*).

Dose. See Table 3.

Adults (maximum): 10 mg/kg (600 mg), once weekly during the continuation phase of treatment. Data have suggested that a dose of 900 mg is well tolerated but the clinical efficacy of this dose has not been established (*52*).

Children: The drug is not approved for use in children.

Preparation. Tablet (150 mg, film coated).

Adverse effects.

The adverse effects of rifapentine are similar to those associated with RIF. Rifapentine is an inducer of multiple hepatic enzymes and therefore may increase metabolism of coadministered drugs that are metabolized by these enzymes (see Section 7: Drug Interactions).

Use in pregnancy. There is not sufficient information to recommend the use of rifapentine for pregnant women.

CNS penetration. There are no data on CSF concentrations of rifapentine.

Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease .) The pharmacokinetics of rifapentine have not been evaluated in patients with renal impairment. Although only about 17% of an administered dose is excreted via the kidneys, the clinical significance of impaired renal function in the disposition of rifapentine is not known.

Use in hepatic disease. (See Section 8.8: Hepatic Disease.) The pharmacokinetics of rifapentine and its 25-desacetyl metabolite were similar among patients with various degrees of hepatic impairment and not different from those in healthy volunteers, even though the elimination of these compounds is primarily via the liver (*53*). The clinical significance of impaired hepatic function in the disposition of rifapentine and its 25-desacetyl metabolite is not known.

Monitoring. Monitoring is similar to that for RIF. Drug interactions involving rifapentine are being investigated and are likely to be similar to those of RIF.

3.1.5. Pyrazinamide

Role in treatment regimen. Pyrazinamide (PZA) is a first-line agent for the treatment of all forms of tuberculosis caused by organisms with known or presumed susceptibility to the drug. The drug is believed to exert greatest activity against the population of dormant or semidormant organisms contained within macrophages or the acidic environment of caseous foci (*54*).

Dose. See Tables 3 and 4.

Adults: 20–25 mg/kg per day. Recommended adult dosages by weight, using whole tablets, are listed in Table 4.

Children (maximum): 15–30 mg/kg (2.0 g) daily; 50 mg/kg twice weekly (2.0 g).

Preparations. Tablets (500 mg, scored).

Adverse effects.

Hepatotoxicity: Early studies (*55,56*) using doses of 40–70 mg/kg per day reported high rates of hepatotoxicity. However, in treatment trials with multiple other drugs, including INH, liver toxicity has been rare at doses of 25 mg/kg per day or less (*15,34,57*). In one study, however, hepatotoxicity attributable to PZA used in standard doses occurred at a rate of about 1% (*58*).

Gastrointestinal symptoms (nausea, vomiting): Mild anorexia and nausea are common at standard doses. Vomiting and severe nausea are rare except at high doses (*59*).

Nongouty polyarthralgia: Polyarthralgias may occur in up to 40% of patients receiving daily doses of PZA. This rarely requires dosage adjustment or discontinuation of the drug (*60*). The pain usually responds to aspirin or other nonsteroidal antiinflammatory agents. In clinical trials of PZA in the initial intensive phase of treatment, athralgias were not noted to be a significant problem (*15,61*).

Asymptomatic hyperuricemia: This is an expected effect of the drug and is generally without adverse consequence (*15,62*).

Acute gouty arthritis: Acute gout is rare except in patients with preexisting gout (*63*), generally a contraindication to the use of the drug.

Transient morbilliform rash: This is usually self-limited and is not an indication for discontinuation of the drug.

Dermatitis: PZA may cause photosensitive dermatitis (*59*).

Use in pregnancy. There is little information about the safety of PZA in pregnancy. However, when there are sound reasons to utilize a 6-month course of treatment, the benefits of PZA may outweigh the possible (but unquantified) risk. The WHO and the IUATLD recommend this drug for use in pregnant women with tuberculosis (see Section 10: Treatment of Tuberculosis in Low-Income Countries: Recommendations of the WHO and the IUATLD).

CNS penetration. The drug passes freely into the CSF, achieving concentrations equivalent to those in serum (*64*).

Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) PZA is cleared primarily by the liver, but its metabolites are excreted in the urine and may accumulate in patients with renal insufficiency (*65*). The dose may, therefore, need to be reduced in patients with renal insufficiency. It should be administered at a reduced dose (25–35 mg/kg) three times a week after dialysis in patients with end-stage renal disease (Table 15) (*26*). The risk of hyperuricemia caused by PZA is increased in patients with renal insufficiency.

Use in hepatic disease. (See Section 8.8: Hepatic Disease.) Although the frequency is slightly lower than with INH or RIF, the drug can cause liver injury that may be severe and prolonged. If the drug is used in patients with underlying liver disease, laboratory and clinical monitoring should be increased.

Monitoring. Serum uric acid measurements are not recommended as a routine but may serve as a surrogate marker for compliance. Liver chemistry monitoring should be performed when the drug is used in patients with underlying liver disease or when it is used with rifampin in treating latent tuberculosis infection.

3.1.6. Ethambutol

Role in treatment regimen. Ethambutol (EMB) is a first-line drug for treating all forms of tuberculosis. It is included in initial treatment regimens primarily to prevent emergence of RIF resistance when primary resistance to INH may be present. Ethambutol is generally not recommended for routine use in children whose visual acuity cannot be monitored. However, if a child has adult-type tuberculosis or disease that is suspected or proven to be caused by organisms that are resistant to either INH or RIF, EMB should be used (see Section 8.2: Children and Adolescents, and Table 6).

Dose. See Tables 3 and 5.

Adults: 15–20 mg/kg per day: Table 5 lists recommended dosages for adults, using whole tablets.

Children (maximum): 15–20 mg/kg per day (2.5 g); 50 mg/kg twice weekly (2.5 g). The drug can be used safely in older children but should be used with caution in children in whom visual acuity cannot be monitored (generally less than 5 years of age) (*66*). In younger children EMB can be used if there is concern with resistance to INH or RIF (Table 6).

Preparations. Tablets (100 mg, 400 mg) for oral administration.

Adverse effects.

Retrobulbar neuritis: This is manifested as decreased visual acuity or decreased red-green color discrimination that may affect one or both eyes. The effect is dose related, with minimal risk at a daily dose of 15 mg/kg (*67*). No difference was found in the prevalence of decreased visual acuity between regimens that contained EMB at 15 mg/kg and those not containing the drug (*68*). The risk of optic toxicity is higher at higher doses given daily (18% of patients receiving more than 30 mg/kg per day) and in patients with renal insufficiency. Higher doses can be given safely twice or three times weekly.

Peripheral neuritis: This is a rare adverse effect (*69*).

Cutaneous reactions: Skin reactions requiring discontinuation of the drug occur in 0.2–0.7% of patients (*68*).

Use in pregnancy. EMB is considered safe for use in pregnancy (*70–72*).

CNS penetration. The agent penetrates the meninges in the presence of inflammation but does not have demonstrated efficacy in tuberculous meningitis (*73*).

Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) EMB is cleared primarily by the kidneys. The dose or dosing interval should be adjusted when the creatinine clearance is less than 70 ml/minute (*74*). EMB should be administered at a dose of 15–20 mg/kg three times a week by DOT after dialysis in patients with end-stage renal disease (Table 15) (*26*).

Use in hepatic disease. (See Section 8.8: Hepatic Disease.) EMB can be used safely in patients with hepatic disease.

Monitoring. Patients should have baseline visual acuity testing (Snellen chart) and testing of color discrimination (Ishihara tests). At each monthly visit patients should be questioned regarding possible visual disturbances including blurred vision or scotomata. Monthly testing of visual acuity and color discrimination is recommended for patients taking doses greater than 15–25 mg/kg, patients receiving the drug for longer than 2 months, and any patient with renal insufficiency. Patients should be instructed to contact their physician or public health clinic immediately if they experience a change in vision. EMB should be discontinued immediately and permanently if there are any signs of visual toxicity.

3.1.7. Fixed-dose combination preparations

Role in treatment regimen. Two combined preparations, INH and RIF (Rifamate®) and INH, RIF, and PZA (Rifater®), are available in the United States. These formulations are a means of minimizing inadvertent monotherapy,

Please note: An erratum has been published for this issue. To view the erratum, please click here.

Role of Fixed-Dose Combination Preparations

Fixed-dose combination preparations minimize inadvertent monotherapy and may decrease the frequency of acquired drug resistance and medication errors. These preparations should generally be used when therapy cannot be administered under DOT.

particularly when DOT is not possible, and, therefore, may decrease the risk of acquired drug resistance (*75*). The use of fixed-dose formulations may reduce the number of pills that must be taken daily. Constituent drugs are combined in proportions compatible with daily treatment regimens. Formulations for intermittent administration are not available in the United States.

Preparations and dose.

Rifamate®: As sold in North America, each capsule contains RIF (300 mg) and INH (150 mg); thus, the daily dose is two capsules (600 mg of RIF and 300 mg of INH). Two capsules of Rifamate® plus two 300-mg tablets of INH are used by some programs for intermittent therapy given twice weekly as DOT.

Rifater®: Each tablet contains RIF (120 mg), INH (50 mg), and PZA (300 mg). The daily dose is based on weight as follows: 44 kg or less, four tablets; 45–54 kg, five tablets; 55 kg or more, six tablets. To obtain an adequate dose of PZA in persons weighing more than 90 kg additional PZA tablets must be given.

Adverse effects. See comments under individual drugs above.

Use in pregnancy. Rifamate® may be used in daily treatment of pregnant women. Rifater® should not be used because it contains PZA.

CNS penetration. See comments under individual drugs above.

Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) Rifamate® may be used in persons with renal insufficiency. Rifater® should not be used because of the potential need for adjustment of the dose of PZA.

Use in hepatic disease. (See Section 8.8: Hepatic Disease.) In patients with underlying hepatic disease it is advisable to treat with single-drug formulations until safety in an individual patient can be determined and a stable regimen established.

3.2. Second-Line Drugs

3.2.1. Cycloserine

Role in treatment regimen. Cycloserine (*76,77*) is a second-line drug that is used for treating patients with drug-resistant tuberculosis caused by organisms with known or presumed susceptibility to the agent. It may also be used on a temporary basis for patients with acute hepatitis in combination with other nonhepatotoxic drugs.

Dose. See Table 3.

Adults (maximum): 10–15 mg/kg per day (1,000 mg), usually 500–750 mg/day given in two doses. Clinicians with experience with cycloserine indicate that toxicity is more common at doses over 500 mg/day. Serum concentration measurements aiming for a peak concentration of 20–35 mg/ml are often useful in determining the optimum dose for a given patient. There are no data to support intermittent administration.

Children (maximum): 10–15 mg/kg per day (1.0 g/day).

Preparations. Capsules (250 mg).

Adverse effects.

Central nervous system effects: The central nervous system effects range from mild reactions, such as headache or restlessness, to severe reactions, such as psychosis and seizures. The drug may exacerbate underlying seizure disorders or mental illness. Seizures have been reported to occur in up to 16% of patients receiving 500 mg twice daily but in only 3% when receiving 500 mg once daily (*78*). Pyridoxine may help prevent and treat neurotoxic side effects and is usually given in a dosage of 100–200 mg/day (*79*). Rarely, cycloserine may cause peripheral neuritis.

Use in pregnancy. Cycloserine crosses the placenta. There are limited data on safety in pregnancy; thus, it should be used in pregnant women only when there are no suitable alternatives (*77*).

CNS penetration. Concentrations in CSF approach those in serum (*77*).

Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) The drug can accumulate in patients with impaired renal function and should be used cautiously in such patients. Generally, the dose should be reduced and serum concentrations measured. Cycloserine should not be used in patients having a creatinine clearance of less than 50 ml/minute unless the patient is receiving hemodialysis. For patients being hemodialyzed the dose should be 500 mg three times a week or 250 mg daily (Table 15). Serum concentrations of the drug should be measured and the dose adjusted accordingly.

Use in hepatic disease. (See Section 8.8: Hepatic Disease.) There are no precautions except for patients with alcohol-related hepatitis in whom there is an increased risk of seizures (*77*).

Monitoring. Neuropsychiatric status should be assessed at least at monthly intervals and more frequently if symptoms

develop. As noted above, measurements of serum concentrations may be necessary until an appropriate dose is established. For patients taking phenytoin, serum concentrations of phenytoin should be measured.

3.2.2. Ethionamide

Role in treatment. Ethionamide (*76,77*) is a second-line drug that is used for patients with drug-resistant tuberculosis disease caused by organisms that have demonstrated or presumed susceptibility to the drug.

Dose: See Table 3.

Adults (maximum): 15–20 mg/kg per day (1.0 g/day), usually 500–750 mg/day in a single daily dose or two divided doses. The single daily dose can be given at bedtime or with the main meal. There are no data to support intermittent dosing.

Children (maximum): 15–20 mg/kg per day (1.0 g/day).

Preparations: Tablets (250 mg).

Adverse reactions.

Gastrointestinal effects: Ethionamide commonly causes profound gastrointestinal side effects, including a metallic taste, nausea, vomiting (that is often severe), loss of appetite, and abdominal pain (*80*). Symptoms may improve if doses are taken with food or at bedtime.

Hepatotoxicity: Ethionamide is similar in structure to INH and may cause similar side effects. Hepatotoxicity occurs in about 2% of patients taking the drug (*81,82*).

Neurotoxicity: Neurotoxicity, including peripheral neuritis, optic neuritis, anxiety, depression, and psychosis, has been reported in 1–2% of patients taking shorter courses of the drug with higher rates reported with prolonged treatment (*83,84*).

Endocrine effects: Endocrine disturbances, including gynecomastia, alopecia, hypothyroidism, and impotence, have been described (*85,86*). Diabetes may be more difficult to manage in patients taking ethionamide (*77*).

Use in pregnancy. Ethionamide crosses the placenta and is teratogenic in laboratory animals. It should not be used in pregnancy.

CNS penetration. CSF concentrations are equal to those in serum (*77*).

Use in renal disease. (See Section 8.7: Renal Insufficiency and End-stage Renal Disease.) For patients having a creatinine clearance of less than 30 ml/minute or who are receiving hemodialysis the dose should be reduced to 250–500 mg/day (Table 15).

Use in hepatic disease. (See Section 8.8: Hepatic Disease.) Ethionamide should be used with caution in patients with underlying liver disease.

Monitoring. Liver function tests should be obtained at baseline and, if there is underlying liver disease, at monthly intervals. The studies should be repeated if symptoms occur. Thyroid-stimulating hormone should be measured at baseline and at monthly intervals.

3.2.3. Streptomycin

Role in treatment regimen. Streptomycin (SM) (*76,77,87–89*) and EMB have been shown to be approximately equivalent when used in the initial phase of treatment with 6-month regimens. However, among patients likely to have acquired *M. tuberculosis* in a high-incidence country, the relatively high rate of resistance to SM limits its usefulness.

Dose. See Table 3.

Adults (maximum): 15 mg/kg per day (1 g/day) parenterally, usually given as a single daily dose (5–7 days/week) initially, and then reducing to two or three times a week after the first 2–4 months or after culture conversion, depending on the efficacy of the other drugs in the regimen (*90*). For persons over 59 years of age, the dose should be reduced to 10 mg/kg per day (750 mg). The dosing frequency should be reduced (i.e., 12–15 mg/kg per dose two or three times per week) in persons with renal insufficiency (see below: Use in Renal Disease) (*91,92*).

Children (maximum): 20–40 mg/kg per day (1 g/day).

Preparations. Aqueous solution in vials of 1 g (*93*).

Adverse effects.

Ototoxicity: The most important adverse reaction caused by SM is ototoxicity, including vestibular and hearing disturbances. The risk is increased with age (*94*) or concomitant use of loop-inhibiting diuretics (furosemide, ethacrynic acid). The risk of ototoxicity increases with increasing single doses and with the cumulative dose, especially above 100–120 g.

Neurotoxicity: SM relatively commonly causes circumoral parasthesias immediately after injection. Rarely, it may interact with muscle relaxants to cause postoperative respiratory muscle weakness.

Nephrotoxicity: Nephrotoxicity occurs less commonly with SM than with amikacin, kanamycin, or capreomycin (*95*). Renal insufficiency requiring discontinuation occurs in about 2% of patients (*96*).

Use in pregnancy. SM is contraindicated in pregnancy because of the risk of fetal hearing loss (*77,97,98*).

CNS penetration. There is only slight diffusion of SM into CSF, even in patients with meningitis (*77,99*)

Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) SM should be used with caution in patients with renal function impairment because of the increased risk of both ototoxicity and nephrotoxicity. Because clearance is almost exclusively by the kidney, dosing

adjustments are essential in patients with underlying renal insufficiency, including the elderly and those undergoing hemodialysis. In such patients, the dosing frequency should be reduced to two or three times weekly, but the milligram dose should be maintained at 12–15 mg/kg per dose to take advantage of the concentration-dependent bactericidal effect (Table 15) (*91,92*). Smaller doses may reduce the efficacy of this drug. The drug should be given after dialysis to facilitate DOT and to avoid premature removal of the drug (*100*). Serum drug concentrations should be monitored to avoid toxicity (*91*).

Use in hepatic disease. (See Section 8.8: Hepatic Disease.) No precautions are necessary.

Monitoring. An audiogram, vestibular testing, Romberg testing, and serum creatinine measurement should be performed at baseline. Assessments of renal function, and questioning regarding auditory or vestibular symptoms, should be performed monthly. An audiogram and vestibular testing should be repeated if there are symptoms of eighth nerve toxicity.

3.2.4. Amikacin and kanamycin

Role in treatment regimen. Amikacin and kanamycin (*76,77,101*) are two closely related injectable second-line drugs that are used for patients with drug-resistant tuberculosis whose isolate has demonstrated or presumed susceptibility to the agents. There is nearly always complete cross-resistance between the two drugs, but most SM-resistant strains are susceptible to both (*102*). Because it is used to treat a number of other types of infections, amikacin may be more easily obtained, and serum drug concentration measurements are readily available.

Dose. See Table 3.

Adults (maximum): 15 mg/kg per day (1.0 g/day), intramuscular or intravenous, usually given as a single daily dose (5–7 days/week) initially, and then reducing to two or three times a week after the first 2–4 months or after culture conversion, depending on the efficacy of the other drugs in the regimen (*90*). For persons greater than 59 years of age the dose should be reduced to 10 mg/kg per day (750 mg). The dosing frequency should be reduced (i.e., 12–15 mg/kg per dose, two or three times per week) in persons with renal insufficiency (see below: Use in Renal Disease) (*91,92*).

Children (maximum): 15–30 mg/kg per day (1 g/day) intramuscular or intravenous as a single daily dose.

Preparations. Aqueous solution for intramuscular or intravenous injection in vials of 500 mg and 1 g.

Adverse effects.

Ototoxicity: Amikacin and kanamycin may cause deafness, but they cause less vestibular dysfunction than SM (*103,104*). Ototoxicity is more common with concurrent use of diuretics. In one report high-frequency hearing loss occurred in 24% of patients receiving amikacin, with higher rates occurring among those receiving longer treatment and/or higher doses (*105*), whereas a review of the literature found only 1.5% hearing loss (*106*).

Nephrotoxicity: Amikacin and kanamycin may be more nephrotoxic than SM (*95*). Renal impairment was seen in 8.7% of patients receiving amikacin, with a higher frequency in patients with initially increased creatinine levels, patients receiving larger total doses, and patients receiving other nephrotoxic agents. A frequency of 3.4% was reported in patients with no risk factors (*106,107*).

Use in pregnancy. Both amikacin and kanamycin are contraindicated in pregnant women because of risk of fetal nephrotoxicity and congenital hearing loss (*77*).

CNS penetration. Only low concentrations of the drugs are found in CSF, although slightly higher concentrations have been found in the presence of meningitis (*77*).

Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) Amikacin and kanamycin should be used with caution in patients with renal function impairment because of the increased risk of both ototoxicity and nephrotoxicity. Because clearance is almost exclusively by the kidney, dosing adjustments are essential in patients with underlying renal insufficiency, including the elderly and those receiving hemodialysis. In such patients, the dosing frequency should be reduced to two or three times per week, but the dose should be maintained at 12–15 mg/kg to take advantage of the concentration-dependent bactericidal effect (Table 15) (*91,92*). Smaller doses may reduce the efficacy of this drug. The drug should be given after dialysis to facilitate DOT and to avoid premature removal of the drug (*100*). Serum drug concentrations should be monitored to avoid toxicity (*91*).

Use in hepatic disease. (See Section 8.8: Hepatic Disease.) No precautions are necessary.

Monitoring. Monitoring should be performed as described for SM. An advantage of amikacin is that serum concentration measurements can be obtained routinely. Patients with severe hepatic disease, because of predisposition to hepatorenal syndrome, may be at greater risk for nephrotoxicity from amikacin/kanamycin and should have renal function monitored closely.

3.2.5. Capreomycin

Role in treatment. Capreomycin is a second-line injectable drug that is used for patients with drug-resistant tuberculosis caused by organisms that have known or presumed susceptibility to the drug (*108*).

Dose. See Table 3.

Adults (maximum): 15 mg/kg per day (1.0 g/day), usually given as a single daily dose five to seven times a week, and reduced to two or three times a week after the first 2–4 months or after culture conversion, depending on the efficacy of the other drugs in the regimen (*90*). For persons greater than 59 years of age the dose should be reduced to 10 mg/kg per day (750 mg). The dosing frequency should be reduced to 12–15 mg/kg two or three times per week in persons with renal insufficiency (see below: Use In Renal Disease) (*91,92*).

Children (maximum): 15–30 mg/kg per day (1 g/day) as a single daily or twice weekly dose.

Preparations. Capreomycin is available in vials of 1 g for both intramuscular and intravenous administration.

Adverse effects.

Nephrotoxicity: Nephrotoxic effects may result in reduced creatinine clearance or potassium and magnesium depletion. Proteinuria is common (*109*). Significant renal toxicity requiring discontinuation of the drug has been reported to occur in 20–25% of patients (*110,111*).

Ototoxicity: Vestibular disturbances, tinnitus, and deafness appear to occur more often in elderly persons or those with preexisting renal impairment (*111*).

Use in pregnancy. Capreomycin should be avoided in pregnancy because of risk of fetal nephrotoxicity and congenital hearing loss (*77*).

CNS penetration. Capreomycin does not penetrate into the CSF (*77*).

Use in renal disease. (see Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) Capreomycin should be used with caution in patients with renal function impairment because of the increased risk of both ototoxicity and nephrotoxicity (*112*). Because capreomycin is nearly entirely cleared by the kidneys, dosing adjustments are essential in patients with underlying renal insufficiency and end-stage renal disease, including patients undergoing hemodialysis. In such patients, the dosing frequency should be reduced to two or three times weekly, but the milligram dose should be maintained at 12–15 mg/kg per dose to take advantage of the concentration-dependent bactericidal effect (Table 15) (*91,92*). Smaller doses may reduce the efficacy of this drug. The drug should be given after dialysis to facilitate DOT and avoid premature removal of the drug (*100,113*). Serum drug concentrations should be monitored to avoid toxicity (*91*).

Use in hepatic disease. (See Section 8.8: Hepatic Disease.) No precautions are necessary.

Monitoring. Monitoring should be performed as described for SM. In addition, serum potassium and magnesium concentrations should be measured at baseline and at least at monthly intervals.

3.2.6. *p*-Aminosalicylic acid

Role in treatment. *p*-Aminosalicylic acid (PAS) is an oral agent used in treatment of drug-resistant tuberculosis caused by organisms that are susceptible to the drug.

Dose. See Table 3.

Adults: 8–12 g/day in two or three doses. For PAS granules, 4 g three times daily has been the usual dosage (*114,115*). However, it has been shown that administration of 4 g twice daily is adequate to achieve the target serum concentration (*116*).

Children: 200–300 mg/kg per day in two to four divided doses (*117*).

Preparations. The only available formulation in the United States is granules in 4-g packets (Paser Granules®) (*118*). It was previously thought that the granules needed to be taken with acidic food (*115*); however, more recent data suggest that this is not necessary (C. Peloquin, personal communication). Tablets (500 mg) are still available in some countries. A solution for intravenous administration is available in Europe (*119,120*).

Adverse effects.

Hepatotoxicity: In a review of 7,492 patients being treated for tuberculosis, 38 (0.5%) developed hepatitis, of which 28 cases (0.3%) were attributed at least in part to PAS (*121*).

Gastrointestinal distress: This is the most common side effect of PAS (*122*). In a large study of INH and PAS 11% of patients had drug toxicity, mainly gastrointestinal intolerance to PAS (*114*). The incidence of gastrointestinal side effects is less with lower doses (8 g daily) and with the granular formulation of the drug.

Malabsorption syndrome: This is characterized by steatorrhea and low serum folate levels (*123*).

Hypothyroidism: This is a common side effect, especially with prolonged administration or concomitant use of ethionamide. It may be accompanied by goiter formation. Thyroid hormone replacement may be required. Thyroid function returns to normal after discontinuation of the drug (*124*).

Coagulopathy: A doubling of the prothrombin time that seemed to be lessened by coadministration of streptomycin has been reported (*125*).

Use in pregnancy. No studies have been done in humans; however, PAS has been used safely in pregnancy. The drug should be used only if there are no alternatives (see below) for a pregnant woman who has multidrug-resistant tuberculosis.

CNS penetration. In the presence of inflamed meninges, PAS concentrations are between 10–50% of those achieved in serum (*119*). The drug has marginal efficacy in meningitis.

Use in renal disease. (See Section 8.7: Renal Insufficiency and End-Stage Renal Disease.) Approximately 80% of the drug is excreted in the urine (*118*). Unless there is no alternative,

PAS is contraindicated in severe renal insufficiency because of the accumulation of the acetylated form (*123,126,127*). Because both PAS and acetyl-PAS are removed by dialysis, the drug should be given after dialysis to facilitate DOT and avoid premature removal of the drug (*126*).

Use in hepatic disease. (See Section 8.8: Hepatic Disease.) The clearance of PAS is not substantially altered in liver disease, suggesting that the drug may be used in usual doses but with increased laboratory and clinical monitoring (*127*).

Monitoring. Hepatic enzymes and thyroid function should be measured at baseline. With prolonged therapy (i.e., more than 3 months) thyroid function should be checked every 3 months.

3.2.7. Fluoroquinolones

Role in treatment regimen. Of the fluoroquinolones (*128–131*), levofloxacin, moxifloxacin, and gatifloxacin have the most activity against *M. tuberculosis.* On the basis of cumulative experience suggesting a good safety profile with long-term use of levofloxacin, this drug is the preferred oral agent for treating drug-resistant tuberculosis caused by organisms known or presumed to be sensitive to this class of drugs, or when first-line agents cannot be used because of intolerance. Data on long-term safety and tolerability of moxifloxacin and gatifloxacin, especially at doses above 400 mg/day, are limited. Cross-resistance has been demonstrated among ciprofloxacin, ofloxacin, and levofloxacin and presumably is a class effect (*132*). Fluoroquinolones should not be considered first-line agents for the treatment of drug-susceptible tuberculosis except in patients who are intolerant of first-line drugs.

Dose. (See Table 3.) The doses given are for levofloxacin.

Adults: 500–1,000 mg daily.

Children: The long-term (more than several weeks) use of fluoroquinolones in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. However, most experts agree that the drug should be considered for children with MDR tuberculosis. The optimal dose is not known.

Preparations (Levofloxacin). Tablets (250 mg, 500 mg, 750 mg); aqueous solution (500 mg) for intravenous administration.

Adverse effects. The adverse effects (*133*) cited are for levofloxacin.

Gastrointestinal disturbance: Nausea and bloating occur in 0.5–1.8% of patients taking the drug.

Neurologic effects: Dizziness, insomnia, tremulousness, and headache occur in 0.5% of patients.

Cutaneous reactions: Rash, pruritis, and photosensitivity occur in 0.2–0.4% of patients.

Use in pregnancy. This class of drugs should be avoided in pregnancy because of teratogenic effects (*119,134*).

CNS penetration. The concentration in CSF after administration of a standard dose of levofloxacin is 16–20% of that in serum (*135*).

Interference with absorption. Because antacids and other medications containing divalent cations markedly decrease absorption of fluoroquinolones, it is critical that any fluoroquinolone not be administered within 2 hours of such medications (see Section 7.1: Interactions Affecting Antituberculosis Drugs).

Use in renal disease. (See Section 8.7: Renal Insufficiency and End Stage Renal Disease.) The drug is cleared primarily (80%) by the kidney (*135*). Dosage adjustment (750–1,000 mg three times a week) is recommended if creatinine clearance is less than 50 ml/minute (Table 15) (*136*). It is not cleared by hemodialysis; supplemental doses after dialysis are not necessary (*135*).

Use in hepatic disease. Drug levels are not affected by hepatic disease (*135*). It is presumed to be safe for use in the setting of severe liver disease, but as with all drugs, should be used with caution.

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4. Principles of Antituberculosis Chemotherapy

4.1. Combination Chemotherapy

The primary goals of antituberculosis chemotherapy are to kill tubercle bacilli rapidly, prevent the emergence of drug resistance, and eliminate persistent bacilli from the host's tissues to prevent relapse (*1*). To accomplish these goals, multiple antituberculosis drugs must be taken for a sufficiently long time. The theoretical model of chemotherapy for tuberculosis is founded on current understanding of the biology of *M. tuberculosis* in the host and on the specific activities of antituberculosis drugs. This model is supported by data from numerous in vivo and in vitro studies.

Effects of Antituberculosis Chemotherapy

Antituberculosis chemotherapy is designed to kill tubercle bacilli rapidly, minimize the potential for the organisms to develop drug resistance, and sterilize the host's tissues. The achievement of these effects requires that a combination of agents with specific activities be administered for a sufficiently long period of time. As a consequence of these effects, the patient is cured and has only a small likelihood of relapse.

It is theorized that there are three separate subpopulations of *M. tuberculosis* within the host. These populations are defined by their growth characteristics and the milieu in which they are located (*1*). The largest of the subpopulations consists of rapidly growing extracellular bacilli that reside mainly in cavities. This subpopulation, because of its size, is most likely to harbor organisms with random mutations that confer drug resistance. The frequency of these mutations that confer resistance is about 10^{-6} for INH and SM, 10^{-8} for RIF, and 10^{-5} for EMB; thus, the frequency of concurrent mutations to both INH and RIF, for example, would be 10^{-14}, making simultaneous resistance to both drugs in an untreated patient a highly unlikely event (*2*).

INH has been shown to possess the most potent ability to kill rapidly multiplying *M. tuberculosis* during the initial part of therapy (early bactericidal activity), thereby rapidly decreasing infectiousness (*3–5*). It is followed in this regard by EMB, RIF, and SM. PZA has weak early bactericidal activity during the first 2 weeks of treatment (*3,6*). Drugs that have potent early bactericidal activity reduce the chance of resistance developing within the bacillary population.

Early experience in clinical trials demonstrated that multiple agents are necessary to prevent the emergence of a drug-resistant population as a consequence of the selection pressure from administration of a single agent. Shortly after the discovery of SM, it was demonstrated that treatment with this agent alone resulted in treatment failure and drug resistance (*7*). Subsequently, it was shown that the combination of PAS and SM substantially lessened the likelihood of acquired resistance and treatment failure (*8*). In modern regimens both INH and RIF have considerable ability to prevent the emergence of drug resistance when given with another drug. EMB and SM are also effective in preventing the emergence of drug resistance, whereas the activity of PZA in this regard is poor (*9,10*). For this reason PZA should not be used with only one other agent when treating active tuberculosis.

The rapidly dividing population of bacilli is eliminated early in effective therapy as shown by the early clinical responses and clearing of live bacilli from sputum within 2 months in about 80% of patients. The remaining subpopulations of *M. tuberculosis* account for treatment failures and relapses, especially when the duration of therapy is inadequate. These residual populations include organisms that are growing more slowly, often in the acidic environment provided by areas of necrosis, and a group that is characterized by having spurts of growth interspersed with periods of dormancy. The sterilizing activity of a drug is defined by its ability to kill bacilli, mainly in these two subpopulations that persist beyond the early months of therapy, thus decreasing the risk of relapse (*1*). The use of drugs that have good sterilizing properties is essential for regimens as short as 6 months. RIF and PZA have the greatest sterilizing activity followed by INH and SM (*11,12*). The sterilizing activity of RIF persists throughout the course of therapy, but this does not appear to be true for PZA. When given in RIF-containing regimens, PZA provides additive sterilizing activity only during the initial 2 months of therapy. The sterilizing activity of PZA may not be so limited in regimens where RIF cannot be used or is not effective, so regimens for MDR tuberculosis may include PZA for the full course of treatment if the isolate is susceptible to this agent.

4.2. Optimum Duration of Treatment

Truly effective chemotherapy for tuberculosis became available with the introduction of INH in the early 1950s. Adding INH to SM and PAS increased cure rates from about 70 to 95% but required treatment for 18–24 months (*13*). Eventually, EMB replaced PAS as the companion agent for INH (*14*). Subsequent investigations of combination chemotherapy sought to identify regimens that were shorter and that could be given intermittently.

The British Medical Research Council (BMRC) in East Africa (*15*) conducted the first large-scale multicenter study of short-course (6-month) regimens. This study demonstrated that the addition of RIF or PZA to a base regimen of daily SM and INH increased the proportion of patients whose sputum cultures were negative by 2 months after the initiation of treatment and significantly reduced the relapse rate. Moreover, the relapse rate of the short-course regimens was no greater than that of the standard 18-month regimen containing SM, INH, and thiacetazone (a drug used in many countries in place of PAS or EMB). In Hong Kong, administration of a 9-month regimen of SM, INH, and PZA daily, twice weekly, or three times weekly was associated with a relapse rate of only 5–6% (*16*). Unfortunately, all short-course regimens that did not include RIF required fully supervised therapy and SM had to be used for the entire 9 months. Subsequent investigations conducted by the British Thoracic Association demonstrated that SM (or EMB) was necessary only for the first 2 months

to achieve excellent results with a 9-month treatment duration, using INH and RIF throughout (*17,18*). The BMRC conducted studies in Hong Kong proving that EMB was roughly as effective as SM in the initial phase of therapy, thereby demonstrating that an all-oral regimen was effective (*19*).

The addition of PZA to a regimen containing INH and RIF enabled further shortening of the duration of therapy to 6 months. The British Thoracic Association demonstrated that a regimen of INH and RIF for 6 months, supplemented during the first 2 months with PZA and either EMB or SM, was as effective as a 9-month regimen of INH and RIF with EMB in the first 2 months (*18*). Administration of PZA beyond the initial 2 months in an RIF-containing regimen had no additional benefit. The efficacy of the treatment regimens was similar regardless of whether PZA was given for 2, 4, or 6 months (*20*).

Subsequent studies of 6-month regimens have served to refine the approach used currently. USPHS Trial 21 compared self-administered INH and RIF for 6 months plus PZA given during the initial 2 months with INH and RIF for 9 months (*21*). EMB was added only if INH resistance was suspected. Patients taking the 6-month PZA-containing regimen had negative sputum cultures sooner after treatment was started than those treated for 9 months without PZA and relapse rates were similar for the two regimens (3.5 versus 2.8%).

Investigators in Denver reported a low relapse rate (1.6%) when using a 62-dose, directly observed, 6-month regimen that consisted of 2 weeks of daily INH, RIF, PZA, and SM, 6 weeks of the same four drugs given twice weekly, and 18 weeks of twice weekly INH and RIF (*22*).

Regimens less than 6 months in duration have been shown to have unacceptably high relapse rates among patients with smear-positive pulmonary tuberculosis (*23,24*). However, in a study in Hong Kong among patients with smear-negative, culture-positive tuberculosis, the relapse rate was about 2% when using a 4-month regimen of daily SM, INH, RIF, and PZA (*25*); among smear-negative, culture-negative cases, the relapse rate was only 1%. In Arkansas, patients with tuberculosis who had negative smears and cultures were treated with INH and RIF given daily for 1 month followed by 3 months of twice weekly INH and RIF (*26*). Only 3 of 126 (2.4%) patients developed active tuberculosis during 3.5 years of follow-up. Thus, it appears that a 4-month, INH- and RIF-containing regimen is effective in culture-negative tuberculosis (see Section 8.4: Culture-Negative Pulmonary Tuberculosis in Adults).

4.3. Intermittent Drug Administration

Nonadherence to the antituberculosis treatment regimen is well known to be the most common cause of treatment failure, relapse, and the emergence of drug resistance. Administration of therapy on an intermittent basis, as opposed to daily dosing, facilitates supervision of therapy, thereby improving the outcome. The concept of intermittent administration of antituberculosis drugs developed from early clinical observations and was supported by subsequent laboratory investigations. First, it was noted that a single daily dose of 400 mg of INH was more effective than the same total dose given in two divided doses (*27*). Second, in an early study from Madras, investigators demonstrated that fully supervised twice weekly therapy could be delivered to nonhospitalized patients and that the results were better than with a conventional self-administered daily regimen (*28*). These findings, plus the laboratory results noted below, led to a series of clinical trials that compared daily and intermittent dosing of antituberculosis medications. In all of these studies, intermittent regimens were demonstrated to be as effective as daily regimens and no more toxic (*20*).

In the laboratory it was noted that in vitro exposure of tubercle bacilli to drugs was followed by a lag period of several days before growth began again (postantibiotic effect) (*29–31*). Thus, it was concluded that maintaining continuous inhibitory drug concentrations was not necessary to kill or inhibit growth of *M. tuberculosis*. Studies in guinea pigs substantiated that INH could be given at intervals as long as 4 days without loss of efficacy; however, there was a significant decrease in activity with an 8-day dosing interval (*30,31*).

The concept of intermittent drug administration continues to evolve. Studies have demonstrated that the frequency of drug administration in the continuation phase of treatment may be decreased to once a week when using INH and rifapentine for certain highly selected patients (*32–34*). Because of the newness of these findings the data are presented in some detail.

The results from three open-label, randomized clinical trials indicate that rifapentine given with INH once a week is safe and effective when used for the treatment of selected, HIV-negative patients with pulmonary tuberculosis. In a study performed in Hong Kong, patients with pulmonary tuberculosis were allocated at random to receive 600 mg of rifapentine and 900 mg of INH given either once every week or once every 2 of 3 weeks for 4 months after completion of a standard 2-month initial phase (*32*). Overall, about 11% of patients in the two rifapentine arms failed or relapsed during a 5-year follow-up period, compared with 4% of the patients who received three times weekly INH–RIF (control arm) in the continuation phase of treatment. Omitting every third dose of INH–rifapentine did not appreciably increase the relapse rate, indicating that modest nonadherence may have a negligible effect. Multivariate analyses showed that the significant prognostic factors were treatment arm, radiographic extent of

disease (all three regimens), and sex (women fared better than men). The frequency of failures and relapses was also greater in all three arms if the 2-month culture was positive.

The pivotal study for drug registration was conducted in North America and South Africa among HIV-negative patients with pulmonary tuberculosis (*33*). Patients in the experimental arm received directly observed twice weekly rifapentine together with daily self-administered INH, PZA, and EMB in the initial 2 months, followed by 4 months of once weekly directly observed rifapentine and INH. Patients in the control arm received a standard four-drug initial phase, followed by twice weekly INH–RIF. Relapse rates during 2 years of follow-up were similar to those seen in the Hong Kong study (8.2% relapse in the experimental arm versus 4.4% in the control arm), and cavitary disease, sputum culture positivity at the end of the initial phase, and nonadherence with INH, EMB, and PZA in the experimental arm were significantly associated with an increased probability of relapse.

The third study was conducted by the CDC Tuberculosis Trials Consortium, and employed a design similar to the Hong Kong trial, in which HIV-negative patients were allocated at random after successful completion of standard 2-month initial phase therapy (*34*). Again, results, as measured by rates of failure/relapse, were remarkably similar to the first two trials, 9.2% in the experimental (INH–rifapentine once weekly) arm compared with 5.6% in the control (INH–RIF twice weekly) arm. However, as in the South Africa study, relapse was significantly associated with the presence of cavitary lesions seen on the initial chest film and sputum culture positivity at 2 months, both of which were more common in the rifapentine arm. With adjustment for these factors, the difference in outcome in the two arms was not statistically significant. Relapse rates among patients who did not have cavitary disease and had negative sputum cultures at 2 months were low in both treatment arms. However, in patients who had both cavitation and a positive culture at 2 months the relapse rate in the rifapentine arm was 22% and in the twice weekly INH–RIF arm was 21% (Table 11). In all of the cited studies, rifapentine was well tolerated, with the adverse events being similar to those occurring with RIF.

A small number of HIV–positive patients were enrolled in the CDC study, but this arm was closed after the development of acquired rifampin resistance among relapse cases in the rifapentine arm (*35*).

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TABLE 11. Percentage of culture-positive relapse* by continuation phase regimen, radiographic status, and 2-month sputum culture: USPHS Study 22

Continuation phase, INH–RIF twice weekly†			Continuation phase, INH–RPT once weekly†		
	Culture-positive at 2 months			Culture-positive at 2 months	
Cavity	Yes	No	Cavity	Yes	No
Yes	20.8 (48)‡	4.7 (150)	Yes	22.2 (72)	9.1 (154)
No	5.9 (17)	1.7 (181)	No	11.8 (17)	1.9 (162)

Definition of abbreviations: INH = Isoniazid; RIF = rifampin; RPT = rifapentine.
Source: Tuberculosis Trials Consortium. Rifapentine and isoniazid once a week versus rifampin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomized clinical trial. Lancet 2002;360:528–534 and additional data (A. Vernon, personal communication).
*Culture-positive relapse with restriction fragment length polymorphism match to initial isolate.
†INH–RIF = twice weekly isoniazid–rifampin for 16 weeks; INH–RPT = once weekly isoniazid–rifapentine for 16 weeks.
‡Denominators in parentheses: number enrolled, completing treatment per protocol, and assessed for relapse.

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5. Recommended Treatment Regimens

5.1. Evidence-based Rating System

To assist in making informed treatment decisions based on the most credible research results, evidence-based ratings have been assigned to the treatment recommendations (Table 1). The ratings system is the same as that used in the recommendations for treating latent tuberculosis infection, in which a letter indicating the strength of the recommendation, and a roman numeral indicating the quality of the evidence supporting the recommendation, are assigned to each regimen (*1*). Thus, clinicians can use the ratings to differentiate among recommendations based on data from clinical trials and those based on the opinions of experts familiar with the relevant clinical practice and scientific rationale for such practice when clinical trial data are not available.

5.2. Recommended Regimens

There are four basic regimens recommended for treating adults with tuberculosis caused by organisms that are known or presumed to be susceptible to INH, RIF, PZA, and EMB (Table 2). As noted below, children, depending on the

circumstances, may not receive EMB in the initial phase of a 6-month regimen, but the regimens are otherwise identical. Each regimen has an initial phase of 2 months, followed by a choice of several options for the continuation phase of either 4 or 7 months. In Table 2 the initial phase is denoted by a number (1, 2, 3, or 4) and the options for the continuation phase are denoted by the respective number and a letter designation (a, b, or c). DOT is the preferred initial management strategy for all regimens and should be used whenever feasible. All patients being given drugs less than 7 days per week (5, 3, or 2 days/week) must receive DOT.

5.2.1. Six-month regimens

The current minimal acceptable duration of treatment for all children and adults with culture-positive tuberculosis is 6 months (26 weeks). The initial phase of a 6-month regimen for adults should consist of a 2-month period of INH, RIF, PZA, and EMB given daily throughout (Regimen 1), daily for 2 weeks followed by two times weekly for 6 weeks (Regimen 2), or three times a week (Regimen 3). The minimum number of doses is specified in Table 2. On the basis of substantial clinical experience, 5 day-a-week drug administration by DOT is considered to be equivalent to 7 day-a-week administration; thus, either may be considered "daily." Although administration of antituberculosis drugs by DOT at 5 days/week, rather than 7 days, has been reported in a large number of studies it has not been compared with 7-day administration in a clinical trial and therefore is rated AIII.

The recommendation that a four-drug regimen be used initially for all patients is based on the current proportion of new tuberculosis cases caused by organisms that are resistant to INH (*2*). This recommendation is supported by a retrospective analysis of data from various BMRC studies indicating that in the presence of INH resistance there were fewer treatment failures and relapses if a regimen containing four drugs, INH, RIF, PZA, and EMB, was used in the initial phase (*3*). However, if therapy is being initiated after drug susceptibility test results are known and the organisms are susceptible to INH and RIF, EMB is not necessary. EMB can be discontinued as soon as the results of drug susceptibility studies demonstrate that the isolate is susceptible to the first-line agents. In most situations these results are not available before 6–8 weeks after treatment is begun.

The continuation phase of treatment should consist of INH and RIF given for a minimum of 4 months (18 weeks). Patients should be treated until they have received the specified total number of doses for the treatment regimen (Table 2). The continuation phase can be given daily (Regimen 1a), twice weekly (Regimens 1b and 2a), or three times weekly (Regimen 3a). The continuation phase should be extended for an additional 3 months for patients who have cavitation on the initial or follow-up chest radiograph and are culture-positive at the time of completion of the initial phase of treatment (2 months). Patients who are HIV negative, who do not have cavities on the chest radiograph, and who have negative sputum AFB smears at completion of the initial phase of treatment may be treated with once weekly INH and rifapentine in the continuation phase for 4 months. If the culture of the sputum obtained at 2 months is positive, observational data and expert opinion suggest that the continuation phase of once weekly INH and rifapentine should be 7 months (*4*).

5.2.2. Nine-month regimen

If PZA cannot be included in the initial regimen, or if the isolate is determined to be resistant to PZA (an unusual circumstance, except for *Mycobacterium bovis* and *M. bovis* var. BCG), a regimen consisting of INH, RIF, and EMB should be given for the initial 2 months (Regimen 4) followed by INH and RIF for 7 months given either daily or twice weekly (Regimens 4a and 4b).

5.2.3. Alternative regimens

In some cases, either because of intolerance or drug resistance, the above-described regimens cannot be used. In these instances, an alternative regimen may be required. In a retrospective analysis of the combined results of clinical trials conducted by the BMRC it was concluded that, in the presence of initial resistance to INH, if a four-drug regimen containing RIF and PZA was used in the initial phase and RIF was used throughout a 4-month continuation phase there were no treatment failures and 7% relapses compared with 4% relapses among patients with fully susceptible strains (*3*). Data from a Hong Kong BMRC study suggest that in the presence of INH resistance results are better when PZA is used throughout (*5*). On the basis of these data, when INH cannot be used or the organisms are resistant to INH, a 6-month regimen of RIF, PZA, and EMB is nearly as efficacious as an INH-containing regimen (Rating BI) (*3*). Alternatively, RIF and EMB for 12 months may be used, preferably with PZA during at least the initial 2 months (Rating BII) (*5,6*). If RIF is not used, INH, EMB, and FQN should be given for a minimum of 12–18 months supplemented with PZA during at least the initial 2 months (Rating BIII). An injectable agent may also be included for the initial 2–3 months for patients with more extensive disease or to shorten the duration (e.g., to 12 months), (*7,8*).

Levofloxacin, moxifloxacin, or gatifloxacin may be useful in alternative regimens, but the potential role of a fluoroquinolone and optimal length of therapy have not been defined (*9,10*). In situations in which several of the first-line

agents cannot be used because of intolerance, regimens based on the principles described for treating multiple drug-resistant tuberculosis (Section 9.3: Management of Tuberculosis Caused by Drug-Resistant Organisms) should be used.

5.3. Deciding to Initiate Treatment

The decision to initiate combination chemotherapy for tuberculosis should be based on epidemiologic information, clinical and radiographic features of the patient, and the results of the initial series of AFB smears (preferably three) and, subsequently, cultures for mycobacteria. Rapid amplification tests, if used, can also confirm the diagnosis of tuberculosis more quickly than cultures. On the basis of this information, the likelihood that a given patient has tuberculosis can be estimated. For example, a patient who has emigrated recently from a high-incidence country, has a history of cough and weight loss, and has characteristic findings on chest radiograph should be considered highly likely to have tuberculosis. In such situations combination drug therapy should be initiated, even before AFB smear and mycobacterial culture results are known. Empirical treatment with a four-drug regimen should be initiated promptly when a patient is seriously ill with a disorder that is thought possibly to be tuberculosis. Initiation of treatment should not be delayed because of negative AFB smears for patients in whom tuberculosis is suspected and who have a life-threatening condition. Disseminated (miliary) tuberculosis, for example, is often associated with negative sputum AFB smears. Likewise, for a patient with suspected tuberculosis and a high risk of transmitting *M. tuberculosis* if, in fact, she or he had the disease, combination chemotherapy should be initiated in advance of microbiological confirmation of the diagnosis to minimize potential transmission.

A positive AFB smear provides strong inferential evidence for the diagnosis of tuberculosis. If the diagnosis is confirmed by isolation of *M. tuberculosis* or a positive nucleic acid amplification test, or is strongly inferred from clinical or radiographic improvement consistent with a response to treatment, the regimen can be continued to complete a standard course of therapy (Figure 1). A PPD-tuberculin skin test may be done at the time of initial evaluation, but a negative test does not exclude the diagnosis of active tuberculosis. However, a positive skin test supports the diagnosis of culture-negative pulmonary tuberculosis or, in persons with stable abnormal chest radiographs consistent with inactive tuberculosis, a diagnosis of latent tuberculosis infection (see below).

If the cultures are negative, the PPD-tuberculin skin test is positive (5 mm or greater induration), and there is no response to treatment, the options are as follows: 1) stop treatment if RIF and PZA have been given for at least 2 months; 2) continue treatment with RIF, with or without INH, for a total of 4 months; or 3) continue treatment with INH for a total of 9 months (*11*). All three of these options provide adequate therapy for persons with prior tuberculosis once active disease has been excluded.

If clinical suspicion for active tuberculosis is low, the options are to begin treatment with combination chemotherapy or to defer treatment until additional data have been obtained to clarify the situation (usually within 2 months) (Figure 2, top). Even when the suspicion of active tuberculosis is low, treatment for latent tuberculosis infection with a single drug should not be initiated until active tuberculosis has been excluded.

In low-suspicion patients not initially treated, if cultures remain negative, the PPD-tuberculin skin test is positive (5 mm or greater induration), and the chest radiograph is unchanged after 2 months, there are three treatment options (Figure 2, top) (*11*). The preferred options are INH for 9 months or RIF, with or without INH, for 4 months. RIF and PZA for a total of 2 months can be used for patients not likely to complete a longer regimen and who can be monitored closely. However, this last regimen has been associated with an increased risk of hepatotoxicity and should be used only in the limited circumstances described (*12,13*). An advantage of the early use of combination chemotherapy is that, once active disease is excluded by negative cultures and lack of clinical or radiographic response to treatment, the patient will have completed 2 months of combination treatment that can be applied to the total duration of treatment recommended for latent tuberculosis infection (Figure 2, bottom).

5.4. Baseline and Follow-Up Evaluations

Patients suspected of having tuberculosis should have appropriate specimens collected for microscopic examination and mycobacterial culture. When the lung is the site of disease, three sputum specimens should be obtained 8–24 hours apart. In patients who are not producing sputum spontaneously, induction of sputum using aerosolized hypertonic saline or bronchoscopy (performed under appropriate infection control procedures) may be necessary to obtain specimens. Susceptibility testing for INH, RIF, and EMB should be performed on an initial positive culture, regardless of the source. Second-line drug susceptibility testing should be done only in reference laboratories and be limited to specimens from patients who have had prior therapy, have been in contact of a patient with known drug resistance, have demonstrated resistance to rifampin or two other first-line drugs, or who have positive cultures after more than 3 months of treatment.

At the time treatment is initiated, in addition to the microbiologic examinations, it is recommended that all patients with

tuberculosis have counseling and testing for HIV infection (*14*). Patients with epidemiologic factors suggesting a risk for hepatitis B or C, for example, injection drug use, birth in Asia or Africa, or HIV infection, should have serologic tests for these viruses (*15,16*). HIV-infected patients should also undergo $CD4^+$ lymphocyte count measurement. Measurements of AST, bilirubin, alkaline phosphatase, and serum creatinine and a platelet count should be obtained for all adults. Testing of visual acuity (Snellen chart) and color vision (Ishihara tests) should be performed when EMB is to be used.

During treatment of patients with pulmonary tuberculosis, at a minimum, a sputum specimen for AFB smear and culture should be obtained at monthly intervals until two consecutive specimens are negative on culture. As described subsequently, important decisions concerning the continuation-phase regimen hinge on the microbiological status at the end of the initial phase of treatment, thus, obtaining sputum specimens at this juncture is critical, if sputum conversion to negative has not already been documented. For patients who had positive AFB smears at the time of diagnosis, follow-up smears may be obtained at more frequent intervals (e.g., every 2 weeks until two consecutive specimens are negative) to provide an early assessment of the response to treatment, especially for patients in situations in which the risk of transmission is high. On occasion, AFB-positive sputa are culture negative; this occurs most frequently among patients with far advanced cavitary tuberculosis after the first months of treatment. It is thought that these organisms are dead and that their presence is not a sign of treatment failure, even if noted later in treatment. However, repeat cultures should be obtained to confirm that the earlier culture result was correct and not a false negative.

Drug susceptibility tests should be repeated on isolates from patients who have positive cultures after 3 months of treatment. As described in Section 9.2 (Treatment Failure), patients who have positive cultures after 4 months of treatment should be considered as having failed treatment and managed accordingly.

For patients with extrapulmonary tuberculosis the frequency and kinds of evaluations will depend on the sites involved and the ease with which specimens can be obtained.

In addition to the microbiological evaluations, it is essential that patients have clinical evaluations at least monthly to identify possible adverse effects of the antituberculosis medications and to assess adherence.

For patients with positive cultures at diagnosis, a repeat chest radiograph at completion of 2 months of treatment may be useful but is not essential. A chest radiograph at completion of therapy provides a baseline against which subsequent examinations can be compared, but, as with the 2-month examination, it is not essential. When the initial sputum cultures are negative, a presumptive diagnosis can be made if radiographic improvement is noted, generally by the time 2 months of treatment has been completed. Thus, in patients with negative initial cultures, a chest radiograph is necessary after 2 months of treatment and a radiograph at completion of treatment is desirable. Generally, follow-up after completion of therapy is not necessary.

As a routine, it is not necessary to monitor liver or renal function or platelet count for patients being treated with first-line drugs unless there were abnormalities at baseline or there are clinical reasons to obtain the measurements. Patients who have stable abnormalities of hepatic or renal function at baseline should have repeat measurements early in the course of treatment, then less frequently to ensure that there has not been worsening. Patients receiving EMB should be questioned regarding visual disturbances at monthly intervals; monthly repeat testing of visual acuity and color vision is recommended for patients receiving an EMB dose exceeding 15–20 mg/kg (the recommended range) and for patients receiving the drug for more than 2 months. Monitoring tests for the individual second-line drugs are listed in Section 3: Drugs in Current Use.

5.5. Identification and Management of Patients at Increased Risk of Relapse

The result of a sputum culture at the conclusion of the initial phase of treatment (2 months) has been shown to correlate with the likelihood of relapse after completion of treatment for pulmonary tuberculosis. In seven clinical trials performed by the BMRC, the regimens that had the highest proportion of patients with a positive sputum culture at 2 months after treatment was initiated were associated with a higher likelihood of relapse within 2 years (*17*). Of greater relevance to the current recommendations, data from USPHS Trial 22 comparing once weekly rifapentine and INH with twice weekly RIF and INH, showed an increased rate of relapse in patients who had a positive culture at 2 months in both study arms (*18*). Cavitation on the initial chest radiograph was also an independent risk factor for relapse. In patients in the control arm (twice weekly INH–RIF) the presence of both cavitation and a positive culture at completion of 2 months of therapy

Patients At Increased Risk of Relapse

Patients who have cavitation on initial chest radiograph and who have a positive culture at completion of 2 months of therapy are at substantially increased risk of relapse. For these patients it is recommended that the continuation phase of treatment be prolonged to 7 months, making a total treatment period of 9 months.

was associated with a 21% rate of relapse, compared with 2% for patients who had neither risk factor (Table 11). Similar findings were reported in a retrospective analysis of data from BMRC trials (*17*) and from a USPHS trial conducted in Poland (*19*).

The most effective means of decreasing the likelihood of relapse for patients at increased risk has not yet been determined by clinical trials. However, in a controlled trial of treatment for silicotuberculosis in Hong Kong, prolongation of the continuation phase from 4 to 6 months decreased the rate of relapse from 22 to 7% ($p < 0.025$) (*20*). Also in studies from Hong Kong, it was found that increasing the duration of PZA beyond the 2-month initial phase did not improve the efficacy of RIF-containing regimens (*21*). It has been reported that for patients at high risk of relapse, prolongation of the once weekly INH–rifapentine continuation phase from 4 to 7 months resulted in significantly better results compared with patients in an earlier trial (*4*).

In view of this evidence and on the basis of expert opinion, it is recommended that treatment for patients who have cavitation noted on the initial chest radiograph and who have positive cultures at completion of 2 months of therapy should be extended with INH and RIF for an additional 3 months for a total of 9 months (Rating AIII).

In USPHS Study 22 patients treated with INH and RIF twice weekly in the continuation phase who had *either* cavitation on the initial chest radiograph *or* a positive culture at 2 months had approximately a 5–6% rate of relapse (Table 11) (*18*). This rate of adverse outcomes is not deemed to be sufficient to recommend prolongation of the continuation phase; however, patients with one or the other of these risk factors should be monitored more closely and consideration given to lengthening treatment if there are suggestions of a poor response. Additional factors to be considered in deciding to prolong treatment in patients with either cavitation or a positive culture at 2 months (but not both) might include being more than 10% underweight at diagnosis, having HIV infection, or having extensive involvement on chest radiograph.

Patients with noncavitary pulmonary tuberculosis and a negative AFB smear at 2 months who are started on the once weekly rifapentine–INH continuation phase and are subsequently found to be culture positive at 2 months should have treatment extended by an additional 3 months for a total of 9 months.

5.6. Definition of Completion of Therapy

Treatment for a defined duration without accounting for the number of doses taken can result in undertreatment. Therefore, the determination of whether or not treatment has been completed is based on the total number of doses taken—not solely on the duration of therapy (Table 2). For example, the 6-month daily (given 7 days/week) regimen should consist of at least 182 doses of INH and RIF, and 56 doses of PZA. If the drugs are administered by DOT at 5 days/week, the minimum number of doses is 130. A similar reduction in the target number of doses for 5-day-a-week administration applies to any of the regimens with a daily component.

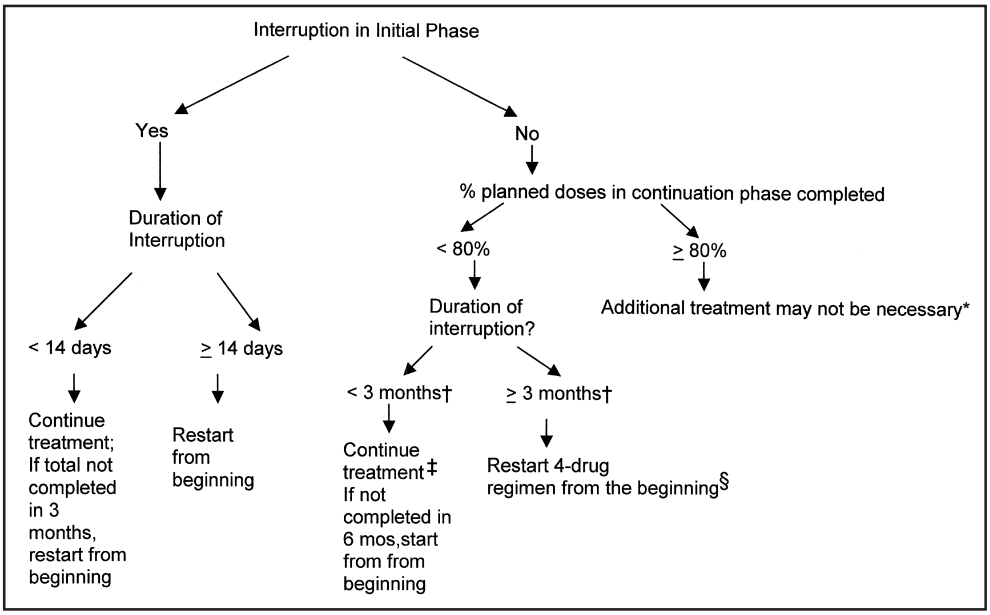
In some cases, either because of drug toxicity or nonadherence to the regimen, the specified number of doses cannot be administered within the targeted time period. In such cases, it is recommended that all of the specified number of doses for the initial phase be delivered within 3 months and those for the 4-month continuation phase be delivered within 6 months, so that the 6-month regimen should be completed within 9 months. If these targets are not met the patient must be considered to have interrupted therapy and be managed as described below.

5.7. Interruptions in Therapy

Interruptions in therapy are common in the treatment of tuberculosis. When interruptions occur, the person responsible for supervision must decide whether to restart a complete course of treatment or simply to continue as intended originally. This decision depends in part on whether the interruption occurred during the initial or the continuation phase of therapy. In general, the earlier the break in therapy and the longer its duration, the more serious the effect and the greater the need to restart the treatment from the beginning. Continuous treatment is more important in the initial phase of therapy, when there is the highest bacillary population and the chance of developing drug resistance is greatest. During the continuation phase, the number of bacilli is much smaller and the goal of therapy is to kill the persisting organisms. The duration of the interruption and the bacteriological status of the patient before and after the interruption are also important considerations.

There is no evidence on which to base detailed recommendations for managing interruptions in treatment, and no recommendations will cover all of the situations that may arise. The following approach (summarized in Figure 5), modified from the New York City Bureau of Tuberculosis Control Clinical Policies and Protocols (*22*), is presented as an example. If the interruption occurs during the initial phase of treatment and the lapse is 14 days or more in duration, treatment should be restarted from the beginning. However, if the lapse is less than 14 days, the treatment regimen should be continued. In either instance the total number of doses targeted for the initial phase should be given. If the interruption in treatment occurs during the continuation phase after the patient has received more than 80% of the planned total continuation

FIGURE 5. Management of treatment interruptions



* Patients who were initially AFB smear-positive should receive additional therapy.
† Recheck smears and cultures (if positive, check drug susceptibility results). Start DOT if not already being used.
‡ If repeat culture is positive, restart four-drug regimen while waiting for drug susceptibility results. If repeat culture is negative, continue therapy to complete regimen within 9 months of original start date.
§ If repeat culture is positive, continue four-drug regimen while waiting for drug susceptibility results. If repeat culture is negative, consider stopping therapy if patient has received a total of 9 months of therapy.

phase doses given by DOT, further treatment may not be necessary if the patient's sputum was AFB smear negative on initial presentation. However, for patients who were smear positive initially, continued treatment to complete the planned total number of doses is warranted. If the patient has received less than 80% of the planned total doses and the lapse is 3 months or more in duration, treatment should be restarted from the beginning. If the lapse is less than 3 months in duration, treatment should be continued to complete a full course.

At the time the patient is returned to treatment sputum cultures should be obtained and repeat drug susceptibility testing performed. If the cultures are still positive, the treatment regimen should be restarted. If sputum cultures are negative the patient could be treated as having culture-negative tuberculosis and given an additional 4 months of combination chemotherapy. Regardless of the timing and duration of the interruption, DOT should be used. If the patient was already being managed with DOT, additional measures will be necessary to ensure completion of therapy.

Consultation with an expert is recommended to assist in managing treatment interruptions.

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6. Practical Aspects of Treatment

6.1. Drug Administration

The first-line antituberculosis medications should be administered together as single dose rather than in divided doses. A single dose leads to higher, and potentially more effective, peak serum concentrations. Administering a single daily dose also facilitates using DOT. Ingestion with food delays or moderately decreases the absorption of antituberculosis drugs (*1*). However, given the wide therapeutic margin of the first-line agents, the effects of food are of little clinical significance. Thus, if patients have epigastric distress or nausea with the first-line drugs, dosing with food is recommended. Administration with food is preferable to splitting a dose or changing to a second-line drug. The absorption of INH can be substantially decreased when the drug is ingested with glucose or lactose. Because of this effect, the commercial preparation of INH elixir uses sorbitol for flavor, rather than glucose or lactose. However, sorbitol can cause diarrhea, limiting the acceptability of the commercial INH elixir. Administration of crushed INH tablets in a food with relatively low concentrations of glucose, such as applesauce, has not been formally evaluated, but has been used successfully by many providers.

Antacids have minimal effects on the absorption of the first-line antituberculosis drugs. With the exception of fluoroquinolones, there is little information regarding the effect of food and antacids on the second-line antituberculosis drugs. In the absence of data, it is preferable to administer the drugs on an empty stomach if they are tolerated. However, antacids and other medications containing divalent cations markedly decrease the absorption of the fluoroquinolones, an interaction that has been associated with failure of antibiotic therapy (*2,3*). Therefore, it is critical that any fluoroquinolone not be administered within 2 hours of a dose of antacids, the chewable tablet form of didanosine, sucralfate, iron, magnesium, calcium, zinc, or vitamins or dietary supplements (e.g., Ensure®, Sustical®) containing a significant amount of these cations.

Parenteral therapy is indicated for severely ill patients who cannot take oral therapy and may be useful for the uncommon patient for whom poor absorption has been documented. Preparations of INH, RIF, the aminoglycosides, capreomycin, and most fluoroquinolones are available for intravenous administration.

6.2. Fixed-Dose Combination Preparations

There are two fixed-dose combination preparations currently available for use in the United States, a combination of INH and RIF (Rifamate®) and a combination of INH, RIF, and PZA (Rifater®) (see Section 3: Drugs in Current Use). (A four-drug combination of INH, RIF, EMB, and PZA is available in some countries.) Two tablets of Rifamate® provide conventional daily doses of both INH (300 mg) and RIF (600 mg). The Rifater® tablet that is available in the United States contains INH (50 mg), RIF (120 mg), and PZA (300 mg). Six tablets of Rifater® would provide INH (300 mg) RIF (720 mg), and PZA (1,800 mg). The RIF dose is higher than is used typically in the United States because the RIF is less bioavailable in this formulation. These fixed-dose combinations have been formulated for use in daily therapy, although some programs use Rifamate® plus INH tablets for twice weekly treatment. It should be noted that the dose of PZA in Rifater® is such that additional PZA tablets will be required to provide an adequate dose for persons weighing more than 90 kg.

Although there is no evidence indicating that fixed-dose combination medications are superior to individual drugs, expert opinion suggests that these formulations should be used when DOT is given daily and when DOT is not possible. Moreover, they are strongly recommended in international recommendations of the WHO and IUATLD. The theoretical advantage of reducing the risk of inadvertent monotherapy, the ease of administration, and the potential for reducing medication errors make them preferable to individual medications in many instances. When prescribing a fixed-dose combination preparation, care must be taken because of the

similarity of the trade names of RIF (Rifadin®) and the fixed-dose combinations (Rifamate®, Rifater®).

6.3. Management of Common Adverse Effects

As is true with all medications, combination chemotherapy for tuberculosis is associated with a predictable incidence of adverse effects, some mild, some serious. A comprehensive list of reported adverse reactions and their frequency is described in Section 3: Drugs in Current Use.

Mild adverse effects can generally be managed with symptomatic therapy, whereas with more severe effects the offending drug or drugs must be discontinued. Although it is important to be attuned to the potential for adverse effects it is at least equally important that first-line drugs not be stopped without adequate justification.

The following is a summary, based largely on clinical experience and expert opinion, of the approaches that should be taken in managing the common adverse effects of tuberculosis treatment. Proper management of more serious adverse reactions often requires expert consultation.

6.3.1. Gastrointestinal upset: nausea, vomiting, poor appetite, abdominal pain

Gastrointestinal reactions are common, particularly in the first few weeks of therapy. Many of the antituberculosis drugs can cause gastrointestinal upset (*4*). In the presence of gastrointestinal symptoms serum AST and bilirubin should be measured. If the AST level is less than three times the upper limit of normal, the symptoms are assumed not to be due to hepatic toxicity. However, if the AST level is three or more times the upper limit of normal the symptoms should be assumed to represent hepatic toxicity, and the patient should be evaluated as described below.

The initial approach to gastrointestinal intolerance, not associated with hepatic toxicity, is to change the hour of drug administration and/or to administer the drugs with food. If patients are taking daily DOT, the timing of the drug administration should be altered, preferably to be closer to mealtime. Alternatively, food can be taken at the time of DOT administration. (In many programs food is offered as an incentive with DOT.) Patients receiving self-administered therapy can take the medications at bedtime. If gastrointestinal intolerance persists it may be best for all medications to be taken with meals.

6.3.2. Rash

All drugs used in treating tuberculosis can cause a rash. The response to a patient with a rash depends on its severity. The rash may be minor, affecting a limited area or being predominantly manifested as itching, in which case antihistamines should be given for symptomatic relief, but all antituberculosis medications can be continued. A petechial rash may suggest thrombocytopenia in patients taking RIF (*5*). The platelet count should be checked and, if low, RIF hypersensitivity should be presumed to be the cause. RIF should be stopped and the platelet count monitored until it returns to baseline; RIF should not be restarted. If there is a generalized erythematous rash, especially if it is associated with fever and/or mucous membrane involvement, all drugs should be stopped immediately. If the patient has severe tuberculosis, three new drugs (e.g., an aminoglycoside and two oral agents) should be started. When the rash is substantially improved the medications can be restarted one by one, at intervals of 2–3 days. RIF should be restarted first (because it is the least likely to cause rash, and it is the most important agent), followed by INH, and then EMB or PZA. If the rash recurs the last drug added should be stopped. If no rash appears after the first three drugs have been restarted, the fourth drug should not be restarted unless the rash was relatively mild and the fourth drug is considered essential for therapy.

6.3.3. Drug fever

Recurrence of fever in a patient who has been receiving therapy for several weeks should suggest drug fever, especially if the patient is showing microbiological and radiographic improvement. It should be noted, however, that fever from tuberculosis may persist for as long as 2 months after therapy has been initiated (*6*). Fever may also be a manifestation of a paradoxical reaction, especially in patients with HIV infection (see Section 8.1: HIV Infection) (*7*). The clinical hallmark of drug fever is that the patient looks and feels well despite having a high fever (often greater than 39°C). There is no specific pattern to the fever. Eosinophilia may or may not be present.

The first step in management of a possible drug fever is to ensure that there is no superinfection or worsening of tuberculosis. If these potential causes are excluded all drugs should be stopped. Drug-related fever usually will resolve within 24 hours. Patients with severe tuberculosis should be given at least three new drugs in the interim. Once the fever has resolved, the same protocol as described above for restarting drugs in the presence of a rash should be followed.

6.3.4. Hepatitis

(Management of patients with baseline abnormal liver function is described in Section 8.8: Hepatic Disease.) Three of the first-line antituberculosis drugs, INH, RIF, and PZA, can cause drug-induced liver injury (AST level three or more times the upper limit of normal in the presence of symptoms, or five or more times the upper limit of normal in the absence of

symptoms) (*8*). If the AST level is less than 5 times the upper limit of normal, toxicity can be considered mild, an AST level 5–10 times normal defines moderate toxicity, and an AST level greater than 10 times normal (i.e., greater than 500 IU) is severe (*9*). In addition to AST elevation, occasionally there are disproportionate increases in bilirubin and alkaline phosphatase. This pattern is more consistent with rifampin hepatotoxicity

It is important to note that an asymptomatic increase in AST concentration occurs in nearly 20% of patients treated with the standard four-drug regimen (*10*). In the absence of symptoms therapy should *not* be altered because of modest asymptomatic elevations of AST, but the frequency of clinical and laboratory monitoring should be increased. In most patients, asymptomatic aminotransferase elevations resolve spontaneously. However, if AST levels are more than five times the upper limit of normal (with or without symptoms) or more than three times normal in the presence of symptoms, hepatotoxic drugs should be stopped immediately and the patient evaluated carefully. Similarly, a significant increase in bilirubin and/or alkaline phosphatase is cause for a prompt evaluation. Serologic testing for hepatitis A, B, and C should be performed and the patient questioned carefully regarding symptoms suggestive of biliary tract disease and exposures to other potential hepatotoxins, particularly alcohol and hepatotoxic medications. Drug-induced hepatitis is usually a diagnosis of exclusion but in view of the frequency with which other possible causes are present in any given patient, determining the cause may be difficult.

Because the schedule for restarting antituberculosis medications is slower with hepatitis than for rash or drug fever it is generally prudent to give at least three nonhepatotoxic antituberculosis drugs until the specific cause of hepatotoxicity can be determined and an appropriate longer term regimen begun. The suspect antituberculosis medications should be restarted one at a time after the AST concentration returns to less than two times the upper limit of normal. (In patients with elevated baseline AST from preexisting liver disease, drugs should be restarted when the AST returns to near baseline levels.) Because RIF is much less likely to cause hepatotoxicity than is INH or PZA (Table 10) (*10*) and is the most effective agent, it should be restarted first. If there is no increase in AST after about 1 week, INH may be restarted. PZA can be started 1 week after INH if AST does not increase. If symptoms recur or AST increases the last drug added should be stopped. If RIF and INH are tolerated, and hepatitis was severe, PZA should be assumed to be responsible and should be discontinued. In this last circumstance, depending on the number of doses of PZA taken, severity of disease, and bacteriological status, therapy might be extended to 9 months.

6.4. Serum Drug Concentration Measurements

The first-line drugs (INH, RIF, PZA, and EMB) have relatively predictable pharmacokinetics (*11,12*) and are highly efficacious when given in standard doses as DOT (*13,14*). Rarely, patients may have poor absorption or altered metabolism of the first-line drugs, resulting in failure of therapy (*15,16*) Second-line agents have a much narrower therapeutic window (the range of concentrations having reliable activity against *M. tuberculosis* but rarely causing toxicity) than the first-line drugs, and the consequences of treatment failure of drug-resistant tuberculosis may be difficult to manage. These considerations suggest several clinical situations in which therapeutic drug monitoring may be helpful: 1) patients with treatment failure that is not explained by nonadherence or drug resistance, 2) persons with medical conditions that may result in abnormal pharmacokinetics of the first-line drugs, and 3) the management of multidrug-resistant tuberculosis with second-line drugs. Be aware, however, that there are many uncertainties about the use of therapeutic drug monitoring in tuberculosis treatment. An important limitation is the lack of sufficient data to formulate clinically validated therapeutic ranges for antituberculosis agents. One response to the lack of clinically derived therapeutic ranges for the rifamycins is to use the distribution of concentrations achieved in healthy volunteers as the therapeutic range. However, in practice this approach has been quite problematic. For example, serum concentrations of the first-line drugs among HIV-infected patients with active tuberculosis are frequently lower than those in healthy volunteers (*17,18*), but HIV-related tuberculosis responds well to standard tuberculosis treatment regimens (*19,20*).

The disadvantages of therapeutic drug monitoring are as follows: 1) the time necessary, from both patients and providers, to obtain and ship blood samples, and 2) the relatively high cost of measuring serum drug concentrations.

Until more data are available, it seems prudent to restrict therapeutic drug monitoring for the first-line drugs to patients who are having an inadequate response to DOT (that is not due to nonadherence or drug resistance) or evidence of severe gastrointestinal or metabolic abnormalities. Examples of such circumstances include severe gastroparesis, short-bowel syndrome, chronic diarrhea with malabsorption, and renal insufficiency. As described above, patients with HIV-related tuberculosis may have an increased incidence of malabsorption of antituberculosis drugs (although some studies have contrary findings) (*21,22*). Even if true, this tendency for lower drug concentrations among patients with HIV-related tuberculosis is not sufficient to warrant routine therapeutic drug monitoring in this population.

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7. Drug Interactions

7.1. Interactions Affecting Antituberculosis Drugs

Drug–drug interactions can result in changes in the concentrations of one or both of the drugs involved. In the case of the antituberculosis drugs, there are relatively few interactions that substantially change the concentrations of the antituberculosis drugs; much more often the antituberculosis drugs cause clinically relevant changes in the concentrations of other drugs. The exceptions to this general rule are rifabutin and the fluoroquinolones.

Rifabutin is partially metabolized by cytochrome P450 (CYP) 3A. Inhibitors of CYP3A increase serum concentrations of rifabutin and one of its metabolites (25-*O*-desacetyl-rifabutin), sometimes to toxic levels. For example, administration of ritonavir, a potent CYP3A inhibitor, with the standard daily dose of rifabutin (300 mg) increases the serum concentrations of rifabutin (4-fold increase) and 25-*O*-desacetyl-rifabutin (35-fold increase) (*1*) and is associated with increased rates of leukopenia, arthralgias, skin discoloration, and uveitis (*2*), all recognized to be toxic effects of rifabutin or one of its metabolites (*3,4*). Conversely, administering rifabutin with a CYP3A inducer decreases its concentrations, perhaps to ineffective levels. For example, efavirenz, a potent antiretroviral drug, decreases rifabutin serum concentrations by approximately one-third (*5*).

Recommendations for making dose adjustments of rifabutin when it is given with commonly used CYP3A inhibitors and inducers are available (*6,7*). However, the complexity of these interactions and the rapidly changing nature of antiretroviral therapy strongly suggest that the management of cases of HIV-related tuberculosis should involve a physician with experience in this field.

Absorption of the fluoroquinolones is markedly decreased by ingestion with medications containing divalent cations (calcium, iron, zinc), including antacids (*8,9*); supplements or vitamins containing calcium, iron or zinc (*10*), sucralfate (*11*); and the chewable tablet formulation of didanosine (*12*). These drug interactions can be avoided by assuring that medications containing divalent cations are ingested at least 2 hours apart from doses of fluoroquinolones (*13*).

7.2. Effects of Antituberculosis Drugs on Other Drugs

7.2.1. Drug interactions due to rifamycins

The drugs used to treat tuberculosis affect the metabolism of many other drugs, and can result in a lack of efficacy (interactions with the rifamycins) or toxicity (interactions with isoniazid and the fluoroquinolones). Most of the clinically relevant drug–drug interactions involving the antituberculosis drugs are due to the effect of the rifamycins (rifampin, rifabutin, and rifapentine) on the metabolism of other drugs. All of the rifamycins are inducers of a variety of metabolic pathways, particularly those involving the various isozymes of the cytochrome P450 system (*14–18*). By inducing the activity of metabolic enzymes, rifamycin therapy results in a decrease in the serum concentrations of many drugs, sometimes to levels that are subtherapeutic. The rifamycins differ substantially in their potency as enzyme inducers; rifampin is the most potent, rifapentine is intermediate, and rifabutin is the least potent enzyme inducer (*19*).

The well-described, clinically relevant drug–drug interactions involving the rifamycins are presented in Table 12 (*1,5,15,20–88*). However, it is important to note that many possible interactions involving the rifamycins have not been investigated fully and additional clinically relevant interactions undoubtedly will be described. Therefore, it is important to check all concomitant medications for possible, as well as confirmed, drug–drug interactions with rifamycins.

Some of these drug–drug interactions can be managed with close clinical or laboratory monitoring and dose increases of the medication(s) affected by the rifamycins (Table 12). In other cases, the magnitude of the decrease in concentrations of a concomitant medication may be such that serum concentrations cannot be restored by a dose increase. If the dose of a medication is increased to compensate for the effect of a rifamycin, it is critical to remember that the dose of this drug will probably need to be decreased within the 2 weeks after the rifamycin is discontinued and its inductive effect resolves.

In some situations, rifabutin can sometimes be used in place of rifampin, if there is an unacceptable drug–drug interaction between rifampin and another drug, such as cyclosporine (*51*) and most of the HIV-1 protease inhibitors (*89*). All the rifamycins may cause unacceptable decreases in the serum concentrations of certain drugs, such as delavirdine (*26,27,90*), ketoconazole and itraconazole (*34,91*).

7.2.2. Drug interactions due to isoniazid

Isoniazid is a relatively potent inhibitor of several cytochrome P450 isozymes (CYP2C9, CYP2C19, and CYP2E1) (*92*), but has minimal effect on CYP3A (*20*). As an inhibitor, isoniazid can increase concentrations of some drugs to the point of toxicity. The clearest examples of toxicity due to the inhibitory activity of isoniazid are the anticonvulsants, phenytoin (*93,94*) and carbamazepine (*95,96*). Isoniazid also increases concentrations of benzodiazepines metabolized by oxidation, such as diazepam (*85*) and triazolam (*97*), but not those metabolized by conjugation, such as oxazepam (*97*). It is worth noting that rifampin has the opposite effect on the serum concentrations of many of these drugs. The available data demonstrate that the inductive effect of rifampin outweighs the inhibitory effect of isoniazid, so that the overall effect of combined therapy with rifampin and isoniazid is a decrease in the concentrations of drugs such as phenytoin (*59*) and diazepam (*85*).

Isoniazid may increase toxicity of other drugs—acetaminophen (*98*), valproate (*99*), serotonergic antidepressants (*100*), disulfiram (*101*), warfarin (*102*), and theophylline (*103*)—but these potential interactions have not been well studied.

7.2.3. Drug interactions due to fluoroquinolones

Ciprofloxacin (*104*) inhibits the metabolism of theophylline and can cause clinical theophylline toxicity (*105*). However, levofloxacin (*106*), gatifloxacin (*107*), and moxifloxacin (*108*) do not affect theophylline metabolism.

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(Includes references cited in Table 12.)

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TABLE 12. Clinically significant drug–drug interactions involving the rifamycins*

Drug class	Drugs whose concentrations are substantially decreased by rifamycins (references)	Comments
Antiinfectives	HIV-1 protease inhibitors (saquinavir, indinavir, nelfinavir, amprenavir, ritonavir, lopinavir/ritonavir) (*1,20–25*)	Can be used with rifabutin. Ritonavir, 400–600 mg twice daily, probably can be used with rifampin. The combination of saquinavir and ritonavir can also be used with rifampin.
	Nonnucleoside reverse transcriptase inhibitors Delavirdine (*26,27*) Nevirapine (*28*) Efavirenz (*29*)	Delavirdine should not be used with any rifamycin. Doses of nevirapine (*28*) and efavirenz (*29*) need to be increased if given with rifampin, no dose increase needed if given with rifabutin (*5*).
	Macrolide antibiotics (clarithromycin, erythromycin) (*30–32*)	Azithromycin has no significant interaction with rifamycins.
	Doxycycline (*33*)	May require use of a drug other than doxycycline.
	Azole antifungal agents (ketoconazole, itraconazole, voriconazole) (*34–38*)	Itraconazole, ketoconazole, and voriconazole concentrations may be subtherapeutic with any of the rifamycins. Fluconazole can be used with rifamycins, but the dose of fluconazole may have to be increased.
	Atovaquone (*39*)	Consider alternate form of *Pneumocystis carinii* treatment or prophylaxis.
	Chloramphenicol (*40*)	Consider an alternative antibiotic.
	Mefloquine (*41*)	Consider alternate form of malaria prophylaxis.
Hormone therapy	Ethinylestradiol, norethindrone (*42–44*)	Women of reproductive potential on oral contraceptives should be advised to add a barrier method of contraception when taking a rifamycin.
	Tamoxifen (*45*)	May require alternate therapy or use of a nonrifamycin-containing regimen.
	Levothyroxine (*46,47*)	Monitoring of serum TSH recommended; may require increased dose of levothyroxine.
Narcotics	Methadone (*48,49*)	Rifampin and rifapentine use may require methadone dose increase; rifabutin infrequently causes methadone withdrawal.
Anticoagulants	Warfarin (*50*)	Monitor prothrombin time; may require two- to threefold dose increase.
Immunosuppressive agents	Cyclosporine, tacrolimus (*51–53*)	Rifabutin may allow concomitant use of cyclosporine and a rifamycin; monitoring of cyclosporine serum concentrations may assist with dosing.
	Corticosteroids (*54–57*)	Monitor clinically; may require two- to threefold increase in corticosteroid dose (*58*).
Anticonvulsants	Phenytoin (*59*), lamotrigine (*60*)	Therapeutic drug monitoring recommended; may require anticonvulsant dose increase.
Cardiovascular agents	Verapamil (*61*), nifedipine (*62,63*), diltiazem (a similar interaction is also predicted for felodipine and nisoldipine)	Clinical monitoring recommended; may require change to an alternate cardiovascular agent.
	Propranolol (*64*), metoporol (*65*)	Clinical monitoring recommended; may require dose increase or change to an alternate cardiovascular drug.
	Enalapril (*66*), losartan (*67*)	Monitor clinically; may require a dose increase or use of an alternate cardiovascular drug.
	Digoxin (among patients with renal insufficiency) (*68*), digitoxin (*69*)	Therapeutic drug monitoring recommended; may require digoxin or digitoxin dose increase.
	Quinidine (*70,71*)	Therapeutic drug monitoring recommended; may require quinidine dose increase.
	Mexilitine (*72*), tocainide (*73*), propafenone (*15*)	Clinical monitoring recommended; may require change to an alternate cardiovascular drug.
Bronchodilators	Theophylline (*74*)	Therapeutic drug monitoring recommended; may require theophylline dose increase.
Sulfonylurea hypoglycemics	Tolbutamide, chlorpropamide, glyburide, glimepiride, repaglinide (*75–79*)	Monitor blood glucose; may require dose increase or change to an alternate hypoglycemic drug.
Hypolipidemics	Simvastatin (*80*), fluvastatin (*81*)	Monitor hypolipidemic effect; may require use of an alternate hypolipidemic drug.
Psychotropic drugs	Nortriptyline (*82*)	Therapeutic drug monitoring recommended; may require dose increase or change to alternate psychotropic drug.
	Haloperidol (*83*), quetiapine (*84*)	Monitor clinically; may require a dose increase or use of an alternate psychotropic drug.
	Benzodiazepines (e.g., diazepam [*85*], triazolam [*86*]), zolpidem (*87*), buspirone (*88*)	Monitor clinically; may require a dose increase or use of an alternate psychotropic drug.

* For reference citations refer to Section 7.2.

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8. Treatment in Special Situations

8.1. HIV Infection

Treatment of tuberculosis in patients with HIV infection follows the same principles as treatment of HIV-uninfected patients. However, there are several important differences between patients with and without HIV infection. These differences include the potential for drug interactions, especially between the rifamycins and antiretroviral agents, paradoxical reactions that may be interpreted as clinical worsening, and the potential for the development of acquired resistance to rifamycins when treated with highly intermittent therapy.

8.1.1. Clinical trials of treatment for tuberculosis in HIV-infected patients

There have been seven prospective studies of 6-month regimens for the treatment of pulmonary tuberculosis in patients with HIV infection for which recurrence data were reported. Four of the studies were randomized, controlled trials (*1–4*),

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The treatment of tuberculosis in persons with HIV infection is essentially the same as for patients without HIV infection. There are two important exceptions to this generalization: 1) Once weekly INH–rifapentine in the continuation phase should not be used in any HIV-infected patient; and 2) twice weekly INH–RIF or rifabutin should not be used for patients with $CD4^+$ lymphocyte counts less than 100/µl. Providers must be alert to the potential for interactions among many of the antiretroviral drugs and the rifamycins. Paradoxical reactions that mimic worsening of tuberculosis are more common in patients with HIV infection and may complicate therapy.

and three were observational in nature (*5,6*). These studies differed somewhat in design, patient population, eligibility criteria, frequency of dosing, treatment supervision, and outcome definitions; therefore, it is difficult to provide meaningful cross-study comparisons. All of the studies reported a good early clinical response to therapy and the time required for sputum culture conversion from positive to negative and treatment failure rates were similar to these indices of treatment efficacy in patients without HIV infection.

