Drug Resistant TB

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Detroit TB Program / Wayne State University School of Medicine
Tri-State TB Intensive Workshop
Detroit, MI
July 18, 2019

1

Disclosures

- Financial – none
- 10 medications are approved by the FDA for TB
  - INH, RIF, Rifapentine, PZA, EMB, Streptomycin, Cycloserine, Ethionamide, PAS, Bedaquiline
  - All other drugs discussed here are NOT FDA approved for TB

2

Objectives

- When you ***think TB*** you will ***think drug resistance***
- When your patient has a higher than normal chance of having drug resistant TB you will know to ***rapidly confirm*** it or rule it out
- When you suspect or know that your patient has drug resistant TB you will know how to develop a ***treatment plan***

3

Topics

- Introduction – uncertainties, resources, definitions
- Epidemiology / costs
- Origin of drug resistant TB – man made
- Diagnostic testing – rapid, genetic testing
- Building a treatment regimen
  - Mono Resistant TB
  - Poly Resistant TB
  - Multi-Drug Resistant TB

4

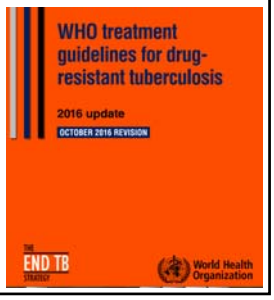
Uncertainties. Resources. Definitions.

INTRODUCTION

5

Introductory Remarks

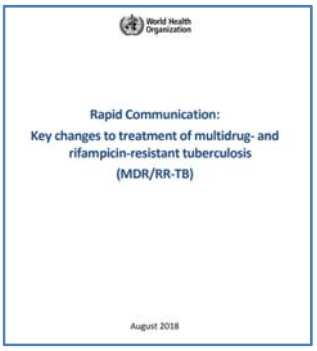
- Adequate data in the form of randomized controlled trials is limited
- Recommendations for treatment are sometimes based on expert opinion, which can vary
- Each case has its own complexities; complications should be expected, anticipated, and discussed
- This is a moving field
  - WHO Guideline Development Group convened July 16-20, 2018 to update 2016 guidelines



6

Rapid Communication: Box 4.7 Page 109 August 2018

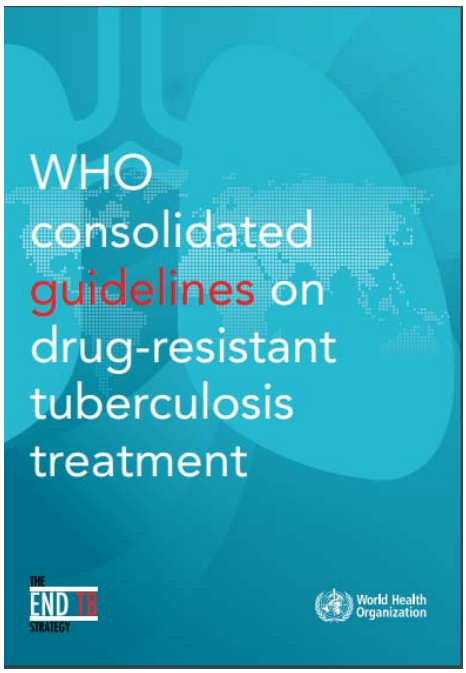
- Priority 1 drugs for MDR-TB
  - Levofloxacin (Lfx) or Moxifloxacin (Mfx)
  - Bedaquiline (Bdq)
  - Linezolid (Lzd)
- "Longer" all-oral regimens are acceptable for some patients
- Inclusion of injectables is no longer required
  - ~~*Kanamycin, Capreomycin*~~ no longer recommended



7

2019

- Replaces 8 prior guidelines developed 2011-2018
  - Incorporates & supersedes them
- Methodology GRADE / PICO questions
- MDR/RR-TB regimens
  - **Shorter standardized regimen** 9-12 months conditionally recommended
    - 2018 STREAM trial – Mfx, Eto, Z, E, Cfz, Hh
    - Without DR to FLQ, Am, Z, Eto
  - **Longer regimen**
    - ≥ 18 months
- Updates weight-based drug dosage schedules



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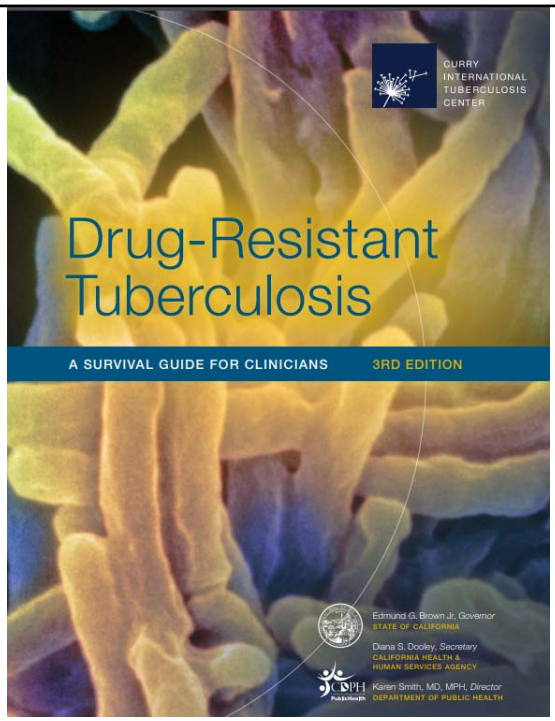


Published 2016

Represents best practice in 2015

New ATS, CDC, IDSA drug resistant TB guidelines are in process

9

Definitions / Abbreviations (1)

- MDR-TB: Multidrug-resistant TB
  - Any TB resistant to **at least** isoniazid (H) and rifampin (R)
- Pre-XDR-TB: Pre-extensively drug-resistant TB
  - A type of MDR-TB that is also resistant to either a fluoroquinolone (FLQ) or 1 of 3 injectables (amikacin [Am], ~~*kanamycin, capreomycin*~~)
- XDR-TB: Extensively drug-resistant TB
  - A type of MDR-TB that is also resistant to both a FLQ and 1 of 3 injectables (Am, ~~*kanamycin, capreomycin*~~)

