Transmission and Pathogenesis of Tuberculosis

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Learning Objectives

- Explain how TB is spread (transmission)
- Explain the difference between latent TB infection (LTBI) and active TB disease
- Explain how LTBI develops (pathogenesis)
- Explain how active TB disease develops (pathogenesis)

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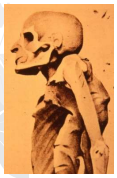

TB History Timeline

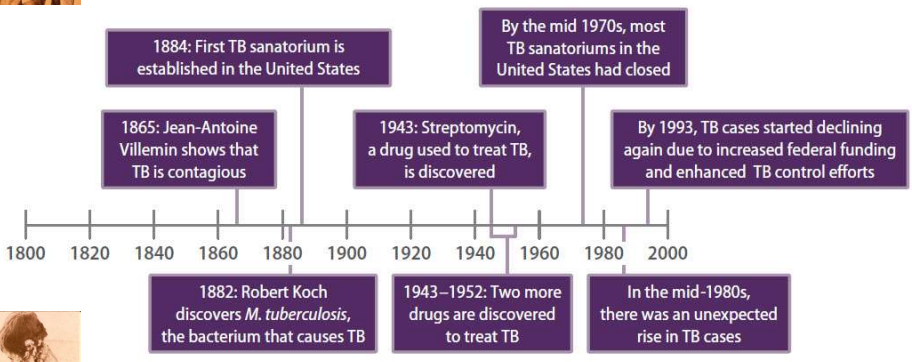

Figure 1.1 Timeline of major events in the history of TB.

CDC.gov – Transmission and Pathogenesis of Tuberculosis

Definitions

Transmission = Spread of an organism, such as *M. tuberculosis*, from one person to another (an event).

Infectiousness = the characteristic of the disease that concerns the ease with which it is transmitted (a capacity)

Pathogenesis = the way an infection or disease develops in the body.

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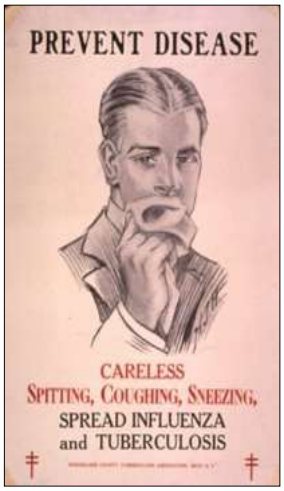
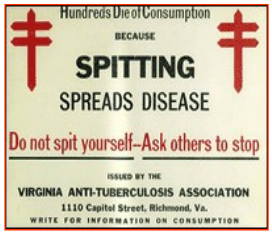
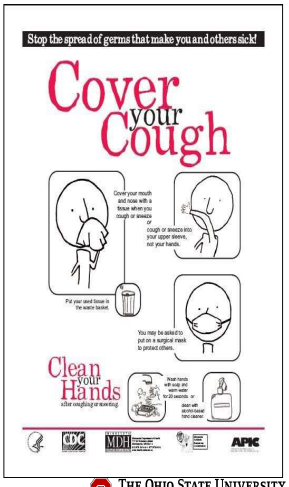
Early Disease Prevention → Modern Cough Etiquette







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Elderly Patient with Chronic Cough & Weight Loss

HOPI

- 74 year-old female
- Seen in Emergency Room with complaints of shortness of breath and progressive weakness
- Increasing shortness of breath over the last 4 days
- Associated with fevers, chills, cough, with purulent sputum
- Family noted history of cough and weight loss over last several months

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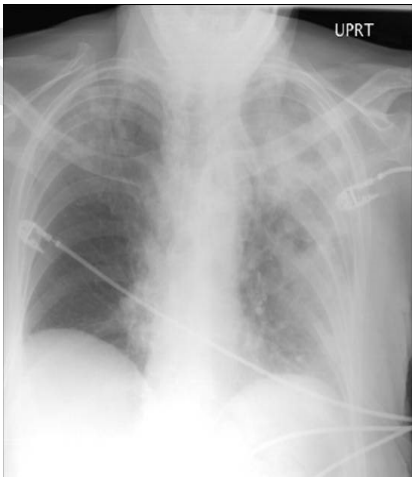
CXR