Recurrence rates have varied among studies, with most reporting rates of 5% or less (*2,3,5,6*). In one study from the Democratic Republic of Congo (formerly Zaire), in which the recurrence rate in the 6-month arm was 9% compared with 3% in the 12-month arm, nonadherence in the continuation phase and/or exogenous reinfection may have contributed to the higher recurrence rate (*1*). In a randomized trial of once weekly INH-rifapentine versus twice weekly INH–RIF in the continuation phase of therapy, 5 of 30 (17%) HIV-infected patients receiving treatment in the once weekly arm relapsed compared with 3 of 31 (10%) patients in the twice weekly INH–RIF arm (*4*). Four of the five relapsed patients in the once weekly group had resistance to rifampin alone compared with none in the standard treatment arm. Because of the small sample size in the standard treatment arm, it is difficult to interpret the relapse rate of 10%.

In an observational study of twice weekly INH–rifabutin among HIV-infected tuberculosis patients also receiving antiretroviral therapy, 7 of 156 patients failed treatment or relapsed (*7*). Although the life table rate of failure/relapse was low (4.6%), *M. tuberculosis* isolated from all five of these patients was resistant to RIF alone. The phenomenon of acquired rifampin monoresistance was also seen in a trial of largely twice weekly INH–RIF therapy, albeit at a lower rate (*3*). In all of these studies, acquired RIF resistance occurred only among patients with $CD4^+$ cell counts <100 cells/µl. Acquired rifampin resistance has not been seen in trials where RIF was given daily.

A consistent finding in the treatment studies has been a high mortality rate among HIV-seropositive patients. In most studies the cause of death is difficult to ascertain. Early mortality may be related to advanced tuberculosis, but deaths during the continuation phase of therapy are usually due to other AIDS-related conditions. Mortality during treatment among HIV-infected patients with tuberculosis has been associated with advanced HIV disease (*1,3,6,8*). However, the use of effective antiretroviral therapy during the treatment of tuberculosis in persons with HIV infection may improve treatment outcomes and, thus, is recommended, as described subsequently (*9*).

A major concern in treating tuberculosis in the setting of HIV infection is the interaction of RIF with antiretroviral agents (see Section 7: Drug Interactions, and Table 12). As described previously, rifabutin is highly active against *M. tuberculosis* but has less of an effect in inducing hepatic microsomal enzymes than RIF. Data from clinical trials suggest that rifabutin and RIF-based regimens are equally efficacious. Gonzalez-Montaner and colleagues (*10*) reported the first randomized clinical trial comparing rifabutin (150 and 300 mg) with RIF in a 6-month regimen in persons without HIV infection. The outcomes were highly favorable in both groups and there were few adverse reactions.

Investigators from South Africa reported a randomized, open-label trial comparing rifabutin with RIF in a standard four-drug regimen administered with DOT (*11*). Although patients did not have HIV testing performed, the HIV seroprevalence was reportedly low at the time of the study. In the continuation phase, the medications were given twice weekly. By 2 months after treatment was begun, 88% of the patients in the RIF arm and 92% of those given rifabutin had negative sputum cultures. The relapse rate was 3.8% in the RIF group versus 5.1% in the rifabutin group (p = NS).

Only one study examining the effectiveness of rifabutin included HIV-infected patients (*12*). A single blind randomized study of 50 HIV-infected patients in Uganda compared a fully supervised regimen of RIF versus rifabutin together with INH, EMB, and PZA. Time to sputum conversion was similar between groups when controlling for baseline characteristics. Relapse data were not available.

Investigators in Uganda have reported a higher mortality rate among HIV-infected patients treated with regimens that did not contain RIF. Wallis and associates (*13*) reported that a

non-RIF-containing regimen was associated with shortened survival compared with an RIF-based regimen. In addition to the higher mortality associated with non-RIF-based regimens, other studies have demonstrated unacceptably high recurrence rates in the setting of HIV infection (*14,15*). Thus, every effort should be made to use a rifamycin-based regimen for the entire course of therapy in persons with HIV infection.

8.1.2. Treatment recommendations

Recommendations for the treatment of tuberculosis in HIV-infected adults are, with two exceptions, identical to those for HIV-uninfected adults: a 6-month regimen consisting of an initial phase of INH, RIF, PZA, and EMB given for 2 months followed by INH and RIF for 4 months when the disease is caused by organisms that are known or presumed to be susceptible to the first-line agents. This regimen may be given by daily or intermittent administration as listed in Table 1 and described in Section 5.2: Recommended Regimens. However, on the basis of data showing an increased frequency of rifamycin resistance among patients having $CD4^+$ cell counts <100/µl, it is recommended that patients with advanced HIV disease be treated with daily or three times weekly therapy in the continuation phase (Rating AIII) (*16*). Twice weekly drug administration in the continuation phase should not be used in patients with $CD4^+$ cell counts <100/µl. Twice weekly therapy may be considered in patients with less advanced immunosuppression ($CD4^+$ cell counts ≥100/µl). Once weekly administration of INH–rifapentine in the continuation phase should not be used in any patient with HIV infection.

Six months should be considered the minimum duration of treatment for adults, even for patients with culture-negative tuberculosis. If there is evidence of a slow or suboptimal response (e.g., cultures are still positive after 2 months of therapy), prolongation of the continuation phase to 7 months (a total of 9 months treatment) should be strongly considered. DOT and other adherence-promoting strategies should be used in all patients with HIV-related tuberculosis. Although there are no data on which to base recommendations, the American Academy of Pediatrics recommends that for HIV-infected children the minimum duration of therapy be 9 months (*17*).

All patients with tuberculosis should be advised to undergo voluntary counseling and HIV testing. Efforts should be made to engage all patients with a new diagnosis of HIV infection in HIV care during their treatment for tuberculosis. Ideally, patients should be managed by physicians who are expert in the treatment of tuberculosis/HIV coinfection. If the HIV care provider and tuberculosis care provider are not the same person, communication between them is essential and should occur frequently throughout the course of treatment.

8.1.3. Safety and tolerability

The frequency of antituberculosis drug-related toxicity in patients with HIV infection has varied from study to study. In a retrospective study from San Francisco, 18% of HIV-seropositive patients with tuberculosis had a change of regimen because of adverse drug reactions (*18*). RIF was the drug implicated most commonly, producing an adverse reaction in 12% of the patients. In the Democratic Republic of Congo, 11% of the seropositive patients developed a rash but in none was the treatment interrupted (*1*). Paresthesia developed in 21% of the cases, suggesting the need for pyridoxine when treating tuberculosis in persons with HIV infection.

Other investigators have reported low rates of significant adverse reactions (*3,5,6,19*). In the three times weekly regimen studied in Haiti, there were no differences in adverse events between HIV-infected and uninfected patients (*6*). In HIV-infected patients it is often difficult to distinguish an adverse reaction to antituberculosis drugs from the effects of associated conditions or reactions to any of the many medications that are often being taken concurrently. Because of the difficulties in diagnosing a drug reaction and in determining the responsible agent, the first-line antituberculosis drugs (especially INH or RIF) should not be stopped permanently without strong evidence that the antituberculosis drug was the cause of the reaction. In such situations consultation with an expert in treating tuberculosis in persons with HIV infection is recommended.

In a study reported by Ungo and associates (*20*), it was demonstrated that the relative risk of developing drug-induced hepatoxicity in tuberculosis patients with hepatitis C virus or HIV infection was 5- and 4-fold, respectively, compared with a 14-fold relative risk in patients with both hepatitis C virus and HIV infections. This finding was not confirmed in a study from Baltimore, in which rates of transaminase elevation were not greater in patients with HIV and hepatitis C virus who were given INH (*21*). Current IDSA and USPHS guidelines recommend screening all HIV-infected patients for hepatitis C virus (*22*). Until more data are available it is probably prudent to provide more frequent clinical and laboratory monitoring, as described for patients with preexisting liver disease, for patients with HIV infection or hepatitis C virus infection who are being treated for tuberculosis.

8.1.4. Concurrent administration of antiretroviral agents and rifamycins

Most patients with tuberculosis have relatively advanced HIV disease and, thus, antiretroviral therapy is indicated (*23*). Antiretroviral therapy should not be withheld simply because the patient is being treated for tuberculosis, if it is otherwise

indicated. Nevertheless, it is not advisable to begin both antiretroviral therapy and combination chemotherapy for tuberculosis at nearly the same time. So doing may involve as many as eight new drugs with interactions and overlapping toxicities that would be difficult to evaluate. Although there are few data on which to base recommendations, expert opinion suggests that treatment for tuberculosis should be initiated first.

Although antiretroviral therapy has a dramatic effect in decreasing progression of HIV disease (decreasing $CD4^+$ cell counts, new opportunistic infections, or death), among patients with HIV-related tuberculosis, the use of antiretroviral therapy in the setting of tuberculosis therapy is complex. In those patients not already receiving antiretroviral therapy, early initiation of antiretroviral therapy may decrease HIV disease progression, but is also associated with a high incidence of side effects and paradoxical reactions, some severe enough to warrant discontinuation of both antiretroviral and antituberculosis drugs (*9*). In addition, starting so many new medications in a short time period may present a tremendous adherence challenge for patients adjusting to the diagnoses of both tuberculosis and AIDS. Delaying the initiation of antiretroviral therapy until 4–8 weeks after starting antituberculosis therapy has the potential advantages of being better able to ascribe a specific cause for a drug side effect, decreasing the severity of paradoxical reactions, and decreasing the adherence difficulties for the patient. Until there have been controlled studies evaluating the optimal time for starting antiretroviral therapy in patients with HIV infection and tuberculosis, this decision should be individualized, based on the patient's initial response to treatment for tuberculosis, occurrence of side effects, and ready availability of multidrug antiretroviral therapy. For patients with $CD4^+$ cell counts >350 cells/µl, the antiretroviral regimen could be initiated at any time after tuberculosis treatment was begun, based on current recommendations (*23*). For patients who are already receiving an antiretroviral regimen, treatment should generally be continued, although the regimen may need to be modified on the basis of the risk of drug–drug interactions, as described in Section 7: Drug Interactions.

Even though drug interactions are common, a rifamycin should not be excluded from the tuberculosis treatment regimen for fear of interactions with some antiretroviral agents. The exclusion of a rifamycin from the treatment regimen is likely to delay sputum conversion, will prolong the duration of therapy, and possibly result in a poorer outcome (*24*). As noted in Section 7, Drug Interactions, rifabutin has fewer interactions than RIF and should be used if these categories of antiretroviral agents are being administered.

The categories of antiretroviral agents available currently are nucleoside reverse transcriptase inhibitors (NRTIs), nucleotide reverse transcriptase inhibitors (NtRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). The NRTIs and NtRTIs do not have clinically significant drug interactions with the standard antituberculosis medications; thus, drugs in these categories can be used together with rifamycins without any dose adjustment being necessary. However, the PIs and NNRTIs, depending on the specific drug, may either inhibit or induce cytochrome P450 isoenzymes (CYP450). Thus, these drugs may alter the serum concentration of rifabutin, as described in Section 7.1: Interactions Affecting Antituberculosis Drugs.

When rifabutin is combined with antiretroviral agents, its dose and the dose of the antiretroviral agents may require adjustment. A report described the successful use of rifabutin with an antiretroviral regimen containing PIs (*25*). All 25 patients became culture negative by 2 months and no relapses were reported after a median follow-up of 13 months. Moreover, the circulating HIV RNA levels decreased significantly, with 20 of 25 patients achieving viral loads of less than 500 copies/ml. Thus, it appears that both tuberculosis and HIV can be treated successfully with concurrent use of a rifabutin-based regimen and potent combinations of antiretroviral agents.

Previous guidelines from CDC specifically stated that RIF was contraindicated in patients who were taking any PI or NNRTI (*26*). However, new data indicate that RIF can be used for the treatment of tuberculosis with certain combinations of antiretroviral agents (*27,28*). As recommended by CDC (*27*), rifampin can be used with a regimen of efavirenz and two NRTIs, with ritonavir and one or more NRTIs, with ritonavir and saquinavir (either hard-gel or soft-gel capsule), and with a triple nucleoside regimen. As new antiretroviral agents and more pharmacokinetic data become available, these recommendations are likely to be modified. Because these recommendations are frequently revised, obtaining the most up-to-date information from the CDC website, http://www.cdc.gov/nchstp/tb/, is advised. Updated information on antiretroviral drugs and drug interactions, compiled by Medscape, can be found at http://www.medscape.com/updates/quickguide.

When starting NNRTIs or PIs for tuberculosis patients receiving RIF, a 2-week "washout" period is generally recommended between the last dose of RIF and the first dose of PIs or NNRTIs to allow for reduction of the enzyme-inducing activity of RIF. During this time, rifabutin may be started to ensure that the tuberculosis treatment regimen is adequate. For patients already receiving antiretroviral agents at the time

treatment for tuberculosis is begun, an assessment of the antiretroviral regimen should be undertaken and, if necessary, changes made to ensure optimum treatment of the HIV infection during tuberculosis therapy. Conversely, the determination of whether to use RIF and the dose of the rifamycin must take into account the antiretroviral regimen.

8.1.5. Paradoxical reaction

On occasion, patients have a temporary exacerbation of symptoms, signs, or radiographic manifestations of tuberculosis (paradoxical reaction) after beginning antituberculosis treatment. Worsening of this sort occurs in patients without HIV infection, especially with lymphadenitis, but it is more common among HIV-infected patients. These reactions presumably develop as a consequence of reconstitution of immune responsiveness brought about by antiretroviral therapy or, perhaps, by treatment of the tuberculosis itself. Narita and colleagues (*29*) reported that among HIV-infected patients who were taking antiretroviral agents, 36% developed paradoxical worsening after beginning treatment for tuberculosis compared with 7% of those who were not taking antiretroviral drugs. In contrast, Wendel and colleagues (*30*) reported that only 7% of HIV-infected patients with tuberculosis developed paradoxical worsening and the reactions were not associated with antiretroviral therapy. Signs of a paradoxical reaction may include high fevers, increase in size and inflammation of involved lymph nodes, new lymphadenopathy, expanding central nervous system lesions, worsening of pulmonary parenchymal infiltrations, and increasing pleural effusions. Such findings should be attributed to a paradoxical reaction only after a thorough evaluation has excluded other possible causes, especially tuberculosis treatment failure.

A paradoxical reaction that is not severe should be treated symptomatically without a change in antituberculosis or antiretroviral therapy. Although approaches to the management of severe reactions, such as high fever, airway compromise from enlarging lymph nodes, enlarging serosal fluid collections, and sepsis syndrome, have not been studied, expert opinion suggests that prednisone or methylprednisolone be started at a dose of about 1 mg/kg and gradually reduced after 1 to 2 weeks.

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8.2. Children and Adolescents

Children most commonly develop tuberculosis as a complication of the initial infection with *M. tuberculosis* (primary tuberculosis). Radiographically, primary tuberculosis is characterized by intrathoracic adenopathy, mid- and lower lung zone infiltrates, and the absence of cavitation. However, children, occasionally, and adolescents, more frequently, develop adult-type tuberculosis (upper lobe infiltration and cavitation associated with sputum production). The lesions of primary tuberculosis have a smaller number of *M. tuberculosis* organisms than those of adult-type pulmonary tuberculosis; thus, treatment failure, relapse, and development of secondary resistance are rare phenomena among children.

Because it is more difficult to isolate *M. tuberculosis* from a child with pulmonary tuberculosis than from an adult, it is frequently necessary to rely on the results of culture and susceptibility tests of specimens from the person presumed to be the source of the infection in the child to guide the choice of drugs for the child. In children in whom drug resistance is suspected or for whom no source case isolate is available, attempts to isolate organisms via three early morning gastric aspirations (optimally during hospitalization), bronchoalveolar lavage, or tissue biopsy must be considered.

Because tuberculosis in infants and children younger than 4 years of age is more likely to disseminate, treatment should be started as soon as the diagnosis is suspected. Asymptomatic children with a positive PPD-tuberculin skin test and an abnormal chest radiograph (atelectasis, parenchymal infiltrate, or hilar adenopathy) should receive combination chemotherapy, usually with INH, RIF, and PZA as initial therapy.

Several controlled and observational trials of 6-month therapy in children with pulmonary tuberculosis caused by organisms known or presumed to be susceptible to the first-line drugs have been published (*1–9*). Six months of therapy with INH and RIF has been shown to be effective for hilar adenopathy and pulmonary disease caused by drug-susceptible organisms (*5,6*). However, most studies used 6 months of daily treatment with INH and RIF, supplemented during the first 2 weeks to 2 months with PZA. This three-drug combination has a success rate of greater than 95% and a rate of adverse effects of less than 2%. Two studies used twice or three times weekly therapy from the beginning with good results (*1,7*).

Many experts prefer to treat children with three (rather than four) drugs in the initial phase because the bacillary population is low, because many infants and children cannot tolerate the pill burden required with four oral drugs, and because of the difficulty in performing visual acuity tests in young children who are being treated with EMB. In children suspected or known to have been infected with an *M. tuberculosis* strain that is fully susceptible, the initial phase should consist of INH, RIF, and PZA. If the susceptibility of the presumed infecting strain is not known and the likelihood of failure is low (primary tuberculosis), some experts prefer to use three drugs.

However, children and adolescents with adult-type pulmonary tuberculosis, as defined above, should be treated with the four-drug initial phase regimen, unless the infecting strain is known to be susceptible (*10*). When epidemiologic circumstances (Table 6) suggest an increased risk of drug-resistant organisms being present, EMB can be used safely in a dose of about 15–20 mg/kg per day, even in children too young for routine eye testing. Older children should have monthly evaluations of visual acuity and color discrimination while taking EMB. SM, kanamycin, or amikacin can be used as the fourth drug, when necessary.

The usual doses for daily and twice weekly treatment in children are listed in Section 3, Drugs in Current Use, and shown in Table 3. Three times weekly therapy is not recommended for children. Pyridoxine is recommended for infants, children, and adolescents who are being treated with INH and who have nutritional deficiencies, symptomatic HIV infection, or who are breastfeeding.

DOT should be used for all children with tuberculosis. The lack of pediatric dosage forms of most antituberculosis medications necessitates using crushed pills and suspensions. Even when drugs are given under DOT, tolerance of the medications must be monitored closely. Parents should not be relied on to supervise DOT.

Because of the difficulties in isolating *M. tuberculosis* from children, bacteriological examinations are less useful in evaluating the response to treatment and clinical and radiographic examinations are of relatively greater importance. However, hilar adenopathy and resultant atelectasis may require 2–3 years to resolve. Thus, a persisting abnormality on chest radiographs is not necessarily a criterion for extending continuing therapy. Recognition of treatment failure or relapse in a child is subject to the same difficulties as making a diagnosis. Thus, clinical and radiographic worsening may not be accompanied by positive AFB smears or mycobacterial cultures. A decision to modify the drug regimen should not be made lightly, but often must be made on clinical grounds only.

In general, extrapulmonary tuberculosis in children can be treated with the same regimens as pulmonary disease. Exceptions may be disseminated disease, and meningitis, for which there are inadequate data to support 6-month therapy. A fourth drug is recommended in the initial phase when there is disseminated tuberculosis. The recommended duration is 9–12 months.

The optimal treatment of pulmonary tuberculosis in children and adolescents with HIV infection is unknown. The American Academy of Pediatrics recommends that initial therapy should always include at least three drugs (INH and RIF, plus PZA for the first 2 months), and the total duration of therapy should be at least 9 months (*11*).

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8.3. Extrapulmonary Tuberculosis

Tuberculosis can involve virtually any organ or tissue in the body. Nonpulmonary sites tend to be more common among children and persons with impaired immunity. To establish the diagnosis of extrapulmonary tuberculosis, appropriate specimens including pleural fluid; pericardial or peritoneal fluid; pleural, pericardial, and peritoneal biopsy specimens; lymph node tissue; and bone marrow, bone, blood, urine, brain, or cerebrospinal fluid should be obtained for AFB staining, mycobacterial culture, and drug susceptibility testing (*1*). Tissue specimens should also be examined microscopically, after routine and AFB staining, but the absence of AFB and of granulomas or even failure to culture *M. tuberculosis* does not exclude the diagnosis of tuberculosis. Bacteriological evaluation of the response to treatment in extrapulmonary tuberculosis is often limited by the difficulty in obtaining follow-up specimens. Thus, response often must be judged on the basis of clinical and radiographic findings.

The basic principles that underlie the treatment of pulmonary tuberculosis also apply to extrapulmonary forms of the disease. Although many fewer treatment studies have examined treatment of extrapulmonary tuberculosis, compared with pulmonary disease, increasing evidence, including some

randomized controlled trials, suggests that 6- to 9-month regimens that include INH and RIF are effective (*2–16*). Therefore, among patients with extrapulmonary tuberculosis, a 6- to 9-month regimen (2 months of INH, RIF, PZA, and EMB followed by 4–7 months of INH and RIF) is recommended as initial therapy unless the organisms are known or strongly suspected of being resistant to the first-line drugs. If PZA cannot be used in the initial phase, the continuation phase must be increased to 7 months, as described for pulmonary tuberculosis.

The exception to the recommendation for a 6- to 9-month regimen is tuberculous meningitis, for which the optimal length of therapy has not been established, but some experts recommend 9–12 months.

Although in extrapulmonary tuberculosis there have not been controlled trials of the various patterns of intermittent drug administration listed in Table 2, expert opinion suggests that all could be used, with the exception of INH–rifapentine once weekly in the continuation phase. Given the lack of experience with this regimen, it is not recommended currently for treating extrapulmonary tuberculosis.

Corticosteroid treatment is a useful adjunct in treating some forms of extrapulmonary tuberculosis, specifically meningitis and pericarditis caused by drug-susceptible organisms. Evidence-based recommendations on the duration of treatment for extrapulmonary tuberculosis and the use of corticosteriods are shown in Table 13.

8.3.1. Lymph node tuberculosis

A 6-month regimen as described in Section 5, Recommended Treatment Regimens, and Table 2 is recommended for initial treatment of all patients with tuberculous lymphadenitis caused by drug-susceptible organisms (*2–6*). Affected lymph nodes may enlarge while patients are receiving appropriate therapy or after the end of treatment without any evidence of bacteriological relapse (*3,5,17,18*). On occasion, new nodes can appear during or after treatment as well. Therapeutic lymph node excision is not indicated except in unusual circumstances. For large lymph nodes that are fluctuant and appear to be about to drain spontaneously, aspiration or incision and drainage appears to be beneficial, although this approach has not been examined systematically (Rating BIII). It should be noted that the majority of cases of lymphatic mycobacterial disease in children born in the United States are caused by nontuberculous mycobacteria.

8.3.2. Bone and joint tuberculosis

Several studies have examined treatment of bone and joint tuberculosis and have shown that 6- to 9-month regimens containing RIF are at least as effective as 18-month regimens that do not contain RIF (*13–15*) Because of the difficulties in assessing response, however, some experts tend to favor the 9-month duration. A randomized trial performed primarily among ambulatory patients by the Medical Research Council Working Party on Tuberculosis of the Spine (*13*) demonstrated no additional benefit of surgical debridement or radical operation (resection of the spinal focus and bone grafting) in combination with chemotherapy compared with chemotherapy alone. Myelopathy with or without functional impairment most often responds to chemotherapy. In two Medical Research Council studies conducted in Korea, 24 of 30 patients in one study (*14*) and 74 of 85 patients in an earlier study (*19*) had complete resolution of myelopathy or complete functional recovery when treated medically. In some circumstances, however, surgery appears to be beneficial and may be indicated. Such situations include failure to respond to chemotherapy with evidence of ongoing infection, the relief of cord compression in patients with persistence or recurrence of neurologic deficits, or instability of the spine.

8.3.3. Pericardial tuberculosis

For patients with pericardial tuberculosis, a 6-month regimen is recommended. Corticosteroids are recommended as adjunctive therapy for tuberculous pericarditis during the first 11 weeks of antituberculosis therapy. In a randomized, double-blind, controlled trial, patients in the later effusive–constrictive phase who received prednisolone had a

TABLE 13. Evidence-based* guidelines for the treatment of extrapulmonary tuberculosis and adjunctive use of corticosteriods†

Site	Length of therapy (mo)	Rating (duration)	Corticosteroids‡	Rating (corticosteroids)
Lymph node	6	AI	Not recommended	DIII
Bone and joint	6–9	AI	Not recommended	DIII
Pleural disease	6	AII	Not recommended	DI
Pericarditis	6	AII	Strongly recommended	AI
CNS tuberculosis including meningitis	9–12	BII	Strongly recommended	AI
Disseminated disease	6	AII	Not recommended	DIII
Genitourinary	6	AII	Not recommended	DIII
Peritoneal	6	AII	Not recommended	DIII

* For rating system, see Table 1.
† Duration of therapy for extrapulmonary tuberculosis caused by drug-resistant organisms is not known.
‡ Corticosteroid preparations vary among studies. See Section 8.3 for specific recommendations.

significantly more rapid clinical resolution compared with patients given placebo. Prednisolone-treated patients also had a lower mortality (2 of 53 [4%] versus 7 of 61 [11%]) and needed pericardiectomy less frequently (11 of 53 [21%] versus 18 of 61 [30%]), but the differences did not reach statistical significance (*8*). Prednisolone did not reduce the risk of constrictive pericarditis. In a second prospective, double-blind, randomized trial of adjunctive prednisolone therapy involving patients with effusive pericarditis (i.e., more acute disease), prednisolone reduced the need for repeated pericardiocentesis (7 of 76 [9%] versus 17 of 74 [23%]; $p < 0.05$) and was associated with a significantly lower mortality (2 of 76 [3%] died among those who received prednisolone compared with 10 of 74 [14%] among those not given prednisolone; $p < 0.05$) (*9*). As before, there was no statistically significant impact on progression to constriction or in the need for pericardiectomy. An additional small randomized trial by Hakim and associates (*20*) performed in HIV-infected patients with tuberculous pericarditis also demonstrated that prednisolone therapy was associated with a reduced risk of mortality.

On the basis of these studies, it is recommended that daily adjunctive prednisolone or prednisone treatment be given to adults and children with tuberculous pericarditis. For adults the prednisone dose is 60 mg/day (or the equivalent dose of prednisolone) given for 4 weeks, followed by 30 mg/day for 4 weeks, 15 mg/day for 2 weeks, and finally 5 mg/day for week 11 (the final week). Children should be treated with doses proportionate to their weight, beginning with about 1 mg/kg body weight and decreasing the dose as described for adults.

8.3.4. Pleural tuberculosis

A 6-month regimen is also recommended for treating pleural tuberculosis. A number of studies have examined the role of corticosteroid therapy for tuberculous pleural effusions (*21*), but only two have been prospective, double blind, and randomized (*7,22*). In both of these studies, prednisone (or prednisolone) administration did not reduce the development of residual pleural thickening. Lee and associates (*22*) found that patients with pleural tuberculosis who received prednisone had a significantly more rapid resolution of symptoms such as fever, chest pain, and dyspnea than patients given placebo. Patients who received prednisone had a more rapid radiographic resolution of the effusions. In the study by Wyser and colleagues (*7*), all patients had complete drainage of the effusion performed at the time of the diagnostic procedure; patients were then allocated at random to receive adjunctive oral prednisone or placebo for 6 weeks. The complete drainage led to a rapid resolution of symptoms, and the added benefit of corticosteroids on symptoms was minimal.

Tuberculous empyema, a chronic, active infection of the pleural space containing a large number of tubercle bacilli, usually occurs when a cavity ruptures into the pleural space. Treatment consists of drainage (often requiring a surgical procedure) and antituberculous chemotherapy. Surgery, when needed, should be undertaken by experienced thoracic surgeons (*23*). The optimum duration of treatment for this unusual form of tuberculosis has not been established.

8.3.5. Tuberculous meningitis

Before the advent of effective antituberculosis chemotherapy, tuberculous meningitis was uniformly fatal. Tuberculous meningitis remains a potentially devastating disease that is associated with a high morbidity and mortality, despite prompt initiation of adequate chemotherapy (*24–29*). HIV-infected patients appear to be at increased risk for developing tuberculous meningitis but the clinical features and outcomes of the disease are similar to those in patients without HIV infection (*24–26,29*). Patients presenting with more severe neurologic impairment such as drowsiness, obtundation, or coma have a greater risk of neurologic sequelae and a higher mortality. Chemotherapy should be initiated with INH, RIF, PZA, and EMB in an initial 2-month phase. INH and RIF, as well as the aminoglycosides, capreomycin, and the fluoroquinolones are available in parenteral forms for patients with altered mental status who may not be able to take oral medications.

After 2 months of four-drug therapy for meningitis caused by susceptible strains, PZA and EMB may be discontinued, and INH and RIF continued for an additional 7–10 months, although the optimal duration of chemotherapy is not defined, and there are no data from randomized, controlled trials to serve as the basis of recommendations. Repeated lumbar punctures should be considered to monitor changes in CSF cell count, glucose, and protein, especially in the early course of therapy.

Differences in regimens among patient groups and in the use of corticosteroid therapy have made meta-analysis of published treatment trials impossible (*30*). Some authors have advocated longer courses of therapy, up to 2 years (*28,31*), whereas others have suggested that short-course RIF-based regimens for 6 to 9 months may be adequate therapy (*10,32,33*). It has been reported that some patients being treated for tuberculous meningitis develop tuberculomas during therapy, perhaps as a form of paradoxical reaction; however, this does not necessarily indicate treatment failure.

A number of investigators have examined the role of adjunctive corticosteroid therapy in the treatment of tuberculous meningitis (*21,34–41*), but many of these are limited by small sample size or use of a regimen that did not include RIF. There are no large, prospective, randomized, controlled trials

of adjunctive corticosteroid use for tuberculous meningitis in which an RIF-based regimen has been used. Six of eight controlled trials noted a benefit of corticosteroid therapy in terms of survival, frequency of sequelae, or both. In the study conducted by Girgis and coworkers (*34*), the greatest benefit was for patients with Stage II disease (lethargic) on presentation (4 of 27 [15%] of those who received dexamethasone died versus 14 of 35 [40%] in the control group; $p < 0.02$). For patients presenting with coma (Stage III), there was no significant difference in survival between those who received dexamethasone and control patients (28 of 44 [64%] mortality for the dexamethasone group versus 35 of 46 [76%] for control subjects). However, the small sample size may have precluded finding an effect. Likewise, there were too few patients with Stage I disease (alert) on entry to determine the effectiveness of dexamethasone for this less severely ill group.

On the basis of the available data, albeit limited, adjunctive corticosteroid therapy with dexamethasone is recommended for all patients, particularly those with a decreased level of consciousness, with tuberculous meningitis. The recommended regimen is dexamethasone in an initial dose of 8 mg/day for children weighing less than 25 kg and 12 mg/day for children weighing 25 kg or more and for adults. The initial dose is given for 3 weeks and then decreased gradually during the following 3 weeks.

8.3.6. Disseminated tuberculosis

A 6-month regimen is recommended for tuberculosis at multiple sites and for miliary tuberculosis, although there are limited data from controlled clinical trials addressing this issue. (The AAP recommends 9 months of treatment for children with disseminated tuberculosis.) Expert opinion suggests that corticosteroid therapy may be useful for treating respiratory failure caused by disseminated tuberculosis but there are no data to support its use.

8.3.7. Genitourinary tuberculosis

Renal tuberculosis is treated primarily with medical therapy (*12,42–46*), and a 6-month regimen is recommended. If ureteral obstruction occurs, procedures to relieve the obstruction are indicated. In cases of hydronephrosis and progressive renal insufficiency due to obstruction, renal drainage by stenting or nephrostomy is recommended (*42*). The use of corticosteriods in addition to stenting for the treatment of ureteric stenosis is discussed in the urologic literature but the efficacy of steroids in this setting is unclear. Nephrectomy is not usually indicated for the treatment of uncomplicated renal tuberculosis but should be considered when there is a nonfunctioning or poorly functioning kidney, particularly if hypertension or continuous flank pain is present. Tuberculosis of either the female or male genital tract responds well to standard chemotherapy, and surgery is needed only for residual large tubo-ovarian abscesses.

A positive urine culture for *M. tuberculosis* occurs relatively commonly as an incidental finding among patients with pulmonary or disseminated disease, especially those with HIV infection. The positive culture may occur in the absence of any abnormalities on urinalysis and does not necessarily represent genitourinary tract involvement.

8.3.8. Abdominal tuberculosis

A 6-month regimen is recommended for patients with peritoneal or intestinal tuberculosis (*47,48*). There are insufficient data to recommend adjunctive corticosteroid therapy in the treatment of tuberculous peritonitis (*21*). In a small study of peritoneal tuberculosis alternate patients received adjunctive corticosteroid therapy for 4 months (total of 23 steroid recipients) (*49*). Fibrotic complications were noted in 4 of 24 in the control group and in none of those in the steroid group (23 patients), but the difference was not statistically significant.

8.3.9. Other sites of involvement

As noted above, tuberculosis can involve any organ or tissue. In treating tuberculosis in sites other than those mentioned, the basic principles of therapy apply, but experts should be consulted for specific advice concerning individual patients.

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8.4. Culture-Negative Pulmonary Tuberculosis in Adults

Failure to isolate *M. tuberculosis* from appropriately collected specimens in persons who, because of clinical or radiographic findings, are suspected of having pulmonary tuberculosis does not exclude a diagnosis of active tuberculosis. For the United States as a whole, about 17% of the reported new cases of pulmonary tuberculosis have negative cultures (*1*). Low bacillary populations, temporal variations in the number of bacilli being expelled, and errors in specimen processing all may result in failure to isolate organisms from patients who have active tuberculosis. It should be emphasized that alternative diagnoses must be considered carefully and appropriate diagnostic studies undertaken in patients who have what appears to be culture-negative tuberculosis. At a minimum, patients suspected of having pulmonary tuberculosis should have three sputum specimens (using sputum induction with hypertonic saline if necessary) for AFB smears and cultures for mycobacteria as part of the diagnostic evaluation. Depending on the clinical features and differential diagnosis, other diagnostic testing, such as bronchoscopy with bronchoalveolar lavage and biopsy, should be considered before making a presumptive diagnosis of culture-negative tuberculosis.

Patients who, on the basis of careful clinical and radiographic evaluation, are thought to have pulmonary tuberculosis should have treatment initiated with INH, RIF, PZA, and EMB even when the initial sputum smears are negative. If *M. tuberculosis* is isolated in culture, treatment for active disease should be continued. Patients who have negative cultures but who still are presumed to have pulmonary tuberculosis should have a thorough follow-up clinical and radiographic evaluation at the time 2 months of therapy has been completed to determine whether there has been a response that can be attributed to antituberculosis treatment. If there is either clinical or radiographic improvement and no other etiology is identified, treatment should be continued for active tuberculosis. A 4-month, INH and RIF regimen for culture-negative tuberculosis has been demonstrated to be successful with only 1.2% relapses during an average follow-up of 44 months (*2*). However, because the results of cultures may not be known for 3–8 weeks and because of the possibility of drug resistance, initiation of two-drug therapy with INH and RIF alone is not recommended, but the continuation phase can be shortened to 2 months using INH and RIF (Figure 2).

On occasion, patients who are being evaluated for pulmonary tuberculosis will be found to have positive AFB smears but negative cultures. There are several potential explanations for this occurrence, including the possibilities that the acid-fast organisms are nontuberculous and difficult to culture, that they are nonviable tubercle bacilli, and that they are the result of laboratory error. The approach taken in such cases should be individualized on the basis of clinical and radiographic findings. If suspicion of tuberculosis is high and the patient has positive AFB smears, even with negative cultures, he/she should be treated as if the culture is positive, using one of the recommended regimens.

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8.5. Radiographic Evidence of Prior Tuberculosis: Inactive Tuberculosis

Persons with a positive tuberculin PPD skin test who have radiographic findings consistent with prior pulmonary tuberculosis (ATS/CDC Class 4) (*1*) and who have not been treated are at increased risk for the subsequent development of active tuberculosis (*2–4*). The radiographic findings that constitute evidence of prior tuberculosis are apical fibronodular infiltrations, often with volume loss. Case rates among such persons in one study were about 2.5 times those of persons infected with *M. tuberculosis* who did not have chest radiographic abnormalities (*3*). Persons with radiographic findings of healed primary tuberculosis (e.g., calcified solitary pulmonary nodules, calcified hilar lymph nodes, and pleural thickening) are not at increased risk for tuberculosis compared with other persons with latent tuberculosis infection.

Patients should not be classified as having radiographic evidence of prior tuberculosis if another disease is found to account for the radiographic findings. The activity of tuberculosis cannot be determined from a single chest radiograph, and unless there are previous radiographs showing that the abnormality has not changed, it is recommended that sputum examination, using sputum induction if necessary, be performed to assess the possibility of active tuberculosis. Once active tuberculosis has been excluded by sputum culture, these persons are high-priority candidates for treatment of latent tuberculosis infection (*5*).

The optimum treatment for patients with latent tuberculosis infection and abnormal chest radiographs consistent with prior tuberculosis has been examined in several studies. A placebo-controlled trial conducted by the IUATLD (*2*) compared the efficacy of 3, 6, and 12 months of INH in preventing

active tuberculosis for persons with latent tuberculosis infection who had chest radiographs showing fibrotic lesions consistent with inactive tuberculosis. Among those receiving INH for at least 6 months, the incidence of tuberculosis was significantly reduced compared with those given placebo. In patients with fibrotic lesions greater than 2 cm in diameter INH given for 12 months was significantly better than 6 months (89 versus 67% reduction). A reanalysis of data from a community-based study of persons with abnormal radiographs felt to represent inactive tuberculosis showed that the efficacy of INH decreased significantly if less than 9 months of the drug was taken, but that further protection was not conferred if the duration was extended from 9 to 12 months (*6*). On the basis of these data, guidelines for treatment of latent tuberculosis infection recommend 9 months of INH for persons with abnormal chest radiographs consistent with prior tuberculosis (*5*). Additional treatment regimens are RIF (with or without INH) for 4 months, and RIF and PZA for 2 months (for persons who are unlikely to complete a longer course and who can be monitored carefully) (*5*) (Table 14). A study comparing the cost-effectiveness of INH and RIF with INH alone in treating this category of patient showed that 4 months of INH and RIF was cost saving compared with INH alone, and the cost savings increased as the prevalence of infection with strains resistant to INH increased (*7*).

Instances of severe and fatal liver disease have been reported in patients taking RIF and PZA for treatment of latent tuberculosis infection (*8*). In addition, the frequency of hepatotoxicity has been shown to be greater with RIF–PZA than with INH alone (7.7% Grade 3 or 4 hepatotoxicity with RIF–PZA compared with 1% for INH; p = 0.001) (*9*). In view of these data, the regimen should be used with caution and with careful monitoring, measuring serum AST and bilirubin at baseline and after 2, 4, and 6 weeks of treatment. RIF–PZA is not recommended for patients with underlying liver disease or a history of alcoholism, or for those who have had hepatotoxicity from INH. The regimen should be reserved for patients who are not likely to complete a longer course of treatment and who can be monitored carefully.

TABLE 14. Summary of evidence* for treatment of persons with radiographic evidence of prior tuberculosis and negative sputum cultures not treated previously

	Rating/evidence	
Treatment regimen	**HIV negative**	**HIV positive**
INH for 9 mo	AII	AII
RIF with or without INH for 4 mo	BII	BIII
RIF and PZA for 2 mo	CIII	BI

Definition of abbreviations: INH = isoniazid; PZA = pyrazinamide; RIF = rifampin.
* For rating system, see Table 1.

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8.6. Pregnancy and Breastfeeding

Untreated tuberculosis represents a far greater hazard to a pregnant woman and her fetus than does treatment of the disease. Infants born to women with untreated tuberculosis may be of lower birth weight than those born to women without tuberculosis and, rarely, the infant may acquire congenital tuberculosis (*1–3*). Thus, treatment of a pregnant woman with suspected tuberculosis should be started if the probability of tuberculosis is moderate to high. The initial treatment regimen should consist of INH, RIF, and EMB. SM should *not* be substituted for EMB. Although PZA is recommended for routine use in pregnant women by the WHO (*4*) and the IUATLD (*5*), the drug has not been recommended for general use in pregnant women in the United States because of insufficient data to determine safety. However, some public health jurisdictions in the United States have used PZA in pregnant women without reported adverse events (*1*). If PZA is not included in the initial treatment regimen, the minimum duration of therapy is 9 months. Pyridoxine, 25 mg/day, should be given to pregnant women who are receiving INH.

INH, RIF, and EMB cross the placenta, but none has been shown to have teratogenic effects (*6*). SM, the only antituberculosis drug documented to have harmful effects on the human fetus, interferes with development of the ear and may cause congenital deafness. In 40 pregnancies among women being treated with SM, 17% of the babies had eighth nerve damage with deficits ranging from mild hearing loss to bilateral deafness (*6,7*). Kanamycin, amikacin, and capreomycin presumably share this toxic potential; however, there is little specific information on the fetal effects of these three drugs. PAS was used commonly with INH in the past and there was no indication of teratogenicity among babies whose mothers had received these two drugs (*2*). There are not enough data to determine the risk of cycloserine or ethionamide, although one report described nonspecific teratogenic effects attributed to ethionamide (*8*). The fluoroquinolones have been associated with arthropathies in young animals; therefore, they should be avoided if possible in pregnant women (*6*).

In general, administration of antituberculosis drugs is not an indication for termination of pregnancy (*2*). However, in women who are being treated for drug-resistant tuberculosis, counseling concerning the risk to the fetus should be provided because of the known and unknown risks of the second-line agents.

Breastfeeding should not be discouraged for women being treated with first-line agents, because the small concentrations of these drugs in breast milk do not produce toxic effects in the nursing infant (*9*). Conversely, drugs in breast milk should not be considered to serve as effective treatment for active tuberculosis or latent tuberculosis infection in a nursing infant. Supplementary pyridoxine is recommended for the nursing mother receiving INH. The administration of the fluoroquinolones during breastfeeding is not recommended, although, as of 1998, there have been no reported cases of adverse reactions in infants breast fed by women taking these drugs (*6*).

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8.7. Renal Insufficiency and End-stage Renal Disease

Renal insufficiency complicates the management of tuberculosis because some antituberculosis medications are cleared by the kidneys. Management may be further complicated by the removal of some antituberculosis agents via hemodialysis. Thus, some alteration in dosing antituberculosis medications is commonly necessary in patients with renal insufficiency and end-stage renal disease (ESRD) receiving hemodialysis (Table 15). Decreasing the dose of selected antituberculosis drugs may not be the best method of treating tuberculosis because, although toxicity may be avoided, the peak serum concentrations may be too low. Therefore, instead of decreasing the dose of the antituberculosis agent, increasing the dosing interval is recommended (*1*). The general approach described in Table 15 involves either estimating or measuring creatinine clearance. Administration of drugs that are cleared by the kidneys to patients having a creatinine clearance of less than 30 ml/minute and those receiving hemodialysis are managed in the same manner, with an increase in dosing interval (C. Peloquin, personal communication). There are insufficient data to guide dosing recommendations for patients having a reduced creatinine clearance but not less than 30 ml/minute. In such patients standard doses should be used, but measurement of serum concentrations should be considered to avoid toxicity.

RIF and INH are metabolized by the liver, so conventional dosing may be used in the setting of renal insufficiency (*1–5*). PZA is also metabolized by the liver but its metabolites (pyrazinoic acid and 5-hydroxy-pyrazinoic acid) may accumulate in patients with renal insufficiency (*3,6*). EMB is about 80% cleared by the kidneys and may accumulate in patients with renal insufficiency (*7*). A longer interval between doses with three times a week administration is recommended for PZA and EMB (*3,7*). INH, EMB, and PZA (as well as its metabolites) are cleared by hemodialysis to some degree, but only PZA and presumably its metabolites are dialyzed to a significant degree (*3*). RIF is not cleared by hemodialysis because of its high molecular weight, wide distribution into tissues, high degree of protein binding, and rapid hepatic metabolism (*3*). Therefore, supplemental dosing is not necessary for INH, RIF, or EMB. If PZA is given after

TABLE 15. Dosing recommendations for adult patients with reduced renal function and for adult patients receiving hemodialysis

Drug	Change in frequency?	Recommended dose and frequency for patients with creatinine clearance <30 ml/min or for patients receiving hemodialysis
Isoniazid	No change	300 mg once daily, or 900 mg three times per week
Rifampin	No change	600 mg once daily, or 600 mg three times per week
Pyrazinamide	Yes	25–35 mg/kg per dose three times per week (not daily)
Ethambutol	Yes	15–25 mg/kg per dose three times per week (not daily)
Levofloxacin	Yes	750–1,000 mg per dose three times per week (not daily)
Cycloserine	Yes	250 mg once daily, or 500 mg/dose three times per week*
Ethionamide	No change	250-500 mg/dose daily
p-Aminosalicylic acid	No change	4 g/dose, twice daily
Streptomycin	Yes	12–15 mg/kg per dose two or three times per week (not daily)
Capreomycin	Yes	12–15 mg/kg per dose two or three times per week (not daily)
Kanamycin	Yes	12–15 mg/kg per dose two or three times per week (not daily)
Amikacin	Yes	12–15 mg/kg per dose two or three times per week (not daily)

Standard doses are given unless there is intolerance.
The medications should be given after hemodialysis on the day of hemodialysis.
Monitoring of serum drug concentrations should be considered to ensure adequate drug absorption, without excessive accumulation, and to assist in avoiding toxicity.
Data currently are not available for patients receiving peritoneal dialysis. Until data become available, begin with doses recommended for patients receiving hemodialysis and verify adequacy of dosing, using serum concentration monitoring.
* The appropriateness of 250-mg daily doses has not been established. There should be careful monitoring for evidence of neurotoxicity (see Section 3).

hemodialysis, supplemental dosing is not required. In general, antituberculosis drugs should be given after hemodialysis to avoid any loss of the drugs during hemodialysis, and to facilitate DOT.

Doses of streptomycin, kanamycin, amikacin, and capreomycin must be adjusted in patients with renal failure because the kidneys excrete essentially all of these drugs. Approximately 40% of the dose is removed with hemodialysis when these drugs are given just before hemodialysis (*8*). Far less drug is likely to be removed once the drugs have had time to distribute throughout the body, and some accumulation of the drugs should be anticipated. As with EMB and PZA, the dosing interval should be increased. In general, the dose should not be reduced because the drugs exhibit concentration-dependent bactericidal action (*9*), and smaller doses may reduce drug efficacy. Ethionamide is not cleared by the kidneys, nor is the drug removed with hemodialysis, so no dose adjustment is necessary (*10*). PAS is modestly cleared by hemodialysis (6.3%) but its metabolite, acetyl-PAS, is substantially removed by hemodialysis; twice daily dosing (4 g) should be adequate if the granule formulation is used (Jacobus Pharmaceuticals) (*10*). Cycloserine is excreted primarily by the kidney, and is cleared by hemodialysis (56%). Thus, an increase in the dosing interval is necessary to avoid accumulation between hemodialysis sessions, and the drug should be given after hemodialysis to avoid underdosing (*10*). The fluoroquinolones undergo some degree of renal clearance that varies from drug to drug. For example, levofloxacin undergoes greater renal clearance than moxifloxacin (*11*). It should be noted that the fluoroquinolone dosing recommendations for end-stage renal disease provided by the manufacturers were developed for treating pyogenic bacterial infections. These recommendations may not be applicable to the treatment of tuberculosis in patients with end-stage renal disease.

As noted above, administration of all antituberculosis drugs immediately after hemodialysis will facilitate DOT (three times per week) and avoid premature removal of the drugs (*2*). It is important to monitor serum drug concentrations in persons with renal insufficiency who are taking cycloserine, EMB, or any of the injectable agents to minimize dose-related toxicity, while providing effective doses. Clinicians also should be aware that patients with end-stage renal disease may have additional clinical conditions, such as diabetes mellitus with gastroparesis, that may affect the absorption of the antituberculosis drugs, or they may be taking concurrent medications that interact with these drugs. Under these circumstances a careful clinical and pharmacologic assessment is necessary, and, in selected cases, serum drug concentration measurements may be used to assist in determining the optimum dose of the antituberculosis drugs (*9*). Finally, data currently do not exist for patients receiving peritoneal dialysis. Because the drug removal mechanisms differ between hemodialysis and peritoneal dialysis, it cannot be assumed that all of the recommendations in Table 15 will apply to peritoneal dialysis. Such patients may require close monitoring, including measurements of the serum concentrations of the antituberculosis drugs.

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8.8. Hepatic Disease

The treatment of tuberculosis in patients with unstable or advanced liver disease is problematic for several reasons. First, the likelihood of drug-induced hepatitis may be greater. Second, the implications of drug-induced hepatitis for patients with marginal hepatic reserve are potentially serious, even life-threatening. Finally, fluctuations in the biochemical indicators of liver function (with/without symptoms) related to the preexisting liver disease confound monitoring for drug-induced hepatitis. Thus, clinicians may consider regimens with fewer potentially hepatotoxic agents in patients with advanced or unstable liver disease, and expert consultation is advisable in treating such patients. It should be noted that tuberculosis itself may involve the liver, causing abnormal liver function; thus, not all abnormalities in liver function tests noted at baseline should be attributed to causes other than tuberculosis. The hepatic abnormalities caused by tuberculosis will improve with effective treatment.

Possible treatment regimens in the setting of liver disease include the following.

8.8.1. Treatment without INH

As described in Section 5.2, Alternative Regimens, analysis of data from several studies conducted by the BMRC in patients with smear-positive pulmonary tuberculosis demonstrated high levels of efficacy with 6-month regimens despite in vitro resistance to INH so long as the initial phase contained four drugs and RIF was used throughout the 6 months (*1*). Subsequent studies by the Hong Kong Chest Service and the BMRC suggested that results were improved when PZA was used throughout the 6 months (*2*). Thus, it is reasonable to employ an initial phase regimen of RIF, PZA, and EMB followed by a continuation phase of RIF, EMB, and PZA (Rating BII). Although this regimen has two potentially hepatotoxic medications, it has the advantage of retaining the 6-month duration.

8.8.2. Treatment without PZA

Although the frequency of PZA-induced hepatitis is slightly less than occurs with INH or RIF, the liver injury induced by this drug may be severe and prolonged (*3*). Therefore, one might elect to employ a regimen with an initial phase of INH, RIF, and EMB for 2 months followed by a continuation phase of INH and RIF for 7 months, for a total of 9 months (Table 2, Regimen 4).

8.8.3. Regimens with only one potentially hepatotoxic drug

For patients with advanced liver disease, a regimen with only one potential hepatotoxic drug might be selected. Generally, RIF should be retained. Additional agents in such regimens could include EMB, a fluoroquinolone, cycloserine, and injectable agents. The duration of treatment with such regimens should be 12–18 months, depending on the extent of the disease and the response (Rating CIII). Consultation is advised in such situations.

8.8.4. Regimens with no potentially hepatotoxic drugs

In the setting of severe unstable liver disease, a regimen with no hepatotoxic agents might be necessary. Such a regimen might include SM, EMB, a fluoroquinolone, and another second-line oral drug. There are no data that provide guidance as to the choice of agents or the duration of treatment or that indicate the effectiveness of such a regimen. Expert opinion suggests that a regimen of this sort should be given for 18–24 months (Rating CIII). Consultation should always be obtained before embarking on such a treatment plan.

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8.9. Other Associated Disorders

Tuberculosis commonly occurs in association with other diseases or conditions. An associated disorder may alter immune responsiveness, thereby causing a predisposition to tuberculosis, or simply may be a disorder that occurs frequently in the same social and cultural milieu as tuberculosis. Examples of the former class of disorders include HIV infection, hematologic or reticuloendothelial malignancies, immunosuppressive therapy, chronic renal failure, poorly controlled, insulin-dependent diabetes mellitus, and malnutrition. Silicosis, by impairing pulmonary macrophage function, is a unique example of local immune dysfunction.

The latter group of disorders includes chronic alcoholism and its secondary effects, other substance abuse, and psychiatric illnesses, among others. All of these conditions may influence the organization, supervision, and outcome of therapy (discussed in Section 2: Organization and Supervision of Treatment). The response of immunocompromised patients to treatment may not be as good as would be expected in a person with normal immunity, although in patients with HIV infection the response to treatment is not impaired Nevertheless, therapeutic decisions for the immunocompromised host should be more individualized, taking into account the severity of tuberculosis and the response to treatment. When possible, steps should be taken to correct the immune deficiency. In patients with silicotuberculosis there are data demonstrating that the rate of cure is improved if the continuation phase is extended for at least 2 months (*1,2*).

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9. Management of Relapse, Treatment Failure, and Drug Resistance

9.1. Relapse

Relapse refers to the circumstance in which a patient becomes and remains culture-negative while receiving antituberculosis drugs but, at some point after completion of therapy, either becomes culture-positive again or experiences clinical or radiographic deterioration consistent with active tuberculosis. In such patients vigorous efforts should be made to establish a diagnosis and to obtain microbiological confirmation of the relapse to enable testing for drug resistance. True relapses are due to failure of chemotherapy to sterilize the host tissues, thereby enabling endogenous recrudescence of the original infection. In some hyperendemic settings, however, exogenous reinfection with a new strain of *M. tuberculosis* may be responsible for the apparent relapse (*1*).

Microbiological Confirmation of Relapse Should be Pursued Vigorously.

Relapses may occur with either drug-resistant or drug-susceptible strains of *M. tuberculosis*. To confirm that a true relapse has occurred and to obtain drug susceptibility tests, microbiological confirmation of relapse should be pursued vigorously.

Patients who are most likely to have true relapses are those with extensive tuberculosis whose sputum cultures remain positive after 2 months of chemotherapy (*2–4*). Most patients relapse within the first 6–12 months after completion of therapy. In nearly all patients with tuberculosis caused by drug-susceptible organisms who were treated with rifamycin-containing regimens using DOT, relapses occur with susceptible organisms (*5,6*). However, in patients who received self-administered therapy or a nonrifamycin regimen and who have a relapse, the risk of acquired drug resistance is substantial. In addition, if initial drug susceptibility testing was not performed and the patient fails or relapses with a rifamycin-containing regimen given by DOT, there is a high likelihood that the organisms were resistant from the outset.

Among patients who received self-administered therapy, the risk of erratic drug administration leading to relapse with resistant organisms is greater. In view of these considerations, the selection of empirical treatment regimens for patients with relapses should be based on the prior treatment scheme. For patients with tuberculosis that was caused by drug-susceptible organisms, who were treated by DOT, and who have relapses, retreatment using the standard four-drug initial phase regimen may be appropriate, at least until the results of susceptibility tests are known. For patients who did not receive DOT or are known to have had irregular treatment in the past, it is prudent to infer a higher risk of acquired drug resistance and begin an expanded regimen (see below). The expanded regimen is indicated especially in patients with impaired immunity, limited respiratory reserve, central nervous system involvement, or other life-threatening circumstances, that is, cases in which treatment with an inadequate regimen could have severe consequences.

For the relatively few patients in whom epidemiologic circumstances provide a strong suspicion of exogenous reinfection as the cause of apparent relapse, the choice of a regimen is influenced by the drug susceptibility pattern of the presumed

source case. If the presumed source case is known to have tuberculosis caused by drug-susceptible organisms, resumption of a standard four-drug initial phase may be indicated. However, if the likely source case is known to have drug-resistant organisms, an empirically expanded regimen based on the resistance profile of the putative source case may be suitable.

There are no clinical trials to guide the choice of agents to include in expanded empirical regimens for presumed drug resistance; however, expert opinion indicates that such regimens should generally employ INH, RIF, and PZA plus an additional three agents, based on the probability of in vitro susceptibility. Usual agents would include EMB, a fluoroquinolone, and an injectable agent such as SM (if not used previously, and the initial isolate was susceptible) amikacin, kanamycin or capreomycin, with or without other drugs.

9.2. Treatment Failure

Treatment failure is defined as continued or recurrently positive cultures in a patient receiving appropriate chemotherapy. Among patients with drug-susceptible pulmonary tuberculosis, even with extensive lung cavitation, 90–95% will be culture-negative after 3 months of treatment with a regimen that contains INH and RIF. During this time the vast majority of patients show clinical improvement, including defervescence, reduced cough, and weight gain. Thus, patients with persistently positive cultures after 3 months of chemotherapy, with or without on-going symptoms, should be evaluated carefully to attempt to identify the cause of the delayed response. Patients whose sputum cultures remain positive after 4 months of treatment are considered to have failed treatment.

Never Add a Single Drug To a Failing Regimen

Treatment failure is defined by continued or recurrent positive cultures after 4 months of treatment in patients in whom medication ingestion was assured. Patients with treatment failure should be assumed, until proven otherwise, to have drug-resistant organisms and be treated with multiple agents that they have not received before. A single drug should never be added to a failing regimen. So doing risks development of resistance to the new drug, further complicating management.

There are multiple potential reasons for treatment failure. If the patient is not receiving DOT, the most likely explanation for persistently positive cultures is nonadherence to the drug regimen. Among patients receiving DOT, cryptic nonadherence (spitting out or deliberately regurgitating pills) or failure of the health care system to reliably deliver the drugs may be the cause. Other potential reasons include unrecognized drug resistance (Was initial drug-susceptibility testing done? Was it reported accurately?), malabsorption (prior resectional surgery of the stomach or small intestine, taking tuberculosis medication with antacids or other drugs/substances that might bind or interfere with drug absorption (see Section 6.1: Drug Administration, and Section 7.1: Interactions Affecting Antituberculosis Drugs), or simply an extreme biologic variation (For unclear reasons, rare "normal" patients may experience very protracted disease including persistently positive cultures or prolonged symptoms in the face of chemotherapy that would be expected to be effective). Laboratory error should also be considered as a possible reason for a positive culture in a patient who is doing well. Recent reports document cross contamination or mislabeling of specimens as a source for some of these unexpectedly positive cultures (*7,8*).

Clinicians should be alert, as well, to the possibility of transient clinical or radiographic worsening (paradoxical reactions), despite appropriate therapy that would eventually result in cure. Examples of this include ongoing inflammation at sites of lymphadenitis, worsened abnormalities on chest radiographs after several months of treatment, or the new appearance of pleural effusions during therapy for pulmonary tuberculosis (*9–11*). Such paradoxical worsening during treatment occurs more commonly but not exclusively in persons with HIV infection (*12–14*) (see Section 8.1: HIV Infection).

For patients who meet criteria for treatment failure, the possible reasons listed above should be addressed promptly. If clinicians are not familiar with the management of drug-resistant tuberculosis, prompt referral to, or consultation with a specialty center is indicated. If treatment failure is presumed to be due to drug resistance and the patient does not have severe tuberculosis, one may either initiate an empirical retreatment regimen or wait for drug susceptibility results from a recent isolate. If the patient is seriously ill or has a positive sputum AFB smear, an empirical regimen that would be anticipated to be effective should be started immediately and continued until susceptibility tests are available to guide therapy. For patients who have failed treatment, mycobacterial isolates should be sent promptly to a reference laboratory for susceptibility testing for both first- and second-line drugs.

A fundamental principle in managing patients who have failed treatment is that a single new drug should never be added to a failing regimen; so doing may lead to acquired resistance to the added drug. In such cases, it is generally prudent to add at least three new drugs to which susceptibility could logically

be inferred to lessen the probability of further acquired resistance. As noted previously there are no clinical trials to guide the choice of an empirical regimen; however, expert opinion indicates that empirical retreatment regimens might include a fluoroquinolone such as levofloxacin, an injectable agent such as SM (if not used previously and the isolate was susceptible initially), amikacin, kanamycin, or capreomycin, and an oral agent such as PAS, cycloserine, or ethionamide (Rating AIII). When drug susceptibility results are available, the regimen should be adjusted according to the results.

9.3. Management of Tuberculosis Caused by Drug-Resistant Organisms

Tubercle bacilli are continually undergoing spontaneous mutations that create resistance to individual antituberculosis drugs. However, the frequency of these single mutations is sufficiently low that with appropriate combination chemotherapy that is reliably ingested, clinically significant resistance will not develop (see Section 4.1: Combination Chemotherapy) (*15*). Most commonly the development of acquired drug resistance occurs when there is a large bacillary population, such as in pulmonary cavities, when an inadequate drug regimen is prescribed (inappropriate drugs, insufficient dosage) or when there is a combined failure of both the patient and the provider to ensure that an adequate regimen is taken (*16*). Rarely, malabsorption of one or more antituberculosis drugs may account for acquired resistance. Drug resistance is much more likely to occur in cavitary pulmonary tuberculosis because of the immense number of rapidly multiplying bacilli in the cavity(ies) (*17*). During extended or repeated treatment, resistance to multiple agents may evolve. Patients with acquired drug resistance may transmit their strains to others who, if they develop tuberculosis, will have primary drug resistance.

Request Consultation

Treatment of tuberculosis caused by drug-resistant organisms should be done by or in close consultation with an expert in the management of these difficult situations. Second-line regimens often represent the patient's last best hope for being cured. Inappropriate management can, thus, have life-threatening consequences.

Drug resistance in a patient with newly diagnosed tuberculosis may be suspected on the basis of historical (previous treatment) or epidemiologic information (contact with a known drug-resistant case or coming from a region in which drug resistance is common) (*18,19*). In such situations it is prudent to employ an empirically expanded regimen, as described previously, especially if the patient is seriously ill (Table 16). Drug resistance can be proven only by drug-susceptibility testing performed in a competent laboratory (Table17). The steps taken when resistance is shown to be present are of critical importance. Patients harboring strains of *M. tuberculosis* resistant to both INH and RIF (MDR) are at high risk for treatment failure and further acquired resistance; they must be referred immediately to a specialist or consultation obtained from specialized treatment centers. Patients with strains resistant to RIF alone have a better prognosis than MDR cases, but also are at increased risk for failure and additional resistance. Thus, their management should also be subject to special scrutiny.

Definitive randomized or controlled studies have not been performed among patients with the various patterns of drug resistance. In the absence of ideal evidence, practices in the treatment of patients are based on a mixture of general principles, extrapolations and expert opinion. The WHO and IUATLD have formulated standard algorithmic regimens for the management of treatment failure or chronic cases, largely based on the principles listed below, as well as on expert opinion (*20,21*). This approach is best suited to regions without in vitro susceptibility testing capacity and access to the full array of retreatment medications, but it is not appropriate for industrialized nations with more ample resources (*22,23*).

Guidelines for management of patients with tuberculosis caused by drug-resistant organisms are based on the following guidelines, all of which are rated A III:

- A single new drug should never be added to a failing regimen.
- When initiating or revising therapy, always attempt to employ at least three previously unused drugs to which there is in vitro susceptibility. One of these should be an injectable agent.
- Do not limit the regimen to three agents if other previously unused drugs that are likely to be active are available. In patients with MDR organisms in whom there is resistance to first-line agents in addition to INH and RIF, regimens employing four to six medications appear to be associated with better results (*24–26*).
- Patients should receive either hospital-based or domiciliary DOT. The implications of treatment failure and further acquired resistance are such that these cases should receive highest priority for DOT.
- Intermittent therapy should not be used in treating tuberculosis caused by drug-resistant organisms, except perhaps for injectable agents after an initial period (usually 2–3 months) of daily therapy.

TABLE 16. Potential regimens for the management of patients with drug-resistant pulmonary tuberculosis

Pattern of drug resistance	Suggested regimen	Duration of treatment (mo)	Comments
INH (± SM)	RIF, PZA, EMB (an FQN may strengthen the regimen for patients with extensive disease)	6	In BMRC trials, 6-mo regimens have yielded ≥95% success rates despite resistance to INH if four drugs were used in the initial phase and RIF plus EMB or SM was used throughout.* Additional studies suggested that results were best if PZA was also used throughout the 6 mo (Rating BII).† Fluoroquinolones were not employed in BMRC studies, but may strengthen the regimen for patients with more extensive disease (Rating BIII). INH should be stopped in cases of INH resistance (see text for additional discussion).
INH and RIF (± SM)	FQN, PZA, EMB, IA, ± alternative agent	18–24	In such cases, extended treatment is needed to lessen the risk of relapse. In cases with extensive disease, the use of an additional agent (alternative agents) may be prudent to lessen the risk of failure and additional acquired drug resistance. Resectional surgery may be appropriate (see text).
INH, RIF (± SM), and EMB or PZA	FQN (EMB or PZA if active), IA, and two alternative agents	24	Use the first-line agents to which there is susceptibility. Add two or more alternative agents in case of extensive disease. Surgery should be considered (see text).
RIF	INH, EMB, FQN, supplemented with PZA for the first 2 months (an IA may be included for the first 2–3 months for patients with extensive disease)	12–18	Daily and three times weekly regimens of INH, PZA, and SM given for 9 mo were effective in a BMRC trial‡ (Rating BI). However, extended use of an injectable agent may not be feasible. It is not known if EMB would be as effective as SM in these regimens. An all-oral regimen for 12–18 mo should be effective (Rating BIII). But for more extensive disease and/or to shorten duration (e.g., to 12 months), an injectable agent may be added in the initial 2 mo of therapy (Rating BIII).

Definition of abbreviations: BMRC = British Medical Research Council; EMB = ethambutol; FQN = fluoroquinolone; IA = injectable agent; INH = isoniazid; PZA = pyrazinamide; RIF = rifampin; SM = streptomycin.
FQN = Fluoroquinolone; most experience involves ofloxacin, levofloxacin, or ciprofloxacin.
IA = Injectable agent; may include aminoglycosides (streptomycin, amikacin, or kanamycin) or the polypeptide capreomycin.
Alternative agents = Ethionamide, cycloserine, *p*-aminosalicylic acid, clarithromycin, amoxicillin-clavulanate, linezolid.
* **Source:** Mitchison DA, Nunn AJ. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. Am Rev Respir Dis 1986;133:423–430.
† **Source:** Hong Kong Chest Service, British Medical Research Council. Five-year follow-up of a controlled trial of five 6 month regimens of chemotherapy for tuberculosis. Am Rev Respir Dis 1987;136:1339–1342.
‡ **Source:** Hong Kong Chest Service, British Medical Research Council. Controlled trial of 6-month and 9-month regimens of daily and intermittent streptomycin plus isoniazid plus pyrazinamide for pulmonary tuberculosis in Hong Kong. Am Rev Respir Dis 1977;115:727–735.

- The use of drugs to which there is demonstrated in vitro resistance is not encouraged because there is little or no efficacy of these drugs (assuming the test results are accurate), and usually, alternative medications are available. However, the clinical significance and effectiveness of the use of INH in the setting of low-level INH resistance is unclear (see Section 9.5). It should be noted that the use of INH was associated with better survival rates in patients with the strain-W variety of MDR *M. tuberculosis* that was susceptible to higher concentrations of INH (*27*).
- Resistance to RIF is associated in nearly all instances with cross-resistance to rifabutin and rifapentine (*28*). Rare strains with RIF resistance retain susceptibility to rifabutin; this is associated with uncommon mutations of the RNA-polymerase locus in the bacillus (*29*). However, unless in vitro susceptibility to rifabutin is demonstrated, this agent should not be employed in cases with RIF resistance. Cross-resistance between RIF and rifapentine appears almost universal (*28*).
- There is no cross-resistance between SM and the other injectable agents: amikacin, kanamycin, and capreomycin (although resistance to all may occur as independent events); however, cross-resistance between amikacin and kanamycin is universal (*24*). Simultaneous use of two injectable agents is not recommended due to the absence of proof of efficacy and potential amplification of drug toxicity.
- Determination of resistance to PZA is technically problematic and, thus, is not made in many laboratories. However, resistance to PZA is uncommon in the absence of resistance to other first-line drugs (*30*). If monoresistance to PZA is observed, consideration must be given to the possibility that the etiologic agent is *M. bovis*, not *M. tuberculosis* (*M. bovis* is genotypically resistant to PZA

TABLE 17. Recommended drug concentrations* for susceptibility testing

Drug	Proportion method		Broth-based systems			
	7H10 Agar	7H11 Agar	Radiometric (BACTEC)	ESP Myco	MGIT	BacT/ALERT MB†
First-line drugs						
Isoniazid	0.2‡	0.2‡	0.1‡	0.1‡	0.1	0.09
Isoniazid (high)	1.0	1.0	0.4	0.4	0.4	0.4
Rifampin§	1.0‡	1.0	2.0‡	1.0‡	1.0	0.9
Ethambutol	5.0‡	7.5	2.5‡	5.0‡	5.0	2.3
Pyrazinamide	NR	NR	100.0‡	—	100.0	200.0
Second-line drugs						
Streptomycin	2.0‡	2.0	2.0‡	—	1.0	0.9
Streptomycin (high)	10.0	10.0	6.0	—	4.0	—
Ethambutol (high)¶	10.0	10.0	7.5	—	7.5	—
Capreomycin	10.0	10.0				
Ethionamide	5.0	10.0				
Kanamycin#	5.0	6.0				
Ofloxacin	2.0	2.0				
p-Aminosalicylic acid	2.0	8.0				
Rifabutin**	0.5	0.5				

Definition of abbreviations: ESP Myco = ESP (Extra Sensing Power) Culture System II; BacT/ALERT MB = BacT/ALERT MB susceptibility kit; MGIT = mycobacterial growth indicator tube; NR = not recommended.

Source: Adapted from Woods GL. Susceptibility testing for mycobacteria. Clin Infect Dis 2000;31:1209–1215; National Committee for Clinical Laboratory Standards (NCCLS). Susceptibility testing of mycobacteria, *Nocardia*, and other aerobic actinomycetes, 2nd edition. Tentative standard M24-T2. Wayne, PA: National Committee for Clinical Laboratory Standards; 2000. Available at http://www.nccls.org/microbiology.htm

* Concentration in micrograms per milliliter.

† BacT/ALERT MB is not currently FDA approved for susceptibility tests.

‡ Critical concentration of the drug in this medium.

§ Rifampin is the class agent for rifapentene.

¶ Isolates of *M. tuberculosis* that are resistant to rifampin or resistant to any two primary drugs should be tested for susceptibility to the secondary drugs. In addition, the NCCLS recommends a higher concentration of ethambutol (i.e., 10 mg/ml in both 7H10 and 7H11 agar) should be tested.

\# Kanamycin is the class agent for amikacin.

** Some investigators also test a higher concentration (usually 1.0 or 2.0 mg/ml) of rifabutin.

and is not distinguished from *M. tuberculosis* by nucleic acid hybridization–probe assays that are commonly used for identification).

Table 16 contains regimens suggested for use in patients with various patterns of drug-resistant tuberculosis.

9.4. Role of Surgery in MDR Tuberculosis

The role of resectional surgery in the management of patients with extensive pulmonary MDR tuberculosis has not been established in randomized studies. In one series, patients with severe drug resistance (on average, having resistance to more than 5 drugs) appeared to benefit from the resection of cavitary or badly damaged lung tissue when compared with historical controls (*31*). In contrast, other clinicians have reported patients with drug resistance having similar cure rates without surgery (*25,32*). The disparity in these reports may be due to long-standing disease with extensive fibrosis in the former group. If surgery is to be done, it should be performed by an experienced surgeon after the patient has received several months of intensive chemotherapy. Even with successful resection, 12–24 additional months of chemotherapy, using drugs to which there is demonstrated susceptibility, should be given.

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9.5 Laboratory Considerations in Determining Drug Resistance

Susceptibility testing of *M. tuberculosis* is critical for appropriate patient management and should be performed on an initial isolate from all patients from whom *M. tuberculosis* is recovered (*1*). Public health laboratories routinely will perform susceptibility testing on initial isolates but, often, private laboratories do not perform such testing unless specifically requested to do so by the physician. As noted previously, susceptibility testing should be repeated if the patient still has a positive culture result after 3 months of therapy or again develops positive cultures after a period of negative cultures (*2*). Antimicrobial susceptibility testing should be performed using a standard methodology, such as that recommended by the National Committee for Clinical Laboratory Standards (*3*). The second edition of a tentative standard (M24-T2) for sus-

Obtaining Drug Susceptibility Tests

Drug susceptibility testing for INH, RIF and EMB should be performed on an initial isolate of *M. tuberculosis* from all patients. Susceptibility testing for first-line and second line drugs should be performed for all patients with possible treatment failure or relapse. Most public health laboratories will perform initial susceptibility tests without a specific request, but this may not be true for private laboratories. Testing for susceptibility to the second-line drugs should be performed only in reference laboratories.

ceptibility testing of mycobacteria was published by the National Committee for Clinical Laboratory Standards in 2000 (*3*).

Susceptibility of *M. tuberculosis* is determined by evaluating the ability of an isolate to grow on agar or in broth containing a single "critical" concentration of a drug (*2*). The agar proportion method has been proposed as the reference method for all antituberculosis drugs except pyrazinamide, in which case the BACTEC broth-based methodology is the reference method (*3*). With the agar proportion method, resistance is defined as growth on the drug-containing plate that is more than 1% of the growth on the non–drug-containing plate (*4*). Because the agar method requires up to 6 weeks to yield results, it is recommended that initial susceptibility testing of *M. tuberculosis* isolates to first-line antituberculosis drugs be performed using more rapid broth-based methods (e.g., BACTEC and others). The goal, as stated by CDC, is to have culture and susceptibility results (to first-line drugs) available within 28 days of receipt of a clinical specimen (*5*). The critical concentrations recommended by the National Committee for Clinical Laboratory Standards for agar proportion method and "equivalent" concentrations for broth-based testing methods are shown in Table 17 (*2,3*).

The National Committee for Clinical Laboratory Standards recommends that susceptibility testing be performed for INH (two concentrations) and RIF and EMB (one concentration each) using a broth-based method on all initial *M. tuberculosis* isolates. Pyrazinamide testing may be done if there is a sufficiently high prevalence of PZA resistance. It is also recommended that the full panel of drugs (including second-line drugs) be tested when there is resistance to RIF alone or to two or more drugs. Testing of second-line drugs is performed using the agar proportion method, generally by public health laboratories. Secondary antituberculous drugs used for testing are capreomycin, ethionamide, kanamycin (which also predicts amikacin susceptibility), ofloxacin (used to assess fluoroquinolone activity), PAS, rifabutin, and SM (*3*). For second-line drug testing, a second concentration of EMB is also recommended. Susceptibility testing for cycloserine is not recommended because of the technical problems associated with the test.

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10. Treatment Of Tuberculosis in Low-Income Countries: Recommendations and Guidelines of the WHO and the IUATLD

This brief summary of the differences between the recommendations for treatment of tuberculosis in high-income, low-incidence countries and low-income, high incidence countries is presented to provide an international context for the ATS/CDC/IDSA guidelines. As tuberculosis in low-incidence countries, such as the United States, becomes more and more a reflection of the situation in high-incidence countries, it is important that health care providers in low-incidence countries have an understanding of the differences in the approaches used and the reasons for these differences so as to be better equipped to treat the increasing proportion of patients from high-incidence countries (*1*). As noted at the outset of this document, the ATS/CDC/IDSA recommendations cannot be assumed to be applicable under all epidemiologic and economic circumstances. The incidence of tuberculosis and the resources with which to confront it to an important extent determine the approaches used.

A number of differences exist between these new ATS/CDC/IDSA recommendations, and the current tuberculosis treatment recommendations of WHO (*2*) and IUATLD (*3*), the two major sets of international guidelines. Rather than being recommendations per se, the IUATLD document presents a distillation of IUATLD practice, validated in the field. The WHO and the IUATLD documents target, in general, countries in which mycobacterial culture and susceptibility testing and radiographic examinations are not widely available. These organizations recommend a tuberculosis control strategy called "DOTS" (Directly Observed Treatment, Short-Course) in which direct observation of therapy ("DOT" in the current statement) is only one of five key elements (*4*). The boxed insert lists the elements of DOTS strategy.

Selected important differences among the recommendations are summarized below. Some of the differences arise from variations in strategies, based on availability of resources, whereas others, such as the use of twice weekly regimens, arise from different interpretations of common elements, for example, whether DOT is used throughout the entire course of therapy or is limited to the initial phase.

10.1. Microbiological Tests for Diagnosis and Evaluation of Response

The WHO and the IUATLD recommend diagnosis and classification of cases and assessment of response based on sputum AFB smears. The AFB smear is emphasized because access to reliable culture facilities is limited in many countries. In addition, the AFB smear identifies patients who are most likely to transmit the organism. Susceptibility testing for new patients is not recommended because of cost, limited applicability and lack of facilities. However, susceptibility testing is recommended by the WHO for patients who fail (sputum smear–positive in month 5 of treatment or later during the course of treatment) the initial treatment regimen, and for those who fail a supervised retreatment regimen. Regarding follow-up, it is recommended by the WHO and the IUATLD that patients who have initial positive smears have repeat smears examined at 2 months, 5 months, and at completion of treatment (either 6 or 8 months). The IUATLD recommends that for patients who have positive smears at 2 months, the initial phase should be extended for 1 month.

Five Components of the DOTS Strategy

- Government commitment to sustained TB control activities.
- Case detection by sputum smear microscopy among symptomatic patients self-reporting to health services.
- Standardized treatment regimen of 6–8 months for at least all confirmed sputum smear positive cases, with directly observed treatment (DOT) for at least the initial 2 months.
- A regular, uninterrupted supply of all essential antituberculosis drugs.
- A standardized recording and reporting system that allows assessment of treatment results for each patient and of the TB control program overall.

10.2. Use of Chest Radiographs in Diagnosis and Follow-Up of Patients Being Treated

In many parts of the world radiographs are not readily available. Moreover, because the highest priority for treatment is the highly infectious sputum smear–positive patient, there is concern that treatment based on radiographic findings alone is an inefficient use of resources. Thus, chest radiography is recommended by both the WHO and the IUATLD only for patients with negative sputum smears and is not recommended at all for follow-up.

10.3. Initial Treatment Regimens

The WHO recommends a single initial phase of daily INH, RIF, PZA, and EMB (or SM) for 2 months followed by a continuation phase of either daily or three times a week INH and RIF, all given by DOT, for 4 months or daily INH and EMB for 6 months (self-administered). The WHO specifically discourages programs from using twice weekly regimens, the reason being that there is a lesser margin of safety if a dose or doses are missed.

The IUATLD recommends a 2-month initial phase of INH, RIF, PZA, and EMB given by DOT, followed by a 6-month continuation phase of daily INH and thiacetazone, self-administered. For patients with HIV infection the IUATLD recommends EMB in place of thiaocetazone. The IUATLD also recommends a 12-month regimen with a 2-month initial phase of INH, SM, and thioacetazone given daily and a 10-month continuation phase of daily INH and thioacetazone. This regimen is intended to be used for patients who have negative smears or when the 8-month regimen is not available.

The rationale for the 8-month regimen recommendation is that it is felt that RIF should always be given by DOT; yet, many programs cannot afford to provide the supervision required by DOT for the full 6 months of treatment. The 8-month regimen is less efficacious in patients with drug-susceptible tuberculosis, but use of this regimen will likely preserve RIF for use in retreatment regimens. In addition to the issue of supervision, the 8-month regimen's continuation phase of INH and EMB costs about 27% less than a 4-month continuation phase of daily INH and RIF.

10.4. Approach to Previously Treated Patients

The WHO and the IUATLD recommend a standardized regimen for patients who have relapsed, had interrupted treatment, or have failed treatment. (The approach to this last group of patients is currently under discussion at the WHO.) The regimen consists of an initial phase of INH, RIF, PZA, EMB, and SM given daily for 2 months and then 1 month of daily INH, RIF, PZA, and EMB. The continuation phase consists of 5 months of daily INH, RIF, and EMB.

Patients who have failed supervised retreatment are considered "chronic" cases and are highly likely to have tuberculosis caused by MDR organisms. Susceptibility testing and a tailored regimen using second-line drugs based on the test results are recommended by the WHO, if testing and second-line drugs are available (*5*). The IUATLD recommendations do not address the issue.

The issue of chronic cases is an area of considerable controversy (*6*). In countries with sufficient resources, such as the

United States, individualized retreatment regimens, based on drug susceptibility patterns, as described in Section 9, Management of Relapse, Treatment Failure, and Drug Resistance, are recommended. However, in countries without the capacity to obtain susceptibility tests, individualized regimens cannot be prescribed. Nevertheless, at least one group has demonstrated that in a high-incidence, low-income country (Peru) treatment with individualized regimens is feasible and effective (*7*).

10.5. Monitoring of Outcomes of Therapy

Both the WHO and the IUATLD recommend a formal system for monitoring outcomes of treatment that classifies all cases into one of six categories (cured, completed without proof of cure, failed, died, defaulted, or transferred out). The assessment of cure is based on clinical response and on sputum AFB smear (or culture when available) at completion of treatment. The analysis of these outcomes is by temporal cohorts and enables identification of programmatic shortcomings.

10.6. Recommended Doses of Antituberculosis Drugs

The WHO recommends 10 mg/kg as the dose for three times weekly INH, whereas the ATS/CDC/IDSA recommend 15 mg/kg (Table 3). There is no difference in the daily doses recommended for adults (5 mg/kg per day to a maximum of 300 mg/day), but the ATS/CDC/IDSA recommend a higher dose for children (10–15 mg/kg per day), based primarily on the expert opinion of pediatricians. The IUATLD recommendations are based on the number of pills required for three weight ranges resulting in a dose of about 5 mg/kg up to 300 mg/day.

The clinical trials of the BMRC that established the efficacy of three times weekly regimens all used an INH dose of 15 mg/kg. The 10-mg/kg INH dose for thrice-weekly regimens was extrapolated by the WHO and the IUATLD (with assistance from global experts), and was chosen to maintain the weekly amount of INH approximately equal to that of the daily or twice weekly regimens.

10.7. Drugs/Preparations Not Available in the United States

Thioacetazone, which formerly was commonly used, is still available in most parts of the world, but is used less frequently. However, thioacetazone remains listed as an "essential" first-line drug by the WHO and is a component of the recommended IUATLD first-line regimen. Combination preparations not available in the United States but listed by the WHO include the following: INH (150 mg) and EMB (400 mg); INH (100 mg) and thioacetazone (50 mg); and INH (75 mg), RIF (150 mg), PZA (400 mg), and EMB (275 mg). The IUATLD recommends using only combination preparations of INH and RIF or INH and thiacetazone.

10.8. Treating Pregnant Women

Both the WHO and the IUATLD include PZA in the regimen for treating pregnant women, in the absence of data indicating that there are adverse consequences.

10.9. Management of Common Adverse Reactions

Neither baseline nor follow-up testing is recommended by the WHO and the IUATLD. It is recommended that patients be taught to recognize the symptoms associated with drug toxicity and to report them promptly.

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11. Research Agenda for Tuberculosis Treatment

11.1. New Antituberculosis Drugs

New antituberculosis drugs are needed for three reasons: to shorten or otherwise simplify treatment of tuberculosis caused by drug-susceptible organisms, to improve the treatment of patients with MDR tuberculosis, and to provide more effective and efficient treatment of latent tuberculosis infection (LTBI) (*1*). Although treatment regimens for drug-susceptible tuberculosis are effective, they must be administered for a minimum of 6 months to achieve optimal results.

Nonadherence to this relatively lengthy course of treatment remains a major problem. To address the problem of nonadherence, DOT (as a component of the DOTS strategy) is recommended as a standard of care worldwide. However, the administrative and financial burden of providing DOT for all patients is considerable. Thus, new drugs that would permit significant shortening of treatment are urgently needed, as are drugs that could enable effective treatment to be given at dosing intervals of 1 week or more.

Rates of multidrug-resistant tuberculosis are alarmingly high in several countries (*2*), and even in countries, such as the United States, where the rates are low and decreasing, the occasional case presents an often extremely difficult treatment problem (see Section 9: Management of Relapse, Treatment Failure, and Drug Resistance). Current treatment regimens for drug-resistant tuberculosis utilize drugs that are less effective, more toxic, and more expensive than those used for standard treatment. Moreover, these treatment regimens often have to be given for 18–24 months. Although new drugs that are effective against resistant organisms would alone not solve the problem of drug resistance, their judicious use would greatly improve the treatment for many patients.

Finally, the United States and several other low-incidence countries have embarked on plans to eliminate tuberculosis. An important component of an elimination strategy is the identification and treatment of persons with LTBI who are at high risk of developing tuberculosis (*3*). In the United States the most commonly used LTBI treatment regimen is INH given for 9 months; however, poor adherence to this regimen imposes a major limitation on its effectiveness. A shorter LTBI treatment regimen with RIF and PZA appears to be effective, but reports have indicated that toxicity may be unacceptably high (*4*). Thus, new drugs to provide for safe and effective "short-course" LTBI treatment are a major need.

No truly novel compounds that are likely to have a significant impact on tuberculosis treatment are presently available for clinical study. However, further work to optimize the effectiveness of once weekly rifapentine regimens and investigate the role of newer fluoroquinolones in the treatment of drug-susceptible tuberculosis is warranted. As noted above, once weekly rifapentine–INH is recommended only in the continuation phase for HIV-negative patients with noncavitary pulmonary tuberculosis who have negative sputum smears at completion of 2 months of treatment. Two approaches to improve intermittent rifapentine regimens have been suggested by experimental studies: increasing the rifapentine dosage (*5*), and adding moxifloxacin as a companion drug to provide better protection against the development of drug resistance and enhance the sterilizing activity of the regimen (*6*). Other data from a clinical trial of ofloxacin suggest that fluoroquinolones have the potential to significantly shorten treatment (*7*). Of the newer fluoroquinolones with more potent activity against *M. tuberculosis*, moxifloxacin appears to be the most promising.

Other compounds that might become available for clinical evaluation in the future include the nitroimidazopyrans that are chemically related to metronidazole, for which activity against dormant *M. tuberculosis* has been suggested; oxazolidinones such as linezolid; and drugs that target isocitrate lyase, an enzyme that may be necessary for the establishment of latent tuberculosis infection (*8*). The nitroimidazopyran compound PA-824 has bactericidal activity comparable to that of INH and appears to act as well on bacilli maintained in an anaerobic environment (*9*). However, additional preclinical evaluation of PA-824 is needed before clinical studies could begin. Although linezolid, a drug that is marketed for the treatment of selected acute bacterial infections, does have demonstrated activity against *M. tuberculosis*, other compounds in that class may be more suited for the treatment of tuberculosis (*10*).

11.2. Other Interventions To Improve the Efficacy of Treatment

A number of other approaches have been suggested that might lead to improved treatment outcome, including alternative drug delivery systems and a variety of methods of immunomodulation and immunotherapy. Experimental studies have demonstrated that effective serum concentrations of INH and PZA can be provided through incorporation of drug into slow-release, biodegradable polymers that are implanted subcutaneously (*11*). However, there has been little apparent commercial interest in pursuing this approach. Liposomal encapsulation of antituberculosis drugs has been suggested as an approach to direct drug to the proposed site of infection (i.e., the macrophage) providing for more effective and better tolerated therapy, as well as for more widely spaced treatment. Similarly, incorporation of drug into inhalable microparticles may reduce dose requirements, minimize toxicity, and deliver drug to infected alveolar macrophages. Although experimental studies have suggested that these approaches might be effective, little clinical work has been done in these areas (*11,12*).

Because of possible detrimental effects of the cytokine, tumor necrosis factor-α, in HIV-associated tuberculosis, there has been some interest in the use of drugs, such as thalidomide and pentoxifylline, that block tumor necrosis factor-α production. Studies have shown that administration of thalidomide improves weight gain in both HIV-positive and HIV-negative tuberculosis patients (*13*). Pentoxifylline has been associated with reductions in circulating HIV viral load in

patients with tuberculosis (*14*). However, the potential side effects of these drugs may outweigh possible benefits. A more promising intervention is the administration of "protective" cytokines, such as aerosolized interferon-γ and subcutaneous interleukin-2, that have shown activity as adjuncts to chemotherapy in patients with multidrug-resistant tuberculosis (*15,16*). Another method of immunomodulation, the use of heat-killed preparations of *M. vaccae* as a therapeutic vaccine, has not shown clinically significant benefits when carefully evaluated in randomized clinical trials (*17*). Nonetheless, there continues to be interest in this approach, especially for patients with advanced drug-resistant tuberculosis. Other vaccines that have been shown to lead to expression of protective cytokines have shown more promise in experimental studies (*18*). Finally, a study suggested that the administration of Vitamin A and zinc to patients with pulmonary tuberculosis is associated with an increased rate of sputum conversion and improvement in chest radiographs (*19*). Further assessment of nutritional supplements in tuberculosis treatment may be indicated.