10

Definitions / Abbreviations (2)

- RR-TB: Rifampin-resistant TB
- MDR/RR-TB: WHO guidelines refer to rifampin or rifampin and isoniazid resistant TB
- Transmitted drug resistance (primary): TB in a person not previously treated for TB (new* TB case)
- Acquired drug resistance (secondary): TB in a person previously treated for TB (previously treated** TB case)
  - New case* = < 1 month treatment
  - Previously treated** = treatment for ≥1 month
    - Resistance can be created by 1 month of inappropriate treatment
  - Primary & secondary are old terms

11

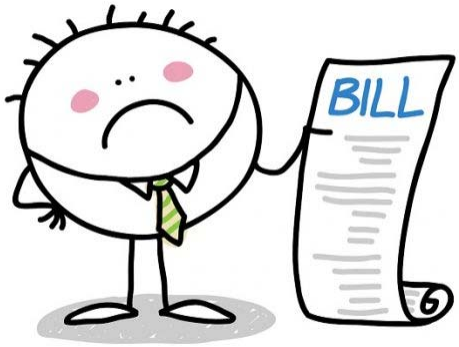
Definitions / Abbreviations (3)

- Mono or isolated resistance – resistance to 1 drug
  - INH mono-resistance is common, rifampin less so
  - PZA (Z) mono-resistance suggests *M. bovis* (including BCG), or other MTB complex species (*M. canettii*)
- Poly-resistant TB – resistance to >1 first line drug, but not INH and RIF together
- First line drugs are H, R, Z, Ethambutol (E)

12

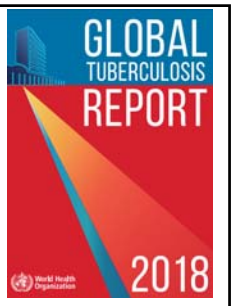
Statistics. Costs.

EPIDEMIOLOGY



13

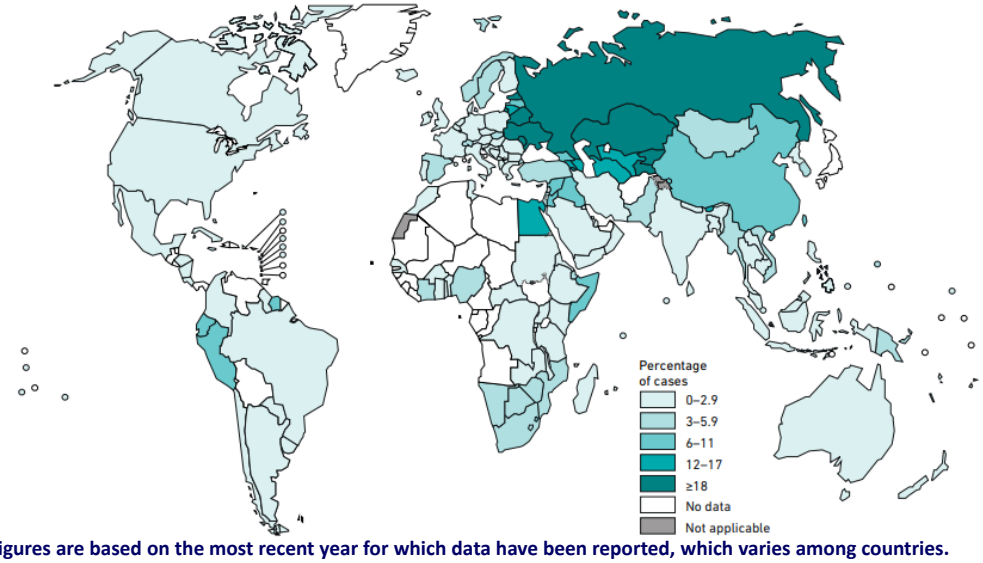
Global Epidemiology 2017



- 457,000 cases of MDR-TB
- 101,000 additional cases of RR-TB
- 47% of the MDR/RR-TB cases were from
  - India (24%), China (13%), & the Russian Federation (10%)
- 8.5% of the MDR/RR-TB cases were XDR-TB
- **3.5% new and 18% previously treated TB cases were MDR/RR**
- 240,000 (43%) MDR/RR cases died
- 139,114 (25%) MDR/RR cases started treatment
  - 55% were successfully treated

14

% MDR/RR-TB in new TB cases



Figures are based on the most recent year for which data have been reported, which varies among countries.
Data from 2002 - 2018

World Health Organization | GLOBAL TB PROGRAMME | END TB

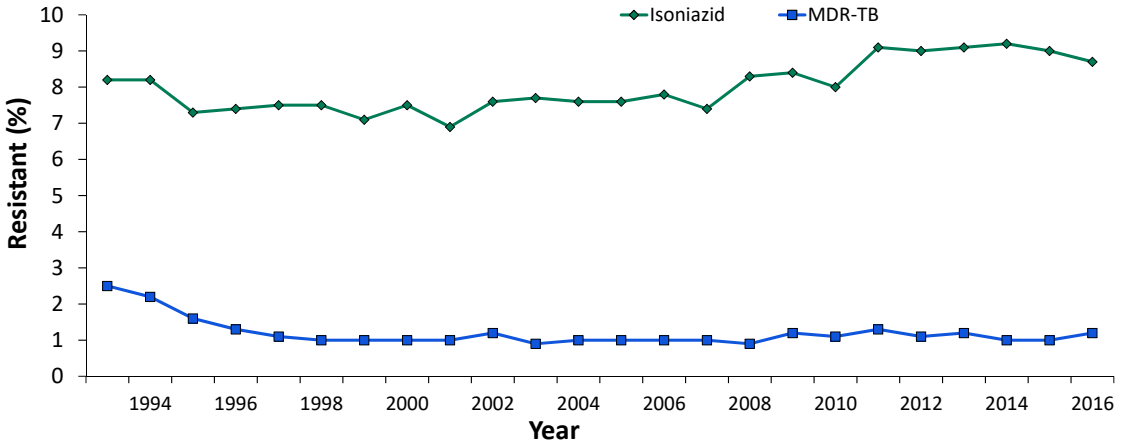
15

Epidemiology – U.S.A. 2017

- 128 cases of MDR-TB (including 3 XDR) = 1.9% cases with DST done
- Only 26 (20.3%) of the MDR cases had prior TB treatment
- 110 (85.9%) of the MDR cases, including all the XDR ones, were in non-U.S. born persons