Admission

8 months prior to admission

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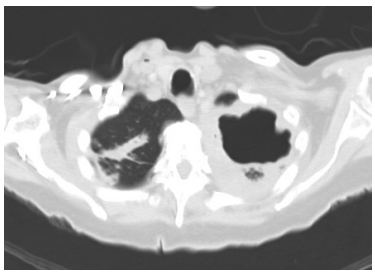

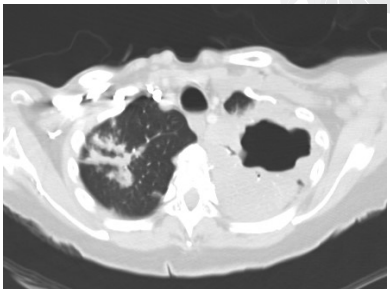

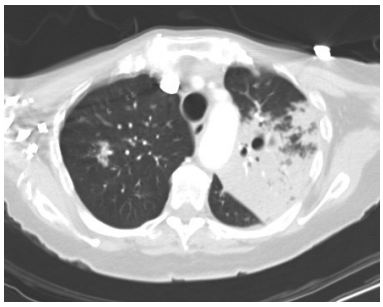

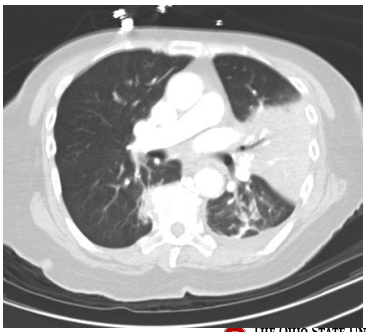

CT Scan: Extensive air-space disease left apical, post cavitary

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Hospital Course

- Admitted to inpatient ward – Community Acquired Pneumonia
- Treated: ampicillin/sulbactam/azithromycin
- Respiratory failure→Intubated 24 hours later
- Blood and routine sputum cultures negative.
- Bronchial alveloar lavage (BAL)

5/5 respiratory specimens
"Heavy AFB Positive"

•**Family History**
–**Patient's mother died productive cough and weight loss**

Case 1: Transmission Questions

- Where and how was she infected?
- Is she infectious?
- Who has been exposed?

TB Facts

- TB is contagious and spreads through the air
- if not treated, each person with active TB infects ~ 10 to 15 people every year
- Every one second someone is newly infected with TB

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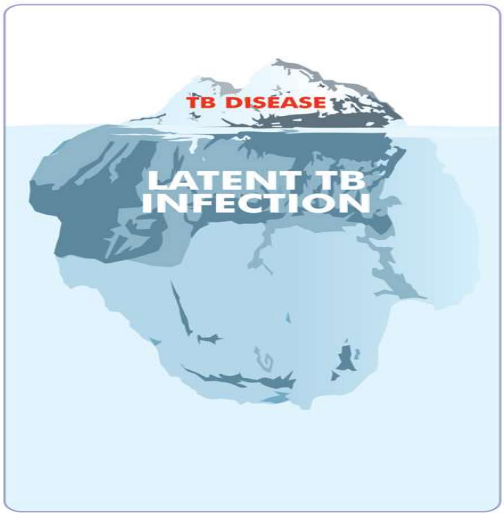
WHO

The Hidden Epidemic – Latent TB Infection



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•**Two billion people, 1/3 of the world's total population, are infected with TB**

• **One in 10** people infected with TB bacilli will develop active TB

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CDC Tuberculosis (TB) Transmission and Pathogenesis Video

https://www.youtube.com/watch?v=9112brXCOVc

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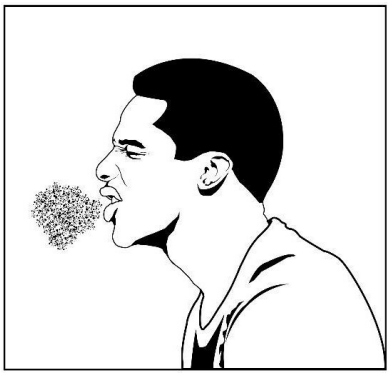
TB Transmission

- **TB is spread person to person through the air via droplet nuclei**
- ***M. tuberculosis* may be expelled when an infectious person:**
  - **Coughs**
  - **Speaks**
  - **Sings**
- **Transmission occurs when another person inhales droplet nuclei**