11.2.1. Better methods to identify and manage high- and low-risk patients

As noted above, sputum culture positivity at 2 months appears to be a marker for an increased risk of relapse for patients with pulmonary tuberculosis. Surrogate markers that could be measured earlier in therapy and have a greater sensitivity and specificity for a poor outcome could better select high risk patients for more intensive or longer therapy, thus minimizing the likelihood of relapse. Studies of several molecular markers in the sputum have shown promise and deserve further evaluation (*20*). Conversely, markers that reliably identify patients at lower risk of an adverse treatment outcome would be helpful to select patients for less intense or shorter treatment. Whether or not low-risk patients can be treated with shorter regimens using currently available drugs is a topic of considerable importance.

11.2.2. Health services research to facilitate treatment administration and improve treatment outcome

Although DOT (as a component of DOTS) is widely advocated as a universal standard of care for tuberculosis treatment, many tuberculosis control programs do not have the resources to provide DOT for all patients. Moreover, some programs have achieved excellent results by targeting DOT to patients known or suspected of being at increased risk for nonadherence. Further evaluation of alternatives to universal DOT is needed.

Finally, although limited work has been done in the area of behavioral studies of tuberculosis patients and providers, an ambitious research agenda established in the mid-1990s has not been implemented and should be revisited (21).

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Goal and Objectives

This *MMWR* provides recommendations regarding treatment for tuberculosis (TB) infection in the United States. These recommendations were developed by the American Thoracic Society, CDC staff, and the Infectious Disease Society of America. The goal of this report is to provide guidance for health-care providers and public health professionals regarding the treatment for active TB among adults and children in the United States. Upon completion of this educational activity, the reader should be able to 1) describe the principles of antituberculosis chemotherapy; 2) describe the current recommendations for treating tuberculosis; 3) describe how to treat TB in special situations; 4) describe precautions regarding treatment regimens for TB; and 5) describe how to manage disease relapse, treatment failure, and drug resistance.

To receive continuing education credit, please answer all of the following questions.

1. Which of the following groups should be given high priority for directly observed therapy (DOT)?

A. Persons with current or prior substance abuse.
B. Persons with memory impairment.
C. Persons having pulmonary TB with positive sputum smears.
D. Persons who have been previously treated for latent TB infection.
E. All of the above groups.

2. Which of the following statements is false concerning sputum cultures?

A. Sputum cultures should be obtained at the end of the initial treatment phase.
B. Patients with positive cultures at diagnosis must have a repeat chest radiograph at 2 months.
C. If a positive culture is obtained at 2 months in a patient with initial chest cavitation, the total treatment regimen should be extended to 9 months.
D. Cultures that are initially positive should undergo susceptibility testing for isoniazid, rifampin, and ethambutol.

3. Which of the following is the preferred treatment regimen for TB among HIV-positive persons?

A. Daily isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by once weekly isoniazid and rifapentine for 4 months.
B. Daily isoniazid, rifampin, and ethambutol for 2 months, followed by daily isoniazid and rifampin for 4 months.
C. Daily isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by daily isoniazid and rifampin for 4 months.
D. Daily isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by thrice weekly isoniazid and rifampin for 4 months.

4. Which of the following is the preferred treatment regimen for TB among children?

A. Thrice weekly isoniazid, ethambutol, and rifapentine for 2 months, followed by thrice weekly isoniazid and rifapentine for 4 months.
B. Daily isoniazid and rifampin supplemented with pyrazinamide for 2 months, followed by daily isoniazid and rifampin for 4 months.
C. Daily isoniazid, rifampin, and ethambutol for 2 months, followed by daily isoniazid and rifapentine for 4 months.
D. Daily isoniazid, rifampin, streptomycin, and ethambutol for 2 months, followed by thrice weekly isoniazid and rifampin for 4 months.

5. Which of the following statements is true concerning management of adverse effects?

A. If a patient with severe TB experiences a rash or fever, three new drugs should be administered in the interim before medications are restarted one by one.
B. Rifampin should be excluded from the treatment regimen for patients who experience drug-induced hepatitis.
C. Patients experiencing adverse effects from first-line drugs should switch to second-line drugs.
D. Modest asymptomatic elevations of aspartate aminotransferase (AST) require changing the treatment regimen.

6. Which of the following is a clinically relevant drug–drug interaction?

A. Rifabutin and CYP3A inducers.
B. Isoniazid and certain anticonvulsants.
C. Rifampin and the majority of human immunodeficiency virus type 1(HIV-1) protease-inhibitors.
D. Ciprofloxacin and theophylline.
E. All of the above.

7. Which of the following statements is true concerning interruptions in treatment?

A. The duration of interruptions in treatment alone determines whether the regimen should be restarted.
B. Continuous treatment is more important in the continuation phase of therapy.
C. DOT is not necessary for brief interruptions in treatment.
D. Patients who complete >80% of the planned total doses in the continuation phase may not need additional treatment.

8. Which of the following regimens is preferred for treatment of persons with radiographic evidence of prior TB and negative sputum cultures who were not treated previously?

A. Isoniazid and pyrazinamide for 4 months.
B. Isoniazid for 9 months.
C. Rifampin and pyrazinamide for 2 months.
D. Rifampin with or without isoniazid for 4 months.

9. Which of the following guidelines is not recommended for the management of patients with multidrug-resistant TB?

A. When initiating therapy, ≥3 previously unused drugs that have in vitro susceptibility should be used.
B. An injectable agent should be included in the treatment regimen.
C. In cases of rifampin resistance, rifabutin and rifapentine should be included in the treatment regimen.
D. Patients should receive either hospital-based or domiciliary DOT.

10. Which of the following is a component of a patient-centered management system?

A DOT as the main strategy.
B. The public health system with ultimate responsibility for patient care.
C. Culturally sensitive patient education materials.
D. Availability of social service assistance.
E. All of the above.

11. Indicate your work setting.

A. State/local health department.
B. Other public health setting.
C. Hospital clinic/private practice.
D. Managed care organization.
E. Academic institution.
F. Other.

12. Which best describes your professional activities?

A. Physician.
B. Nurse.
C. Health educator.
D. TB control staff.
E. Other.

13. I plan to use these recommendations as the basis for . . . (*Indicate all that apply.*)

A. health education materials.
B. insurance reimbursement policies.
C. local practice guidelines.
D. public policy.
E. other.

14. Each month, approximately how many patients with TB do you treat?

A. None.
B. 1–5.
C. 6–20.
D. 21–50.
E. 51–100.
F. >100.

15. How much time did you spend reading this report and completing the exam?

A. <2.0 hours.
B. ≥2.0 hours but <3.0 hours.
C. ≥3.0 hours but <4.0.
D. ≥4.0 hours.

16. After reading this report, I am confident I can describe the principles of antituberculosis chemotherapy.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

17. After reading this report, I am confident I can describe the current recommendations for treating TB.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

18. After reading this report, I am confident I can describe how to treat TB in special situations.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

19. After reading this report, I am confident I can describe precautions regarding treatment regimens for TB.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

20. After reading this report, I am confident I can describe how to manage disease relapse, treatment failure, and drug resistance.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

(Continued on pg CE-4)

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June 20, 2006/Vol. 52/No. RR-11
Treatment of Tuberculosis
American Thoracic Society, CDC, and Infectious Diseases Society of America

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1. [ ] A [ ] B [ ] C [ ] D [ ] E
2. [ ] A [ ] B [ ] C [ ] D
3. [ ] A [ ] B [ ] C [ ] D
4. [ ] A [ ] B [ ] C [ ] D
5. [ ] A [ ] B [ ] C [ ] D
6. [ ] A [ ] B [ ] C [ ] D [ ] E
7. [ ] A [ ] B [ ] C [ ] D
8. [ ] A [ ] B [ ] C [ ] D
9. [ ] A [ ] B [ ] C [ ] D
10. [ ] A [ ] B [ ] C [ ] D [ ] E
11. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F
12. [ ] A [ ] B [ ] C [ ] D [ ] E
13. [ ] A [ ] B [ ] C [ ] D [ ] E
14. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F
15. [ ] A [ ] B [ ] C [ ] D
16. [ ] A [ ] B [ ] C [ ] D [ ] E
17. [ ] A [ ] B [ ] C [ ] D [ ] E
18. [ ] A [ ] B [ ] C [ ] D [ ] E
19. [ ] A [ ] B [ ] C [ ] D [ ] E
20. [ ] A [ ] B [ ] C [ ] D [ ] E
21. [ ] A [ ] B [ ] C [ ] D [ ] E
22. [ ] A [ ] B [ ] C [ ] D [ ] E
23. [ ] A [ ] B [ ] C [ ] D [ ] E
24. [ ] A [ ] B [ ] C [ ] D [ ] E
25. [ ] A [ ] B [ ] C [ ] D [ ] E
26. [ ] A [ ] B [ ] C [ ] D [ ] E
27. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F

Signature *Date I Completed Exam*

21. The objectives are relevant to the goal of this report.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

22. The teaching strategies used in this report (text, figures, boxes, and tables) were useful.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

23. Overall, the presentation of the report enhanced my ability to understand the material.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

24. These recommendations will affect my practice.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

25. The content of this activity was appropriate for my educational needs.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

26. The availability of continuing education credit influenced my decision to read this report.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

27. How did you learn about this continuing education activity?

A. Internet.
B. Advertisement (e.g., fact sheet, *MMWR* cover, newsletter, or journal).
C. Coworker/supervisor.
D. Conference presentation.
E. *MMWR* subscription.
F. Other.

Correct answers for questions 1–10.
1. E; 2. B; 3. C; 4. B; 5. A; 6. E; 7. D; 8. B; 9. C; 10. E.

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Notice to Readers

National Birth Defects Prevention Month and National Folic Acid Awareness Week

January is National Birth Defects Prevention Month, and January 24–30 is National Folic Acid Awareness Week. Birth defects affect approximately 120,000 (one in 33) newborns in the United States each year; they are the leading cause of infant mortality and contribute substantially to illness and long-term disability. Lifetime costs for those infants born in a single year with one or more of the 17 most clinically important birth defects has been estimated to total $6 billion (*1*).

Health-care professionals can help prevent birth defects by encouraging women of childbearing age to follow healthy preconceptional and prenatal practices, including taking multivitamins containing folic acid and avoiding alcohol consumption. Taking the B vitamin folic acid before and during early pregnancy can prevent serious birth defects of the spine and brain (i.e., neural tube defects). The rates of such birth defects declined 26% after folic acid was first added to cereal-grain products in 1998. However, approximately 3,000 pregnancies each year in the United States continue to be affected by these defects (*2*). Similarly, alcohol consumption in pregnancy is widely known as a cause of fetal alcohol spectrum disorders, yet some women continue to consume alcohol during pregnancy (*3*).

Information on CDC activities regarding birth defects is available at http://www.cdc.gov/ncbddd. Information on Birth Defects Prevention Month is available from the March of Dimes (http://www.marchofdimes.com) and the National Birth Defects Prevention Network (http://www.nbdpn.org/nbdpn/bdpm2005.html). Information on National Folic Acid Awareness Week is available from the National Council on Folic Acid (http://www.folicacidinfo.org).

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Errata: Vol. 52, No. RR-11

In the *MMWR Recommendations and Reports*, "Treatment of Tuberculosis: American Thoracic Society, CDC, and Infectious Diseases Society of America," two errors occurred. In Table 3 (pages 4–5), the subheading of the second column under "Doses" should read, "1x/wk." On page 25, column 2, in section 3.2.1 Cycloserine, the adult dosage should read, "Serum concentration measurements aiming for a peak concentration of 20–35 mg/l are often useful in determining the optimum dose for a given patient."

MMWR™

Morbidity and Mortality Weekly Report

Recommendations and Reports December 30, 2005 / Vol. 54 / No. RR-17

Guidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in Health-Care Settings, 2005

INSIDE: Continuing Education Examination

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

The *MMWR* series of publications is published by the Coordinating Center for Health Information and Service, Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services, Atlanta, GA 30333.

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Guidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in Health-Care Settings, 2005

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Summary

In 1994, CDC published the Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Facilities, 1994. *The guidelines were issued in response to 1) a resurgence of tuberculosis (TB) disease that occurred in the United States in the mid-1980s and early 1990s, 2) the documentation of several high-profile health-care–associated (previously termed "nosocomial") outbreaks related to an increase in the prevalence of TB disease and human immunodeficiency virus (HIV) coinfection, 3) lapses in infection-control practices, 4) delays in the diagnosis and treatment of persons with infectious TB disease, and 5) the appearance and transmission of multidrug-resistant (MDR) TB strains. The 1994 guidelines, which followed statements issued in 1982 and 1990, presented recommendations for TB-infection control based on a risk assessment process that classified health-care facilities according to categories of TB risk, with a corresponding series of administrative, environmental, and respiratory-protection control measures.*

The TB infection-control measures recommended by CDC in 1994 were implemented widely in health-care facilities in the United States. The result has been a decrease in the number of TB outbreaks in health-care settings reported to CDC and a reduction in health-care–associated transmission of Mycobacterium tuberculosis *to patients and health-care workers (HCWs). Concurrent with this success, mobilization of the nation's TB-control programs succeeded in reversing the upsurge in reported cases of TB disease, and case rates have declined in the subsequent 10 years. Findings indicate that although the 2004 TB rate was the lowest recorded in the United States since national reporting began in 1953, the declines in rates for 2003 (2.3%) and 2004 (3.2%) were the smallest since 1993. In addition, TB infection rates greater than the U.S. average continue to be reported in certain racial/ethnic populations. The threat of MDR TB is decreasing, and the transmission of* M. tuberculosis *in health-care settings continues to decrease because of implementation of infection-control measures and reductions in community rates of TB.*

Given the changes in epidemiology and a request by the Advisory Council for the Elimination of Tuberculosis (ACET) for review and update of the 1994 TB infection-control document, CDC has reassessed the TB infection-control guidelines for health-care settings. This report updates TB control recommendations reflecting shifts in the epidemiology of TB, advances in scientific understanding, and changes in health-care practice that have occurred in the United States during the preceding decade. In the context of diminished risk for health-care–associated transmission of M. tuberculosis, *this document places emphasis on actions to maintain momentum and expertise needed to avert another TB resurgence and to eliminate the lingering threat to HCWs, which is mainly from patients or others with unsuspected and undiagnosed infectious TB disease. CDC prepared the current guidelines in consultation with experts in TB, infection control, environmental control, respiratory protection, and occupational health. The new guidelines have been expanded to address a broader concept; health-care–associated settings go beyond the previously defined facilities. The term "health-care setting" includes many types, such as inpatient settings, outpatient settings, TB clinics, settings in correctional facilities in which health care is delivered, settings in which home-based health-care and emergency medical services are provided, and laboratories handling clinical specimens that might contain* M. tuberculosis. *The term "setting" has been chosen over the term "facility," used in the previous guidelines, to broaden the potential places for which these guidelines apply.*

The material in this report originated in the National Center for HIV, STD, and TB Prevention, Kevin Fenton, MD, PhD, Director; and the Division of Tuberculosis Elimination, Kenneth G. Castro, MD, Director.
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Introduction

Overview

In 1994, CDC published the *Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health Care Facilities, 1994* (*1*). The guidelines were issued in response to 1) a resurgence of tuberculosis (TB) disease that occurred in the United States in the mid-1980s and early 1990s, 2) the

documentation of multiple high-profile health-care–associated (previously "nosocomial") outbreaks related to an increase in the prevalence of TB disease and human immunodeficiency virus (HIV) coinfection, 3) lapses in infection-control practices, 4) delays in the diagnosis and treatment of persons with infectious TB disease (*2,3*), and 5) the appearance and transmission of multidrug-resistant (MDR) TB strains (*4,5*).

The 1994 guidelines, which followed CDC statements issued in 1982 and 1990 (*1,6,7*), presented recommendations for TB infection control based on a risk assessment process. In this process, health-care facilities were classified according to categories of TB risk,with a corresponding series of environmental and respiratory-protection control measures.

The TB infection-control measures recommended by CDC in 1994 were implemented widely in health-care facilities nationwide (*8–15*). As a result, a decrease has occurred in 1) the number of TB outbreaks in health-care settings reported to CDC and 2) health-care–associated transmission of *M. tuberculosis* to patients and health-care workers (HCWs) (*9,16–23*). Concurrent with this success, mobilization of the nation's TB-control programs succeeded in reversing the upsurge in reported cases of TB disease, and case rates have declined in the subsequent 10 years (*4,5*). Findings indicate that although the 2004 TB rate was the lowest recorded in the United States since national reporting began in 1953, the declines in rates for 2003 (2.3%) and 2004 (3.2%) were the lowest since 1993. In addition, TB rates higher than the U.S. average continue to be reported in certain racial/ethnic populations (*24*). The threat of MDR TB is decreasing, and the transmission of *M. tuberculosis* in health-care settings continues to decrease because of implementation of infection-control measures and reductions in community rates of TB (*4,5,25*).

Despite the general decline in TB rates in recent years, a marked geographic variation in TB case rates persists, which means that HCWs in different areas face different risks (*10*). In 2004, case rates varied per 100,000 population: 1.0 in Wyoming, 7.1 in New York, 8.3 in California, and 14.6 in the District of Columbia (*26*). In addition, despite the progress in the United States, the 2004 rate of 4.9 per 100,000 population remained higher than the 2000 goal of 3.5. This goal was established as part of the national strategic plan for TB elimination; the final goal is <1 case per 1,000,000 population by 2010 (*4,5,26*).

Given the changes in epidemiology and a request by the Advisory Council for the Elimination of Tuberculosis (ACET) for review and updating of the 1994 TB infection-control document, CDC has reassessed the TB infection-control guidelines for health-care settings. This report updates TB-control recommendations, reflecting shifts in the epidemiology of TB (*27*), advances in scientific understanding, and changes in health-care practice that have occurred in the United States in the previous decade (*28*). In the context of diminished risk for health-care–associated transmission of *M. tuberculosis*, this report emphasizes actions to maintain momentum and expertise needed to avert another TB resurgence and eliminate the lingering threat to HCWs, which is primarily from patients or other persons with unsuspected and undiagnosed infectious TB disease.

CDC prepared the guidelines in this report in consultation with experts in TB, infection control, environmental control, respiratory protection, and occupational health. This report replaces all previous CDC guidelines for TB infection control in health-care settings (*1,6,7*). Primary references citing evidence-based science are used in this report to support explanatory material and recommendations. Review articles, which include primary references, are used for editorial style and brevity.

The following changes differentiate this report from previous guidelines:

- The risk assessment process includes the assessment of additional aspects of infection control.
- The term "tuberculin skin tests" (TSTs) is used instead of purified protein derivative (PPD).
- The whole-blood interferon gamma release assay (IGRA), QuantiFERON®-TB Gold test (QFT-G) (Cellestis Limited, Carnegie, Victoria, Australia), is a Food and Drug Administration (FDA)–approved in vitro cytokine-based assay for cell-mediated immune reactivity to *M. tuberculosis* and might be used instead of TST in TB screening programs for HCWs. This IGRA is an example of a blood assay for *M. tuberculosis* (BAMT).
- The frequency of TB screening for HCWs has been decreased in various settings, and the criteria for determination of screening frequency have been changed.
- The scope of settings in which the guidelines apply has been broadened to include laboratories and additional outpatient and nontraditional facility-based settings.
- Criteria for serial testing for *M. tuberculosis* infection of HCWs are more clearly defined. In certain settings, this change will decrease the number of HCWs who need serial TB screening.
- These recommendations usually apply to an entire health-care setting rather than areas within a setting.
- New terms, airborne infection precautions (airborne precautions) and airborne infection isolation room (AII room), are introduced.

- Recommendations for annual respirator training, initial respirator fit testing, and periodic respirator fit testing have been added.
- The evidence of the need for respirator fit testing is summarized.
- Information on ultraviolet germicidal irradiation (UVGI) and room-air recirculation units has been expanded.
- Additional information regarding MDR TB and HIV infection has been included.

In accordance with relevant local, state, and federal laws, implementation of all recommendations must safeguard the confidentiality and civil rights of all HCWs and patients who have been infected with *M. tuberculosis* and TB disease.

The 1994 CDC guidelines were aimed primarily at hospital-based facilities, which frequently refer to a physical building or set of buildings. The 2005 guidelines have been expanded to address a broader concept. Setting has been chosen instead of "facility" to expand the scope of potential places for which these guidelines apply (Appendix A). "Setting" is used to describe any relationship (physical or organizational) in which HCWs might share air space with persons with TB disease or in which HCWs might be in contact with clinical specimens. Various setting types might be present in a single facility. Health-care settings include inpatient settings, outpatient settings, and nontraditional facility-based settings.

- Inpatient settings include patient rooms, emergency departments (EDs), intensive care units (ICUs), surgical suites, laboratories, laboratory procedure areas, bronchoscopy suites, sputum induction or inhalation therapy rooms, autopsy suites, and embalming rooms.
- Outpatient settings include TB treatment facilities, medical offices, ambulatory-care settings, dialysis units, and dental-care settings.
- Nontraditional facility-based settings include emergency medical service (EMS), medical settings in correctional facilities (e.g., prisons, jails, and detention centers), home-based health-care and outreach settings, long-term–care settings (e.g., hospice-skilled nursing facilities), and homeless shelters. Other settings in which suspected and confirmed TB patients might be encountered might include cafeterias, general stores, kitchens, laundry areas, maintenance shops, pharmacies, and law enforcement settings.

HCWs Who Should Be Included in a TB Surveillance Program

HCWs refer to all paid and unpaid persons working in health-care settings who have the potential for exposure to *M. tuberculosis* through air space shared with persons with infectious TB disease. Part time, temporary, contract, and full-time HCWs should be included in TB screening programs. All HCWs who have duties that involve face-to-face contact with patients with suspected or confirmed TB disease (including transport staff) should be included in a TB screening program.

The following are HCWs who should be included in a TB screening program:

- Administrators or managers
- Bronchoscopy staff
- Chaplains
- Clerical staff
- Computer programmers
- Construction staff
- Correctional officers
- Craft or repair staff
- Dental staff
- Dietician or dietary staff
- ED staff
- Engineers
- Food service staff
- Health aides
- Health and safety staff
- Housekeeping or custodial staff
- Homeless shelter staff
- Infection-control staff
- ICU staff
- Janitorial staff
- Laboratory staff
- Maintenance staff
- Morgue staff
- Nurses
- Outreach staff
- Pathology laboratory staff
- Patient transport staff, including EMS
- Pediatric staff
- Pharmacists
- Phlebotomists
- Physical and occupational therapists
- Physicians (assistant, attending, fellow, resident, or intern), including
  - — anesthesiologists
  - — pathologists
  - — psychiatrists
  - — psychologists
- Public health educators or teachers
- Public safety staff
- Radiology staff
- Respiratory therapists
- Scientists
- Social workers

- Students (e.g., medical, nursing, technicians, and allied health)
- Technicians (e.g., health, laboratory, radiology, and animal)
- Veterinarians
- Volunteers

In addition, HCWs who perform any of the following activities should also be included in the TB screening program.

- entering patient rooms or treatment rooms whether or not a patient is present;
- participating in aerosol-generating or aerosol-producing procedures (e.g., bronchoscopy, sputum induction, and administration of aerosolized medications) (*29*);
- participating in suspected or confirmed *M. tuberculosis* specimen processing; or
- installing, maintaining, or replacing environmental controls in areas in which persons with TB disease are encountered.

Pathogenesis, Epidemiology, and Transmission of *M. tuberculosis*

M. tuberculosis is carried in airborne particles called droplet nuclei that can be generated when persons who have pulmonary or laryngeal TB disease cough, sneeze, shout, or sing (*30,31*). The particles are approximately 1–5 μm; normal air currents can keep them airborne for prolonged periods and spread them throughout a room or building (*32*). *M. tuberculosis* is usually transmitted only through air, not by surface contact. After the droplet nuclei are in the alveoli, local infection might be established, followed by dissemination to draining lymphatics and hematogenous spread throughout the body (*33*). Infection occurs when a susceptible person inhales droplet nuclei containing *M. tuberculosis*, and the droplet nuclei traverse the mouth or nasal passages, upper respiratory tract, and bronchi to reach the alveoli. Persons with TB pleural effusions might also have concurrent unsuspected pulmonary or laryngeal TB disease.

Usually within 2–12 weeks after initial infection with *M. tuberculosis*, the immune response limits additional multiplication of the tubercle bacilli, and immunologic test results for *M. tuberculosis* infection become positive. However, certain bacilli remain in the body and are viable for multiple years. This condition is referred to as latent tuberculosis infection (LTBI). Persons with LTBI are asymptomatic (they have no symptoms of TB disease) and are not infectious.

In the United States, LTBI has been diagnosed traditionally based on a PPD-based TST result after TB disease has been excluded. In vitro cytokine-based immunoassays for the detection of *M. tuberculosis* infection have been the focus of intense research and development. One such blood assay for *M. tuberculosis* (or BAMT) is an IGRA, the QuantiFERON®-TB test (QFT), and the subsequently developed version, QFT-G. The QFT-G measures cell-mediated immune responses to peptides from two *M. tuberculosis* proteins that are not present in any Bacille Calmette-Guérin (BCG) vaccine strain and that are absent from the majority of nontuberculous mycobacteria (NTM), also known as mycobacteria other than TB (MOTT). QFT-G was approved by FDA in 2005 and is an available option for detecting *M. tuberculosis* infection. CDC recommendations for the United States regarding QFT and QFT-G have been published (*34,35*). Because this field is rapidly evolving, in this report, BAMT will be used generically to refer to the test currently available in the United States.

Additional cytokine-based immunoassays are under development and might be useful in the diagnosis of *M. tuberculosis* infection. Future FDA-licensed products in combination with CDC-issued recommendations might provide additional diagnostic alternatives. The latest CDC recommendations for guidance on diagnostic use of these and related technologies are available at http://www.cdc.gov/nchstp/tb/pubs/mmwrhtml/Maj_guide/Diagnosis.htm.

Typically, approximately 5%–10% of persons who become infected with *M. tuberculosis* and who are not treated for LTBI will develop TB disease during their lifetimes (*1*). The risk for progression of LTBI to TB disease is highest during the first several years after infection (*36–38*).

Persons at Highest Risk for Exposure to and Infection with *M. tuberculosis*

Characteristics of persons exposed to *M. tuberculosis* that might affect the risk for infection are not as well defined. The probability that a person who is exposed to *M. tuberculosis* will become infected depends primarily on the concentration of infectious droplet nuclei in the air and the duration of exposure to a person with infectious TB disease. The closer the proximity and the longer the duration of exposure, the higher the risk is for being infected.

Close contacts are persons who share the same air space in a household or other enclosed environment for a prolonged period (days or weeks, not minutes or hours) with a person with pulmonary TB disease (*39*). A suspect TB patient is a person in whom a diagnosis of TB disease is being considered, whether or not antituberculosis treatment has been started. Persons generally should not remain a suspect TB patient for >3 months (*30,39*).

In addition to close contacts, the following persons are also at higher risk for exposure to and infection with *M. tuberculosis.* Persons listed who are also close contacts should be top priority.

- Foreign-born persons, including children, especially those who have arrived to the United States within 5 years after

moving from geographic areas with a high incidence of TB disease (e.g., Africa, Asia, Eastern Europe, Latin America, and Russia) or who frequently travel to countries with a high prevalence of TB disease.
- Residents and employees of congregate settings that are high risk (e.g., correctional facilities, long-term–care facilities [LTCFs], and homeless shelters).
- HCWs who serve patients who are at high risk.
- HCWs with unprotected exposure to a patient with TB disease before the identification and correct airborne precautions of the patient.
- Certain populations who are medically underserved and who have low income, as defined locally.
- Populations at high risk who are defined locally as having an increased incidence of TB disease.
- Infants, children, and adolescents exposed to adults in high-risk categories.

Persons Whose Condition is at High Risk for Progression From LTBI to TB Disease

The following persons are at high risk for progressing from LTBI to TB disease:
- persons infected with HIV;
- persons infected with *M. tuberculosis* within the previous 2 years;
- infants and children aged <4 years;
- persons with any of the following clinical conditions or other immunocompromising conditions
  — silicosis,
  — diabetes mellitus,
  — chronic renal failure,
  — certain hematologic disorders (leukemias and lymphomas),
  — other specific malignancies (e.g., carcinoma of the head, neck, or lung),
  — body weight ≥10% below ideal body weight,
  — prolonged corticosteroid use,
  — other immunosuppressive treatments (including tumor necrosis factor-alpha [TNF-α] antagonists),
  — organ transplant,
  — end-stage renal disease (ESRD), and
  — intestinal bypass or gastrectomy; and
- persons with a history of untreated or inadequately treated TB disease, including persons with chest radiograph findings consistent with previous TB disease.

Persons who use tobacco or alcohol (*40,41*), illegal drugs, including injection drugs and crack cocaine (*42–47*), might also be at increased risk for infection and disease. However, because of multiple other potential risk factors that commonly occur among such persons, use of these substances has been difficult to identify as separate risk factors.

HIV infection is the greatest risk factor for progression from LTBI to TB disease (*22,39,48,49*). Therefore, voluntary HIV counseling, testing, and referral should be routinely offered to all persons at risk for LTBI (*1,50,51*). Health-care settings should be particularly aware of the need for preventing transmission of *M. tuberculosis* in settings in which persons infected with HIV might be encountered or might work (*52*).

All HCWs should be informed regarding the risk for developing TB disease after being infected with *M. tuberculosis* (*1*). However, the rate of TB disease among persons who are HIV-infected and untreated for LTBI in the United States is substantially higher, ranging from 1.7–7.9 TB cases per 100 person-years (*53*). Persons infected with HIV who are already severely immunocompromised and who become newly infected with *M. tuberculosis* have a greater risk for developing TB disease, compared with newly infected persons without HIV infection (*39,53–57*).

The percentage of patients with TB disease who are HIV-infected is decreasing in the United States because of improved infection-control practices and better diagnosis and treatment of both HIV infection and TB. With increased voluntary HIV counseling and testing and the increasing use of treatment for LTBI, TB disease will probably continue to decrease among HIV-infected persons in the United States (*58*). Because the risk for disease is particularly high among HIV-infected persons with *M. tuberculosis* infection, HIV-infected contacts of persons with infectious pulmonary or laryngeal TB disease must be evaluated for *M. tuberculosis* infection, including the exclusion of TB disease, as soon as possible after learning of exposure (*39,49,53*).

Vaccination with BCG probably does not affect the risk for infection after exposure, but it might decrease the risk for progression from infection with *M. tuberculosis* to TB disease, preventing the development of miliary and meningeal disease in infants and young children (*59,60*). Although HIV infection increases the likelihood of progression from LTBI to TB disease (*39,49*), whether HIV infection increases the risk for becoming infected if exposed to *M. tuberculosis* is not known.

Characteristics of a Patient with TB Disease That Increase the Risk for Infectiousness

The following characteristics exist in a patient with TB disease that increases the risk for infectiousness:
- presence of cough;
- cavitation on chest radiograph;
- positive acid-fast bacilli (AFB) sputum smear result;
- respiratory tract disease with involvement of the larynx (substantially infectious);
- respiratory tract disease with involvement of the lung or pleura (exclusively pleural involvement is less infectious);

- failure to cover the mouth and nose when coughing;
- incorrect, lack of, or short duration of antituberculosis treatment; and
- undergoing cough-inducing or aerosol-generating procedures (e.g., bronchoscopy, sputum induction, and administration of aerosolized medications) (*29*).

Environmental Factors That Increase the Risk for Probability of Transmission of *M. tuberculosis*

The probability of the risk for transmission of *M. tuberculosis* is increased as a result of various environmental factors.

- Exposure to TB in small, enclosed spaces.
- Inadequate local or general ventilation that results in insufficient dilution or removal of infectious droplet nuclei.
- Recirculation of air containing infectious droplet nuclei.
- Inadequate cleaning and disinfection of medical equipment.
- Improper procedures for handling specimens.

Risk for Health-Care–Associated Transmission of *M. tuberculosis*

Transmission of *M. tuberculosis* is a risk in health-care settings (*57,61–79*). The magnitude of the risk varies by setting, occupational group, prevalence of TB in the community, patient population, and effectiveness of TB infection-control measures. Health-care–associated transmission of *M. tuberculosis* has been linked to close contact with persons with TB disease during aerosol-generating or aerosol-producing procedures, including bronchoscopy (*29,63,80–82*), endotracheal intubation, suctioning (*66*), other respiratory procedures (*8,9,83–86*), open abscess irrigation (*69,83*), autopsy (*71,72,77*), sputum induction, and aerosol treatments that induce coughing (*87–90*).

Of the reported TB outbreaks in health-care settings, multiple outbreaks involved transmission of MDR TB strains to both patients and HCWs (*56,57,70,87,91–94*). The majority of the patients and certain HCWs were HIV-infected, and progression to TB and MDR TB disease was rapid. Factors contributing to these outbreaks included delayed diagnosis of TB disease, delayed initiation and inadequate airborne precautions, lapses in AII practices and precautions for cough-inducing and aerosol-generating procedures, and lack of adequate respiratory protection. Multiple studies suggest that the decline in health-care–associated transmission observed in specific institutions is associated with the rigorous implementation of infection-control measures (*11,12,18–20,23, 95–97*). Because various interventions were implemented simultaneously, the effectiveness of each intervention could not be determined.

After the release of the 1994 CDC infection-control guidelines, increased implementation of recommended infection-control measures occurred and was documented in multiple national surveys (*13,15,98,99*). In a survey of approximately 1,000 hospitals, a TST program was present in nearly all sites, and 70% reported having an AII room (*13*). Other surveys have documented improvement in the proportion of AII rooms meeting CDC criteria and proportion of HCWs using CDC-recommended respiratory protection and receiving serial TST (*15,98*). A survey of New York City hospitals with high caseloads of TB disease indicated 1) a decrease in the time that patients with TB disease spent in EDs before being transferred to a hospital room, 2) an increase in the proportion of patients initially placed in AII rooms, 3) an increase in the proportion of patients started on recommended antituberculosis treatment and reported to the local or state health department, and 4) an increase in the use of recommended respiratory protection and environmental controls (*99*). Reports of increased implementation of recommended TB infection controls combined with decreased reports of outbreaks of TB disease in health-care settings suggest that the recommended controls are effective in reducing and preventing health-care–associated transmission of *M. tuberculosis* (*28*).

Less information is available regarding the implementation of CDC-recommended TB infection-control measures in settings other than hospitals. One study identified major barriers to implementation that contribute to the costs of a TST program in health departments and hospitals, including personnel costs, HCWs' time off from work for TST administration and reading, and training and education of HCWs (*100*). Outbreaks have occurred in outpatient settings (i.e., private physicians' offices and pediatric settings) where the guidelines were not followed (*101–103*). CDC-recommended TB infection-control measures are implemented in correctional facilities, and certain variations might relate to resources, expertise, and oversight (*104–106*).

Fundamentals of TB Infection Control

One of the most critical risks for health-care–associated transmission of *M. tuberculosis* in health-care settings is from patients with unrecognized TB disease who are not promptly handled with appropriate airborne precautions (*56,57,93,104*) or who are moved from an AII room too soon (e.g., patients with unrecognized TB and MDR TB) (*94*). In the United States, the problem of MDR TB, which was amplified by health-care–associated transmission, has been substantially reduced by the use of standardized antituberculosis treatment regimens in the initial phase of therapy, rapid drug-susceptibility testing, directly observed therapy (DOT), and

improved infection-control practices (*1*). DOT is an adherence-enhancing strategy in which an HCW or other specially trained health professional watches a patient swallow each dose of medication and records the dates that the administration was observed. DOT is the standard of care for all patients with TB disease and should be used for all doses during the course of therapy for TB disease and for LTBI, whenever feasible.

All health-care settings need a TB infection-control program designed to ensure prompt detection, airborne precautions, and treatment of persons who have suspected or confirmed TB disease (or prompt referral of persons who have suspected TB disease for settings in which persons with TB disease are not expected to be encountered). Such a program is based on a three-level hierarchy of controls, including administrative, environmental, and respiratory protection (*86,107,108*).

Administrative Controls

The first and most important level of TB controls is the use of administrative measures to reduce the risk for exposure to persons who might have TB disease. Administrative controls consist of the following activities:

- assigning responsibility for TB infection control in the setting;
- conducting a TB risk assessment of the setting;
- developing and instituting a written TB infection-control plan to ensure prompt detection, airborne precautions, and treatment of persons who have suspected or confirmed TB disease;
- ensuring the timely availability of recommended laboratory processing, testing, and reporting of results to the ordering physician and infection-control team;
- implementing effective work practices for the management of patients with suspected or confirmed TB disease;
- ensuring proper cleaning and sterilization or disinfection of potentially contaminated equipment (usually endoscopes);
- training and educating HCWs regarding TB, with specific focus on prevention, transmission, and symptoms;
- screening and evaluating HCWs who are at risk for TB disease or who might be exposed to *M. tuberculosis* (i.e., TB screening program);
- applying epidemiologic-based prevention principles, including the use of setting-related infection-control data;
- using appropriate signage advising respiratory hygiene and cough etiquette; and
- coordinating efforts with the local or state health department.

HCWs with TB disease should be allowed to return to work when they 1) have had three negative AFB sputum smear results (*109–112*) collected 8–24 hours apart, with at least one being an early morning specimen because respiratory secretions pool overnight; and 2) have responded to antituberculosis treatment that will probably be effective based on susceptibility results. In addition, HCWs with TB disease should be allowed to return to work when a physician knowledgeable and experienced in managing TB disease determines that HCWs are noninfectious (see Treatment Procedures for LTBI and TB Disease). Consideration should also be given to the type of setting and the potential risk to patients (e.g., general medical office versus HIV clinic) (see Supplements, Estimating the Infectiousness of a TB Patient; Diagnostic Procedures for LTBI and TB Disease; and Treatment Procedures for LTBI and TB Disease).

Environmental Controls

The second level of the hierarchy is the use of environmental controls to prevent the spread and reduce the concentration of infectious droplet nuclei in ambient air.

Primary environmental controls consist of controlling the source of infection by using local exhaust ventilation (e.g., hoods, tents, or booths) and diluting and removing contaminated air by using general ventilation

Secondary environmental controls consist of controlling the airflow to prevent contamination of air in areas adjacent to the source (AII rooms) and cleaning the air by using high efficiency particulate air (HEPA), filtration, or UVGI.

Respiratory-Protection Controls

The first two control levels minimize the number of areas in which exposure to *M. tuberculosis* might occur and, therefore, minimize the number of persons exposed. These control levels also reduce, but do not eliminate, the risk for exposure in the limited areas in which exposure can still occur. Because persons entering these areas might be exposed to *M. tuberculosis*, the third level of the hierarchy is the use of respiratory protective equipment in situations that pose a high risk for exposure. Use of respiratory protection can further reduce risk for exposure of HCWs to infectious droplet nuclei that have been expelled into the air from a patient with infectious TB disease (see Respiratory Protection). The following measures can be taken to reduce the risk for exposure:

- implementing a respiratory-protection program,
- training HCWs on respiratory protection, and
- training patients on respiratory hygiene and cough etiquette procedures.

Relevance to Biologic Terrorism Preparedness

MDR *M. tuberculosis* is classified as a category C agent of biologic terrorism (*113*). Implementation of the TB infection-control guidelines described in this document is essential for preventing and controlling transmission of *M. tuberculosis* in health-care settings. Additional information is at http://www.bt.cdc.gov and http://www.idsociety.org/bt/toc.htm (*114*).

Recommendations for Preventing Transmission of *M. tuberculosis* in Health-Care Settings

TB Infection-Control Program

Every health-care setting should have a TB infection-control plan that is part of an overall infection-control program. The specific details of the TB infection-control program will differ, depending on whether patients with suspected or confirmed TB disease might be encountered in the setting or whether patients with suspected or confirmed TB disease will be transferred to another health-care setting. Administrators making this distinction should obtain medical and epidemiologic consultation from state and local health departments.

TB Infection-Control Program for Settings in Which Patients with Suspected or Confirmed TB Disease Are Expected To Be Encountered

The TB infection-control program should consist of administrative controls, environmental controls, and a respiratory-protection program. Every setting in which services are provided to persons who have suspected or confirmed infectious TB disease, including laboratories and nontraditional facility-based settings, should have a TB infection-control plan. The following steps should be taken to establish a TB infection-control program in these settings:

1. Assign supervisory responsibility for the TB infection-control program to a designated person or group with expertise in LTBI and TB disease, infection control, occupational health, environmental controls, and respiratory protection. Give the supervisor or supervisory body the support and authority to conduct a TB risk assessment, implement and enforce TB infection-control policies, and ensure recommended training and education of HCWs.
   - Train the persons responsible for implementing and enforcing the TB infection-control program.
   - Designate one person with a back-up as the TB resource person to whom questions and problems should be addressed, if supervisory responsibility is assigned to a committee.
2. Develop a written TB infection-control plan that outlines a protocol for the prompt recognition and initiation of airborne precautions of persons with suspected or confirmed TB disease, and update it annually.
3. Conduct a problem evaluation (see Problem Evaluation) if a case of suspected or confirmed TB disease is not promptly recognized and appropriate airborne precautions not initiated, or if administrative, environmental, or respiratory-protection controls fail.
4. Perform a contact investigation in collaboration with the local or state health department if health-care–associated transmission of *M. tuberculosis* is suspected (*115*). Implement and monitor corrective action.
5. Collaborate with the local or state health department to develop administrative controls consisting of the risk assessment, the written TB infection-control plan, management of patients with suspected or confirmed TB disease, training and education of HCWs, screening and evaluation of HCWs, problem evaluation, and coordination.
6. Implement and maintain environmental controls, including AII room(s) (see Environmental Controls).
7. Implement a respiratory-protection program.
8. Perform ongoing training and education of HCWs (see Suggested Components of an Initial TB Training and Education Program for HCWs).
9. Create a plan for accepting patients who have suspected or confirmed TB disease if they are transferred from another setting.

TB Infection-Control Program for Settings in Which Patients with Suspected or Confirmed TB Disease Are Not Expected To Be Encountered

Settings in whichT patients might stay before transfer should still have a TB infection-control program in place consisting of administrative, environmental, and respiratory-protection controls. The following steps should be taken to establish a TB infection-control program in these settings:

1. Assign responsibility for the TB infection-control program to appropriate personnel.
2. Develop a written TB infection-control plan that outlines a protocol for the prompt recognition and transfer of persons who have suspected or confirmed TB disease to another health-care setting. The plan should indicate procedures to follow to separate persons with suspected or confirmed infectious TB disease from other persons

in the setting until the time of transfer. Evaluate the plan annually, if possible, to ensure that the setting remains one in which persons who have suspected or confirmed TB disease are not encountered and that they are promptly transferred.

3. Conduct a problem evaluation (see Problem Evaluation) if a case of suspected or confirmed TB disease is not promptly recognized, separated from others, and transferred.
4. Perform an investigation in collaboration with the local or state health department if health-care–associated transmission of *M. tuberculosis* is suspected.
5. Collaborate with the local or state health department to develop administrative controls consisting of the risk assessment and the written TB infection-control plan.

TB Risk Assessment

Every health-care setting should conduct initial and ongoing evaluations of the risk for transmission of *M. tuberculosis*, regardless of whether or not patients with suspected or confirmed TB disease are expected to be encountered in the setting. The TB risk assessment determines the types of administrative, environmental, and respiratory-protection controls needed for a setting and serves as an ongoing evaluation tool of the quality of TB infection control and for the identification of needed improvements in infection-control measures. Part of the risk assessment is similar to a program review that is conducted by the local TB-control program (*42*). The TB Risk Assessment Worksheet (Appendix B) can be used as a guide for conducting a risk assessment. This worksheet frequently does not specify values for acceptable performance indicators because of the lack of scientific data.

TB Risk Assessment for Settings in Which Patients with Suspected or Confirmed TB Disease Are Expected To Be Encountered

The initial and ongoing risk assessment for these settings should consist of the following steps:

1. Review the community profile of TB disease in collaboration with the state or local health department.
2. Consult the local or state TB-control program to obtain epidemiologic surveillance data necessary to conduct a TB risk assessment for the health-care setting.
3. Review the number of patients with suspected or confirmed TB disease who have been encountered in the setting during at least the previous 5 years.
4. Determine if persons with unrecognized TB disease have been admitted to or were encountered in the setting during the previous 5 years.
5. Determine which HCWs need to be included in a TB screening program and the frequency of screening (based on risk classification) (Appendix C).
6. Ensure the prompt recognition and evaluation of suspected episodes of health-care–associated transmission of *M. tuberculosis*.
7. Identify areas in the setting with an increased risk for health-care–associated transmission of *M. tuberculosis*, and target them for improved TB infection controls.
8. Assess the number of AII rooms needed for the setting. The risk classification for the setting should help to make this determination, depending on the number of TB patients examined. At least one AII room is needed for settings in which TB patients stay while they are being treated, and additional AII rooms might be needed, depending on the magnitude of patient-days of cases of suspected or confirmed TB disease. Additional AII rooms might be considered if options are limited for transferring patients with suspected or confirmed TB disease to other settings with AII rooms.
9. Determine the types of environmental controls needed other than AII rooms (see TB Airborne Precautions).
10. Determine which HCWs need to be included in the respiratory-protection program.
11. Conduct periodic reassessments (annually, if possible) to ensure
    - proper implementation of the TB infection-control plan,
    - prompt detection and evaluation of suspected TB cases,
    - prompt initiation of airborne precautions of suspected infectious TB cases,
    - recommended medical management of patients with suspected or confirmed TB disease (*31*),
    - functional environmental controls,
    - implementation of the respiratory-protection program, and
    - ongoing HCW training and education regarding TB.
12. Recognize and correct lapses in infection control.

TB Risk Assessment for Settings in Which Patients with Suspected or Confirmed TB Disease Are Not Expected To Be Encountered

The initial and ongoing risk assessment for these settings should consist of the following steps:

1. Review the community profile of TB disease in collaboration with the local or state health department.
2. Consult the local or state TB-control program to obtain epidemiologic surveillance data necessary to conduct a TB risk assessment for the health-care setting.
3. Determine if persons with unrecognized TB disease were encountered in the setting during the previous 5 years.

4. Determine if any HCWs need to be included in the TB screening program.
5. Determine the types of environmental controls that are currently in place, and determine if any are needed in the setting (see Environmental Controls; Appendices A and D).
6. Document procedures that ensure the prompt recognition and evaluation of suspected episodes of health-care–associated transmission of *M. tuberculosis*.
7. Conduct periodic reassessments (annually, if possible) to ensure 1) proper implementation of the TB infection-control plan; 2) prompt detection and evaluation of suspected TB cases; 3) prompt initiation of airborne precautions of suspected infectious TB cases before transfer; 4) prompt transfer of suspected infectious TB cases; 5) proper functioning of environmental controls, as applicable; and 6) ongoing TB training and education for HCWs.
8. Recognize and correct lapses in infection control.

Use of Risk Classification to Determine Need for TB Screening and Frequency of Screening HCWs

Risk classification should be used as part of the risk assessment to determine the need for a TB screening program for HCWs and the frequency of screening (Appendix C). A risk classification usually should be determined for the entire setting. However, in certain settings (e.g., health-care organizations that encompass multiple sites or types of services), specific areas defined by geography, functional units, patient population, job type, or location within the setting might have separate risk classifications. Examples of assigning risk classifications have been provided (see Risk Classification Examples).

TB Screening Risk Classifications

The three TB screening risk classifications are low risk, medium risk, and potential ongoing transmission. The classification of low risk should be applied to settings in which persons with TB disease are not expected to be encountered, and, therefore, exposure to *M. tuberculosis* is unlikely. This classification should also be applied to HCWs who will never be exposed to persons with TB disease or to clinical specimens that might contain *M. tuberculosis.*

The classification of medium risk should be applied to settings in which the risk assessment has determined that HCWs will or will possibly be exposed to persons with TB disease or to clinical specimens that might contain *M. tuberculosis*.

The classification of potential ongoing transmission should be temporarily applied to any setting (or group of HCWs) if evidence suggestive of person-to-person (e.g., patient-to-patient, patient-to-HCW, HCW-to-patient, or HCW-to-HCW) transmission of *M. tuberculosis* has occurred in the setting during the preceding year. Evidence of person-to-person transmission of *M. tuberculosis* includes 1) clusters of TST or BAMT conversions, 2) HCW with confirmed TB disease, 3) increased rates of TST or BAMT conversions, 4) unrecognized TB disease in patients or HCWs, or 5) recognition of an identical strain of *M. tuberculosis* in patients or HCWs with TB disease identified by deoxyribonucleic acid (DNA) fingerprinting.

If uncertainty exists regarding whether to classify a setting as low risk or medium risk, the setting typically should be classified as medium risk.

TB Screening Procedures for Settings (or HCWs) Classified as Low Risk

- All HCWs should receive baseline TB screening upon hire, using two-step TST or a single BAMT to test for infection with *M. tuberculosis*.
- After baseline testing for infection with *M. tuberculosis*, additional TB screening is not necessary unless an exposure to *M. tuberculosis* occurs.
- HCWs with a baseline positive or newly positive test result for *M. tuberculosis* infection (i.e., TST or BAMT) or documentation of treatment for LTBI or TB disease should receive one chest radiograph result to exclude TB disease (or an interpretable copy within a reasonable time frame, such as 6 months). Repeat radiographs are not needed unless symptoms or signs of TB disease develop or unless recommended by a clinician (*39,116*).

TB Screening Procedures for Settings (or HCWs) Classified as Medium Risk

- All HCWs should receive baseline TB screening upon hire, using two-step TST or a single BAMT to test for infection with *M. tuberculosis*.
- After baseline testing for infection with *M. tuberculosis*, HCWs should receive TB screening annually (i.e., symptom screen for all HCWs and testing for infection with *M. tuberculosis* for HCWs with baseline negative test results).
- HCWs with a baseline positive or newly positive test result for *M. tuberculosis* infection or documentation of previous treatment for LTBI or TB disease should receive one chest radiograph result to exclude TB disease. Instead of participating in serial testing, HCWs should receive a symptom screen annually. This screen should be accomplished by educating the HCW about symptoms of TB disease and instructing the HCW to report any such symptoms immediately to the occupational health unit. Treat-

ment for LTBI should be considered in accordance with CDC guidelines (*39*).

TB Screening Procedures for Settings (or HCWs) Classified as Potential Ongoing Transmission

- Testing for infection with *M. tuberculosis* might need to be performed every 8–10 weeks until lapses in infection control have been corrected, and no additional evidence of ongoing transmission is apparent.
- The classification of potential ongoing transmission should be used as a temporary classification only. It warrants immediate investigation and corrective steps. After a determination that ongoing transmission has ceased, the setting should be reclassified as medium risk. Maintaining the classification of medium risk for at least 1 year is recommended.

Settings Adopting BAMT for Use in TB Screening

Settings that use TST as part of TB screening and want to adopt BAMT can do so directly (without any overlapping TST) or in conjunction with a period of evaluation (e.g., 1 or 2 years) during which time both TST and BAMT are used. Baseline testing for BAMT would be established as a single step test. As with the TST, BAMT results should be recorded in detail. The details should include date of blood draw, result in specific units, and the laboratory interpretation (positive, negative, or indeterminate—and the concentration of cytokine measured, for example, interferon-gamma [IFN-γ]).

Risk Classification Examples

Inpatient Settings with More Than 200 Beds

If less than six TB patients for the preceding year, classify as low risk. If greater than or equal to six TB patients for the preceeding year, classify as medium risk.

Inpatient Settings with Less Than 200 Beds

If less than three TB patients for the proceeding year, classify as low risk. If greater than or equal to three TB patients for the preceeding year, classify as medium risk.

Outpatient, Outreach, and Home-Based Health-Care Settings

If less than three TB patients for the preceding year, classify as low risk. If greater than or equal to three TB patients for the preceeding year, classify as medium risk.

Hypothetical Risk Classification Examples

The following hypothetical situations illustrate how assessment data are used to assign a risk classification. The risk classifications are for settings in which patients with suspected or confirmed infectious TB disease are expected to be encountered.

Example A. The setting is a 150-bed hospital located in a small city. During the preceding year, the hospital admitted two patients with a diagnosis of TB disease. One was admitted directly to an AII room, and one stayed on a medical ward for 2 days before being placed in an AII room. A contact investigation of exposed HCWs by hospital infection-control personnel in consultation with the state or local health department did not identify any health-care–associated transmission-. Risk classification: low risk.

Example B. The setting is an ambulatory-care site in which a TB clinic is held 2 days per week. During the preceding year, care was delivered to six patients with TB disease and approximately 50 persons with LTBI. No instances of transmission of *M. tuberculosis* were noted. Risk classification: medium risk (because it is a TB clinic).

Example C. The setting is a large publicly funded hospital in a major metropolitan area. The hospital admits an average of 150 patients with TB disease each year, comprising 35% of the city burden. The setting has a strong TB infection-control program (i.e., annually updates infection-control plan, fully implements infection-control plan, and has enough AII rooms [see Environmental Controls]) and an annual conversion rate (for tests for *M. tuberculosis* infection) among HCWs of 0.5%. No evidence of health-care–associated transmission is apparent. The hospital has strong collaborative linkages with the state or local health department. Risk classification: medium risk (with close ongoing surveillance for episodes of transmission from unrecognized cases of TB disease, test conversions for *M. tuberculosis* infection in HCWs as a result of health-care–associated transmission, and specific groups or areas in which a higher risk for health-care–associated transmission exists).

Example D. The setting is an inpatient area of a correctional facility. A proportion of the inmates were born in countries where TB disease is endemic. Two cases of TB disease were diagnosed in inmates during the preceding year. Risk classification: medium risk (Correctional facilities should be classified as at least medium risk).

Example E. A hospital located in a large city admits 35 patients with TB disease per year, uses QFT-G to measure *M. tuberculosis* infection, and has an overall HCW *M. tuberculosis* infection test conversion rate of 1.0%. However, on annual testing, three of the 20 respiratory therapists tested had QFT-G conversions, for a rate of 15%. All of the respiratory therapists who tested positive received medical evaluations, had TB disease excluded, were diagnosed with LTBI, and were offered and completed a course of treatment for LTBI. None of the respiratory therapists had known exposures to

M. tuberculosis outside the hospital. The problem evaluation revealed that 1) the respiratory therapists who converted had spent part of their time in the pulmonary function laboratory where induced sputum specimens were collected, and 2) the ventilation in the laboratory was inadequate. Risk classification: potential ongoing transmission for the respiratory therapists (because of evidence of health-care–associated transmission). The rest of the setting was classified as medium risk. To address the problem, booths were installed for sputum induction. On subsequent testing for *M. tuberculosis* infection, no conversions were noted at the repeat testing 3 months later, and the respiratory therapists were then reclassified back to medium risk.

Example F. The setting is an ambulatory-care center associated with a large health maintenance organization (HMO). The patient volume is high, and the HMO is located in the inner city where TB rates are the highest in the state. During the preceding year, one patient who was known to have TB disease was evaluated at the center. The person was recognized as a TB patient on his first visit and was promptly triaged to an ED with an AII room capacity. While in the ambulatory-care center, the patient was held in an area separate from HCWs and other patients and instructed to wear a surgical or procedure mask, if possible. QFT-G was used for infection-control surveillance purposes, and a contact investigation was conducted among exposed staff, and no QFT-G conversions were noted. Risk classification: low risk.

Example G. The setting is a clinic for the care of persons infected with HIV. The clinic serves a large metropolitan area and a patient population of 2,000. The clinic has an AII room and a TB infection-control program. All patients are screened for TB disease upon enrollment, and airborne precautions are promptly initiated for anyone with respiratory complaints while the patient is being evaluated. During the preceding year, seven patients who were encountered in the clinic were subsequently determined to have TB disease. All patients were promptly put into an AII room, and no contact investigations were performed. The local health department was promptly notified in all cases. Annual TST has determined a conversion rate of 0.3%, which is low compared with the rate of the hospital with which the clinic is associated. Risk classification: medium risk (because persons infected with HIV might be encountered).

Example H. A home health-care agency employs 125 workers, many of whom perform duties, including nursing, physical therapy, and basic home care. The agency did not care for any patients with suspected or confirmed TB disease during the preceding year. Approximately 30% of the agency's workers are foreign-born, many of whom have immigrated within the previous 5 years. At baseline two-step testing, four had a positive initial TST result, and two had a positive second-step TST result. All except one of these workers was foreign-born. Upon further screening, none were determined to have TB disease. The home health-care agency is based in a major metropolitan area and delivers care to a community where the majority persons are poor and medically underserved and TB case rates are higher than the community as a whole. Risk classification: low risk (because HCWs might be from populations at higher risk for LTBI and subsequent progression to TB disease because of foreign birth and recent immigration or HIV-infected clients might be overrepresented, medium risk could be considered).

Screening HCWs Who Transfer to Other Health-Care Settings

All HCWs should receive baseline TB screening, even in settings considered to be low risk. Infection-control plans should address HCWs who transfer from one health-care setting to another and consider that the transferring HCWs might be at an equivalent or higher risk for exposure in different settings. Infection-control plans might need to be customized to balance the assessed risks and the efficacy of the plan based on consideration of various logistical factors. Guidance is provided based on different scenarios.

Because some institutions might adopt BAMT for the purposes of testing for *M. tuberculosis* infection, infection-control programs might be confronted with interpreting historic and current TST and BAMT results when HCWs transfer to a different setting. On a case-by-case basis, expert medical opinion might be needed to interpret results and refer patients with discordant BAMT and TST baseline results. Therefore, infection-control programs should keep all records when documenting previous test results. For example, an infection-control program using a BAMT strategy should request and keep historic TST results of a HCW transferring from a previous setting. Even if the HCW is transferring from a setting that used BAMT to a setting that uses BAMT, historic TST results might be needed when in the future the HCW transfers to a setting that uses TST. Similarly, historic BAMT results might be needed when the HCW transfers from a setting that used TST to a setting that uses BAMT.

HCWs transferring from low-risk to low-risk settings. After a baseline result for infection with *M. tuberculosis* is established and documented, serial testing for *M. tuberculosis* infection is not necessary.

HCWs transferring from low-risk to medium-risk settings. After a baseline result for infection with *M. tuberculosis* is established and documented, annual TB screening (includ-

ing a symptom screen and TST or BAMT for persons with previously negative test results) should be performed.

HCWs transferring from low- or medium-risk settings to settings with a temporary classification of potential ongoing transmission. After a baseline result for infection with *M. tuberculosis* is established, a decision should be made regarding follow-up screening on an individual basis. If transmission seems to be ongoing, consider including the HCW in the screenings every 8–10 weeks until a determination has been made that ongoing transmission has ceased. When the setting is reclassified back to medium-risk, annual TB screening should be resumed.

Calculation and Use of Conversion Rates for *M. tuberculosis* Infection

The *M. tuberculosis* infection conversion rate is the percentage of HCWs whose test result for *M. tuberculosis* infection has converted within a specified period. Timely detection of *M. tuberculosis* infection in HCWs not only facilitates treatment for LTBI, but also can indicate the need for a source case investigation and a revision of the risk assessment for the setting. Conversion in test results for *M. tuberculosis*, regardless of the testing method used, is usually interpreted as presumptive evidence of new *M. tuberculosis* infection, and recent infections are associated with an increased risk for progression to TB disease.

For administrative purposes, a TST conversion is ≥10 mm increase in the size of the TST induration during a 2-year period in 1) an HCW with a documented negative (<10 mm) baseline two-step TST result or 2) a person who is not an HCW with a negative (<10 mm) TST result within 2 years.

In settings conducting serial testing for *M. tuberculosis* infection (medium-risk settings), use the to estimate the risk for test conversion in HCWs.

- Calculate a conversion rate by dividing the number of conversions among HCWs in the setting in a specified period (numerator) by the number of HCWs who received tests in the setting over the same period (denominator) multiplied by 100 (see Use of Conversion Test Data for *M. tuberculosis* Infection To Identify Lapses in Infection Control).
- Identify areas or groups in the setting with a potentially high risk for *M. tuberculosis* transmission by comparing conversion rates in HCWs with potential exposure to patients with TB disease to conversion rates in HCWs for whom health-care–associated exposure to *M. tuberculosis* is not probable.

Use of Conversion Test Data for *M. tuberculosis* Infection To Identify Lapses in Infection Control

- Conversion rates above the baseline level (which will be different in each setting) should instigate an investigation to evaluate the likelihood of health-care–associated transmission. When testing for *M. tuberculosis* infection, conversions are determined to be the result of well-documented community exposure or probable false-positive test results; the risk classification of the setting does not need to be adjusted.
- For settings that no longer perform serial testing for *M. tuberculosis* infection among HCWs, reassessment of the risk for the setting is essential to ensure that the infection-control program is effective. The setting should have ongoing communication with the local or state health department regarding incidence and epidemiology of TB in the population served and should ensure that timely contact investigations are performed for HCWs or patients with unprotected exposure to a person with TB disease.

Example Calculation of Conversion Rates

Medical Center A is classified as medium risk and uses TST for annual screening. At the end of 2004, a total of 10,051 persons were designated as HCWs. Of these, 9,246 had negative baseline test results for *M. tuberculosis* infection. Of the HCWs tested, 10 experienced an increase in TST result by ≥10 mm. The overall setting conversion rate for 2004 is 0.11%. If five of the 10 HCWs whose test results converted were among the 100 HCWs employed in the ICU of Hospital X (in Medical Center A), then the ICU setting-specific conversion rate for 2004 is 5%.

Evaluation of HCWs for LTBI should include information from a serial testing program, but this information must be interpreted as only one part of a full assessment. TST or BAMT conversion criteria for administrative (surveillance) purposes are not applicable for medical evaluation of HCWs for the diagnosis of LTBI (see Supplement, Surveillance and Detection of *M. tuberculosis* Infections in Health-Care Workers [HCWs]).

Evaluation of TB Infection-Control Procedures and Identification of Problems

Annual evaluations of the TB infection-control plan are needed to ensure the proper implementation of the plan and to recognize and correct lapses in infection control. Previous hospital admissions and outpatient visits of patients with TB disease should be noted before the onset of TB symptoms. Medical records of a sample of patients with suspected and confirmed

TB disease who were treated or examined at the setting should be reviewed to identify possible problems in TB infection control. The review should be based on the factors listed on the TB Risk Assessment Worksheet (Appendix B).

- Time interval from suspicion of TB until initiation of airborne precautions and antituberculosis treatment.
  - suspicion of TB disease and patient triage to proper AII room or referral center for settings that do not provide care for patients with suspected or confirmed TB disease;
  - admission until TB disease was suspected;
  - admission until medical evaluation for TB disease was performed;
  - admission until specimens for AFB smears and polymerase chain reaction (PCR)–based nucleic acid amplification (NAA) tests for *M. tuberculosis* were ordered;
  - admission until specimens for mycobacterial culture were ordered;
  - ordering of AFB smears, NAA tests, and mycobacterial culture until specimens were collected;
  - collection of specimens until performance and AFB smear results were reported;
  - collection of specimens until performance and culture results were reported;
  - collection of specimens until species identification was reported;
  - collection of specimens until drug-susceptibility test results were reported;
  - admission until airborne precautions were initiated; and
  - admission until antituberculosis treatment was initiated.
- Duration of airborne precautions.
- Measurement of meeting criteria for discontinuing airborne precautions. Certain patients might be correctly discharged from an AII room to home.
- Patient history of previous admission.
- Adequacy of antituberculosis treatment regimens.
- Adequacy of procedures for collection of follow-up sputum specimens.
- Adequacy of discharge planning.
- Number of visits to outpatient setting from the start of symptoms until TB disease was suspected (for outpatient settings).

Work practices related to airborne precautions should be observed to determine if employers are enforcing all practices, if HCWs are adhering to infection-control policies, and if patient adherence to airborne precautions is being enforced. Data from the case reviews and observations in the annual risk assessment should be used to determine the need to modify 1) protocols for identifying and initiating prompt airborne precautions for patients with suspected or confirmed infectious TB disease, 2) protocols for patient management, 3) laboratory procedures, or 4) TB training and education programs for HCWs.

Environmental Assessment

- Data from the most recent environmental evaluation should be reviewed to determine if recommended environmental controls are in place (see Suggested Components of an Initial TB Training and Education Program for HCWs).
- Environmental control maintenance procedures and logs should not be reviewed to determine if maintenance is conducted properly and regularly.
- Environmental control design specifications should be compared with guidelines from the American Institute of Architects (AIA) and other ventilation guidelines (*117,118*) (see Risk Classification Examples) and the installed system performance.
- Environmental data should be used to assist building managers and engineers in evaluating the performance of the installed system.
- The number and types of aerosol-generating or aerosol-producing procedures (e.g., specimen processing and manipulation, bronchoscopy, sputum induction, and administration of aerosolized medications) performed in the setting should be assessed.
- The number of AII rooms should be suitable for the setting based on AIA Guidelines and the setting risk assessment. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has adapted the AIA guidelines when accrediting facilities (*118*).

Suggested Components of an Initial TB Training and Education Program for HCWs

The following are suggested components of an initial TB training and education program:

1. Clinical Information

- Basic concepts of *M. tuberculosis* transmission, pathogenesis, and diagnosis, including the difference between LTBI and TB disease and the possibility of reinfection after previous infection with *M. tuberculosis* or TB disease.
- Symptoms and signs of TB disease and the importance of a high index of suspicion for patients or HCWs with these symptoms.
- Indications for initiation of airborne precautions of inpatients with suspected or confirmed TB disease.
- Policies and indications for discontinuing airborne precautions.

- Principles of treatment for LTBI and for TB disease (indications, use, effectiveness, and potential adverse effects).

2. Epidemiology of TB

- Epidemiology of TB in the local community, the United States, and worldwide.
- Risk factors for TB disease.

3. Infection-Control Practices to Prevent and Detect *M. tuberculosis* Transmission in Health-Care Settings

- Overview of the TB infection-control program.
- Potential for occupational exposure to infectious TB disease in health-care settings.
- Principles and practices of infection control to reduce the risk for transmission of *M. tuberculosis*, including the hierarchy of TB infection-control measures, written policies and procedures, monitoring, and control measures for HCWs at increased risk for exposure to *M. tuberculosis.*
- Rationale for infection-control measures and documentation evaluating the effect of these measures in reducing occupational TB risk exposure and *M. tuberculosis* transmission.
- Reasons for testing for *M. tuberculosis* infection, importance of a positive test result for *M. tuberculosis* infection, importance of participation in a TB screening program, and importance of retaining documentation of previous test result for *M. tuberculosis* infection, chest radiograph results, and treatment for LTBI and TB disease.
- Efficacy and safety of BCG vaccination and principles of screening for *M. tuberculosis* infection and interpretation in BCG recipients.
- Procedures for investigating an *M. tuberculosis* infection test conversion or TB disease occurring in the workplace.
- Joint responsibility of HCWs and employers to ensure prompt medical evaluation after *M. tuberculosis* test conversion or development of symptoms or signs of TB disease in HCWs.
- Role of HCW in preventing transmission of *M. tuberculosis.*
- Responsibility of HCWs to promptly report a diagnosis of TB disease to the setting's administration and infection-control program.
- Responsibility of clinicians and the infection-control program to report to the state or local health department a suspected case of TB disease in a patient (including autopsy findings) or HCW.
- Responsibilities and policies of the setting, the local health department, and the state health department to ensure confidentiality for HCWs with TB disease or LTBI.
- Responsibility of the setting to inform EMS staff who transported a patient with suspected or confirmed TB disease.
- Responsibilities and policies of the setting to ensure that an HCW with TB disease is noninfectious before returning to duty.
- Importance of completing therapy for LTBI or TB disease to protect the HCW's health and to reduce the risk to others.
- Proper implementation and monitoring of environmental controls (see Environmental Controls).
- Training for safe collection, management, and disposal of clinical specimens.
- Required Occupational Safety and Health Administration (OSHA) record keeping on HCW test conversions for *M. tuberculosis* infection.
- Record-keeping and surveillance of TB cases among patients in the setting.
- Proper use of (see Respiratory Protection) and the need to inform the infection-control program of factors that might affect the efficacy of respiratory protection as required by OSHA.
- Success of adherence to infection-control practices in decreasing the risk for transmission of *M. tuberculosis* in health-care settings.

4. TB and Immunocompromising Conditions

- Relationship between infection with *M. tuberculosis* and medical conditions and treatments that can lead to impaired immunity.
- Available tests and counseling and referrals for persons with HIV infection, diabetes, and other immunocompromising conditions associated with an increased risk for progression to TB disease.
- Procedures for informing employee health or infection-control personnel of medical conditions associated with immunosuppression.
- Policies on voluntary work reassignment options for immunocompromised HCWs.
- Applicable confidentiality safeguards of the health-care setting, locality, and state.

5. TB and Public Health

- Role of the local and state health department's TB-control program in screening for LTBI and TB disease, providing treatment, conducting contact investigations and outbreak investigations, and providing education, counseling, and responses to public inquiries.
- Roles of CDC and of OSHA.

- Availability of information, advice, and counseling from community sources, including universities, local experts, and hotlines.
- Responsibility of the setting's clinicians and infection-control program to promptly report to the state or local health department a case of suspected TB disease or a cluster of TST or BAMT conversions.
- Responsibility of the setting's clinicians and infection-control program to promptly report to the state or local health department a person with suspected or confirmed TB disease who leaves the setting against medical advice.

Managing Patients Who Have Suspected or Confirmed TB Disease: General Recommendations

The primary TB risk to HCWs is the undiagnosed or unsuspected patient with infectious TB disease. A high index of suspicion for TB disease and rapid implementation of precautions are essential to prevent and interrupt transmission. Specific precautions will vary depending on the setting.

Prompt Triage

Within health-care settings, protocols should be implemented and enforced to promptly identify, separate from others, and either transfer or manage persons who have suspected or confirmed infectious TB disease. When patients' medical histories are taken, all patients should be routinely asked about 1) a history of TB exposure, infection, or disease; 2) symptoms or signs of TB disease; and 3) medical conditions that increase their risk for TB disease (see Supplements, Diagnostic Procedures for LTBI and TB Disease; and Treatment Procedures for LTBI and TB Disease). The medical evaluation should include an interview conducted in the patient's primary language, with the assistance of a qualified medical interpreter, if necessary. HCWs who are the first point of contact should be trained to ask questions that will facilitate detection of persons who have suspected or confirmed infectious TB disease. For assistance with language interpretation, contact the local and state health department. Interpretation resources are also available (*119*) at http://www.atanet.org; http://www. languageline.com; and http://www.ncihc.org.

A diagnosis of respiratory TB disease should be considered for any patient with symptoms or signs of infection in the lung, pleura, or airways (including larynx), including coughing for >3 weeks, loss of appetite, unexplained weight loss, night sweats, bloody sputum or hemoptysis, hoarseness, fever, fatigue, or chest pain. The index of suspicion for TB disease will vary by geographic area and will depend on the population served by the setting. The index of suspicion should be substantially high for geographic areas and groups of patients characterized by high TB incidence (*26*).

Special steps should be taken in settings other than TB clinics. Patients with symptoms suggestive of undiagnosed or inadequately treated TB disease should be promptly referred so that they can receive a medical evaluation. These patients should not be kept in the setting any longer than required to arrange a referral or transfer to an AII room. While in the setting, symptomatic patients should wear a surgical or procedure mask, if possible, and should be instructed to observe strict respiratory hygiene and cough etiquette procedures (see Glossary) (*120–122*).

Immunocompromised persons, including those who are HIV-infected, with infectious TB disease should be physically separated from other persons to protect both themselves and others. To avoid exposing HIV-infected or otherwise severely immunocompromised persons to *M. tuberculosis*, consider location and scheduling issues to avoid exposure.

TB Airborne Precautions

Within health-care settings, TB airborne precautions should be initiated for any patient who has symptoms or signs of TB disease, or who has documented infectious TB disease and has not completed antituberculosis treatment. For patients placed in AII rooms because of suspected infectious TB disease of the lungs, airway, or larynx, airborne precautions may be discontinued when infectious TB disease is considered unlikely and either 1) another diagnosis is made that explains the clinical syndrome or 2) the patient has three consecutive, negative AFB sputum smear results (*109–112,123*). Each of the three sputum specimens should be collected in 8–24-hour intervals (*124*), and at least one specimen should be an early morning specimen because respiratory secretions pool overnight. Generally, this method will allow patients with negative sputum smear results to be released from airborne precautions in 2 days.

The classification of the risk assessment of the health-care setting is used to determine how many AII rooms each setting needs, depending on the number of TB patients examined. At least one AII room is needed for settings in which TB patients stay while they are being treated, and additional AII rooms might be needed depending on the magnitude of patient-days of persons with suspected or confirmed TB disease (*118*). Additional rooms might be considered if options are limited for transferring patients with suspected or confirmed TB disease to other settings with AII rooms. For example, for a hospital with 120 beds, a minimum of one AII room is needed, possibly more, depending on how many TB patients are examined in 1 year.

TB Airborne Precautions for Settings in Which Patients with Suspected or Confirmed TB Disease Are Expected To Be Encountered

Settings that plan to evaluate and manage patients with TB disease should have at least one AII room or enclosure that meets AII requirements (see Environmental Controls; and Supplement, Environmental Controls). These settings should develop written policies that specify 1) indications for airborne precautions, 2) persons authorized to initiate and discontinue airborne precautions, 3) specific airborne precautions, 4) AII room-monitoring procedures, 5) procedures for managing patients who do not adhere to airborne precautions, and 6) criteria for discontinuing airborne precautions.

A high index of suspicion should be maintained for TB disease. If a patient has suspected or confirmed TB disease, airborne precautions should be promptly initiated. Persons with suspected or confirmed TB disease who are inpatients should remain in AII rooms until they are determined to be noninfectious and have demonstrated a clinical response to a standard multidrug antituberculosis treatment regimen or until an alternative diagnosis is made. If the alternative diagnosis cannot be clearly established, even with three negative sputum smear results, empiric treatment of TB disease should strongly be considered (see Supplement, Estimating the Infectiousness of a TB Patient). Outpatients with suspected or confirmed infectious TB disease should remain in AII rooms until they are transferred or until their visit is complete.

TB Airborne Precautions for Settings in Which Patients with Suspected or Confirmed TB Disease Are Not Expected To Be Encountered

Settings in which patients with suspected or confirmed TB disease are not expected to be encountered do not need an AII room or a respiratory-protection program for the prevention of transmission of *M. tuberculosis*. However, follow the following steps in these settings.

A written protocol should be developed for referring patients with suspected or confirmed TB disease to a collaborating referral setting in which the patient can be evaluated and managed properly. The referral setting should provide documentation of intent to collaborate. The protocol should be reviewed routinely and revised as needed.

Patients with suspected or confirmed TB disease should be placed in an AII room, if available, or in a room that meets the requirements for an AII room, or in a separate room with the door closed, apart from other patients and not in an open waiting area. Adequate time should elapse to ensure removal of *M. tuberculosis*–contaminated room air before allowing entry by staff or another patient (see Environmental Controls; Tables 1 and 2).

If an AII room is not available, persons with suspected or confirmed infectious TB disease should wear a surgical or procedure mask, if possible. Patients should be instructed to keep the mask on and to change the mask if it becomes wet. If patients cannot tolerate a mask, they should observe strict respiratory hygiene and cough etiquette procedures.

AII Room Practices

AII rooms should be single-patient rooms in which environmental factors and entry of visitors and HCWs are controlled to minimize the transmission of *M. tuberculosis*. All HCWs who enter an AII room should wear at least N95 disposable respirators (see Respiratory Protection). Visitors may be offered respiratory protection (i.e., N95) and should be instructed by HCWs on the use of the respirator before entering an AII room. AII rooms have specific requirements for controlled ventilation, negative pressure, and air filtration (*118*) (see Environmental Controls). Each inpatient AII room should have a private bathroom.

Settings with AII Rooms

Health-care personnel settings with AII rooms should

- keep doors to AII rooms closed except when patients, HCWs, or others must enter or exit the room (*118*);
- maintain enough AII rooms to provide airborne precautions of all patients who have suspected or confirmed TB disease. Estimate the number of AII rooms needed based on the results of the risk assessment for the setting;
- monitor and record direction of airflow (i.e., negative pressure) in the room on a daily basis, while the room is being used for TB airborne precautions. Record results in an electronic or readily retrievable document;
- consider grouping AII rooms in one part of the health-care setting to limit costs, reduce the possibility of transmitting *M. tuberculosis* to other patients, facilitate the care of TB patients, and facilitate the installation and maintenance of optimal environmental controls (particularly ventilation). Depending on the architecture and the environmental control systems of a particular setting, AII rooms might be grouped either horizontally (e.g., a wing of a facility) or vertically (e.g., the last few rooms of separate floors of a facility);
- perform diagnostic and treatment procedures (e.g., sputum collection and inhalation therapy) in an AII room.
- ensure patient adherence to airborne precautions. In their primary language, with the assistance of a qualified medical interpreter, if necessary, educate patients (and family and visitors) who are placed in an AII room about *M. tuberculosis* transmission and the reasons for airborne precautions. For assistance with language interpretation,

contact the local and state health department. Interpretation resources are available (*119*) at http://www.atanet.org; http://www.languageline.com; and http://www.ncihc.org. Facilitate patient adherence by using incentives (e.g., provide telephones, televisions, or radios in AII rooms; and grant special dietary requests) and other measures. Address problems that could interfere with adherence (e.g., management of withdrawal from addictive substances, including tobacco); and

- ensure that patients with suspected or confirmed infectious TB disease who must be transported to another area of the setting or to another setting for a medically essential procedure bypass the waiting area and wear a surgical or procedure mask, if possible. Drivers, HCWs, and other staff who are transporting persons with suspected or confirmed infectious TB disease might consider wearing an N95 respirator. Schedule procedures on patients with TB disease when a minimum number of HCWs and other patients are present and as the last procedure of the day to maximize the time available for removal of airborne contamination (see Environmental Controls; Tables 1 and 2).

Diagnostic Procedures

Diagnostic procedures should be performed in settings with appropriate infection-control capabilities. The following recommendations should be applied for diagnosing TB disease and for evaluating patients for potential infectiousness.

Clinical Diagnosis

A complete medical history should be obtained, including symptoms of TB disease, previous TB disease and treatment, previous history of infection with *M. tuberculosis*, and previous treatment of LTBI or exposure to persons with TB disease. A physical examination should be performed, including chest radiograph, microscopic examination, culture, and, when indicated, NAA testing of sputum (*39,53,125,126*). If possible, sputum induction with aerosol inhalation is preferred, particularly when the patient cannot produce sputum. Gastric aspiration might be necessary for those patients, particularly children, who cannot produce sputum, even with aerosol inhalation (*127–130*). Bronchoscopy might be needed for specimen collection, especially if sputum specimens have been nondiagnostic and doubt exists as to the diagnosis (*90,111, 127,128,131–134*).

All patients with suspected or confirmed infectious TB disease should be placed under airborne precautions until they have been determined to be noninfectious (see Supplement, Estimating the Infectiousness of a TB Patient). Adult and adolescent patients who might be infectious include persons who are coughing; have cavitation on chest radiograph; have positive AFB sputum smear results; have respiratory tract disease with involvement of the lung, pleura or airways, including larynx, who fail to cover the mouth and nose when coughing; are not on antituberculosis treatment or are on incorrect antituberculosis treatment; or are undergoing cough-inducing or aerosol-generating procedures (e.g., sputum induction, bronchoscopy, and airway suction) (*30,135*).

Persons diagnosed with extrapulmonary TB disease should be evaluated for the presence of concurrent pulmonary TB disease. An additional concern in infection control with children relates to adult household members and visitors who might be the source case (*136*). Pediatric patients, including adolescents, who might be infectious include those who have extensive pulmonary or laryngeal involvement, prolonged cough, positive sputum AFB smears results, cavitary TB on chest radiograph (as is typically observed in immunocompetent adults with TB disease), or those for whom cough-inducing or aerosol-generating procedures are performed (*136,137*).

Although children are uncommonly infectious, pediatric patients should be evaluated for infectiousness by using the same criteria as for adults (i.e., on the basis of pulmonary or laryngeal involvement). Patients with suspected or confirmed TB disease should be immediately reported to the local public health authorities so that arrangements can be made for tracking their treatment to completion, preferably through a case management system, so that DOT can be arranged and standard procedures for identifying and evaluating TB contacts can be initiated. Coordinate efforts with the local or state health department to arrange treatment and long-term follow-up and evaluation of contacts.

Laboratory Diagnosis

To produce the highest quality laboratory results, laboratories performing mycobacteriologic tests should be skilled in both the laboratory and the administrative aspects of specimen processing. Laboratories should use or have prompt access to the most rapid methods available: 1) fluorescent microscopy and concentration for AFB smears; 2) rapid NAA testing for direct detection of *M. tuberculosis* in patient specimens (*125*); 3) solid and rapid broth culture methods for isolation of mycobacteria; 4) nucleic acid probes or high pressure liquid chromatography (HPLC) for species identification; and 5) rapid broth culture methods for drug susceptibility testing. Laboratories should incorporate other more rapid or sensitive tests as they become available, practical, and affordable (see Supplement, Diagnostic Procedures for LTBI and TB Disease) (*138,139*).

In accordance with local and state laws and regulations, a system should be in place to ensure that laboratories report

any positive results from any specimens to clinicians within 24 hours of obtaining the result (*139,140*). Certain settings perform AFB smears on-site for rapid results (and results should be reported to clinicians within 24 hours) and then send specimens or cultures to a referral laboratory for identification and drug-susceptibility testing. This referral practice can speed the receipt of smear results but delay culture identification and drug-susceptibility results. Settings that cannot provide the full range of mycobacteriologic testing services should contract with their referral laboratories to ensure rapid results while maintaining proficiency for on-site testing. In addition, referral laboratories should be instructed to store isolates in case additional testing is necessary.

All drug susceptibility results on *M. tuberculosis* isolates should be reported to the local or state health department as soon as these results are available. Laboratories that rarely receive specimens for mycobacteriologic analysis should refer specimens to a laboratory that performs these tests routinely. The reference laboratory should provide rapid testing and reporting. Out-of-state reference laboratories should provide all results to the local or state health department from which the specimen originated.

Special Considerations for Persons Who Are at High Risk for TB Disease or in Whom TB Disease Might Be Difficult to Diagnose

The probability of TB disease is higher among patients who 1) previously had TB disease or were exposed to *M. tuberculosis*, 2) belong to a group at high risk for TB disease or, 3) have a positive TST or BAMT result. TB disease is strongly suggested if the diagnostic evaluation reveals symptoms or signs of TB disease, a chest radiograph consistent with TB disease, or AFB in sputum or from any other specimen. TB disease can occur simultaneously in immunocompromised persons who have pulmonary infections caused by other organisms (e.g., *Pneumocystis jaroveci* [formerly *P. carinii*] and *M. avium* complex) and should be considered in the diagnostic evaluation of all such patients with symptoms or signs of TB disease (*53*).

TB disease can be difficult to diagnose in persons who have HIV infection (*49*) (or other conditions associated with severe suppression of cell mediated immunity) because of nonclassical or normal radiographic presentation or the simultaneous occurrence of other pulmonary infections (e.g., *P. jaroveci or M. avium* complex) (*2*). Patients who are HIV-infected are also at greater risk for having extrapulmonary TB (*2*). The difficulty in diagnosing TB disease in HIV-infected can be compounded by the possible lower sensitivity and specificity of sputum smear results for detecting AFB (*53,141*) and the overgrowth of cultures with *M. avium* complex in specimens from patients infected with both *M. tuberculosis* and *M. avium* complex. The TST in patients with advanced HIV infection is unreliable and cannot be used in clinical decision making (*35,53,142*).

For immunocompromised patients who have respiratory symptoms or signs that are attributed initially to infections or conditions other than TB disease, conduct an evaluation for coexisting TB disease. If the patient does not respond to recommended treatment for the presumed cause of the pulmonary abnormalities, repeat the evaluation (see Supplement, Diagnostic Procedures for LTBI and TB Disease). In certain settings in which immunocompromised patients and patients with TB disease are examined, implementing airborne precautions might be prudent for all persons at high risk. These persons include those infected with HIV who have an abnormal chest radiograph or respiratory symptoms, symptomatic foreign-born persons who have immigrated within the previous 5 years from TB-endemic countries, and persons with pulmonary infiltrates on chest radiograph, or symptoms or signs of TB disease.

Initiation of Treatment

For patients who have confirmed TB disease or who are considered highly probable to have TB disease, promptly start antituberculosis treatment in accordance with current guidelines (see Supplements, Diagnostic Procedures for LTBI and TB Disease; and Treatment Procedures for LTBI and TB Disease) (*31*). In accordance with local and state regulations, local health departments should be notified of all cases of suspected TB.

DOT is the standard of care for all patients with TB disease and should be used for all doses during the course of therapy for treatment of TB disease. All inpatient medication should be administered by DOT and reported to the state or local health department. Rates of relapse and development of drug-resistance are decreased when DOT is used (*143–145*). All patients on intermittent (i.e., once or twice per week) treatment for TB disease or LTBI should receive DOT. Settings should collaborate with the local or state health department on decisions concerning inpatient DOT and arrangements for outpatient DOT (*31*).

Managing Patients Who Have Suspected or Confirmed TB Disease: Considerations for Special Circumstances and Settings

The recommendations for preventing transmission of *M. tuberculosis* are applicable to all health-care settings, including those that have been described (Appendix A). These settings should each have independent risk assessments if they

are stand-alone settings, or each setting should have a detailed section written as part of the risk assessment for the overall setting.

Minimum Requirements

The specific precautions for the settings included in this section vary, depending on the setting.

Inpatient Settings

Emergency Departments (EDs)

The symptoms of TB disease are usually symptoms for which patients might seek treatment in EDs. Because TB symptoms are common and nonspecific, infectious TB disease could be encountered in these settings. The use of ED-based TB screening has not been demonstrated to be consistently effective (*146*).

The amount of time patients with suspected or confirmed infectious TB disease spend in EDs and urgent-care settings should be minimized. Patients with suspected or confirmed infectious TB disease should be promptly identified, evaluated, and separated from other patients. Ideally, such patients should be placed in an AII room. When an AII room is not available, use a room with effective general ventilation, and use air cleaning technologies (e.g., a portable HEPA filtration system), if available, or transfer the patient to a setting or area with recommended infection-control capacity. Facility engineering personnel with expertise in heating, ventilation, and air conditioning (HVAC) and air handlers have evaluated how this option is applied to ensure no over pressurization of return air or unwanted alternations exists in design of air flow in the zone.

EDs with a high volume of patients with suspected or confirmed TB disease should have at least one AII room (see TB Risk Assessment). Air-cleaning technologies (e.g., HEPA filtration and UVGI) can be used to increase equivalent air changes per hour (ACH) in waiting areas (Table 1). HCWs entering an AII room or any room with a patient with infectious TB disease should wear at least an N95 disposable respirator. After a patient with suspected or confirmed TB disease exits a room, allow adequate time to elapse to ensure removal of *M. tuberculosis*-contaminated room air before allowing entry by staff or another patient (see Environmental Controls; Tables 1 and 2).