16

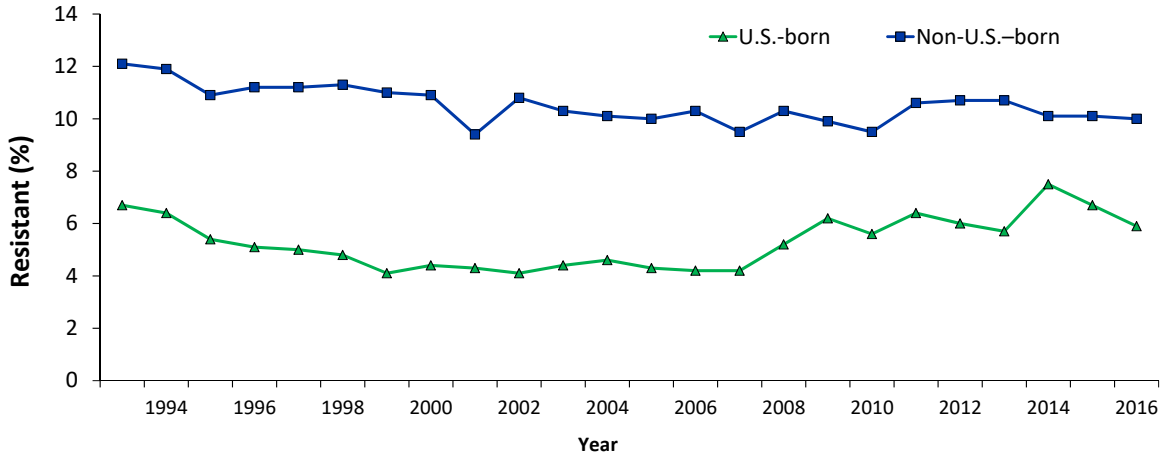
Primary Anti-TB Drug Resistance, United States, 1993–2016*



* As of June 21, 2017.
Note: Based on initial isolates from persons with no prior history of TB; multidrug-resistant TB (MDR-TB) is defined as resistance to at least isoniazid and rifampin.

17

Primary Isoniazid Resistance Among U.S.-Born versus Non-U.S.–Born Persons, United States, 1993–2016*



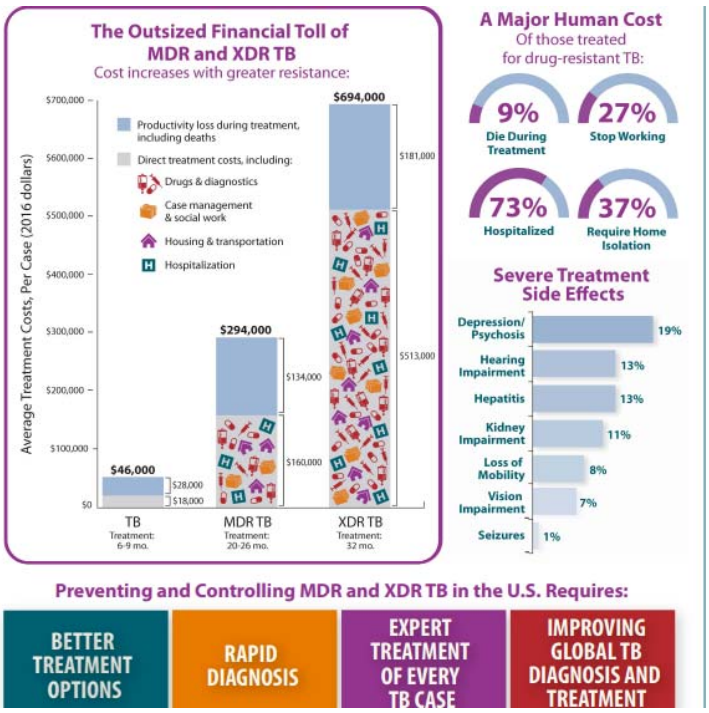
* As of June 21, 2017.
Note: Based on initial isolates from persons with no prior history of TB.

18

November, 2017

Direct costs
DS-TB $18,000
MDR-TB $160,000
XDR-TB $513,000

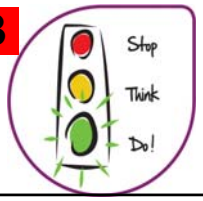
Financial Toxicity



19

First Conclusions

- Rates and numbers of MDR-TB cases are low but costs, morbidity, and mortality are staggeringly high
- Preventing or recognizing DR should be part of initial TB management
- Estimating likelihood of DR is essential to good care
  - Country of origin and residence help determine risk
  - Persons treated previously for TB have a higher risk
- **Consider risk of resistance before initiating TB therapy**



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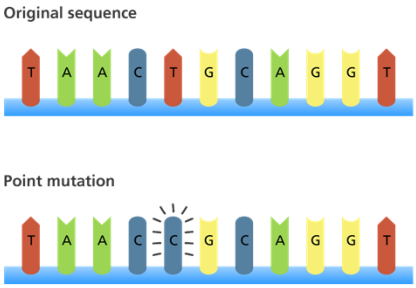
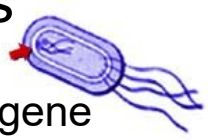


Genetic mutations. Selective pressure. Made by humans.