CDC.gov – Transmission and Pathogenesis of Tuberculosis

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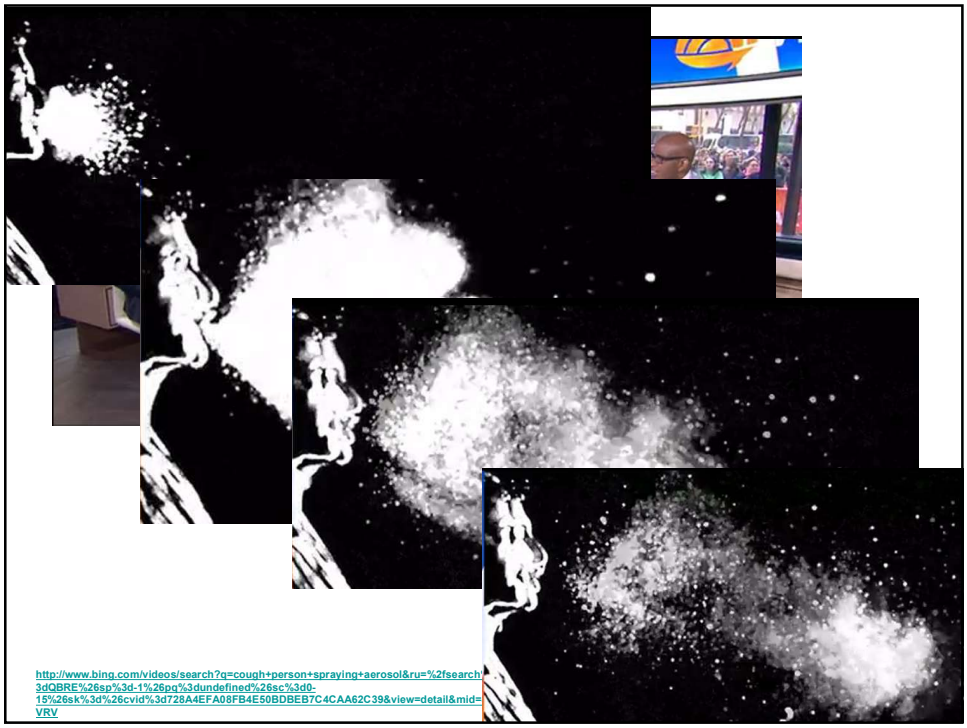
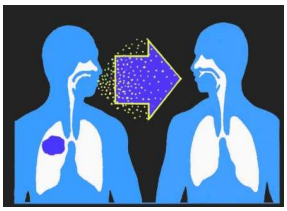


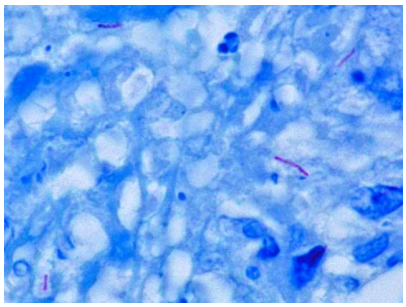
http://www.bing.com/videos/search?q=cough+person+spraying+aerosol&ru=%2fsearch%3dQBRE%26sp%3d-1%26pq%3dundefined%26sc%3d0-15%26sk%3d%26cvid%3d728A4EFA08FB4E50BDBEB7C4CAA62C39&view=detail&mid=VRV

Factors InfluencingTransmission

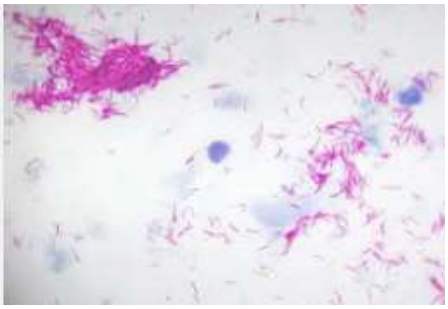
- Transmission is airborne from patients with <u>active</u> pulmonary TB
- Infectiousness of source patient
  - Vehicle: droplet nucleus (coughing, talking, sneezing); size (1-5 μm)
  - Quantity of organisms; high with cavitary disease
- Duration of exposure
- Virulence of *M. tuberculosis* strain
- Environment: spread is enhanced by crowded, poorly ventilated conditions