Before a patient leaves an AII room, perform an assessment of 1) the patient's need to discontinue airborne precautions, 2) the risk for transmission and the patient's ability to observe strict respiratory hygiene, and 3) cough etiquette procedures. Patients with suspected or confirmed infectious TB who are outside an AII room should wear a surgical or procedure mask, if possible. Patients who cannot tolerate masks because of medical conditions should observe strict respiratory hygiene and cough etiquette procedures.

TABLE 1. Air changes per hour (ACH) and time required for removal efficiencies of 99% and 99.9% of airborne contaminants*

	Minutes required for removal efficiency†	
ACH	99%	99.9%
2	138	207
4	69	104
6	46	69
12	23	35
15	18	28
20	7	14
50	3	6
400	<1	1

* This table can be used to estimate the time necessary to clear the air of airborne *Mycobacterium tuberculosis* after the source patient leaves the area or when aerosol-producing procedures are complete.
† Time in minutes to reduce the airborne concentration by 99% or 99.9%.

Intensive Care Units (ICUs)

Patients with infectious TB disease might become sick enough to require admission to an ICU. Place ICU patients with suspected or confirmed infectious TB disease in an AII room, if possible. ICUs with a high volume of patients with suspected or confirmed TB disease should have at least one AII room (see TB Risk Assessment Worksheet) [Appendix B]. Air-cleaning technologies (e.g., HEPA filtration and UVGI) can be used to increase equivalent ACH in waiting areas (see Environmental Controls).

HCWs entering an AII room or any room with a patient with infectious TB disease should wear at least an N95 disposable respirator. To help reduce the risk for contaminating a ventilator or discharging *M. tuberculosis* into the ambient air when mechanically ventilating (i.e., with a ventilator or manual resuscitator) a patient with suspected or confirmed TB disease, place a bacterial filter on the patient's endotracheal tube (or at the expiratory side of the breathing circuit of a ventilator) (*147–151*). In selecting a bacterial filter, give preference to models specified by the manufacturer to filter particles 0.3 μm in size in both the unloaded and loaded states with a filter efficiency of >95% (i.e., filter penetration of <5%) at the maximum design flow rates of the ventilator for the service life of the filter, as specified by the manufacturer.

Surgical Suites

Surgical suites require special infection-control considerations for preventing transmission of *M. tuberculosis*. Normally, the direction of airflow should be from the operating room (OR) to the hallway (positive pressure) to minimize contamination of the surgical field. Certain hospitals have procedure rooms with reversible airflow or pressure, whereas others have positive-pressure rooms with a negative pressure anteroom.

Surgical staff, particularly those close to the surgical field, should use respiratory protection (e.g., a valveless N95 disposable respirator) to protect themselves and the patient undergoing surgery.

When possible, postpone non-urgent surgical procedures on patients with suspected or confirmed TB disease until the patient is determined to be noninfectious or determined to not have TB disease. When surgery cannot be postponed, procedures should be performed in a surgical suite with recommended ventilation controls. Procedures should be scheduled for patients with suspected or confirmed TB disease when a minimum number of HCWs and other patients are present in the surgical suite, and at the end of the day to maximize the time available for removal of airborne contamination (see Environmental Controls; Tables 1 and 2).

If a surgical suite or an OR has an anteroom, the anteroom should be either 1) positive pressure compared with both the corridor and the suite or OR (with filtered supply air) or 2) negative pressure compared with both the corridor and the suite or OR. In the usual design in which an OR has no anteroom, keep the doors to the OR closed, and minimize traffic into and out of the room and in the corridor. Using additional air-cleaning technologies (e.g., UVGI) should be considered to increase the equivalent ACH. Air-cleaning systems can be placed in the room or in surrounding areas to minimize contamination of the surroundings after the procedure (*114*) (see Environmental Controls).

Ventilation in the OR should be designed to provide a sterile environment in the surgical field while preventing contaminated air from flowing to other areas in the health-care setting. Personnel steps should be taken to reduce the risk for contaminating ventilator or anesthesia equipment or discharging tubercle bacilli into the ambient air when operating on a patient with suspected or confirmed TB disease (*152*). A bacterial filter should be placed on the patient's endotracheal tube (or at the expiratory side of the breathing circuit of a ventilator or anesthesia machine, if used) (*147–151*). When selecting a bacterial filter, give preference to models specified by the manufacturer to filter particles 0.3 µm in size in both the unloaded and loaded states with a filter efficiency of ≥95% (i.e., filter penetration of <5%) at the maximum design flow rates of the ventilator for the service life of the filter, as specified by the manufacturer.

When surgical procedures (or other procedures that require a sterile field) are performed on patients with suspected or confirmed infectious TB, respiratory protection should be worn by HCWs to protect the sterile field from the respiratory secretions of HCWs and to protect HCWs from the infectious droplet nuclei generated from the patient. When selecting respiratory protection, do not use valved or positive-pressure respirators, because they do not protect the sterile field. A respirator with a valveless filtering facepiece (e.g., N95 disposable respirator) should be used.

Postoperative recovery of a patient with suspected or confirmed TB disease should be in an AII room in any location where the patient is recovering (*118*). If an AII or comparable room is not available for surgery or postoperative recovery, air-cleaning technologies (e.g., HEPA filtration and UVGI) can be used to increase the number of equivalent ACH (see Environmental Controls); however, the infection-control committee should be involved in the selection and placement of these supplemental controls.

Laboratories

Staff who work in laboratories that handle clinical specimens encounter risks not typically present in other areas of a health-care setting (*153–155*). Laboratories that handle TB specimens include 1) pass-through facilities that forward specimens to reference laboratories for analysis; 2) diagnostic laboratories that process specimens and perform acid-fast staining and primary culture for *M. tuberculosis*; and 3) facilities that perform extensive identification, subtyping, and susceptibility studies.

Procedures involving the manipulation of specimens or cultures containing *M. tuberculosis* introduce additional substantial risks that must be addressed in an effective TB infection-control program. Personnel who work with mycobacteriology specimens should be thoroughly trained in methods that minimize the production of aerosols and undergo periodic competency testing to include direct observation of their work practices. Risks for transmission of *M. tuberculosis* in laboratories include aerosol formation during any specimen or isolate manipulation and percutaneous inoculation from accidental exposures. Biosafety recommendations for laboratories performing diagnostic testing for TB have been published (*74,75,138,156,157*).

In laboratories affiliated with a health-care setting (e.g., a hospital) and in free-standing laboratories, the laboratory director, in collaboration with the infection-control staff for the setting, and in consultation with the state TB laboratory, should develop a risk-based infection-control plan for the laboratory that minimizes the risk for exposure to *M. tuberculosis*. Consider factors including 1) incidence of TB disease (including drug-resistant TB) in the community and in patients served by settings that submit specimens to the laboratory, 2) design of the laboratory, 3) level of TB diagnostic service offered, 4) number of specimens processed, and 5) whether or not aerosol-generating or aerosol-producing procedures are performed and the frequency at which they are performed. Referral laboratories should store isolates in case additional testing is necessary.

Biosafety level (BSL)-2 practices and procedures, containment equipment, and facilities are required for nonaerosol-producing manipulations of clinical specimens (e.g., preparing direct smears for acid-fast staining when done in conjunction with training and periodic checking of competency) (*138*). All specimens suspected of containing *M. tuberculosis* (including specimens processed for other microorganisms) should be handled in a Class I or II biological safety cabinet (BSC) (*158,159*). Conduct all aerosol-generating activities (e.g., inoculating culture media, setting up biochemical and antimicrobic susceptibility tests, opening centrifuge cups, and performing sonication) in a Class I or II BSC (*158*).

For laboratories that are considered at least medium risk (Appendix C), conduct testing for *M. tuberculosis* infection at least annually among laboratorians who perform TB diagnostics or manipulate specimens from which *M. tuberculosis* is commonly isolated (e.g., sputum, lower respiratory secretions, or tissues) (Appendix D). More frequent testing for *M. tuberculosis* is recommended in the event of a documented conversion among laboratory staff or a laboratory accident that poses a risk for exposure to *M. tuberculosis* (e.g., malfunction of a centrifuge leading to aerosolization of a sample).

Based on the risk assessment for the laboratory, employees should use personal protective equipment (including respiratory protection) recommended by local regulations for each activity. For activities that have a low risk for generating aerosols, standard personal protective equipment consists of protective laboratory coats, gowns, or smocks designed specifically for use in the laboratory. Protective garments should be left in the laboratory before going to nonlaboratory areas.

For all laboratory procedures, disposable gloves should be worn. Gloves should be disposed of when work is completed, the gloves are overtly contaminated, or the integrity of the glove is compromised. Local or state regulations should determine procedures for the disposal of gloves. Face protection (e.g., goggles, full-facepiece respirator, face shield, or other splatter guard) should also be used when manipulating specimens inside or outside a BSC. Use respiratory protection when performing procedures that can result in aerosolization outside a BSC. The minimum level of respiratory protection is an N95 filtering facepiece respirator. Laboratory workers who use respiratory protection should be provided with the same training on respirator use and care and the same fit testing as other HCWs.

After documented laboratory accidents, conduct an investigation of exposed laboratory workers. Laboratories in which specimens for mycobacteriologic studies (e.g., AFB smears and cultures) are processed should follow the AIA and CDC/National Institute of Health guidelines (*118,159*) (see Environmental Controls). BSL-3 practices, containment equipment, and facilities are recommended for the propagation and manipulation of cultures of *M. tuberculosis* complex (including *M. bovis*) and for animal studies in which primates that are experimentally or naturally infected with *M. tuberculosis* or *M. bovis* are used. Animal studies in which guinea pigs or mice are used can be conducted at animal BSL-2. Aerosol infection methods are recommended to be conducted at BSL-3 (*159*).

Bronchoscopy Suites

Because bronchoscopy is a cough-inducing procedure that might be performed on patients with suspected or confirmed TB disease, bronchoscopy suites require special attention (*29,81,160,161*). Bronchoscopy can result in the transmission of *M. tuberculosis* either through the airborne route (*29,63,81,86,162*) or a contaminated bronchoscope (*80,82,163–170*). Closed and effectively filtered ventilatory circuitry and minimizing opening of such circuitry in intubated and mechanically ventilated patients might minimize exposure (see Intensive Care Units) (*149*).

If possible, avoid bronchoscopy on patients with suspected or confirmed TB disease or postpone the procedure until the patient is determined to be noninfectious, by confirmation of the three negative AFB sputum smear results (*109–112*). When collection of spontaneous sputum specimen is not adequate or possible, sputum induction has been demonstrated to be equivalent to bronchoscopy for obtaining specimens for culture (*110*). Bronchoscopy might have the advantage of confirmation of the diagnosis with histologic specimens, collection of additional specimens, including post bronchoscopy sputum that might increase the diagnostic yield, and the opportunity to confirm an alternate diagnosis. If the diagnosis of TB disease is suspected, consideration should be given to empiric antituberculosis treatment.

A physical examination should be performed, and a chest radiograph, microscopic examination, culture, and NAA testing of sputum or other relevant specimens should also be obtained, including gastric aspirates (*125*), as indicated (*53,126,131,130*). Because 15%–20% of patients with TB disease have negative TST results, a negative TST result is of limited value in the evaluation of the patient with suspected TB disease, particularly in patients from high TB incidence groups in whom TST positive rates exceed 30% (*31*).

Whenever feasible, perform bronchoscopy in a room that meets the ventilation requirements for an AII room (same as the AIA guidelines parameters for bronchoscopy rooms) (see Environmental Controls). Air-cleaning technologies (e.g., HEPA filtration and UVGI) can be used to increase equivalent ACH.

If sputum specimens must be obtained and the patient cannot produce sputum, consider sputum induction before bron-

choscopy (*111*). In a patient who is intubated and mechanically ventilated, minimize the opening of circuitry. At least N95 respirators should be worn by HCWs while present during a bronchoscopy procedure on a patient with suspected or confirmed infectious TB disease. Because of the increased risk for *M. tuberculosis* transmission during the performance of bronchoscopy procedures on patients with TB disease, consider using a higher level of respiratory protection than an N95 disposable respirator (e.g., an elastomeric full-facepiece respirator or a powered air-purifying respirator [PAPR] [*29*]) (see Respiratory Protection).

After bronchoscopy is performed on a patient with suspected or confirmed infectious TB disease, allow adequate time to elapse to ensure removal of *M. tuberculosis*–contaminated room air before performing another procedure in the same room (see Environmental Controls; Tables 1 and 2). During the period after bronchoscopy when the patient is still coughing, collect at least one sputum for AFB to increase the yield of the procedure. Patients with suspected or confirmed TB disease who are undergoing bronchoscopy should be kept in an AII room until coughing subsides.

Sputum Induction and Inhalation Therapy Rooms

Sputum induction and inhalation therapy induces coughing, which increases the potential for transmission of *M. tuberculosis* (*87,88,90*). Therefore, appropriate precautions should be taken when working with patients with suspected or confirmed TB disease. Sputum induction procedures for persons with suspected or confirmed TB disease should be considered after determination that self-produced sputum collection is inadequate and that the AFB smear result on other specimens collected is negative. HCWs who order or perform sputum induction or inhalation therapy in an environment without proper controls for the purpose of diagnosing conditions other than TB disease should assess the patient's risk for TB disease.

Cough-inducing or aerosol-generating procedures in patients with diagnosed TB should be conducted only after an assessment of infectiousness has been considered for each patient and should be conducted in an environment with proper controls. Sputum induction should be performed by using local exhaust ventilation (e.g., booths with special ventilation) or alternatively in a room that meets or exceeds the requirements of an AII room (see Environmental Controls) (*90*). At least an N95 disposable respirator should be worn by HCWs performing sputum inductions or inhalation therapy on a patient with suspected or confirmed infectious TB disease. Based on the risk assessment, consideration should be given to using a higher level of respiratory protection (e.g., an elastomeric full-facepiece respirator or a PAPR) (see Respiratory Protection) (*90*).

After sputum induction or inhalation therapy is performed on a patient with suspected or confirmed infectious TB disease, allow adequate time to elapse to ensure removal of *M. tuberculosis*–contaminated room air before performing another procedure in the same room (see Environmental Controls; Tables 1 and 2). Patients with suspected or confirmed TB disease who are undergoing sputum induction or inhalation therapy should be kept in an AII room until coughing subsides.

Autopsy Suites

Autopsies performed on bodies with suspected or confirmed TB disease can pose a high risk for transmission of *M. tuberculosis*, particularly during the performance of aerosol-generating procedures (e.g., median sternotomy). Persons who handle bodies might be at risk for transmission of *M. tuberculosis* (*77,78,171–177*). Because certain procedures performed as part of an autopsy might generate infectious aerosols, special airborne precautions are required.

Autopsies should not be performed on bodies with suspected or confirmed TB disease without adequate protection for those performing the autopsy procedures. Settings in which autopsies are performed should meet or exceed the requirements of an AII room, if possible (see Environmental Controls), and the drawing in the American Conference of Governmental Industrial Hygienists® (ACGIH) Industrial Ventilation Manual VS-99-07 (*178*). Air should be exhausted to the outside of the building. Air-cleaning technologies (e.g., HEPA filtration or UVGI) can be used to increase the number of equivalent ACH (see Environmental Controls).

As an added administrative measure, when performing autopsies on bodies with suspected or confirmed TB disease, coordination between attending physicians and pathologists is needed to ensure proper infection control and specimen collection. The use of local exhaust ventilation should be considered to reduce exposures to infectious aerosols (e.g., when using a saw, including Striker saw). For HCWs performing an autopsy on a body with suspected or confirmed TB disease, at least N95 disposable respirators should be worn (see Respiratory Protection). Based on the risk assessment, consider using a higher level of respiratory protection than an N95 disposable respirator (e.g., an elastomeric full-facepiece respirator or a PAPR) (see Respiratory Protection).

After an autopsy is performed on a body with suspected or confirmed TB disease, allow adequate time to elapse to ensure removal of *M. tuberculosis*–contaminated room air before performing another procedure in the same room (see Environmental Controls; Tables 1 and 2). If time delay is not feasible, the autopsy staff should continue to wear respirators while they are in the room.

Embalming Rooms

Embalming procedures performed on bodies with suspected or confirmed TB disease can pose a high risk for transmission of *M. tuberculosis*, particularly during the performance of aerosol-generating procedures. Persons who handle corpses might be at risk for transmission of *M. tuberculosis* (*77,78,171–176*). Because certain procedures performed as part of embalming might generate infectious aerosols, special airborne precautions are required.

Embalming should not be performed on bodies with suspected or confirmed TB disease without adequate protection for the persons performing the procedures. Settings in which embalming is performed should meet or exceed the requirements of an AII room, if possible (see Environmental Controls), and the drawing in the ACGIH Industrial Ventilation Manual VS-99-07 (*178*). Air should be exhausted to the outside of the building. Air-cleaning technologies (e.g., HEPA filtration or UVGI) can be used to increase the number of equivalent ACH (see Environmental Controls). The use of local exhaust ventilation should be considered to reduce exposures to infectious aerosols (e.g., when using a saw, including Striker saw) and vapors from embalming fluids.

When HCWs embalm a body with suspected or confirmed TB disease, at least N95 disposable respirators should be worn (see Respiratory Protection). Based on the risk assessment, consider using a higher level of respiratory protection than an N95 disposable respirator (e.g., an elastomeric full-facepiece respirator or a PAPR) (see Respiratory Protection).

After embalming is performed on a body with suspected or confirmed TB disease, allow adequate time to elapse to ensure removal of *M. tuberculosis*–contaminated room air before performing another procedure in the same room (see Environmental Controls). If time delay is not feasible, the embalming staff should continue to wear respirators while in the room.

Outpatient Settings

Outpatient settings might include TB treatment facilities, dental-care settings, medical offices, ambulatory-care settings, and dialysis units. Environmental controls should be implemented based on the types of activities that are performed in the setting.

TB Treatment Facilities

TB treatment facilities might include TB clinics, infectious disease clinics, or pulmonary clinics. TB clinics and other settings in which patients with TB disease and LTBI are examined on a regular basis require special attention. The same principles of triage used in EDs and ambulatory-care settings (see Minimum Requirements) should be applied to TB treatment facilities. These principles include prompt identification, evaluation, and airborne precautions of patients with suspected or confirmed infectious TB disease.

All TB clinic staff, including outreach workers, should be screened for *M. tuberculosis* infection (Appendix C). Patients with suspected or confirmed infectious TB disease should be physically separated from all patients, but especially from those with HIV infection and other immunocompromising conditions that increase the likelihood of development of TB disease if infected. Immunosuppressed patients with suspected or confirmed infectious TB disease need to be physically separated from others to protect both the patient and others. Appointments should be scheduled to avoid exposing HIV-infected or otherwise severely immunocompromised persons to *M. tuberculosis*. Certain times of the day should be designated for appointments for patients with infectious TB disease or treat them in locations in areas in which immunocompromised persons are not treated.

Persons with suspected or confirmed infectious TB disease should be promptly placed in an AII room to minimize exposure in the waiting room and other areas of the clinic, and they should be instructed to observe strict respiratory hygiene and cough etiquette procedures. Clinics that provide care for patients with suspected or confirmed infectious TB disease should have at least one AII room. The need for additional AII rooms should be based on the risk assessment for the setting.

All cough-inducing and aerosol-generating procedures should be performed using environmental controls (e.g., in a booth or an AII room) (see Environmental Controls). Patients should be left in the booth or AII room until coughing subsides. Another patient or HCW should not be allowed to enter the booth or AII room until sufficient time has elapsed for adequate removal of *M. tuberculosis*-contaminated air (see Environmental Controls). A respiratory-protection program should be implemented for all HCWs who work in the TB clinic and who enter AII rooms, visit areas in which persons with suspected or confirmed TB disease are located, or transport patients with suspected or confirmed TB disease in vehicles. When persons with suspected or confirmed infectious TB disease are in the TB clinic and not in an AII room, they should wear a surgical or procedure mask, if possible.

Medical Offices and Ambulatory-Care Settings

The symptoms of TB disease are usually symptoms for which patients might seek treatment in a medical office. Therefore, infectious TB disease could possibly be encountered in certain medical offices and ambulatory-care settings.

Because of the potential for *M. tuberculosis* transmission in medical offices and ambulatory-care settings, follow the general recommendations for management of patients with suspected or confirmed TB disease and the specific

recommendations for EDs (see Intensive Care Units [ICUs]). The risk assessment may be used to determine the need for or selection of environmental controls and the frequency of testing HCWs for *M. tuberculosis* infection.

Dialysis Units

Certain patients with TB disease need chronic dialysis for treatment of ESRD (*179–181*). The incidence of TB disease and infection in patients with ESRD might be higher than in the general population (*181–183*) and might be compounded by the overlapping risks for ESRD and TB disease among patients with diabetes mellitus (*39*). In addition, certain dialysis patients or patients who are otherwise immunocompromised (e.g., patients with organ transplants) might be on immunosuppressive medications (*162,183*). Patients with ESRD who need chronic dialysis should have at least one test for *M. tuberculosis* infection to determine the need for treatment of LTBI. Annual re-screening is indicated if ongoing exposure of ESRD patients to *M. tuberculosis* is probable.

Hemodialysis procedures should be performed on hospitalized patients with suspected or confirmed TB disease in an AII room. Dialysis staff should use recommended respiratory protection, at least an N95 disposable respirator. Patients with suspected or confirmed TB disease who need chronic hemodialysis might need referral to a hospital or other setting with the ability to perform dialysis procedures in an AII room until the patient is no longer infectious or another diagnosis is made. Certain antituberculosis medications are prescribed differently for hemodialysis patients (*31*).

Dental-Care Settings

The generation of droplet nuclei containing *M. tuberculosis* as a result of dental procedures has not been demonstrated (*184*). Nonetheless, oral manipulations during dental procedures could stimulate coughing and dispersal of infectious particles. Patients and dental HCWs share the same air space for varying periods, which contributes to the potential for transmission of *M. tuberculosis* in dental settings (*185*). For example, during primarily routine dental procedures in a dental setting, MDR TB might have been transmitted between two dental workers (*186*).

To prevent the transmission of *M. tuberculosis* in dental-care settings, certain recommendations should be followed (*187,188*). Infection-control policies for each dental health-care setting should be developed, based on the community TB risk assessment (see TB Risk Assessment Worksheet [Appendix B]), and the periodically should be reviewed annually, if possible. The policies should include appropriate screening for LTBI and TB disease for dental HCWs, education on the risk for transmission to the dental HCWs, and provisions for detection and management of patients who have suspected or confirmed TB disease.

When taking a patient's initial medical history and at periodic updates, dental HCWs should routinely document whether the patient has symptoms or signs of TB disease. If urgent dental care must be provided for a patient who has suspected or confirmed infectious TB disease, dental care should be provided in a setting that meets the requirements for an AII room (see Environmental Controls). Respiratory protection (at least N95 disposable respirator) should be used while performing procedures on such patients.

In dental health-care settings that routinely provide care to populations at high risk for TB disease, using engineering controls (e.g., portable HEPA units) similar to those used in waiting rooms or clinic areas of health-care settings with a comparable community-risk profile might be beneficial.

During clinical assessment and evaluation, a patient with suspected or confirmed TB disease should be instructed to observe strict respiratory hygiene and cough etiquette procedures (*122*). The patient should also wear a surgical or procedure mask, if possible. Non-urgent dental treatment should be postponed, and these patients should be promptly referred to an appropriate medical setting for evaluation of possible infectiousness. In addition, these patients should be kept in the dental health-care setting no longer than required to arrange a referral.

Nontraditional Facility-Based Settings

Nontraditional facility-based settings include EMS, medical settings in correctional facilities, home-based health-care and outreach settings, long-term–care settings (e.g., hospices and skilled nursing facilities), and homeless shelters. Environmental controls should be implemented based on the types of activities that are performed in the setting.

TB is more common in the homeless population than in the general population (*189–192*). Because persons who visit homeless shelters frequently share exposure and risk characteristics of TB patients who are treated in outpatient clinics, homeless shelters with clinics should observe the same TB infection-control measures as outpatient clinics. ACET has developed recommendations to assist health-care providers, health departments, shelter operators and workers, social service agencies, and homeless persons to prevent and control TB in this population (*189*).

Emergency Medical Services (EMS)

Although the overall risk is low (*193*), documented transmission of *M. tuberculosis* has occurred in EMS occupational settings (*194*), and approaches to reduce this risk have been described (*193,195*). EMS personnel should be included in a

comprehensive screening program to test for *M. tuberculosis* infection and provide baseline screening and follow-up testing as indicated by the risk classification of the setting. Persons with suspected or confirmed infectious TB disease who are transported in an ambulance should wear a surgical or procedure mask, if possible, and drivers, HCWs, and other staff who are transporting the patient might consider wearing an N95 respirator.

The ambulance ventilation system should be operated in the nonrecirculating mode, and the maximum amount of outdoor air should be provided to facilitate dilution. If the vehicle has a rear exhaust fan, use this fan during transport. If the vehicle is equipped with a supplemental recirculating ventilation unit that passes air through HEPA filters before returning it to the vehicle, use this unit to increase the number of ACH (*188*). Air should flow from the cab (front of vehicle), over the patient, and out the rear exhaust fan. If an ambulance is not used, the ventilation system for the vehicle should bring in as much outdoor air as possible, and the system should be set to nonrecirculating. If possible, physically isolate the cab from the rest of the vehicle, and place the patient in the rear seat (*194*).

EMS personnel should be included in the follow-up contact investigations of patients with infectious TB disease. The Ryan White Comprehensive AIDS Resource Emergency Act of 1990 (Public law 101–381) mandates notification of EMS personnel after they have been exposed to a patient with suspected or confirmed infectious TB disease (Title 42 U.S. Code 1994) (http://hab.hrsa.gov/data2/adap/introduction.htm).

Medical Settings in Correctional Facilities

TB is a substantial health concern in correctional facilities; employees and inmates are at high risk (*105,196–205*). TB outbreaks in correctional facilities can lead to transmission in surrounding communities (*201,206,207*). ACET recommends that all correctional facilities have a written TB infection-control plan (*196*), and multiple studies indicate that screening correctional employees and inmates is a vital TB control measure (*204,208,209*).

The higher risk for *M. tuberculosis* transmission in health-care settings in correctional facilities (including jails and prisons) is a result of the disproportionate number of inmates with risk factors for TB infection and TB disease (*203,210*). Compared with the general population, TB prevalence is higher among inmates and is associated with a higher prevalence of HIV infection (*197*), increased illicit substance use, lower socioeconomic status (*201*), and their presence in settings that are at high risk for transmission of *M. tuberculosis*.

A TB infection-control plan should be developed specifically for that setting, even if the institution is part of a multifacility system (*196,211*). Medical settings in correctional facilities should be classified as at least medium risk; therefore, all correctional facility health-care personnel and other staff, including correctional officers should be screened for TB at least annually (*201,203,208*).

Correctional facilities should collaborate with the local or state health department to decide on TB contact investigations and discharge planning (*105,212*) and to provide TB training and education to inmates and employees (*196*). Corrections staff should be educated regarding symptoms and signs of TB disease and encouraged to facilitate prompt evaluation of inmates with suspected infectious TB disease (*206*).

At least one AII room should be available in the correctional facility. Any inmate with suspected or confirmed infectious TB disease should be placed in an AII room immediately or transferred to a setting with an AII room; base the number of additional AII rooms needed on the risk assessment for the setting. Sputum samples should be collected in sputum induction booths or AII rooms, not in inmates' cells. Sputum collection can also be performed safely outside, away from other persons, windows, and ventilation intakes.

Inmates with suspected or confirmed infectious TB disease who must be transported outside an AII room for medically essential procedures should wear a surgical or procedure mask during transport, if possible. If risk assessment indicates the need for respiratory protection, drivers, medical or security staff, and others who are transporting patients with suspected or confirmed infectious TB disease in an enclosed vehicle should consider wearing an N95 disposable respirator.

A respiratory-protection program, including training, education, and fit-testing in the correctional facility's TB infection-control program should be implemented. Correctional facilities should maintain a tracking system for inmate TB screening and treatment and establish a mechanism for sharing this information with state and local health departments and other correctional facilities (*196,201*). Confidentiality of inmates should be ensured the confidentiality of inmates during screening for symptoms or signs of TB disease and risk factors.

Home-Based Health-Care and Outreach Settings

Transmission of *M. tuberculosis* has been documented in staff who work in home-based health-care and outreach settings (*213,214*). The setting's infection-control plan should include training that reminds HCWs who provide medical services in the homes of patients or other outreach settings of the importance of early evaluation of symptoms or signs of TB disease for early detection and treatment of TB disease. Training should also include the role of the HCW in educating patients regarding the importance of reporting symptoms

or signs of TB disease and the importance of reporting any adverse effects to treatment for LTBI or TB disease.

HCWs who provide medical services in the homes of patients with suspected or confirmed TB disease can help prevent transmission of *M. tuberculosis* by 1) educating patients and other household members regarding the importance of taking medications as prescribed, 2) facilitating medical evaluation of symptoms or signs of TB disease, and 3) administering DOT, including DOT for treatment of LTBI, whenever feasible.

HCWs who provide medical services in the homes of patients should not perform cough-inducing or aerosol-generating procedures on patients with suspected or confirmed infectious TB disease, because recommended infection controls probably will not be in place. Sputum collection should be performed outdoors, away from other persons, windows, and ventilation intakes.

HCWs who provide medical services in the homes of patients with suspected or confirmed infectious TB disease should instruct TB patients to observe strict respiratory hygiene and cough etiquette procedures. HCWs who enter homes of persons with suspected or confirmed infectious TB disease or who transport such persons in an enclosed vehicle should consider wearing at least an N95 disposable respirator (see Respiratory Protection).

Long-Term–Care Facilities (LTCFs)

Infection with *M. tuberculosis* poses a health risk to patients, HCWs, visitors, and volunteers in LTCFs (e.g., hospices and skilled nursing facilities) (*215,216*). Transmission of *M. tuberculosis* has occurred in LTCF (*217–220*), and pulmonary TB disease has been documented in HIV-infected patients and other immunocompromised persons residing in hospices (*218,221,222*). New employees and residents to these settings should receive a symptom screen and possibly a test for *M. tuberculosis* infection to exclude a diagnosis of TB disease (see TB Risk Assessment Worksheet).

LTCFs must have adequate administrative and environmental controls, including airborne precautions capabilities and a respiratory-protection program, if they accept patients with suspected or confirmed infectious TB disease. The setting should have 1) a written protocol for the early identification of patients with symptoms or signs of TB disease and 2) procedures for referring these patients to a setting where they can be evaluated and managed. Patients with suspected or confirmed infectious TB disease should not stay in LTCFs unless adequate administrative and environmental controls and a respiratory-protection program are in place. Persons with TB disease who are determined to be noninfectious can remain in the LTCF and do not need to be in an AII room.

Training and Educating HCWs

HCW training and education regarding infection with *M. tuberculosis* and TB disease is an essential part of administrative controls in a TB surveillance or infection-control program. Training physicians and nurse managers is especially essential because of the leadership role they frequently fulfill in infection control. HCW training and education can increase adherence to TB infection-control measures. Training and education should emphasize the increased risks posed by an undiagnosed person with TB disease in a health-care setting and the specific measures to reduce this risk. HCWs receive various types of training; therefore, combining training for TB infection control with other related trainings might be preferable.

Initial TB Training and Education

The setting should document that all HCWs, including physicians, have received initial TB training relevant to their work setting and additional occupation-specific education. The level and detail of baseline training will vary according to the responsibilities of the HCW and the risk classification of the setting.

Educational materials on TB training are available from various sources at no cost in printed copy, on videotape (*223*), on compact discs, and the Internet. The local or state health department should have access to additional materials and resources and might be able to help develop a setting-specific TB education program. Suggested components of a baseline TB training program for HCWs have been described previously. CDC's TB website provides information regarding training and education materials (http://www.cdc.gov/tb). Additional training and education materials are available on CDC's TB Education and Training Resources website (http://www.findtbresources.org) and on other TB-related websites and resources (Appendix E).

Physicians, trainees, students, and other HCWs who work in a health-care setting but do not receive payment from that setting should receive baseline training in TB infection-control policies and practices, the TB screening program, and procedures for reporting an *M. tuberculosis* infection test conversion or diagnosis of TB disease. Initial TB training should be provided before the HCW starts working.

Follow-Up TB Training and Education

All settings should conduct an annual evaluation of the need for follow-up training and education for HCWs based on the number of untrained and new HCWs, changes in the organization and services of the setting, and availability of new TB infection-control information.

If a potential or known exposure to *M. tuberculosis* occurs in the setting, prevention and control measures should include retraining HCWs in the infection-control procedures established to prevent the recurrence of exposure. If a potential or known exposure results in a newly recognized positive TST or BAMT result, test conversion, or diagnosis of TB disease, education should include information on 1) transmission of *M. tuberculosis*, 2) noninfectiousness of HCWs with LTBI, and 3) potential infectiousness of HCWs with TB disease.

OSHA requires annual respiratory-protection training for HCWs who use respiratory devices (see Respiratory Protection). HCWs in settings with a classification of potential ongoing transmission should receive additional training and education on 1) symptoms and signs of TB disease, 2) *M. tuberculosis* transmission, 3) infection-control policies, 4) importance of TB screening for HCWs, and 5) responsibilities of employers and employees regarding *M. tuberculosis* infection test conversion and diagnosis of TB disease.

TB Infection-Control Surveillance

HCW Screening Programs for TB Support Surveillance and Clinical Care

TB screening programs provide critical information for caring for individual HCWs and information that facilitates detection of *M. tuberculosis* transmission. The screening program consists of four major components: 1) baseline testing for *M. tuberculosis* infection, 2) serial testing for *M. tuberculosis* infection, 3) serial screening for symptoms or signs of TB disease, and 4) TB training and education.

Surveillance data from HCWs can protect both HCWs and patients. Screening can prevent future transmission by identifying lapses in infection control and expediting treatment for persons with LTBI or TB disease. Tests to screen for *M. tuberculosis* infection should be administered, interpreted, and recorded according to procedures in this report (see Supplement, Diagnostic Procedures for LTBI and TB Disease). Protection of privacy and maintenance of confidentiality of HCW test results should be ensured. Methods to screen for infection with *M. tuberculosis* are available (*30,31,39*).

Baseline Testing for *M. tuberculosis* Infection

Baseline testing for *M. tuberculosis* infection is recommended for all newly hired HCWs, regardless of the risk classification of the setting and can be conducted with the TST or BAMT. Baseline testing is also recommended for persons who will receive serial TB screening (e.g., residents or staff of correctional facilities or LTCFs) (*39,224*). Certain settings, with the support of the infection-control committee, might choose not to perform baseline or serial TB screening for HCWs who will never be in contact with or have shared air space with patients who have TB disease (e.g., telephone operators who work in a separate building from patients) or who will never be in contact with clinical specimens that might contain *M. tuberculosis*.

Baseline test results 1) provide a basis for comparison in the event of a potential or known exposure to *M. tuberculosis* and 2) facilitate the detection and treatment of LTBI or TB disease in an HCW before employment begins and reduces the risk to patients and other HCWs. If TST is used for baseline testing, two-step testing is recommended for HCWs whose initial TST results are negative (*39,224*). If the first-step TST result is negative, the second-step TST should be administered 1–3 weeks after the first TST result was read. If either 1) the baseline first-step TST result is positive or 2) the first-step TST result is negative but the second-step TST result is positive, TB disease should be excluded, and if it is excluded, then the HCW should be evaluated for treatment of LTBI. If the first and second-step TST results are both negative, the person is classified as not infected with *M. tuberculosis*.

If the second test result of a two-step TST is not read within 48–72 hours, administer a TST as soon as possible (even if several months have elapsed) and ensure that the result is read within 48–72 hours (*39*). Certain studies indicate that positive TST reactions might still be measurable from 4–7 days after testing (*225,226*). However, if a patient fails to return within 72 hours and has a negative test result, the TST should be repeated (*42*).

A positive result to the second step of a baseline two-step TST is probably caused by boosting as opposed to recent infection with *M. tuberculosis*. These responses might result from remote infections with *M. tuberculosis*, infection with an NTM (also known as MOTT), or previous BCG vaccination. Two-step testing will minimize the possibility that boosting will lead to an unwarranted suspicion of transmission of *M. tuberculosis* with subsequent testing. A second TST is not needed if the HCW has a documented TST result from any time during the previous 12 months (see Baseline Testing for *M. tuberculosis* Infection After TST Within the Previous 12 Months).

A positive TST reaction as a result of BCG wanes after 5 years. Therefore, HCWs with previous BCG vaccination will frequently have a negative TST result (*74,227–232*). Because HCWs with a history of BCG are frequently from high TB-prevalence countries, positive test results for *M. tuberculosis* infection in HCWs with previous BCG vaccination should be interpreted as representing infection with *M. tuberculosis* (*74,227–233*). Although BCG reduces the occurrence of severe forms of TB disease in children and overall might reduce the risk for progression from LTBI to TB disease (*234,235*),

BCG is not thought to prevent *M. tuberculosis* infection (*236*). Test results for *M. tuberculosis* infection for HCWs with a history of BCG should be interpreted by using the same diagnostic cut points used for HCWs without a history of BCG vaccination.

BAMT does not require two-step testing and is more specific than skin testing. BAMT that uses *M. tuberculosis*-specific antigens (e.g., QFT-G) are not expected to result in false-positive results in persons vaccinated with BCG. Baseline test results should be documented, preferably within 10 days of HCWs starting employment.

Baseline Testing for *M. tuberculosis* Infection After TST Within the Previous 12 Months

A second TST is not needed if the HCW has a documented TST result from any time during the previous 12 months. If a newly employed HCW has had a documented negative TST result within the previous 12 months, a single TST can be administered in the new setting (Box 1). This additional TST represents the second stage of two-step testing. The second test decreases the possibility that boosting on later testing will lead to incorrect suspicion of transmission of *M. tuberculosis* in the setting.

A recent TST (performed in ≤12 months) is not a contraindication to a subsequent TST unless the test was associated with severe ulceration or anaphylactic shock, which are substantially rare adverse events (*30,237–239*). Multiple TSTs are safe and do not increase the risk for a false-positive result or a TST conversion in persons without infection with mycobacteria (*39*).

Baseline Documentation of a History of TB Disease, a Previously Positive Test Result for *M. tuberculosis* Infection, or Completion of Treatment for LTBI or TB Disease

Additional tests for *M. tuberculosis* infection do not need to be performed for HCWs with a documented history of TB disease, documented previously positive test result for *M. tuberculosis* infection, or documented completion of treatment for LTBI or TB disease. Documentation of a previously positive test result for *M. tuberculosis* infection can be substituted for a baseline test result if the documentation includes a recorded TST result in millimeters (or BAMT result), including the concentration of cytokine measured (e.g., IFN-γ). All other HCWs should undergo baseline testing for *M. tuberculosis* infection to ensure that the test result on record in the setting has been performed and measured using the recommended diagnostic the recommended procedures (see Supplement, Diagnostic Procedures for LTBI and TB Disease).

BOX 1. Indications for two-step tuberculin skin tests (TSTs)

Situation	Recommended testing
No previous TST result	Two-step baseline TSTs
Previous negative TST result (documented or not) >12 months before new employment	Two-step baseline TSTs
Previous documented negative TST result ≤12 months before new employment	Single TST needed for baseline testing; this test will be the second-step
≥2 previous documented negative TSTs but most recent TST >12 months before new employment	Single TST; two-step testing is not necessary
Previous documented positive TST result	No TST
Previous undocumented positive TST result*	Two-step baseline TST(s)
Previous BCG† vaccination	Two-step baseline TST(s)
Programs that use serial BAMT,§ including QFT¶ (or the previous version QFT)	See Supplement, Use of QFT-G** for Diagnosing *M. tuberculosis* Infections in Health-Care Workers (HCWs)

* For newly hired health-c are workers and other persons who will be tested on a routine basis (e.g., residents or staff of correctional or long-term–care facilities), a previous TST is not a contraindication to a subsequent TST, unless the test was associated with severe ulceration or anaphylactic shock, which are substantially rare adverse events. If the previous positive TST result is not documented, administer two-step TSTs or offer BAMT. **SOURCES:** Aventis Pasteur. Tuberculin purified protein derivative (Mantoux) Tubersol® diagnostic antigen. Toronto, Ontario, Canada: Aventis Pasteur; 2001. Parkdale Pharmaceuticals. APLISOL (Tuberculin purified protein derivative, diluted [stabilized solution]). Diagnostic antigen for intradermal injection only. Rochester, MI: Parkdale Pharmaceuticals; 2002. Froeschle JE, Ruben FL, Bloh AM. Immediate hypersensitivity reactions after use of tuberculin skin testing. Clin Infect Dis 2002;34:E12–3.

† Bacille Calmette-Guérin.

§ Blood assay for *Mycobacterium tuberculosis.*

¶ QuantiFERON®-TB test.

** QuantiFERON®-TB Gold test.

A recent TST (performed in ≤12 months) is not a contraindication to the administration of an additional test unless the TST was associated with severe ulceration or anaphylactic shock, which are substantially rare adverse events (*30,237,238*). However, the recent test might complicate interpretation of subsequent test results because of the possibility of boosting.

Serial Follow-Up of TB Screening and Testing for *M. tuberculosis* Infection

The need for serial follow-up screening for groups of HCWs with negative test results for *M. tuberculosis* infection is an institutional decision that is based on the setting's risk classification. This decision and changes over time based on updated risk assessments should be official and documented. If a serial follow-up screening program is required, the risk assessment for the setting (see TB Risk Assessment Worksheet [Appendix B]) will determine which HCWs should be included in the program and the frequency of screening. Two-step TST testing should not be performed for follow-up testing.

If possible, stagger follow-up screening (rather than testing all HCWs at the same time each year) so that all HCWs who work in the same area or profession are not tested in the same month. Staggered screening of HCWs (e.g., on the anniversary of their employment or on their birthdays) increases opportunities for early recognition of infection-control problems that can lead to conversions in test results for *M. tuberculosis* infection. Processing aggregate analysis of TB screening data on a periodic regular basis is important for detecting problems.

HCWs with a Newly Recognized Positive Test Result for *M. tuberculosis* Infection or Symptoms or Signs of TB Disease

Clinical Evaluation

Any HCW with a newly recognized positive test result for *M. tuberculosis* infection, test conversion, or symptoms or signs of TB disease should be promptly evaluated. The evaluation should be arranged with employee health, the local or state health department, or a personal physician. Any physicians who evaluate HCWs with suspected TB disease should be familiar with current diagnostic and therapeutic guidelines for LTBI and TB disease (*31,39*).

The definitions for positive test results for *M. tuberculosis* infection and test conversion in HCWs are included in this report (see Supplement, Diagnostic Procedures for LTBI and TB Disease). Symptoms of disease in the lung, pleura, or airways, and the larynx include coughing for >3 weeks, loss of appetite, unexplained weight loss, night sweats, bloody sputum or hemoptysis, hoarseness, fever, fatigue, or chest pain. The evaluation should include a clinical examination and symptom screen (a procedure used during a clinical evaluation in which patients are asked if they have experienced any symptoms or signs of TB disease), chest radiograph, and collection of sputum specimens.

If TB disease is diagnosed, begin antituberculosis treatment immediately, according to published guidelines (*31*). The diagnosing clinician (who might not be a physician with the institution's infection-control program) should notify the local or state health department in accordance with disease reporting laws, which generally specify a 24-hour time limit.

If TB disease is excluded, offer the HCW treatment for LTBI in accordance with published guidelines (see Supplements, Diagnostic Procedures for LTBI and TB Disease; and Treatment Procedures for LTBI and TB Disease [*39,240*]). If the HCW has already completed treatment for LTBI and is part of a TB screening program, instead of participating in serial skin testing, the HCW should be monitored for symptoms of TB disease and should receive any available training, which should include information on the symptoms of TB disease and instructing the HCW to report any such symptoms immediately to occupational health. In addition, annual symptom screens should be performed, which can be administered as part of other HCW screening and education efforts. Treatment for LTBI should be offered to HCWs who are eligible (*39*).

HCWs with a previously negative test result who have an increase of ≥10 mm induration when examined on follow-up testing probably have acquired *M. tuberculosis* infection and should be evaluated for TB disease. When disease is excluded, HCWs should be treated for LTBI unless medically contraindicated (*39,240*).

Chest Radiography

HCWs with a baseline positive or newly positive TST or BAMT result should receive one chest radiograph to exclude a diagnosis of TB disease (or an interpretable copy within a reasonable time frame, such as 6 months). After this baseline chest radiograph is performed and the result is documented, repeat radiographs are not needed unless symptoms or signs of TB disease develop or a clinician recommends a repeat chest radiograph (*39,116*). Instead of participating in serial testing for *M. tuberculosis* infection, HCWs with a positive test result for *M. tuberculosis* infection should receive a symptom screen. The frequency of this symptom screen should be determined by the risk classification for the setting.

Serial follow-up chest radiographs are not recommended for HCWs with documentation of a previously positive test result for *M. tuberculosis* infection, treatment for LTBI or TB disease, or for asymptomatic HCWs with negative test results for *M. tuberculosis* infection. HCWs who have a previously positive test result for *M. tuberculosis* infection and who change

jobs should carry documentation of a baseline chest radiograph result (and the positive test result for *M. tuberculosis* infection) to their new employers.

Workplace Restrictions

HCWs with a baseline positive or newly positive test result for *M. tuberculosis* infection should receive one chest radiograph result to exclude TB disease (or an interpretable copy within a reasonable time frame, such as 6 months).

HCWs with confirmed infectious pulmonary, laryngeal, endobroncheal, or tracheal TB disease, or a draining TB skin lesion pose a risk to patients, HCWs, and others. Such HCWs should be excluded from the workplace and should be allowed to return to work when the following criteria have been met: 1) three consecutive sputum samples (*109–112*) collected in 8–24-hour intervals that are negative, with at least one sample from an early morning specimen (because respiratory secretions pool overnight); 2) the person has responded to antituberculosis treatment that will probably be effective (can be based on susceptibility results); and 3) the person is determined to be noninfectious by a physician knowledgeable and experienced in managing TB disease (see Supplements, Estimating the Infectiousness of a TB Patient; Diagnostic Procedures for LTBI and TB Disease; and Treatment Procedures for LTBI and TB Disease).

HCWs with extrapulmonary TB disease usually do not need to be excluded from the workplace as long as no involvement of the respiratory track has occurred. They can be confirmed as noninfectious and can continue to work if documented evidence is available that indicates that concurrent pulmonary TB disease has been excluded.

HCWs receiving treatment for LTBI can return to work immediately. HCWs with LTBI who cannot take or do not accept or complete a full course of treatment for LTBI should not be excluded from the workplace. They should be counseled regarding the risk for developing TB disease and instructed to report any TB symptoms immediately to the occupational health unit.

HCWs who have a documented positive TST or BAMT result and who leave employment should be counseled again, if possible, regarding the risk for developing TB disease and instructed to seek prompt evaluation with the local health department or their primary care physician if symptoms of TB disease develop. Consider mailing letters to former HCWs who have LTBI. This information should be recorded in the HCWs' employee health record when they leave employment.

Asymptomatic HCWs with a baseline positive or newly positive TST or BAMT result do not need to be excluded from the workplace. Treatment for LTBI should be considered in accordance with CDC guidelines (*39*).

Identification of Source Cases and Recording of Drug-Susceptibility Patterns

If an HCW experiences a conversion in a test result for *M. tuberculosis* infection, evaluate the HCW for a history of suspected or known exposure to *M. tuberculosis* to determine the potential source. When the source case is identified, also identify the drug susceptibility pattern of the *M. tuberculosis* isolate from the source. The drug-susceptibility pattern should be recorded in the HCW's medical or employee health record to guide the treatment of LTBI or TB disease, if indicated.

HCWs with Medical Conditions Associated with Increased Risk for Progression to TB Disease

In settings in which HCWs are severely immunocompromised, additional precautions must be taken. HIV infection is the highest risk factor for progression from LTBI to TB disease (*22,39,42,49*). Other immunocompromising conditions, including diabetes mellitus, certain cancers, and certain drug treatments, also increase the risk for rapid progression from LTBI to TB disease. TB disease can also adversely affect the clinical course of HIV infection and acquired immunodeficiency syndrome (AIDS) and can complicate HIV treatment (*31,39,53*).

Serial TB screening beyond that indicated by the risk classification for the setting is not indicated for persons with the majority of medical conditions that suppress the immune system or otherwise increase the risk for infection with *M. tuberculosis* progressing to TB disease (*58*). However, consideration should be given to repeating the TST for HIV-infected persons whose initial TST result was negative and whose immune function has improved in response to highly active antiretroviral therapy (HAART) (i.e., those whose CD4-T lymphocyte count has increased to >200 cells/mL).

All HCWs should, however, be encouraged during their initial TB training to determine if they have such a medical condition and should be aware that receiving medical treatment can improve cell-mediated immunity. HCWs should be informed concerning the availability of counseling, testing, and referral for HIV (*50,51*). In addition, HCWs should know whether they are immunocompromised, and they should be aware of the risks from exposure to *M. tuberculosis* (*1*). In certain cases, reassignment to areas in which exposure is minimized or nonexistent might be medically advisable or desirable.

Immunocompromised HCWs should have the option of an assignment in an area or activity where the risk for exposure to *M. tuberculosis* is low. This choice is a personal decision for the immunocompromised HCW (*241*) (http://www.eeoc.gov/laws/ada.html). Health-care settings should provide education and follow infection-control recommendations (*70*).

Information provided by HCWs regarding their immune status and request for voluntary work assignments should be treated confidentially, according to written procedures on the confidential handling of such information. All HCWs should be made aware of these procedures at the time of employment and during initial TB training and education.

Problem Evaluation

Contact investigations might be initiated in response to 1) conversions in test results in HCWs for *M. tuberculosis* infection, 2) diagnosis of TB disease in an HCW, 3) suspected person-to-person transmission of *M. tuberculosis*, 4) lapses in TB infection-control practices that expose HCWs and patients to *M. tuberculosis*, or 5) possible TB outbreaks identified using automated laboratory systems (*242*). In these situations, the objectives of a contact investigation might be to 1) determine the likelihood that transmission of *M. tuberculosis* has occurred; 2) determine the extent of *M. tuberculosis* transmission; 3) identify persons who were exposed, and, if possible, the sources of potential transmission; 4) identify factors that could have contributed to transmission, including failure of environmental infection-control measures, failure to follow infection-control procedures, or inadequacy of current measures or procedures; 5) implement recommended interventions; 6) evaluate the effectiveness of the interventions; and 7) ensure that exposure to *M. tuberculosis* has been terminated and that the conditions leading to exposure have been eliminated.

Earlier recognition of a setting in which *M. tuberculosis* transmission has occurred could be facilitated through innovative approaches to TB contact investigations (e.g., network analysis and genetic typing of isolates). Network analysis makes use of information (e.g., shared locations within a setting that might not be collected in traditional TB contact investigations) (*45*). This type of information might be useful during contact investigations involving hospitals or correctional settings to identify any shared wards, hospital rooms, or cells. Genotyping of isolates is universally available in the United States and is a useful adjunct in the investigation of *M. tuberculosis* transmission (*44,89,243,244*). Because the situations prompting an investigation are likely to vary, investigations should be tailored to the individual circumstances. Recommendations provide general guidance for conducting contact investigations (*34,115*).

General Recommendations for Investigating Conversions in Test Results for *M. tuberculosis* Infection in HCWs

A test conversion might need to be reported to the health department, depending on state and local regulations. Problem evaluation during contact investigations should be accomplished through cooperation between infection-control personnel, occupational health, and the local or state TB-control program. If a test conversion in an HCW is detected as a result of serial screening and the source is not apparent, conduct a source case investigation to determine the probable source and the likelihood that transmission occurred in the health-care setting (*115*).

Lapses in TB infection control that might have contributed to the transmission of *M. tuberculosis* should be corrected. Test conversions and TB disease among HCWs should be recorded and reported, according to OSHA requirements (http://www.osha.gov/recordkeeping). Consult *Recording and Reporting Occupational Injuries and Illness* (OSHA standard 29 Code of Federal Regulations [CFR], 1904) to determine recording and reporting requirements (*245*).

Investigating Conversions in Test Results for *M. tuberculosis* Infection in HCWs: Probable Source Outside the Health-Care Setting

If a test conversion in an HCW is detected and exposure outside the health-care setting has been documented by the corresponding local or state health department, terminate the investigation within the health-care setting.

Investigating Conversions in Test Results for *M. tuberculosis* Infection in HCWs: Known Source in the Health-Care Setting

An investigation of a test conversion should be performed in collaboration with the local or state health department. If a conversion in an HCW is detected and the HCW's history does not document exposure outside the health-care setting but does identify a probable source in the setting, the following steps should be taken: 1) identify and evaluate close contacts of the suspected source case, including other patients and visitors; 2) determine possible reasons for the exposure; 3) implement interventions to correct the lapse(s) in infection control; and 4) immediately screen HCWs and patients if they were close contacts to the source case. For exposed HCWs and patients in a setting that has chosen to screen for infection with *M. tuberculosis* by using the TST, the following steps should be taken:

- administer a symptom screen;
- administer a TST to those who had previously negative TST results; baseline two-step TST should not be performed in contact investigations;
- repeat the TST and symptom screen 8–10 weeks after the end of exposure, if the initial TST result is negative (*33*);
- administer a symptom screen, if the baseline TST result is positive;
- promptly evaluate (including a chest radiograph) the exposed person for TB disease, if the symptom screen or the initial 8–10-week follow-up TST result is positive; and
- conduct additional medical and diagnostic evaluation (which includes a judgment about the extent of exposure) for LTBI, if TB disease is excluded;

If no additional conversions in the test results for *M. tuberculosis* are detected in the follow-up testing, terminate the investigation. If additional conversions in the tests for *M. tuberculosis* are detected in the follow-up testing, transmission might still be occurring, and additional actions are needed: 1) implement a classification of potential ongoing transmission for the specific setting or group of HCWs; 2) the initial cluster of test conversions should be reported promptly to the local or state health department; 3) possible reasons for exposure and transmission; should be reassessed and 4) the degree of adherence to the interventions implemented should be evaluated.

Repeat testing for *M. tuberculosis* infection should be repeated 8–10 weeks after the end of exposure for HCW contacts who previously had negative test results, and the circle of contacts should be expanded to include other persons who might have been exposed. If no additional TST conversions are detected on the second round of follow-up testing, terminate the investigation. If additional TST conversions are detected on the second round of follow-up testing, maintain a classification of potential ongoing transmission and consult the local or state health department or other persons with expertise in TB infection control for assistance.

The classification of potential ongoing transmission should be used as a temporary classification only. This classification warrants immediate investigation and corrective steps. After determination has been made that ongoing transmission has ceased, the setting should be reclassified as medium risk. Maintaining the classification of medium risk for at least 1 year is recommended.

Investigating a Conversion of a Test Result for *M. tuberculosis* Infection in an HCW with an Unknown Exposure

If a test conversion in an HCW is detected and the HCW's history does not document exposure outside the health-care setting and does not identify a probable source of exposure in the setting, additional investigation to identify a probable source in the health-care setting is warranted.

If no source case is identified, estimate the interval during which the HCW might have been infected. The interval is usually 8–10 weeks before the most recent negative test result through 2 weeks before the first positive test result. Laboratory and infection-control records should be reviewed to identify all patients (and any HCWs) who have had suspected or confirmed infectious TB disease and who might have transmitted *M. tuberculosis* to the HCW. If the investigation identifies a probable source, identify and evaluate contacts of the suspected source. Close contacts should be the highest priority for screening.

The following steps should be taken in a setting that uses TST or BAMT to screen for *M. tuberculosis*: 1) administer a symptom screen and the test routinely used in the setting (i.e., TST or BAMT) to persons who previously had negative results; 2) if the initial result is negative, the test and symptom screen should be repeated 8–10 weeks after the end of exposure; 3) if the symptom screen, the first test result, or the 8–10-week follow-up test result is positive, the presumed exposed person should be promptly evaluated for TB disease, including the use of a chest radiograph; and 4) if TB disease is excluded, additional medical and diagnostic evaluation for LTBI is needed, which includes a judgment regarding the extent of exposure (see Investigating Conversions in Test Results for *M. tuberculosis* Infection in HCWs: Known Source in the Health-Care Setting).

Investigations That Do Not Identify a Probable Source

If serial TB screening is performed in the setting, review the results of screening of other HCWs in the same area of the health-care setting or same occupational group. If serial TB screening is not performed in the setting or if insufficient numbers of recent results are available, conduct additional TB screening of other HCWs in the same area or occupational group. If the review and screening yield no additional test conversions, and no evidence to indicate health-care–associated transmission exists, then the investigation should be terminated.

Whether HCW test conversions resulted from exposure in the setting or elsewhere or whether true infection with *M. tuberculosis* has even occurred is uncertain. However, the absence of other data implicating health-care–associated transmission suggests that the conversion could have resulted from 1) unrecognized exposure to *M. tuberculosis* outside the health-care setting; 2) cross reactivity with another antigen (e.g., BCG or nontuberculous mycobacteria); or 3) errors in applying, reading, or interpreting the test result for *M. tuberculosis*

infection. If the review and screening identify additional test conversions, health-care–associated transmission is more probable.

Evaluation of the patient identification process, TB infection-control policies and practices, and environmental controls to identify lapses that could have led to exposure and transmission should be conducted. If no problems are identified, a classification of potential ongoing transmission should be identified, and the local or state health department or other persons with expertise in TB infection control should be consulted for assistance. If problems are identified, implement recommended interventions and repeat testing for *M. tuberculosis* infection 8–10 weeks after the end of exposure for HCWs with negative test results. If no additional test conversions are detected in the follow-up testing, terminate the investigation.

Conversions in Test Results for *M. tuberculosis* Infection Detected in Follow-Up Testing

In follow-up testing, a classification of potential ongoing transmission should be maintained. Possible reasons for exposure and transmission should be reassessed, and the appropriateness of and degree of adherence to the interventions implemented should be evaluated. For HCWs with negative test results, repeat testing for *M. tuberculosis* infection 8–10 weeks after the end of exposure. The local or state health department or other persons with expertise in TB infection control should be consulted.

If no additional conversions are detected during the second round of follow-up testing, terminate the investigation. If additional conversions are detected, continue a classification of potential ongoing transmission and consult the local or state health department or other persons with expertise in TB infection control.

The classification of potential ongoing transmission should be used as a temporary classification only. This classification warrants immediate investigation and corrective steps. After a determination that ongoing transmission has ceased, the setting should be reclassified as medium risk. Maintaining the classification of medium risk for at least 1 year is recommended.

Investigating a Case of TB Disease in an HCW

Occupational health services and other physicians in the setting should have procedures for immediately notifying the local administrators or infection-control personnel if an HCW is diagnosed with TB disease so that a problem evaluation can be initiated. If an HCW is diagnosed with TB disease and does not have a previously documented positive test result for *M. tuberculosis* infection, conduct an investigation to identify the probable sources and circumstances for transmission (see General Recommendations for Investigating Conversions in Test Results for *M. tuberculosis* Infection in HCWs). If an HCW is diagnosed with TB disease, regardless of previous test result status, an additional investigation must be conducted to ascertain whether the disease was transmitted from this HCW to others, including other HCWs, patients, and visitors.

The potential infectiousness of the HCW, if potentially infectious, and the probable period of infectiousness (see Contact Investigations) should be determined. For HCWs with suspected or confirmed infectious TB disease, conduct an investigation that includes 1) identification of contacts (e.g., other HCWs, patients, and visitors), 2) evaluation of contacts for LTBI and TB disease, and 3) notification of the local or state health department for consultation and investigation of community contacts who were exposed outside the health-care setting.

M. tuberculosis genotyping should be performed so that the results are promptly available. *M. tuberculosis* results are useful adjuncts to epidemiologically based public health investigations of contacts and possible source cases (especially in determining the role of laboratory contamination) (*89,166,243,246–261*). When confidentiality laws prevent the local or state health department from communicating information regarding a patient's identity, health department staff should work with hospital staff and legal counsel, and the HCW to determine how the hospital can be notified without breaching confidentiality.

Investigating Possible Patient-to-Patient Transmission of *M. tuberculosis*

Information concerning TB cases among patients in the setting should be routinely recorded for risk classification and risk assessment purposes. Documented information by location and date should include results of sputum smear and culture, chest radiograph, drug-susceptibility testing, and adequacy of infection-control measures.

Each time a patient with suspected or confirmed TB disease is encountered in a health-care setting, an assessment of the situation should be made and the focus should be on 1) a determination of infectiousness of the patient, 2) confirmation of compliance with local public health reporting requirements (including the prompt reporting of a person with suspected TB disease as required), and 3) assessment of the adequacy of infection control.

A contact investigation should be initiated in situations where infection control is inadequate and the patient is infectious. Patients with positive AFB sputum smear results are more infectious than patients with negative AFB sputum smear results, but the possibility exists that patients with negative sputum smear results might be infectious (*262*). Patients with

negative AFB sputum smear results but who undergo aerosol-generating or aerosol-producing procedures (including bronchoscopy) without adequate infection-control measures create a potential for exposure. All investigations should be conducted in consultation with the local public health department.

If serial surveillance of these cases reveals one of the following conditions, patient-to-patient transmission might have occurred, and a contact investigation should be initiated:

- A high proportion of patients with TB disease were admitted to or examined in the setting during the year preceding onset of their TB disease, especially when TB disease is identified in patients who were otherwise unlikely to be exposed to *M. tuberculosis*.
- An increase occurred in the number of TB patients diagnosed with drug-resistant TB, compared with the previous year.
- Isolates from multiple patients had identical and characteristic drug susceptibility or DNA fingerprint patterns.

Surveillance of TB Cases in Patients Indicates Possible Patient-to-Patient Transmission of *M. tuberculosis*

Health-care settings should collaborate with the local or state health department to conduct an investigation. For settings in which HCWs are serially tested for *M. tuberculosis* infection, review HCW records to determine whether an increase in the number of conversions in test results for *M. tuberculosis* infection has occurred. Patient surveillance data and medical records should be reviewed for additional cases of TB disease. Settings should look for possible exposures from previous or current admissions that might have exposed patients with newly diagnosed TB disease to other patients with TB disease, determining if the patients were admitted to the same room or area, or if they received the same procedure or went to the same treatment area on the same day.

If the investigation suggests that transmission has occurred, possible causes of transmission of *M. tuberculosis* (e.g., delayed diagnosis of TB disease, institutional barriers to implementing timely and correct airborne precautions, and inadequate environmental controls) should be evaluated. Possible exposure to other patients or HCWs should be determined, and if exposure has occurred, these persons should be evaluated for LTBI and TB disease (i.e., test for *M. tuberculosis* infection and administer a symptom screen).

If the local or state health department was not previously contacted, settings should notify the health department so that a community contact investigation can be initiated, if necessary. The possibility of laboratory errors in diagnosis or the contamination of bronchoscopes (*82,169*) or other equipment should be considered (*136*).

Contact Investigations

The primary goal of contact investigations are to identify secondary cases of TB disease and LTBI among contacts so that therapy can be initiated as needed (*263–265*). Contact investigations should be collaboratively conducted by both infection-control personnel and local TB-control program personnel.

Initiating a Contact Investigation

A contact investigation should be initiated when 1) a person with TB disease has been examined at a health-care setting, and TB disease was not diagnosed and reported quickly, resulting in failure to apply recommended TB infection controls; 2) environmental controls or other infection-control measures have malfunctioned while a person with TB disease was in the setting; or 3) an HCW develops TB disease and exposes other persons in the setting.

As soon as TB disease is diagnosed or a problem is recognized, standard public health practice should be implemented to prioritize the identification of other patients, HCWs, and visitors who might have been exposed to the index case before TB infection-control measures were correctly applied (*52*). Visitors of these patients might also be contacts or the source case.

The following activities should be implemented in collaboration with or by the local or state health department (*34,266*): 1) interview the index case and all persons who might have been exposed; review the medical records of the index case; determine the exposure sites (i.e., where the index case lived, worked, visited, or was hospitalized before being placed under airborne precautions); and determine the infectious period of the index case, which is the period during which a person with TB disease is considered contagious and most capable of transmitting *M. tuberculosis* to others.

For programmatic purposes, for patients with positive AFB sputum smear results, the infectious period can be considered to begin 3 months before the collection date of the first positive AFB sputum smear result or the symptom onset date (whichever is earlier). The end of the infectious period is the date the patient is placed under airborne precautions or the date of collection of the first of consistently negative AFB sputum smear results (whichever is earlier). For patients with negative AFB sputum smear results, the infectious period can begin 1 month before the symptom onset date and end when the patient is placed under airborne precautions.

The exposure period, the time during which a person shared the same air space with a person with TB disease for each contact, should be determined as well as whether transmission occurred from the index patient to persons with whom the index patient had intense contact. In addition, the following should be determined: 1) intensity of the exposure based

on proximity; 2) overlap with the infectious period of the index case; 3) duration of exposure, 4) presence or absence of infection-control measures, 5) infectiousness of the index case; 6) performance of procedures that could increase the risk for transmission during contact (e.g., sputum induction, bronchoscopy, and airway suction); and 7) the exposed cohort of contacts for TB screening.

The most intensely exposed HCWs and patients should be screened as soon as possible after exposure to *M. tuberculosis* has occurred and 8–10 weeks after the end of exposure if the initial TST result is negative. Close contacts should be the highest priority for screening.

For HCWs and patients who are presumed to have been exposed in a setting that screens for infection with *M. tuberculosis* using the TST, the following activities should be implemented:

- performing a symptom screen;
- administering a TST to those who previously had negative TST results;
- repeating the TST and symptom screen 8–10 weeks after the end of exposure, if the initial TST result is negative;
- promptly evaluating the HCW for TB disease, including performing a chest radiograph, if the symptom screen or the initial or 8–10-week follow-up TST result is positive; and
- providing additional medical and diagnostic evaluation for LTBI, including determining the extent of exposure, if TB disease is excluded.

For HCWs and patients who are presumed to have been exposed in a setting that screens for infection with *M. tuberculosis* using the BAMT, the following activities should be implemented (see Supplement, Surveillance and Detection of *M. tuberculosis* Infections in Health-Care Settings). If the most intensely exposed persons have test conversions or positive test results for *M. tuberculosis* infection in the absence of a previous history of a positive test result or TB disease, expand the investigation to evaluate persons with whom the index patient had less contact. If the evaluation of the most intensely exposed contacts yields no evidence of transmission, expanding testing to others is not necessary.

Exposed persons with documented previously positive test results for *M. tuberculosis* infection do not require either repeat testing for *M. tuberculosis* infection or a chest radiograph (unless they are immunocompromised or otherwise at high risk for TB disease), but they should receive a symptom screen. If the person has symptoms of TB disease, 1) record the symptoms in the HCW's medical chart or employee health record, 2) perform a chest radiograph, 3) perform a full medical evaluation, and 4) obtain sputum samples for smear and culture, if indicated.

The setting should determine the reason(s) that a TB diagnosis or initiation of airborne precautions was delayed or procedures failed, which led to transmission of *M. tuberculosis* in the setting. Reasons and corrective actions taken should be recorded, including changes in policies, procedures, and TB training and education practices.

Collaboration with the Local or State Health Department

For assistance with the planning and implementation of TB-control activities in the health-care setting and for names of experts to help with policies, procedures, and program evaluation, settings should coordinate with the local or state TB-control program . By law, the local or state health department must be notified when TB disease is suspected or confirmed in a patient or HCW so that follow up can be arranged and a community contact investigation can be conducted. The local or state health department should be notified as early as possible before the patient is discharged to facilitate followup and continuation of therapy by DOT (*31*). For inpatient settings, coordinate a discharge plan with the patient (including a patient who is an HCW with TB disease) and the TB-control program of the local or state health department.

Environmental Controls

Environmental controls are the second line of defense in the TB infection-control program, after administrative controls. Environmental controls include technologies for the removal or inactivation of airborne *M. tuberculosis*. These technologies include local exhaust ventilation, general ventilation, HEPA filtration, and UVGI. These controls help to prevent the spread and reduce the concentration of infectious droplet nuclei in the air. A summary of environmental controls and their use in prevention of transmission of *M. tuberculosis* is provided in this report (see Supplement, Environmental Controls), including detailed information concerning the application of environmental controls.

Local Exhaust Ventilation

Local exhaust ventilation is a source-control technique used for capturing airborne contaminants (e.g., infectious droplet nuclei or other infectious particles) before they are dispersed into the general environment. In local exhaust ventilation methods, external hoods, enclosing booths, and tents are used. Local exhaust ventilation (e.g., enclosed, ventilated booth) should be used for cough-inducing and aerosol-generating procedures. When local exhaust is not feasible, perform cough-inducing and aerosol-generating procedures in a room that meets the requirements for an AII room.

General Ventilation

General ventilation systems dilute and remove contaminated air and control airflow patterns in a room or setting. An engineer or other professional with expertise in ventilation should be included as part of the staff of the health-care setting or hire a consultant with expertise in ventilation engineering specific to health-care settings. Ventilation systems should be designed to meet all applicable federal, state, and local requirements.

A single-pass ventilation system is the preferred choice in areas in which infectious airborne droplet nuclei might be present (e.g., AII rooms). Use HEPA filtration if recirculation of air is necessary.

AII rooms in existing health-care settings should have an airflow of ≥6 ACH. When feasible, the airflow should be increased to 12 ACH by 1) adjusting or modifying the ventilation system or 2) using air-cleaning methods (e.g., room-air recirculation units containing HEPA filters or UVGI systems that increase the equivalent ACH). New construction or renovation of health-care settings should be designed so that AII rooms achieve an airflow of ≥12 ACH. Ventilation rates for other areas in health-care settings should meet certain specifications (see Risk Classification Examples). If a variable air volume (VAV) ventilation system is used in an AII room, design the system to maintain the room under negative pressure at all times. The VAV system minimum set point must be adequate to maintain the recommended mechanical and outdoor ACH and a negative pressure >0.01 inch of water gauge compared with adjacent areas.

Based on the risk assessment for the setting, the required number of AII rooms, other negative-pressure rooms, and local exhaust devices should be determined. The location of these rooms and devices will depend partially on where recommended ventilation conditions can be achieved. Grouping AII rooms in one area might facilitate the care of patients with TB disease and the installation and maintenance of optimal environmental controls.

AII rooms should be checked for negative pressure by using smoke tubes or other visual checks before occupancy, and these rooms should be checked daily when occupied by a patient with suspected or confirmed TB disease. Design, construct, and maintain general ventilation systems so that air flows from clean to less clean (more contaminated) areas. In addition, design general ventilation systems to provide optimal airflow patterns within rooms and to prevent air stagnation or short-circuiting of air from the supply area to the exhaust area.

Health-care settings serving populations with a high prevalence of TB disease might need to improve the existing general ventilation system or use air-cleaning technologies in general-use areas (e.g., waiting rooms, EMS areas, and radiology suites). Applicable approaches include 1) single-pass, nonrecirculating systems that exhaust air to the outside, 2) recirculation systems that pass air through HEPA filters before recirculating it to the general ventilation system, and 3) room-air recirculation units with HEPA filters and UVGI systems.

Air-Cleaning Methods

High-Efficiency Particulate Air (HEPA) Filters

HEPA filters can be used to filter infectious droplet nuclei from the air and must be used 1) when discharging air from local exhaust ventilation booths or enclosures directly into the surrounding room or area and 2) when discharging air from an AII room (or other negative-pressure room) into the general ventilation system (e.g., in settings in which the ventilation system or building configuration makes venting the exhaust to the outside impossible).

HEPA filters can be used to remove infectious droplet nuclei from air that is recirculated in a setting or exhausted directly to the outside. HEPA filters can also be used as a safety measure in exhaust ducts to remove droplet nuclei from air being discharged to the outside. Air can be recirculated through HEPA filters in areas in which 1) no general ventilation system is present, 2) an existing system is incapable of providing sufficient ACH, or 3) air-cleaning (particulate removal) without affecting the fresh-air supply or negative-pressure system is desired. Such uses can increase the number of equivalent ACH in the room or area.

Recirculation of HEPA filtered air can be achieved by exhausting air from the room into a duct, passing it through a HEPA filter installed in the duct, and returning it to the room or the general ventilation system. In addition, recirculation can be achieved by filtering air through HEPA recirculation systems installed on the wall or ceiling of the room or filtering air through portable room-air recirculation units.

To ensure adequate functioning, install HEPA filters carefully and maintain the filters according to the instructions of the manufacturer. Maintain written records of all prefilter and HEPA maintenance and monitoring (*114*). Manufacturers of room-air recirculation units should provide installation instructions and documentation of the filtration efficiency and of the overall efficiency of the unit in removing airborne particles from a space of a given size.

UVGI

UVGI is an air-cleaning technology that can be used in a room or corridor to irradiate the air in the upper portion of the room (upper-air irradiation) and is installed in a duct to irradiate air passing through the duct (duct irradiation) or incorporated into room air-recirculation units. UVGI can be used in

ducts that recirculate air back into the same room or in ducts that exhaust air directly to the outside. However, UVGI should not be used in place of HEPA filters when discharging air from isolation booths or enclosures directly into the surrounding room or area or when discharging air from an AII room into the general ventilation system. Effective use of UVGI ensures that *M. tuberculosis,* as contained in an infectious droplet, is exposed to a sufficient dose of ultraviolet-C (UV-C) radiation at 253.7 nanometers (nm) to result in inactivation. Because dose is a function of irradiance and time, the effectiveness of any application is determined by its ability to deliver sufficient irradiance for enough time to result in inactivation of the organism within the infectious droplet. Achieving a sufficient dose can be difficult with airborne inactivation because the exposure time can be substantially limited; therefore, attaining sufficient irradiance is essential.

For each system, follow design guidelines to maximize UVGI effectiveness in equivalent ACH. Because air velocity, air mixing, relative humidity, UVGI intensity, and lamp position all affect the efficacy of UVGI systems, consult a UVGI system designer before purchasing and installing a UVGI system. Experts who might be consulted include industrial hygienists, engineers, and health physicists.

To function properly and minimize potential hazards to HCWs and other room occupants, upper-air UVGI systems should be properly installed, maintained, and labeled. A person knowledgeable in the use of ultraviolet (UV) radiometers or actinometers should monitor UV irradiance levels to ensure that exposures in the work area are within safe exposure levels. UV irradiance levels in the upper-air, where the air disinfection is occurring, should also be monitored to determine that irradiance levels are within the desired effectiveness range.

UVGI tubes should be changed and cleaned according to the instructions of the manufacturer or when irradiance measurements indicate that output is reduced below effective levels. In settings that use UVGI systems, education of HCWs should include 1) basic principles of UVGI systems (mechanism and limitations), 2) potential hazardous effects of UVGI if overexposure occurs, 3) potential for photosensitivity associated with certain medical conditions or use of certain medications, and 4) the importance of maintenance procedures and record-keeping. In settings that use UVGI systems, patients and visitors should be informed of the purpose of UVGI systems and be warned about the potential hazards and safety precautions.

Program Issues

Personnel from engineering, maintenance, safety and infection control, and environmental health should collaborate to ensure the optimal selection, installation, operation, and maintenance of environmental controls. A written maintenance plan should be developed that outlines the responsibility and authority for maintenance of the environmental controls and addresses HCW training needs. Standard operating procedures should include the notification of infection-control personnel before performing maintenance on ventilation systems servicing TB patient-care areas.

Personnel should schedule routine preventive maintenance for all components of the ventilation systems (e.g., fans, filters, ducts, supply diffusers, and exhaust grills) and air-cleaning devices. Quality control (QC) checks should be conducted to verify that environmental controls are operating as designed and that records are current. Provisions for emergency electrical power should be made so that the performance of essential environmental controls is not interrupted during a power failure.

Respiratory Protection

The first two levels of the infection-control hierarchy, administrative and environmental controls, minimize the number of areas in which exposure to *M. tuberculosis* might occur. In addition, these administrative and environmental controls also reduce, but do not eliminate, the risk in the few areas in which exposures can still occur (e.g., AII rooms and rooms where cough-inducing or aerosol-generating procedures are performed). Because persons entering these areas might be exposed to airborne *M. tuberculosis*, the third level of the hierarchy is the use of respiratory protective equipment in situations that pose a high risk for exposure (see Supplement, Respiratory Protection).

On October 17, 1997, OSHA published a proposed standard for occupational exposure to *M. tuberculosis* (*267*). On December 31, 2003, OSHA announced the termination of rulemaking for a TB standard (*268*). Previous OSHA policy permitted the use of any Part 84 particulate filter respirator for protection against TB disease (*269*). Respirator use for TB had been regulated by OSHA under CFR Title 29, Part 1910.139 (29CFR1910.139) (*270*) and compliance policy directive (CPL) 2.106 (Enforcement Procedures and Scheduling for Occupational Exposure to Tuberculosis). Respirator use for TB is regulated under the general industry standard for respiratory protection (29 CFR 1910.134, http://www.osha.gov/SLTC/respiratoryprotection/index.html) (*271*). General information concerning respiratory protection for aerosols, including *M. tuberculosis*, has been published (*272–274*).

Indications for Use

Respiratory protection should be used by the following persons:

- all persons, including HCWs and visitors, entering rooms in which patients with suspected or confirmed infectious TB disease are being isolated;
- persons present during cough-inducing or aerosol-generating procedures performed on patients with suspected or confirmed infectious TB disease; and
- persons in other settings in which administrative and environmental controls probably will not protect them from inhaling infectious airborne droplet nuclei. These persons might also include persons who transport patients with suspected or confirmed infectious TB disease in vehicles (e.g., EMS vehicles or, ideally, ambulances) and persons who provide urgent surgical or dental care to patients with suspected or confirmed infectious TB disease (see Supplement, Estimating the Infectiousness of a TB Patient).

Laboratorians conducting aerosol-producing procedures might require respiratory protection. A decision concerning use of respiratory protection in laboratories should be made on an individual basis, depending on the type of ventilation in use for the laboratory procedure and the likelihood of aerosolization of viable mycobacteria that might result from the laboratory procedure.

Respiratory-Protection Program

OSHA requires health-care settings in which HCWs use respiratory protection to develop, implement, and maintain a respiratory-protection program. All HCWs who use respiratory protection should be included in the program (see Supplement, Respiratory Protection).

Training HCWs

Annual training regarding multiple topics should be conducted for HCWs, including the nature, extent, and hazards of TB disease in the health-care setting. The training can be conducted in conjunction with other related training regarding infectious disease associated with airborne transmission. In addition, training topics should include the 1) risk assessment process and its relation to the respirator program, including signs and symbols used to indicate that respirators are required in certain areas and the reasons for using respirators; 2) environmental controls used to prevent the spread and reduce the concentration of infectious droplet nuclei; 3) selection of a particular respirator for a given hazard (see Selection of Respirators); 4) operation, capabilities, and limitations of respirators; 5) cautions regarding facial hair and respirator use (*275,276*); and 6) OSHA regulations regarding respirators, including assessment of employees' knowledge.

Trainees should be provided opportunities to handle and wear a respirator until they become proficient (see Fit Testing). Trainees should also be provided with 1) copies or summaries of lecture materials for use as references and 2) instructions to refer all respirator problems immediately to the respiratory program administrator.

Selection of Respirators

Respiratory protective devices used in health-care settings for protection against *M. tuberculosis* should meet the following criteria (*277,278*):

- certified by CDC/National Institute for Occupational Safety and Health (NIOSH) as a nonpowered particulate filter respirator (N-, R-, or P-95, 99, or 100), including disposable respirators, or PAPRs with high efficiency filters (*279*);
- ability to adequately fit respirator wearers (e.g., a fit factor of >100 for disposable and half-mask respirators) who are included in a respiratory-protection program; and
- ability to fit the different facial sizes and characteristics of HCWs. (This criterion can usually be met by making respirators available in different sizes and models.)

The fit of filtering facepiece respirators varies because of different facial types and respirator characteristics (*10,280–289*). Assistance with selection of respirators should be obtained through consultation with respirator fit-testing experts, CDC, occupational health and infection-control professional organizations, peer-reviewed research, respirator manufacturers, and advanced respirator training courses.

Fit Testing

A fit test is used to determine which respirator fits the user adequately and to ensure that the user knows when the respirator fits properly. After a risk assessment is conducted to validate the need for respiratory protection, perform fit testing during the initial respiratory-protection program training and periodically thereafter in accordance with federal, state, and local regulations (http://www.osha.gov/SLTC/respiratory protection/index.html).

Fit testing provides a means to determine which respirator model and size fits the wearer best and to confirm that the wearer can don the respirator properly to achieve a good fit. Periodic fit testing for respirators used in TB environments can serve as an effective training tool in conjunction with the content included in employee training and retraining. The frequency of periodic fit testing should be supplemented by the occurrence of 1) risk for transmission of *M. tuberculosis*, 2) facial features of the wearer, 3) medical condition that would affect respiratory function, 4) physical characteristics of respirator (despite the same model number), or 5) model or size of the assigned respirator (*281*).

Respirator Options: General Recommendations

In situations that require respiratory protection, the minimum respiratory protection device is a filtering facepiece (nonpowered, air-purifying, half-facepiece) respirator (e.g., an N95 disposable respirator). This CDC/NIOSH-certified respirator meets the minimum filtration performance for respiratory protection in areas in which patients with suspected or confirmed TB disease might be encountered. For situations in which the risk for exposure to *M. tuberculosis* is especially high because of cough-inducing and aerosol-generating procedures, more protective respirators might be needed (see Respirator Options: Special Circumstances).

Respirator Options: Special Circumstances

Visitors to AII rooms and other areas with patients who have suspected or confirmed infectious TB disease may be offered respirators and should be instructed by an HCW on the use of the respirator before entering an AII room (Supplement, Frequently Asked Questions [FAQs] User-Seal Check in Respiratory Protection section). Particulate respirators vary substantially by model, and fit testing is usually not easily available to visitors.

The risk assessment for the setting might identify a limited number of circumstances (e.g., bronchoscopy or autopsy on persons with suspected or confirmed TB disease and selected laboratory procedures) for which a level of respiratory protection that exceeds the minimum level provided by an N95 disposable respirator should be considered. In such circumstances, consider providing HCWs with a level of respiratory protection that both exceeds the minimum criteria and is compatible with patient care delivery. Such protection might include more protective respirators (e.g., full-facepiece respirators or PAPRs) (see Supplement, Respiratory Protection). Detailed information regarding these and other respirators has been published (*272,273,278,290*).

In certain settings, HCWs might be at risk for both inhalation exposure to *M. tuberculosis* and mucous membrane exposure to bloodborne pathogens. In these situations, the HCW might wear a nonfluid-resistant respirator with a full-face shield or the combination product surgical mask/N95 disposable respirator to achieve both respiratory protection and fluid protection.

When surgical procedures (or other procedures requiring a sterile field) are performed on persons with suspected or confirmed infectious TB disease, respiratory protection worn by HCWs must also protect the surgical field. The patient should be protected from the HCW's respiratory secretions and the HCW from infectious droplet nuclei that might be expelled by the patient or generated by the procedure. Respirators with exhalation valves and PAPRs do not protect the sterile field.

Settings in which patients with suspected or confirmed infectious TB disease will not be encountered do not need a respiratory-protection program for exposure to *M. tuberculosis*. However, these settings should have written protocols for the early identification of persons with symptoms or signs of TB disease and procedures for referring these patients to a setting where they can be evaluated and managed. Filtering facepiece respirators should also be available for emergency use by HCWs who might be exposed to persons with suspected or confirmed TB disease before transfer. In addition, respirators and the associated respiratory-protection program might be needed to protect HCWs from other infectious diseases or exposures to harmful vapors and gases. Their availability or projected need for other exposures should be considered in the selection of respirators for protection against TB to minimize replication of effort.

Surgical or procedure masks are designed to prevent respiratory secretions of the wearer from entering the air. To reduce the expulsion of droplet nuclei into the air, persons with suspected or confirmed TB disease should be instructed to observe respiratory hygiene and cough etiquette procedures (*122*) and should wear a surgical or procedure mask, if possible, when they are not in AII rooms. These patients do not need to wear particulate respirators.

Patients with suspected or confirmed TB disease should never wear any kind of respiratory protection that has an exhalation valve. This type of respirator does not prevent droplet nuclei from being expelled into the air.

Cough-Inducing and Aerosol-Generating Procedures

General Recommendations

Procedures that involve instrumentation of the lower respiratory tract or induction of sputum can increase the likelihood that droplet nuclei will be expelled into the air. These cough-inducing procedures include endotracheal intubation, suctioning, diagnostic sputum induction, aerosol treatments (e.g., pentamidine therapy and nebulized treatments), bronchoscopy, and laryngoscopy, gastric aspiration and nasogastric tube placement can also induce cough in certain patients. Other procedures that can generate aerosols include irrigating TB abscesses, homogenizing or lyophilizing tissue, performing autopsies on cadavers with untreated TB disease, and other processing of tissue that might contain tubercle bacilli and TB laboratory procedures.

If possible, postpone cough-inducing or aerosol-generating procedures on patients with suspected or confirmed infectious TB disease unless the procedure can be performed with recommended precautions. When a cough-inducing or aerosol-generating procedure must be performed on a patient with suspected or confirmed infectious TB disease, use a local exhaust ventilation device (e.g., booth or special enclosure). If using this device is not feasible, perform the procedure in a room that meets the ventilation requirements for an AII room.

After completion of cough-inducing procedures, keep patients in the AII room or enclosure until coughing subsides. Patients should be given tissues and instructed to cover the mouth and nose with tissues when coughing. Tissues should be disposed of in accordance with the infection-control plan.

Before the booth, enclosure, or room is used for another patient, allow enough time for the removal of ≥99% of airborne contaminants. This interval will vary based on the efficiency of the ventilation or filtration system (see Supplement, Environmental Controls; Table 2).

For postoperative recovery, do not place the patient in a recovery room with other patients; place the patient in a room that meets the ventilation requirements for an AII room. If the room does not meet the ventilation requirements for an AII room, air-cleaning technologies (e.g., HEPA filtration and UVGI) can be used to increase the number of equivalent ACH (see Supplement, Environmental Controls).

Perform all manipulations of suspected or confirmed *M. tuberculosis* specimens that might generate aerosols in a BSC. When in rooms or enclosures in which cough-inducing or aerosol-generating procedures are being performed, respiratory protection should be worn.

Special Considerations for Bronchoscopy

Bronchoscopy can result in the transmission of *M. tuberculosis* either through the airborne route (*63,81,86,162*) or a contaminated bronchoscope (*80,82,163–169*). Whenever feasible, perform bronchoscopy in a room that meets the ventilation requirements for an AII room (see Supplement, Environmental Controls). Air-cleaning technologies can be used to increase equivalent ACH. If a bronchoscopy must be performed in a positive-pressure room (e.g., OR), exclude TB disease before performing the procedure. Examine three spontaneous or induced sputum specimens for AFB (if possible) to exclude a diagnosis of TB disease before bronchoscopy is considered as a diagnostic procedure (*110,291*).

In a patient who is intubated and mechanically ventilated, minimize the opening of circuitry. For HCWs present during bronchoscopic procedures on patients with suspected or confirmed TB disease, a respirator with a level of protection of at

TABLE 2. Ventilation recommendations for selected areas in new or renovated health-care settings

Health-care setting	Minimum mechanical ACH*	Minimum outdoor ACH*	Air movement relative to adjacent areas	Air exhausted directly outdoors†
Microbiology laboratory	6	§	In	Yes
Anteroom to AII¶ room	10	§	In/Out	Yes
AII room**††	12	2	In	Yes
Autopsy suite	12	§	In	Yes
Bronchoscopy room	12	2	In	Yes
Emergency department and radiology waiting rooms	12–15§§	2	In	Yes
Operating room or surgical room	15¶¶	3§§	Out	§
	25***	15¶¶		
		5***		

SOURCES: CDC. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care facilities, 1994. MMWR 1994;43(No. RR-13). American Society of Heating, Refrigerating, and Air-Conditioning Engineers, Inc. Health care facilities [Chapter 7]. 2003 ASHRAE handbook: HVAC applications. Atlanta, GA: American Society of Heating, Refrigerating, and Air-Conditioning Engineers, Inc.; 2003:7.1–7.14.