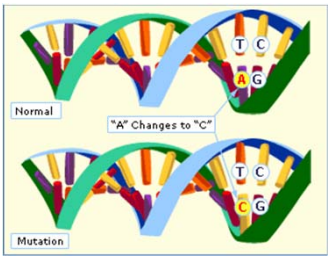
ORIGINS OF DRUG RESISTANT TB

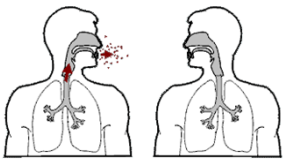
21

How TB drug resistance develops



- Mechanism: Spontaneous mutations in resistance gene
  - Single nucleotide substitutions lead to mutations in a gene, conferring resistance to a specific antibiotic
- Selective pressure
  - Inappropriate treatment => acquired DR
  - Clinical drug resistance is man-made
- Transmission to contact => transmitted DR

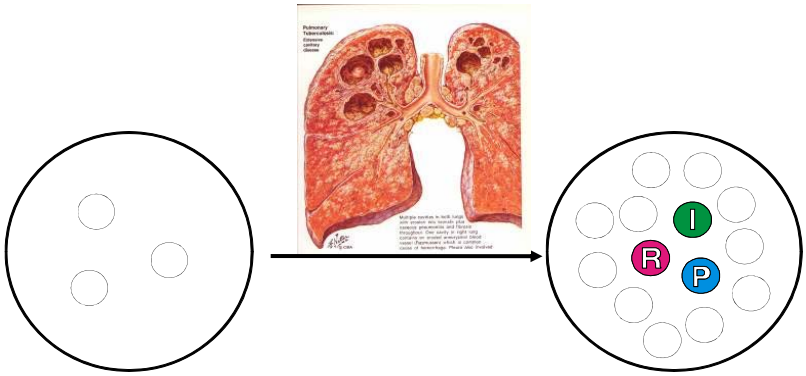




Adenine **Thymine** **Guanine** **Cytosine**

22

- Spontaneous mutations develop as bacilli proliferate to >10^8 (100,000,000)
- Typical TB cavity contains 10^7 to 10^9 organisms



23

- Without selective pressure from inappropriate antibiotic use, a single bacillus will not be resistant to 2 antibiotics.

DRUG	PREVALENCE
ISONIAZID	3.5 X 10^{-6} .0000035
RIFAMPIN	1.2 X 10^{-8} .000000012
PYRAZINAMIDE	1.0 X 10^{-5} .00001

- The prevalence of resistance to INH and Rifampin would be 3.5 x 10^{-6} x 1.2 x 10^{-8} = 4.2 x 10^{-14}

24

Some Resistance Genes

- INH
  - KatG
  - inhA
  - kasA

80% of resistance

- RIF
  - rpoB

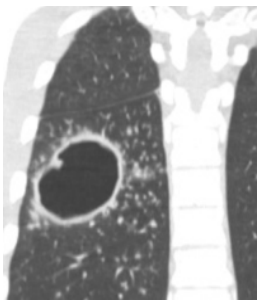
>95% of resistance

- PZA
  - pncA
- EMB
  - embB
  - ubiA

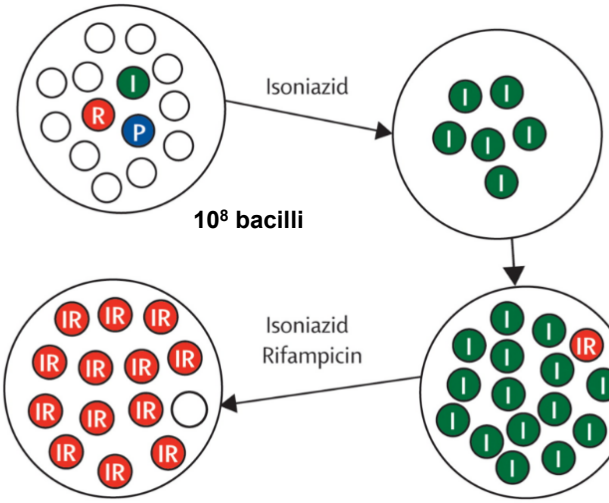
- SM (aminocyclitol glycoside)
  - rrs
  - rpsL
- Fluoroquinolones*
  - gyrA, gyrB
- Kanamycin*, Amikacin*
  - its
- Linezolid*
  - rplC
- Ethionamide (analog INH)
  - ethA
- PAS
  - thyA
  - ribD

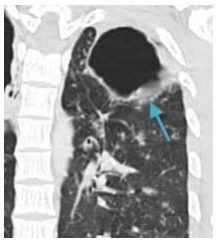
25

Creation of MDR-TB
"Previously Treated" or "Acquired"



10^8 bacilli





10^8 bacilli

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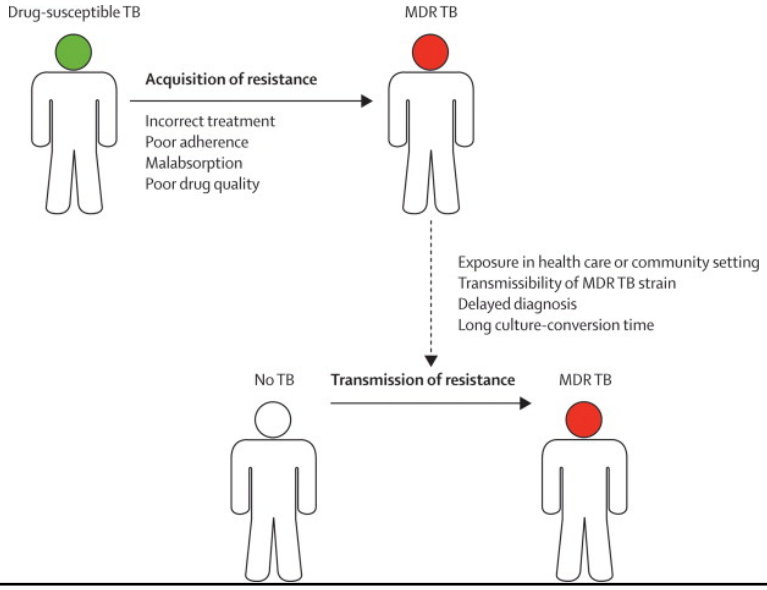
26

Transmission of MDR TB
"MDR in New Case" or "Transmitted MDR"



27

2nd Set of Conclusions (1)