Less Transmission



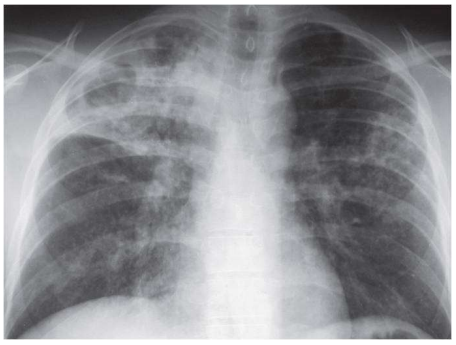
More Transmission



Christopher Vinnard

Less Transmission

More Transmission



Christopher Vinnard

Less Transmission More Transmission

SAMJ, S. Afr. med. j. vol.102 n.8 Cape Town Aug. 2012

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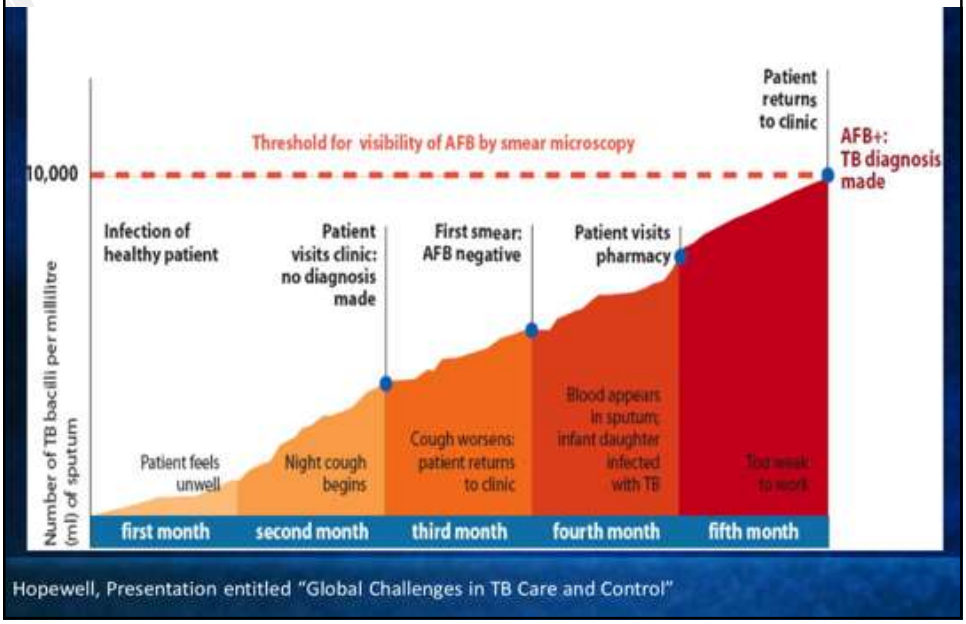
Delayed Diagnosis & Increased Transmission



Hopewell, Presentation entitled "Global Challenges in TB Care and Control"

Reducing TB transmission

- **The best way to stop transmission is to:**
  - **Provide effective <u>treatment</u> to infectious persons as soon as possible**
    - **Decreases bacterial burden**
    - **Decreases symptoms**
    - **2 weeks of effective therapy decreases contagion dramatically**
  - **<u>Isolate</u> infectious persons while contagious**
    - **Smear negative samples implies less contagion**
      - **Smear negative, on therapy, clinically improving---? Discontinue isolation**
    - **Zero transmission occurs once the index case is culture negative**

Slide courtesy Dr. E. Jane Carter

"The patient in the next bed is highly infectious. Thank God for these curtains."