* Air changes per hour.

† If it is not possible to exhaust all the air to the outdoors in existing or renovated facilities, the air can be recirculated after passing through high efficiency particulate air (HEPA) filtration.

§ American National Standards Institute (ANSI)/American Society of Heating, Refrigerating, and Air-Conditioning Engineers, Inc. (ASHRAE). Standard 62.1-2004, Ventilation for Acceptable Indoor Air Quality, should be consulted for outside air recommendations in areas that are not specified. **SOURCE:** ANSI/ASHRAE. Standard 62.1-2004—ventilation for acceptable indoor air quality. Atlanta, GA: ASHRAE; 2004.

¶ Airborne infection isolation.

** Settings with existing AII rooms should have an airflow of ≥6 mechanical ACH; air-cleaning devices can be used to increase the equivalent ACH.

†† Patients requiring a protective environment room (e.g., severely immunocompromised patients) who also have TB disease require protection from common airborne infectious microorganisms.

§§ Recommendation of the American Institute of Architects (AIA) (air is recirculated through HEPA filters). **SOURCE:** AIA. Guidelines for design and construction of hospital and health care facilities. Washington, DC: AIA; 2001.

¶¶ Recommendation of ASHRAE (100% exhaust). **SOURCE:** ANSI/ASHRAE. Standard 62.1-2004—ventilation for acceptable indoor air quality. Atlanta, GA: ASHRAE; 2004.

*** Recommendation of ASHRAE (air is recirculated through HEPA filters). **SOURCE:** ANSI/ASHRAE. Standard 62.1-2004—ventilation for acceptable indoor air quality. Atlanta, GA: ASHRAE; 2004.

least an N95 disposable respirator should be worn. Protection greater than an N95 disposable respirator (e.g., a full-facepiece elastomeric respirator or PAPR) should be considered.

Special Considerations for Administration of Aerosolized Pentamidine and Other Medications

Patients receiving aerosolized pentamidine (or other aerosolized medications) who are immunocompromised and have a confirmed or suspected pulmonary infection (i.e., pneumocystis pneumonia [PCP] or pneumonia caused by *P. jaroveci,* formerly *P. carinii*) are also at risk for TB disease. Patients receiving other aerosolized medications might have an immunocompromising condition that puts them at greater risk for TB disease. Patients should be screened for TB disease before initiating prophylaxis with aerosolized pentamidine; a medical history, test for infection with *M. tuberculosis*, and a chest radiograph should be performed.

Before each subsequent treatment with aerosolized pentamidine, screen patients for symptoms or signs of TB disease. If symptoms or signs are present, evaluate the patient for TB disease. Patients with suspected or confirmed TB disease should be administered oral prophylaxis for *P. jaroveci* instead of aerosolized pentamidine if clinically practical. Patients receiving other aerosolized medication might have immunocompromising conditions; therefore, if warranted, they should be similarly screened and evaluated, and treatment with oral medications should be considered.

Supplements

Estimating the Infectiousness of a TB Patient

General Principles

Transmission of *M. tuberculosis* is most likely to result from exposure to persons who have 1) unsuspected pulmonary TB disease and are not receiving antituberculosis treatment, 2) diagnosed TB disease and are receiving inadequate therapy, or 3) diagnosed TB disease and are early in the course of effective therapy. Administration of effective antituberculosis treatment has been associated with decreased infectiousness among persons who have TB disease (*292*). Effective treatment reduces coughing, the amount of sputum produced, the number of organisms in the sputum, and the viability of the organisms in the sputum. However, the duration of therapy required to decrease or eliminate infectiousness varies (*293*). Certain TB patients are never infectious, whereas those with unrecognized or inadequately treated drug-resistant TB disease might remain infectious for weeks or months (*2,3,87,94,162,294–297*). In one study, 17% of transmission occurred from persons with negative AFB smear results (*262*). Rapid laboratory methods, including PCR-based techniques, can decrease diagnostic delay and reduce the duration of infectiousness (*298*).

The infectiousness of patients with TB correlates with the number of organisms they expel into the air (*299*). The number of organisms expelled are related to the following factors: 1) presence of cough lasting >3 weeks; 2) cavitation on chest radiograph; 3) positive AFB sputum smear result; 4) respiratory tract disease with involvement of the lung or airways, including larynx; 5) failure to cover the mouth and nose when coughing; 6) lack of incorrect or short duration of antituberculosis treatment (*300*); or 7) undergoing cough-inducing or aerosol-generating procedures (e.g., sputum induction, bronchoscopy, and airway suction). Closed and effectively filtered ventilatory circuitry and minimized opening of such circuitry in intubated and mechanically ventilated patients might minimize exposure (see Intensive Care Units [ICUs]).

Persons with extrapulmonary TB disease usually are not infectious unless they have concomitant pulmonary disease, nonpulmonary disease located in the oral cavity or the larynx, or extrapulmonary disease that includes an open abscess or lesion in which the concentration of organisms is high, especially if drainage from the abscess or lesion is extensive, or if aerosolization of drainage fluid is performed (*69,72,77, 83,301*). Persons with TB pleural effusions might also have concurrent unsuspected pulmonary or laryngeal TB disease. These patients should be considered infectious until pulmonary TB disease is excluded. Patients with suspected TB pleural effusions or extrapulmonary TB disease should be considered pulmonary TB suspects until concomitant pulmonary disease is excluded (*302*).

Although children with TB disease usually are less likely than adults to be infectious, transmission from young children can occur (*135,137*). Therefore, children and adolescents with TB disease should be evaluated for infectiousness by using the majority of the same criteria as for adults. These criteria include presence of cough lasting >3 weeks; cavitation on chest radiograph; or respiratory tract disease with involvement of lungs, airways, or larynx. Infectiousness would be increased if the patient were on nonstandard or short duration of antituberculosis treatment (*300*) or undergoing cough-inducing or aerosol-generating procedures (e.g., sputum induction, bronchoscopy, and airway suction). Although gastric lavage is useful in the diagnosis of pediatric TB disease, the grade of the positive AFB smear result does not correlate with infectiousness. Pediatric patients who might be infectious include those who are not on antituberculosis treatment,

who have just been started on treatment or are on inadequate treatment, and who have extensive pulmonary or laryngeal involvement (i.e., coughing >3 weeks, cavitary TB disease, positive AFB sputum smear results, or undergoing cough-inducing or aerosol-generating procedures). Children who have typical primary TB lesions on chest radiograph and do not have any of these indicators of infectiousness might not need to be placed in an AII room.

No data exist on the transmission of *M. tuberculosis* and its association with the collection of gastric aspirate specimens. Children who do not have predictors for infectiousness do not need to have gastric aspirates obtained in an AII room or other special enclosure; however, the procedure should not be performed in an area in which persons infected with HIV might be exposed. Because the source case for pediatric TB patients might be a member of the infected child's family, parents and other visitors of all hospitalized pediatric TB patients should be screened for TB disease as soon as possible to ensure that they do not become sources of health-care–associated transmission of *M. tuberculosis* (*303–306*).

Patients who have suspected or confirmed TB disease and who are not on antituberculosis treatment usually should be considered infectious if characteristics include

- presence of cough;
- cavitation on chest radiograph;
- positive AFB sputum smear result;
- respiratory tract disease with involvement of the lung or airways, including larynx;
- failure to cover the mouth and nose when coughing; and
- undergoing cough-inducing or aerosol-generating procedures (e.g., sputum induction, bronchoscopy, and airway suction).

If a patient with one or more of these characteristics is on standard multidrug therapy with documented clinical improvement usually in connection with smear conversion over multiple weeks, the risk for infectiousness is reduced.

Suspected TB Disease

For patients placed under airborne precautions because of suspected infectious TB disease of the lungs, airway, or larynx, airborne precautions can be discontinued when infectious TB disease is considered unlikely and either 1) another diagnosis is made that explains the clinical syndrome or 2) the patient has three negative AFB sputum smear results (*109–112*). Each of the three consecutive sputum specimens should be collected in 8–24-hour intervals (*124*), and at least one specimen should be an early morning specimen because respiratory secretions pool overnight. Generally, this method will allow patients with negative sputum smear results to be released from airborne precautions in 2 days.

Hospitalized patients for whom the suspicion of TB disease remains after the collection of three negative AFB sputum smear results should not be released from airborne precautions until they are on standard multidrug antituberculosis treatment and are clinically improving. If the patient is believed to not have TB disease because of an alternate diagnosis or because clinical information is not consistent with TB disease, airborne precautions may be discontinued. Therefore, a patient suspected of having TB disease of the lung, airway, or larynx is symptomatic with cough and not responding clinically to antituberculosis treatment should not be released from an AII room into a non-AII room, and additional sputum specimens should be collected for AFB examination until three negative AFB sputum smear results are obtained (*30,31*). Additional diagnostic approaches might need to be considered (e.g., sputum induction) and, after sufficient time on treatment, bronchoscopy.

Confirmed TB Disease

A patient who has drug-susceptible TB of the lung, airway, or larynx, who is on standard multidrug antituberculosis treatment, and who has had a substantial clinical and bacteriologic response to therapy (i.e., reduction in cough, resolution of fever, and progressively decreasing quantity of AFB on smear result) is probably no longer infectious. However, because culture and drug-susceptibility results are not usually known when the decision to discontinue airborne precautions is made, all patients with suspected TB disease should remain under airborne precautions while they are hospitalized until they have had three consecutive negative AFB sputum smear results, each collected in 8–24-hour intervals, with at least one being an early morning specimen; have received standard multidrug antituberculosis treatment (minimum of 2 weeks); and have demonstrated clinical improvement.

Discharge to Home of Patients with Suspected or Confirmed TB Disease

If a hospitalized patient who has suspected or confirmed TB disease is deemed medically stable (including patients with positive AFB sputum smear results indicating pulmonary TB disease), the patient can be discharged from the hospital before converting the positive AFB sputum smear results to negative AFB sputum smear results, if the following parameters have been met:

- a specific plan exists for follow-up care with the local TB-control program;
- the patient has been started on a standard multidrug antituberculosis treatment regimen, and DOT has been arranged;

- no infants and children aged <4 years or persons with immunocompromising conditions are present in the household;
- all immunocompetent household members have been previously exposed to the patient; and
- the patient is willing to not travel outside of the home except for health-care–associated visits until the patient has negative sputum smear results.

Patients with suspected or confirmed infectious TB disease should not be released to health-care settings or homes in which the patient can expose others who are at high risk for progressing to TB disease if infected (e.g., persons infected with HIV or infants and children aged <4 years). Coordination with the local health department TB program is indicated in such circumstances.

Drug-Resistant TB Disease

Because the consequences of transmission of MDR TB are severe, certain infection-control practitioners might choose to keep persons with suspected or confirmed MDR TB disease under airborne precautions during the entire hospitalization or until culture conversion is documented, regardless of sputum smear results. The role of drug resistance in transmission is complex. Transmission of drug-resistant organisms to persons with and without HIV infection has been documented (*54,307–309*). In certain cases, transmission from patients with TB disease caused by drug-resistant organisms might be extensive because of prolonged infectiousness as a result of delays in diagnosis and delays in initiation of effective therapy (*53,94,98,101,255,310,311*).

HIV-Associated TB Disease

Although multiple TB outbreaks among HIV-infected persons have been reported (*51,52,99*), the risk for transmission does not appear to be increased from patients with TB disease and HIV infection, compared with TB patients without HIV infection (*54,312–315*). Whether persons infected with HIV are more likely to be infected with *M. tuberculosis* if exposed is unclear; however, after infected with *M. tuberculosis*, the risk for progression to TB disease in persons infected with HIV is high (*316*). Progression to TB disease can be rapid, as soon as 1 month after exposure (*51,53,54,101*).

Diagnostic Procedures for LTBI and TB Disease

LTBI is a condition that develops after exposure to a person with infectious TB disease, and subsequent infection with *M. tuberculosis* occurs where the bacilli are alive but inactive in the body. Persons who have LTBI but who do not have TB disease are asymptomatic (i.e., have no symptoms), do not feel sick, and cannot spread TB to other persons.

Use of QFT-G for Diagnosing *M. tuberculosis* Infections in Health-Care Workers (HCWs)

In the United States, LTBI has been traditionally diagnosed based on a positive TST result after TB disease has been excluded. In vitro cytokine-based immunoassays for the detection of *M. tuberculosis* infection have been the focus of intense research and development. This document uses the term "BAMT" to refer to blood assay for *M. tuberculosis* infection currently available in the United States.

TB disease should be considered for any patient who has symptoms or signs of disease, including coughing for >3 weeks, loss of appetite, unexplained weight loss, night sweats, bloody sputum or hemoptysis, hoarseness, fever, fatigue, or chest pain. The index of suspicion for TB disease will vary by individual risk factors, geographic area, and prevalence of TB disease in the population served by the health-care setting. Persons exposed to patients with infectious TB disease might acquire LTBI, depending on host immunity and the degree and duration of exposure. Diagnostic tests for TB disease include chest radiography and laboratory tests of sputum (examination for AFB and culture). The treatment of persons with TB disease involves vital aspects of TB control by stopping transmission of *M. tuberculosis* and preventing persons with LTBI from developing infectious TB disease (*36*).

In the majority of the U.S. population, targeted testing for LTBI and TB disease is performed to identify persons with LTBI and TB disease who would benefit from treatment. Therefore, all testing activities should be accompanied by a plan for follow-up care of persons with LTBI or TB disease. A decision to test for infection with *M. tuberculosis* should be based on a commitment to treat LTBI after a medical examination (*39*). Health-care agencies or other settings should consult with the local or state health department before starting a program to test HCWs for *M. tuberculosis* infection. This step ensures that adequate provisions are in place for the evaluation and treatment of persons whose test results are positive, including the medical supervision of the course of treatment for those who are treated for LTBI or TB disease.

Groups that are not at high risk for LTBI or TB disease should not be tested routinely because testing in populations at low risk diverts resources from other priority activities. In addition, testing persons at low risk for *M. tuberculosis* infection is discouraged because a substantial proportion of persons from populations at low risk who have positive TST results might actually have false-positive TST results and might not represent true infection with *M. tuberculosis* (*39,316*). Testing for infection with *M. tuberculosis* should be performed for

well-defined groups at high risk. These groups can be divided into two categories: 1) persons at higher risk for exposure to and infection with *M. tuberculosis* and 2) persons at higher risk for progression from LTBI to TB disease (see TB Infection-Control Program for Settings in Which Patients with Suspected or Confirmed TB Disease Are Expected To Be Encountered; and TB Infection-Control Program for Settings in Which Patients with Suspected or Confirmed TB Disease Are Not Expected To Be Encountered).

Flexibility is needed in defining high-priority groups for TB screening. The changing epidemiology of TB indicates that the risk for TB among groups currently considered as high priority might decrease over time, and groups currently not identified originally as being at high risk might be considered as high priority.

Use of Tuberculin Skin Test (TST) for Diagnosing *M. tuberculosis* Infections in HCWs

The TST is frequently the first step of a TB diagnostic evaluation that might lead to diagnosing LTBI. Although currently available preparations of PPD used in TST are <100% sensitive and specific for the detection of LTBI, the TST is currently the most widely used diagnostic test for *M. tuberculosis* infection in the United States. The TST is less sensitive in patients who have TB disease.

The TST, like all medical tests, is subject to variability (*74,228,317*), but many of the inherent variations in administering and reading TST results can be avoided by training and attention to detail (*318*). Details of TST administration and TST result reading procedures are suggested in this report to improve the technical aspects of TST placement and reading, thus reducing observer variations and improving test reliability (Appendix F). These checklists were developed for the National Health and Nutrition Examination Survey (NHANES) to standardize TST placement and reading for research purposes. The suggested TST training recommendations are not mandatory.

Adherence to TST

Operational policies, procedures, and practices at healthcare settings can enhance HCW adherence to serial TST. In 2002, one focus group study identified potential barriers and facilitators to adherence with routine TST (*319*). HCWs identified structural factors (e.g., inconvenient TST screening schedules and locations and long waiting times) that negatively affected adherence. Facilitators to help HCWs adhere to routine TST included active follow-up by supervisors and occupational health staff and work-site visits for TST screening. Misinformation and stigma concerning TB also emerged in the discussions, indicating the need for additional training and education for HCWs.

Administering the TST

For each patient, a risk assessment should be conducted that takes into consideration recent exposure to *M. tuberculosis*, clinical conditions that increase risk for TB disease if infected, and the program's capacity to deliver treatment for LTBI to determine if the TST should be administered.

The recommended method for TST is the Mantoux method (Appendix F) (*223,318,320–322*). Mantoux TST training materials supporting the guidance in this report are available at http://www.cdc.gov/tb (*223,318,320–325*). Multipuncture tests (e.g., Tine® tests) are not as reliable as the Mantoux method of skin testing and should not be used as a diagnostic test in the United States (*30*). Contact the state and local health department for TST resources.

Reading the TST Result

The TST result should be read by a designated, trained HCW 48–72 hours after the TST is placed (*39,326,327*). If the TST was not read between 48–72 hours, ideally, another TST should be placed as soon as possible and read within 48–72 hours (*39*). Certain studies indicate that positive TST reactions might still be measurable from 4–7 days after testing (*225,226,328*). However, if a patient fails to return within 72 hours and has a negative test result, the TST should be repeated (*42*). Patients and HCWs should not be allowed to read their own TST results. HCWs do not typically measure their own TST results reliably (*48*).

Reading the TST result consists of first determining the presence or absence of induration (hard, dense, and raised formation) and, if induration is present, measuring the diameter of induration transverse (perpendicular) to the long axis of the forearm (Figure 1) (*39,318*). Erythema or redness of the skin should not be considered when reading a TST result (Appendix F).

Interpreting TST Results

The positive-predictive value of a TST is the probability that a person with a positive TST result is actually infected with *M. tuberculosis*. The positive predictive value is dependent on the prevalence of infection with *M. tuberculosis* in the population being tested and the sensitivity and specificity of the test (*228,329,330*).

In populations with a low prevalence of *M. tuberculosis* infection, the probability that a positive TST result represents true infection with *M. tuberculosis* can be substantially low, especially if the cut point is set too low (i.e., the test is not adequately specific and a low prevalence exists in the population). In populations with a high prevalence of infection with

FIGURE 1. The tuberculin skin test result in this picture should be recorded as 16 mm. The "0" mm ruler line is inside the edge of the left dot.

M. tuberculosis and inadequate test specificity, the probability that a positive TST result using the same cut point represents true infection with *M. tuberculosis* is much higher.

Interpreting TST Results in HCWs

TST result interpretation depends on two factors: 1) measured TST induration in millimeters and 2) the person's risk for being infected with *M. tuberculosis* and risk for progression to TB disease if infected.

The purpose of the test (Box 2) should be used to determine whether the TST result should be classified as positive or negative. A TST result with no induration (0 mm) or a measured induration below the defined cut point for each category is considered to signify absence of infection with *M. tuberculosis*.

In the context of TST screening as part of a TB infection-control program, the interpretation of TST results occurs in two distinct parts. The first is the interpretation by standard criteria, without regard to personal risk factors or setting-specific factors of the TST results for infection control, surveillance, and referral purposes. The second is the interpretation by individualized criteria to determine the need for treatment of LTBI.

Determining the need for treatment of LTBI is a subsequent and separate task. For infection-control and surveillance purposes, TST results should be interpreted and recorded under strict criteria, without considering setting-based or personal risk factors (see Supplement, Diagnostic Procedures for LTBI and TB Disease). Any HCW with a positive TST result from serial TB screening should be referred to a medical provider for an evaluation and to determine the need for treatment of LTBI based on individual risk (see Supplements, Diagnostic Procedures for LTBI and TB Disease; and Treatment Procedures for LTBI and TB Disease; Box 2).

Interpreting the TST Result for Infection Control and Surveillance

On baseline TST testing, a TST result of ≥10 mm is considered positive for the majority of HCWs, and a TST result of ≥5 mm is considered positive for HCWs who are infected with HIV or who have other immunocompromising conditions (see Supplement, Diagnostic Procedures for LTBI and TB Disease; Box 2). All HCWs with positive baseline TST results should be referred for medical and diagnostic evaluation; additional skin testing does not need to be performed.

On serial screening for the purposes of infection-control surveillance, TST results indicating an increase of ≥10 mm within 2 years should be interpreted and recorded as a TST

BOX 2. Interpretations of tuberculin skin test (TST) and QuantiFERON®-TB test (QFT) results according to the purpose of testing for *Mycobacterium tuberculosis* infection in a health-care setting

Purpose of testing	TST	QFT
1. Baseline	1. ≥10 mm is considered a positive result (either first- or second-step)	1. Positive (only one-step)
2. Serial testing without known exposure	2. Increase of ≥10 mm is considered a positive result (TST conversion)	2. Change from negative to positive (QFT conversion)
3. Known exposure (close contact)	3. ≥5 mm is considered a positive result in persons who have a baseline TST result of 0 mm; an increase of ≥10 mm is considered a positive result in persons with a negative baseline TST result or previous follow-up screening TST result of ≥0 mm	3. Change to positive

conversion. For the purposes of assessing and monitoring infection control, TST conversion rates should be regularly determined. Health-care settings with a substantial number of HCWs to be tested might have systems in place that can accurately determine the TST conversion rate every month (e.g., from among a group of HCWs tested annually), whereas smaller settings might have imprecise estimates of their TST conversion rate even with annual assessments.

The precision of the setting's TST conversion rate and any analysis assessing change from baseline TST results will depend on the number and frequency of HCWs tested. These factors should be considered when establishing a regular interval for TB screening for HCWs.

After a known exposure in a health-care setting, close HCW contacts who have TST results of ≥5 mm should be considered to have positive TST results, which should be interpreted as new infections only in HCWs whose previous TST result is 0 mm. However, HCWs 1) with a baseline or follow-up TST result of >0 mm but <10 mm with a health-care–associated exposure to *M. tuberculosis* and 2) who then have an increase of ≥10 mm should be considered to have a TST conversion because of a new infection (see Supplement, Diagnostic Procedures for LTBI and TB Disease; Box 2).

In a contact investigation, a follow-up TST should be administered 8–10 weeks after the end of exposure (rather than 1–3 weeks later, as in two-step testing). In this instance, a change from a negative TST result to a positive TST result should not be interpreted as a boosted reaction. The change in the TST result indicates a TST conversion, recent exposure, transmission, and infection.

All HCWs who are immunocompromised should be referred for a medical and diagnostic evaluation for any TST result of ≥5 mm on baseline or follow-up screening. Because infection-control staff will usually not know the immune status of the HCWs being tested, HCWs who have TST results of 5–9 mm should be advised that such results can be an indication for referral for medical evaluation for HCWs who have HIV infection or other causes of severe immunosuppression.

After an HCW has met criteria for a positive TST result, including HCWs who will not receive treatment for LTBI, repeat TSTs are not necessary because the results would not provide any additional information (*30*). This approach applies to HCWs who have positive TST results but who will not receive treatment for LTBI after medical evaluation. For future TB screening in settings that are medium risk, instead of participating in serial skin testing, the HCW should receive a medical evaluation and a symptom screen annually.

Interpreting the TST Result for Medical and Diagnostic Referral and Evaluation

HCWs who have positive TST results and who meet the criteria for referral should have a medical and diagnostic evaluation. For HCWs who are at low risk (e.g., those from low-incidence settings), a baseline result of ≥15 mm of induration (instead of ≥10 mm) might possibly be the cut point. The criteria used to determine the need for treatment of LTBI has been presented (Box 2).

When making decisions for the diagnosis and treatment of LTBI, setting-based risk factors (e.g., the prevalence of TB disease and personal risk factors such as having an immunocompromising condition or known contact with a TB case) should be assessed when choosing the cut point for a positive TST result. The medical evaluation can occur in different settings, including an occupational health clinic, local or state health department, or private medical clinic (Box 2)

When 15 mm is used as the cut point, TST results of 10–14 mm can be considered clinically negative (*331*). These HCWs should not have repeat TST, and the referring physician might not recommend treatment for LTBI. This issue of false-positive TST results might be especially true in areas of the country where the prevalence of infection with NTM is high.

HCWs who have TST results of 5–9 mm on baseline two-step testing should be advised that such results might be an indication for treatment of LTBI if the HCW is a contact of a person with infectious TB disease, has HIV infection, or has other causes of severe immunosuppression (e.g., organ transplant and receipt of the equivalent of ≥15 mg/day of prednisone for ≥1 month). The risk for TB disease in persons treated with corticosteroids increases with higher dose and longer duration of corticosteroid use. TNF-α antagonists also substantially increase the risk for progression to TB disease in persons with LTBI (*332*).

HCWs with negative baseline two-step TST results who are referred for medical evaluation for an increase of ≥10 mm induration on follow-up TST screening, including those who are otherwise at low risk for TB disease, probably acquired *M. tuberculosis* infection since receiving the previous TST and should be evaluated for TB disease. If disease is excluded, the HCW should be offered treatment for LTBI if they have no contraindication to treatment (Box 2).

QC Program for Techniques for TST Administration and Reading TST Results

Random variation (i.e., differences in procedural techniques) in TST administration and reading TST results can cause false-positive or false-negative TST results. Many of the variations in administering and reading TST results can be avoided by

conducting training and maintaining attention to details. HCWs who are responsible for TST procedures should be trained to reduce variation by following standardized operational procedures and should be observed by an expert TST trainer. All TST procedures (i.e., administering, reading, and recording the results) should be supervised and controlled to detect and correct variation. Corrective actions might include coaching and demonstration by the TST trainer. Annual re-training is recommended for HCWs responsible for administering and reading TST results.

One strategy to identify TST procedure variation is to use a QC tool (see Supplement, Diagnostic Procedures for LTBI and TB Disease; Appendix F). The expert TST trainer should observe the procedures and indicate procedural variation on the observation checklists. An expert trainer includes persons who have documented training experience.

QC for Administering TST by the Mantoux Method

Ideally, the TST trainer should participate in QC TST administrations with other TST trainers to maintain TST trainer certification. State regulations specify who is qualified to administer the test by injection. The TST trainer should first ensure antigen stability by maintaining the manufacturer's recommended cold chain (i.e., controlling antigen exposure to heat and light from the time it is out of refrigeration until the time it is placed back into refrigeration or until the vial is empty or expired). The TST trainer should prevent infection during an injection by preparing the skin and preventing contamination of solution, needle, and syringe.

The TST trainer should prevent antigen administration errors by controlling the five rights of administration: 1) right antigen; 2) right dose; 3) right patient; 4) right route; and 5) right time for TST administration, reading, and clinical evaluation (*333*). Finally, the TST trainer should observe and coach the HCW trainee in administering multiple intradermal injections by the Mantoux method. The TST trainer should record procedural variation on the observation checklist (see Supplement, Diagnostic Procedures for LTBI and TB Disease; Appendix F). TST training and coaching should continue until more than 10 correct skin test placements (i.e., >6 mm wheal) are achieved.

For training purposes, normal saline for injection can be used instead of PPD for intradermal injections. Volunteers are usually other HCWs who agree to be tested. Attempt to recruit volunteers who have known positive TST results so the trainees can practice reading positive TST results. A previous TST is not a contraindication to a subsequent TST unless the test was associated with severe ulceration or anaphylactic shock, which are substantially rare adverse events (*30,237,238*).

Model TST Training Program

A model TST training program for placing TST and reading TST results has been produced by NHANES (*326*). The number of hours, sessions, and blinded independent duplicate reading (BIDR) readings should be determined by the setting's TB risk assessment. The following information can be useful for a model TST training program.

Initial training for a TST placer ideally consists of three components.

- Introductory lecture and demonstration by an expert TST placer or trainer. An expert TST trainer is a qualified HCW who has received training on administering multiple TST and reading multiple TST results (consider 3 hours of lecture).
- Supervised practical work using procedural checklists observed and coached by the expert TST trainer (see Supplement, Diagnostic Procedures for LTBI and TB Disease; Appendix F) (consider 9 hours of practical work).
- Administration of more than 10 total skin tests on volunteers by using injectable saline and producing more than 10 wheals that measure 6–10 mm.

TST training should include supervised TST administration, which is a procedure in which an expert TST trainer supervises a TST trainee during all steps on the procedural observation checklist for TST administration (see Supplement, Diagnostic Procedures for LTBI and TB Disease; Appendix F). Wheal size should be checked for all supervised TST administrations, and skin tests should be repeated if wheal size is inadequate (i.e., <6 mm). TST training and coaching should continue until more than10 correct skin test placements (i.e., >6 mm wheal) are achieved.

QC for Reading TST Results by the Palpation Method

The TST trainer should participate in QC readings with other TST trainers to maintain TST trainer certification. When training HCWs to read TST results, providing measurable TST responses is helpful (i.e., attempt to recruit volunteers who have known positive TST results so that the trainees can practice reading positive TST results).

TST readers should correctly read both measurable (>0 mm) and nonmeasurable responses (0 mm) (e.g., consider reading more than 20 TST results [at least 10 measurable and at least 10 nonmeasurable], if possible). The TST trainer should observe and coach the HCW in reading multiple TST results by the Palpation method and should record procedure variation on the observation checklist (see Supplement, Diagnostic Procedures for LTBI and TB Disease; Appendix F).

The TST trainer should conduct BIDRs for comparison with the HCW's reading. BIDRs are performed when two or more consecutive TST readers immediately measure the same

TST result by standard procedures, without consulting or observing one another's readings, and record results independently (may use recommended procedural observation checklist; Appendix F). BIDRs help ensure that TST readers continue to read TST results correctly.

Initial training for a TST reader ideally should consist of multiple components.

- Receiving an introductory lecture and demonstration by an expert TST reader. Training materials are available from CDC (*223,318*) and CDC-sponsored Regional Model and Training Centers and should also be available at the local or state health department (consider 6 hours for lecture and demonstration).
- Receiving four sessions of supervised practical work using procedural checklists (observed and coached by an expert TST reader) (consider16 hours of practical work).
- Performing BIDR readings (consider more than 80, if possible). TST trainers should attempt to organize the sessions so that at least 50% of the TST results read have a result of >0 mm according to the expert TST reader.
- Performing BIDR readings on the last day of TST training (consider more than 30 BIDR readings out of the total 80 readings, if possible). TST trainers should attempt to ensure that at least 25% of persons tested have a TST result of >0 mm, according to the expert TST reader.
- Missing no more than two items on the procedural observation checklist (Appendix F) for three random observations by an expert TST reader.
- Performing all procedures on the checklist correctly during the final observation.

TST training and coaching should continue until the HCW is able to perform all procedures correctly and until a satisfactory measurement is achieved (i.e., the trainer and the trainee read the TST results within 2 mm of each other). For example, if the trainer reads the TST result as 11 mm (this might be considered the gold standard reading), the trainee's reading should be between 9–13 mm to be considered correct. Only a single measurement, in millimeters, should be recorded (not 11 mm x 11 mm or 11 mm x 15 mm). QC Procedural Observation Checklists (Appendix F) are recommended by CDC as a tool for use during TST training.

Special Considerations in TST

Anergy. The absence of a reaction to a TST does not exclude a diagnosis of TB disease or infection with *M. tuberculosis*. In immunocompromised persons, delayed-type hypersensitivity (DTH) responses (e.g., tuberculin reactions) can decrease or disappear more rapidly, and a limited number of otherwise healthy persons apparently are incapable of reacting to tuberculin even after diagnosed infection with *M. tuberculosis*. This condition, called anergy, can be caused by multiple factors (e.g., advanced HIV infection, measles infection, sarcoidosis, poor nutrition, certain medications, vaccinations, TB disease itself, and other factors) (*307,334–338*). However, anergy skin in conjunction with skin testing is no longer recommended routinely for screening for *M. tuberculosis* infection (*336*).

Anergy testing is not useful in screening for diagnosing LTBI or asymptomatic TB disease (*339*). In addition, anergy testing is not routinely recommended for anyone infected with HIV or who is otherwise immunocompromised, because TST results alone, positive or negative, are not sensitive or specific enough to guide clinical decision making (*336*).

Reconstitution of DTH in HIV-infected persons taking antiretroviral therapy (ART). In one prospective study (*340*), TB patients who initially had negative TST results had positive TST results after initiation of HAART. HCWs must be aware of the potential public health and clinical implications of restored TST reactivity among persons who have not been diagnosed with TB disease but who might have LTBI. After the initiation of HAART repeat testing for infection with *M. tuberculosis* is recommended for HIV-infected persons previously known to have negative TST results (*58*). Recommendations on the prevention and treatment of TB in HIV-infected persons have been published (*39,53,240*).

Pregnancy. Tens of thousands of pregnant women have received TST since the test was developed, and no documented episodes of TST-related fetal harm have been reported (*341*). No evidence exists that the TST has adverse effects on the pregnant mother or fetus (*39*). Pregnant HCWs should be included in serial skin testing as part of an infection-control program or a contact investigation because no contraindication for skin testing exists (*342*). Guidelines issued by the American College of Obstetricians and Gynecologists (ACOG) emphasize that postponement of the diagnosis of infection with *M. tuberculosis* during pregnancy is unacceptable (*343*).

Booster phenomenon and two-step testing. In certain persons with LTBI, the DTH responsible for TST reactions wanes over time. Repeated TST can elicit a reaction called boosting in which an initial TST result is negative, but a subsequent TST result is positive. For example, a TST administered years after infection with *M. tuberculosis* can produce a false-negative result. This TST might stimulate (or boost) the person's ability to react to tuberculin, resulting in a positive result to a subsequent test (including the second step of a two-step procedure) (*36,74,316,342,343*). With serial testing, a boosted reaction on a subsequent TST might be misinterpreted as a newly acquired infection, compared with the false-negative result from the initial TST. Misinterpretation of a

boosted reaction as a new infection with *M. tuberculosis* or TST conversion might prompt unnecessary investigations to find the source case, unnecessary treatment for the person tested, and unnecessary testing of other HCWs. The booster phenomenon can occur in anyone, but it is more likely to occur in older persons, persons with remote infection with *M. tuberculosis* (i.e., infected years ago), persons infected with NTM, and persons with previous BCG vaccination (*39,229,234,344,345*).

All newly employed HCWs who will be screened with TST should receive baseline two-step TST upon hire, unless they have documentation of either a positive TST result or treatment for LTBI or TB disease (*39,224*). Any setting might have HCWs at risk for boosting, and a rate of boosting even as low as 1% can result in unnecessary investigation of transmission. Therefore, two-step TSTs are needed to establish a baseline for persons who will receive serial TST (e.g., residents or staff of correctional facilities or LTCFs). This procedure is especially important for settings that are classified as low risk where testing is indicated only upon exposure. A reliable baseline test result is necessary to detect health-care–associated transmission of *M. tuberculosis*. Guidance for baseline TST for HCWs is included in this report (Box 2). To estimate the frequency of boosting in a particular setting, a four-appointment schedule of TST administration and reading (i.e., appointments for TST administration and reading both TST results) is necessary, rather than the three-appointment schedule (i.e., appointments for the administration of both tests, with reading of the second-step TST result only) (*196*).

Two-step testing should be used only for baseline screening, not in contact investigations. In a contact investigation, for persons with a negative TST, a follow-up test should be administered 8–10 weeks after the end of exposure (rather than 1–3 weeks later, as in a two-step TST). In this instance, a change from a negative to a positive TST result suggests that recent exposure, transmission, and infection occurred and should not be interpreted as a boosted response.

After a known exposure in a health-care setting (close contact to a patient or HCW with infectious TB disease), TST results of ≥5 mm should be considered positive and interpreted as a new infection in HCWs whose previous TST result is 0 mm. If an HCW has a baseline or follow-up TST result of >0 mm but ≤10 mm, a health-care–associated exposure to *M. tuberculosis,* and an increase in the TST size of >10 mm, the result should be interpreted as the HCW having a TST conversion because of new infection.

BCG vaccination. In the United States, vaccination with BCG is not recommended routinely for anyone, including HCWs or children (*227*). Previous BCG vaccination is not a contraindication to having a TST or two-step skin testing administered. HCWs with previous BCG vaccination should receive baseline and serial skin testing in the same manner as those without BCG vaccination (*233*) (see Supplement, Diagnostic Procedures for LTBI and TB Disease; Box 1).

Previous BCG vaccination can lead to boosting in baseline two-step testing in certain persons (*74,231,344–346*). Distinguishing a boosted TST reaction resulting from BCG vaccination (a false-positive TST result) and a TST result because of previous infection with *M. tuberculosis* (true positive TST result) is not possible (*39*). Infection-control programs should refer HCWs with positive TST results for medical evaluation as soon as possible (see Supplement, Diagnostic Procedures for LTBI and TB Disease; Box 2).

Previous BCG vaccination increases the probability of a boosted reaction that will probably be uncovered on initial two-step skin testing. For an HCW with a negative baseline two-step TST result who is a known contact of a patient who has suspected or confirmed infectious TB disease, treatment for LTBI should be considered if the follow-up TST result is ≥5 mm, regardless of BCG vaccination status.

PPD preparations for diagnosing infection with *M. tuberculosis*. Two PPD preparations are available in the United States: Tubersol® (Aventis Pasteur, Swiftwater, Pennsylvania) (*237*) and APLISOL® (Parkdale Pharmaceuticals, Rochester, Michigan) (*238*). Compared with the U.S. reference PPD, no difference exists in TST interpretation between the two preparations (*347*). However, when Tubersol and Aplisol were compared with each other, a slight difference in reactivity was observed. Aplisol produced slightly larger reactions than Tubersol, but this difference was not statistically significant (*347*). The difference in specificity, 98% versus 99%, is limited. However, when applied in large institutional settings that test thousands of workers annually who are at low risk for infection with *M. tuberculosis*, this difference in specificity might affect the rate of positive TST results observed.

TB screening programs should use one antigen consistently and should realize that changes in products might make serial changes in TST results difficult to interpret. In one report, systematic changes in product use resulted in a cluster of pseudoconversions that were believed to have erroneously indicated a health-care–associated outbreak (*348*). Persons responsible for making decisions about the choice of pharmacy products should seek advice from the local or state health department's TB infection-control program before switching PPD preparations and should inform program staff of any changes.

Chest Radiography

Chest radiographic abnormalities can suggest pulmonary TB disease. Radiographic abnormalities that are consistent with

pulmonary TB disease include upper-lobe infiltration, cavitation, and effusion. Infiltrates can be patchy or nodular and observed in the apical (in the top part of the lungs) or subapical posterior upper lobes or superior segment of the lower lobes in the lungs. HCWs who have positive test results for *M. tuberculosis* infection or symptoms or signs of TB disease, regardless of test results for *M. tuberculosis* infection, should have a chest radiograph performed to exclude a diagnosis of TB disease. However, a chest radiograph is not a substitute for tests for *M. tuberculosis* infection in a serial TB screening program for HCWs.

Persons who have LTBI or cured TB disease should not have repeat chest radiographs performed routinely (*116*). Repeat radiographs are not needed unless symptoms or signs of TB disease develop or a clinician recommends a repeat chest radiograph (*39,116*).

A chest radiograph to exclude pulmonary TB disease is indicated for all persons being considered for treatment of LTBI. If chest radiographs do not indicate pulmonary TB and if no symptoms or signs of TB disease are present, persons with a positive test result for infection with *M. tuberculosis* might be candidates for treatment of LTBI. In persons with LTBI, the chest radiograph is usually normal, although it might demonstrate abnormalities consistent with previous healed TB disease or other pulmonary conditions. In patients with symptoms or signs of TB disease, pulmonary infiltrates might only be apparent on a computed tomography (CT) scan. Previous, healed TB disease can produce radiographic findings that might differ from those associated with current TB disease, although a substantial overlap might exist. These findings include nodules, fibrotic scars, calcified granulomas, or basal pleural thickening. Nodules and fibrotic scars might contain slowly multiplying tubercle bacilli and pose a high risk for progression to TB disease. Calcified nodular lesions (calcified granulomas) and apical pleural thickening pose a lower risk for progression to TB disease (*31*).

Chest Radiography and Pregnancy

Because TB disease is dangerous to both mother and fetus, pregnant women who have a positive TST result or who are suspected of having TB disease, as indicated by symptoms or other concerns, should receive chest radiographs (with shielding consistent with safety guidelines) as soon as feasible, even during the first trimester of pregnancy (*31,39,341*).

Chest Radiography and HIV-Infected Persons

The radiographic presentation of pulmonary TB in persons infected with HIV might be apical; however, apical cavitary disease is less common among such patients. More common chest radiograph findings for HIV-infected persons are infiltrates in any lung zone, mediastinal or hilar adenopathy, or, occasionally, a normal chest radiograph. Typical and cavitary lesions are usually observed in patients with higher CD4 counts, and more atypical patterns are observed in patients with lower CD4 counts (*31,49,94,142,349–354*). In patients with symptoms and signs of TB, a negative chest radiograph result does not exclude TB. Such patients might be candidates for airborne precautions during medical evaluation.

Evaluation of Sputum Samples

Sputum examination is a critical diagnostic procedure for pulmonary TB disease (*30*) and is indicated for the following persons:

- anyone suspected of having pulmonary or laryngeal TB disease;
- persons with chest radiograph findings consistent with TB disease (current, previous, or healed TB);
- persons with symptoms of infection in the lung, pleura, or airways, including larynx;
- HIV-infected persons with any respiratory symptoms or signs, regardless of chest radiograph findings; and
- persons suspected of having pulmonary TB disease for whom bronchoscopy is planned.

Sputum Specimen Collection

Persons requiring sputum collection for smear and culture should have at least three consecutive sputum specimens obtained, each collected in 8–24-hours intervals (*124*), with at least one being an early morning specimen (*355*). Specimens should be collected in a sputum induction booth or in an AII room. In resource-limited settings without environmental containment or when an AII room is not available, sputum collection can be performed safely outside of a building, away from other persons, windows, and ventilation intakes. Patients should be instructed on how to produce an adequate sputum specimen (containing little saliva) and should be supervised and observed by an HCW during the collection of sputum, if possible (*30*). If the patient's specimen is determined to be inadequate, it should still be sent for bacteriologic testing, although the inadequate nature of the specimen should be recorded. The HCW should wear an N95 disposable respirator during sputum collection.

Sputum Induction

For patients who are unable to produce an adequate sputum specimen, expectoration can be induced by inhalation of an aerosol of warm, hypertonic saline. Because sputum induction is a cough-inducing procedure, pre-treatment with a bronchodilator should be considered in patients with a history of asthma or other chronic obstructive airway diseases.

Medical assistance and bronchodilator medication should be available during any sputum induction in the event of induced bronchospasm (*109,356,357*).

The patient should be seated in a small, well-ventilated sputum induction booth or in an AII room (see Environmental Controls; and Supplement, Environmental Controls). For best results, an ultrasonic nebulizer that generates an aerosol of approximately 5 mL/minute should be used. A 3% hypertonic saline is commercially available, and its safety has been demonstrated. At least 30 mL of 3% saline should be administered; administration of smaller volumes will have a lower yield. Higher concentrations can be used with an adjustment in the dose and closer monitoring for adverse effects.

Patients should be instructed to breathe deeply and cough intermittently. Sputum induction should be continued for up to 15 minutes or until an adequate specimen (containing little saliva) is produced. Induced sputum will often be clear and watery. Any expectorated material produced should be labeled as expectorated sputum and sent to the laboratory.

Laboratory Examination

Detection of AFB in stained smears by microscopy can provide the first bacteriologic indication of TB disease. Laboratories should report any positive smear results within 24 hours of receipt of the specimen (*30*). A positive result for AFB in a sputum smear is predictive of increased infectiousness. Smears allow presumptive detection of mycobacteria, but definitive identification, strain typing, and drug-susceptibility testing of *M. tuberculosis* require that a culture be performed (*30*). Negative AFB sputum smear results do not exclude a diagnosis of TB disease, especially if clinical suspicion of disease is high. In the United States, approximately 63% of patients with reported positive sputum culture results have positive AFB sputum smear results (*26*).

A culture of sputum or other clinical specimen that contains *M. tuberculosis* provides a definitive diagnosis of TB disease. In the majority of cases, identification of *M. tuberculosis* and drug-susceptibility results are available within 28 days (or 4–6 weeks) when recommended rapid methods such as liquid culture and DNA probes are used. Negative culture results are obtained in approximately 14% of patients with confirmed pulmonary TB disease (*4,5*). Testing sputum with rapid techniques (e.g., NAA) facilitates the rapid detection and identification of *M. tuberculosis* but should not replace culture and drug-susceptibility testing in patients with suspected TB disease (*30,125,358*). Mixed mycobacterial infection can obscure the identification of *M. tuberculosis* during the laboratory evaluation (e.g., because of cross-contamination or dual infections) and can be distinguished by the use of mycobacterial species-specific DNA probes (*359*). Examination of colony morphology on solid culture media can also be useful.

Drug-susceptibility tests should be performed on initial isolates from all patients to assist in identifying an effective antituberculosis treatment regimen. Drug-susceptibility tests should be repeated if sputum specimens continue to be culture-positive after 3 months of antituberculosis treatment or if culture results become positive for *M. tuberculosis* after a period of negative culture results (*30,31*).

Bronchoscopy

If possible, bronchoscopy should be avoided in patients with a clinical syndrome consistent with pulmonary or laryngeal TB disease because bronchoscopy substantially increases the risk for transmission either through an airborne route (*63,80,81,162,360*) or a contaminated bronchoscope (*80,82,163–169*), including in persons with negative AFB sputum smear results. Microscopic examination of three consecutive sputum specimens obtained in 8–24-hour intervals, with at least one obtained in the early morning, is recommended instead of bronchoscopy, if possible. In a patient who is intubated and mechanically ventilated, closed circuitry can reduce the risk for exposure.

If the suspicion for pulmonary TB disease is high or if the patient is seriously ill with a disorder, either pulmonary or extrapulmonary, that is believed to be TB disease, multidrug antituberculosis treatment using one of the recommended regimens should be initiated promptly, frequently before AFB smear results are known (*31*). Obtaining three sputum samples is safer than performing bronchoscopy. For AFB smear and culture results, three sputum samples have an increased yield compared with a single specimen (*110,357*), and induced specimens have better yield than specimens obtained without induction. Sputum induction is well-tolerated (*90,109,132, 133,357,361,362*), even in children (*134,356*), and sputum specimens (either spontaneous or induced) should be obtained in all cases before a bronchoscopy (*109,356,363,364*).

In circumstances where a person who is suspected of having TB disease is not on a standard antituberculosis treatment regimen and the sputum smear results (possibly including induced specimens) are negative and a reasonably high suspicion for TB disease remains, additional consideration to initiate treatment for TB disease should be given. If the underlying cause of a radiographic abnormality remains unknown, additional evaluation with bronchoscopy might be indicated; however, in cases where TB disease remains a diagnostic possibility, initiation of a standard antituberculosis treatment regimen for a period before bronchoscopy might reduce the risk for transmission. Bronchoscopy might be valuable in establishing the diagnosis; in addition, a positive culture result can be both of

clinical and public health importance to obtain drug-susceptibility results. Bronchoscopy in patients with suspected or confirmed TB disease should not be undertaken until after consideration of the risks for transmission of *M. tuberculosis* (*30,63,81,162,360*). If bronchoscopy is performed, because it is a cough-inducing procedure, additional sputum samples for AFB smear and culture should be collected after the procedure to increase the diagnostic yield.

Treatment Procedures for LTBI and TB Disease

Treatment for LTBI

Treatment for LTBI is essential to control and eliminate TB disease in the United States because it substantially reduces the risk that infection with *M. tuberculosis* will progress to TB disease (*10,28*). Certain groups of persons are at substantially high risk for developing TB disease after being infected, and every effort should be made to begin treatment for LTBI and to ensure that those persons complete the entire course of treatment (see Supplement, Treatment Procedures for LTBI and TB Disease; Box 2).

Before beginning treatment of LTBI, a diagnosis of TB disease should be excluded by history, medical examination, chest radiography, and, when indicated, bacteriologic studies. In addition, before offering treatment of LTBI, ensure that the patient has not experienced adverse reactions with previous isoniazid (INH) treatment (*215*).

Candidates for Treatment of LTBI

Persons in the following groups at high risk should be administered treatment for LTBI if their TST result is ≥5 mm, regardless of age (*31,39*):

- persons infected with HIV,
- recent contacts with a person with TB disease,
- persons with fibrotic changes on chest radiograph consistent with previous TB disease,
- organ transplant recipients, and
- other immunosuppressed persons (e.g., persons receiving ≥15 mg/day of prednisone for ≥1 month).

Persons in the following groups at high risk should be considered for treatment of LTBI if their TST result is ≥10 mm, or if the BAMT result is positive:

- persons with TST or BAMT conversions;
- persons born or who have lived in developing countries or countries with a high-incidence of TB disease;
- persons who inject illicit drugs;
- residents and employees in congregate settings that are at high risk (i.e., correctional facilities and LTCFs [e.g., hospices and skilled nursing facilities]), hospitals and other health-care facilities, residential settings for persons with HIV/AIDS or other immunocompromising conditions, and homeless shelters;
- personnel from mycobacteriology laboratories;
- persons with any of the following clinical conditions or other immunocompromising conditions that place them at high risk for TB disease:
  - — silicosis,
  - — diabetes mellitus,
  - — chronic renal failure,
  - — certain hematologic disorders (e.g., leukemias and lymphomas),
  - — other specific malignancies (e.g., carcinoma of the head, neck, or lung),
  - — unexplained weight loss of ≥10% of ideal body weight,
  - — gastrectomy, or
  - — jejunoileal bypass;
- persons living in areas with high incidence of TB disease;
- children aged <4 years; and
- infants, children, and adolescents exposed to adults at high risk for developing TB disease.

Persons who use tobacco or alcohol (*40,41*), illegal drugs, including injection drugs and crack cocaine (*43–48*), might also be at increased risk for infection and disease, but because of the multiple other potential risk factors that commonly occur among such persons, use of these substances has been difficult to identify as separate risk factors.

Persons with no known risk factors for TB disease can be considered for treatment of LTBI if their TST result is ≥15 mm. However, programs to screen HCWs for infection with *M. tuberculosis* should only be conducted among groups at high risk. All testing activities should be accompanied by a plan for follow-up care for persons with LTBI or, if it is found, TB disease. A decision to test for infection with *M. tuberculosis* should be based on a commitment to treat LTBI after a medical examination (*39*).

Persons who might not be good candidates for treatment of LTBI include those with a previous history of liver injury or a history of excessive alcohol consumption. Active hepatitis and ESLD are relative contraindications to the use of INH for treatment of LTBI (*39,240*). If the decision is made to treat such patients, baseline and follow-up monitoring of serum aminotransaminases should be considered.

For persons who have previous positive TST or BAMT results and who completed treatment for LTBI previously, treating them again is not necessary. Documentation of completed therapy for LTBI is critical. Instead of participating in serial skin testing, the HCW should receive a medical evaluation and a symptom screen annually. A symptom screen is a procedure used during a clinical evaluation in which patients

are asked if they have experienced any departure from normal in function, appearance, or sensation related to TB disease (e.g., cough)..

Screening HCWs for infection with *M. tuberculosis* is an essential administrative measure for the control of transmission of *M. tuberculosis* in health-care settings. By conducting TB screening, ongoing transmission of *M. tuberculosis* can be detected, and future transmission can be prevented by identifying lapses in infection control and identifying persons infected with *M. tuberculosis* and TB disease. The majority of individual HCWs, however, do not have the risk factors for progression to disease that serve as the basis for the current recommendations for targeted testing and treatment of LTBI. The majority of HCWs in the United States do not provide care in areas in which the prevalence of TB is high. Therefore, HCWs should be tested, as determined by risk classification for the health-care setting, and can be categorized as having a positive test result or conversion for *M. tuberculosis* infection. HCWS can be categorized as part of the TB infection-control program for the purpose of surveillance and referral, but they might not necessarily be a candidate for treatment of LTBI.

In the context of TST screening as part of an infection-control program, the interpretation of TST results in HCWs occurs in multiple steps. HCWs should receive baseline two-step TST testing (see Supplement, Diagnostic Procedures for LTBI and TB Disease; Box 2). In the context of BAMT screening, HCWs should receive only one baseline test.

HCWs should receive serial screening for infection with *M. tuberculosis* (either TST or BAMT), as determined by the health-care setting's risk classification (Appendix D). For infection-control purposes, the results of the testing should be recorded and interpreted as part of the TB infection-control program as either a 1) negative TST result, 2) previously documented positive TST or BAMT result, or 3) TST or BAMT conversion. All recordings should also document the size of the induration in millimeters, not simply as negative or positive. BAMT results should be recorded in detail. The details should include date of blood draw, result in specific units, and the laboratory interpretation (positive, negative, or indeterminate—and the concentration of cytokine measured [e.g., IFN-γ]).

To determine whether treatment for LTBI should be indicated, HCWs should be referred for medical and diagnostic evaluation according to the TST result criteria (Box 2). In conjunction with a medical and diagnostic evaluation, HCWs with positive test results for *M. tuberculosis* should be considered for treatment of LTBI (Box 2) after TB disease has been excluded by further medical evaluation. HCWs cannot be compelled to take treatment for LTBI, but they should be encouraged to do so if they are eligible for treatment.

HCWs' TST or BAMT results might be considered positive as part of the TB infection-control program for the purposes of surveillance and referral (i.e., meet the criterion for a conversion), and this occurrence is important to note. However, not all of these HCWs may be considered candidates for treatment of LTBI, according to the individual medical and diagnostic evaluation. After an HCW has been classified as having a positive result or conversion for *M. tuberculosis* infection, additional testing is not necessary.

Treatment Regimens for LTBI

For persons suspected of having LTBI, treatment of LTBI should not begin until TB disease has been excluded. Persons highly suspected of having TB disease should receive the standard multidrug antituberculosis treatment regimen for TB disease until the diagnosis is confirmed or excluded. Standard regimens for the treatment of LTBI have been presented (Table 3); however, modifications to those regimens should be considered under certain circumstances, including HIV infection, suspected drug resistance, and pregnancy (*47,365*).

Reports of severe liver injury and death associated with the combination of rifampin and pyrazinamide (RZ) for treatment of LTBI (*366–368*) prompted the American Thoracic Society and CDC to revise previous recommendations (*39,53*) to indicate that RZ generally should not be offered for the treatment of LTBI (*240*). If the potential benefits substantially outweigh the demonstrated risk for severe liver injury and death associated with this regimen and the patient has no contraindications, a physician with experience treating LTBI and TB disease should be consulted before using this regimen (*246*). Clinicians should continue the appropriate use of rifampin and pyrazinamide in standard multidrug antituberculosis treatment regimens for the treatment of TB disease (*31*).

TABLE 3. Standard drug regimens for treatment of latent TB infection (LTBI)*

Drugs	Months of duration	Interval	Minimum no. of standard doses*
Isoniazid (INH)	9†	Daily	270
		Twice weekly	76
INH	6	Daily	180
		Twice weekly	52
Rifampin (RIF)	4	Daily	120
Rifampin/Pyrazinamide (RIF/PZA or RZ)	§	§	§

* **SOURCE:** American Thoracic Society, CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR 2000;49(No. RR-6).

†Nine months of INH is preferred, but 6 months of INH or 4 months of rifampin are acceptable alternatives.

§Generally should not be offered for treatment of LTBI. **SOURCE:** CDC. Update: adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection—United States, 2003. MMWR 2003;52:735–9.

For all regimens for treatment of LTBI, nonadherence to intermittent dosing (i.e., once or twice weekly) results in a larger proportion of total doses missed than daily dosing. DOT should be used for all doses during the course of treatment of LTBI whenever feasible. Collaborate with the local or state health department on decisions regarding DOT arrangements (*31*).

Contacts of patients with drug-susceptible TB disease. Persons with a previously negative TST or BAMT result who are contacts of patients with drug-susceptible TB disease and who subsequently have a positive TST result (≥5 mm) or positive BAMT result should be evaluated for treatment of LTBI, regardless of age. The majority of persons who are infected with *M. tuberculosis* will have a positive TST result within 6 weeks of exposure (*74,228,369–371*). Therefore, contacts of patients with drug-susceptible TB disease with negative TST (or BAMT) results should be retested 8–10 weeks after the end of exposure to a patient with suspected or confirmed TB disease. Persons infected with *M. tuberculosis* should be advised that they possibly can be reinfected with *M. tuberculosis* if re-exposed (*246,372–375*). Persons infected with HIV, persons receiving immunosuppressive therapy, regardless of TST result, and persons with a previous positive TST or BAMT result who are close contacts of a person with suspected or confirmed TB disease should be considered for treatment of LTBI.

The interpretation of TST results is more complicated in a contact investigation among HCWs who have negative baseline TST results from two-step testing but where the induration was >0 mm on the baseline TST or subsequent serial testing. Differences in the TST results between the contact investigation and previous baseline and serial TST could be a result of 1) inter-test variability in reaction size; 2) intervening exposure to NTM, BCG, or *M. tuberculosis*; and 3) reversion. In practice, TST, only inter-test variability and exposure to or infection with NTM or *M. tuberculosis* are likely.

Treatment of LTBI should not be started until a diagnosis of TB disease has been excluded. If uncertainty exists concerning the presence of TB disease because of an ambiguous chest radiograph, a standard multidrug antituberculosis treatment regimen can be started and adjusted as necessary based on the results of sputum cultures and the patient's clinical response (*31*). If cultures are obtained without initiating therapy, treatment for LTBI should not be initiated until all culture results are reported as negative.

Contacts of patients with drug-resistant TB disease. Treatment for LTBI caused by drug-resistant or MDR TB disease is complex and should be conducted in consultation with the local or state health department's infection-control program and experts in the medical management of drug-resistant TB. In certain instances, medical decision making for the person with LTBI will benefit from the results of drug susceptibility testing of the isolate of the index TB case. Treatment should be guided by susceptibility test results from the isolate to which the patient was exposed and presumed to be infected (*31,376,377*).

Pretreatment Evaluation and Monitoring of Treatment

The pretreatment evaluation of persons who are targeted for treatment of LTBI provides an opportunity for healthcare providers to 1) establish rapport with patients; 2) discuss details of the patient's risk for progression from LTBI to TB disease; 3) explain the benefits of treatment and the importance of adhering to the drug regimen; 4) review possible adverse effects of the regimen, including interactions with other medications; and 5) establish an optimal follow-up plan.

Monitoring for adverse effects of antituberculosis medications must be individualized. Persons receiving treatment for LTBI should be specifically instructed to look for symptoms associated with the most common reactions to the medications they are taking (*39*). Laboratory testing should be performed to evaluate possible adverse effects (*31,39*). Routine laboratory monitoring during treatment of LTBI is indicated for patients with abnormal baseline test results and for persons with a risk for hepatic disease. Baseline laboratory testing is indicated for persons infected with HIV, pregnant women, women in the immediate postpartum period (usually within 3 months of delivery), persons with a history of liver disease, persons who use alcohol regularly, and those who have or are at risk for chronic liver disease.

All patients being treated for LTBI should be clinically monitored at least monthly, including a brief clinical assessment conducted in the person's primary language for signs of hepatitis (e.g., nausea, vomiting, abdominal pain, jaundice, and yellow or brown urine). Patients receiving treatment for LTBI should be advised about the adverse effects of the drugs and the need for prompt cessation of treatment and clinical evaluation if adverse effects occur.

Because of the risk for serious hepatic toxicity and death, the use of the combination of RZ for the treatment of LTBI generally should not be offered. If RZ is used, a physician with experience treating LTBI and TB disease should be consulted before the use of this regimen. In addition, more extensive biochemical and clinical monitoring is recommended (*240*).

Treatment for TB Disease

Suspected or confirmed TB cases must be reported to the local or state health department in accordance with laws and regulations. Case management for TB disease should be coor-

dinated with officials of the local or state health department. Regimens for treatment of TB disease must contain multiple drugs to which the organisms are susceptible. For persons with TB disease, treatment with a single drug can lead to the development of mycobacterial resistance to that drug. Similarly, adding a single drug to a failing antituberculosis treatment regimen can lead to resistance to the added drug (*31*).

For the majority of patients, the preferred regimen for treating TB disease consists of an initiation 2-month phase of four drugs (INH, rifampin, pyrazinamide, and ethambutol) and at least a 4-month continuation phase of INH and rifampin (for a minimum total treatment of 6 months). Ethambutol may be discontinued if supporting drug susceptibility results are available. Completion of therapy is based on the number of doses taken within a maximal period and not simply 6 months (*31*). Persons with cavitary pulmonary TB disease and positive culture results of sputum specimens at the completion of 2 months of therapy should receive a longer (7-month continuation) phase because of the significantly higher rate of relapse (*31*).

TB treatment regimens might need to be altered for persons infected with HIV who are on ART (*49*). Whenever feasible, the care of persons with both TB disease and HIV infection should be provided by or in consultation with experts in the management of both TB and HIV-related disease (*31*). To prevent the emergence of rifampin-resistant organisms, persons with TB disease, HIV infection, and CD4 cell counts of <100 cells/mm^3 should not be treated with highly intermittent (i.e., once or twice weekly) regimens. These patients should receive daily treatment during the intensive phase by DOT (if feasible) and daily or three times weekly by DOT during the continuation phase (*378*). Detailed information on TB treatment for persons infected with HIV has been published and is available (http://www.dhfs.state.wi.us/AIDS-HIV/Resources/Overviews/AIDS_HIV.htm, http://www.hiv-druginteractions.org, and http://www.cdc.gov/nchstp/tb/TB_HIV_Drugs/TOC.htm) and published (*31,53*).

Drug-susceptibility testing should be performed on all initial isolates from patients with TB disease. When results from drug-susceptibility tests become available, the antituberculosis treatment regimen should be reassessed, and the drugs used in combination should be adjusted accordingly (*376,377,379–381*). If drug resistance is present, clinicians who are not experts in the management of patients with drug-resistant TB disease should seek expert consultation (*31*) and collaborate with the local or state health department for treatment decisions.

The major determinant of the outcome of treatment is adherence to the drug regimen. Therefore, careful attention should be paid to measures designed to enable and foster adherence (*31,319,382*). DOT is an adherence-enhancing strategy in which a trained HCW or other specially trained person watches a patient swallow each dose of medication and records the dates that the DOT was observed. DOT is the standard of care for all patients with TB disease and should be used for all doses during the course of therapy for TB disease and for LTBI, whenever feasible. Plans for DOT should be coordinated with the local or state health department (*31*).

Reporting Serious Adverse Events

HCWs should report serious adverse events associated with the administration of tuberculin antigen or treatment of LTBI or TB disease to the FDA MedWatch (Adverse Event Reporting System) [AERS], telephone: 800-FDA-1088, fax: 800-FDA-0178, http://www.fda.gov/medwatch. Report Form 3500, Physicians' Desk Reference. Specific instructions for the types of adverse events that should be reported are included in MedWatch report forms.

Surveillance and Detection of *M. tuberculosis* Infections in Health-Care Settings

In the United States, LTBI has been traditionally diagnosed on the basis of a positive PPD-based TST result after TB disease has been excluded. In vitro cytokine-based immunoassays for the detection of *M. tuberculosis* infection have been the focus of research and development. One such BAMT is QFT (which is PPD-based) and the subsequently developed version, QFT-G. QFT-G measures cell-mediated immune responses to peptides representative of two *M. tuberculosis* proteins that are not present in any BCG vaccine strain and are absent from the majority of nontuberculosis mycobacteria. This assay was approved by FDA in 2005 and is an available option for detecting *M. tuberculosis* infection. CDC recommendations for the United States on QFT and QFT-G have been published (*35*).

QFT-G is an in vitro test based on measuring interferon-gamma (IFN-γ) released in heparinized whole blood when incubated overnight with mitogen (serving as a positive control), Nil (i.e., all reagents except antigens, which sets a baseline), and peptide simulating ESAT-6 (6-kDa early secretory antigenic target) and CFP-10 (10-kDa culture filtrate protein) (measured independently), two different proteins with similar amino acid sequences specific for *M. tuberculosis* (Box 3). The sequences of ESAT-6 and CFP-10 are not related to each other. The genes encoding these two proteins are usually found next to each other in an operon (i.e., are coexpressed and translated from an mRNA product containing both genes). Although mycobacterial genomes contain multiple copies of each family, QFT-G and Elispot detect immunoreactivity associated only with the ESAT-6 protein

BOX 3. Interpretation of QuantiFERON®-TB Gold test (QFT-G) results

QFT-G result	Interpretation
Positive	
ESAT-6 or CFP-10* responsiveness detected	*Mycobacterium tuberculosis* infection probable
Negative	
No ESAT-6 and CFP-10 responsiveness detected	*M. tuberculosis* infection unlikely, but cannot be excluded, especially when 1. any illness is consistent with TB disease, and 2. the likelihood of progression to TB disease is increased (e.g., because of immunosuppression)
Indeterminate	Test not interpretable

* ESAT-6 is a 6-kDa early secretory antigenic target, and CFP-10 is 10-kDa culture filtrate protein.

and CFP-10 protein encoded by the genes in the region of deletion (RDI). In addition, virulence attributes are associated with the RD1 genes only and not the other homologues.

Specific antigens of these two proteins are found in *M. tuberculosis*–complex organisms (i.e., *M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microti*, *and M. canetti, M. caprae,* and *M. pinnipedii*), but not in the majority of other mycobacteria or in vaccine-variant *M. bovis*, BCG. Lymphocytes from the majority of persons who have been infected by *M. tuberculosis* complex indicate their sensitivity to ESAT-6 or CFP-10 by releasing IFN-γ, whereas infection by the majority of other mycobacteria, including BCG, does not appear to cause this sensitivity.

The blood tests using IFN-γ methods require one less patient visit, assess responsiveness to *M. tuberculosis* antigens, and do not boost anamnestic immune responses. Interpretation of the BAMT result is less subjective than interpretation of a skin test result, and the BAMT result might be affected less by previous BCG vaccination and sensitization to environmental mycobacteria (e.g., *M. avium* complex) than the PPD-based TST. BAMT might be more efficient and cost effective than TST (*35*). Screening programs that use BAMT might eliminate the need for two-step testing because this test does not boost sensitization.

Other cytokine-based immunoassays are under development and might be useful in the diagnosis of *M. tuberculosis* infection. Future FDA-approved products, in combination with CDC-issued recommendations, might provide additional diagnostic alternatives. For guidance on the use of these and related technologies, CDC plans to periodically publish recommendations on the diagnosis of *M. tuberculosis* infection. BAMT can be used in both testing and infection-control surveillance programs for HCWs.

Baseline Testing with BAMT

For the purposes of establishing a baseline, a single negative BAMT result is sufficient evidence that the HCW is probably not infected with *M. tuberculosis* (Box 1). However, cautions regarding making medical care decisions for persons whose conditions are at increased risk for progressing to TB disease from *M. tuberculosis* infection have been presented (Box 4).

If BAMT is used for baseline testing of HCWs, including those in settings that are low risk, one negative BAMT result is sufficient to demonstrate that the HCW is not infected with *M. tuberculosis* (Box 2). Perform and document the baseline BAMT result preferably within 10 days of starting employment. HCWs with positive baseline results should be referred for a medical and diagnostic evaluation to exclude TB disease and then treatment for LTBI should be considered in accordance with CDC guidelines. Persons with a positive BAMT result do not need to be tested again for surveillance. For HCWs who have indeterminate test results, providers should consult the responsible laboratorian for advice on interpreting the result and making additional decisions (*383*).

Serial Testing with BAMT for Infection-Control Surveillance

When using BAMT for serial testing, a conversion for administrative purposes is a change from a negative to a positive result (Box 2). For HCWs who have indeterminate test results, providers should consult the responsible laboratorian for advice on interpreting the result and making additional decisions (*383*). Persons with indeterminate results should not be counted for administrative calculations of conversion rates.

BOX 4. Conditions requiring caution in interpreting negative QuantiFERON®-TB Gold test results

- Human immunodeficiency virus infection or acquired immunodeficiency syndrome
- Immunosuppressive drugs, including those used for managing organ transplantation
- TNF*-α
- Diabetes mellitus
- Silicosis
- Chronic renal failure
- Certain hematological disorders (e.g., leukemias and lymphomas)
- Other specific malignancies (e.g., carcinoma of the head, neck, or lung)

* Tumor necrosis factor.

Exposure of HCWs and Patients to *M. tuberculosis*

Known and Presumed Exposure

For HCWs with known and presumed exposure to *M. tuberculosis*, administer a symptom screen and obtain the BAMT result. A BAMT conversion probably indicates recent *M. tuberculosis* infection; therefore, TB disease must be excluded. Experience with BAMT in contact investigations is limited. Specific attention is needed in the management of certain populations (e.g., infants and children aged <4 years and immunocompromised persons, including those who are HIV-infected) (Box 4).

If the symptom screen or the BAMT result is positive, the exposed person should be evaluated for TB disease promptly, which includes a chest radiograph. If TB disease is excluded, additional medical and diagnostic evaluation for LTBI is needed, which includes a judgment regarding the extent of exposure.

Performing QFT-G

The QFT-G should be performed as described in the product insert provided with the BAMT kit. This insert is also available from the manufacturer's website (http://www.cellestis.com).

Interpretation of BAMT Results and Referral for Evaluation

HCWs who meet the criteria for referral should have a medical and diagnostic evaluation (see Supplements, Estimating the Infectiousness of a TB Patient; Diagnostic Procedures for LTBI and TB Disease; and Treatment Procedures for LTBI and TB Disease). The factors affecting treatment decisions during medical and diagnostic evaluation by risk for infection with *M. tuberculosis* have been presented (Box 5). In addition, because BAMT and other indirect tests for *M. tuberculosis* infection are diagnostic aids, the test results must be interpreted in the context of epidemiologic, historical, physical, and diagnostic findings. A higher likelihood of infection, as estimated from historical or epidemiologic details (e.g., exposure to *M. tuberculosis*) or because of the presence of an illness consistent with TB disease, increases the predictive value of a positive result. Setting-based risk factors (e.g., the prevalence of TB disease in the setting) should be considered when making decisions regarding the diagnosis and treatment of LTBI.

Medical conditions that impair or alter immune function (Box 4) decrease the predictive value of a negative result, and additional diagnostic methods (e.g., bacteriology, radiography, and histology) are required as evidence before excluding *M. tuberculosis* infection when the BAMT result is negative. Medical evaluations can occur in different settings, including an occupational health clinic, local or state health department, hospital, or private medical clinic.

Indeterminate QFT-G results are reported for either of two test conditions.

- The IFN-γ responses to all antigens (ESAT-6, CFP-10, and mitogen) are below a cut-off threshold. The weak response to mitogen could be caused by nonstandard storage or transportation of the blood sample, by laboratory errors, or by lymphocytic insensitivity caused by immune dysfunction.

OR,

- The IFN-γ response to the Nil exceeds a specified threshold, and the responses to both ESAT-6 and CFP-10 do not exceed the response to Nil by at least 50%. This response could be caused by nonstandard storage or transportation, laboratory errors, or circulating IFN-γ, which can be increased in ill HCWs or patients. For HCWs who have indeterminate test results, providers should consult the responsible laboratorian for advice on interpreting the result and making further decisions (*383*).

Interpreting the BAMT Result for Infection Control and Surveillance

BAMT conversion rates should be determined routinely. The precision of the BAMT conversion rate will depend, in part, on the number of HCWs tested, which should be considered when establishing a regular interval for evaluation and monitoring of HCWs with BAMT. Health-care settings with a substantial number of HCWs might have testing schedules that can accurately determine the BAMT conversion rate each month (i.e., from annual results of an HCW cohort tested within the given month), if testing is staggered throughout the year. BAMT conversion rates are more difficult to calculate in settings with fewer test results.

BOX 5. Factors affecting treatment decisions during the medical and diagnostic evaluation, by tuberculin skin test (TST) result

TST result ≥5 mm is positive	TST result ≥10 mm is positive	TST result ≥15 mm is positive*
• Persons infected with HIV†	• Recent immigrants (i.e., within the previous 5 years) from countries with a high incidence of TB disease	• Persons with no known risk factors for TB disease
• Recent contacts of a person with tuberculosis (TB) disease	• Persons who inject illicit drugs	• HCWs who are otherwise at low risk for TB disease and who received baseline testing at the beginning of employment as part of a TB screening program**
• Persons with fibrotic changes on chest radiograph consistent with previous TB disease	• Residents and employees (including health-care workers [HCWs])** of the following congregate settings — hospitals and other health-care facilities — long-term–care facilities (e.g., hospices and skilled nursing facilities) — residential facilities for patients with AIDS†† or other immunocompromising conditions — correctional facilities — homeless shelters	
• Organ transplant recipients and other immunosuppressed persons (e.g., persons receiving ≥15 mg/day of prednisone for ≥1 month)§	• Mycobacteriology laboratory personnel	
• TB suspects¶	• Persons with any of the following clinical conditions or immunocompromising conditions that place them at high risk for TB disease — diabetes mellitus — silicosis — chronic renal failure — certain hematologic disorders (e.g., leukemias and lymphomas) — other specific malignancies (e.g., carcinoma of the head, neck, or lung) — unexplained weight loss of ≥10% of ideal body weight — gastrectomy — jejunoileal bypass	
	• Persons living in areas with high incidence of TB disease	
	• Children aged <4 years	
	• Infants, children, and adolescents exposed to adults at high risk for developing TB disease	
	• Locally identified groups at high risk	

* TST results ≥15 mm is positive in anyone. These persons should receive a symptom screen and do not need be tested again. They should be evaluated for TB disease, and if disease is excluded, they should be offered treatment for latent TB infection (LTBI) if they have no contraindication to treatment.

† Human immunodeficiency virus.

§ The risk for TB disease in persons treated with corticosteroids increases with higher doses and longer duration of corticosteroid use.

¶ Persons with suspected TB disease can be treated based on the medical and diagnostic evaluation, regardless of the TST results.

** For HCWs who are otherwise at low risk for LTBI and progression to TB disease if infected and who received baseline testing at the beginning of employment as part of a TB infection-control screening program, a TST result of ≥15 mm (instead of ≥10 mm) is considered to be positive. Although a result of ≥10 mm on baseline or follow-up testing is considered a positive result for HCWs for the purposes of referral for medical and diagnostic evaluation, if the TST result is 10–14 mm on baseline or follow-up testing, the referring clinician might not recommend treatment of LTBI. **SOURCE:** Marsh BJ, SanVicente J, vonReyn F. Utility of dual skin tests to evaluate tuberculin skin test reactions of 10 to 14 mm in health-care workers. Infect Control Hosp Epidemiol 2003;24:821–4.

†† Acquired immunodeficiency syndrome.

QC Program for the BAMT

Multiple processes are necessary to assure quality BAMT results: specimen collection, transport and handling, and conducting the test in the laboratory. BAMT must meet performance parameters for a valid test result to be achieved. QC is an ongoing laboratory issue. The infection-control team should assist the laboratory in assuring that all requisite conditions are present. The laboratory performing the BAMT will be required to validate its performance of the test before processing clinical samples. State and federal laboratory requirements regulate laboratory-testing procedures.

Additional Considerations

An indeterminate QFT-G result does not mean that the test has failed; it indicates that the specimen has inadequate responsiveness for the test to be performed. This result might reflect the condition of the HCW or patient, who, for example, might be immunosuppressed. Alternatively, the specimen might have been handled incorrectly. For HCWs who have indeterminate test results, providers should consult the responsible laboratorian for advice on interpreting the result and making further decisions (*383*). Skin testing for cutaneous anergy is not useful in screening for asymptomatic LTBI or for diagnosing TB disease (*339*).

QFT-G use with HIV-infected persons taking ART. The effect of HIV infection and of ART on the performance of the QFT-G have not been fully evaluated.

Persons aged <17 years or pregnant women. The use of the QFT-G has not been evaluated in persons aged <17 years or pregnant women (*35*).

Booster phenomenon and BAMT. BAMT does not involve the injection of any substance into the persons being tested and is not affected by the booster phenomenon.

BCG vaccination. In the United States, vaccination with BCG is not routinely recommended (*227*). However, BCG is the most commonly used vaccine in the world. Foreign-born persons are commonly employed in the United States as HCWs. Previous BCG vaccination is not a contraindication to having a BAMT performed. BCG does not influence BAMT results with the version of the test approved in 2005 (i.e., QFT-G). HCWs who have received BCG vaccination should receive a baseline BAMT in the same manner as those without BCG vaccination, and the test result should be interpreted without reference to BCG.

Environmental Controls

Overview

Environmental controls include the following technologies to remove or inactivate *M. tuberculosis*: local exhaust ventilation, general ventilation, HEPA filtration, and UVGI. These controls help to prevent the spread and reduce the concentration of airborne infectious droplet nuclei. Environmental controls are the second line of defense in the TB infection-control program, and they work in harmony with administrative controls.

The reduction of occupational exposures to *M. tuberculosis* can be facilitated through the effective use of environmental controls at the source of exposure (e.g., coughing patient or laboratory specimen) or in the general workplace environment. Source control is amenable to situations where the source has been identified and the generation of the contaminant is localized. Source-control techniques can prevent or reduce the spread of infectious droplet nuclei into the air by collecting infectious particles as they are released. These techniques are especially critical during procedures that will probably generate infectious aerosols (e.g., bronchoscopy, sputum induction, endotracheal intubation, suctioning, irrigating TB abscesses, aerosol treatments, autopsies on cadavers with untreated TB disease, and certain laboratory specimen manipulations) and when patients with infectious TB disease are coughing or sneezing.

Unsuspected and undiagnosed cases of infectious TB disease are believed to represent a substantial proportion of the current risk to HCWs (*10,85*). In such situations, source control is not a feasible option. Instead, general ventilation and air cleaning must be relied upon for control. General ventilation can be used to dilute the air and remove air contaminants and to control airflow patterns in rooms or in a health-care setting. Air-cleaning technologies include HEPA filtration to reduce the concentration of *M. tuberculosis* droplet nuclei and UVGI to kill or inactivate the microorganisms so that they no longer pose a risk for infection.

Ventilation systems for health-care settings should be designed, and modified when necessary, by ventilation engineers in collaboration with infection-control practitioners and occupational health staff. Recommendations for designing and operating ventilation systems have been published (*117,118,178*). The multiple types and conditions for use of ventilation systems in health-care settings and the needs of persons in these settings preclude the provision of extensive guidance in this document.

The information (see Environmental Controls; and Supplement, Environmental Controls) is conceptual and intended to educate HCWs regarding environmental controls and how these controls can be used in the TB infection-control program. This information should not be used in place of consultation with experts who can give advice on ventilation system design, selection, installation, and maintenance. Because environmental controls will fail if they are not properly operated and maintained, routine training and education of staff are key components to a successful TB infection-control

program. These guidelines do not specifically address mechanical ventilators in detail (see Intensive Care Units [ICUs]).

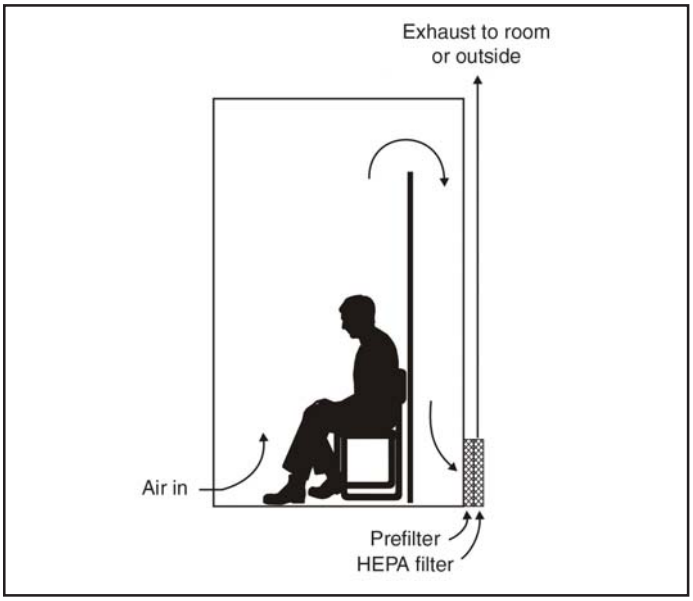
Local Exhaust Ventilation

Local exhaust ventilation captures airborne contaminants at or near their source and removes the contaminants without exposing persons in the area to infectious agents. This method is considered the most efficient way to remove airborne contaminants because it captures them before they can disperse. In local exhaust devices, hoods are typically used. Two types of hoods are 1) enclosing devices, in which the hood either partially or fully encloses the infectious source; and 2) exterior devices, in which the infectious source is near but outside the hood. Fully enclosed hoods, booths, or tents are always preferable to exterior devices because of their superior ability to prevent contaminants from escaping into the HCW's breathing space. Descriptions of both enclosing and exterior devices have been published (*178*).

Enclosing Devices

Enclosing devices for local exhaust ventilation include 1) booths for sputum induction or administration of aerosolized medications (see Environmental Controls; Figure 2), 2) tents or hoods for enclosing and isolating a patient, and 3) BSCs (*165*). These devices are available in various configurations. The simplest device is a tent placed over the patient; the tent has an exhaust connection to the room-discharge exhaust system. The most complex device is an enclosure with a self-contained airflow and recirculation system (see Environmental Controls; Figure 2).

FIGURE 2. An enclosing booth designed to sweep air past a patient with tuberculosis disease and collect the infectious droplet nuclei on a high efficiency particular air (HEPA) filter



Tents and booths should have sufficient airflow to remove at least 99% of airborne particles during the interval between the departure of one patient and the arrival of the next (see Environmental Controls; Table 1). The time required to remove 99% or 99.9% of airborne particles from an enclosed space depends on 1) the number of ACH, which is a function of the volume (number of cubic feet of air) in the room or booth and the rate at which air is exiting the room or booth at the intake source; 2) the location of the ventilation inlet and outlet; and 3) the configuration of the room or booth. The surfaces of tents and booths should be periodically cleaned in accordance with recommendations and guidance from the manufacturers (see Supplement, Cleaning, Disinfecting, and Sterilizing Patient-Care Equipment and Rooms).

Exterior Devices

Exterior devices for local exhaust ventilation are usually hoods that are near to but not enclosing an infectious patient. The airflow produced by these devices should be sufficient to prevent cross-currents of air near the patient's face from allowing droplet nuclei to escape. Whenever possible, the patient should face directly into the opening of the hood to direct any coughing or sneezing into the hood. The device should maintain an air velocity of 200 feet per minute (fpm) at the patient's breathing zone to ensure the capture of droplet nuclei. Smoke tubes should be used to verify that the control velocity at the typical location of the patient's breathing zone is adequate to provide capture for the condition of highest expected cross-drafts and then the patient's breathing zone should be maintained at this location for the duration of the treatment.

Discharge of Exhaust from Booths, Tents, and Hoods

Air from booths, tents, and hoods is either discharged into the room in which the device is located or to the outside. If the exhaust air is discharged into the room, a HEPA filter should be incorporated at the discharge duct or vent of the device. The exhaust fan should be located on the discharge side of the HEPA filter to ensure that the air pressure in the filter housing and booth is negative compared with adjacent areas. Uncontaminated air from the room will flow into the booth through all openings, preventing infectious droplet nuclei in the booth from escaping into the room. Additional information on the installation, maintenance, and monitoring of HEPA filters is included in this report (Appendix A).

The majority of commercially available booths, tents, and hoods are fitted with HEPA filters; additional HEPA filtration is not needed with these devices. If a device does not

incorporate a HEPA filter, the air from the device should be exhausted directly to the outside and away from air-intake vents, persons, and animals, in accordance with applicable federal, state, and local regulations on environmental discharges.

General Ventilation

General ventilation is used to 1) dilute and remove contaminated air, 2) control the direction of airflow in a health-care setting, and 3) control airflow patterns in rooms.

Dilution and Removal of Contaminated Air

General ventilation maintains air quality by both air dilution and removal of airborne contaminants. Uncontaminated supply air mixes with contaminated room air (dilution), and air is subsequently removed from the room by the exhaust system (removal). These processes reduce the concentration of droplet nuclei in the room air.

Ventilation systems for air dilution and removal. Two types of general ventilation systems are used to dilute and remove contaminated air: single-pass air systems and recirculating air systems.

In a single-pass air system, the supply air is either outside air that has been heated or cooled or air that is uncontaminated from a central system that supplies multiple areas. After air passes through the room or area, 100% of the air is exhausted to the outside. A single-pass system is the preferred choice for an AII room because the system prevents contaminated air from being recirculated to other areas of the health-care setting. In a recirculating air system, a limited portion of the exhaust air is discharged directly to the outside and replaced with fresh outside air, which mixes with the portion of exhaust air that was not discharged. If the resulting air mixture is not treated, it can contain a substantial proportion of contaminated air when it is recirculated to areas serviced by the system. This air mixture can be recirculated into the general ventilation, and infectious particles can be carried from contaminated areas to uncontaminated areas. Alternatively, the air mixture could be recirculated in a specific room or area so that other areas are not affected. The use of air-cleaning technologies for removing or inactivating infectious particles in recirculated air systems has been discussed (Appendix A).

Delivery of general ventilation. General ventilation is delivered by either constant air volume (CAV) systems or VAV systems. In general, CAV systems are best for AII rooms and other negative-pressure rooms because the negative-pressure differential is easier to maintain. VAV systems are acceptable if provisions are made to maintain the minimum mechanical and outside ACH and a negative pressure $\geq$0.01 inch of water gauge compared with adjacent areas at all times.

Ventilation rates. Recommended ventilation rates (air change rates) for health-care settings are usually expressed in numbers of ACH, which is the ratio of the volume of air entering the room per hour to the room volume. ACH equals the exhaust airflow (Q cubic feet per minute [cfm]) divided by the room volume (∀ cubic feet) multiplied by 60.

$$ACH = (Q \div \forall) \times 60$$

Ventilation recommendations for selected areas in new or renovated health-care settings have been presented (Table 2). These recommendations have been adapted from those published by AIA (*118*). The feasibility of achieving a specific ventilation rate depends on the construction and operational requirements of the ventilation system and might differ for retrofitted and newly constructed facilities. The expense and effort of achieving a high ventilation rate might be reasonable for new construction but less reasonable when retrofitting an existing setting.

In existing settings, air-cleaning technologies (e.g., fixed or portable room-air recirculation units [also called portable air cleaners] or UVGI) can be used to increase the equivalent ACH. This equivalent ventilation concept has been used to compare microbial inactivation by UVGI with particle-removal by mechanical ventilation (*384,385*) and to compare particle removal by HEPA filtration of recirculated air with particle removal by mechanical ventilation. The equivalent ventilation approach does not, however, negate the requirement to provide sufficient fresh outside air for occupant comfort (see Supplement, Environmental Controls; Table 2).

To dilute the concentration of normal room-air contaminants and minimize odors, a portion of the supply air should come from the outdoors (see Supplement, Environmental Controls, Table 2). Health-care settings should consult the American Society of Heating, Refrigerating, and Air-Conditioning Engineers, Inc. (ASHRAE), Standard 62.1, Ventilation for Acceptable Indoor Air Quality, for outside air recommendations in areas not listed in this report (*386*).

Control of Airflow Direction in a Health-Care Setting

Airflow direction is controlled in health-care settings to contain contaminated air and prevent its spread to uncontaminated areas.