- One should suspect resistance in those with prior treatment that was inappropriate
  - Wrong drugs, doses, regimens
  - Intermittent therapy with missed doses
  - Interrupted, erratic treatment
  - Noncompliance, no DOT, patient taking some medicines & not others
  - Possibility of malabsorption
    - Critically ill patient given oral medications
  - Bad medications

28

2nd Set of Conclusions (2)

- Consider resistance most likely in these circumstances
  - Extensive cavitary disease (more organisms)
  - Poor clinical response to therapy after 2 months
  - Positive cultures after 3 months of therapy or after conversion
  - Contact with a person with resistant disease
  - Emigration from or travel to (>1 month) region with high prevalence/incidence of DR
  - HIV – higher rates of RR-TB
- Taking a good history is essential to preventing or worsening DR and for selecting drugs for treatment

29

2nd Set of Conclusions (3)

- Never treat TB with a single agent
- Never add a single agent to a failing regimen (patient not improving or getting worse) unless you know the drug susceptibilities

30

Contact laboratory. Work with local health department / state. Consult experts, COE.

IF YOU SUSPECT RESISTANCE TEST FOR RESISTANCE

31

Think resistance? Test for resistance! (1)

- Conventional, growth-based DST is a gold standard, but
  - Slow
  - Growth detection and identification take several weeks; DST an additional 1-3 weeks
- DST for 1st line drugs (INH, RIF, EMB, PZA) should be done for
  - All new TB isolates
  - Positive cultures after 3 months of therapy
  - Positive cultures after a period of negative ones

32

Think resistance? Test for resistance! (2)

- DST should be done for 2^{o} drugs for all cases of RR
- Talk to lab to make sure appropriate testing for 2^{o} drugs is done

33

Think resistance? Test for resistance! (3)

- Xpert® MTB/RIF (FDA approved) and Xpert® MTB/RIF Ultra
  - Point of care assay to detect MTB complex (NAAT)* and mutations of the gene *rpo*B, known to confer RIF-R (Molecular Beacon)
  - Time to result is 1.5-2 hours
  - Ultra – better detection of MTB complex in paucibacillary specimens; more reliable detection of *rpo*B mutations that => RR
  - If RR is detected, confirmation should be obtained with a sequencing-based method unless patient has clear risk
    - "Silent" mutations which don't => resistance may be picked up (false positive)

***Nucleic Acid Amplification Test**

34

Think resistance? Test for resistance! (4)

- Line-probe assays
- Sequencing-based assays
  - Pyrosequencing
    - California Public Health Lab
  - CDC Molecular Detection of Drug Resistance (MDDR) service
    - Sanger sequencing
  - Whole Genome Sequencing
- Communicate – local lab, public health lab, local health department, state TB program, COE - to make sure proper and timely testing is done!

35

Pyrosequencing (PSQ) for XDR TB Screening

At MDL, CA Department of Public Health

Contact: **Dr. Desmond** (ed.desmond@cdph.ca.gov; **510-412-3781**) or
Grace Lin (grace.lin@cdph.ca.gov; **510-412-3929**)

PSQ is a rapid screening technique for molecular detection of drug resistance. For confirmation of PSQ results, culture-based drug susceptibility testing should be performed.

Intended use	Pyrosequencing (PSQ) provides: • Identification of ***M. tuberculosis*** complex (MTBC). • Screening for resistance to INH, RIF, quinolones and injectable drugs.					
Date of implementation	3-26-2012					
Testing schedule	The assay is performed 3-4 times a week. If urgent, additional runs can be scheduled. Turnaround time: 1-3 days.					
Principle	The test involves two steps: 1. Use PCR to amplify the target sequences. 2. Use **pyrosequencing** technology to perform realtime sequencing. The sequencer, PyroMark Q96ID, dispenses one kind of dNTP at a time according to the order specified by the assay. If the dNTP being dispensed is complementary to the first available base in the DNA template, the dNTP will anneal to the template and pyrophosphate (ppi) will be generated. The ppi will trigger a cascade of chemical reactions and result in the emission of light. The light generated is proportional to the dNTP incorporated. The identity of dNTP incorporated represents the base(s) sequenced. The sequence grows when the incorporation of dNTP complementary to the DNA template occurs until the end of the dispensation of dNTPs.					
Specimens	**Sediments: NALC-NaOH processed specimens, at least 0.5 ml, and AFB-smear positive (1+ or greater).** Ship with cold packs. **Cultures: solid media** or **broth (0.5-1 ml)**. Ship at room temperature or with cold packs.					
Molecular targets	INH	*katG* (codon 312-316), *inhA* promoter and *ahpC-oxyR* intergenic region				
	RIF	*rpoB* core region from codons 507 to 533.				
	Quinolones	*gyrA* from codons 88 to 95.				
	Injectable drugs	*rrs*, 1397 to 1406				
Performance characterization (130 isolates + 115	DST results by MGIT 960 (KAN: by agar proportion)					
	INH (n =245) 0.1 µg/ml	RIF (n = 239) 1.0 µg/ml	Quinolones (n=125)	AMK (n =120) 1.5 µg/ml	CAP (n=119) 3.0 µg/ml	KAN (n=55) 5 µg/ml

36

Drugs: Genes Tested

INH: inhA, katG

RIF: rpoB

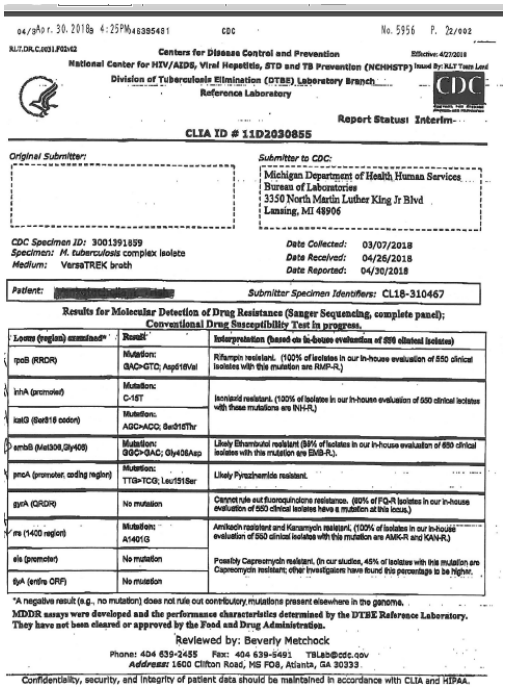
Ethambutol: embB

PZA: pncA

Fluoroquinolones: gyrA

Amikacin, Kanamycin, Capreomycin:

rrs, eis, tlyA



Centers for Disease Control and Prevention
National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention (NCHHSTP)
Division of Tuberculosis Elimination (DTBE) Laboratory Branch
Reference Laboratory