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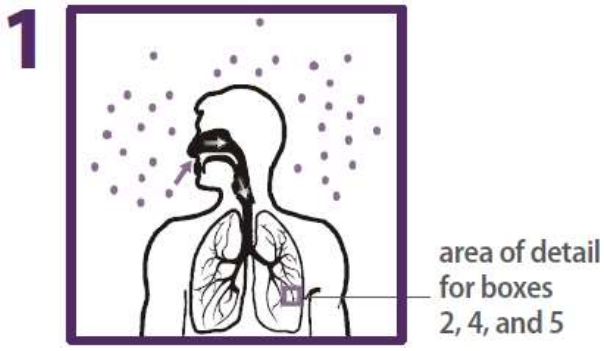
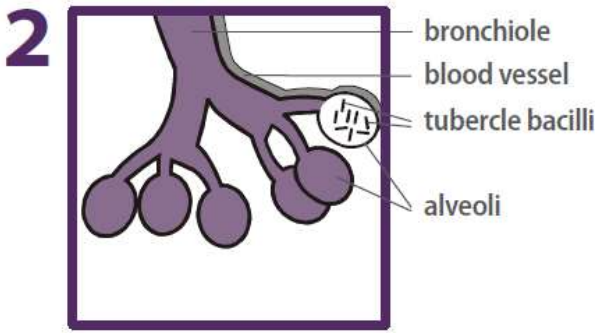
TB Pathogenesis



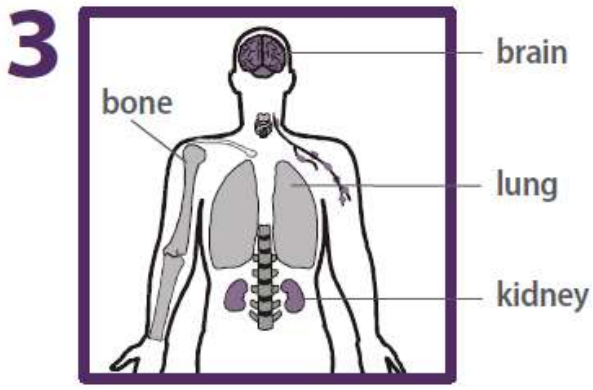
Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to small air sacs (alveoli)

TB Pathogenesis



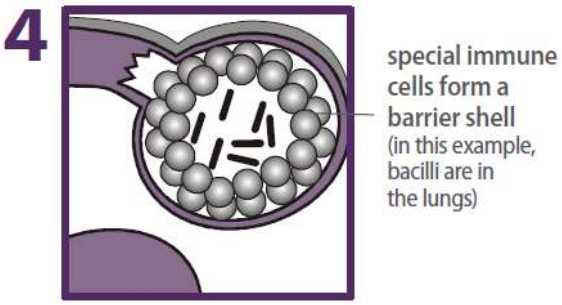
Tubercle bacilli multiply in alveoli, where infection begins

TB Pathogenesis



A small number of tubercle bacilli enter bloodstream and spread throughout body

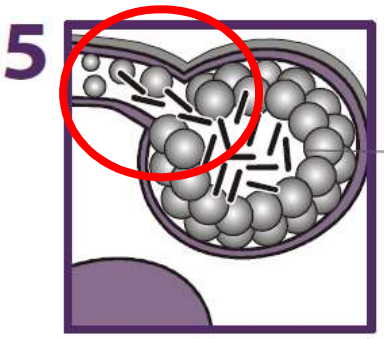
TB Pathogenesis
LTBI



- **Within 2 to 8 weeks the immune system produces special immune cells called macrophages that surround the tubercle bacilli**
- **These cells form a barrier shell that keeps the bacilli contained and under control (LTBI)**

TB Pathogenesis

TB Disease



- **If the immune system CANNOT keep tubercle bacilli under control, bacilli begin to multiply rapidly and cause TB disease**
- **This process can occur in different places in the body**

Active TB Disease

Pulmonary

- Lungs

Extrapulmonary

- Lymphatic system
- Kidney
- Central nervous system
- Bones (Potts)
- Disseminated (miliary TB)