Directional airflow. The general ventilation system should be designed and balanced so that air flows from less contaminated (more clean) to more contaminated (less clean) areas (*118,117*). For example, air should flow from corridors (cleaner areas) into AII rooms (less clean areas) to prevent the spread of contaminants. In certain rooms in which surgical and invasive procedures are performed and in protective environment (PE) rooms, the direction of airflow should be from the room

to the hallway. Environmental control recommendations for situations involving the care and treatment of patients with TB disease in ORs and PE rooms have been presented (see Other Selected Settings). Cough-inducing or aerosol-generating procedures should not be performed on patients with suspected or confirmed TB disease in rooms where air flows from the room to the hallway.

Negative pressure for achieving directional airflow. The direction of airflow is controlled by creating a lower (negative) pressure in the area into which the flow of air is desired. Negative pressure is the approximate air-pressure difference between two areas in a health-care setting. For air to flow from one area to another, the air pressure in the two areas must be different. Air will flow from a higher pressure area to a lower pressure area. A room that is under negative pressure has a lower pressure than adjacent areas, which keeps air flowing from the adjacent rooms or areas into the room. Negative pressure is achieved by exhausting air at a higher volumetric rate than the rate that the air is being supplied.

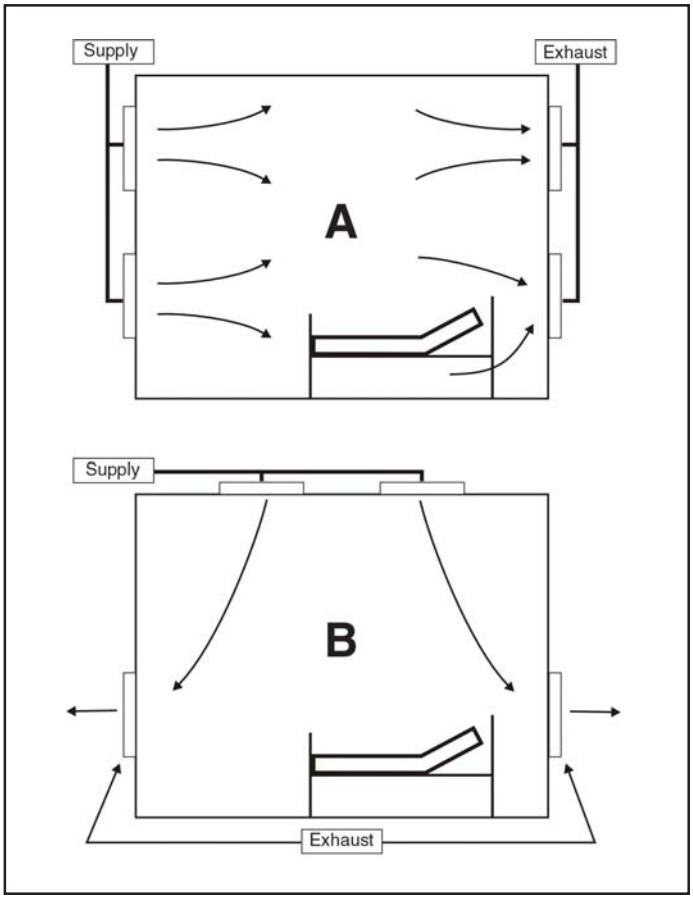
Control of Airflow Patterns in Rooms

General ventilation systems should be designed to provide controlled patterns of airflow in rooms and to prevent air stagnation or short-circuiting of air from the supply to the exhaust (i.e., passage of air directly from the air supply to the exhaust). To provide controlled airflow patterns, the air supply and exhaust should be located so that clean air flows first to parts of the room where HCWs probably work and then across the infectious source and into the exhaust. Therefore, HCWs are not positioned between the infectious source and the exhaust. This configuration is not always possible but should be used whenever feasible.

One way to achieve a controlled airflow pattern is to supply air at the side of the room opposite the patient and exhaust it from the side where the patient is located (see Environmental Controls; Figure 3). Another method, which is most effective when the supply air is cooler than the room air, is to supply air near the ceiling and exhaust it near the floor (see Supplements, Environmental Controls; Figure 3). Care must be taken to ensure that furniture or moveable equipment does not block the low exhausts. Airflow patterns are affected by air temperature differentials, location of the supply diffusers and exhaust grilles, location of furniture, movement of HCWs and patients, and the configuration of the space.

If the room ventilation is not designed for a plug-flow type of airflow pattern (Figure 3), then adequate mixing must be maintained to minimize air stagnation. The majority of rooms with properly installed supply diffusers and exhaust grilles will have adequate mixing. A qualitative measure of mixing is the visualization of air movement with smoke tubes at multiple locations in the room. Smoke movement in all areas of the room indicates good mixing. Additional sophisticated studies can be conducted by using a tracer gas to quantify air-mixing and air-exchange rates.

FIGURE 3. Room airflow patterns designed to provide mixing of air and prevent short-circuiting*



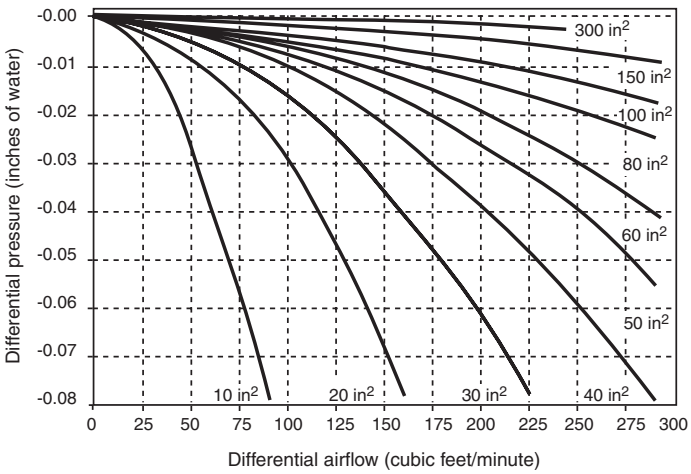
* Short-circuiting is the passage of air directly from the air supply to the exhaust.

If areas of air stagnation are present, air mixing can be improved by adding a circulating fan or repositioning the supply and exhaust vents. Room-air recirculation units positioned in the room or installed above the ceiling can also improve air mixing. If supply or exhaust vents circulating fans or room-air recirculation units are placed incorrectly, HCWs might not be adequately protected.

Achieving Negative Pressure in Rooms

Negative pressure is needed to control the direction of airflow between selected rooms in a health-care setting and their adjacent spaces to prevent contaminated air from escaping from the room into other areas (*118*) (Figure 4). Control of a room's differential airflow and total leakage area is critical to achieving and maintaining negative pressure. Differential air-

FIGURE 4. Empirical relation between differential airflow, differential pressure, and leakage areas*



* Black solid lines indicate leakage areas. **SOURCE:** Hayden II CS, Fischbach TJ, Johnston OE, Hughes RT, Jensen PA. A model for calculating leakage areas into negative pressure isolation rooms. Cincinnati, OH: US Department of Health and Human Services, CDC; 1996.

flow, differential pressure, and leakage area are interrelated. This relation is illustrated (Figure 4) and is expressed in an empirical equation (*387*).

$$A_E = 0.01138 * (\Delta Q^{1.170}/\Delta P^{0.602})$$

In the equation, AE is the leakage area in square inches; DQ is the differential airflow rate in cfm; and DP is the differential pressure drop in inches of water gauge. This empirical equation was used (Figure 4), which indicates that changing one parameter will influence one or both of the other parameters. For example, the control of differential pressure can frequently be improved by increasing the air tightness or seal of a room, HVAC system, and ensuring continuous monitoring. In a room that is already substantially tight (e.g., with 10 square inches of leakage), however, a small change in differential pressure will have a substantial affect on differential airflow. Similarly, a room with a more substantial leakage area (e.g., 300 square inches of leakage) requires a higher differential airflow rate to achieve a pressure differential of 0.01 inch of water gauge. Reducing the leakage in a room with 300 square inches of leakage can help achieve a pressure differential of 0.01 inch of water gauge (Figure 4). If the leakage area is reduced to approximately 40 square inches, a pressure differential of 0.01 inch of water gauge can be achieved by exhausting approximately 100 cubic feet per minute (cfm) more air from the room than is supplied to the room.

Room leakage can occur through cracks or spaces near doors, windows, ceiling, and utility connections. Steps should be taken to minimize these leaks. Changes in the performance of the HVAC system will affect the pressure differential in a room and can potentially cause a negative-pressure room to become positive-pressure. Therefore, each of these parameters requires close monitoring to ensure that minor changes in the performance of the HVAC system do not adversely affect the entire system (*388,389*).

Pressure differential. To achieve negative pressure in a room that has a normally functioning ventilation system, first measure and balance the supply and exhaust airflows to achieve an exhaust flow higher than the supply flow. Next, measure the pressure differential across the closed door. Although the minimum pressure difference needed for airflow into a room is substantially small (regarding 0.001 inch of water gauge), a pressure differential of ≥0.01 inch of water gauge (2.5 Pascals [Pa]) is recommended. This higher pressure differential is easier to measure and offers a margin of safety for maintaining negative pressure as the pressure in surrounding areas changes because of the opening and closing of doors, operation of elevators, stack effect (rising of warm air, similar to a chimney), ventilation system fluctuations, and other factors. The higher pressurization value is consistent with the most recent AIA recommendations for airborne precautions in health-care settings (*118*) and is the generally accepted level of negative pressurization for microbiology and biomedical laboratories (*390*).

Opening doors and windows can substantially affect the negative pressure in an AII room. Infection-control criteria requires AII room windows and doors to remain closed, except when doors must be opened for persons to enter or leave the room. Keeping certain doors in the corridor outside the AII rooms closed might be necessary to maintain the negative-pressure differential between an AII room and the corridor. Pressurization cannot be maintained in rooms or spaces that are not enclosed.

If ≥0.01 inch of water gauge is not achieved and cannot be achieved by increasing the flow differential (within the limits of the ventilation system), the room should be inspected for leakage. The total room leakage is based on the previously measured pressure, and air flow differentials can be estimated (Figure 4). If the room leakage is too substantial (e.g., 300 square inches), maintaining a negative-pressure differential as high as 0.01 inch of water gauge might be difficult. A lower value is acceptable if air-pressure monitoring indicates that negative pressure is always maintained (or airflow indicators consistently demonstrate that air is flowing in the desired direction). If negative pressure cannot be maintained, the leakage area might need to be reduced by sealing cracks around windows or replacing porous suspended ceiling panels with gasketed or sealed solid panels.

Because negative pressure in an AII room can be affected by even minimal changes in the operation of the ventilation sys-

tem, negative pressure can be difficult to maintain with a VAV ventilation system. To maintain negative pressure, a VAV supply system should be coupled with a compensating exhaust system that increases when the supply flow rate increases. Alternatively, the exhaust can be set at a fixed rate that ensures negative pressure throughout the VAV supply cycle. The VAV minimum flow rate must also be adequate to maintain the recommended minimum mechanical and outdoor ACH (see Supplement, Environmental Controls; Table 2).

Alternate methods for achieving negative pressure. An anteroom is not a substitute for negative pressure in an AII room. However, an anteroom can reduce the escape of droplet nuclei during the opening and closing of the door to an AII room and can buffer an AII room from pressure fluctuations in the corridor. To function properly, an anteroom must have more air exhausted from the room than supplied to remove *M. tuberculosis* that can enter from the AII room. An anteroom can also have its own supply diffuser, if needed, to balance the pressure with the corridor. If an anteroom is unventilated or not properly ventilated, it will function only as a lesser contaminated vestibule between the AII room and the corridor and might not prevent the escape of droplet nuclei into the corridor. To adjust airflow and pressure differentials, health-care settings should consult a ventilation engineer who is knowledgeable regarding all applicable regulations, including building fire codes.

If the desired negative pressure cannot be achieved because a room does not have a separate ventilation system or a system that can provide the proper airflow, steps should be taken to provide a method to discharge air from an AII room. One method to achieve negative pressure in a room is to add a supplemental exhaust unit. If an AII room has a window or an outside wall, a small exhaust fan can be used. An engineer should be consulted to evaluate the potential for negative effects on surrounding areas (e.g., disruption of exhaust airflow in adjoining bathrooms) and to ensure the provision of the recommended amounts of outdoor air. The exhaust must not be discharged where it can immediately re-enter the building or pose a hazard to persons outside.

Fixed room-air recirculation systems (i.e., systems that recirculate the air in an entire AII room) can be designed to achieve negative pressure by discharging a portion of the air to the outside. Some portable room-air recirculation units are also designed to discharge air to the outside to achieve negative pressure. These air cleaners must be designed specifically for this purpose.

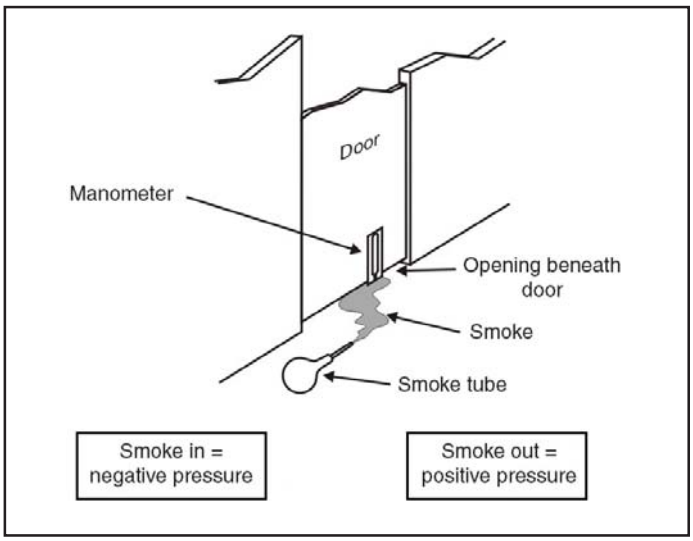
Monitoring negative pressure. Negative pressure must be monitored to ensure that air is always flowing from the corridor (or surrounding area) into the AII room. Negative pressure can be monitored either continuously or periodically. Monitoring methods include chemical aerosols (e.g., smoke tube), differential pressure-sensing devices (e.g., manometer), and physical indicators (e.g., flutter strips).

A chemical aerosol resembling smoke can be used to observe airflow between a room and the surrounding area, or within a room. Devices called smoke tubes generate the chemical aerosol resembling smoke, which follows the local air currents wherever it is released. To check the negative pressure in a room, hold a smoke tube approximately 2 inches in front of the base of the closed door of the AII room or in front of the air transfer grille, if the door has such a feature. Hold the smoke tube parallel to the door. A small amount of smoke should be generated slowly to ensure that the velocity of smoke emanating from the tube does not overpower the air velocity (see Supplement, Environmental Controls; Figure 5). If the room is under negative pressure, the smoke will travel into the room (from higher to lower pressure). If the room is not under negative pressure, the smoke will be blown outward or stay in front of the door. Room air cleaners in the room should be operating. Persons using smoke tubes should avoid inhaling the smoke, because direct inhalation of high concentrations of the smoke can be irritating (*391*) (Figure 5).

Manometers are used to monitor negative pressure. They provide either periodic (noncontinuous) pressure measurements or continuous pressure monitoring. A continuous monitoring indicator can simply be a visible or audible warning signal indicating that air pressure is positive. Both periodic and continuous pressure detectors generate a digital or analog signal that can be recorded for later verification or used to automatically adjust the room's ventilation control system.

Physical indicators (e.g., flutter strips) are occasionally used to provide a continuous visual sign that a room is under nega-

FIGURE 5. Smoke tube testing and manometer placement to determine the direction of airflow into and out of a room



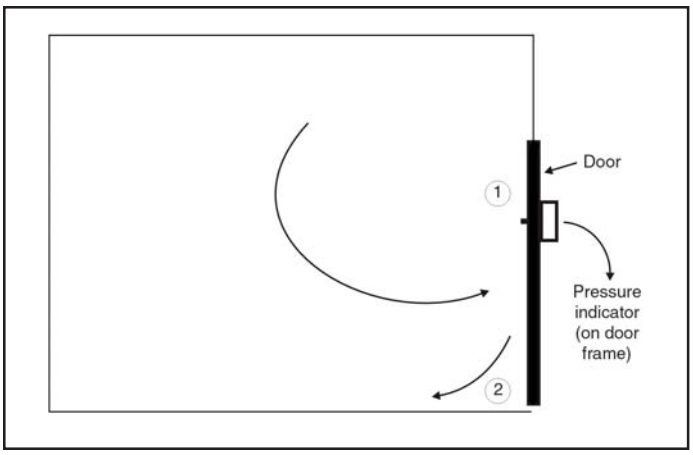
tive pressure. These simple and inexpensive devices are placed directly in the door and can be useful in identifying a pressure differential problem.

Pressure-measuring devices should sense the pressure just inside the airflow path into the AII room (e.g., at the base of the door). Unusual airflow patterns can cause pressure variations. For example, the air can be under negative pressure at the middle of a door and under positive pressure at the base of the same door. The ideal location of a pressure-measuring device has been illustrated (Figure 6). If the pressure-sensing ports of the device cannot be located directly across the airflow path, validating that the negative pressure at the sensing point is and remains the same as the negative pressure across the flow path might be necessary.

Pressure-sensing devices should incorporate an audible warning with a time delay to indicate an open door. When a door is open, the negative pressure cannot be maintained, but this situation should not generate an alarm unless the door is left open. Therefore, the time delay should allow adequate time for persons to enter or leave an AII room without activating the alarm.

The pressure differentials used to achieve low negative pressure (<0.005 inch) require the use of substantially sensitive mechanical devices, electronic devices, or pressure gauges to ensure accurate measurements. Pressure-measuring and monitoring devices can give false readings if the calibration has drifted. For example, a sensor might indicate that the room pressure is slightly negative compared with the corridor, but, because air current momentum effects or "drift" of the electrical signal, air might actually be flowing out of the AII room through the opening at the base of the door. In one study of 38 AII rooms with electrical or mechanical devices to continuously monitor air pressurization, one half had airflow at the door in the opposite direction of that indicated by the continuous monitors (*392*). The investigators attributed this problem to instrument limitations and device malfunction. A negative pressure differential of ≥0.01 inch of water gauge (compared with the previously recommended 0.001 inch of water gauge) might help to minimize this problem.

FIGURE 6. Cross-sectional view of a room indicating the location of negative pressure measurement*



* Airflow pressure at location 1 might differ from that at location 2. Measure pressure at location 2 for correct indication of negative pressure.

Periodic checks are required to maintain the desired negative pressure and the optimal operation of monitoring devices.

- AII rooms should be checked for negative pressure before occupancy.
- When occupied by a patient, an AII room should be checked daily with smoke tubes or other visual checks for negative pressure.
- If pressure-sensing devices are used in AII rooms occupied by patients with suspected or confirmed TB disease, negative pressure should be checked daily by using smoke tubes or other visual checks.
- If the AII rooms are not being used for patients who have suspected or confirmed TB disease but potentially could be used for such patients, the negative pressure should be checked monthly.
- Laboratories should be checked daily for negative pressure.

AII Rooms and Other Negative-Pressure Rooms

AII rooms are used to 1) separate patients who probably have infectious TB from other persons, 2) provide an environment in which environmental factors are controlled to reduce the concentration of droplet nuclei, and 3) prevent the escape of droplet nuclei from such rooms into adjacent areas using directional airflow. Other negative-pressure rooms include bronchoscopy suites, sputum induction rooms, selected examination and treatment rooms, autopsy suites, and clinical laboratories.

Preventing the escape of droplet nuclei. AII rooms used for TB isolation should be single-patient rooms with negative pressure, compared with the corridor or other areas connected to the room. Opening doors and windows can substantially affect the negative pressure in an AII room. Infection-control criteria require AII room windows and doors to remain closed, except when doors must be opened for persons to enter or leave the room. It might also be necessary to keep certain doors in the corridor outside the AII rooms closed and also might be necessary to maintain the negative-pressure differential between an AII room and the corridor. The use of self-closing doors is recommended. The openings in the room (e.g., windows, and electrical and plumbing entries) should be sealed as much as possible, with the exception of a small gap (1/8–1/2 inch) at the base of the door to provide a controlled airflow path. Proper use of negative pressure will prevent contaminated air from escaping the room (*393,394*).

Reducing the concentration of droplet nuclei. AII rooms in existing health-care settings should have an airflow of ≥6 mechanical ACH. Whenever feasible, this airflow rate should be increased to ≥12 mechanical ACH by adjusting or modifying the ventilation system or should be increased to ≥12 equivalent ACH by supplementing with air-cleaning technologies (e.g., fixed or portable room-air recirculation systems or UVGI systems). New construction or renovation of existing health-care settings should be designed so that AII rooms achieve a total air change rate of ≥12 mechanical ACH. These recommendations are consistent with guidelines by ASHRAE and AIA that recommend ≥12 mechanical ACH for AII rooms (*117,118)*. Ventilation recommendations for other negative-pressure rooms in new or renovated health-care settings have been presented (see Risk Classification Examples).

To dilute the concentration of normal room air contaminants and minimize odors, a portion of the supply air should come from the outdoors. A minimum of 2 ACH of outdoor air should be provided to AII rooms and other negative-pressure rooms (*117,118*).

Exhaust from AII rooms and other negative-pressure rooms. Air from AII rooms and other negative-pressure rooms for patients with suspected or confirmed TB disease should be exhausted directly to the outside and away from air-intake vents, persons, and animals, in accordance with applicable federal, state, and local regulations on environmental discharges. Exhaust ducts should be located away from areas (e.g., sidewalks or windows that can be opened). Ventilation system exhaust discharges and inlets should be designed to prevent the re-entry of exhausted air. Wind blowing over a building creates a substantially turbulent recirculation zone that can cause exhausted air to re-enter the building. Exhaust flow should be discharged above this zone. Design guidelines for proper placement of exhaust ducts have been published (*395*). If recirculation of air from such rooms into the general ventilation system is unavoidable, the air should be passed through a HEPA filter before recirculation.

Alternatives to negative-pressure rooms. AII can also be achieved by the use of negative-pressure enclosures (e.g., tents or booths). These enclosures can provide patient isolation in EDs and medical testing and treatment areas and can supplement AII in designated negative-pressure rooms.

Other Selected Settings

Operating rooms, autopsy suites, sputum-induction rooms, and aerosolized treatment rooms pose potential hazards from infectious aerosols generated during procedures on patients with TB disease (*72,90,396–398*). Recommended administrative, environmental, and respiratory-protection controls for these and other selected settings have been summarized (Appendix B). Additional or specialized TB infection controls that are applicable to special circumstances and types of health-care delivery settings have also been described (see Managing Patients Who Have Suspected or Confirmed TB Disease: Considerations for Special Circumstances and Settings). Ventilation recommendations for these settings in new or renovated health-care facilities have been included in this report (Table 2). Existing facilities might need to augment the current ventilation system or use the air-cleaning methods to increase the number of equivalent ACH.

Patients with TB disease who also require a PE room (e.g., severely immunocompromised patients) are special cases. These patients require protection from common airborne infectious microorganisms and must be placed in a room that has HEPA-filtered supply air and is under positive pressure compared with its surroundings (*118*). If an anteroom is not available, the use of other air-cleaning methods should be considered to increase the equivalent ACH. The air-cleaning systems can be placed in the room and in surrounding areas to minimize contamination of the surroundings. Similar controls can be used in ORs that are used for patients with TB disease because these rooms must be maintained under positive pressure, compared with their surroundings to maintain a sterile field.

Air-Cleaning Methods

HEPA Filtration

HEPA filtration can be used to supplement other recommended ventilation measures by providing a minimum removal efficiency of 99.97% of particles equal 0.3 µm in diameter. This air-cleaning method is considered an adjunct to other ventilation measures. Used alone, this method neither provides outside air for occupant comfort nor satisfies other recommended ventilation measures (e.g., using source control whenever possible and minimizing the spread of contaminants in a setting through control of airflow patterns and pressure differentials).

HEPA filters have been demonstrated to reduce the concentration of *Aspergillus* spores (range in size: 5–6 µm) to below measurable levels (*399–401*). Because infective droplet nuclei generated by TB patients are believed to range from 1–5 µm in diameter (*300*) (comparable in size to Aspergillus spores) (*402*), HEPA filters will remove *M. tuberculosis*–containing infectious droplet nuclei from contaminated air. HEPA filters can be used to clean air before it is 1) exhausted to the outside, 2) recirculated to other areas of a health-care setting, or 3) recirculated in an AII room. Because electrostatic filters can degrade over time with exposure to humid environments and ambient aerosols (*403*), their use in sys-

tems that recirculate air back into the general ventilation system from AII rooms and treatment rooms should be avoided. If used, the filter manufacturer should be consulted regarding the performance of the filter to ensure that it maintains the desired filtration efficiency over time and with loading.

Use of HEPA filtration when exhausting air to the outside. HEPA filters can be used as an added safety measure to clean air from AII rooms and local exhaust devices (e.g., booths, tents, and hoods) before exhausting it to the outside. This added measure is not necessary, however, if the exhaust air cannot re-enter the ventilation system supply and does not pose a risk to persons and animals where it is exhausted.

Exhaust air frequently is not discharged directly to the outside; instead, the air is directed through heat-recovery devices (e.g., heat wheels or radiator-like devices). Heat wheels are frequently used to reduce the costs of operating ventilation systems (*404*). As the wheel rotates, energy is transferred into or removed from the supply inlet air stream. If a heat wheel is used with a system, a HEPA filter should also be used. The HEPA filter should be placed upstream from the heat wheel because of the potential for leakage across the seals separating the inlet and exhaust chambers and the theoretical possibility that droplet nuclei might be impacted on the wheel by the exhaust air and subsequently stripped off into the supply air.

Recirculation of HEPA-filtered air. Air from AII rooms and other negative-pressure rooms should be exhausted directly to the outside. In certain instances, however, recirculation of air into the general ventilation system from such rooms is unavoidable (e.g., settings in which the ventilation system or building configuration causes venting the exhaust to the outside impossible). In such cases, HEPA filters should be installed in the exhaust duct exiting the room to remove infectious organisms from the air before it is returned to the general ventilation system.

Person room-air recirculation can be used in areas in which no general ventilation system exists, where an existing system is incapable of providing sufficient ACH, or where air-cleaning (particulate removal) is desired without affecting the fresh air supply or negative-pressure system. Recirculation of HEPA-filtered air in a room can be achieved by 1) exhausting air from the room into a duct, passing it through a HEPA filter installed in the duct, and returning it to the room (see Supplement, Environmental Controls; Figure 7); *2*) filtering air through HEPA recirculation systems installed on the wall or ceiling of the room (see Supplement, Environmental Controls; Figure 8); or 3) filtering air through portable HEPA recirculation systems. In this report, the first two approaches are referred to as fixed room-air recirculation systems because the recirculation systems are not easily movable.

FIGURE 7. Fixed ducted room-air recirculation system using a high efficiency particulate air (HEPA) filter inside an air duct

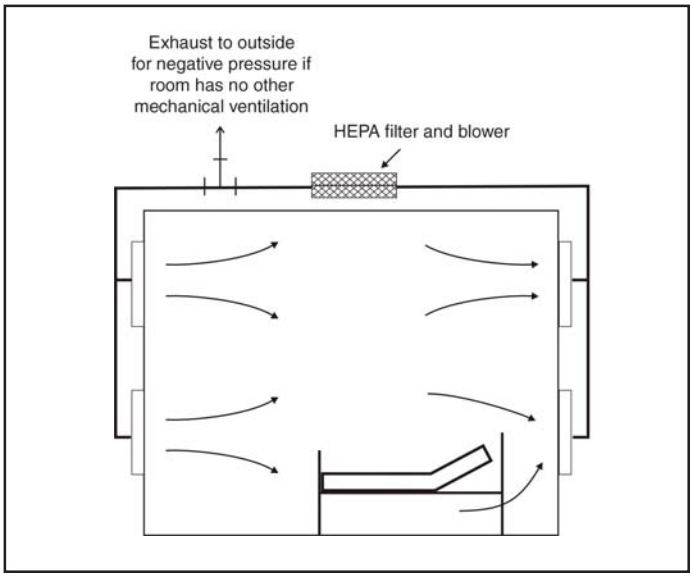
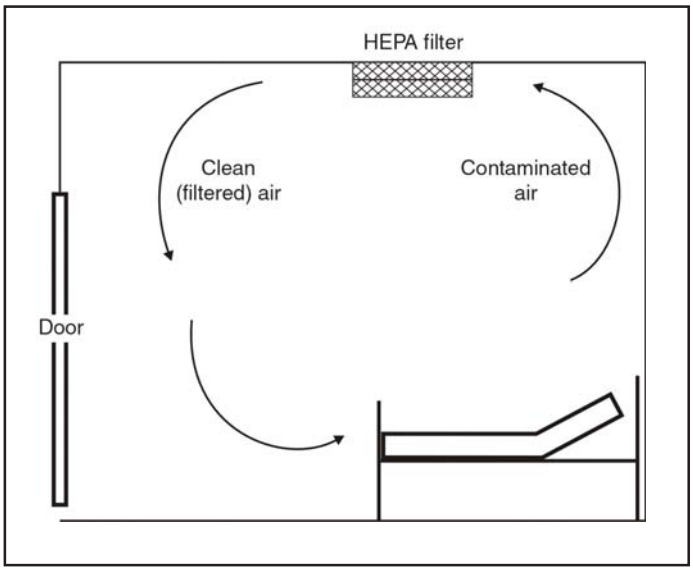


FIGURE 8. Fixed ceiling-mounted room-air recirculation system using a high efficiency particulate air (HEPA) filter



Fixed room-air recirculation systems. The preferred method of recirculating HEPA-filtered air is by using a built-in system in which air is exhausted from the room into a duct, filtered through a HEPA filter, and returned to the room (see Supplement Environmental Controls; Figure 7). This technique can add equivalent ACH in areas in which the recommended minimum ACH is difficult to meet with general ventilation. This equivalent ventilation concept compares particle removal by HEPA filtration of the recirculated air with particle clearance from exhaust ventilation. Because the air

does not have to be conditioned, airflow rates that are higher than those produced by the general ventilation system can usually be achieved. An alternative is to install HEPA filtration units on the wall or ceiling (see Supplement, Environmental Controls; Figure 8).

Fixed recirculation systems are preferred to portable (free-standing) units because they can be installed with a higher degree of reliability. In addition, certain fixed systems have a higher airflow capacity than portable systems, and the potential for short-circuiting of air is reduced as the distance between the air intake and exhaust is increased.

Portable room-air recirculation systems. Portable room-air recirculation units with HEPA filters (also called portable air cleaners) can be considered when 1) a room has no general ventilation system, 2) the system cannot provide adequate ACH, or 3) increased effectiveness in airflow is needed. Effectiveness depends on the ability of the portable room-air recirculation unit to circulate as much of the air in the room as possible through the HEPA filter. Effectiveness can vary depending on the room's configuration, the furniture and persons in the room, the placement of the HEPA filtration unit compared with the supply diffusers and exhaust grilles, and the degree of mixing of air within the room.

Portable room-air recirculation units have been demonstrated to be effective in removing bioaerosols and aerosolized particles from room air (*405–410*). Findings indicate that various commercially available units are useful in reducing the concentration of airborne particles and are therefore helpful in reducing airborne disease transmission. The performance of 14 units was evaluated for volumetric airflow, airborne particle reduction, noise level, and other parameters (*406*). The range of volumetric airflow rates is 110 cfm–1,152 cfm, and the equivalent ACH range was an average of 8–22 in a standard-sized, substantially well-mixed, single-patient room. Recommendations were provided to make subsequent models safer, more effective, quieter, and easier to use and service. Purchasers should be aware that the majority of manufacturer specifications indicated flow rates of free-wheeling fans and not the fan under the load of a filter.

Portable HEPA filtration units should be designed to 1) achieve ≥12 equivalent ACH, 2) ensure adequate air mixing in all areas of the rooms, and 3) be compatible with the ventilation system. An estimate of the ability of the unit to circulate the air in a room can be made by visualizing airflow patterns (estimating room air mixing [see Supplements, Environmental Controls; and General Ventilation]). If the air movement is adequate in all areas of the room, the unit should be effective.

If portable devices are used, units with high volumetric airflow rates that provide maximum flow through the HEPA filter are preferred. Placement should be selected to optimize the recirculation of AII room air through the HEPA filter. Careful consideration must be given to obstacles (e.g., furnishings, medical equipment, and walls) that could disrupt airflow and to system specifications (e.g., physical dimensions, airflow capacity, locations of air inlet and exhaust, and noise) to maximize performance of the units, minimize short-circuiting of air, and reduce the probability that the units will be switched off by room occupants.

Installing, maintaining, and monitoring HEPA filters. The performance of HEPA filters depends on proper installation, testing, and meticulous maintenance (*411*), especially if the system recirculates air to other parts of the health-care setting. Improper design, installation, or maintenance could allow infectious particles to circumvent filtration and escape into the general ventilation system (*117*). These failures also could impede proper ventilation performance.

HEPA filters should be installed to prevent leakage between filter segments and between the filter bed and its frame. A regularly scheduled maintenance program is required to monitor filters for possible leakage and filter loading. A quantitative filter performance test (e.g., the dioctyl phthalate penetration test [*412,413*]) should be performed at the initial installation and each time the filter is changed. Records should be maintained for all filter changes and testing. A leakage test using a particle counter or photometer should be performed every 6–12 months for filters in general-use areas and in areas with systems that will probably be contaminated with *M. tuberculosis* (e.g., AII rooms).

A manometer or other pressure-sensing device should be installed in the filter system to provide an accurate and objective means of determining the need for filter replacement. Pressure-drop characteristics of the filter are supplied by the manufacturer. Installation of the filter should allow for maintenance that will not contaminate the delivery system or the area served. For general infection-control purposes, special care should be taken to avoid jarring or dropping the filter element during or after removal.

The scheduled maintenance program should include procedures for installation, removal, and disposal of filter elements. HEPA filter maintenance should be performed only by adequately trained personnel and only while the ventilation system or room-air recirculation unit is not being operated.

Laboratory studies indicate that re-aerosolization of viable mycobacteria from filter material (HEPA filters and N95 disposable respirator filter media) is not probable under normal conditions (*414–416*). Although these studies indicate that *M. tuberculosis* becoming an airborne hazard is not probable after it is removed by a HEPA filter (or other high efficiency filter material), the risks associated with handling loaded HEPA

filters in ventilation systems under field-use conditions have not been evaluated. Therefore, persons performing maintenance and replacing filters on any ventilation system that is probably contaminated with *M. tuberculosis* should wear a respirator (see Respiratory Protection) in addition to eye protection and gloves. When feasible, HEPA filters can be disinfected in 10% bleach solution or other appropriate mycobacteriacide before removal (*417*). In addition, filter housing and ducts leading to the housing should be labeled clearly with the words "TB-Contaminated Air" or other similar warnings. Disposal of filters and other potentially contaminated materials should be in accordance with applicable local or state regulations.

One or more lower-efficiency disposable pre-filters installed upstream can extend the life of a HEPA filter by at least 25%. If the disposable filter is replaced by a 90% extended surface filter, the life of the HEPA filter can be extended by approximately 900% (*178*). Pre-filters should be handled and disposed of in the same manner as the HEPA filter.

UVGI

UVGI is a form of electromagnetic radiation with wavelengths between the blue region of the visible spectrum and the radiograph region. UV-C radiation (short wavelengths; range: 100–280 nm) (*418*) can be produced by various artificial sources (e.g., arc lamps and metal halide lamps). The majority of commercially available UV lamps used for germicidal purposes are low-pressure mercury vapor lamps that emit radiant energy in the UV-C range, predominantly at a wavelength of 253.7 nm (*418*).

Research has demonstrated that UVGI is effective in killing or inactivating *M. tuberculosis* under experimental conditions (*292,385,419–423*) and in reducing transmission of other infectious agents in hospitals (*424*), military housing (*425*), and classrooms (*426–428*). Because of the results of multiple studies (*384,429–432*) and the experiences of clinicians and mycobacteriologists during the preceding decades, UVGI has been recommended as a supplement or adjunct to other TB infection-control and ventilation measures in settings in which the need to kill or inactivate *M. tuberculosis* is essential (*6,7,196,433,434*). UVGI alone does not provide outside air or circulate interior air, both of which are essential in achieving acceptable air quality in occupied spaces.

Applications of UVGI. UVGI is considered a method of air cleaning because it can kill or inactivate microorganisms so that they are no longer able to replicate and form colonies. UVGI is not a substitute for HEPA filtration before exhausting the air from AII rooms back into the general circulation. UVGI lamps can be placed in ducts, fixed or portable room air-recirculation units, or upper-air irradiation systems. The use of this air-cleaning technique has increased, particularly in substantial open areas in which unsuspected or undiagnosed patients with TB disease might be present (e.g., ED waiting rooms, shelters, and correctional facilities), and the costs of conditioning substantial volumes of outdoor air are prohibitive.

For each UVGI system, guidelines should be followed to maximize effectiveness. Effectiveness can be expressed in terms of an equivalent air change rate (*427,435–437*), comparing the ability of UVGI to inactivate organisms with removal through general ventilation. Initially, understanding and characterizing the application for which UVGI will be used is vital. Because the effectiveness of UVGI systems will vary, the use of UVGI must be carefully evaluated and the level of efficacy clearly defined and monitored.

The effective use of UVGI is associated with exposure of *M. tuberculosis*, as contained in an infectious droplet, to a sufficient dose of UV-C at 253.7 nm to ensure inactivation. Because dose is a function of irradiance and time, the effectiveness of any application is determined by its ability to deliver sufficient irradiance for enough time to result in inactivation of the organism within the infectious droplet. Achieving a sufficient dose can be difficult with airborne inactivation because the exposure time can be substantially limited; therefore, attaining sufficient irradiance is essential.

The number of persons who are properly trained in the design and installation of UVGI systems is limited. One critical recommendation is that health-care facility managers consult a UVGI system designer to address safety and efficacy considerations before such a system is procured and installed. Experts who can be consulted include industrial hygienists, engineers, and health physicists.

Duct irradiation. Duct irradiation is designed to kill or inactivate *M. tuberculosis* without exposing persons to UVGI. In duct irradiation systems, UVGI lamps are placed inside ducts to disinfect the exhaust air from AII rooms or other areas in which *M. tuberculosis* might be present before it is recirculated to the same room (desirable) or to other areas served by the system (less desirable). When UVGI duct systems are not properly designed, installed, and maintained, high levels of UVGI can be produced in the duct that can potentially cause high UVGI exposures during maintenance operations.

Duct-irradiation systems depend on the circulation of as much of the room air as possible through the duct. Velocity profiles and mixing are important factors in determining the UVGI dose received by airborne particles. Design velocity for a typical UVGI unit is approximately 400 fpm (*438*). The particle residence time must be sufficient for inactivation of the microorganisms.

Duct irradiation can be used in three ways.

- Ventilation systems serving AII rooms to recirculate air from the room, through a duct containing UV lamps, and back into the same room. UVGI duct systems should not be used either in place of HEPA filters, if air from AII rooms must be recirculated to other areas of a setting, or as a substitute for HEPA filtration of air from booths, tents, or hoods used for cough-inducing or aerosol-generating procedures.
- Return air ducts serving patient rooms, waiting rooms, EDs, and general-use areas in which patients with undiagnosed TB disease could potentially contaminate the recirculated air.
- Recirculating ventilation systems serving rooms or areas in which ceiling heights are too low for the safe and effective use of upper-air UVGI.

Upper-air irradiation. In upper-air irradiation, UVGI lamp fixtures are suspended from the ceiling and installed on walls. The base of the lamps are shielded to direct the radiation upward and outward to create an intense zone of UVGI in the upper air while minimizing the levels of UVGI in the lower part of the room where the occupants are located. The system depends on air mixing to move the air from the lower part of the room to the upper part where microbial-contaminated air can be irradiated.

A major consideration is the placement of UVGI fixtures to achieve sufficient irradiance of the upper-air space. The ceiling should be high enough (≥8 feet) for a substantial volume of upper air to be irradiated without overexposing occupants in the lower part of the room to UVGI. System designers must consider the mechanical ventilation system, room geometry, and emission characteristics of the entire fixture.

Upper-air UVGI can be used in various settings.

- AII rooms and rooms in which aerosol-generating or aerosol-producing procedures (e.g., bronchoscopy, sputum induction, and administration of aerosolized medications) are performed.
- Patient rooms, waiting rooms, EDs, corridors, central areas, and other substantial areas in which patients with undiagnosed TB disease could potentially contaminate the air.
- Operating rooms and adjacent corridors where procedures are performed on patients with TB disease.
- Medical settings in correctional facilities.

UVGI-containing–portable room air cleaners. In portable room air-recirculation units containing UVGI, a fan moves a volume of room air across UVGI lamps to disinfect the air before it is recirculated back to the room. Some portable units contain both a HEPA filter (or other high efficiency filter) and UVGI lamps.

In addition to the guidelines described for the use of portable room air-recirculation systems containing HEPA filtration, consideration must be given to the volume of room air that passes through the unit, the UVGI levels, particle residence time, and filtration efficiency (for devices with a filter). One study in which a bioaerosol chamber was used demonstrated that portable room air cleaners with UVGI lamps as the primary air-cleaning mechanism are effective (>99%) in inactivating or killing airborne vegetative bacteria (*439*). Additional studies need to be performed in rooms with portable air cleaners that rely only on UVGI for air cleaning.

Portable room air cleaners with UVGI can be used in 1) AII rooms as an adjunct method of air cleaning and 2) waiting rooms, EDs, corridors, central areas, or other substantial areas in which patients with undiagnosed TB disease could potentially contaminate the air.

Effectiveness of UVGI. Air mixing, air velocity, relative humidity, UVGI intensity, and lamp configuration affect the efficacy of all UVGI applications. For example, with upper-air systems, airborne microorganisms in the lower, occupied areas of the room must move to the upper part of the room to be killed or inactivated by upper-air UVGI. Air mixing can occur through convection caused by temperature differences, fans, location of supply and exhaust ducts, or movement of persons.

Air-mixing. UVGI has been demonstrated to be effective in killing bacteria in the upper-air applications under conditions in which air mixing was accomplished primarily by convection. In a 1976 study on aerosolization of *M. bovis.* BCG (a surrogate for *M. tuberculosis*) in a room without mechanical ventilation that relied primarily on convection and infiltration resulted in 10–25 equivalent ACH, depending on the number of UVGI fixtures used (*384*). Other early studies examined the effect of air-mixing on UVGI efficacy (*440,441*). These studies indicated that the efficacy of UVGI was substantially increased if cold supply air relative to the lower portion of the room entered through diffusers in the ceiling. The findings indicated that substantial temperature gradients between the upper and lower portions of the room favored (cold air in the upper portion of the room) or inhibited (hot air in the upper portion of the room) vertical mixing of air between the two zones.

When large-bladed ceiling fans were used to promote mixing in the experimental room, the ability of UVGI to inactivate *Serratia marcescens*, an organism known to be highly sensitive to UVGI, was doubled (*442,443*). Similar effects were reported in studies conducted during 2000–2002 in which louvered

UVGI fixtures were used. One study documented an increase in UVGI effectiveness of 16% at 2 ACH and 33% at 6 ACH when a mixing fan was used (*444*). Another study conducted in a simulated health-care room determined that 1) at 0 ACH, a high degree of efficacy of upper-air UVGI was achieved in the absence or presence of mixing fans when no temperature gradient was created; and 2) at 6 ACH, bringing in warm air at the ceiling resulted in a temperature gradient with cooler room air near the floor and a UVGI efficacy of only 9% (*422*). Turning on box fans under these winter conditions increased UVGI efficacy nearly 10-fold (to 89%) (*445*).

To reduce variability in upper-air UVGI efficacy caused by temperature gradients in the room, a fan should be routinely used to continually mix the air, unless the room has been determined to be well mixed under various conditions of operation. Use of a fan would also reduce or remove the variable winter versus summer ACH requirements for optimal upper-air UVGI efficacy (*446*).

Relative humidity. In studies conducted in bioaerosol chambers, the ability of UVGI to kill or inactivate microorganisms declined substantially when the relative humidity exceeded 60% (*447–450*). In room studies, declines in the ability of upper-air UVGI to kill or inactivate microorganisms at high relative humidity (65%, 75%, and 100%) (*384,422*) have also been reported. The exact mechanism responsible for the reduced effectiveness of UVGI at these higher levels of relative humidity is unknown but does not appear to be related to changes in UV irradiance levels. Relative humidity changes from 55%–90% resulted in no corresponding changes in measured UVGI levels (*437*). In another study, an increase in relative humidity from 25%–67% did not reduce UVGI levels (*422*). Bacteria have been demonstrated to absorb substantial amounts of water from the air as the relative humidity increases. At high humidity, the UV irradiance levels required to inactivate bacteria might approach the higher levels that are needed for liquid suspensions of bacteria (*448*). The ability of bacteria to repair UVGI damage to their DNA through photoreactivation has also been reported to increase as relative humidity increases (*422,448*).

For optimal efficacy of upper-air UVGI, relative humidity should be maintained at ≤60%, a level that is consistent with recommendations for providing acceptable indoor air quality and minimizing environmental microbial contamination in indoor environments (*386,451*).

Ventilation rates. The relation between ventilation and UVGI has also been evaluated. Certain predicted inactivation rates have been calculated and published for varying flow rates, UV intensity, and distances from the lamp, based on radiative heat transfer theory (*438*). In room studies with substantially well-mixed air, ventilation rates (0 ACH, 3 ACH, and 6 ACH) were combined with various irradiation levels of upper-air UVGI. All experiments were conducted at 50% relative humidity and 70° F (21.2° C). When *M. parafortuitum* is used as a surrogate for *M. tuberculosis*, ventilation rates usually had no adverse effect on the efficiency of upper-air UVGI. The combined effect of both environmental controls was primarily additive in this artificial environment, with possibly a small loss of upper-air UVGI efficiency at 6 ACH (*422*). Therefore, ventilation rates of up to 6 ACH in a substantially well-mixed room might achieve ≥12 ACH (mechanical ACH plus equivalent ACH) by combining these rates with the appropriate level of upper-air irradiation (*422*). Higher ventilation rates (>6 ACH) might, however, decrease the time the air is irradiated and, therefore, decrease the killing of bacteria (*429,452*).

Ventilation rates up to six mechanical ACH do not appear to adversely affect the performance of upper-air UVGI in a substantially well-mixed room. Additional studies are needed to examine the combined effects of mechanical ventilation and UVGI at higher room-air exchange rates.

UVGI intensity. UVGI intensity field plays a primary role in the performance of upper-air UVGI systems. The UVGI dose received by microorganisms is a function of UVGI times duration of exposure. Intensity is influenced by the lamp wattage, distance from the lamp, surface area, and presence of reflective surfaces. The number of lamps, location, and UVGI level needed in a room depends on the room's geometry, area, and volume, and the location of supply air diffusers (*422,436*). UVGI fixtures should be spaced to reduce overlap while maintaining an even irradiance zone in the upper air.

The emission profile of a fixture is a vital determinant of UVGI effectiveness. Information regarding total UVGI output for a given fixture (lamp plus housing and louvers) should be requested from the manufacturer and used for comparison when selecting UVGI systems. Information concerning only the UVGI output of the lamp is inadequate; the lamp output will be higher than the output for the fixture because of losses from reflectors and nonreflecting surfaces and the presence of louvers and other obstructions (*436,437*). In addition, information provided by the manufacturer reflects ideal laboratory conditions; damage to fixtures or improper installation will affect UV output. Because old or dust-covered UVGI lamps are less effective, routine maintenance and cleaning of UVGI lamps and fixtures is essential. UVGI system designers should consider room geometry, fixture output, room ventilation, and the desired level of equivalent ACH in determining the types, numbers, and placement of UVGI fixtures in a room to achieve target irradiance levels in the upper air.

Health and safety issues. Short-term overexposure to UV radiation can cause erythema (i.e., abnormal redness of the skin), photokeratitis (inflammation of the cornea), and con-

junctivitis (i.e., inflammation of the conjunctiva) (*453*). Symptoms of photokeratitis and conjunctivitis include a feeling of sand in the eyes, tearing, and sensitivity to light. Photokeratitis and conjunctivitis are reversible conditions, but they can be debilitating while they run their course. Because the health effects of UVGI are usually not evident until after exposure has ended (typically 6–12 hours later), HCWs might not recognize them as occupational injuries.

In 1992, UV-C (100–280 nm) radiation was classified by the International Agency for Research on Cancer as "probably carcinogenic to humans (Group 2A)" (*454*). This classification was based on studies indicating that UV-C radiation can induce skin cancers in animals and create DNA damage, chromosomal aberrations, and sister chromatid exchange and transformation in human cells in vitro. In addition, DNA damage in mammalian skin cells in vivo can be caused. In the animal studies, a contribution of UV-C radiation to the tumor effects could not be excluded, but the effects were higher than expected for UV-B radiation alone (*454*). Certain studies have demonstrated that UV radiation can activate HIV gene promoters (i.e., genes in HIV that prompt replication of the virus) in laboratory samples of human cells (*455–460*). The potential for UV-C radiation to cause cancer and promote HIV in humans is unknown, but skin penetration might be an important factor. According to certain reports, only 20% of incident 250 nm UV penetrates the stratum corneum, compared with approximately 30–60% of 300 nm UV (UV-B) radiation (*461*).

In upper-air UVGI systems, fixtures must be designed and installed to ensure that UVGI exposures to occupants are below current safe exposure levels. Health-hazard evaluations have identified potential problems at some settings using UVGI systems. These problems include overexposure of HCWs to UVGI and inadequate maintenance, training, labeling, and use of personal protective equipment (PPE) (*398,462,463*).

An improperly maintained (unshielded) germicidal lamp was believed to be the cause of dermatosis or photokeratitis in five HCWs in an ED (*464*) and three HCWs who were inadvertently exposed to an unshielded UVGI lamp in a room that had been converted from a sputum induction room to an office (*465*). These case reports highlight the importance of posting warning signs to identify the presence of UVGI (see Supplement, Labeling and Posting) and are reminders that shielding should be used to minimize UVGI exposures to occupants in the lower room. In the majority of applications, properly designed, installed, and maintained UVGI fixtures provide protection from the majority of, if not all, the direct UVGI in the lower room. However, radiation reflected from glass, polished metal, and high-gloss ceramic paints can be harmful to persons in the room, particularly if more than one UVGI fixture is in use. Surfaces in irradiated rooms that can reflect UVGI into occupied areas of the room should be covered with non-UV–reflecting material.

Although more studies need to be conducted, lightweight clothing made of tightly woven fabric and UV-absorbing sunscreens with solar-protection factors (SPFs) of ≥15 might help protect photosensitive persons. Plastic eyewear containing a UV inhibitor that prevents the transmission of ≥95% of UV radiation in the 210–405 nm range is commercially available. HCWs should be advised that any eye or skin irritation that develops after UVGI exposure should be evaluated by an occupational health professional.

Exposure criteria. In 1972, CDC published a recommended exposure limit (REL) for occupational exposure to UV radiation (*453*). REL is intended to protect HCWs from the acute effects of UV light exposure. Photosensitive persons and those exposed concomitantly to photoactive chemicals might not be protected by the recommended standard.

The CDC/NIOSH REL for UV radiation is wavelength dependent because different wavelengths have different adverse effects on the skin and eyes (*453*). At 254 nm, the predominant wavelength for germicidal UV lamps, the CDC/NIOSH REL is 0.006 joules per square centimeter (J/cm2) for a daily 8-hour work shift. ACGIH has a Threshold Limit Value® for UV radiation that is identical to the REL for this spectral region (*466*). HCWs frequently do not stay in one place in the setting during the course of their work and, therefore, are not exposed to UV irradiance levels for 8 hours. Permissible exposure times (PET) for HCWs with unprotected eyes and skin can be calculated for various irradiance levels as follows:

$$\text{PET (seconds)} = \frac{\text{0.006 J/cm2 (the CDC/NIOSH REL at 254 nm)}}{\text{Measured irradiance level (at 254 nm) in W/cm}^2}$$

Exposures exceeding the CDC/NIOSH REL require the use of PPE to protect the skin and eyes.

Labeling, Maintenance, and Monitoring

Labeling and posting. Health-care settings should post warning signs on UV lamps and wherever high-intensity (i.e., UVGI exposure greater than the REL) UVGI irradiation is present to alert maintenance staff, HCWs, and the general public of the hazard. The warning signs should be written in the languages of the affected persons (Box 6).

Maintenance. Because the UVGI output of the lamps decline with age, a schedule for replacing the lamps should be developed in accordance with manufacturer recommendations. The schedule can be determined from a time-use log, a system based on cumulative time, or routinely (e.g., at least annually). UVGI lamps should be checked monthly for dust

BOX 6. Examples of ultraviolet germicidal irradiation (UVGI) signs

- Wall sign for upper-air UVGI

CAUTION
ULTRAVIOLET ENERGY
SWITCH OFF LAMPS BEFORE
ENTERING UPPER ROOM

- General warning posted near UVGI lamps

CAUTION
ULTRAVIOLET ENERGY
PROTECT EYES AND SKIN

- Warning posted on the door of air handlers where UVGI is present in ductwork

CAUTION
ULTRAVIOLET ENERGY IN DUCT
DO NOT SWITCH OFF SAFETY BUTTON
OR ACTIVATE LAMPS WITH DOOR OPEN

build-up, which lessens radiation output. A dirty UVGI lamp should be allowed to cool and then should be cleaned in accordance with the manufacturer recommendations so that no residue remains.

UVGI lamps should be replaced if they stop glowing, if they flicker, or if the measured irradiance (see Supplement, Environmental Controls) drops below the performance criteria or minimum design criterion set forth by the design engineers. Maintenance personnel must switch off all UVGI lamps before entering the upper part of the room or before accessing ducts for any purpose. Only limited seconds of direct exposure to the intense UVGI in the upper-air space or in ducts can cause dermatosis or photokeratitis. Protective clothing and equipment (e.g., gloves, goggles, face shield, and sunscreen) should be worn if exposure greater than the recommended levels is possible or if UVGI radiation levels are unknown.

Banks of UVGI lamps can be installed in ventilation system ducts. Safety devices and lock-out or tag-out protocols should be used on access doors to eliminate exposures of maintenance personnel. For duct irradiation systems, the access door for servicing the lamps should have an inspection window through which the lamps are checked periodically for dust build-up and to ensure that they are functioning properly. The access door should have a warning sign written in appropriate languages to alert maintenance personnel to the health hazard of looking directly at bare UV lamps. The lock for this door should have an automatic electric switch or other device that turns off the lamps when the door is opened.

Types of fixtures used in upper-air irradiation include wall-mounted, corner-mounted, and ceiling-mounted fixtures that have louvers or baffles to block downward radiation and ceiling-mounted fixtures that have baffles to block radiation below the horizontal plane of the fixtures. If possible, light switches that can be locked should be used to prevent injury to persons who might unintentionally turn the lamps on during maintenance procedures. Because lamps must be discarded after use, consideration should be given to selecting germicidal lamps that are manufactured with relatively low amounts (i.e., $\leq$5 mg) of mercury. UVGI products should be listed with the Underwriters Laboratories (UL) or Electrical Testing Laboratories (ETL) for their specific application and installed in accordance with the National Electric Code.

Monitoring. UVGI intensity should be measured by an industrial hygienist or other person knowledgeable in the use of UV radiometers with a detector designed to be most sensitive at 254 nm. Equipment used to measure UVGI should be maintained and calibrated on a regular schedule, as recommended by the manufacturer.

UVGI should be measured in the lower room to ensure that exposures to occupants are below levels that could result in acute skin and eye effects. The monitoring should consider typical duties and locations of the HCWs and should be done at eye level. At a minimum, UVGI levels should be measured at the time of initial installation and whenever fixtures are moved or other changes are made to the system that could affect UVGI. Changes to the room include those that might result in higher exposures to occupants (e.g., addition of UV-reflecting materials or painting of walls and ceiling). UVGI monitoring information, lamp maintenance, meter calibration, and lamp and fixture change-outs should be recorded.

UVGI measurements should also be made in the upper air to define the area that is being irradiated and determine if target irradiance levels are met (*467*). Measurements can be made using UVGI radiometers or other techniques (e.g., spherical actinometry), which measures the UVGI in an omnidirectional manner to estimate the energy to which microorganisms would be exposed (*468*). Because high levels of UVGI can be measured in the upper air, persons making the measurements should use adequate skin and eye protection. UVGI radiation levels close to the fixture source can have permissible exposure times on the order of seconds or minutes for HCWs with unprotected eyes and skin. Therefore, overexposures can occur with brief UVGI exposures in the upper air (or in ventilation system ducts where banks of unshielded UV lamps are placed) in HCWs who are not adequately protected.

Upper-air UVGI systems and portable room-air recirculation units. A study in 2002 examined the relation between three portable room-air recirculation units with different capture or inactivation mechanisms and an upper-air UVGI system in a simulated health-care room (*409*). The study determined that the equivalent ACH produced by the recirculation units and produced by the upper-air UVGI system were approximately additive. For example, one test using aerosolized *M. parafortuitum* provided an equivalent ACH for UVGI of 17 and an equivalent ACH for the recirculation unit of 11; the total experimentally measured equivalent ACH for the two systems was 27. Therefore, the use of portable room-air recirculation units in conjunction with upper-air UVGI systems might increase the overall removal of *M. tuberculosis* droplet nuclei from room air.

Environmental Controls: Program Concerns

To be most effective, environmental controls must be installed, operated, and maintained correctly. Ongoing maintenance is a critical part of infection control that should be addressed in the written TB infection-control plan. The plan should outline the responsibility and authority for maintenance and address staff training needs. At one hospital, improperly functioning ventilation controls were believed to be an important factor in the transmission of MDR TB disease to three patients and a correctional officer, three of whom died (*469*). In three other multihospital studies evaluating the performance of AII rooms, failure to routinely monitor air-pressure differentials or a failure of the continuous monitoring devices installed in the AII rooms resulted in a substantial percentage of the rooms being under positive pressure (*57,392,470,471*).

Routine preventive maintenance should be scheduled and should include all components of the ventilation systems (e.g., fans, filters, ducts, supply diffusers, and exhaust grilles) and any air-cleaning devices in use. Performance monitoring should be conducted to verify that environmental controls are operating as designed. Performance monitoring can include 1) directional airflow assessments using smoke tubes and use of pressure monitoring devices that are sensitive to pressures as low as approximately 0.005 inch of water gauge and 2) measurement of supply and exhaust airflows to compare with recommended air change rates for the respective areas of the setting. Records should be kept to document all preventive maintenance and repairs.

Standard procedures should be established to ensure that maintenance staff notifies infection-control personnel before performing maintenance on ventilation systems servicing patient-care areas. Similarly, infection-control staff should request assistance from maintenance personnel in checking the operational status of AII rooms and local exhaust devices (e.g., booths, hoods, and tents) before use. A protocol that is well-written and followed will help to prevent unnecessary exposures of HCWs and patients to infectious aerosols. Proper labeling of ventilation system components (e.g., ducts, fans, and filters) will help identify air-flow paths. Clearly labeling which fan services a given area will help to prevent accidental shutdowns (*472*).

In addition, provisions should be made for emergency power to avoid interruptions in the performance of essential environmental controls during a power failure.

Respiratory Protection

Considerations for Selection of Respirators

The overall effectiveness of respiratory protection is affected by 1) the level of respiratory protection selected (e.g., the assigned protection factor), 2) the fit characteristics of the respirator model, 3) the care in donning the respirator, and 4) the adequacy of the fit-testing program. Although data on the effectiveness of respiratory protection from various hazardous airborne materials have been collected, the precise level of effectiveness in protecting HCWs from *M. tuberculosis* transmission in health-care settings has not been determined.

Information on the transmission parameters of *M. tuberculosis* is also incomplete. Neither the smallest infectious dose of *M. tuberculosis* nor the highest level of exposure to *M. tuberculosis* at which transmission will not occur has been defined conclusively (*159,473,474*). In addition, the size distribution of droplet nuclei and the number of particles containing viable *M. tuberculosis* organisms that are expelled by patients with infectious TB disease have not been adequately defined, and accurate methods of measuring the concentration of infectious droplet nuclei in a room have not been developed. Nonetheless, in certain settings (e.g., AII rooms and ambulances during the transport of persons with suspected or confirmed infectious TB disease), administrative and environmental controls alone might not adequately protect HCWs from infectious airborne droplet nuclei.

On October 17, 1997, OSHA published a proposed standard for occupational exposure to *M. tuberculosis* (*267*). On December 31, 2003, OSHA announced the termination of rulemaking for a TB standard (*268*). Previous OSHA policy permitted the use of any Part 84 particulate filter respirator for protection against infection with *M. tuberculosis* (*269*). Respirator usage for TB had been regulated by OSHA under CFR Title 29, Part 1910.139 (29 CFR 1910.139) (*270*) and compliance policy directive (CPL) 2.106 (Enforcement Procedures and Scheduling for Occupational Exposure to Tuberculosis). Respirator usage for TB is now regulated under the

general industry standard for respiratory protection (29 CFR 1910.134) (*271*). General information on respiratory protection for aerosols, including *M. tuberculosis*, has been published (*272–274*).

Performance Criteria for Respirators

Performance criteria for respirators are derived from data on 1) effectiveness of respiratory protection against noninfectious hazardous materials in workplaces other than health-care settings and an interpretation of how these data can be applied to respiratory protection against *M. tuberculosis*, 2) efficiency of respirator filters in filtering biologic aerosols, 3) face-seal leakage, and 4) characteristics of respirators used in conjunction with administrative and environmental controls in outbreak settings to stop transmission of *M. tuberculosis* to HCWs and patients.

Particulate filter respirators certified by CDC/NIOSH, either nonpowered respirators with N95, N99, N100, R95, R99, R100, P95, P99, and P100 filters (including disposable respirators), or PAPRs with high efficiency filters can be used for protection against airborne *M. tuberculosis*.

The most essential attribute of a respirator is the ability to fit the different facial sizes and characteristics of HCWs. Studies have demonstrated that fitting characteristics vary substantially among respirator models. The fit of filtering facepiece respirators varies because of different facial types and respirator characteristics (*10,280–289*). Selection of respirators can be done through consultation with respirator fit-testing experts, CDC, occupational health and infection-control professional organizations, peer-reviewed research, respirator manufacturers, and from advanced respirator training courses. Data have determined that fit characteristics cannot be determined solely by physical appearance of the respirator (*282*).

Types of Respiratory Protection for TB

Respirators encompass a range of devices that vary in complexity from flexible masks covering only the nose and mouth, to units that cover the user's head (e.g., loose-fitting or hooded PAPRs), and to those that have independent air supplies (e.g., airline respirators). Respirators must be selected from those approved by CDC/NIOSH under the provisions of 42 CFR, Part 84 (*475*).

Nonpowered air-purifying respirators. Nine classes of nonpowered, air-purifying, particulate-filter respirators are certified under 42 CFR 84. These include N-, R-, and P-series respirators of 95%, 99%, and 100% (99.7%) filtration efficiency when challenged with 0.3 µm particles (filters are generally least efficient at this size) (see Supplement, Respiratory Protection; Table 4). The N, R, and P classifications are based on the capacity of the filter to withstand exposure to oil. All of these respirators meet or exceed CDC's filtration efficiency performance criteria during the service life of the filter (*1,272,273*).

TABLE 4. Nonpowered air-purifying respirator filter classes certified in 42 CFR* 84

Resistance to efficiency filter degradation	Filter efficiencies†		
	95 (95%)	99 (99%)	100 (99.97%)
N (Not resistant to oil)	N95	N99	N100
R (Resistant to oil)	R95	R99	R100
P (Oil proof)	P95	P99	P100

* Code of Federal Regulations.
† The percentages in parenthesis indicate the minimum allowable laboratory filter efficiency value when challenged with 0.3 µm particles.

Nonpowered air-purifying respirators work by drawing ambient air through the filter during inhalation. Inhalation causes negative pressure to develop in the tight-fitting facepiece and allows air to enter while the particles are captured on the filter. Air leaves the facepiece during exhalation because positive pressure develops in the facepiece and forces air out of the mask through the filter (disposable) or through an exhalation valve (replaceable and certain ones are disposable).

The classes of certified nonpowered air-purifying respirators include both filtering facepiece (disposable) respirators and elastomeric (rubber-like) respirators with filter cartridges. The certification test for filtering facepieces and filter cartridges consists only of a filter performance test. It does not address respirator fit. Although all N-, R-, and P-series respirators are recommended for protection against *M. tuberculosis* infection in health-care settings and other workplaces that are usually free of oil aerosols that could degrade filter efficiency, well-fitting N-series respirators are usually less expensive than R- and P-series respirators (*272,273*). All respirators should be replaced as needed, based on hygiene considerations, increased breathing resistance, time-use limitations specified in the CDC/NIOSH approval guidelines, and respirator damage, in accordance with manufacturer specifications.

PAPRs. PAPR uses a blower that draws air through the filters into the facepiece. PAPRs can be equipped with a tight-fitting or loose-fitting facepiece, a helmet, or a hood. PAPR filters are classified as high efficiency and are different from those presented in this report (Table 4). A hooded PAPR high efficiency filter meets the N100, R100, and P100 criteria at the beginning of their service life. No loading tests using 0.3 µm particles are conducted as part of certification. PAPRs can be useful for persons with facial hair or other conditions that prevent an adequate face to facepiece seal (*476*).

Atmosphere-supplying respirators. Positive-pressure airline (supplied-air) respirators are provided with air from a stationary source (compressor) or an air tank.

Effectiveness of Respiratory-Protection Devices

Data on the effectiveness of respiratory protection against hazardous airborne materials are based on experience in the industrial setting; data on protection against transmission of *M. tuberculosis* in health-care settings are not available. The parameters used to determine the effectiveness of a respiratory protective device are face-seal efficacy and filter efficiency.

Face-seal leakage. Face-seal leakage is the weak link that limits a respirator's protective ability. Excessive face-seal leakage compromises the ability of particulate respirators to protect HCWs from airborne materials (*477*). A proper seal between the respirator's sealing surface and the face of the person wearing the res-pirator is essential for the effective and reliable performance of any tight-fitting, negative-pressure respirator.

For tight-fitting, negative-pressure respirators (e.g., N95 disposable respirators), the amount of face-seal leakage is determined by 1) the fit characteristics of the respirator, 2) the care in donning the respirator, and 3) the adequacy of the fit-testing program. Studies indicate that a well-fitting respirator and a fit test produces better results than a well-fitting respirator without a fit test or a poor-fitting respirator with a fit test. Increased face-seal leakage can result from additional factors, including incorrect facepiece size, failure to follow the manufacturer's instructions at each use, beard growth, perspiration or facial oils that can cause facepiece slippage, improper maintenance, physiological changes of the HCW, and respirator damage.

Face-seal leakage is inherent in tight-fitting negative-pressure respirators. Each time a person wearing a nonpowered particulate respirator inhales, negative pressure (relative to the workplace air) is created inside the facepiece. Because of this negative pressure, air containing contaminants can leak into the respirator through openings at the face-seal interface and avoid the higher-resistance filter material. A half-facepiece respirator, including an N95 disposable respirator, should have <10% leakage. Full facepiece, nonpowered respirators have the same leakage (<2%) as PAPRs with tight-fitting full-facepieces.

The more complex PAPRs and positive-pressure airline respirators reduce or eliminate this negative facepiece pressure and, therefore, reduce leakage into the respirator and enhance protection. A PAPR is equipped with a blower that forcibly draws ambient air through high efficiency filters and then delivers the filtered air to the facepiece. This air is blown into the facepiece at flow rates that generally exceed the expected inhalation flow rates. The pressure inside the facepiece reduces face-seal leakage to low levels, particularly during the relatively low inhalation rates expected in health-care settings. PAPRs with a tight-fitting facepiece have <2% face-seal leakage under routine conditions (*278*). PAPRs with loose-fitting facepieces, hoods, or helmets have <4% inward leakage under routine conditions (*278*). Therefore, a PAPR might offer lower levels of face-seal leakage than nonpowered, half-mask respirators.

Filter penetration. Aerosol penetration through respirator filters depends on at least five independent variables: 1) filtration characteristics for each type of filter, 2) size distribution of the droplets in the aerosol, 3) linear velocity through the filtering material, 4) filter loading (i.e., amount of contaminant deposited on the filter), and 5) electrostatic charges on the filter and on the droplets in the aerosol (*284*).

When N95 disposable respirators are used, filter penetration might approach 5% (50% of the allowable leakage of 10% for an N95 disposable respirator). When high efficiency filters are used in PAPRs or for half-facepiece respirators, filter efficiency is high (effectively 100%), and filter penetration is less of a consideration. Therefore, for high efficiency or 100-series filter respirators, the majority of inward leakage of droplet nuclei occurs at the respirator's faceseal or exhalation valve.

Implementing a Respiratory-Protection Program

If respirators are used in a health-care setting, OSHA requires the development, implementation, administration, and periodic reevaluation of a respiratory-protection program (*271,277,278*). The most critical elements of a respiratory-protection program include 1) assigning of responsibility, 2) training, and 3) fit testing (*1*). All HCWs who use respirators for protection against infection with *M. tuberculosis* should be included in the respiratory-protection program.

Visitors to AII rooms and other areas with patients who have suspected or confirmed infectious TB disease may be offered respirators (e.g., N95 disposable respirators) and should be instructed by an HCW on the use of the respirator before entering an AII room (see Respiratory Protection section for User-Seal Check FAQs). The health-care setting should develop a policy on use of respirators by visitors.

The number of HCWs included in the respiratory- protection program will vary depending on the 1) number of persons who have suspected or confirmed TB disease examined in a setting, 2) number of rooms or areas in which patients with suspected or confirmed infectious TB disease stay or are encountered, and 3) number of HCWs needed to staff these rooms or areas. In settings in which respiratory-protection programs are required, enough HCWs should be included to provide adequate care for patients with suspected or confirmed TB disease. However, administrative measures should be used to limit the number of HCWs exposed to *M. tuberculosis* (see Prompt Triage).

Information on the development and management of a respiratory-protection program is available in technical training courses that cover the basics of respiratory protection. Such courses are offered by OSHA, the American Industrial Hygiene Association, universities, manufacturers, and private contractors. To be effective and reliable, respiratory-protection programs must include at least the following elements (*274,277,278*).

Assignment of Responsibility

One person (the program administrator) must be in charge of the respiratory-protection program and be given the authority and responsibility to manage all aspects of the program. The administrator must have sufficient knowledge (obtained by training or experience) to develop and implement a respiratory-protection program. Preferably, the administrator should have a background in industrial hygiene, safety, health care, or engineering. The administrator should report to the highest official possible (e.g., manager of the safety department, supervisor of nurses, HCWs' health manager, or infection-control manager) and should be allocated sufficient time to administer the respiratory-protection program in addition to other assigned duties.

Standard Operating Procedures

The effectiveness of a respiratory-protection program requires the development of written standard procedures. These procedures should include information and guidance for the proper selection, use, and care of respirators (*274*).

Screening

HCWs should not be assigned a task requiring use of respirators unless they are physically able to perform job duties while wearing the respirator. HCWs who might need to use a respirator should be screened by a physician or other licensed health-care professional for pertinent medical conditions at the time they are hired and then re-screened periodically (*274*). The screening process should begin with a screening questionnaire for pertinent medical conditions, the results of which should be used to identify HCWs who need further evaluation (see Supplement, Respiratory Protection; Appendix G). Unless prescribed by the screening physician, serial physical examination or testing with chest radiographs or spirometry is neither necessary nor required (*287*).

Training

HCWs should be provided annual training on multiple topics.

- Nature, extent, and hazards of TB disease in the health-care setting. This training can be conducted in conjunction with other related training on infectious disease associated with airborne transmission (e.g., severe acute respiratory syndrome [SARS]-coronavirus [CoV] and measles) and with serial TB screening.
- The risk assessment process and its relation to the respirator program.
- Signs and symbols used to demonstrate that respirators are required in an area.
- Reasons for using respirators.
- Environmental controls used to prevent the spread and reduce the concentration of infectious droplet nuclei.
- Reasons for selecting a particular respirator for a given hazard (see Selection of Respirators; and Respirator Options: Special Circumstances).
- Operation, capabilities, and limitations of respirators.
- Respirator care (see Baseline Testing for *M. tuberculosis* Infection After TST Within the Previous 12 Months).
- Cautions regarding facial hair and respirator use.
- Applicable federal, state, and local regulations regarding respirators, including assessment of employees' knowledge.

Trainees should be provided resources as an adjunct to the respiratory-protection program.

- Opportunities to handle and wear a respirator until they are proficient (see Supplement, Fit Testing).
- Educational material for use as references.
- Instructions to refer all respirator problems immediately to the respirator program administrator.

Selection

Filtering facepiece respirators used for protection against *M. tuberculosis* must be selected from those approved by CDC/NIOSH under the provisions of 42 CFR 84 (http://www.cdc.gov/niosh/celintro.html). A listing of CDC/NIOSH-approved disposable particulate respirators (filtering facepieces) is available at http://www.cdc.gov/niosh/npptl/topics/respirators/disp_part. If a health-care setting uses respirators for protection against other regulated hazards (e.g., formaldehyde and ethylene oxide), then these potential exposures should be specifically addressed in the program. Combination product surgical mask/N95 disposable respirators (respirator portion certified by CDC/NIOSH and surgical mask portion listed by FDA) are available that provide both respiratory protection and bloodborne pathogen protection. Selection of respirators can be chosen through consultation with respirator fit-testing experts, CDC, occupational health and infection-control professional organizations, peer-reviewed research, respirator manufacturers, and advanced respirator training courses (*10,280–289*).

Fit Testing

A fit test is used to determine which respirator fits the user adequately and to ensure that the user knows when the respi-

rator fits properly. After a risk assessment is conducted to validate the need for respiratory protection, perform fit testing during the initial respiratory-protection program training and periodically thereafter, in accordance with federal, state, and local regulations.

Fit testing provides a method to determine which respirator model and size fits the wearer best and to confirm that the wearer can properly fit the respirator. Periodic fit testing for respirators used in environments where a risk for *M. tuberculosis* transmission exists can serve as an effective training tool in conjunction with the content included in employee training and retraining. The frequency of periodic fit testing should be supplemented by the occurrence of 1) a risk for transmission of *M. tuberculosis*, 2) a change in facial features of the wearer, 3) a medical condition that would affect respiratory function, 4) physical characteristics of respirator (despite the same model number), or 5) a change in the model or size of the assigned respirator (*281*).

Inspection and Maintenance

Respirator maintenance should be an integral part of an overall respirator program. Maintenance applies both to respirators with replaceable filters and to respirators that are classified as disposable but are reused. Manufacturer instructions for inspecting, cleaning, maintaining, and using (or reuse) respirators should be followed to ensure that the respirator continues to function properly (*278*).

When respirators are used for protection against noninfectious aerosols (e.g., wood dust) that might be present in the air in heavy concentrations, the filter can become obstructed with airborne material. This obstruction in the filter material can result in increased resistance, causing breathing to be uncomfortable. In health-care settings in which respirators are used for protection against biologic aerosols, the concentration of infectious particles in the air is probably low. Thus, the filter in a respirator is unlikely to become obstructed with airborne material. In addition, no evidence exists to indicate that particles that affect the filter material in a respirator are reaerosolized easily. Therefore, the filter material used in respirators in health-care settings might remain functional for weeks. Because electrostatic filter media can degrade, the manufacturer should be contacted for the product's established service life to confirm filter performance.

Respirators with replaceable filters are reusable, and a respirator classified as disposable can be reused by the same HCW as long as it remains functional and is used in accordance with local infection-control procedures. Respirators with replaceable filters and filtering facepiece respirators can be reused by HCWs as long as they have been inspected before each use and are within the specified service life of the manufacturer. If the filter material is physically damaged or soiled or if the manufacturer's service life criterion has been exceeded, the filter (in respirators with replaceable filters) should be changed or the disposable respirator should be discarded according to local regulations. Infection-control personnel should develop standard procedures for storing, reusing, and disposing of respirators that have been designated for disposal.

Evaluation

The respirator program must be evaluated periodically to ensure its continued effectiveness.

Cleaning, Disinfecting, and Sterilizing Patient-Care Equipment and Rooms

General

Medical instruments and equipment, including medical waste, used on patients who have TB disease are usually not involved in the transmission of *M. tuberculosis* (*478–480*). However, transmission of *M. tuberculosis* and pseudo-outbreaks (e.g., contamination of clinical specimens) have been linked to inadequately disinfected bronchoscopes contaminated with *M. tuberculosis* (*80,81,160,163,164,166*). Guidelines for cleaning, disinfecting, and sterilizing flexible endoscopic instruments have been published (*481–485*).

The rationale for cleaning, disinfecting, or sterilizing patient-care instruments and equipment can be understood more readily if medical devices, equipment, and surgical materials are divided into three general categories (*486*). The categories are critical, semicritical, and noncritical and are based on the potential risk for infection if an item remains contaminated at the time of use.

Critical Medical Instruments

Instruments that are introduced directly into the bloodstream or other normally sterile areas of the body (e.g., needles, surgical instruments, cardiac catheters, and implants) are critical medical instruments. These items should be sterile at the time of use.

Semicritical Medical Instruments

Instruments that might come into contact with mucous membranes but do not ordinarily penetrate body surfaces (e.g., noninvasive flexible and rigid fiberoptic endoscopes or bronchoscopes, endotracheal tubes, and anesthesia breathing circuits) are semicritical medical instruments. Although sterilization is preferred for these instruments, high-level disinfection that destroys vegetative microorganisms, the majority of fungal spores, mycobacteria (including tubercle bacilli), and small nonlipid viruses can be used. Meticulous cleaning of

such items before sterilization or high-level disinfection is essential (*481*). When an automated washer is used to clean endoscopes and bronchoscopes, the washer must be compatible with the instruments to be cleaned (*481,487*). High-level disinfection can be accomplished with either manual procedures alone or use of an automated endoscope reprocessor with manual cleaning (*80,481*). In all cases, manual cleaning is an essential first-step in the process to remove debris from the instrument.

Noncritical Medical Instruments or Devices

Instruments or devices that either do not ordinarily touch the patient or touch only the patient's intact skin (e.g., crutches, bed boards, and blood pressure cuffs) are noncritical medical instruments. These items are not associated with transmission of *M. tuberculosis*. When noncritical instruments or equipment are contaminated with blood or body substances, they should be cleaned and then disinfected with a hospital-grade, Environmental Protection Agency (EPA)-registered germicide disinfectant with a label claim for tuberculocidal activity (i.e., an intermediate-level disinfectant). Tuberculocidal activity is not necessary for cleaning agents or low-level disinfectants that are used to clean or disinfect minimally soiled noncritical items and environmental surfaces (e.g., floors, walls, tabletops, and surfaces with minimal hand contact).

Disinfection

The rationale for use of a disinfectant with tuberculocidal activity is to ensure that other potential pathogens with less intrinsic resistance than that of mycobacteria are killed. A common misconception in the use of surface disinfectants in health care relates to the underlying purpose of products labeled as tuberculocidal germicides. Such products will not interrupt and prevent transmission of *M. tuberculosis* in health-care settings, because TB is not acquired from environmental surfaces. The tuberculocidal claim is used as a benchmark by which to measure germicidal potency. Because mycobacteria have the highest intrinsic level of resistance among the vegetative bacteria, viruses, and fungi, any germicide with a tuberculocidal claim on the label (i.e., an intermediate-level disinfectant) is considered capable of inactivating many pathogens, including much less resistant organisms such as the bloodborne pathogens (e.g., hepatitis B virus, hepatitis C virus, and HIV). Rather than the product's specific potency against mycobacteria, a germicide that can activate many pathogens is the basis for protocols and regulations indicating the appropriateness of tuberculocidal chemicals for surface disinfection.

Policies of health-care settings should specify whether cleaning, disinfecting, or sterilizing an item is necessary to decrease the risk for infection. Decisions regarding decontamination processes should be based on the intended use of the item, not on the diagnosis of the condition of the patient for whom the item is used. Selection of chemical disinfectants depends on the intended use, the level of disinfection required, and the structure and material of the item to be disinfected.

The same cleaning procedures used in other rooms in the health-care setting should be used to clean AII rooms. However, personnel should follow airborne precautions while cleaning these rooms when they are still in use. Personal protective equipment is not necessary during the final cleaning of an AII room after a patient has been discharged if the room has been ventilated for the appropriate amount of time (see Supplement, Environmental Controls; Table 2).

Frequently Asked Questions (FAQs)

The following are FAQs regarding TST, QFT-G, BAMT, treatment for LTBI, risk assessment, environmental controls, respiratory protection, and cough-inducing and aerosol-generating procedures.

TST and QFT-G

- **Does having more than one TST placed in 1 year pose any risk?** No risk exists for having TSTs placed multiple times per year.
- **Can repeated TSTs, by themselves, cause the TST result to convert from negative to positive?** No, the TST itself does not cause false-positive results. Exposure to other mycobacteria or BCG vaccination can cause false-positive TST results.
- **What defines a negative TST result?** A TST result of 0 mm or a measurement below the defined cut point for each criteria category is considered a negative TST result (Box 2).
- **What defines a positive TST result?** A TST result of any millimeter reading above or at the defined cut point for each criteria category is considered a positive TST result (Box 2). The cut point (5 mm, 10 mm, and 15 mm) varies according to the purpose of the test (e.g., infection-control surveillance or medical and diagnostic evaluation, or contact investigation versus baseline testing).
- **What defines a false-negative result?** A false-negative TST or QFT-G result is one that is interpreted as negative for a particular purpose (i.e., infection-control surveillance versus medical and diagnostic evaluation) in a person who is actually infected with *M. tuberculosis*. False-negative TST results might be caused by incorrect TST placement (too deeply or too shallow), incorrect reading of the TST result, use of an incorrect antigen, or if the

person being tested is anergic (i.e., unable to respond to the TST because of an immunocompromising condition) or sick with TB disease.

- **What defines a false-positive result?** A false-positive TST or QFT-G result is one that is interpreted as positive for a particular purpose (i.e., infection-control surveillance versus medical and diagnostic evaluation) in a person who is actually not infected with *M. tuberculosis*. False-positive TST results are more likely to occur in persons who have been vaccinated with BCG or who are infected with NTM, also known as mycobacteria other than TB (MOTT). A false-positive TST result might also be caused by incorrect reading of the TST result (reading erythema rather than induration) or use of incorrect antigen (e.g., tetanus toxoid).
- **Is placing a TST on a nursing mother safe?** Yes, placing a TST on a nursing mother is safe.
- **A pregnant HCW in a setting is reluctant to get a TST. Should she be encouraged to have the test administered?** Yes, placing a TST on a pregnant woman is safe. The HCW should be encouraged to have a TST or offered BAMT. The HCW should receive education that 1) pregnancy is not contraindication to having a TST administered and 2) skin testing does not affecting the fetus or the mother. Tens of thousands of pregnant women have received TST since the test was developed, and no documented episodes of TST-related fetal harm have been reported. Guidelines issued by ACOG emphasize that postponement of the application of a TST as indicated and postponement of the diagnosis of infection with *M. tuberculosis* during pregnancy is unacceptable.
- **A pregnant HCW in a setting has a positive TST result and is reluctant to get a chest radiograph. Should she be encouraged to have the chest radiograph performed?** Pregnant women with positive TST results or who are suspected of having TB disease should not be exempted from recommended medical evaluations and radiography. Shielding consistent with safety guidelines should be used even during the first trimester of pregnancy.
- **Are periodic chest radiographs recommended for HCWs (or staff or residents of LTCFs) who have positive TST or BAMT results?** No, persons with positive TST or BAMT results should receive one baseline chest radiograph to exclude a diagnosis of TB disease. Further chest radiographs are not needed unless the patient has symptoms or signs of TB disease or unless ordered by a physician for a specific diagnostic examination. Instead of participating in serial skin testing, HCWs with positive TST results should receive a medical evaluation and a symptom screen. The frequency of this medical evaluation should be determined by the risk assessment for the setting. HCWs who have a previously positive TST result and who change jobs should carry documentation of the TST result and the results of the baseline chest radiograph (and documentation of treatment history for LTBI or TB disease, if applicable) to their new employers.
- **What is boosting?** Boosting is a phenomenon in which a person has a negative TST (i.e., false-negative) result years after infection with *M. tuberculosis* and then a positive subsequent TST result. The positive TST result is caused by a boosted immune response of previous sensitivity rather than by a new infection (false-positive TST conversion). Two-step testing reduces the likelihood of mistaking a boosted reaction for a new infection.
- **What procedure should be followed for a newly hired HCW who had a documented negative TST result 3 months ago at their previous job?** This person should receive one baseline TST upon hire (ideally before the HCW begins assigned duties). The negative TST result from the 3 months preceding new employment (or a documented negative TST result anytime within the previous 12 months) should be considered the first step of the baseline two-step TST. If the HCW does not have documentation of any TST result, the HCW should be tested with baseline two-step TST (one TST upon hire and one TST placed 1–3 weeks after the first TST result was read).
- **Why are two-step TSTs important for the baseline (the beginning of an HCW's employment)?** If TST is used for TB screening (rather than BAMT), performing two-step TST at baseline minimizes the possibility that boosting will lead to suspicion of transmission of *M. tuberculosis* in the setting during a later contact investigation or during serial testing (false-positive TST conversions). HCWs who do not have documentation of a positive TST result or who have not been previously treated for LTBI or TB disease should receive baseline two-step TST.
- **If a person does not return for a TST reading within 48–72 hours, when can a TST be placed on them again?** A TST can be administered again as soon as possible. If the second step of a two-step TST is not read within 48–72 hours, administer a third test as soon as possible (even if multiple months have elapsed), and ensure that the result is read within 48–72 hours.
- **Should a TST reading of ≥10 mm be accepted 7 days after the TST was placed?** If the TST was not read between 48–72 hours, another TST should be placed as soon as possible and read within 48–72 hours. However, certain studies indicate that positive TST reactions might

still be measurable 4–7 days after the TST was placed. If the TST reaction is read as ≥15 mm 7 days after placement, the millimeter result can be recorded and considered to be a positive result.