Report Status: Interim

CLIA ID # 11D2030855

Original Submitter:

Submitter to CDC:
Michigan Department of Health Human Services
Bureau of Laboratories
3350 North Martin Luther King Jr Blvd
Lansing, MI 48906

CDC Specimen ID: 3001391859
Specimen: M. tuberculosis complex isolate
Medium: VersaTREK broth

Date Collected: 03/07/2018
Date Received: 04/25/2018
Date Reported: 04/30/2018

Patient: [redacted] Submitter Specimen Identifiers: CL18-310467

Results for Molecular Detection of Drug Resistance (Sanger Sequencing, complete panel); Conventional Drug Susceptibility Test in progress.

Locus (region) examined*	Result	Interpretation (based on in-house evaluation of 550 clinical isolates)
rpoB (RRDR)	Mutation: GAC>GTC; Asp516Val	Rifampin resistant. (100% of isolates in our in-house evaluation of 550 clinical isolates with this mutation are RMP-R.)
inhA (promoter)	Mutation: C-15T	Isoniazid resistant. (100% of isolates in our in-house evaluation of 550 clinical isolates with these mutations are INH-R.)
katG (Ser315 codon)	Mutation: AGC>ACC; Ser315Thr	
embB (Met306,Gly406)	Mutation: GGC>GAC; Gly406Asp	Likely Ethambutol resistant (88% of isolates in our in-house evaluation of 550 clinical isolates with this mutation are EMB-R.).
pncA (promoter, coding region)	Mutation: TTG>TCG; Leu151Ser	Likely Pyrazinamide resistant.
gyrA (QRDR)	No mutation	Cannot rule out fluoroquinolone resistance. (80% of FQ-R isolates in our in-house evaluation of 550 clinical isolates have a mutation at this locus.)
rrs (1400 region)	Mutation: A1401G	Amikacin resistant and Kanamycin resistant. (100% of isolates in our in-house evaluation of 550 clinical isolates with this mutation are AMK-R and KAN-R.)
eis (promoter)	No mutation	Possibly Capreomycin resistant. (In our studies, 45% of isolates with this mutation are Capreomycin resistant; other investigators have found this percentage to be higher.
tlyA (entire ORF)	No mutation	

*A negative result (e.g., no mutation) does not rule out contributory mutations present elsewhere in the genome.
MDDR assays were developed and the performance characteristics determined by the DTBE Reference Laboratory. They have not been cleared or approved by the Food and Drug Administration.

Reviewed by: Beverly Metchock
Phone: 404 639-2455 Fax: 404 639-5491 TBLab@cdc.gov
Address: 1600 Clifton Road, MS F08, Atlanta, GA 30333

Confidentiality, security, and integrity of patient data should be maintained in accordance with CLIA and HIPAA.

37

Molecular Detection of Drug Resistance (MDDR) Recent TB Patient: South African

LOCUS EXAMINED (region of gene)	RESULT	INTERPRETATION In-House Evaluation of 550 clinical isolates
rpoB (RRDR)	**Mutation**	RMP-R. 100% of our 550 isolates… were RMP-R
inhA (promoter)	**Mutation** C15T	INH-R 100% of our 550 isolates with these mutations were INH-R
katG	**Mutation**	
embB	**Mutation**	Likely EMB-R 88% of our isolates…were EMB-R (***12% were not***)
pncA	**Mutation**	Likely PZA-R
gyrA	No mutation	Cannot R/O FLQ-R 80% of our FLQ-R isolates have a mutation at this locus.***(20% don't!)***
rrs	**Mutation**	AMK-R & KAN-R. 100% of our isolates with this mutation are R
eis	No mutation	Possibly CAP-R 45% of our isolates with this mutation are CAP-R
tlyA	No mutation	

38

Criteria for MDDR testing (1)

1. Increased risk for DR
   A. Born in / lived in high prevalence country >1 month
   B. Contact to someone known to or suspected to have DR
   C. Patient not responding to Rx
   D. Patient with prior Rx and relapse
2. Public or personal health consequences
   A. Congregate setting, many contacts
   B. Age <5, immune compromised
   C. Case has contacts to patients in 2B who need window prophylaxis

39

Criteria for MDDR testing (2)

3. Lab issues
   A. Mixed cultures unlikely to yield results
   B. AFB smear positive / culture negative
   C. Pathology specimens not sent for culture
4. Program priorities

Our patient: from S. Africa, did charity work in very poor areas, visited many homes there. More on this patient later.