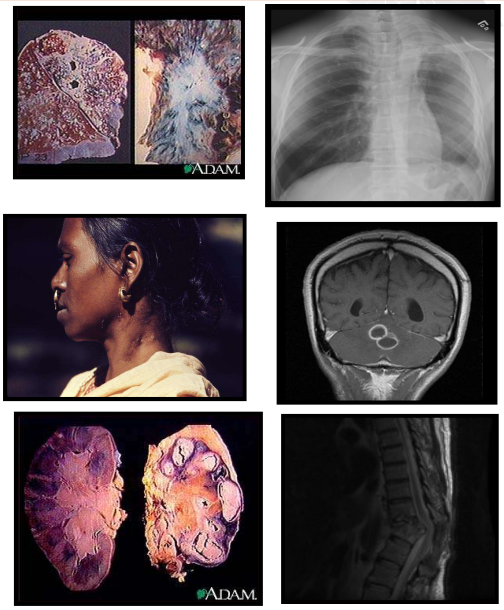


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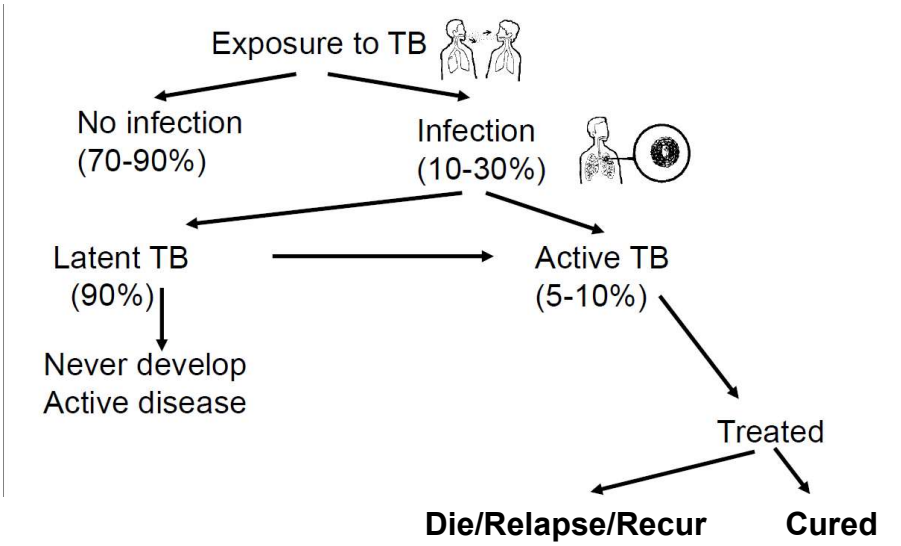
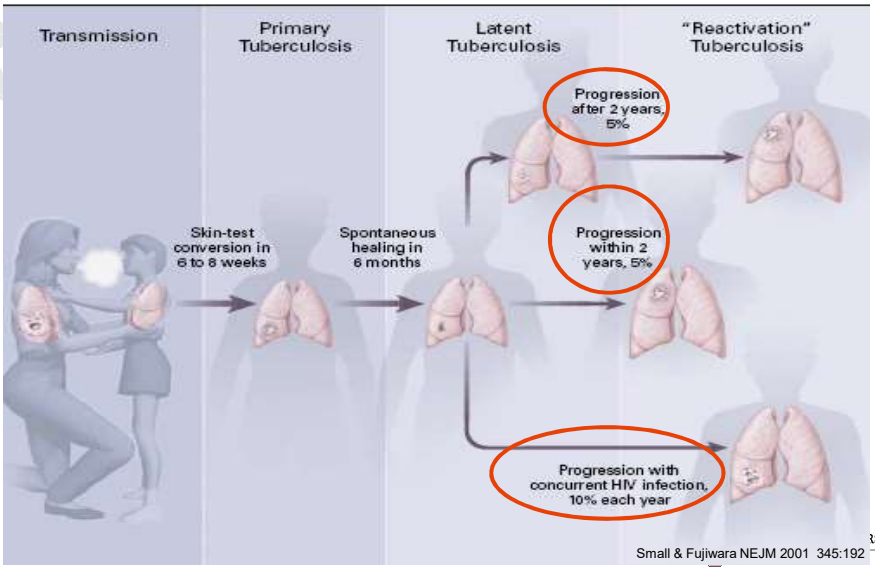
Photo CDC and ADAM