- **Do health-care settings or areas in the United States exist for which baseline two-step skin TST for newly hired HCWs is not needed?** Ideally, all newly hired HCWs who might share air space with patients should receive baseline two-step TST (or one-step BAMT) before starting duties. In certain settings, a choice might be offered not to perform baseline TST on HCWs who will never be in contact with or share air space with patients who have TB disease, or who will never be in contact with clinical specimens (e.g., telephone operators in a separate building from patients).
- **In our setting, workers are hired to provide health care in homes, and they are not medically trained. Two-step skin testing is difficult because of the requirement to return for testing and reading multiple times. Can the two-step TST be omitted?** No, ideally, all HCWs who do not have a previously documented positive TST result or treated LTBI or TB disease should receive two-step baseline skin testing in settings that have elected to use TST for screening. BAMT is a single test procedure. Baseline testing for *M. tuberculosis* infection will ensure that TB disease or LTBI is detected before employment begins and treatment for LTBI or TB disease is offered, if indicated.
- **When performing two-step skin testing, what should be done if the second-step TST is not placed in 1–3 weeks?** Perform the second-step TST as soon as possible, even if several months have passed.
- **Should gloves be worn when placing TST?** Specific CDC recommendations do not exist regarding this topic. If your local area indicates that universal precautions should be practiced with skin testing, the local areas should determine what precautions should be followed in their setting.
- **Is TST QC important?** Yes, performing QC for HCWs during training and retraining of placing and reading TST is important to avoid false-negative and false-positive TST results, and to ensure appropriate treatment decisions.
- **If the longitudinal reading of the induration of the TST result is 12 mm and the horizontal reading is 8 mm, what should be recorded?** The correct TST reading should be recorded as 8 mm (not 12 mm or 8 x 12 mm). For purposes of standardization, only record the millimeters of induration, which should be measured transversely (i.e., perpendicular), to the long axis of the forearm. Erythema (redness) around the TST site should not be read as part of the TST result. Consideration should be given to retesting if the selected area for placement was on or near a muscle margin, scar, heavy hair, veins, or tattoos, which could be barriers to reading the TST result, or consider offering a BAMT. BAMT results should be recorded in detail. The details should include date of blood draw, result in specific units, and the laboratory interpretation (positive, negative, or indeterminate—and the concentration of cytokine measured, e.g., IFN-γ).
- **Should HCWs who report upon hire that they have had a positive TST result or have been previously treated for LTBI or TB disease receive baseline two-step TST when beginning work at a new health-care setting?** Unless the HCW has documentation of a positive TST result or previously treated LTBI or TB disease, they should usually receive baseline two-step testing before starting duties. If documentation is available of a positive TST result, that result can be considered as the baseline TST result for the HCW at the new setting, and additional testing is not needed. Recommendations for testing HCWs who transfer from one setting to another where the risk assessment might be different are presented (see Use of Risk Classification to Determine Need for TB Screening and Frequency of Screening HCWs).
- **If an HCW has a baseline first-step TST result between 0–9 mm, does a second-step TST need to be placed?** Yes, if the baseline first-step TST result is <10 mm, a second-step TST should be applied 1–3 weeks after the first TST result was read. HCWs who are immunocompromised are still subject to the 10 mm cutoff for baseline two-step testing for surveillance purposes but would be referred for medical evaluation for LTBI using the 5 mm cutoff.
- **An HCW in a medium-risk setting who had a two-step baseline TST result of 8 mm is retested 1 year later for serial TB screening and had a TST result of 16 mm. No known exposure to *M. tuberculosis* had occurred. Although the TST is now >10 mm, a ≥10 mm increase did not occur in the TST result to meet the criteria for a TST conversion. How should this reading be interpreted?** The TST result needs to be interpreted from two perspectives: 1) administrative and 2) individual medical interpretation. Because an increase by ≥10 mm did not occur, the result would not be classified as a TST conversion for administrative purposes. However, this HCW should be referred for a medical evaluation. The following criteria are used to determine whether a TST result is positive or negative, considering

individual clinical grounds: 1) absolute measured induration (i.e., ≥5, ≥10, or ≥15 mm induration, depending on the level of risk and purpose of testing); 2) the change in the size of the TST result; 3) time frame of the change; 4) risk for exposure, if any; and 5) occurrence of other documented TST conversions in the setting. For HCWs at low risk for LTBI, TST results of 10–14 mm can be considered negative from a clinical standpoint, and these HCWs should not have repeat TST, because an additional increase in induration of ≥10 mm will not be useful in determining the likelihood of LTBI.

- **Are baseline two-step TST needed for HCWs who begin jobs that involve limited contact with patients (e.g., medical records staff)?** Yes, all HCWs who might share air space with patients should receive baseline two-step TST (or one-time BAMT) before starting duties. However, in certain settings, a choice might be offered not to perform baseline TST on HCWs who will never be in contact with or share air space with patients who have TB disease, or who will never be in contact with clinical specimens (e.g., telephone operators in a separate building from patients).
- **A setting conducts skin testing annually on the anniversary of each HCW's employment. Last year, multiple TST conversions occurred in April; therefore, all HCWs received a TST during that month. In the future, do all HCWs need to be tested annually in April?** No, after a contact investigation is performed, the best and preferred schedule for annual TB screening is on the anniversary of the HCW's employment date or on their birthday (rather than testing all HCWs at the same time each year), because it increases the opportunity for early recognition of infection-control problems that can lead to TST conversions.
- **An HCW who has been vaccinated with BCG is being hired. She states that BCG will make her TST result positive and that she should not have a TST. Should this HCW be exempted from baseline two-step TST?** Unless she has documentation of a positive TST result or previously treated LTBI or TB disease, she should receive baseline two-step TST or one BAMT. Some persons who received BCG never have a positive TST result. For others, the positive reaction wanes after 5 years. U.S. guidelines state that a positive TST result in a person who received BCG should be interpreted as indicating LTBI.
- **Does BCG affect TST results and interpretations?** BCG is the most commonly used vaccine in the world. BCG might cause a positive TST (i.e., false-positive) result initially; however, tuberculin reactivity caused by BCG vaccination typically wanes after 5 years but can be boosted by subsequent TST. No reliable skin test method has been developed to distinguish tuberculin reactions caused by vaccination with BCG from reactions caused by natural mycobacterial infections, although TST reactions of ≥20 mm of induration are not usually caused by BCG.
- **What steps should be taken when an HCW has had a recent BCG vaccination?** When should the TST be placed? A TST may be placed anytime after a BCG vaccination, but a positive TST result after a recent BCG vaccination can be a false-positive result. QFT-G should be used, because the assay test avoids cross reactivity with BCG.
- **A hospital HCW has not had a TST in 18 months because she was on maternity leave and missed her annual TST. She has been employed at the hospital for the previous 5 years. Is two-step testing necessary on her next skin test date?** No, two-step TSTs are needed only to establish a baseline for a specific setting for newly hired HCWs and others who will receive serial TST (e.g., residents or staff of correctional facilities or LTCFs). The HCW should have a single TST or BAMT upon returning to work and should then resume a routine testing schedule on the next normal TST anniversary date.
- **Should two-step testing be performed in a contact investigation for HCWs who have not had a TST within the preceding 12 months?** No, two-step testing should only be used for baseline TST screening and has no role in a contact investigation. In a contact investigation, a follow-up TST should be placed 8–10 weeks after an initial negative TST result is read.
- **What length of time should a person who has had contact with someone with TB disease be included in a contact investigation?** This decision can best be made in consultation with the local TB program, which frequently has experience responding to similar situations. A minimum exposure time has not been established, but the minimum length of contact time with a person who has TB disease necessary for transmission will depend on multiple factors. Begin by estimating the duration of the infectious period (see Supplement, Contact Investigations; and CDC self-training modules [http://www.phppo.cdc.gov/phtn/tbmodules/modules6-9/m6/6-12.htm]). The highest priority for evaluation should be given to 1) persons with a medical risk factor for TB disease (e.g., HIV infection or immunosuppressive therapy); 2) infants and children <4 years; 3) household or congregate setting contacts; and 4) persons present during medical procedures (e.g., bronchoscopies, sputum induction, or autopsies).

In addition, offer TB screening to all persons named by the patient as work or social contacts during the infectious period. Determining whether to broaden the investigation will depend on whether evidence of transmission to any of the above contacts exists (positive TST or BAMT results or conversions), the duration of the potential exposure, and the intensity of the exposure (e.g., in a poorly ventilated environment versus outdoors). If the exposure was to pulmonary TB that was cavitary on chest radiograph or if the patient had positive AFB sputum smear results, usually the minimum exposure duration for a person to be considered a contact would be shorter. Nonetheless, infection with *M. tuberculosis* requires some degree of prolonged or regular exposure (i.e., days to weeks, not just a few hours).

- **If an HCW in a setting has a latex allergy, should this person receive a TST?** A person with a latex allergy can receive a TST when latex-free products are used. Latex allergy can be a contraindication to skin testing if the allergy is severe and the products used to perform the test (e.g., syringe plungers, PPD antigen bottle stopper, and gloves) contain latex. Latex-free products are, however, usually available. If a person with a latex allergy does have a TST performed using products or equipment that contain latex, interpretation of the TST results can be difficult, because the TST reaction might be the result of the latex allergy, reaction to PPD, or a combination of both. Consider repeating the TST using latex-free products or use BAMT.
- **Should the TST site be covered with an adhesive bandage?** No, avoid covering the TST site with anything that might interfere with reading the TST result (e.g., adhesive bandages, cream, ointment, lotion, liquids, and medication).
- **When can a TST be placed if other vaccines are also being administered (e.g., measles, varicella, yellow fever, and smallpox)?** A TST should be administered either on the same day as vaccination with live virus or 4–6 weeks later. Vaccines that might cause a false-negative TST result are measles, varicella, yellow fever, smallpox, BCG, mumps, rubella, oral polio, oral typhoid, and live-attenuated influenza.
- **How frequently should persons in the general public receive TST?** Testing for LTBI in the general public is not necessary unless the person is at risk for exposure to *M. tuberculosis* (e.g., someone who had contact with a person with TB disease) or at increased risk for progression to TB disease [e.g., someone infected with HIV]).
- **Should we use a multiple puncture (Tine®) skin test to perform a TST?** No, in the United States, the Mantoux method of skin testing is the preferred method because it is more accurate than Tine® skin tests. BAMT (currently QFT-G) is also now recommended as a test for *M. tuberculosis* infection.
- **What steps should be taken if an HCW has a baseline TST result of 16 mm and 1 year later the TST result was read as 0 mm?** If documentation existed for the 16 mm result, administering another TST to the HCW subsequently was not necessary. One or both of these TST results could be false results. The first result might have been documented as 16 mm, but perhaps 16 mm of erythema was measured and no induration was present. The second result of 0 mm might have been caused by incorrect administration of the TST (i.e., too deeply or too shallow), or was read and recorded incorrectly if it was actually positive). In this instance, another TST should be placed, or a BAMT should be offered, or if TB disease is suspected, a chest radiograph should be performed.
- **What steps should be taken if the TST is administered intramuscularly instead of intradermally?** QC for administering TST is critical. If the TST is administered intramuscularly (too deeply), repeat the skin test immediately, or offer BAMT.
- **How are annual TST conversion rates for HCWs calculated?** A TST conversion is a change in the result of a test for *M. tuberculosis* infection wherein the condition is interpreted as having progressed from uninfected to infected. Annual TST conversion rates are calculated for a given year by dividing the number of test conversions among HCWs in the setting that year (numerator) by the total number of HCWs who received tests in the setting that year (denominator) multiplied by 100. By calculating annual TST conversion rates, year-to-year comparisons can be used to identify transmission of *M. tuberculosis* that was not previously detected.
- **Where can PPD be obtained?** Local and state health departments can provide PPD antigen for TST without charge to selected targeted testing and treatment programs. Purchase of the antigen and supplies is regulated by local and state laws related to professional licensure.
- **Where can millimeter rulers be obtained to measure TST results?** A TST training kit, which includes a TST training video, guide for facilitators, and a TST millimeter ruler is available free of charge from CDC (https://www2.cdc.gov/nchstp_od/PIWeb/TBorderform.asp). In addition, check with your local or state health department and TST antigen manufacturers.
- **Where can materials be obtained for educating HCWs regarding TB?** A list of TB websites and resources is avail-

able (Appendix E). Local or state health departments should have additional materials and access to resources and might be able to help develop a setting-specific TB education program.

- **Where can self-reading TST cards be obtained that allow HCWs to report their own results?** HCWs and patients should not be allowed to read and report their own TST results; therefore, self-reading cards for reporting TST results are not recommended. All TST results should be read and recorded by a trained TST reader other than the person on whom the TST was placed.

Treatment for LTBI

- **Who should be treated for LTBI?** Persons with LTBI who are at increased risk for developing TB disease should be offered treatment for LTBI regardless of age, if they have no contraindication to the medicine.
- **What are contraindications to treatment of LTBI?** Active hepatitis and ESLD are contraindications to the use of INH for treatment of LTBI. Persons who have these conditions might be eligible for rifampin for 4 months for treatment of LTBI. Because of the substantial and complex drug-drug interactions between rifamycins and HIV protease inhibitors (PI) and nonnucleoside reverse transcriptase inhibitors (NNRTI), clinicians are encouraged to seek expert advice if the concurrent use of these drugs is being considered in persons infected with HIV. Information regarding use of these drugs is available at http://www.cdc.gov/nchstp/tb/tb_hiv_drugs/toc.htm.
- **Do persons need to be in a specific age range to be eligible for treatment of LTBI?** No age restriction for eligibility of treatment for LTBI currently exists. Targeted TST programs should be conducted for persons at high risk, and these programs are discouraged for persons or settings considered to be low risk. However, for infection-control programs that conduct TB screening that includes HCWs who are frequently at low risk, proper medical evaluation needs to be conducted when an HCW with a positive TST result is identified. In this context, age might be a factor in the decision to administer treatment, because older persons are at increased risk for hepatic toxicity caused by INH.
- **What is the preferred regimen for treatment of LTBI?** Nine months of daily INH is the preferred treatment regimen for patients who have LTBI. The 6-month regimen of INH or the 4-month regimen of rifampin are also acceptable alternatives.
- **Why is the 2-month regimen of RZ generally not offered for treatment of LTBI?** Although the 2-month regimen of RZ was previously recommended as an option for the treatment of LTBI, reports of severe liver injury and death prompted the American Thoracic Society and CDC to revise recommendations to indicate that this regimen should generally not be offered for treatment of LTBI.
- **Can sputum specimens collected over a 2-day period that are reported as negative for AFB be used to exclude a diagnosis of TB disease?** Yes, airborne precautions can be discontinued when infectious TB disease is considered unlikely and either 1) another diagnosis is made that explains the clinical syndrome or 2) the patient has three negative AFB sputum smear results (*109–112*). Each of the three consecutive sputum specimens should be collected 8–24 hours apart (*124*), and at least one specimen should be an early morning specimen, because respiratory secretions pool overnight. Generally, this method will allow patients with negative sputum smear results to be released from airborne precautions in 2 days.
- **When does an infectious TB patient become noninfectious?** Historically, health-care professionals have believed that the effect of antituberculosis treatment to reduce infectiousness was virtually immediate; older texts state that patients on antituberculosis treatment are not infectious. Surrogates that are used for noninfectiousness include conversion of positive sputum AFB results to negative AFB results and clinical response to antituberculosis treatment (i.e., improvement of symptoms and chest radiograph result).

Risk Assessment

- **In certain health-care settings (e.g., outpatient clinics or emergency medical settings) where patients are evaluated before a hospitalization during which TB disease is diagnosed, determining the number of TB patients who were encountered can be difficult. How should the risk classification be assigned?** These situations underscore the importance of obtaining an accurate patient history, completing contact investigations for all persons with suspected or confirmed TB disease, and ensuring effective communication to all settings in which persons with TB disease are encountered before diagnosis. Collaboration between infection-control personnel at the setting and the TB-control program staff at the local health department can help with this estimation.
- **At a pediatric hospital, the parents are normally with the child at the time of the TB diagnosis, and the parents can be diagnosed with TB disease at the same time as the child. To determine the number of patients diagnosed at the health-care setting, should the parents with TB disease who are visiting also be included in the total TB patient count?** Only patients with TB

disease who were evaluated or treated in the health-care setting count, not visitors who have TB (unless they were diagnosed at the same setting).

- **In a 160-bed hospital, three HCWs have had TST conversions during a 2-month period, which is usually the number of TST conversions detected in the hospital in 1 year. Should the setting be classified as potential ongoing transmission?** If the HCWs with TST conversions can be linked together in some way, either through a job type, location of work, or DNA fingerprinting, then the classification of potential ongoing transmission might apply to one group of HCWs or one part of the setting. Evidence of ongoing transmission in this setting appears to exist, and a problem evaluation should be conducted to ascertain the reason for the TST conversions (see Problem Evaluation). Reasons could range from an undiagnosed case of TB in the setting to incorrect placement or reading of TST. Early consultation with the local health department and an expert in TB infection control might be helpful in identifying and resolving the problem.
- **If a health-care setting has a risk classification of potential ongoing transmission, how long should that classification be applied?** The classification of potential ongoing transmission should be assigned only on a temporary basis and always warrants a problem evaluation (see Problem Evaluation). After resolution of problems, settings with a classification of potential ongoing transmission should be reclassified as a medium-risk classification for at least 1 year.

Environmental Controls

- **What is the difference between environmental controls and engineering controls ?** "Environmental controls" is a more inclusive term than "engineering controls". Examples of environmental controls are UVGI, HEPA filters and AII rooms. Examples of engineering controls are local exhaust ventilation (e.g., booths, hoods, and tents) and general ventilation (including directional airflow and negative pressure).
- **Is an AII room the same as a negative-pressure isolation room?** "AII room" is an accepted term and is used in the AIA guidelines that describe the purpose for and details of ventilation of AII rooms. An AII room is a special negative-pressure room for the specific purpose of isolating persons who might have suspected or confirmed infectious TB disease from other parts of the setting. Not all negative-pressure rooms are AII rooms, because they might not have the required air flow or differential pressure of an AII room.
- **Our TB clinic only treats persons with LTBI. Do we need an AII room and a respiratory-protection program?** Ideally, yes, because persons with LTBI are at risk for developing TB disease. TB clinics usually should have at least one AII room and a respiratory-protection program. An AII room and a respiratory-protection program might not be needed if 1) each person treated in the clinic will be adequately screened before admission and are determined to not have TB disease, 2) a system exists to promptly detect and triage persons who have symptoms or signs of TB disease, and 3) no cough-inducing procedures will ever be performed in the clinic.
- **Can airborne precautions be discontinued for a patient with suspected TB disease who has positive AFB sputum smear results but has a negative NAA for *M. tuberculosis*?** Yes, if the NAA test result is negative and dual infection with *M. tuberculosis* and another mycobacterial species is not clinically suspected, the patient may be released from airborne precautions. An NAA test is highly sensitive and specific for the identification of *M. tuberculosis* when performed properly on a patient who has a positive AFB sputum smear result.
- **During the winter months at a hospital, inadequate numbers of AII rooms are available for all patients with suspected or confirmed infectious TB disease. Can only two negative sputum smear results be obtained for AFB before releasing patients from airborne precautions?** In general, the criterion for the release of a patient with suspected infectious TB disease from airborne precautions is that infectious TB disease is considered unlikely and either 1) another diagnosis is made that explains the clinical syndrome or 2) the patient has three negative AFB sputum smear results (*109–112*). Each of the three consecutive sputum specimens should be collected 8–24 hours apart (*124*), and at least one specimen should be an early morning specimen. Generally, this method will allow patients with negative sputum smear results to be released from airborne precautions in 2 days. If the number of AII rooms in the setting is inadequate, consider adding one or more AII rooms. Before undertaking this expense, however, ensure that the criteria for placing patients in AII rooms are correct and that the available rooms are not being used for patients in whom infectious TB disease is not suspected. In addition, the following intervals should be reviewed to identify any delays that could be corrected and decrease time for patients in AII rooms: 1) time between admission and ordering of sputum specimens for AFB examination, 2) time between ordering and collecting specimens, and 3)

time between collection of specimens and receipt of results from the laboratory.

- **How many AII rooms are required in a 120-bed hospital?** For a hospital with 120 beds, a minimum of one AII room is needed. Although no available data exist to quantify the number of rooms needed for a given number of cases of suspected or confirmed TB disease, a reasonable choice is one additional AII room for every 200 patient-days of cases of suspected or confirmed TB disease. The setting's risk assessment will help determine the number of AII rooms needed.
- **Who is responsible for ensuring that negative pressure is achieved in AII rooms?** Ensuring that negative pressure is achieved in AII rooms is a function of the infection-control program at each health-care setting. This responsibility may be delegated to engineering, maintenance, or other appropriate staff to perform the actual negative pressure tests. AII rooms should be checked for negative pressure before occupation by a patient with suspected or confirmed infectious TB disease, and when in use by a person with TB disease, negative pressure should be checked daily with smoke tubes or other visual checks.
- **What is the difference between VAV and CAV? How do I determine which settings need them?** VAV is variable air volume, and CAV is constant air volume. These terms refer to how the ventilation system is designed to deliver air to and maintain temperature and relative humidity control within a room. CAV systems usually are best for AII rooms and other negative-pressure rooms, because the negative-pressure differential is easier to maintain. VAV systems are acceptable if provisions are made to maintain the minimum total and outside ACH and a negative pressure $\geq$0.01 inch of water gauge relative to adjacent areas at all times.
- **Why was the differential pressure requirement for an AII room increased from 0.001 inch of water gauge to $\geq$0.01 inch of water gauge?** In an ideal, controlled environment, 0.001 inches of water gauge has been demonstrated to ensure negative pressure in AII rooms. However, AIA and other organizations have demonstrated that a minimum of 0.01 inches of water gauge is needed in certain installations to ensure that negative pressure is consistently achieved.
- **How can a portable HEPA filter unit help control TB?** Portable HEPA filtration units recirculate room air, and the HEPA filters effectively remove all particles from the air in the size range of droplet nuclei, resulting in a dilution of the concentration of infectious particles in the room.

Respiratory Protection

- **What is the difference between a CDC/NIOSH-certified respirator and a surgical or procedure mask?** Respirators are designed to help reduce the wearer's (i.e., HCW's) exposure to airborne particles. The primary purpose of a surgical or procedure mask is to help prevent biologic particles from being expelled into the air by the wearer (i.e., patient).
- **How important is the fit of the respirator?** This step is critical. The fit of a respirator is substantially important. If a respirator does not fit tightly on the face, airborne hazards can penetrate or enter underneath the facepiece seal and into the breathing zone. Before each use, the wearer of a respirator should perform a user-seal check on themselves to minimize contaminant leakage into the facepiece (http://www.cdc.gov/niosh/topics/respirators).
- **How do I perform a respirator user-seal check?** Performing a user-seal check (formerly called "fit check") after redonning the respirator each time is critical to ensure adequate respiratory protection. The seal checks for respirators are described in the respirator user instructions and should be consulted before the respirator is used. The two types of user-seal checks usually are positive-pressure and negative-pressure checks.

  To check positive pressure seal after donning the respirator, the wearer should cover the surface of the respirator with their hands or with a piece of household plastic film and exhale gently. If air is felt escaping around the facepiece, the respirator should be repositioned, and the user-seal check should be performed again. If the wearer does not feel air escaping around the facepiece, the positive pressure user-seal check was successful.

  To check the negative pressure seal after donning the respirator, the wearer should gently inhale, which should create a vacuum, causing the respirator to be drawn in toward the face. If the respirator is not drawn in toward the face or if the wearer feels air leaking around the face seal, the respirator should be removed and examined for any defects (e.g., a small hole or poor molding of the respirator to the face [especially around the nose area]). If no holes are found, the respirator should be repositioned and readjusted, and a second attempt at negative pressure user-seal check should be made. If the check is not successful, try a new respirator.
- **Is performing a user-seal check (formerly called "fit check") on a respirator before each use always necessary?** Yes, performing a user-seal check on respirators before each use is essential to minimize contaminant leakage into the facepiece. Each respirator manufacturer has a rec-

ommended user-seal check procedure that should be followed by the user each time the respirator is worn.

- **What is a respirator fit test and who does fit testing?** A fit test is used to determine which respirator does or does not fit the user adequately and to ensure that the user knows when the respirator fits properly. Fit testing must be performed by a qualified health professional. Fit testing should be performed during the initial respiratory-protection program training and periodically thereafter, based on the risk assessment for the setting and in accordance with applicable federal, state, or local regulations.

  Periodic fit testing for respirators used in TB environments can serve as an effective training tool in conjunction with the content included in employee training and retraining. The frequency of fit testing should be determined by a change in the 1) risk for transmission of *M. tuberculosis*, 2) facial features of the wearer, 3) medical condition that would affect respiratory function, 4) physical characteristics of the respirator (despite the same model number), or 5) model or size of the assigned respirator.
- **What kind of respiratory protection should HCWs use when providing care to persons with suspected or confirmed infectious TB disease in the home?** The recommended respiratory protection for HCWs who provide care in the homes of patients with suspected or confirmed infectious TB disease is at least an N95 respirator.
- **What kind of respiratory protection should HCWs use when transporting patients with suspected or confirmed infectious TB disease?** The risk assessment for the setting should consider the potential for shared air. Drivers, HCWs and other staff who are transporting patients with suspected or confirmed infectious TB disease in an enclosed vehicle should consider wearing an N95 disposable respirator. If the patient has symptoms or signs of infectious TB disease (e.g., productive cough or positive AFB sputum smear result), the patient should wear a surgical or procedure mask, if possible, during transport, in waiting areas, or when other persons are present. Patients who cannot tolerate masks because of medical conditions should observe strict respiratory hygiene and cough etiquette procedures.
- **What type of respiratory protection should be used in the operating room (OR) by HCWs with facial hair or other factors that preclude proper fitting of an N95 respirator?** Will wearing a surgical or procedure mask underneath a PAPR solve this problem? HCWs with facial hair should not wear negative pressure respirators (e.g., N95 disposable respirators that require a tight faceseal). In the OR, HCWs with facial hair who are caring for a person with suspected or confirmed infectious TB disease should consult their infection-control committee and respirator manufactures regarding optimal respiratory protection and adequate infection-control measures. The HCW in this case might wear a surgical or procedure mask to protect the surgical field underneath a loose-fitting PAPR. However, the user cannot be assured of proper operation unless the PAPR's manufacturer tested the PAPR over a surgical or procedure mask or N95 respirator. All respiratory-protection equipment should be used in accordance with the manufacturer's instructions.
- **Should bacterial filters be used routinely on the breathing circuits of all ventilators and anesthesia equipment on patients with suspected or confirmed infectious TB disease?** Yes, bacterial filters should be used routinely on the exhalation breathing circuits of patients with suspected or confirmed infectious TB disease to prevent exhaled air containing infectious droplet nuclei from contaminating the room air. Filters should be used on mechanical ventilators and also on hand-held ventilating bags (i.e., manual resuscitators [e.g., ambu-bags®]). The bacterial filter should be specified by the manufacturer to filter particles 0.3 μm in both the unloaded and the loaded states, with a filter efficiency of ≥95% (i.e., filter penetration of <5%) at the maximum design flow rates of the ventilator.
- **Who should not wear an N95 respirator?** Any HCW who is restricted from using a respirator because of medical reasons should not wear one nor should persons who cannot pass a fit test because of the presence of facial hair or other condition that interferes with the seal of the respirator to the face.
- **How long can I use my respirator for TB exposures before I discard it?** Disposable respirators can be functional for weeks to months and reused by the same HCW. Reuse is limited by hygiene, damage, and breathing resistance, and manufacturer instructions should be considered.
- **Should persons who perform maintenance on and replace filters on any ventilation system that is likely to be contaminated with *M. tuberculosis*** wear a respirator? Laboratory studies indicate that re-aerosolization of viable mycobacteria from HEPA filters and N95 disposable respirator filter media is unlikely under normal conditions; however, the risks associated with handling loaded HEPA filters in ventilation systems under field-use conditions have not been evaluated. Therefore, persons performing maintenance and replacing filters on any ventilation system that is likely to be contaminated with

M. tuberculosis should wear a respirator (see Respiratory Protection) and adhere to local recommendations for eye protection and gloves.

Cough-Inducing and Aerosol-Generating Procedures

- **Should a bronchoscopic procedure be performed on a patient with TB disease?** If possible, bronchoscopic procedures should be avoided for patients with 1) a clinical syndrome consistent with infectious pulmonary or laryngeal TB disease and 2) in persons with positive AFB sputum smear results, because bronchoscopic procedures substantially increase the risk for transmission either through an airborne route or a contaminated bronchoscope. If the diagnosis of TB is suspected, consideration should be given to empiric antituberculosis treatment, but a bronchoscopic procedure might have the advantage of confirmation of the diagnosis with histologic specimens; collection of additional specimens, including post bronchoscopy sputum that can increase the diagnostic yield and increase the opportunity to confirm an alternate diagnosis. Microscopic examination of three consecutive sputum specimens obtained at least 8 hours apart is recommended instead of bronchoscopy.
- **For ORs without an AII room, postoperative recovery is usually in the OR suite.** Is this location acceptable? If the OR has an anteroom, this location is acceptable. Reversible flow rooms (OR or isolation) are not recommended by CDC, AIA, or ASHRAE.

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Terms and Abbreviations Used in this Report

ACET	Advisory Council for the Elimination of Tuberculosis
ACGIH	American Conference of Governmental Industrial Hygienists
ACH	Air changes per hour
ACOG	American College of Obstetricians and Gynecologists
AERS	Adverse event reporting system
AFB	Acid-fast bacilli
AIA	American Institute of Architects
AIDS	Acquired immunodeficiency syndrome
AII	Airborne infection isolation
ALA	American Lung Association
ALT	Alanine aminotransferase
ANSI	American National Standards Institute
APF	Assigned protection factor
APIC	Association for Professionals in Infection Control and Epidemiology, Inc.
ART	Antiretroviral therapy
ASHRAE	American Society of Heating, Refrigerating, and Air-Conditioning Engineers, Inc.
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BAMT	Blood assay for *Mycobacterium tuberculosis*
BCG	Bacille Calmette-Guérin
BIDR	Blinded independent duplicate reading
BMBL	Biosafety in Microbiological and Biomedical Laboratories
BSL	Biosafety level
BSC	Biological safety cabinet
CAV	Constant air volume
CDC	Centers for Disease Control and Prevention
CEL	Certified equipment list
CFM	Cubic feet per minute
CFR	Code of Federal Regulations
CoV	Coronavirus
CPL	Compliance policy directive

CT	Computed tomography
DHHS	U.S. Department of Health and Human Services
DNA	Deoxyribonucleic acid
DTBE	Division of Tuberculosis Elimination
DOT	Directly observed therapy
DTH	Delayed-type hypersensitivity
ED	Emergency department
EMS	Emergency medical service
EPA	Environmental Protection Agency
ESRD	End-stage renal disease
ETL	Electrical Testing Laboratories
FDA	U.S. Food and Drug Administration
FGI	Facility Guideline Institute
FPM	Feet per minute
HAART	Highly active antiretroviral therapy
HCW	Health-care worker
HEPA	High-efficiency particulate air
HIV	Human immunodeficiency virus
HMO	Health maintenance organization
HPLC	High-pressure liquid chromatograph
HVAC	Heating, ventilation, air conditioning
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
IFN-γ	Inteferon-gamma
IGRA	Interferon gamma release assay
INH	Isoniazid
IUATLD	International Union Against Tuberculosis and Lung Disease
JCAHO	Joint Commission on Accreditation of Healthcare Organizations
LTBI	Latent tuberculosis infection
MDR TB	Multidrug-resistant tuberculosis
MOTT	Mycobacterium other than tuberculosis
NAA	Nucleic acid amplification
NCID	National Center for Infectious Diseases

NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NM	Nanometer
NNRTI	Nonnucleoside reverse transcriptase inhibitors
NPIN	National Prevention Information Network
NTCA	National Tuberculosis Controllers Association
NTM	Nontuberculous mycobacteria
OR	Operating room
OSHA	Occupational Safety and Health Administration
PAPR	Powered air-purifying respirator
PCP	*Pneumocystis pneumonia*
PCR	Polymerase chain reaction
PE	Protective environment
PET	Permissible exposure time
PI	Protease inhibitor
PPD	Purified protein derivative
PPE	Personal protective equipment
QC	Quality control
QFT	QuantiFERON®-TB test
QFT-G	QuantiFERON®- TB Gold test
QLFT	Qualitative fit test
QNFT	Quantitative fit test
REL	Recommended exposure limit
RFLP	Restriction fragment length polymorphism
RNA	Ribonucleic acid
RZ	Rifampin and pyrazinamide
SARS	Severe acute respiratory syndrome
SGOT	Serum glutamic-oxalacetic transaminase*
SGPT	Serum glutamic-pyruvic transaminase†
SWPF	Simulated workplace protection factor
TB	Tuberculosis
TNF-α	Tumor necrosis factor-alpha

TU	Tuberculin unit
TST	Tuberculin skin test
UL	Underwriters Laboratories
UV	Ultraviolet
UVGI	Ultraviolet germicidal irradiation
VAV	Variable air volume
WHO	World Health Organization
WPF	Workplace protection factor

* Older term for AST.
† Older term for ALT.

Glossary of Definitions

acid-fast bacilli (AFB) examination	A laboratory test that involves microscopic examination of a stained smear of a patient specimen (usually sputum) to determine if mycobacteria are present. A presumptive diagnosis of pulmonary tuberculosis (TB) can be made with a positive AFB sputum smear result; however, approximately 50% of patients with TB disease of the lungs have negative AFB sputum smear results. The diagnosis of TB disease is usually not confirmed until *Mycobacterium tuberculosis* is identified in culture or by a positive nucleic acid amplification (NAA) test result.
administrative controls	Managerial measures that reduce the risk for exposure to persons who might have TB disease. Examples include coordinating efforts with the local or state health department; conducting a TB risk assessment for the setting; developing and instituting a written TB infection-control plan to ensure prompt detection, airborne infection isolation (AII), and treatment of persons with suspected or confirmed TB disease; and screening and evaluating health-care workers (HCWs) who are at risk for TB disease or who might be exposed to *M. tuberculosis.*
aerosol	Dispersions of particles in a gaseous medium (e.g., air). Droplet nuclei are an example of particles that are expelled by a person with an infectious disease (e.g., by coughing, sneezing, or singing). For *M. tuberculosis*, the droplet nuclei are approximately 1–5 μm. Because of their small size, the droplet nuclei can remain suspended in the air for substantial periods and can transmit *M. tuberculosis* to other persons.
air change rate	Ratio of the airflow in volume units per hour to the volume of the space under consideration in identical volume units, usually expressed in air changes per hour (ACH).
air change rate (equivalent)	Ratio of the volumetric air loss rate associated with an environmental control (or combination of controls) (e.g., an air cleaner or ultraviolet germicidal irradiation [UVGI] system) divided by the volume of the room where the control has been applied. The equivalent air change rate is useful for describing the rate at which bioaerosols are removed by means other than ventilation.
air change rate (mechanical)	Ratio of the airflow to the space volume per unit time, usually expressed in air changes per hour (ACH).
air changes per hour (ACH)	Air change rate expressed as the number of air exchange units per hour.
airborne infection isolation (AII) precautions	The isolation of patients infected with organisms spread through airborne droplet nuclei 1–5 μm in diameter. This isolation area receives substantial ACH ($\geq$12 ACH for new construction since 2001 and $\geq$6 ACH for construction before 2001) and is under negative pressure (i.e., the direction of the air flow is from the outside adjacent space [e.g., the corridor] into the room). The air in an AII room is preferably exhausted to the outside, but can be recirculated if the return air is filtered through an high efficiency particulate respirator (HEPA) filter.
AII room	A room designed to maintain AII. Formerly called negative pressure isolation room, an AII room is a single-occupancy patient-care room used to isolate persons with suspected or confirmed infectious TB disease. Environmental factors are controlled in AII rooms to minimize the transmission of infectious agents that are usually spread from person-to-person by droplet nuclei associated with coughing or aerosolization of contaminated fluids. AII rooms should provide negative pressure in the room (so that air flows under the door gap into the room), an air flow rate of 6–12 ACH, and direct exhaust of air from the room to the outside of the building or recirculation of air through a HEPA filter.

American Institute of Architects/ Facility Guideline Institute (AIA/FGI)	A professional organization that develops standards for building design and construction, including ventilation parameters, and enforced by the Joint Commission on Accreditation of Healthcare Organizations.
American Society of Heating, Refrigerating, and Air-Conditioning Engineers, Inc. (ASHRAE)	A professional organization that develops guidelines for building ventilation.
aminotransaminases	Also called transaminases. Used to assess for hepatotoxicity in persons taking antituberculosis medications and include aspartate amino transferase (AST), serum glutamic oxalacetic transaminase, formerly SGOT, and amino alanine transferase, formerly ALT.
aminotransferases	Also called transaminases. Used to assess for hepatotoxicity in persons taking antituberculosis medications and include aspartate amino transferase (AST) (formerly serum glutamic oxalacetic transaminase) and amino alanine transferase (ALT) (formerly serum glutamic pyruvic transaminase).
anaphylactic shock	An often severe and sometimes fatal systemic reaction upon a second exposure to a specific antigen (as wasp venom or penicillin) after previous sensitization that is characterized especially by respiratory symptoms, fainting, itching, and hives.
anemometer	An instrument used to measure the velocity (speed) of air.
anergy	A condition in which a person has a diminished ability to exhibit delayed T-cell hypersensitivity to antigens because of a condition or situation resulting in altered immune function. An inability to react to a skin test is called cutaneous anergy. Skin tests for anergy (i.e., control antigens) have poor predictive value and are not recommended.
anteroom	Small room leading from a corridor into an AII room. An anteroom is separated from both the AII room and the corridor by doors. An anteroom can act as an airlock, preventing the escape of contaminants from the AII room into the corridor.
apical	Relating to or located at the tip (an apex).
assigned protection factor (APF)	The minimum anticipated protection provided by a properly worn and functioning respirator or class of respirators.
asymptomatic	Neither causing nor exhibiting signs or symptoms of disease.
Bacille Calmette-Guérin (BCG)	A vaccine for TB named after the French scientists Calmette and Guérin used in most countries where TB disease is endemic. The vaccine is effective in preventing disseminated and meningeal TB disease in infants and young children. It may have approximately 50% efficacy for preventing pulmonary TB disease in adults.
baseline TB screening	Screening HCWs for LTBI and TB disease at the beginning of employment. TB screening includes a symptom screen for all HCWs, and tuberculin skin tests (TSTs) or blood assay for *Mycobacterium tuberculosis* (BAMT) for those with previous negative test results for *M. tuberculosis* infection.
baseline TST or baseline BAMT	The TST or BAMT is administered at the beginning of employment to newly hired HCWs. If the TST method is used, for HCWs who have not had a documented negative test result for *M. tuberculosis* during the preceding 12 months, the baseline TST result should be obtained by using the two-step method. BAMT baseline testing does not need the two-step method.

biological safety cabinet (BSC)	A ventilated box that provides HCWs with a degree of protection against hazardous aerosols that are generated within it. BSC is the principal device used to contain infectious splashes or aerosols generated by multiple microbiology processes. BSC provides physical barriers and directional airflow to carry hazards away from the HCW. Maintenance is an essential part of ensuring proper BCS function.
Biosafety in Microbiological and Biomedical Laboratories (BMBL)	A publication of the U.S. Public Health Service that describes the combinations of standard and special microbiology practices, safety equipment, and facilities constituting biosafety levels (BSLs) 1–4, which are recommended for work with various infectious agents in laboratory settings. The recommendations are advisory and intended to provide a voluntary guide or code of practice.
biosafety levels (BSLs)	Four BSLs are described in Section III of BMBL that comprise combinations of laboratory practices and techniques, safety equipment, and laboratory settings.
blinded independent duplicate reading (BIDR)	Process in which two or more TST readers immediately measure the same TST result by standard procedures, without consulting or observing one another's readings, and record results. BIDRs help ensure that TST readers continue to read TST results correctly.
blood assay for *Mycobacterium tuberculosis* (BAMT)	A general term to refer to recently developed in vitro diagnostic tests that assess for the presence of infection with *M. tuberculosis*. This term includes, but is not limited to, IFN-γ release assays (IGRA). In the United States, the currently available test is QuantiFERON®-TB Gold test (QFT-G).
BAMT converter	A change from a negative to a positive BAMT result over a 2-year period.
boosting	When nonspecific or remote sensitivity to tuberculin purified protein derivative (PPD) in the skin test wanes or disappears over time, subsequent TSTs can restore the sensitivity. This process is called boosting or the booster phenomenon. An initially small TST reaction size is followed by a substantial reaction size on a later test, and this increase in millimeters of induration can be confused with a conversion or a recent *M. tuberculosis* infection. Two-step testing is used to distinguish new infections from boosted reactions in infection-control surveillance programs.
bronchoscopy	A procedure for examining the lower respiratory tract in which the end of the endoscopic instrument is inserted through the mouth or nose (or tracheostomy) and into the respiratory tree. Bronchoscopy can be used to obtain diagnostic specimens. Bronchoscopy also creates a high risk for *M. tuberculosis* transmission to HCWs if it is performed on an untreated patient who has TB disease (even if the patient has negative AFB smear results) because it is a cough-inducing procedure.
case	A particular instance of a disease (e.g., TB). A case is detected, documented, and reported.
cavity (pulmonary)	A hole in the lung parenchyma, usually not involving the pleural space. Although a lung cavity can develop from multiple causes, and its appearance is similar regardless of its cause, in pulmonary TB disease, cavitation results from the destruction of pulmonary tissue by direct bacterial invasion and an immune interaction triggered by *M. tuberculosis*. A TB cavity substantial enough to see with a normal chest radiograph predicts infectiousness.
clinical examination	A physical evaluation of the clinical status of a patient by a physician or equivalent practitioner.
close contact (TB)	A person who has shared the same air space in a household or other enclosed environment for a prolonged period (days or weeks, not minutes or hours) with a person with suspected or confirmed TB disease. Close contacts have also been referred to as high-priority contacts because they have the highest risk for infection with *M. tuberculosis*.

cluster (TB)	A group of patients with LTBI or TB disease that are linked by epidemiologic, location, or genotyping data. Two or more TST conversions within a short period can be a cluster of TB disease and might suggest transmission within the setting. A genotyping cluster is two or more cases with isolates that have an identical genotyping pattern.
combination product surgical mask/N95 disposable respirator	Product certified by CDC's National Institute for Occupational Safety and Health (NIOSH) and cleared by the Food and Drug Administration (FDA) that provides both respiratory protection and bloodborne pathogen protection.
constant air volume (CAV)	A descriptor for an air-handling system which, as the name implies, supplies and exhausts air at a constant flow rate. The flow rate does not change over time based on temperature load or other parameters.
contact (TB)	Refers to someone who was exposed to *M. tuberculosis* infection by sharing air space with an infectious TB patient.
contact investigation	Procedures that occur when a case of infectious TB is identified, including finding persons (contacts) exposed to the case, testing and evaluation of contacts to identify LTBI or TB disease, and treatment of these persons, as indicated.
contagious	Describes a characteristic of a disease that can be transmitted from one living being to another through direct contact or indirect contact; communicable. The agent responsible for the contagious character of a disease is also described as being infectious; the usual culprits are microorganisms.
contraindication	Any condition, especially any condition of disease, which renders a certain line of treatment improper or undesirable.
conversion	See TST conversion.
conversion rate	The percentage of a population with a converted test result (TST or BAMT) for *M. tuberculosis* within a specified period. This is calculated by dividing the number of conversions among eligible HCWs in the setting in a specified period (numerator) by the number of HCWs who received tests in the setting over the same period (denominator) multiplied by 100.
culture	Growth of microorganisms in the laboratory performed for detection and identification in sputum or other body fluids and tissues. This test usually takes 2–4 weeks for mycobacteria to grow (2–4 days for most other bacteria).
cough etiquette	See respiratory hygiene and cough ettiquette.
cross contamination	When organisms from one sample are introduced into another sample, causing a false-positive result.
delayed-type hypersensitivity (DTH)	Cell-mediated inflammatory reaction to an antigen, which is recognized by the immune system usually because of previous exposure to the same antigen or similar ones. Cell-mediated reactions are contrasted with an antibody (or humoral) response. DTH typically peaks at 48–72 hours after exposure to the antigen.
deoxyribonucleic acid	DNA fingerprinting is a clinical laboratory technique used to distinguish between different strains of M. tuberculosis and to help assess the likelihood of TB transmission.
differential pressure	A measurable difference in air pressure that creates a directional airflow between adjacent compartmentalized spaces.

directly observed therapy (DOT)	Adherence-enhancing strategy in which an HCW or other trained person watches a patient swallow each dose of medication. DOT is the standard care for all patients with TB disease and is a preferred option for patients treated for LTBI.
disposable respirator	A respirator designed to be used and then discarded; also known as a filtering-facepiece respirator. Respirators should be discarded after excessive resistance, physical damage, or hygiene considerations.
droplet nuclei	Microscopic particles produced when a person coughs, sneezes, shouts, or sings. These particles can remain suspended in the air for prolonged periods and can be carried on normal air currents in a room and beyond to adjacent spaces or areas receiving exhaust air.
drug-susceptibility test	A laboratory determination to assess whether an *M. tuberculosis* complex isolate is susceptible or resistant to antituberculosis drugs that are added to mycobacterial growth medium or are detected genetically. The results predict whether a specific drug is likely to be effective in treating TB disease caused by that isolate.
environmental control measures	Physical or mechanical measures (as opposed to administrative control measures) used to reduce the risk for transmission of *M. tuberculosis*. Examples include ventilation, filtration, ultraviolet lamps, AII rooms, and local exhaust ventilation devices.
epidemiologic cluster	A closely grouped series of cases in time or place.
erythema	Abnormal redness of the skin. Erythema can develop around a TST site but should not be read as part of the TST result.
expert TST trainer	A designated instructor who has documented TST training experience. This may include having received training on placing and reading multiple TST results.
exposed cohorts	Groups of persons (e.g., family members, co-workers, friends, club, team or choir members, persons in correctional facilities, or homeless shelter residents) who have shared the same air space with the suspected patient with TB disease during the infectious period. A person in the exposed cohort is a contact. See also contact and close contact.
exposure	The condition of being subjected to something (e.g., an infectious agent) that could have an effect. A person exposed to *M. tuberculosis* does not necessarily become infected. See also transmission.
exposure period	The coincident period when a contact shared the same air space as the index TB patient during the infectious period.
exposure site	A location that the index patient visited during the infectious period (e.g., school, bar, bus, or residence).
extrapulmonary TB	TB disease in any part of the body other than the lungs (e.g., kidney, spine, or lymph nodes). The presence of extrapulmonary disease does not exclude pulmonary TB disease.
false-negative TST or BAMT result	A TST or BAMT result that is interpreted as negative in a person who is actually infected with *M. tuberculosis*.
false-positive TST or BAMT result	A TST or BAMT result that is interpreted as positive in a person who is not actually infected with *M. tuberculosis*. A false-positive TST result is more likely to occur in persons who have been vaccinated with BCG or who are infected with nontuberculous mycobacteria (NTM).
facility	A physical building or set of buildings.

filtering-facepiece respirator	A type of air purifying respirator that uses a filter as an integral part of the facepiece or with the entire facepiece composed of the filtering medium.
fit check	See user-seal check.
fit factor	A quantitative estimate of the fit of a particular respirator to a specific person; typically estimates the ratio of the concentration of a substance in ambient air to its concentration inside the respirator when worn.
fit test	The use of a protocol to qualitatively or quantitatively evaluate the fit of a respirator on a person. See also QLFT and QNFT.
flutter strips	Physical indicators used to provide a continuous visual sign that a room is under negative pressure. These simple and inexpensive devices are placed directly in the door and can be useful in identifying a pressure differential problem.
genotype	The DNA pattern of *M. tuberculosis* used to discriminate among different strains.
health-care–associated	Broader term used instead of "nosocomial."
health-care setting	A place where health care is delivered.
health-care workers (HCWs)	All paid and unpaid persons working in health-care settings.
heating, ventilating, or air conditioning (HVAC)	Mechanical systems that provide either collectively or individually heating, ventilating, or air conditioning for comfort within or associated with a building.
high efficiency particulate air (HEPA) filter	A filter that is certified to remove ≥99.97% of particles 0.3 μm in size, including *M. tuberculosis*–containing droplet nuclei; the filter can be either portable or stationary. Use of HEPA filters in building ventilation systems requires expertise in installation and maintenance.
high-pressure liquid chromatograph (HPLC)	Laboratory method used to identify *Mycobacterium* species by analysis of species-specific fatty acids called mycolic acids, which are present in the cell walls of mycobacteria.
human immunodeficiency virus (HIV) infection	Infection with the virus that causes acquired immunodeficiency syndrome (AIDS). A person with both LTBI and HIV infection is at high risk for developing TB disease.
hemoptysis	The expectoration or coughing up of blood or blood-tinged sputum; one of the symptoms of pulmonary TB disease. Hemoptysis can also be observed in other pulmonary conditions (e.g., lung cancer).
hypersensitivity	A state in which the body reacts with an exaggerated immune response to a foreign substance. Hypersensitivity reactions are classified as immediate or delayed, types I and IV, respectively. See also delayed-type hypersensitivity.
immunocompromised and immunosuppressed	Describes conditions in which at least part of the immune system is functioning at less than normal capacity. According to certain style experts, "immunocompromised" is the broader term, and "immunosuppressed" is restricted to conditions with iatrogenic causes, including treatments for another condition.
incentive	A gift given to patients to encourage or acknowledge their adherence to treatment.
incidence	The number of new events or cases of disease that develop during a specified period.
index case	The first person with TB disease who is identified in a particular setting. This person might be an indicator of a potential public health problem and is not necessarily the source case. See also source case or patient.

induration	The firmness in the skin test reaction; produced by immune-cell infiltration in response to the tuberculin antigen that was introduced into the skin. Induration is measured transversely by palpation, and the result is recorded in millimeters. The measurement is compared with guidelines to determine whether the test result is classified as positive or negative.
infection with *M. tuberculosis*	In some persons who are exposed to and who inhale *M. tuberculosis* bacteria, the bacteria are not promptly cleared by respiratory defense systems, and the bacteria multiply and are spread throughout the body, thereby infecting the exposed person. In the majority of persons who become infected, the body is able to fight the bacteria to stop the bacteria from growing, further establishing a latent state. The bacteria are inactive, but they remain alive in the body and can become active later. In other persons, the infection with *M. tuberculosis* can progress to TB disease more promptly. *M. tuberculosis* infection encompasses both latent TB infection and TB disease. See also latent TB infection and reinfection.
infectious	See contagious.
infectious droplet nuclei	Droplet nuclei produced by an infectious TB patient that can carry tubercle bacteria and be inhaled by others. Although usually produced from patients with pulmonary TB through coughing, aerosol-generating procedures can also generate infectious droplet nuclei.
infectious period	The period during which a person with TB disease might have transmitted *M. tuberculosis* organisms to others. For patients with positive AFB sputum smear results, the infectious period begins 3 months before the collection date of the first positive smear result or the symptom onset date (whichever is earlier) and ends when the patient is placed into AII or the date of collection for the first of consistently negative smear results. For patients with negative AFB sputum smear results, the infectious period extends from 1 month before the symptom onset date and ends when the patient is placed into AII (whichever was earlier).
interferon-γ release assays (IGRA)	A type of an ex vivo test that detects cell-mediated immune response to this cytokine. In the United States, QFT-G is a currently available IGRA.
isoniazid (INH)	A highly active antituberculosis chemotherapeutic agent that is a cornerstone of treatment for TB disease and the cornerstone of treatment for LTBI.
laryngeal TB	A form of TB disease that involves the larynx and can be highly infectious.
latent TB infection (LTBI)	Infection with *M. tuberculosis* without symptoms or signs of disease have manifested. See also infection with *M. tuberculosis*.
manometer	An instrument used to measure pressure differentials (i.e., pressure inside an AII room relative to the corridor of the room).
Mantoux method	A skin test performed by intradermally injecting 0.1 mL of PPD tuberculin solution into the volar or dorsal surface of the forearm. This method is the recommended method for TST.
mask	A device worn over the nose and mouth of a person with suspected or confirmed infectious TB disease to prevent infectious particles from being released into room air.
mechanical ACH	Air change rate based on only the mechanical ventilation flowrates.
medical evaluation	An examination to diagnose TB disease or LTBI, to select treatment, and to assess response to therapy. A medical evaluation can include medical history and TB symptom screen, clinical or physical examination, screening and diagnostic tests (e.g., TSTs, chest radiographs, bacteriologic examination, and HIV testing), counseling, and treatment referrals.
meningeal TB	A serious form of TB disease involving the meningies, the covering of the brain. Meningeal TB can result in serious neurologic complications.

miliary TB	A serious form of TB disease sometimes referred to as disseminated TB. A dangerous and difficult form to diagnose of rapidly progressing TB disease that extends throughout the body. Uniformly fatal if untreated; in certain instances, it is diagnosed too late to save a life. Certain patients with this condition have normal findings or ordinary infiltrates on the chest radiograph.
mitogen	A substance that stimulates the growth of certain white blood cells. Mitogen is used as a positive control in BAMT tests.
multidrug-resistant tuberculosis (MDR TB)	TB disease caused by *M. tuberculosis* organisms that are resistant to at least INH and rifampin.
mycobacteria other than tuberculosis (MOTT)	See NTM.
Mycobacterium tuberculosis	The namesake member organism of *M. tuberculosis* complex and the most common causative infectious agent of TB disease in humans. In certain instances, the species name refers to the entire *M. tuberculosis* complex, which includes *M. bovis* and *M. african, M. microti, M. canetii, M. caprae,* and *M. pinnipedii*.
M. tuberculosis culture	A laboratory test in which the organism is grown from a submitted specimen (e.g., sputum) to determine the presence of *M. tuberculosis*. In the absence of cross-contamination, a positive culture confirms the diagnosis of TB disease.
N95 disposable respirator	An air-purifying, filtering-facepiece respirator that is ≥95% efficient at removing 0.3 μm particles and is not resistant to oil. See also respirator.
negative pressure	The difference in air-pressure between two areas. A room that is under negative pressure has a lower pressure than adjacent areas, which keeps air from flowing out of the room and into adjacent rooms or areas. Also used to describe a nonpowered respirator. See also AII and AII room.
nontuberculous mycobacteria (NTM)	Refers to mycobacterium species other than those included as part of *M. tuberculosis* complex. Although valid from a laboratory perspective, the term can be misleading because certain types of NTM cause disease with pathologic and clinical manifestations similar to TB disease. Another term for NTM is mycobacterium other than tuberculosis (MOTT). NTM are environmental mycobacteria.
nosocomial	Acquired in a hospital. The broader term "health-care–associated" is used in this report.
nucleic acid amplification (NAA)	Laboratory method used to target and amplify a single DNA or RNA sequence usually for detecting and identifying a microorganism. The NAA tests for *M. tuberculosis* complex are sensitive and specific and can accelerate the confirmation of pulmonary TB disease.
periodic fit testing	Repetition of fit testing performed in accordance with federal, state, and local regulations. Additional fit testing should be used when 1) a new model of respirator is used, 2) a physical characteristic of the user changes, or 3) when the user or respiratory program administrator is uncertain that the HCW is obtaining an adequate fit.
pleural effusion	Abnormal accumulation of fluid between the lining of the lung and the chest wall. Persons with TB pleural effusions might also have concurrent unsuspected pulmonary or laryngeal TB disease. These patients should be considered contagious until infectious TB disease is excluded.
polymerase chain reaction (PCR)	A system for in vitro amplification of DNA that can be used for diagnosis of infections.

positive predictive value of a TST	The probability that a person with a positive TST result is actually infected with *M. tuberculosis*. The positive predictive value is dependent on the prevalence of infection with *M. tuberculosis* in the population being tested and on the sensitivity and specificity of the test.
potential ongoing transmission	A risk classification for TB screening, including testing for *M. tuberculosis* infection when evidence of ongoing transmission of *M. tuberculosis* is apparent in the setting. Testing might need to be performed every 8–10 weeks until lapses in infection controls have been corrected, and no further evidence of ongoing transmission is apparent. Use potential ongoing transmission as a temporary risk classification only. After corrective steps are taken, reclassify the setting as medium risk. Maintaining the classification of medium risk for at least 1 year is recommended.
powered air-purifying respirator (PAPR)	A respirator equipped with a tight-fitting facepiece (rubber facepiece) or loose-fitting facepiece (hood or helmet), breathing tube, air-purifying filter, cartridge or canister, and a fan. Air is drawn through the air-purifying element and pushed through the breathing tube and into the facepiece, hood, or helmet by the fan. Loose-fitting PAPRs (e.g., hoods or helmets) might be useful for persons with facial hair because they do not require a tight seal with the face.
prevalence	The proportion of persons in a population who have a disease at a specific time.
protection factor	A general term for three specific terms: 1) APF, 2) SWPF, and 3) WPF. These terms refer to different methods of defining adequacy of respirator fit. See also APF, SWPF, and WPF.
pulmonary TB	TB disease that occurs in the lung parenchyma, usually producing a cough that lasts >3 weeks.
purified protein derivative (PPD) tuberculin	A material used in diagnostic tests for detecting infection with *M. tuberculosis*. In the United States, PPD solution is approved for administration as an intradermal injection (5 TU per 0.1 mL), a diagnostic aid for LTBI (see TST). In addition, PPD tuberculin was one of the antigens in the first-generation QFT.
qualitative fit test (QLFT)	A pass-fail fit test to assess the adequacy of respirator fit that relies on the response of the person to the test agent.
quality control (QC)	A function to ensure that project tools and procedures are reviewed and verified according to project standards.
QFT and QFT-G	Types of BAMT that are in vitro cytokine assays that detects cell-mediated immune response (see also DTH) to *M. tuberculosis* in heparinized whole blood from venipuncture. This test requires only a single patient encounter, and the result can be ready within 1 day. In 2005, QuantiFERON®-TB was replaced by QuantiFERON®-TB Gold (QFT-G), which has greater specificity because of antigen selection. QFT-G appears to be capable of distinguishing between the sensitization caused by *M. tuberculosis* infection and that caused by BCG vaccination.
quantitative fit test (QNFT)	An assessment of the adequacy of respirator fit by numerically measuring the amount of leakage into the respirator.
recirculation	Ventilation in which all or the majority of the air exhausted from an area is returned to the same area or other areas of the setting.
recommended exposure limit (REL)	The occupational exposure limit established by CDC/NIOSH. RELs are intended to suggest levels of exposure to which the majority of HCWs can be exposed without experiencing adverse health effects.

reinfection	A second infection that follows from a previous infection by the same causative agent. Frequently used when referring to an episode of TB disease resulting from a subsequent infection with *M. tuberculosis* and a different genotype.
resistance	The ability of certain strains of mycobacteria, including *M. tuberculosis*, to grow and multiply in the presence of certain drugs that ordinarily kill or suppress them. Such strains are referred to as drug-resistant strains and cause drug-resistant TB disease. See also multidrug-resistant TB.
respirator	A CDC/NIOSH-approved device worn to prevent inhalation of airborne contaminants.
respiratory hygiene and cough etiquette	Procedures by which patients with suspected or confirmed infectious TB disease can minimize the spread of infectious droplet nuclei by decreasing the number of infectious particles that are released into the environment. Patients with a cough should be instructed to turn their heads away from persons and to cover their mouth and nose with their hands or preferably a cloth or tissue when coughing or sneezing.
respiratory protection	The third level in the hierarchy of TB infection-control measures after administrative and environmental controls is used because of the risk for exposure.
restriction fragment length polymorphism (RFLP)	A technique by which organisms can be differentiated by analysis of patterns derived from cleavage of their DNA. The similarity of the patterns generated can be used to differentiate strains from one another. See also genotype.
reversion	A subsequent TST or BAMT result that is substantially smaller than a previous test; reversion has been observed to be more likely when the intervening time between TSTs increases.
Rifampin	A highly active antituberculosis chemotherapeutic agent that is a cornerstone of treatment for TB disease.
screening (TB)	Measures used to identify persons who have TB disease or LTBI. See also symptom screen.
secondary (TB) case	A new case of TB disease that is attributed to recent transmission as part of the scenario under investigation. The period for "recent" is not defined but usually will be briefer than 2 years. Technically, all cases are secondary, in that they originate from other contagious cases.
simulated workplace protection factor (SWPF)	A surrogate measure of the workplace protection provided by a respirator.
smear (AFB smear)	A laboratory technique for preparing a specimen so that bacteria can be visualized microscopically. Material from the specimen is spread onto a glass slide and usually dried and stained. Specific smear, stain, and microscopy methods for mycobacteria are designed to optimally detect members of this genus. The slide can be scanned by light or fluorescent high-power microscopy. These methods require ongoing quality assurance for prompt and reliable results. The results for sputum smears usually are reported as numbers of AFB per high-powered microscopy field or as a graded result, from +1 to +4. The quantity of stained organisms predicts infectiousness. See also AFB.
source case or patient	The person or the case that was the original source of infection for secondary cases or contacts. The source case can be, but is not necessarily, the index case.

source case investigation	An investigation to determine the source case could be conducted in at least two circumstances: 1) when a health-care setting detects an unexplained cluster of TST conversions among HCWs or 2) when TB infection or disease is diagnosed in a young child. The purposes of a source case investigation are to ascertain that the source case has been diagnosed and treated, to prevent further *M. tuberculosis* transmission, and to ensure that other contacts of that source case are also evaluated and, if indicated, provided treatment.
source control	A process for preventing or minimizing emission (e.g., aerosolized *M. tuberculosis*) at the place of origin. Examples of source-control methods are booths in which a patient coughs and produces sputum, BSCs in laboratories, and local exhaust ventilation.
spirometry	A procedure used to measure time expired and the volume inspired, and from these measurements, calculations can be made on the effectiveness of the lungs.
sputum	Mucus containing secretions coughed up from inside the lungs. Tests of sputum (e.g., smear and culture) can confirm pulmonary TB disease. Sputum is different from saliva or nasal secretions, which are unsatisfactory specimens for detecting TB disease. However, specimens suspected to be inadequate should still be processed because positive culture results can still be obtained and might be the only bacteriologic indication of disease.
sputum induction	A method used to obtain sputum from a patient who is unable to cough up a specimen spontaneously. The patient inhales a saline mist, which stimulates coughing from deep inside the lungs.
supervised TST administration	A procedure in which an expert TST trainer supervises a TST trainee who performs all procedures on the procedural observation checklist for administering TSTs.
supervised TST reading	A procedure in which an expert TST trainer supervises a TST trainee who performs all procedures on the procedural observation checklist for reading TST results.
suspected TB	A tentative diagnosis of TB that will be confirmed or excluded by subsequent testing. Cases should not remain in this category for longer than 3 months.
symptomatic	A term applied to a patient with health-related complaints (symptoms) that might indicate the presence of disease. In certain instances, the term is applied to a medical condition (e.g., symptomatic pulmonary TB).
symptom screen	A procedure used during a clinical evaluation in which patients are asked if they have experienced any departure from normal in function, appearance, or sensation related to TB disease (e.g., cough).
targeted testing	A strategy to focus testing for infection with *M. tuberculosis* in persons at high risk for LTBI and for those at high risk for progression to TB disease if infected.
tuberculosis (TB) disease	Condition caused by infection with a member of the *M. tuberculosis* complex that has progressed to causing clinical (manifesting symptoms or signs) or subclinical (early stage of disease in which signs or symptoms are not present, but other indications of disease activity are present [see below]) illness. The bacteria can attack any part of the body, but disease is most commonly found in the lungs (pulmonary TB). Pulmonary TB disease can be infectious, whereas extrapulmonary disease (occurring at a body site outside the lungs) is not infectious, except in rare circumstances. When the only clinical finding is specific chest radiographic abnormalities, the condition is termed "inactive TB" and can be differentiated from active TB disease, which is accompanied by symptoms or other indications of disease activity (e.g., the ability to culture reproducing TB organisms from respiratory secretions or specific chest radiographic finding).

TB case	A particular episode of clinical TB disease. Refers only to the disease, not to the person with the disease. According to local laws and regulation, TB cases and suspect TB cases must be reported to the local or state health department.
TB contact	A person who has shared the same air space with a person who has TB disease for a sufficient amount of time to allow possible transmission of *M. tuberculosis*.
TB exposure incident	A situation in which persons (e.g., HCWs, visitors, and inmates) have been exposed to a person with suspected or confirmed infectious TB disease (or to air containing *M. tuberculosis*), without the benefit of effective infection-control measures.
TB infection	See LTBI.
TB infection-control program	A program designed to control transmission of *M. tuberculosis* through early detection, isolation, and treatment of persons with infectious TB. A hierarchy of control measures are used, including 1) administrative controls to reduce the risk for exposure to persons with infectious TB disease and screening for HCWs for LTBI and TB disease, 2) environmental controls to prevent the spread and reduce the concentration of infectious droplet nuclei in the air, and 3) respiratory protection in areas where the risk for exposure to *M. tuberculosis* is high (e.g., AII rooms). A TB infection-control plan should include surveillance of HCWs who have unprotected high-risk exposure to TB patients or their environment of care.
TB screening	An administrative control measure in which evaluation for LTBI and TB disease are performed through initial and serial screening of HCWs, as indicated. Evaluation might comprise TST, BAMT, chest radiograph, and symptom screening. See also symptom screen.
TB screening program	A plan that health-care settings should implement to provide information that is critical in caring for HCWs and information and that facilitates detection of *M. tuberculosis* transmission. The TB screening program comprises four major components: 1) baseline testing for *M. tuberculosis* infection, 2) serial testing for *M. tuberculosis* infection, 3) serial screening for signs or symptoms of TB disease, and 4) TB training and education.
TB risk assessment	An initial and ongoing evaluation of the risk for transmission of *M. tuberculosis* in a particular health-care setting. To perform a risk assessment, the following factors should be considered: the community rate of TB, number of TB patients encountered in the setting, and the speed with which patients with TB disease are suspected, isolated, and evaluated. The TB risk assessment determines the types of administrative and environmental controls and respiratory protection needed for a setting.
transmission	Any mode or mechanism by which an infectious agent is spread from a source through the environment or to a person (or other living organism). In the context of health-care–associated TB infection control, transmission is the airborne conveyance of aerosolized *M. tuberculosis* contained in droplet nuclei from a person with TB disease, usually from the respiratory tract, to another person, resulting in infection.
treatment for LTBI	Treatment that prevents the progression of infection into disease.
tuberculin skin test (TST)	A diagnostic aid for finding *M. tuberculosis* infection. A small dose of tuberculin is injected just beneath the surface of the skin (in the United States by the Mantoux method), and the area is examined for induration by palpation 48–72 hours after the injection. The indurated margins should be read transverse (perpendicular) to the long axis of the forearm. See also Mantoux method and PPD.

TST conversion	A change in the result of a test for *M. tuberculosis* infection wherein the condition is interpreted as having progressed from uninfected to infected. An increase of >10 mm in induration during a maximum of 2 years is defined as a TST conversion for the purposes of a contact investigation. A TST conversion is presumptive evidence of new *M. tuberculosis* infection and poses an increased risk for progression to TB disease. See also conversion.
tubercle bacilli	*M. tuberculosis* organisms.
tuberculin	A precipitate made from a sterile filtrate of *M. tuberculosis* culture medium.
two-step TST	Procedure used for the baseline skin testing of persons who will receive serial TSTs (e.g., HCWs and residents or staff of correctional facilities or long-term–care facilities) to reduce the likelihood of mistaking a boosted reaction for a new infection. If an initial TST result is classified as negative, a second step of a two-step TST should be administered 1–3 weeks after the first TST result was read. If the second TST result is positive, it probably represents a boosted reaction, indicating infection most likely occurred in the past and not recently. If the second TST result is also negative, the person is classified as not infected. Two-step skin testing has no place in contact investigations or in other circumstances in which ongoing transmission of *M. tuberculosis* is suspected.
tumor necrosis factor-alpha (TNF-α)	A small molecule (called a cytokine) discovered in the blood of animals (and humans) with tumors but which has subsequently been determined to be an essential host mediator of infection and inflammation. TNF-α is released when humans are exposed to bacterial products (e.g., lipopolysaccharide) or BCG. Drugs (agents) that block human TNF-α have been demonstrated to increase the risk for progression to TB disease in persons who are latently infected.
ulceration (TST)	A break in the skin or mucosa with loss of surface tissue.
ultraviolet germicidal radiation (UVGI)	Use of ultraviolet germicidal irradiation to kill or inactivate microorganisms.
UVGI lamp	An environmental control measure that includes a lamp that kills or inactivates microorganisms by emitting ultraviolet germicidal irradiation, predominantly at a wavelength of 254 nm (intermediate light waves between visible light and radiographs). UVGI lamps can be used in ceiling or wall fixtures or within air ducts of ventilation systems as an adjunct to other environmental control measures.
user-seal check	Formerly called "fit check." A procedure performed after every respirator is donned to check for proper seal of the respirator.
variable air volume (VAV)	VAV ventilation systems are designed to vary the quantity of air delivered to a space while maintaining a constant supply air temperature to achieve the desired temperature in the occupied space. Minimum levels are mechanical, and outside air is maintained.
vesiculation	An abnormal elevation of the outer layer of skin enclosing a watery liquid; blister.
wheal	A small bump that is produced when a TST is administered. The wheal disappears in approximately 10 minutes after TST placement.
workplace protection factor (WPF)	A measure of the protection provided in the workplace by a properly functioning respirator when correctly worn and used.

Appendix A. Administrative, environmental, and respiratory-protection controls for selected health-care settings

Setting	Administrative controls*	Environmental controls†	Respiratory-protection controls§
Settings in Which Patients with Suspected or Confirmed Infectious Tuberculosis (TB) Disease are not Expected to be Encountered			
Triage only: Initial evaluation of patients who will transfer to another setting	• Implement a written infection-control plan for triage of patients with suspected or confirmed TB disease. Update annually. • Promptly recognize and transfer patients with suspected or confirmed TB disease to a facility that treats persons with TB disease. • Before transferring the patient out of this setting, hold the patient in an area separate from health-care workers (HCWs) and other persons.	• Settings in which patients with suspected or confirmed TB disease are rarely seen and not treated do not need an airborne infection isolation (AII) room. • Place any patient with suspected or confirmed TB disease in an AII room if available or in a separate room with the door closed, away from others and not in a waiting area. • Air-cleaning technologies (e.g., high efficiency particulate air [HEPA] filtration and ultraviolet germicidal irradiation [UVGI] can be used to increase the number of equivalent air changes per hour [ACH]). (see Supplement, Environmental Controls).	• Settings in which patients with suspected or confirmed TB disease are rarely seen and not treated do not need a respiratory-protection program. • If the patient has signs or symptoms of infectious TB disease (positive acid-fast bacilli [AFB] sputum smear result), consider having the patient wear a surgical or procedure mask (if possible) during transport, in waiting areas, or when others are present.
Inpatient Settings in Which Patients with Suspected or Confirmed Infectious TB Disease are Expected to be Encountered			
	• Perform an annual risk assessment for the setting. • Implement a written infection-control plan for the setting and evaluate and update annually. • Provide TB training, education, and screening for HCWs as part of the infection-control plan. • Establish protocols for problem evaluation. • When possible, postpone nonurgent procedures that might put HCWs at risk for possible exposure to *M. tuberculosis* until patients are determined to not have TB disease or are noninfectious. • Collaborate with state or local health departments when appropriate.	• In settings with a high volume of patients with suspected or confirmed TB disease, at least one room should meet requirements for an AII room (see Supplement, Environmental Controls). • Air-cleaning technologies (e.g., HEPA filtration and UVGI) can be used to increase the number of equivalent ACH (see Supplement, Environmental Controls).	• For HCWs, visitors,¶ and others entering the AII room of a patient with suspected or confirmed infectious TB disease, at least N95 disposable respirators should be worn. • If the patient has signs or symptoms of infectious TB disease consider having the patient wear a surgical or procedure mask, if possible, (e.g., if patient is not using a breathing circuit) during transport, in waiting areas, or when others are present.
Patient rooms	• Place patients with suspected or confirmed TB disease in an AII room.	• At least one inpatient room should meet requirements for an AII room to be used for patients with suspected or confirmed infectious TB disease (see Supplement, Environmental Controls). • Air-cleaning technologies (e.g., HEPA filtration and UVGI) can be used to increase the number of equivalent ACH (see Supplement, Environmental Controls; Table 2).	• For HCWs, visitors,¶ and others entering the AII room of a patient with suspected or confirmed infectious TB disease, at least N95 disposable respirators should be worn. • Persons infected with human immunodeficiency virus (HIV) or who have other immunocompromising conditions should especially avoid exposure to persons with TB disease. • If the patient has signs or symptoms of infectious TB disease (positive AFB sputum smear result), consider having the patient wear a surgical or procedure mask, if possible, (e.g., if patient is not using a breathing circuit) during transport, in waiting areas, or when others are present.

Appendix A. (*Continued*) Administrative, environmental, and respiratory-protection controls for selected health-care settings

Setting	Administrative controls*	Environmental controls†	Respiratory-protection controls§
Inpatient Settings in Which Patients with Suspected or Confirmed Infectious TB Disease are Expected to be Encountered			
Emergency departments (EDs)	• Implement a written infection-control plan for triage of patients with suspected or confirmed TB disease. Update annually. • Patients with signs or symptoms of infectious TB disease should be moved to an AII room as soon as possible.	• In settings classified as medium risk or potential ongoing transmission, at least one room should meet requirements for an AII room to be used for patients with suspected or confirmed infectious TB disease (see Supplement, Environmental Controls; Table 2). • Air-cleaning technologies (e.g., HEPA filtration and UVGI) can be used to increase the number of equivalent ACH (see Supplement, Environmental Controls).	• For HCWs, visitors,¶ and others entering the AII room of a patient with suspected or confirmed TB disease, at least N95 disposable respirators should be worn. • If the patient has signs or symptoms of infectious TB disease (positive AFB sputum smear result), consider having the patient wear a surgical or procedure mask, if possible, (e.g., if patient is not using a breathing circuit) during transport, in waiting areas, or when others are present.
Intensive care units (ICUs)	• Place patients with suspected or confirmed infectious TB disease in an AII room, separate from HCWs and other patients, if possible.	• In settings with a high volume of patients with suspected or confirmed TB disease, at least one room should meet requirements for an AII room to be used for such patients (see Supplement, Environmental Controls; Table 2). • Bacterial filters should be used routinely in breathing circuits of patients with suspected or confirmed TB disease and should filter particles 0.3 µm in size in unloaded and loaded situations with a filter efficiency of ≥95%.	• For HCWs, visitors,¶ and others entering the AII room of a patient with suspected or confirmed infectious TB disease, at least N95 disposable respirators should be worn. • If the patient has signs or symptoms of infectious TB disease and is suspected of being contagious (positive AFB sputum smear result), consider having the patient wear a surgical or procedure mask, if possible (e.g., if patient is not using a breathing circuit) during transport, in waiting areas, or when others are present.
Surgical suites	• Schedule a patient with suspected or confirmed TB disease for surgery when a minimum number of HCWs and other patients are present, and as the last surgical case of the day to maximize the time available for removal of airborne contamination (see Supplement, Environmental Controls; Table 1). For postoperative recovery, place patients in a room that meets requirements for an AII room.	• If a surgical suite has an operating room (OR) with an anteroom, that room should be used for TB cases. • If surgery is needed, use a room or suite of rooms that meet requirements for AII rooms (see Supplement, Environmental Controls). • If an AII or comparable room is not available for surgery or postoperative recovery, air-cleaning technologies (e.g., HEPA filtration and UVGI) can be used to increase the number of equivalent ACH (see Supplement, Environmental Controls). • If the health-care setting has an anteroom, reversible flow rooms (OR or isolation) are not recommended by the American Institute of Architects or American Society of Heating, Refrigerating and Air-conditioning Engineers, Inc. • Bacterial filters should be used routinely in breathing circuits of patients with suspected or confirmed TB disease and should filter particles 0.3 µm in size in an unloaded and loaded situation with a filter efficiency of >95%.	• For HCWs present during surgery of a patient with suspected or confirmed infectious TB disease, at least N95 disposable respirators, unvalved, should be worn. • Standard surgical or procedure masks for HCWs might not have fitting or filtering capacity for adequate protection. • If the patient has signs or symptoms of infectious TB disease (positive AFB sputum smear result), consider having the patient wear a surgical or procedure mask, if possible, before and after the procedure. • Valved or positive-pressure respirators should not be used because they do not protect the sterile surgical field.

Appendix A. (*Continued*) Administrative, environmental, and respiratory-protection controls for selected health-care settings

Setting	Administrative controls*	Environmental controls†	Respiratory-protection controls§
Inpatient Settings in Which Patients with Suspected or Confirmed Infectious TB Disease are Expected to be Encountered			
Laboratories**	• Conduct a laboratory-specific risk assessment. • In general, biosafety level (BSL)-2 practices, procedures, containment equipment, and facilities are required for nonaerosol-producing manipulations of clinical specimens. BSL-3 practices, procedures, and containment equipment might be necessary for certain aerosol-generating or aerosol-producing manipulations.	• Environmental controls should meet requirements for clinical microbiology laboratories in accordance with guidelines by Biosafety in Microbiological and Biomedical Laboratories (BMBL) and the AIA. • Perform all manipulation of clinical specimens that could result in aerosolization in a certified class I or II biosafety cabinet (BSC).	• For laboratory workers who manipulate clinical specimens (from patients with suspected or confirmed infectious TB disease) outside of a BSC, at least N95 disposable respirators should be worn.
Bronchoscopy suites††	• Use a dedicated room to perform bronchoscopy procedures. • If a patient with suspected or confirmed infectious TB disease must undergo bronchoscopy, schedule the procedure when a minimum number of HCWs and other patients are present, and schedule the patient at the end of the day. • Do not allow another procedure to be performed in the bronchoscopy suite until sufficient time has elapsed for adequate removal of *M. tuberculosis*–contaminated air (see Supplement, Environmental Controls; Table 1).	• Bronchoscopy suites should meet requirements for an AII room to be used for patients with suspected or confirmed infectious TB disease (see Supplement, Environmental Controls; Table 2). • Air-cleaning technologies (e.g., HEPA filtration and UVGI) can be used to increase the number of equivalent ACH (see Supplement, Environmental Controls). • Closing ventilatory circuitry and minimizing opening of such circuitry of intubated and mechanically ventilated patients might minimize exposure. • Keep patients with suspected or confirmed infectious TB disease in the bronchoscopy suite until coughing subsides.	• For HCWs present during bronchoscopic procedures of a patient with suspected or confirmed infectious TB disease, at least N95 disposable respirators should be worn. Protection greater than an N95 (e.g., a full-facepiece elastomeric respirator or powered air-purifying respirator (PAPR) should be considered. • If the patient has signs or symptoms of infectious TB disease (positive AFB sputum smear result), consider having the patient wear a surgical or procedure mask, if possible, before and after the procedure.
Sputum induction and inhalation therapy rooms	• Implement a written infection-control plan in the setting. Update annually. • Use a dedicated room to perform sputum induction and inhalation therapy. • Schedule sputum induction and inhalation therapy when a minimum number of HCWs and other patients are present, and schedule the patient at the end of the day. • Do not perform another procedure in a booth or room where sputum induction or inhalation therapy on a patient with suspected or confirmed infectious TB disease was performed until sufficient time has elapsed for adequate removal of *M. tuberculosis*-contaminated air (see Supplement, Environmental Controls; Table 1).	• Perform sputum induction and inhalation therapy in booths with special ventilation, if possible. If booths are not available, sputum induction or inhalation therapy rooms should meet requirements for an AII room to be used for patients with suspected or confirmed infectious TB disease (see Supplement, Environmental Controls; Table 2). • Air-cleaning technologies (e.g., HEPA filtration and UVGI) can be used to increase the number of equivalent ACH (see Supplement, Environmental Controls). • Keep patients with suspected or confirmed infectious TB disease in the sputum induction or inhalation therapy room after sputum collection or inhalation therapy until coughing subsides.	• For HCWs present during sputum induction and inhalation therapy of a patient with suspected or confirmed infectious TB disease, a respirator with a level of protection of at least N95 disposable respirators should be worn. Respiratory protection greater than an N95 (e.g., a full-facepiece elastomeric respirator or PAPR) should be considered (see Supplement, Respiratory Protection). • If the patient has signs or symptoms of infectious TB disease (positive AFB sputum smear result), consider having the patient wear a surgical or procedure mask, if possible, before and after the procedure.

Appendix A. (*Continued*) Administrative, environmental, and respiratory-protection controls for selected health-care settings

Setting	Administrative controls*	Environmental controls†	Respiratory-protection controls§
Inpatient Settings in Which Patients with Suspected or Confirmed Infectious TB Disease are Expected to be Encountered			
Autopsy suites	• Ensure proper coordination between attending physician(s) and pathologist(s) for proper infection control and specimen collection during autopsies performed on bodies with suspected or confirmed infectious TB disease. • Allow sufficient time to elapse for adequate removal of *M. tuberculosis*-contaminated air (see Supplement, Environmental Controls; Table 1) before performing another procedure.	• Autopsy suites should meet ACH requirements for an AII room to be used for bodies with suspected or confirmed TB disease (see Supplement, Environmental Controls; Table 2). • Air-cleaning technologies (e.g., HEPA filtration and UVGI) can be used to increase the number of equivalent ACH (see Supplement, Environmental Controls). • Consider using local exhaust ventilation to reduce exposures to infectious aerosols and vapors from embalming fluids.	• For HCWs present during autopsy on bodies with suspected or confirmed infectious TB disease, a respirator with a level of protection of at least an N95 disposable respirator should be worn. Protection greater than an N95 (e.g., a full-facepiece elastomeric respirator or PAPR) should be considered (see Supplement, Respiratory Protection), especially if aerosol generation is likely. • If another procedure cannot be delayed until sufficient time has elapsed for adequate removal of *M. tuberculosis*-contaminated air, staff should continue wearing respiratory protection while in the room (see Supplement, Environmental Controls; Table 1).
Embalming rooms	• Implement a written infection-control plan in the setting. Update annually.	• Embalming rooms should meet ACH requirements for an AII room to be used for bodies with suspected or confirmed TB disease (see Supplement, Environmental Controls; Table 2). • Air-cleaning technologies (e.g., HEPA filtration and UVGI) can be used to increase the number of equivalent ACH (see Supplement, Environmental Controls).	• For staff present during embalming procedures on bodies with suspected or confirmed infectious TB disease, a respirator with a level of protection of at least N95 disposable respirators should be worn. Protection greater than an N95 (e.g., a full-facepiece elastomeric respirator or PAPR) should be considered (see Supplement, Respiratory Protection), especially if aerosol generation is likely. • If another procedure cannot be delayed until sufficient time has elapsed for adequate removal of *M. tuberculosis*-contaminated air, staff should continue wearing respiratory protection while in the room.
Outpatient Settings§§ in Which Patients with Suspected or Confirmed Infectious TB Disease are Expected to be Encountered			
	• Perform an annual risk assessment for the setting. • Develop and implement a written infection-control plan for the setting and evaluate and update annually. • Provide TB training, education, and screening for HCWs as part of the infection-control plan. • Establish protocols for problem evaluation. • Collaborate with state or local health departments when appropriate.	• Environmental controls should be implemented based on the types of activities that are performed. • Patients with suspected or confirmed infectious TB disease requiring transport should be transported as discussed below under Emergency Medical Services (EMS).	• For HCWs, visitors,¶ and others entering an AII room of a patient with suspected or confirmed infectious TB disease, at least N95 disposable respirators should be worn. • If the patient has signs or symptoms of infectious TB disease (positive AFB sputum smear result), consider having the patient wear a surgical or procedure mask, if possible (e.g., if patient is not using a breathing circuit), during transport, in waiting areas, or when others are present. • If risk assessment indicates that respiratory protection is needed, drivers or HCWs who are transporting patients with suspected or confirmed infectious TB disease in an enclosed vehicle should wear at least an N95 disposable respirator. The risk assessment should consider the potential for shared air.

Appendix A. (*Continued*) Administrative, environmental, and respiratory-protection controls for selected health-care settings

Setting	Administrative controls*	Environmental controls†	Respiratory-protection controls§
Outpatient Settings in Which Patients with Suspected or Confirmed Infectious TB Disease are Expected to be Encountered			
TB treatment facilities¶¶	• Physically separate immunosuppressed patients from those with suspected or confirmed infectious TB. • Schedule appointments to avoid exposing HIV-infected or other severely immunocompromised persons to *M. tuberculosis*.	• If patients with TB disease are treated in the clinic, at least one room should meet requirements for an AII room (see Supplement, Environmental Controls; Table 2). • Air-cleaning technologies (e.g., HEPA filtration and UVGI) can be used to increase the number of equivalent ACH (see Supplement, Environmental Controls). • Perform all cough-inducing or aerosol-generating procedures by using environmental controls (e.g., booth) or in an AII room. • Keep patients in the booth or AII room until coughing subsides. • Do not allow another patient to enter the booth or AII room until sufficient time has elapsed for adequate removal of *M. tuberculosis*-contaminated air (see Supplement, Environmental Controls; Table 1).	• For HCWs, visitors,¶ and others entering the AII room of a patient with suspected or confirmed infectious TB disease, at least N95 disposable respirators should be worn. • If the patient has signs or symptoms of infectious TB disease (positive AFB sputum smear result), consider having the patient wear a surgical or procedure mask, if possible, during transport, in waiting areas, or when others are present.
Medical offices and ambulatory-care settings	• Implement a written infection-control plan in the setting. Update annually.	• In medical offices or ambulatory-care settings where patients with TB disease are treated, at least one room should meet requirements for an AII room to be used for patients with suspected or confirmed infectious TB disease (see Supplement, Environmental Controls; Table 2).	• For HCWs in medical offices or ambulatory care settings with patients with suspected or confirmed infectious TB disease, at least N95 disposable respirators should be worn. • If the patient has signs or symptoms of infectious TB disease (positive AFB sputum smear result), consider having the patient wear a surgical or procedure mask, if possible, during transport, in waiting areas, or when others are present.
Dialysis units	• Schedule dialysis for patients with TB disease when a minimum number of HCWs and other patients are present and at the end of the day to maximize the time available for removal of airborne contamination (see Supplement, Environmental Controls; Table 1).	• Perform dialysis for patients with suspected or confirmed infectious TB disease in a room that meets requirements for an AII room (see Supplement, Environmental Controls; Table 2). • Air-cleaning technologies (e.g., HEPA filtration and UVGI) can be used to increase the number of equivalent ACH (see Supplement, Environmental Controls).	• For HCWs, visitors,¶ and others entering the AII room of a patient with suspected or confirmed infectious TB disease, at least N95 disposable respirators should be worn. • If the patient has signs or symptoms of infectious TB disease (positive AFB sputum smear result), consider having the patient wear a surgical or procedure mask, if possible, during transport, in waiting areas, or when others are present. • If risk assessment indicates the need for respiratory protection, drivers or HCWs who are transporting patients with suspected or confirmed infectious TB disease in an enclosed vehicle should wear at least an N95 disposable respirator. The risk assessment should consider the potential for shared air.

Appendix A. (*Continued*) Administrative, environmental, and respiratory-protection controls for selected health-care settings

Setting	Administrative controls*	Environmental controls†	Respiratory-protection controls§
Outpatient Settings in Which Patients with Suspected or Confirmed Infectious TB Disease are Expected to be Encountered			
Dental-care settings	• If possible, postpone dental procedures of patients with suspected or confirmed infectious TB disease until the patient is determined not to have TB disease or to be noninfectious.	• Treat patients with suspected or confirmed infectious TB disease in a room that meets requirements for an AII room (see Supplement, Environmental Controls; Table 2). • Air-cleaning technologies such as HEPA filtration and (e.g., HEPA filtration and UVGI) can be used to increase the number of equivalent ACH (see Supplement, Environmental Controls).	• For dental staff performing procedures on a patient with suspected or confirmed infectious TB disease, at least N95 disposable respirators should be worn.
Nontraditional Facility-Based Settings			
	• Perform an annual risk assessment for the setting. • Develop and implement a written infection-control plan for the setting and evaluate and update annually. • Provide TB training, education, and screening for HCWs as part of the infection-control plan. • Establish protocols for problem evaluation. • Collaborate with state or local health departments when appropriate.	• Environmental controls should be implemented based on the types of activities that are performed (see Supplement, Environmental Controls). • Patients with suspected or confirmed infectious TB disease requiring transport should be transported as discussed in the EMS section.	• For HCWs, visitors,¶ and others entering the AII room of a patient with suspected or confirmed infectious TB disease, at least N95 disposable respirators should be worn. • If the patient has signs or symptoms of infectious TB disease (positive AFB sputum smear result), consider having the patient wear a surgical or procedure mask, if possible (e.g., if patient is not using a breathing circuit), during transport, in waiting areas, or when others are present.
EMS	• Include exposed emergency medical HCWs in the contact investigation of patients with TB disease if administrative, environmental, and respiratory-protection controls for TB infection control were not followed.	• Patients with suspected or confirmed infectious TB disease requiring transport should be transported in an ambulance whenever possible. The ambulance ventilation system should be operated in the non-recirculating mode, and the maximum amount of outdoor air should be provided to facilitate dilution. If the vehicle has a rear exhaust fan, use this fan during transport. Airflow should be from the cab (front of vehicle), over the patient, and out the rear exhaust fan. • If an ambulance is not used, the ventilation system for the vehicle should bring in as much outdoor air as possible, and the system should be set to non-recirculating. If possible, physically isolate the cab from the rest of the vehicle and have the patient sit in the back.	• If risk assessment indicates the need for respiratory protection, drivers or HCWs who are transporting patients with suspected or confirmed infectious TB disease in an enclosed vehicle should wear at least an N95 disposable respirator. The risk assessment should consider the potential for shared air. • If the patient has signs or symptoms of infectious TB disease (positive AFB sputum smear result), consider having the patient wear a surgical or procedure mask, if possible, during transport, in waiting areas, or when others are present.