40

Principals, Classification of drugs, Mono & Poly-Resistant TB, MDR TB

BUILDING AN EFFECTIVE REGIMEN FOR DRUG RESISTANT TB

41

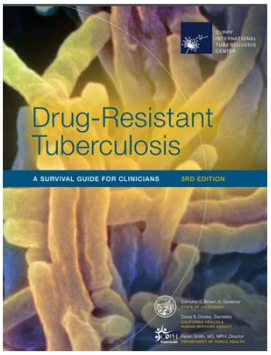
DR-TB: General Considerations (1)

- If resistance suspected consult experts
- Treatment should be daily DOT, not intermittent, with exceptions of
  - Injectables
  - Adjustments for renal failure (PZA, EMB)
  - Specific studied regimens
- Anticipate problems. Discuss with patient. Have monitoring plan
- When to start treatment? For our patient we waited for conventional DST

42

DR-TB: General Considerations (2)

- Decision to treat empirically depends on factors such as
  - How ill the patient is; how contagious
  - How long you expect it to take to get DST results
- While waiting for susceptibility results consider
  - Expanded empiric treatment regimen
    - Four 1st-line drugs plus **2 *or more*** additional ones (p. 67 in Survival Guide)
  - Avoid previously used drugs
  - Consider cross-resistance (p. 76 in Survival Guide)



43

Miscellaneous Items

- Choice of FLQ: Mfx versus Lfx
  - Fewer drug drug interactions with Lfx
  - Mfx is contraindicated with more ARV drugs
    - exception is lamivudine; Lfx interferes with its clearance
  - Rifampin => decrease in plasma concentration & exposure to Mfx
- To shorten TB regimens to 6 months, PZA for 2 months & RIF for 6 months are necessary
- To shorten TB regimens to 9 months, RIF is necessary throughout

44

Mono-Resistant TB
INH

- RIF, EMB, PZA, Lfx for 6 months preferred by WHO
- RIF, EMB, Lfx for 9-12 months when PZA cannot be used

45

Mono-Resistant TB
Rifampin - Rare

- Usually cross resistant to Rifabutin, always to Rifapentine
- Confirm Xpert result with sequencing
- In WHO Guidelines MDR-TB and RR-TB are usually considered the same – (inadequacies of susceptibility tests)
- Preferred regimens (Survival Guide, not discussed by WHO)
  - 1. INH, EMB, PZA, FLQ daily for at least 2 months
    - Then PZA can be stopped or continued
    - Duration 12-18 months or
  - 2. INH, EMB, PZA for 18 months

46

Isolated EMB or PZA Resistance

- Not discussed in WHO Guidelines
- EMB makes no difference
  - Main role is to prevent drug resistance
- PZA: Think *M. bovis*, including BCG, or others in MTB complex (*M. canettii*)
- PZA is essential for shortening Rx time to 6 months
  - INH and Rifampin for 9 months

47

Poly-Resistant-TB

- (Not discussed in WHO Guidelines)
- **INH & EMB**: RIF, PZA, FLQ 6-9 months
- **INH & PZA**: RIF, EMB, FLQ 9-12 months
- **INH, EMB, & PZA**: RIF, FLQ, oral 2nd-line agent, for 9-12 months with injectable for 1st 2-3 months
- **RIF & EMB**: INH, PZA, FLQ for 12-18 months with injectable for 1st 2-3 months
- **RIF & PZA**: INH, EMB, FLQ for 12-18 months with injectable for 1st 2-3 months

48

Regimens

MDR-TB

49

Previous Guidelines

- Intensive phase
  - 6 drugs including an injectable
  - Aim for at least 6 months after culture conversion
- Continuation phase
  - 4 drugs
- Total duration 18 months after culture conversion

50

Bedaquiline (Bdq)

- Diarylquinoline
- FDA approved 28 December 2012
  - 1st TB drug approved since Rifapentine in 1998
- Phase IIb studies by Diacon, et al. 2014
  - Higher mortality (12.6%) than controls (4.9%)
  - 7 patients died, median of 386 days after the last dose
- In a study in France reported by Guglielmetti, et al., 35 patients received Bdq
  - 7 (20%) had increase of ≥60 milliseconds increase in QT interval

51

Bedaquiline (BDQ)

- Dose: 100 mg. capsules
  - 400 mg. daily for 14 days followed by
  - 200 mg. 3 times/week for 22 weeks
- Acquired resistance can occur
- Cross reaction (both directions) with Clofazimine
- Bedaquiline OK for persons ≥ 6 years old according to WHO recommendations
- Approved for 6 months
  - There may be reasons to continue

52

WHO Guidelines for Longer MDR-TB Regimen (≥ 18 months)

- Balance benefits versus harms
- Group medicines in categories A, B, & C
- Based on data from individual patient meta analysis for longer MDR regimens & delamanid trial 2013
- Kanamycin, Capreomycin => poorer outcomes, not recommended
- Clavulonic Acid (in form of amoxicillin- clavulonic acid) is added to every dose of carbapenem & is therefore not counted as an additional drug

53

Grouping of medicines recommended for longer MDR-TB regimens

Group A **Include all three**	**Levofloxacin or Moxifloxacin**	**Lfx or Mfx**
	Bedaquiline	**Bdq**
	Linezolid	**Lzd**
Group B **Include 1 or both**	**Clofazimine**	**Cfz**
	Cycloserine	**Cs**
Group C **Add to complete the regimen or when medicines from group A and B cannot be used** **At least 4 medicines** **At least 3 after Bdg is stopped**	**Ethambutol**	**E**
	Delamanid (NA)	**Dlm**
	Pyraziminamide	**Z**
	Imipenem-cilastin *OR* Meropenem	**Ipm-Cln** **Mpm**
	Amikacin (*OR* Streptomycin)	**Am (S)**
	Ethionamide	**Eto**
	***P*-aminosalicylic acid**	**PAS**

54

Longer MDR-Regimen Duration

- Total duration 18-20 months
- 15-17 months after culture conversion
- Induction phase only if amikacin or streptomycin is used
  - 6-7 months is recommended, if possible

55

- Table 2.2. **Relative risk for (i) <u>treatment failure or relapse</u>** & (ii) **<u>death</u>** (versus treatment success)

56

Lardizabal AA, Khan AN, Bamrah Morris S, Goswami ND. Notes from the Field: Acquisition of Delamanid Under a Compassionate Use Program for Extensively Drug-Resistant Tuberculosis — United States, 2017. MMWR Morb Mortal Wkly Rep 2018;67:996–997. DOI: http://dx.doi.org/10.15585/mmwr.mm6735a6external icon.