Appendix A. (*Continued*) Administrative, environmental, and respiratory-protection controls for selected health-care settings

Setting	Administrative controls*	Environmental controls†	Respiratory-protection controls§
Nontraditional Facility-Based Settings			
Medical settings in correctional facilities	• Follow recommendations for inpatient and outpatient settings as appropriate. In waiting rooms or areas, follow recommendations for TB treatment facilities. • If possible, postpone transporting patients with suspected or confirmed infectious TB disease until they are determined not to have TB disease or to be noninfectious.	• At least one room should meet requirements for an AII room (see Supplement, Environmental Controls; Table 2). • Air-cleaning technologies (e.g., HEPA filtration and UVGI) can be used to increase the number of equivalent ACH (see Supplement, Environmental Controls). • When transporting patients with suspected or confirmed infectious TB disease in a vehicle (ideally an ambulance), if possible, physically isolate the cab (the front seat) from rest of the vehicle, have the patient sit in the back seat, and open the windows.	• For HCWs or others entering the AII room of a patient with suspected or confirmed infectious TB disease, at least N95 disposable respirators should be worn. • If the patient has signs or symptoms of infectious TB disease (positive AFB sputum smear result), consider having the patient wear a surgical or procedure mask, if possible, during transport, in waiting areas, or when others are present.
Home-based health-care and outreach settings	• Patients and household members should be educated regarding the importance of taking medications, respiratory hygiene and cough etiquette procedures, and proper medical evaluation. • If possible, postpone transporting patients with suspected or confirmed infectious TB disease until they are determined not to have TB disease or to be noninfectious. • Certain patients can be instructed to remain at home until they are determined not to have TB disease or to be noninfectious.	• Do not perform cough-inducing or aerosol-generating procedures unless appropriate environmental controls are in place (see Supplement, Environmental Controls), or perform those procedures outside, if possible.	• For HCWs entering the homes of patients with suspected or confirmed infectious TB disease, at least N95 disposable. respirators should be worn. • For HCWs transporting patients with suspected or confirmed infectious TB disease in a vehicle, consider at least an N95 disposable respirator. • If the patient has signs or symptoms of infectious TB disease (positive AFB sputum smear result), consider having the patient wear a surgical or procedure mask, if possible, during transport, in waiting areas, or when others are present.
Long-term–care settings (e.g., hospices and skilled nursing facilities)	• Patients with suspected or confirmed infectious TB disease should not be treated in a long-term–care setting, unless proper administrative and environmental controls and a respiratory-protection program are in place.	• Do not perform cough-inducing or aerosol-generating procedures unless appropriate infection controls are in place (see Supplement, Environmental Controls), or perform those procedures outside, if possible.	• If the patient has signs or symptoms of infectious TB disease (positive AFB sputum smear result), consider having the patient wear a surgical or procedure mask, if possible, during transport, in waiting areas, or when others are present.

* Administrative controls must be implemented to ensure the effectiveness of environmental controls and respiratory-protection programs, and should be in place for all settings where patients with suspected or confirmed TB disease are expected to be encountered. Administrative controls include a written TB infection-control plan (which should be reassessed at least annually), assignment of responsibility for the plan, setting risk assessment, HCW risk classification, HCW training and education, and a TB screening program to test HCWs for infection with *M. tuberculosis*.

† Environmental controls include local exhaust and general ventilation (i.e., achieving negative pressure), using AII rooms, and air-cleaning methods (i.e., HEPA filtration and UVGI).

§ All settings where patients with suspected or confirmed TB disease will be encountered need to have a respiratory-protection program. A respiratory-protection program might not be necessary for settings where patients with TB disease are not encountered or where a procedure exists for the prompt transfer of patients with suspected or confirmed TB disease to a setting where they can be evaluated.

¶ Visitors with suspected or confirmed TB disease should not have contact with patients, including contact with those who have suspected or confirmed TB disease.

** Laboratories that are not based in inpatient settings should observe the same TB infection-control measures as laboratories in inpatient settings.

†† Certain bronchoscopy suites are built to have positive pressure.

§§ Although the majority of these settings are routinely considered “outpatient,” they might be part of inpatient services in certain settings. If so, follow the recommendations for inpatient settings for patient rooms.

¶¶ TB treatment facilities can include TB clinics, infectious disease clinics, or pulmonary clinics.

Appendix B. Tuberculosis (TB) risk assessment worksheet

This model worksheet should be considered for use in performing TB risk assessments for health-care settings and nontraditional facility-based settings. Facilities with more than one type of setting will need to apply this table to each setting.

Scoring: ✓ or Y = Yes X or N = No NA = Not Applicable

_____ **1. Incidence of TB**

a. What is the incidence of TB in your community (county or region served by the health-care setting), and how does it compare with the state and national average?

b. What is the incidence of TB in your facility and specific settings, and how do those rates compare? (Incidence is the number of TB cases in your community during the previous year. A rate of TB cases per 100,000 persons should be obtained for comparison.)* This information can be obtained from the state or local health department.

Rate

Community _____
State _____
National _____
Facility _____
Department 1 _____
Department 2 _____
Department 3 _____

_____ c. Are patients with suspected or confirmed TB disease encountered in your setting (inpatient and outpatient)?

1) If yes, how many are treated in your health-care setting in 1 year? (Review laboratory data, infection-control records, and databases containing discharge diagnoses for this information.)

	No. patients	
Year	**Suspected**	**Confirmed**
1 year ago	_____	_____
2 years ago	_____	_____
5 years ago	_____	_____

2) If no, does your health-care setting have a plan for the triage of patients with suspected or confirmed TB disease?

d. Currently, does your health-care setting have a cluster of persons with confirmed TB disease that might be a result of ongoing transmission of *Mycobacterium tuberculosis*?

2. Risk Classification

a. Inpatient settings

1) How many inpatient beds are in your inpatient setting? Quantity _____

2) How many patients with TB disease are encountered in the inpatient setting in 1 year? (Review laboratory data, infection-control records, and databases containing discharge diagnoses.) Previous year _____ 5 years ago _____

3) Depending on the number of beds and TB patients encountered in 1 year, what is the risk classification for your inpatient setting?

___ Low risk
___ Medium risk
___ Potential ongoing transmission

_____ 4) Does your health-care setting have a plan for triaging patients with suspected or confirmed TB disease?

b. Outpatient settings

1) How many TB patients are evaluated at your outpatient setting in 1 year? (Review laboratory data, infection-control records, and databases containing discharge diagnoses for this information.) Previous year _____ 5 years ago _____

_____ 2) Is your health-care setting a TB clinic? (If yes, a classification of at least medium risk is recommended.)

_____ 3) Does evidence exist that a high incidence of TB disease has been observed in the community that the health-care setting serves?

_____ 4) Does evidence exist of person-to-person transmission in the health-care setting? (Use information from case reports. Determine if any TST or blood assay for *M. tuberculosis* [BAMT] conversions have occurred among health-care workers [HCWs].)

_____ 5) Does evidence exist that ongoing or unresolved health-care–associated transmission has occurred in the health-care setting (based on case reports)?

_____ 6) Does a high incidence of immunocompromised patients or HCWs in the health-care setting exist?

_____ 7) Have patients with drug-resistant TB disease been encountered in your health-care setting within the previous 5 years? Year encountered _____

8) When was the first time a risk classification was done for your health-care setting? Date of classification _____

_____ 9) Considering the items above, would your health-care setting need a higher risk classification?

Appendix B. (*Continued*)Tuberculosis (TB) risk assessment worksheet

_____ 10) Depending on the number of TB patients evaluated in 1 year, what is the risk classification for your outpatient setting (see Appendix C)?
___ Low risk
___ Medium risk
___ Potential ongoing transmission

_____ 11) Does your health-care setting have a plan for the triage of patients with suspected or confirmed TB disease?

c. Nontraditional facility-based settings

1) How many TB patients are encountered at your setting in 1 year?
Previous year _____
5 years ago _____

_____ 2) Does evidence exist that a high incidence of TB disease has been observed in the community that the setting serves?

_____ 3) Does evidence exist of person-to-person transmission in the setting?

_____ 4) Have any recent TST or BAMT conversions occurred among staff or clients?

_____ 5) Is there a high incidence or prevalence of immunocompromised patients or HCWs in the setting?

_____ 6) Have patients with drug-resistant TB disease been encountered in your health-care setting within the previous 5 years?
Year encountered _____

7) When was the first time a risk classification was done for your setting?
Date of classification _____

_____ 8) Considering the items above, would your setting require a higher risk classification?

_____ 9) Does your setting have a plan for the triage of patients with suspected or confirmed TB disease?

_____ 10) Depending on the number of patients with TB disease who are encountered in a nontraditional setting in 1 year, what is the risk classification for your setting (see Appendix C)?
___ Low risk
___ Medium risk
___ Potential ongoing transmission

3. Screening of HCWs for *M. tuberculosis* Infection

_____ a. Does the health-care setting have a TB screening program for HCWs?

If yes, which HCWs are included in the TB screening program? (check all that apply)

___ Physicians
___ Mid-level practitioners (nurse practitioners [NP] and physician's assistants [PA])
___ Nurses
___ Administrators
___ Laboratory workers
___ Respiratory therapists
___ Physical therapists
___ Contract staff
___ Construction or renovation workers
___ Service workers
___ Janitorial staff
___ Maintenance or engineering staff
___ Transportation staff
___ Dietary staff
___ Receptionists
___ Trainees and students
___ Volunteers
___ Others _____

_____ b. Is baseline skin testing performed with two-step TST for HCWs?

_____ c. Is baseline testing performed with QuantiFERON®-TB or other BAMT for HCWs?

d. How frequently are HCWs tested for *M. tuberculosis* infection?
Frequency _____

_____ e. Are *M. tuberculosis* infection test records maintained for HCWs?

_____ f. Where are test records for HCWs maintained?
Location _____

_____ g. Who maintains the records?
Name _____

h. If the setting has a serial TB screening program for HCWs to test for *M. tuberculosis* infection, what are the conversion rates for the previous years?†
1 year ago _____
2 years ago _____
3 years ago _____
4 years ago _____
5 years ago _____

i. Has the test conversion rate for *M. tuberculosis* infection been increasing or decreasing, or has it remained the same over the previous 5 years? (check one)
___ Increasing
___ Decreasing
___ No change in previous 5 years

Appendix B. (*Continued*)Tuberculosis (TB) risk assessment worksheet

_____ j. Do any areas of the health-care setting (e.g., waiting rooms or clinics) or any group of HCWs (e.g., laboratory workers, emergency department staff, respiratory therapists, and HCWs who attend bronchoscopies) have a test conversion rate for *M. tuberculosis* infection that exceeds the health-care setting's annual average? If yes, list. Rate _____

_____ k. For HCWs who have positive test results for *M. tuberculosis* infection and who leave employment at the health setting, are efforts made to communicate test results and recommend follow-up of latent TB infection treatment with the local health department or their primary physician? ___ Not applicable

4. TB Infection-Control Program

_____ a. Does the health-care setting have a written TB infection-control plan?

b. Who is responsible for the infection-control program? Name _____

c. When was the TB infection-control plan first written? Date _____

d. When was the TB infection-control plan last reviewed or updated? Date _____

_____ e. Does the written infection-control plan need to be updated based on the timing of the previous update (i.e., >1 year, changing TB epidemiology of the community or setting, the occurrence of a TB outbreak, change in state or local TB policy, or other factors related to a change in risk for transmission of *M. tuberculosis*)?

_____ f. Does the health-care setting have an infection-control committee (or another committee with infection-control responsibilities)?

1) If yes, which groups are represented on the infection-control committee? (check all that apply)

___ Physicians
___ Nurses
___ Epidemiologists
___ Engineers
___ Pharmacists
___ Laboratory personnel
___ Health and safety staff
___ Administrator
___ Risk assessment
___ Quality control
___ Others (specify)

2) If no, what committee is responsible for infection control in the setting? Committee _____

5. Implementation of TB Infection-Control Plan Based on Review by Infection-Control Committee

_____ a. Has a person been designated to be responsible for implementing an infection-control plan in your health-care setting? If yes, list the name. Name _____

b. Based on a review of the medical records, what is the average number of days for the following:

____ Presentation of patient until collection of specimen.
____ Specimen collection until receipt by laboratory.
____ Receipt of specimen by laboratory until smear results are provided to health-care provider.
____ Diagnosis until initiation of standard antituberculosis treatment.
____ Receipt of specimen by laboratory until culture results are provided to health-care provider.
____ Receipt of specimen by laboratory until drug-susceptibility results are provided to health-care provider.
____ Receipt of drug-susceptibility results until adjustment of antituberculosis treatment, if indicated.
____ Admission of patient to hospital until placement in airborne infection isolation (AII).

c. Through what means (e.g., review of TST or BAMT conversion rates, patient medical records, and time analysis) are lapses in infection control recognized? Means _____

d. What mechanisms are in place to correct lapses in infection control? Mechanisms _____

_____ e. Based on measurement in routine QC exercises, is the infection-control plan being properly implemented?

_____ f. Is ongoing training and education regarding TB infection-control practices provided for HCWs?

Appendix B. (*Continued*)Tuberculosis (TB) risk assessment worksheet

6. Laboratory Processing of TB-Related Specimens, Tests, and Results Based on Laboratory Review

a. Which of the following tests are either conducted in-house at your health-care setting's laboratory or sent out to a reference laboratory? (check all that apply)

In-house	Sent out	
____	____	Acid-fast bacilli (AFB) smears
____	____	Culture using liquid media (e.g., Bactec and MB-BacT)
____	____	Culture using solid media
____	____	Drug-susceptibility testing
____	____	Nucleic acid amplification testing

b. What is the usual transport time for specimens to reach the laboratory for the following tests?
AFB smears _____
Culture using liquid media (e.g., Bactec, MB-BacT) _____
Culture using solid media _____
Drug-susceptibility testing _____
Nucleic acid amplification testing _____
Other (specify) _____

_____ c. Does the laboratory at your health-care setting or the reference laboratory used by your health-care setting report AFB smear results for all patients within 24 hours of receipt of specimen? What is the procedure for weekends?
_____

7. Environmental Controls

a. Which environmental controls are in place in your health-care setting? (check all that apply and describe)

	Environmental control	Description
____	All rooms	_____
____	Local exhaust ventilation (enclosing devices and exterior devices)	_____
____	General ventilation (e.g., single-pass system, recirculation system)	_____
____	Air-cleaning methods (e.g., high efficiency particulate air [HEPA] filtration and ultraviolet germicidal irradiation [UVGI])	_____

b. What are the actual air changes per hour (ACH) and design for various rooms in the setting?

Room	ACH	Design

c. Which of the following local exterior or enclosing devices such as exhaust ventilation devices are used in your health-care setting? (check all that apply)
___ Laboratory hoods
___ Booths for sputum induction
___ Tents or hoods for enclosing patient or procedure

d. What general ventilation systems are used in your health-care setting? (check all that apply)
___ Single-pass system
___ Variable air volume
___ Constant air volume
___ Recirculation system
___ Other _____

e. What air-cleaning methods are used in your health-care setting? (check all that apply)

HEPA filtration	UVGI
___ Fixed room-air recirculation systems	___ Duct irradiation
___ Portable room-air recirculation systems	___ Upper-air irradiation
	___ Portable room-air cleaners

Appendix B. (*Continued*)Tuberculosis (TB) risk assessment worksheet

f. How many AII rooms are in the health-care setting? Quantity _____

g. What ventilation methods are used for AII rooms? (check all that apply)
Primary: (general ventilation)
___ Single-pass heating, ventilating, and air conditioning (HVAC)
___ Recirculating HVAC systems
Secondary (methods to increase equivalent ACH):
___ Fixed room recirculating units
___ HEPA filtration
___ UVGI
___ Other
(specify)_____

_____ h. Does your health-care setting employ, have access to, or collaborate with an environmental engineer (e.g., professional engineer) or other professional with appropriate expertise (e.g., certified industrial hygienist) for consultation on design specifications, installation, maintenance, and evaluation of environmental controls?

_____ i. Are environmental controls regularly checked and maintained with results recorded in maintenance logs?

_____ j. Is the directional airflow in AII rooms checked daily when in use with smoke tubes or visual checks?

_____ k. Are these results readily available?

l. What procedures are in place if the AII room pressure is not negative?
_____

_____ m. Do AII rooms meet the recommended pressure differential of 0.01-inch water column negative to surrounding structures?

8. Respiratory-Protection Program

_____ a. Does your health-care setting have a written respiratory-protection program?

b. Which HCWs are included in the respiratory-protection program? (check all that apply)

___ Physicians
___ Mid-level practitioners (NPs and PAs)
___ Nurses
___ Administrators
___ Laboratory personnel
___ Contract staff
___ Construction or renovation staff
___ Service personnel
___ Janitorial staff
___ Maintenance or engineering staff
___ Transportation staff
___ Dietary staff
___ Students
___ Others (specify) _____

c. Are respirators used in this setting for HCWs working with TB patients? If yes, include manufacturer, model, and specific application (e.g., ABC model 1234 for bronchoscopy and DEF model 5678 for routine contact with infectious TB patients).

Manufacturer	Model	Specific application

_____ d. Is annual respiratory-protection training for HCWs performed by a person with advanced training in respiratory protection?

_____ e. Does your health-care setting provide initial fit testing for HCWs? If yes, when is it conducted? Date _____

_____ f. Does your health-care setting provide periodic fit testing for HCWs? If yes, when and how frequently is it conducted? Date _____ Frequency _____

g. What method of fit testing is used? Method _____

_____ h. Is qualitative fit testing used?

_____ i. Is quantitative fit testing used?

Appendix B. (*Continued*)Tuberculosis (TB) risk assessment worksheet

9. Reassessment of TB Risk

a. How frequently is the TB risk assessment conducted or updated in the health-care setting?

b. When was the last TB risk assessment conducted? Frequency _____

c. What problems were identified during the previous TB risk assessment? Date _____

1) _____

2) _____

3) _____

4) _____

5) _____

d. What actions were taken to address the problems identified during the previous TB risk assessment?

1) _____

2) _____

3) _____

4) _____

5) _____

_____ e. Did the risk classification need to be revised as a result of the last TB risk assessment?

* If the population served by the health-care facility is not representative of the community in which the facility is located, an alternate comparison population might be appropriate.

† Test conversion rate is calculated by dividing the number of conversions among HCWs by the number of HCWs who had previous negative results during a certain period (see Supplement, Surveillance and Detection of *M. tuberculosis* infections in Health-Care Settings).

Appendix C. Risk classifications for health-care settings that serve communities with high incidence of tuberculosis (TB) and recommended frequency of screening for *Mycobacterium tuberculosis* infection among health-care workers (HCWs)*

	Risk classification†		
Setting	**Low risk**	**Medium risk**	**Potential ongoing transmission§**
Inpatient <200 beds	<3 TB patients/year	≥3 TB patients/year	Evidence of ongoing *M. tuberculosis* transmission, regardless of setting
Inpatient ≥200 beds	<6 TB patients/year	≥6 TB patients/year	
Outpatient; and nontraditional facility-based	<3 TB patients/year	≥3 TB patients/year	
TB treatment facilities	Settings in which • persons who will be treated have been demonstrated to have latent TB infection (LTBI) and not TB disease • a system is in place to promptly detect and triage persons who have signs or symptoms of TB disease to a setting in which persons with TB disease are treated • no cough-inducing or aerosol-generating procedures are performed	Settings in which • persons with TB disease are encountered • criteria for low risk is not otherwise met	
Laboratories	Laboratories in which clinical specimens that might contain *M. tuberculosis* are not manipulated	Laboratories in which clinical specimens that might contain *M. tuberculosis* are manipulated	
Recommendations for Screening Frequency			
Baseline two-step TST or one BAMT¶	Yes, for all HCWs upon hire	Yes, for all HCWs upon hire	Yes, for all HCWs upon hire
Serial TST or BAMT screening of HCWs	No**	Every 12 months††	As needed in the investigation of potential ongoing transmission§§
TST or BAMT for HCWs upon unprotected exposure to *M. tuberculosis*	Perform a contact investigation (i.e., administer one TST as soon as possible at the time of exposure, and, if the TST result is negative, place another TST 8–10 weeks after the end of exposure to *M. tuberculosis*)¶¶		

* Health-care workers (HCWs) refers to all paid and unpaid persons working in health-care settings who have the potential for exposure to *M. tuberculosis* through air space shared with persons with TB disease.

† Settings that serve communities with a high incidence of TB disease or that treat populations at high risk (e.g., those with human immunodeficiency virus infection or other immunocompromising conditions) or that treat patients with drug-resistant TB disease might need to be classified as medium risk, even if they meet the low-risk criteria.

§ A classification of potential ongoing transmission should be applied to a specific group of HCWs or to a specific area of the health-care setting in which evidence of ongoing transmission is apparent, if such a group or area can be identified. Otherwise, a classification of potential ongoing transmission should be applied to the entire setting. This classification should be temporary and warrants immediate investigation and corrective steps after a determination has been made that ongoing transmission has ceased. The setting should be reclassified as medium risk, and the recommended timeframe for this medium risk classification is at least 1 year.

¶ All HCWs should have a baseline two-step tuberculin skin test (TST) or one blood assay for *M. tuberculosis* (BAMT) result at each new health-care setting, even if the setting is determined to be low risk. In certain settings, a choice might be made to not perform baseline TB screening or serial TB screening for HCWs who 1) will never be in contact with or have shared air space with patients who have TB disease (e.g., telephone operators who work in a separate building from patients) or 2) will never be in contact with clinical specimens that might contain *M. tuberculosis*. Establishment of a reliable baseline result can be beneficial if subsequent screening is needed after an unexpected exposure to *M. tuberculosis*.

** HCWs whose duties do not include contact with patients or TB specimens do not need to be included in the serial TB screening program.

†† The frequency of testing for infection with *M. tuberculosis* will be determined by the risk assessment for the setting.

§§ During an investigation of potential ongoing transmission of *M. tuberculosis*, testing for *M. tuberculosis* infection should be performed every 8–10 weeks until lapses in infection controls have been corrected and no further evidence of ongoing transmission is apparent.

¶¶ Procedures for contact investigations should not be confused with two-step TST, which is used for newly hired HCWs.

Appendix D. Environmental controls record and evaluation*

Type of environmental control†	No.§	Location in the health-care setting¶	How often maintained**	How often evaluated**	Last evaluation date	Next evaluation due date

* Some settings will not be able to complete all parts of the table. List environmental controls in order of effectiveness.

† For example, ultraviolet germicidal irradiation (UVGI), high-efficiency particulate air (HEPA) filters, or airborne infection isolation (AII) room.

§ Number of UVGI units, HEPA filters, and AII rooms in each location of the health-care setting.

¶ For example, inpatient rooms, emergency departments, bronchoscopy suites, sputum induction rooms, outpatient areas, and waiting areas.

** Daily, weekly, monthly, annually, or other frequency (describe).

Appendix E. Tuberculosis (TB) Internet addresses

CDC Websites

CDC	http://www.cdc.gov
Division of Tuberculosis Elimination (DTBE)	http://www.cdc.gov/tb
Major TB Guidelines	http://www.cdc.gov/nchstp/tb/pubs/mmwrhtml/maj_guide.htm
State TB Program Contact Information	http://www.cdc.gov/nchstp/tb/pubs/tboffices.htm
TB Education and Training Resources	http://www.findtbresources.org
TB Program	http://www.cdc.gov/nchstp/tb/tbwebsites.htm
Division of AIDS, STD, and TB Laboratory Research	http://www.cdc.gov/ncidid/dastlr/TB/default.htm
National Center for Infectious Diseases (NCID)	http://www.cdc.gov/ncid
National Institute for Occupational Safety and Health (NIOSH)	http://www.cdc.gov/niosh/homepage.html
Respirator Information	http://www.cdc.gov/niosh/npptl/topics/respirators
CDC/NIOSH Certified Equipment List (CEL)	http://www.cdc.gov/niosh/npptl/topics/respirators/cel
CDC/NIOSH-Approved Disposable Particulate Respirators (Filtering Facepieces)	http://www.cdc.gov/niosh/npptl/respirators/disp_part/particlist.html
Division of Healthcare Quality Promotion	http://www.cdc.gov/ncidod/hip/enviro/guide.htm
Emergency Preparedness and Response	http://www.bt.cdc.gov

Other U.S. Federal Government Agencies

National Institutes of Health (NIH)	http://www.nih.gov
National Heart, Lung, and Blood Institute	http://www.nhlbi.nih.gov/funding/training/tbaa/index.htm
National Institute of Allergy and Infectious Diseases (NIAID)	http://www.niaid.nih.gov/dmid/tuberculosis
AIDSinfo	http://www.aidsinfo.nih.gov/guidelines
Occupational Safety and Health Administration (OSHA)	http://www.osha.gov; www.osha.gov/qna.pdf
Tuberculosis (OSHA)	http://www.osha.gov/SLTC/tuberculosis/index.html
Recordkeeping (OSHA)	http://www.osha.gov/SLTC/respiratoryprotection/index.html
Respiratory Protection (OSHA)	http://www.osha.gov/recordkeeping
Ryan White Care Act/Wisconsin HIV/AIDS Program	http://www.dhfs.state.wi.us/AIDS-HIV/Resources/Overviews/AIDS HIV.htm
Food and Drug Administration (FDA)	http://www.fda.gov
Safety Information and Adverse Event Reporting System (FDA-AERS)	http://www.fda.gov/medwatch
FDA and CDC Public Health Advisory: Infections from Endoscopes Inadequately Reprocessed by an Automated Endoscope Reprocessing System	http://www.fda.gov/cdrh/safety/endoreprocess.html

Regional Training and Medical Consultation Centers

Francis J. Curry National Tuberculosis Center, San Francisco, California	http://www.nationaltbcenter.edu
Heartland Regional Training Center, San Antonio, Texas	http://www.dshs.state.tx.us/tcid/educationctr.shtm
New Jersey Medical School National Tuberculosis Center Newark, New Jersey	http://www.umdnj.edu/ntbcweb
Southeast Regional Training Center, Gainesville, Florida	http://sntc.medicine.ufl.edu/index.htm

Domestic Organizations

American Lung Association (ALA)	http://www.lungusa.org/diseases/lungtb.html
American Thoracic Society (ATS)	http://www.thoracic.org
Association for Professionals in Infection Control and Epidemiology, Inc. (APIC)	http://www.apic.org
HIV Drug Interactions Organization	http://www.hiv-druginteractions.org
Infectious Disease Society of America/Bioterrorism and Information Resources (IDSA)	http://www.idsociety.org/bt/toc/htm
National Prevention Information Network (NPIN)	http://www.cdcnpin.org/scripts/index.asp
National Tuberculosis Controllers Association (NTCA)	http://www.ntca-tb.org
PharmWeb: Rapid Screening of Tuberculosis Pharmaceuticals	http://www.pharmweb.net/pwmirror/library/pharmwebvlib.html

International Organizations

International Union Against Tuberculosis and Lung Disease (IUATLD)	http://www.iuatld.org/full_picture/en/frameset/frameset.phtml
Stop TB Initiative	http://www.stoptb.org
Tuberculosis Research Center, India	http://www.trc-chennai.org
World Health Organization (WHO) Global TB Program	http://www.who.int/gtb

Appendix E. (*Continued*) Tuberculosis (TB) Internet addresses

State/Area TB and HIV Websites

Alabama ..... http://www.adph.org
Arkansas ..... http://www.epi.alaska.gov
Arizona ..... http://www.hs.state.az.us/phs/oids/tuberculosis/index.htm
California ..... http://www.dhs.ca.gov/ps/dcdc/TBCB/tubindex.htm
Colorado ..... http://www.cdphe.state.co.us/dc/tb/tbhome.asp
Connecticut ..... http://www.dph.state.ct.us
Delaware ..... http://www.state.de.us/dhss/dph/dpc/tuberculosis.html
Florida ..... http://www.doh.state.fl.us/disease_ctrl/tb/WorldTBDay/2004/WTD2004main.html
Georgia ..... http://www.health.state.ga.us/epi
Hawaii ..... http://www.hawaii.gov/doh/resource/comm_dis/tb/index.htm
Iowa ..... http://www.idph.state.ia.us/ch/tb_control.asp
Indiana ..... http://www.in.gov/isdh/programs/tb
Kansas ..... http://www.kdhe.state.ks.us/tb/index.html
Kentucky ..... http://www.chs.state.ky.us/publichealth/TB.htm
Louisiana ..... http://www.oph.dhh.state.la.us/tuberculosis/index.html
Massachusetts ..... http://www.state.ma.us/dph/cdc/tb
Maryland ..... http://www.edcp.org/tb/index.html
Maine ..... http://www.maine.gov/dhs/boh/ddc/tuberculosis.htm
Michigan ..... http://www.michigantb.org
Minnesota ..... http://www.health.state.mn.us/tb
Montana ..... http://www.dphhs.state.mt.us
North Carolina ..... http://www.schs.state.nc.us/epi/tb
North Dakota ..... http://www.ndmtb.com
Nebraska ..... http://www.hhs.state.ne.us/cod/Tuberculosis/tbindex.htm
New Hampshire ..... http://www.dhhs.state.nh.us/DHHS/DHHS_SITE/default.htm
Nevada http://www.health2k.state.nv.us
New York City ..... http://www.nyc.gov/html/doh/html/tb/tb.html
Ohio ..... http://www.odh.state.oh.us
Oklahoma ..... http://www.health.state.ok.us
Oregon ..... http://www.dhs.state.or.us/publichealth/tb
Pennsylvania ..... http://www.dsf.health.state.pa.us
Puerto Rico ..... http://www.salud.gov.pr
Rhode Island ..... http://www.health.ri.gov/disease/communicable/tb_data.htm
South Carolina ..... http://www.scdhec.net/hs/diseasecont/tb/html
South Dakota ..... http://www.state.sd.us/doh/tb
Tennessee http://www2.state.tn.us/health/CEDS/index.htm
Texas ..... http://www.dshs.state.tx.us/idcu/disease/tb
Utah ..... http://health.utah.gov/els/hivaids/tb/tbrefugee.html
Virginia ..... http://www.vdh.virginia.gov/epi/tb
Washington ..... http://www.doh.wa.gov/cfh/tb
Wisconsin ..... http://dhfs.wisconsin.gov/tb
Wyoming ..... http://www.wdh.state.wy.us/tb

Appendix F. Quality control (QC) procedural observation checklists

Quality Control (QC) Procedural Observation Checklist for Placing Tuberculin Skin Tests (TSTs) — Mantoux Method

Date _____ **Trainer (QC by)** _____ **Trainee (TST placed by)** _____

Scoring: ✓ or Y = Yes X or N = No NA = Not Applicable

1. Preliminary

_____ Uses appropriate hand hygiene methods before starting.
_____ Screens patient for contraindications (severe adverse reactions to previous TST).*
_____ Uses well-lit area.

2. Syringe† filled with exactly 0.1 mL of 5 tuberculin units (TU) purified protein derivative (PPD) antigen§

_____ Removes antigen vial from refrigeration and confirms that it is 5 TU PPD antigen.¶
_____ Checks label and expiration date on vial.
_____ Marks opening date on multidose vial.
_____ Fills immediately after vial removed from refrigeration.
_____ Cleans vial stopper with antiseptic swab.
_____ Twists needle onto syringe to ensure tight fit.
_____ Removes needle guard.
_____ Inserts needle into the vial.
_____ Draws slightly over 0.1 mL of 5 TU PPD into syringe.
_____ Removes excess volume or air bubbles to exactly 0.1 mL of 5 TU PPD while needle remains in vial to avoid wasting of antigen.
_____ Removes needle from vial.
_____ Returns antigen vial to the refrigerator immediately after filling.

3. TST administration site selected and cleaned

_____ Selects upper third of forearm with palm up ≥2 inches from elbow, wrist, or other injection site.**
_____ Selects site free from veins, lesions, heavy hair, bruises, scars, and muscle ridge.
_____ Cleans arm site with antiseptic swab using circular motion from center to outside.
_____ Allows site to dry thoroughly before administering antigen.

4. Needle inserted properly to administer antigen

_____ Rests arm on firm, well-lit surface.
_____ Stretches skin slightly.††
_____ Holds needle bevel-up and tip at 5°–15° angle to skin.
_____ Inserts needle in first layer of skin with tip visible beneath skin.
_____ Advances needle until entire bevel is under the first layer of skin.
_____ Releases stretched skin.
_____ Injects entire dose slowly.
_____ Forms wheal, as liquid is injected.
_____ Removes needle without pressing area.
_____ Activates safety feature of device per manufacturer's recommendations, if applicable.
_____ Places used needle and syringe immediately in puncture-resistant container without recapping needle.
_____ Immediately measures wheal to ensure 6–10 mm in diameter (Actual wheal measurement _____mm).
_____ If blood or fluid is present, blots site lightly with gauze or cotton ball.
_____ Discards used gauze or cotton ball according to local standard precautions.
_____ If the TST is administered incorrectly (too deeply or too shallow) and the wheal is inadequate (<6 mm), a new TST should be placed immediately. Applying the second TST on the other arm or in a different area of the same arm (at least 2 inches from the first site) is preferable so that the TST result will be easier to read.
_____ Documents all information required by the setting (e.g., date and time of TST placement, person who placed TST, location of injection site and lot number of tuberculin).
_____ Uses appropriate hand hygiene methods after placing TST.

5. Explanation to the client regarding care instructions for the injection site

_____ The wheal (bump) is normal and will remain about 10 minutes.
_____ Do not touch wheal; avoid scratching.
_____ Avoid pressure or bandage on injection site.
_____ Rare local discomfort and irritation does not require treatment.
_____ May wash with soap and water (without pressure) after 1 hour.
_____ No lotions or liquids on site, except for light washing, as above.
_____ Keeps appointment for reading.

* Severe adverse reactions to the TST are rare but include ulceration, necrosis, vesiculation, or bullae at the test site, or anaphylactic shock, which is substantially rare. These reactions are the only contraindications to having a TST administered.

† Use a ¼–½-inch 27-gauge needle or finer, disposable tuberculin (preferably a safety-type) syringe.

§ Prefilling syringes is not recommended. Tuberculin is absorbed in varying amounts by glass and plastics. To minimize reduction in potency, tuberculin should be administered as soon after the syringe has been filled as possible. Following these procedures will also help avoid contamination. Test doses should always be removed from the vial under strictly aseptic conditions, and the remaining solution should remain refrigerated (not frozen). Tuberculin should be stored in the dark as much as possible and exposure to strong light should be avoided. **SOURCE:** American Thoracic Society, CDC, Infectious Disease Society of America. Diagnostic standards and classification of tuberculosis in adults and children. Am J Respir Crit Care Med 2000;161:1376–95.

¶ Preventing tuberculin antigen and vaccine (e.g., Td toxoid) misadministration is important. Measures should include physical separation of refrigerated products, careful visual inspection and reading of labels, preparation of PPD for patient use only at time of testing, and improved record keeping of lot numbers of antigens, vaccines, and other injectable products. **SOURCE:** CDC. Inadvertent intradermal administration of tetanus toxoid–containing vaccines instead of tuberculosis skin tests. MMWR 2004;53:662–4.

** If neither arm is available or acceptable for testing, the back of the shoulder is a good alternate TST administration site.
SOURCE: National Tuberculosis Controllers Association, National Tuberculosis Nurse Consultant Coalition. Tuberculosis nursing: a comprehensive guide to patient care. Smyrna, GA: National Tuberculosis Controllers Association; 1997.

†† Stretch skin by placing nondominant hand of health-care worker (HCW) on patient's forearm below the needle insertion point and then applying traction in the opposite direction of the needle insertion. Be careful not to place the nondominant hand of the HCW opposite the administration needle if the patient is likely to move during the procedure, which might cause an accidental needle-stick injury. In children and others who are likely to move during the procedure, certain trainers prefer stretching the skin in the opposite direction of the needle insertion by placing the nondominant hand of the HCW under the patient's forearm. This method should not be used for persons with poor skin turgor.

Appendix F. (*Continued*) Quality control (QC) procedural observation checklists

Quality Control (QC) Procedural Observation Checklist for Reading Tuberculin Skin Test (TST) Results — Palpation Method

Date _____ **Trainer (QC by)** _____ **Trainee (TST placed by)** _____

Scoring: ✓ or Y = Yes X or N = No NA = Not Applicable

1. Preliminary

_____ Uses appropriate hand hygiene methods before starting.
_____ Keeps fingernails shorter than fingertips to avoid misreading TST result.
_____ Keeps TST reading materials at hand (eyeliner pencil or ballpoint pen,* and ruler).
_____ Uses well-lit area.
_____ Inspects for the site of the injection.

2. Palpate — finding margin ridges (if any)

_____ Palpates with arm bent at elbow at a 90° angle.
_____ Lightly sweeps 2-inch diameter from injection site in four directions.
_____ Uses zigzag featherlike touch.
_____ Repeats palpation with arm bent at elbow at a 45° angle to determine presence or absence of induration.

If induration is present, continue with these steps†:

3. Placing marks

_____ Holds palm over injection site.
_____ Uses fingertips to find margins of the induration.
_____ Marks the induration by placing small dots on both sides of the induration.
_____ Inspects dots, repeats finger movements toward indurated margin, and adjusts dots if needed.
_____ Marks dots transverse (perpendicular) to long axis of forearm.

4. Placing and reading ruler

_____ Places the "0" ruler line inside the edge of the left dot. Reads the ruler line inside right dot edge (uses lower measurement if between two gradations on millimeter scale) (see Figure 1).
_____ Uses appropriate hand hygiene methods after reading TST.

5. Documenting results

_____ Records all TST results in millimeters, even those classified as negative. Does not record only as "positive" or "negative." Records the absence of induration as "0 mm."
_____ Correctly records results in mm; only a single measured induration in mm should be recorded.
Trainee's measurement _____ mm.
Trainer's (gold standard) measurement _____ mm.
Trainee's result within 2 mm of gold standard reading?§

Yes _____ No _____

NOTE: In rare instances, the reaction might be severe (vesiculation, ulceration, or necrosis of the skin). Report severe adverse events to the FDA MedWatch Adverse Events Reporting System (AERS), telephone: 800-FDA-1088; fax: 800-FDA-0178; http://www.fda.gov/medwatch report form 3500, Physicians' Desk Reference.

* A fine-tipped eyeliner pencil or ballpoint pen can be used as a marker. An eyeliner pencil is useful for TST training and for blinded independent duplicate readings (BIDRs) because the dots are easy to remove with a dot of lubricant (e.g., baby oil). Alternative TST result reading methods have been described, including the pen method.

† If induration is not present, record the TST result as 0 mm and go to the end of this form (Documenting results).

§ For example, if the TST trainer reads the TST result (the gold standard reading) as 11 mm, the trainee's TST reading should be between 9–13 mm to be considered correct. Only a single measured induration in millimeters should be recorded.

Appendix G. Model framework for medical evaluation request and questionnaire for users of N95 disposable respirators

Medical Evaluation Request

1. Today's date _____
2. Your name _____
3. Your age (to nearest year) _____
4. Sex _____ Male _____ Female
5. Your height _____ feet _____ inches
6. Your weight _____ pounds
7. Your job title _____
8. A phone number where you can be reached by the health-care professional who reviews this questionnaire (include area code)
   _____
9. The best time to phone you at this number _____
10. Has your employer told you how to contact the health-care professional who will review this questionnaire? ___ Yes ___ No
11. Check the type of respirator you will use (check all that apply)
    _____ N-, R-, or P-disposable respirator (filter-mask, noncartridge type only)
    _____ Half-facepiece type
    _____ Full-facepiece type
    _____ Powered air-purifying respirator (PAPR) – tight-fitting
    _____ PAPR – loose-fitting
    _____ Other type (supplied-air or self-contained breathing apparatus)
12. Have you worn a respirator? _____ Yes _____ No
    If "yes," what types? _____

Questionnaire for Users of N95 Respirators

Yes	No	
___	___	1. Do you currently or have you smoked tobacco during the previous month? If "yes"
		a. At what age did you start smoking? _____
		b. How long ago did you quit smoking? _____
		c. How many packs per day did or do you smoke? ____
		2. Have you ever had any of the following conditions?
___	___	a. Seizures (fits)
___	___	b. Diabetes (sugar disease)
___	___	c. Allergic reactions that interfere with your breathing
___	___	d. Claustrophobia (fear of closed-in places)
___	___	e. Trouble smelling odors
		3. Have you ever had any of the following pulmonary or lung problems?
___	___	a. Asbestosis
___	___	b. Asthma
___	___	c. Chronic bronchitis
___	___	d. Emphysema
___	___	e. Pneumonia
___	___	f. Tuberculosis
___	___	g. Silicosis
___	___	h. Pneumothorax (collapsed lung)
___	___	i. Lung cancer
___	___	j. Broken ribs
___	___	k. Any chest injuries or surgeries
___	___	l. Any other lung problem that you have been told about
		4. Do you currently have any of the following symptoms of pulmonary or lung illness?
___	___	a. Shortness of breath
___	___	b. Shortness of breath when walking quickly on level ground or walking up a slight hill or incline
___	___	c. Shortness of breath when walking with other people at an ordinary pace on level ground
___	___	d. Have to stop for breath when walking at your own pace on level ground
___	___	e. Shortness of breath when washing or dressing yourself

Yes	No	
		4. (*Continued*)
___	___	f. Shortness of breath that interferes with your job
___	___	g. Coughing that produces phlegm (thick sputum)
___	___	h. Coughing that wakes you early in the morning
___	___	i. Coughing that occurs primarily when you are lying down
___	___	j. Coughing up blood in the last month
___	___	k. Wheezing
___	___	l. Wheezing that interferes with your job
___	___	m. Chest pain when you breathe deeply
___	___	n. Any other symptoms that you think might be related to lung problems
		5. Have you ever had any of the following cardiovascular or heart problems?
___	___	a. Heart attack
___	___	b. Stroke
___	___	c. Angina
___	___	d. Heart failure
___	___	e. Swelling in your legs or feet (not caused by walking)
___	___	f. Heart arrhythmia (heart beating irregularly)
___	___	g. High blood pressure
___	___	h. Any other heart problem that you have been told about
		6. Have you ever had any of the following cardiovascular or heart symptoms?
___	___	a. Frequent pain or tightness in your chest
___	___	b. Pain or tightness in your chest during physical activity
___	___	c. Pain or tightness in your chest that interferes with your job
___	___	d. In the previous 2 years, have you noticed your heart skipping or missing a beat?
___	___	e. Heartburn or indigestion that is not related to eating
___	___	f. Any other symptoms that you think might be related to heart or circulation problems
		7. Do you currently take medication for any of the following problems?
___	___	a. Breathing or lung problems
___	___	b. Heart trouble
___	___	c. Blood pressure
___	___	d. Seizures (fits)
		8. If you have used a respirator, have you ever had any of the following problems? (If you have never used a respirator, check here ___ and go to question 9.)
___	___	a. Eye irritation
___	___	b. Skin allergies or rashes
___	___	c. Anxiety
___	___	d. General weakness or fatigue
___	___	e. Any other problem that interferes with your use of a respirator
___	___	9. Are you currently taking any medications? If yes, list here _____ _____ _____ _____
___	___	10. Would you like to talk with the health-care professional who will review this questionnaire about your answers to this questionnaire?

Please explain "yes" answers (use back of form if necessary)

_____
_____
_____
_____
_____

MMWR™

Morbidity and Mortality Weekly Report

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Continuing Education Activity Sponsored by CDC

Guidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in Health-Care Settings, 2005

EXPIRATION — December 30, 2008

You must complete and return the response form electronically or by mail by **December 30, 2008**, to receive continuing education credit. If you answer all of the questions, you will receive an award letter for 3.5 hours Continuing Medical Education (CME) credit; 0.35 Continuing Education Units (CEUs); 4.0 contact hours Continuing Nursing Education (CNE) credit; or 3.5 contact hours National Commission for Health Education Credentialing (NCHEC) credit. If you return the form electronically, you will receive educational credit immediately. If you mail the form, you will receive educational credit in approximately 30 days. No fees are charged for participating in this continuing education activity.

INSTRUCTIONS

By Internet

1. Read this *MMWR* (Vol. 54, RR-17), which contains the correct answers to the questions beginning on the next page.
2. Go to the *MMWR* Continuing Education Internet site at http://www.cdc.gov/mmwr/cme/conted.html.
3. Select which exam you want to take and select whether you want to register for CME, CEU, CNE, or CHES credit.
4. Fill out and submit the registration form.
5. Select exam questions. To receive continuing education credit, you must answer all of the questions. Questions with more than one correct answer will instruct you to "Indicate all that apply."
6. Submit your answers no later than **December 30, 2008**.
7. Immediately print your Certificate of Completion for your records.

By Mail or Fax

1. Read this *MMWR* (Vol. 54, RR-17), which contains the correct answers to the questions beginning on the next page.
2. Complete all registration information on the response form, including your name, mailing address, phone number, and e-mail address, if available.
3. Indicate whether you are registering for CME, CEU, CNE, or CHES credit.
4. Select your answers to the questions, and mark the corresponding letters on the response form. To receive continuing education credit, you must answer all of the questions. Questions with more than one correct answer will instruct you to "Indicate all that apply."
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   Centers for Disease Control and Prevention
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   Atlanta, GA 30333
6. Your Certificate of Completion will be mailed to you within 30 days.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Goal and Objectives

This report updates tuberculosis (TB) infection-control measures and includes new recommendations for developing, implementing, and evaluating infection-control programs for health-care settings across the continuum of patient care. The goal of this report is to emphasize necessary actions to avert another TB resurgence, eliminate the lingering threat to health-care workers (HCWs) from patients with unsuspected and undiagnosed infectious TB disease, and address health-care associated settings. Upon completion of this educational activity, the reader should be able to 1) describe the three levels of controls in a TB infection-control program designed to prevent *Mycobacterium tuberculosis* transmission in health-care settings; 2) identify administrative measures used to reduce the risk for exposure to persons who might have TB disease; 3) identify appropriate environmental controls used to prevent the spread of infectious droplet nuclei; and 4) identify appropriate use of respiratory protection to reduce the risk for exposure to infectious droplet nuclei that have been expelled into the air from a patient with infectious TB disease.

To receive continuing education credit, please answer all of the following questions.

1. The three levels of controls that should be the foundation for a TB infection-control program are…

A. administrative, environmental, and respiratory protection.
B. risk assessment, environmental, and respiratory protection.
C. administrative, engineering, and respiratory protection.
D. risk assessment, engineering, and environmental.

2. Settings in which persons with TB disease are not expected to be encountered do not need to have a TB infection-control plan.

A. True.
B. False.

3. Which of the following factors are examined when conducting a risk assessment in a health-care setting?

A. Number of patients with TB disease treated per year.
B. Timeliness of the recognition, isolation, and evaluation of patients with suspected or confirmed TB disease.
C. Community rate of TB.
D. Evidence of transmission of *M. tuberculosis.*
E. Types and conditions of the environmental controls present in the facility.
F. All of the above.

4. Baseline testing for *M. tuberculosis* is recommended for all newly hired HCWs who might have contact with persons with suspected or confirmed TB disease, regardless of the risk classification of the setting.

A. True.
B. False.

5. Routine chest radiographs are not recommended for HCWs with positive tuberculosis skin test (TST) or blood assay for *Mycobacterium tuberculosis* (BAMT) results.

A. True.
B. False.

6. Environmental control measures used to prevent the spread and reduce the concentration of airborne infectious droplet nuclei may include which of the following?

A. Implementing a respiratory-protection program.
B. Ensuring proper cleaning and sterilization or disinfection of potentially contaminated equipment.
C. Controlling the source of infection by use of local exhaust ventilation.
D. None of the above.

7. A patient with suspected TB disease can be removed from an airborne infection isolation (AII) room when…

A. another diagnosis is made that describes the clinical syndrome.
B. the patient has been on an antituberculosis treatment regimen for ≥2 weeks.
C. the patient has two consecutive negative acid-fast bacilli (AFB) sputum smear results.
D. the patient's TST or BAMT result reverts to negative.
E. none of the above.

8. All rooms in existing health-care settings should have airflow of ____ air changes per hour (ACH). New construction or renovation of health-care settings should be designed so that All rooms achieve airflow of ____ ACH.

A. ≥3 and ≥6.
B. ≥6 and ≥12.
C. ≥9 and ≥12.
D. ≥12 and ≥24.

9. The frequency of respirator fit testing should be guided by a change in…

A. risk for transmission of *M. tuberculosis*.
B. facial features of the wearer.
C. medical condition that would affect respiratory function.
D. physical characteristics of respirator.
E. model or size of the assigned respirator.
F. all of the above.

10. Respirators should be worn by…

A. all persons entering rooms in which patients with infectious TB disease are being isolated.
B. persons present during cough-inducing or aerosol-generating–procedures being performed on patients with infectious TB disease.
C. persons in settings in which administrative and environmental controls are not likely to be present or effective.
D. all of the above.

11. Which best describes your professional activities?

A. Physician.
B. Nurse.
C. Health educator.
D. Office staff.
E. Other.

12. I plan to use these recommendations as the basis for …(*Indicate all that apply.*)

A. health education materials.
B. insurance reimbursement policies.
C. local practice guidelines.
D. public policy.
E. other.

13. Overall, the length of the journal report was…

A. much too long.
B. a little too long.
C. just right.
D. a little too short.
E. much too short.

14. After reading this report, I am confident I can describe the three levels of controls in a TB infection-control program designed to prevent *M. tuberculosis* transmission in health-care settings.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

15. After reading this report, I am confident I can identify administrative measures used to reduce the risk for exposure to persons who might have TB disease.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

16. After reading this report, I am confident I can identify appropriate environmental controls used to prevent the spread of infectious droplet nuclei.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

17. After reading this report, I am confident I can identify appropriate use of respiratory protection to reduce the risk for exposure to infectious droplet nuclei that have been expelled into the air from a patient with infectious TB disease.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

18. The learning outcomes (objectives) were relevant to the goals of this report.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

19. The instructional strategies used in this report (tables, figures, boxes, and appendices) helped me learn the material.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

(Continued on pg CE-4)

Detach or photocopy.

MMWR Response Form for Continuing Education Credit
December 30, 2005/Vol. 54/No. RR-17
Guidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in Health-Care Settings, 2005

To receive continuing education credit, you must
1. provide your contact information (**please print or type**);
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3. answer all of the test questions;
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5. submit your answer form by **December 30, 2008**.

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Check One
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1.	[ ]A	[ ]B	[ ]C	[ ]D								15.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E														
2.	[ ]A	[ ]B										16.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E														
3.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	[ ]F						17.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E														
4.	[ ]A	[ ]B										18.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E														
5.	[ ]A	[ ]B										19.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E														
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7.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E							21.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E														
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12.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E							26.	[ ]A	[ ]B																	
13.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E							27.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	[ ]F													
14.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E																										

Signature ***Date I Completed Exam***

20. The content was appropriate given the stated objectives of the report.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

21. The content expert(s) demonstrated expertise in the subject matter.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

22. Overall, the quality of the journal report was excellent.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

23. These recommendations will improve the quality of my practice.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

24. The availability of continuing education credit influenced my decision to read this report.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

25. The *MMWR* format was conducive to learning this content.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

26. Do you feel this activity was commercially biased? (*Indicate yes or no; if yes, please explain in the space provided.*)
A. Yes.
B. No.

27. How did you learn about the continuing education activity?
A. Internet.
B. Advertisement (e.g., fact sheet, *MMWR* cover, newsletter, or journal).
C. Coworker/supervisor.
D. Conference presentation.
E. *MMWR* subscription.
F. Other.

Correct answers for questions 1-10.
1. A; 2. B; 3. F; 4. A; 5. A; 6. C; 7. A; 8. B; 9. F; 10. D.

Guidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in Health-Care Settings, 2005

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List of Major Errata in Order of Importance from the
"Guidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in Health-care Settings, 2005"
http://www.cdc.gov/mmwr/pdf/rr/rr5417.pdf

No.	Major Errata	Correction	Page	Column 1 or 2	Paragraph / bullet	Affects interpreta-tion of policy
1	Incorrect insertion of word: "Environmental control maintenance procedures and logs should **not** be reviewed to determine if maintenance is conducted properly and regularly."	"Environmental control maintenance procedures and logs should be reviewed to determine if maintenance is conducted properly and regularly."	14	2	2nd para	Yes
2	Four values in Table 1 are incorrect: **Minutes required for removal efficiency†** **ACH 99% 99.9%** 2 138 207 4 69 104 6 46 69 12 23 35 15 18 28 20 ~~7 14~~ 50 ~~3 6~~ 400 <1 1	**Minutes required for removal efficiency†** **ACH 99% 99.9%** 2 138 207 4 69 104 6 46 69 12 23 35 15 18 28 20 **14** **21** 50 **6** **8** 400 <1 1	20	2	1st para	Yes
3	Word is used incorrectly: "The following are HCWs who **should** be included in a TB screening program:"	"The following are HCWs who **may** be included in a TB screening program:"	3	2	1st sentence before bullets	Yes
4	Incorrect phrase: "In accordance with local and state laws and regulations, a system should be in place to ensure that laboratories report any positive results from any	"In accordance with local and state laws and regulations, a system should be in place to ensure that laboratories report any positive results from any	18	2	Last sentence	Yes

No.	Major Errata	Correction	Page	Column 1 or 2	Paragraph / bullet	Affects interpreta-tion of policy
	specimens to clinicians within 24 hours of **obtaining the result**."	specimens to clinicians within 24 hours of **receipt of the specimen.**"				
5	Word is used incorrectly: "Rather than the product's specific potency against mycobacteria, a germicide that can **activate** many pathogens is the basis for protocols and regulations indicating the appropriateness of tuberculocidal chemicals for surface disinfection."	"Rather than the product's specific potency against mycobacteria, a germicide that can **inactivate** many pathogens is the basis for protocols and regulations indicating the appropriateness of tuberculocidal chemicals for surface disinfection."	80	1	3rd para	Yes
6, 7	The greater than sign (>) is used without the sense of equality, and a space was omitted: "TST training and coaching should continue until more than10 correct skin test placements (i.e., >6 mm wheal) are achieved."	"TST training and coaching should continue until more **than 10** correct skin test placements (i.e., **≥6** mm wheal) are achieved."	48	1	4th para	Yes
8	The greater than sign (>) is used without the sense of equality: "…and an increase in the TST size of >10 mm, the result should be interpreted as the HCW having a TST conversion because of new infection."	"…and an increase in the TST size of **≥10** mm, the result should be interpreted as the HCW having a TST conversion because of new infection."	50	2	2nd to last para	Yes
9	The greater than sign (>) is used without the sense of equality: "An increase of >10 mm in induration during a maximum of 2 years is defined as a TST conversion for the purposes of a contact investigation."	"An increase of **≥10** mm in induration during a maximum of 2 years is defined as a TST conversion for the purposes of a contact investigation."	119	n/a	1st para	Yes

No.	Major Errata	Correction	Page	Column 1 or 2	Paragraph / bullet	Affects interpreta-tion of policy
10	The greater than sign (>) is used without the sense of equality: "…with a filter efficiency of >95%."	"…with a filter efficiency of ≥95%."	122	Environ column	Last line under Surgical Suites	Yes
11	Words are omitted. "Persons in the following groups at high risk should be administered treatment for LTBI if their TST result is ≥5 mm, regardless of age (*31,39*):"	"Persons in the following groups at high risk should be administered treatment for LTBI if their TST result is ≥5 mm, regardless of age (*31,39*), **or if their blood assay for *M. tuberculosis* (BAMT) result is positive.**"	53	1	4th para	Yes
12	Commas are omitted: The number of organisms expelled are related to the following factors: 1) presence of cough lasting >3 weeks…; 6) lack of incorrect or short duration of antituberculosis treatment …"	"The number of organisms expelled are related to the following factors: 1) presence of cough lasting >3 weeks…; 6) lack of**,** incorrect**,** or short duration of antituberculosis treatment …"	42	2	2nd para	Yes
13	Insertion of words: "Infection-control policies for each dental healthcare setting should be developed, based on the community TB risk assessment (see TB Risk Assessment Worksheet [Appendix B]), and **the periodically** should be reviewed annually, if possible."	"Infection-control policies for each dental healthcare setting should be developed, based on the community TB risk assessment (see TB Risk Assessment Worksheet [Appendix B]), and should be reviewed annually, if possible."	25	1	Last para	Yes
14	A clause is omitted: "DOT should be used for all doses during the course of treatment of LTBI whenever feasible."	"DOT should be used for all doses during the course of treatment of LTBI whenever feasible; **however, all patients on intermittent treatment for LTBI (or TB disease)**	55	1	1st para	Yes

No.	Major Errata	Correction	Page	Column 1 or 2	Paragraph / bullet	Affects interpreta-tion of policy
		should receive DOT."				
15	Words are omitted: "To check the negative pressure seal after donning the respirator, the wearer should gently inhale, which should create a vacuum, causing the respirator to be drawn in toward the face."	"To check the negative pressure seal after donning the respirator, the wearer should **cover the surface of the respirator and** gently inhale, which should create a vacuum, causing the respirator to be drawn in toward the face."	87	2	5th para	Yes
16	Words are omitted: "†Test conversion rate is calculated by dividing the number of conversions among HCWs by the number of HCWs who had previous negative results during a certain period."	"†Test conversion rate is calculated by dividing the number of conversions among HCWs by the number of HCWs who **were tested and** had previous negative results during a certain period."	133	n/a	Last footnote	Yes
17	Inserted words in Title of Appendix C: "Risk classifications for health-care settings **that serve communities with high incidence of tuberculosis (TB)** and recommended frequency of screening for *Mycobacterium tuberculosis* infection among health-care workers (HCWs)"	"Risk classifications for various health-care settings and recommended frequency of screening for *Mycobacterium tuberculosis* infection among health-care workers (HCWs)"	134	n/a	n/a	Yes
18	Inserted hyphen: "Nontraditional facility-based settings include … long-term–care settings (e.g., **hospice-skilled** nursing facilities), and homeless shelters."	"Nontraditional facility-based settings include … long-term–care settings (e.g., hospices**,** skilled nursing facilities), and homeless shelters."	3	1	2nd to last para	Yes

No.	Major Errata	Correction	Page	Column 1 or 2	Paragraph / bullet	Affects interpreta-tion of policy
19, 20	Two sections are placed under incorrect headings.	The text under "Use of QFT-G for Diagnosing *M. tuberculosis* Infections in Health-care Workers (HCWs)" should be under "Surveillance and Detection of *M. tuberculosis infections* in Health-care Settings" and vice versa.	44, 56	2 2	1st para 3rd para	No
21	Incorrect wording: "Infection with *M. tuberculosis* poses a health risk to patients, HCWs, visitors, and volunteers in LTCFs (e.g., hospices and skilled nursing facilities)."	"TB disease poses a health risk to patients, HCWs, visitors, and volunteers in LTCFs (e.g., hospices and skilled nursing facilities)."	27	1	4th para	No
22	Incorrect wording: "New employees and residents to these settings should receive a symptom screen and possibly a test for *M. tuberculosis* infection **to exclude a diagnosis of TB disease**."	"New employees to LTCFs should receive baseline TB screening upon hire, using two-step TST or a single BAMT **to test for infection with *M. tuberculosis.*"** "The infection control team may also decide to screen residents to these settings with a symptom screen and possibly a test for *M. tuberculosis* infection."	27	1	4th para	Yes
23	Incorrect references to Supplement and Table 2: "This interval will vary based on the efficiency of the ventilation or filtration system (**see Supplement, Environmental Controls; Table 2**)."	"This interval will vary based on the efficiency of the ventilation or filtration system (**Table 1**)."	41	1	3rd para	No
24	Incorrect references to Supplement		53	1	2nd para	No

No.	Major Errata	Correction	Page	Column 1 or 2	Paragraph / bullet	Affects interpreta-tion of policy
	and Box 2: "Certain groups of persons are at substantially high risk for developing TB disease after being infected, and every effort should be made to begin treatment for LTBI and to ensure that those persons complete the entire course of treatment (**see Supplement, Treatment Procedures for LTBI and TB Disease; Box 2).**"	"Certain groups of persons are at substantially high risk for developing TB disease after being infected, and every effort should be made to begin treatment for LTBI and to ensure that those persons complete the entire course of treatment (**Table 3**)."				
25	Incorrect reference to Appendix D: "HCWs should receive serial screening for infection with *M. tuberculosis* (either TST or BAMT), as determined by the health-care setting's risk classification (**Appendix D**)."	"HCWs should receive serial screening for infection with *M. tuberculosis* (either TST or BAMT), as determined by the health-care setting's risk classification (**Appendix B**).	54	1	4th para	No
26	Commas are omitted: "If supply or exhaust vents circulating fans or room-air recirculation units are placed incorrectly, HCWs might not be adequately protected."	"If supply or exhaust vents**,** circulating fans**,** or room-air recirculation units are placed incorrectly, HCWs might not be adequately protected."	63	2	2nd para	No
27	Incorrect reference to Appendix B: "Recommended administrative, environmental, and respiratory-protection controls for these and other selected settings have been summarized (**Appendix B**)."	"Recommended administrative, environmental, and respiratory-protection controls for these and other selected settings have been summarized (**Appendix A**)."	67	2	1st words	No
28	Incorrect references to Supplement		80	2	2	No

No.	Major Errata	Correction	Page	Column 1 or 2	Paragraph / bullet	Affects interpreta-tion of policy
	and Table 2: "Personal protective equipment is not necessary during the final cleaning of an AII room after a patient has been discharged if the room has been ventilated for the appropriate amount of time **(see Supplement, Environmental Controls; Table 2)."**	"Personal protective equipment is not necessary during the final cleaning of an AII room after a patient has been discharged if the room has been ventilated for the appropriate amount of time (**Table 1**)."				

List of Minor Errata in Order of Page Numbers in the
"Guidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in Health-care Settings, 2005"

	Minor Errata	Correction	Page	Column 1 or 2	Paragraph / bullet	Affect interpreta-tion of policy
1	Words are omitted: "In accordance with relevant local, state, and federal laws, implementation of all recommendations must safeguard the confidentiality and civil rights of all HCWs and patients who have been infected with *M. tuberculosis* and TB disease."	"In accordance with relevant local, state, and federal laws, implementation of all recommendations must safeguard the confidentiality and civil rights of all HCWs and patients who have been infected with *M. tuberculosis* and **who develop** TB disease."	3	1	1st paragraph after bullets	No
2	Period omitted at end of sentence: "Primary environmental controls consist of controlling the source of infection by using local exhaust ventilation (e.g., hoods, tents, or booths) and diluting and removing contaminated air by using general ventilation"	"Primary environmental controls consist of controlling the source of infection by using local exhaust ventilation (e.g., hoods, tents, or booths) and diluting and removing contaminated air by using general ventilation**.**"	7	2	3rd para	No
3	Incorrect comma use: Secondary environmental controls consist of controlling the airflow to prevent contamination of air in areas adjacent to the source (AII rooms) and cleaning the air by using high efficiency particulate air **(HEPA), filtration, or UVGI**.	Should be: Secondary environmental controls consist of controlling the airflow to prevent contamination of air in areas adjacent to the source (AII rooms) and cleaning the air by using high efficiency particulate air (HEPA) filtration or UVGI.	7	2	4th para	No
4	Incorrect abbreviation:		8	2	3rd from	No

	Minor Errata	Correction	Page	Column 1 or 2	Paragraph / bullet	Affect interpreta-tion of policy
	"Settings in **whichT patients** might stay before transfer…"	"Settings in which TB patients might stay before transfer…"			end	
5	Misspelled word: "If less than three TB patients for the **proceeding** year, classify as low risk."	"If less than three TB patients for the preceding year, classify as low risk."	11	1	3rd from end	No
6	Insertion of a hyphen: "A contact investigation of exposed HCWs by hospital infection-control personnel in consultation with the state or local health department did not identify any health-care–associated **transmission-.**"	"A contact investigation of exposed HCWs by hospital infection-control personnel in consultation with the state or local health department did not identify any health-care–associated transmission**."**	11	2	1st para	No
7	Word is omitted: "The home health-care agency is based in a major metropolitan area and delivers care to a community where the majority persons are poor and medically underserved and TB case rates are higher than the community as a whole."	"The home health-care agency is based in a major metropolitan area and delivers care to a community where the majority **of** persons are poor and medically underserved and TB case rates are higher than the community as a whole."	12	2	1st para	No
8	Words are omitted: "In settings conducting serial testing for *M. tuberculosis* infection (medium-risk settings), use the to estimate the risk for test conversion in HCWs."	"In settings conducting serial testing for *M. tuberculosis* infection (medium-risk settings), use the **following steps** to estimate the risk for test conversion in HCWs."	13	1	4th para	No

	Minor Errata	Correction	Page	Column 1 or 2	Paragraph / bullet	Affect interpreta-tion of policy
9	Words are omitted: "When testing for *M. tuberculosis* infection, conversions are determined to be the result of well-documented community exposure or probable false-positive test results; the risk classification of the setting does not need to be adjusted."	"When testing for *M. tuberculosis* infection, **if** conversions are determined to be the result of well-documented community exposure or probable false-positive test results, **then** the risk classification of the setting does not need to be adjusted."	13	2	1st para	No
10, 11	Word is used incorrectly and incorrect verb tense: "Facility engineering personnel with expertise in heating, ventilation, and air conditioning (HVAC) and air handlers have evaluated how this option is applied to ensure no over pressurization of return air or unwanted **alternations exists** in design of air flow in the zone."	"Facility engineering personnel with expertise in heating, ventilation, and air conditioning (HVAC) and air handlers have evaluated how this option is applied to ensure no over pressurization of return air or unwanted **deviations exist** in the design of air flow in the zone."	20	1	4th para	No
12	Insertion of word: "At least one AII room should be available in **the** correctional facility."	"At least one AII room should be available in correctional facilities."	26	2	3rd para	No
13	Insertion of words: "Confidentiality of inmates should be ensured **the confidentiality of inmates during** screening for symptoms or signs of TB disease and risk factors."	"Confidentiality of inmates should be ensured while screening inmates for symptoms or signs of TB disease and risk factors."	26	2	5th para	No
14, 15	Words are omitted and incorrect use of semi-colon:		33	1	1st para after	No

	Minor Errata	Correction	Page	Column 1 or 2	Paragraph / bullet	Affect interpreta-tion of policy
	"If no additional conversions in the test results for *M. tuberculosis* are detected in the follow-up testing, terminate the investigation. If additional conversions in the tests for *M. tuberculosis* are detected in the follow-up testing, transmission might still be occurring, and additional actions are needed:…3) possible reasons for exposure and transmission**;** should be reassessed and …"	"If no additional conversions in the test results for *M. tuberculosis* **infection** are detected in the follow-up testing, terminate the investigation. If additional conversions in the tests for *M. tuberculosis* **infection** are detected in the follow-up testing, transmission might still be occurring, and additional actions are needed:…3) possible reasons for exposure and **transmission should** be reassessed and …"			bullets	
16, 17	Comma and words are omitted: • "promptly evaluate (including a chest radiograph) the exposed person for TB disease, if the symptom screen or the initial 8–10-week follow-up TST result is positive"	Should be: "promptly evaluate (including a chest radiograph) the exposed person for TB disease, if the symptom screen, the initial**, or the** 8–10-week follow-up TST result is positive"	33	1	5th bullet	No
18	Insertion of word: "**Repeat** testing for *M. tuberculosis* infection should be repeated 8–10 weeks after the end of exposure…"	"Testing for *M. tuberculosis* infection should be repeated 8–10 weeks after the end of exposure…"	33	1	2nd after bullets	No
19	Word is used incorrectly: "If no problems are identified, a classification of potential ongoing transmission should be **identified**, and the local or state health department or other persons with	"If no problems are identified, a classification of potential ongoing transmission should be **applied**, and the local or state health department or other persons with expertise in TB	34	1	2nd para	No

	Minor Errata	Correction	Page	Column 1 or 2	Paragraph / bullet	Affect interpreta-tion of policy
	expertise in TB infection control should be consulted for assistance."	infection control should be consulted for assistance."				
20	Incorrect verb tense: "The primary goal of contact investigations **are** to identify secondary cases of TB disease and LTBI among contacts"	"The primary goal of contact investigations **is** to identify secondary cases of TB disease and LTBI among contacts"	35	2	1st para	No
21	Word is used incorrectly: "The frequency of periodic fit testing should be **supplemented** by the occurrence of …"	"The frequency of periodic fit testing should be **determined** by the occurrence of …"	39	2	Last para	No
22	Wording is not consistent with Respiratory Protection Supplement: "Fit testing provides a means to determine which respirator model and size fits the wearer best and to confirm that the wearer can don the respirator properly to achieve a good fit. Periodic fit testing for respirators used in TB environments can serve as an effective training tool in conjunction with the content included in employee training and retraining. The frequency of periodic fit testing should be supplemented by the occurrence of 1) risk for transmission of *M. tuberculosis*, 2) facial features of the wearer, 3) medical condition that would affect respiratory function, 4) physical characteristics of respirator (despite	"Fit testing provides a method to determine which respirator model and size fits the wearer best and to confirm that the wearer can properly fit the respirator. Periodic fit testing for respirators used in environments where a risk for *M. tuberculosis* transmission exists can serve as an effective training tool in conjunction with the content included in employee training and retraining. The frequency of periodic fit testing should be determined by the occurrence of 1) risk for transmission of *M. tuberculosis*, 2) a change in facial features of the wearer, 3) a medical condition that would affect respiratory function, 4) physical characteristics of respirator (despite the same model number), or 5) a	39, 79	39 – 2 79 – 1	Last para 2nd para	No

	Minor Errata	Correction	Page	Column 1 or 2	Paragraph / bullet	Affect interpreta-tion of policy
	the same model number), or 5) model or size of the assigned respirator."	change in the model or size of the assigned respirator."				
23, 24	Incorrect use of comma and period is omitted: "These cough-inducing procedures include endotracheal intubation…bronchoscopy, and laryngoscopy**,** gastric aspiration and nasogastric tube placement can also induce cough in certain patients."	"These cough-inducing procedures include endotracheal intubation…bronchoscopy, and laryngoscopy**.** Gastric aspiration and nasogastric tube placement can also induce cough in certain patients."	40	2	Last para	No
25	Insertion of words: "**The purpose of the test** (Box 2) should be used to determine whether the TST result should be classified as positive or negative."	"Box 2 should be used to determine whether the TST result should be classified as positive or negative."	46	1	Last para	No
26	Incorrect reference to Box 2: "The criteria used to determine the need for treatment of LTBI has been presented (Box 2)."	"The criteria used to determine the need for treatment of LTBI has been presented."	47	2	1st para	No
27, 28	Period is omitted and incorrect reference : "The medical evaluation can occur in different settings, including an occupational health clinic, local or state health department, or private medical clinic (Box 2)"	"The medical evaluation can occur in different settings, including an occupational health clinic, local or state health department, or private medical clinic**.**"	47	2	2nd para	No
29	Space is omitted: "…(consider16 hours of practical	"..(**consider 16** hours of practical	49	1	2nd bullet	No

	Minor Errata	Correction	Page	Column 1 or 2	Paragraph / bullet	Affect interpreta-tion of policy
	work)…"	work)…"				
30	Words are omitted: "For example, the control of differential pressure can frequently be improved by increasing the air tightness or seal of a room, HVAC system, and ensuring continuous monitoring."	"For example, the control of differential pressure can frequently be improved by increasing the air tightness or seal of a room, **maintaining the** HVAC system, and ensuring continuous monitoring."	64	1	2nd para	No
31	The "DQ" and "DP" in the formula are incorrect.	"**Δ**Q" and "**Δ**P"	64	1	2nd para	No
32	Word is used incorrectly: "…however, a small change in differential pressure will have a substantial **affect** on differential airflow."	"…however, a small change in differential pressure will have a substantial **effect** on differential airflow."	64	1	2nd para	No
33	Word is omitted: "HEPA filtration can be used to supplement other recommended ventilation measures by providing a minimum removal efficiency of 99.97% of particles equal 0.3 µm in diameter."	"HEPA filtration can be used to supplement other recommended ventilation measures by providing a minimum removal efficiency of 99.97% of particles equal **to** 0.3 µm in diameter."	67	2	3rd para	No
34	Word is used incorrectly: "**Person** room-air recirculation can be used in areas in which no general ventilation system exists …"	**"Individual** room-air recirculation can be used in areas in which no general ventilation system exists…"	68	1	5th para	No
35	Incorrect verb tense: "The range of volumetric airflow	"The range of volumetric airflow	69	1	4th para	No

	Minor Errata	Correction	Page	Column 1 or 2	Paragraph / bullet	Affect interpreta-tion of policy
	rates **is** 110 cfm–1,152 cfm, and the equivalent ACH range was an average of 8–22 in a standard-sized, substantially well-mixed, single-patient room."	rates **was** 110 cfm–1,152 cfm, and the equivalent ACH range was an average of 8–22 in a standard-sized, substantially well-mixed, single-patient room."				
36	Incorrect use of a period: "In a 1976 study on aerosolization of *M. bovis***.** BCG (a surrogate for *M. tuberculosis*) in a room without mechanical ventilation that relied primarily on convection and infiltration resulted in 10–25 equivalent ACH…"	"In a 1976 study on aerosolization of *M. bovis* BCG (a surrogate for *M. tuberculosis*) in a room without mechanical ventilation that relied primarily on convection and infiltration resulted in 10–25 equivalent ACH…"	71	2	2nd para from end	No
37	Incorrect verb tense: "When *M. parafortuitum* **is** used as a surrogate for *M. tuberculosis*, ventilation rates usually had no adverse effect on the efficiency of upper-air UVGI."	"When *M. parafortuitum* **was** used as a surrogate for *M. tuberculosis*, ventilation rates usually had no adverse effect on the efficiency of upper-air UVGI."	72	2	1st para	No
38	Incorrect verb tense: "Because the UVGI output of the lamps **decline** with age, a schedule for replacing the lamps should be developed in accordance with manufacturer recommendations."	"Because the UVGI output of the lamps **declines** with age, a schedule for replacing the lamps should be developed in accordance with manufacturer recommendations."	73	2	Last para	No
39	Incorrect use of a hyphen: "A proper seal between the respirator's sealing surface and the face of the person wearing the **res-**	"A proper seal between the respirator's sealing surface and the face of the person wearing the **respirator** is essential for the	77	1	2nd para	No

	Minor Errata	Correction	Page	Column 1 or 2	Paragraph / bullet	Affect interpreta-tion of policy
	pirator is essential for the effective and reliable performance of any tight-fitting, negative-pressure respirator."	effective and reliable performance of any tight-fitting, negative-pressure respirator."				
40	Word is used incorrectly: "The frequency of periodic fit testing should be **supplemented** by the occurrence of 1) a risk for transmission of *M. tuberculosis*, 2) a change in facial features of the wearer…"	"The frequency of periodic fit testing should be **determined** by the occurrence of 1) a risk for transmission of *M. tuberculosis*, 2) a change in facial features of the wearer…"	79	1	2nd para	No
41, 42	Word is omitted and incorrect verb tense: "1) pregnancy is not contraindication to having a TST administered and 2) skin testing does not **affecting** the fetus or the mother."	"1) pregnancy is not **a** contraindication to having a TST administered and 2) skin testing does not **affect** the fetus or the mother."	81	1	3rd bulleted question	No
43	Left parenthesis is omitted: "The second result of 0 mm might have been caused by incorrect administration of the TST (i.e., too deeply or too shallow), or was read and recorded incorrectly if it was actually positive)."	"The second result of 0 mm might have been caused by incorrect administration of the TST (i.e., too deeply or too shallow), or was read and recorded incorrectly **(**if it was actually positive)."	84	2	1st bullet	No
44, 45	Insertion of word and comma is omitted: "… collection of additional specimens, including post bronchoscopy sputum **that** can increase the diagnostic yield and	"… collection of additional specimens, including post bronchoscopy sputum**,** can increase the diagnostic yield and increase the	89	1	2nd para	No

	Minor Errata	Correction	Page	Column 1 or 2	Paragraph / bullet	Affect interpreta-tion of policy
	increase the opportunity to confirm an alternate diagnosis.”	opportunity to confirm an alternate diagnosis.”				
46, 47	Incorrect use of comma and inserted word: “… Examples include … developing and instituting a written TB infection-control plan to ensure prompt detection, airborne infection isolation (AII)**, and** treatment of persons with suspected or confirmed TB disease; and screening and evaluating health-care workers (HCWs) who are at risk for TB disease or who might be exposed to *M. tuberculosis.*“	“… Examples include … developing and instituting a written TB infection-control plan to ensure prompt detection, airborne infection isolation (AII)**;** treatment of persons with suspected or confirmed TB disease; and screening and evaluating health-care workers (HCWs) who are at risk for TB disease or who might be exposed to *M. tuberculosis.* “	107	n/a	Definition for “administra-tive controls”	No
48	Words are omitted: “The condition of being subjected to something (e.g., an infectious agent) that could have an effect. A person exposed to *M. tuberculosis* does not necessarily become infected.”	“The condition of being subjected to something (e.g., an infectious agent) that could have an **adverse health** effect. A person exposed to *M. tuberculosis* does not necessarily become infected.”	111	n/a	Definition for “exposure”	No
49	Word is omitted: “See also conversion.”	“See also conversion **rate**.”	119		Definition for “TST conversion’	n/a
50	Page is omitted.	No content is omitted; this page is intentionally blank.	120	n/a	n/a	No
51	Incorrect verb tense: “Keeps appointment for reading.”	“Keep appointment for reading.”	138	2	Last line before bullets	No

Additional Frequently Asked Questions (FAQ) for Clarification of Recommendations in the "Guidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in Health-Care Settings, 2005"

1) **What is an infection-control team?**

   The infection-control team consists of persons who develop and implement infection-control policies for a health-care setting (including, but not limited to, individuals with expertise in infection control, epidemiology, clinical issues [medical doctor, registered nurse], microbiology, engineering, and administrative matters).

2) **An inpatient setting (a hospital) with more than 200 beds and less than six TB patients for the preceding year would be classified as low risk according to the criteria in the guidelines; however, the infection-control team for our setting prefers to continue screening nurses annually. Is that acceptable?**

   Yes, the infection-control team may determine that a higher risk classification is warranted for a specific setting or for a specific group of health-care workers (HCWs). Low-risk settings are free to select recommendations for medium-risk settings, if desired.

3) **Is the model tuberculin skin test (TST) training program used by the National Health and Nutrition Examination Survey (NHANES) described on page 50 of the guidelines required for all settings?**

   No, CDC guidelines are recommendations, they are not requirements. "The suggested TST training recommendations are not mandatory" (from page 45 of the guidelines).

"The number of training hours, sessions, and TST readings should be determined by the setting's TB risk assessment" (p. 48). Settings with a low prevalence of TB may not be able to meet NHANES TST training recommendations.

4) What is the positive cut-point baseline TST result for HCWs?

When making decisions for the diagnosis and treatment of latent tuberculosis infection (LTBI), setting-based risk factors (e.g., the prevalence of TB disease) and personal risk factors (e.g., having an immunocompromising condition or known contact with a TB case) should be assessed when choosing the cut point for a positive TST result.

"For HCWs who are at low risk (e.g., those from low incidence settings), a baseline result of ≥15 mm of induration (instead of ≥10 mm) might possibly be the cut point. When 15 mm is used as the cut point, TST results of 10–14 mm can be considered clinically negative. These HCWs should not have repeat TST, and the referring physician might not recommend treatment for latent tuberculosis infection (LTBI)." (p. 47)

For HCWs who are at medium risk, a baseline TST result of ≥10 mm is considered positive. For HCWs who are known contacts to a person with infectious TB disease (i.e., HCWs who are tested during contact investigations), and for HCWs who are infected with HIV, a TST result of ≥5 mm is considered positive.

5) **How should HCWs in low-risk settings who have positive test results for *M. tuberculosis* infection (positive TST or blood assay for *M. tuberculosis* [BAMT] result) be managed?**

The treating physician, with assistance from the infection-control team, should decide how to manage these HCWs. After a chest radiograph (CXR) is performed to rule out TB disease, the infection-control team may recommend providing an annual symptom screen to HCWs in low-risk settings who have positive test results for *M. tuberculosis* infection and who may or may not have received treatment for LTBI.

6) **The guidelines state (p. 10): "HCWs with a baseline positive or newly positive test result for *M. tuberculosis* infection (i.e., TST or BAMT) or documentation of treatment for LTBI or TB disease should receive one CXR result to exclude TB disease (or an interpretable copy within a reasonable time frame, such as 6 months)." What does "or an interpretable copy within a reasonable time frame, such as 6 months" mean?**

Six months is meant as an example. Individual institutions may set their own parameters. A CXR may be necessary sooner than 6 months, depending on the situation. The treating physician should decide if and when CXRs should be performed.

7) **If a HCW with a newly positive TST or BAMT result has documentation of a recent (1 month ago) negative CXR result would they need an additional CXR?**

If the HCW has symptoms of TB, a CXR would be recommended. If the HCW is immunocompromised, a CXR might be considered. If not, another CXR is not needed

unless recommended by a physician. Again, the treating physician should decide if and when CXRs should be performed.

8) **If a HCW has documentation of a prior positive TST or BAMT result and documentation of a negative CXR result following that, would they need an additional CXR?**

If the HCW has symptoms of TB, a CXR would be recommended. If the HCW is immunocompromised, a CXR might be considered. If not, another CXR is not needed unless recommended by a physician.

9) **How should the duration of the infectious period for TB patients be estimated?**

"For programmatic purposes, for patients with positive AFB sputum smear results, the infectious period can be considered to begin 3 months before the collection date of the first positive AFB sputum smear result or the symptom onset date (whichever is earlier). The end of the infectious period is the date the patient is placed under airborne precautions or the date of collection of the first of consistently negative AFB sputum smear results (whichever is earlier). For patients with negative AFB sputum smear results, the infectious period can begin 1 month before the symptom onset date and end when the patient is placed under airborne precautions" (p. 35).

Please also see Table 2 from CDC's Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis – Recommendations from the National Tuberculosis Controllers Association and CDC, *MMWR* 2005; 54 (p. 7).

http://www.cdc.gov/mmwr/pdf/rr/rr5415.pdf. Table 2 is printed at the end of this document.

10) Is CDC recommending that fit testing should be conducted at least annually in accordance with Occupational Safety and Health Administration (OSHA) 29 Code of Federal Regulations (CFR) 1910.134?

The CDC recommendation regarding fit-testing is: "Perform fit-testing during the initial respiratory-protection program training and periodically thereafter in accordance with federal, state, and local regulations http://www.osha.gov/SLTC/respiratory protection/index.html" (p. 39). The recommendation is for initial and periodic fit testing; however, employees must be cognizant of federal, state, and local regulations.

11) Is a personal respiratory protection program required for low-risk settings?

"Settings in which patients with suspected or confirmed TB disease are not expected to be encountered do not need …a respiratory protection program for the prevention of transmission of *M. tuberculosis"* (p. 17). A personal respiratory protection program is required for all HCWs who will use respirators.

12) Students in our nursing school often change work rotations and may work at different hospitals every 3 months. Would you recommend that nursing students be rescreened each time they change hospitals for a new rotation?

No, routine rescreening every 3 months is not necessary. The infection control team should decide on policies for their specific circumstances. If the nurse is transferring

from low-risk to low-risk settings, "after a baseline result for infection with *M. tuberculosis* is established and documented, serial testing for *M. tuberculosis* infection is not necessary" (p. 12).

If the nurse is transferring **from low-risk to a medium-risk setting**, "after a baseline result for infection with *M. tuberculosis* is established and documented, annual TB screening (including a symptom screen and TST or BAMT for persons with previously negative test results) should be performed" (p. 12 & 13).

If the nurse is transferring from **a medium-risk to a low-risk setting**, after a baseline result for infection with *M. tuberculosis* is established and documented, serial testing for *M. tuberculosis* infection is not necessary.

If the nurse is transferring from **medium-risk to medium risk setting,** after a baseline result for infection with *M. tuberculosis* is established and documented, annual TB screening (including a symptom screen and TST or BAMT for persons with previously negative test results) should be performed.

13) Is directly observed therapy (DOT) recommended for treatment of all persons with TB disease and for all persons with LTBI?

DOT is the ATS-recommended standard of practice for treating TB disease. DOT should be used for all doses during the treatment of TB disease, and it also should be considered for treating LTBI, whenever feasible. CDC's MMWR publication, Guidelines for the

Investigation of Contacts of Persons with Infectious Tuberculosis – Recommendations from the National Tuberculosis Controllers Association and CDC, 2005; 54 (p. 18–19) states: "Although DOT improves completion rates, it is a resource-intensive intervention that might not be feasible for all infected contacts. The following order of priorities is recommended when selecting contacts for DOT (including window-period prophylaxis):

- contacts aged <5 years,
- contacts who are HIV infected or otherwise substantially immunocompromised,
- contacts with a change in their tuberculin *(or BAMT)* status from negative to positive, and
- contacts who might not complete treatment because of social or behavior impediments (e.g., alcohol addiction, chronic mental illness, injection-drug use, unstable housing, or unemployment)"

14) Is the guidance for discontinuing AII intended to apply to direct AFB smears or only to concentrated smears?

A patient may be released from AII based on direct AFB smears. Concentrated AFB smears are more sensitive and hence, would be more stringent.

In addition, the text on one of the slides in the Infection Control guidelines slide set has changed.

This is the link to the slide set: http://www.cdc.gov/tb/pubs/slidesets/InfectionGuidelines/default.htm.

Previously, the last part of slide #123 said:

3. Known exposure
≥5 mm = positive when baseline result is 0 mm; increase of ≥10 mm = positive when baseline result is negative or previous follow-up TST result ≥ 0 mm

It now says (changes are in **bold**):

3. Known exposure **(contact investigation)**
≥5 mm = positive when baseline result is 0 mm; increase of ≥10 mm = positive when baseline **or previous follow-up TST result is >0mm, but <10mm**

TABLE 2. Guidelines for estimating the beginning of the period of infectiousness of persons with tuberculosis (TB), by index case characteristic

Characteristic			
TB symptoms	AFB* sputum smear positive	Cavitary chest radiograph	Recommended minimum beginning of likely period of infectiousness
Yes	No	No	3 months before symptom onset or first positive finding (e.g., abnormal chest radiograph) consistent with TB disease, whichever is longer
Yes	Yes	Yes	3 months before symptom onset or first positive finding consistent with TB disease, whichever is longer
No	No	No	4 weeks before date of suspected diagnosis
No	Yes	Yes	3 months before first positive finding consistent with TB

SOURCE: California Department of Health Services Tuberculosis Control Branch; California Tuberculosis Controllers Association. Contact investigation guidelines. Berkeley, CA; 1998.

*Acid-fast bacilli.