	Medicine	Treatment failure or relapse versus treatment success		Death versus treatment success	
		Number treated	Adjusted odds ratio (95% confidence limits)	Number treated	Adjusted odds ratio (95% confidence limits)
A	Levofloxacin *OR* moxifloxacin	3 143	0.3 (0.1–0.5)	3 551	0.2 (0.1–0.3)
	Bedaquiline	1 391	0.3 (0.2–0.4)	1 480	0.2 (0.2–0.3)
	Linezolid	1 216	0.3 (0.2–0.5)	1 286	0.3 (0.2–0.3)
B	Clofazimine	991	0.3 (0.2–0.5)	1 096	0.4 (0.3–0.6)
	Cycloserine *OR* terizidone	5 483	0.6 (0.4–0.9)	6 160	0.6 (0.5–0.8)
C	Ethambutol	1 163	0.4 (0.1–1.0)	1 245	0.5 (0.1–1.7)
	Delamanid	289	1.1 (0.4–2.8)*	290	1.2 (0.5–3.0)*
	Pyrazinamide	1 248	2.7 (0.7–10.9)	1 272	1.2 (0.1–15.7)
	Imipenem–cilastatin *OR* meropenem	206	0.4 (0.2–0.7)	204	0.2 (0.1–0.5)
	Amikacin	635	0.3 (0.1–0.8)	727	0.7 (0.4–1.2)
	Streptomycin	226	0.5 (0.1–2.1)	238	0.1 (0.0–0.4)
	Ethionamide *OR* prothionamide	2 582	1.6 (0.5–5.5)	2 750	2.0 (0.8–5.3)
	p-aminosalicylic acid	1 564	3.1 (1.1–8.9)	1 609	1.0 (0.6–1.6)
Other medicines	Kanamycin	2 946	1.9 (1.0–3.4)	3 269	1.1 (0.5–2.1)
	Capreomycin	777	2.0 (1.1–3.5)	826	1.4 (0.7–2.8)
	Amoxicillin–clavulanic acid	492	1.7 (1.0–3.0)	534	2.2 (1.3–3.6)

57

WHO Consolidated Guidelines Other recommendations

- Monthly sputum cultures for MDR/RR-TB
- For all patients with HIV, regardless of CD4, receiving 2nd line anti-TB drugs
  - Start of antiretroviral therapy as soon as possible (≤ 8 weeks)
- Elective partial lung resection acceptable
- Care and support of patient
- Ambulatory, decentralized care is best

58

Molecular Detection of Drug Resistance (MDDR) Recent TB Patient: South African

LOCUS EXAMINED (region of gene)	RESULT	INTERPRETATION In-House Evaluation of 550 clinical isolates
rpoB (RRDR)	**Mutation**	RMP-R. 100% of our 550 isolates… were RMP-R
inhA (promoter)	**Mutation** C15T	INH-R 100% of our 550 isolates with these mutations were INH-R
katG	**Mutation**	
embB	**Mutation**	Likely EMB-R 88% of our isolates…were EMB-R ***(12% were not)***
pncA	**Mutation**	Likely PZA-R
gyrA	No mutation	Cannot R/O FLQ-R 80% of our FLQ-R isolates have a mutation at this locus***.(20% don't!)***
rrs	**Mutation**	AMK-R & KAN-R. 100% of our isolates with this mutation are R
eis	No mutation	Possibly CAP-R 45% of our isolates with this mutation are CAP-R
tlyA	No mutation	

59

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	Delamanid (NA)	**Dlm**
	Pyraziminamide	**Z**
	Imipenem-cilastin *OR* Meropenem	**Ipm-Cln** **Mpm**
	Amikacin (*OR* Streptomycin)	**Am (S)**
	Ethionamide	**Eto**
	***P*-aminosalicylic acid**	**PAS**

60

BEDAQUILINE ACCESS GUIDE

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TABLE OF CONTENTS

Contacts 1
Definitions (defined terms are capitalized throughout the document) 2
Bedaquiline Access Statement 3
Purpose of Guide 3
Audience for This Guide 3
Payer Classifications 4
Bedaquiline Access by Payer Classification 5
1. Private Insurance 6
2. State Insured (Medicaid/Medicare/MediCal/Other) 7
3. Covered by Law 8
4. Uninsured Patients 9
The Johnson & Johnson Patient Assistance Foundation (JJPAF) Application 10
Janssen's CarePath for Co-Pays 10
Bedaquiline Resources
Appendix 1: Example Prescription Form
Appendix 2: Summary Table of State Statutes/Laws Governing TB Drug Payment
Appendix 3: Annotated Patient Assistance Application

CONTACTS

Title/Office	Telephone	Email/Webpage
Drug Procurement		
Metro Medical Central Contact	855-691-0963	https://www.metromedical.com
Johnson & Johnson Patient Assistance Program	800-652-6227	http://www.jjpaf.org
Janssen CarePath (for assistance with Co-Payments)	855-846-5392	https://www.janssencarepath.com/hcp *No information currently available on this site for SIRTURO*
Access Issues		
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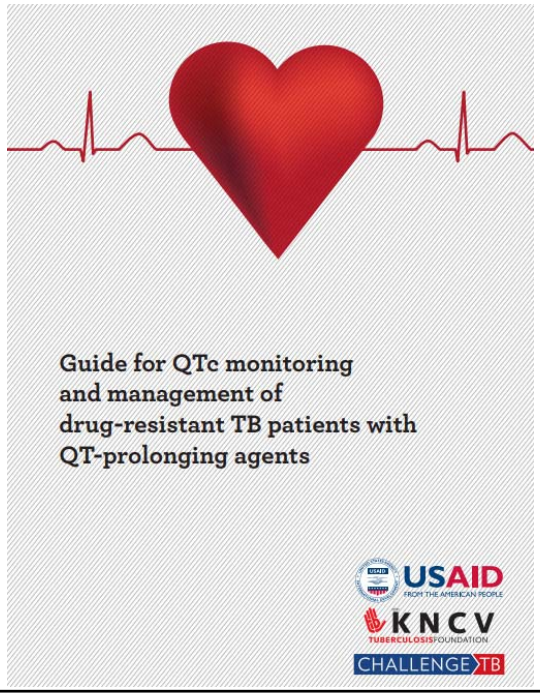
Website Address for this Guide: http://www.tbcontrollers.org/resources/bdq-access/

Version 1.0 04June2019 1



61