Natural History of TB Infection in Patients without HIV

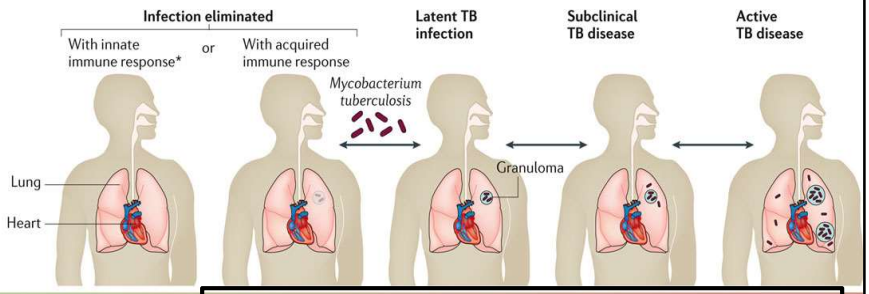


Risk Associated with Development of Active TB Disease



Small & Fujiwara NEJM 2001 345:192

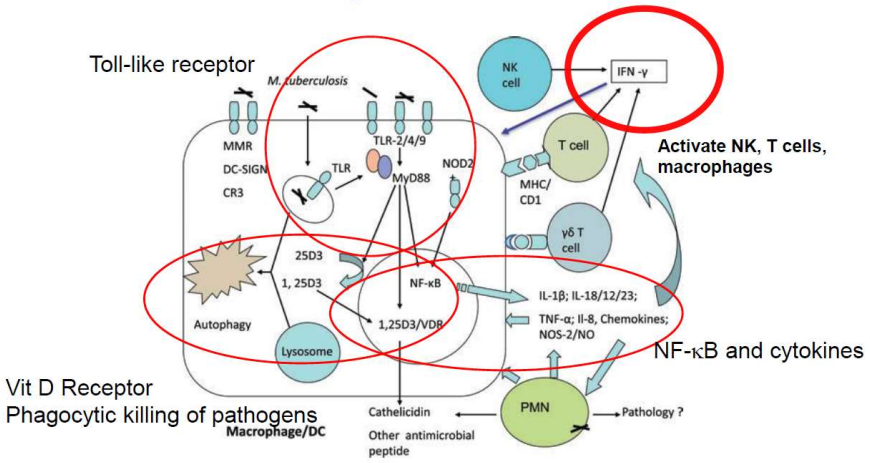
The spectrum of TB: from *M. tuberculosis* infection to active (pulmonary) TB disease



TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

Pai, M. et al. Nat. Rev. Dis. Primers, 2016

Innate Immunity to *M. tuberculosis*



Resp 2010.15:433

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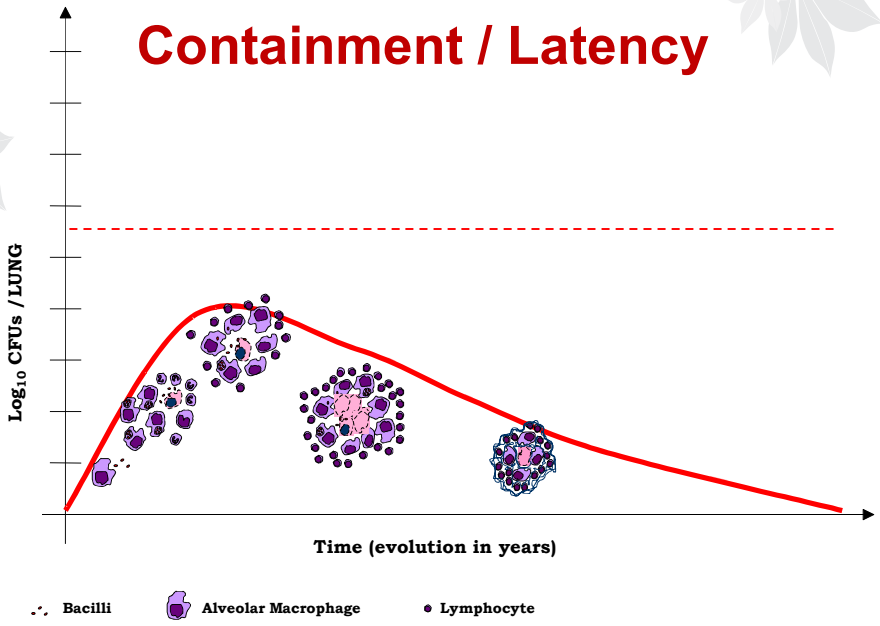
Containment / Latency



Slide courtesy of Joanne Turner

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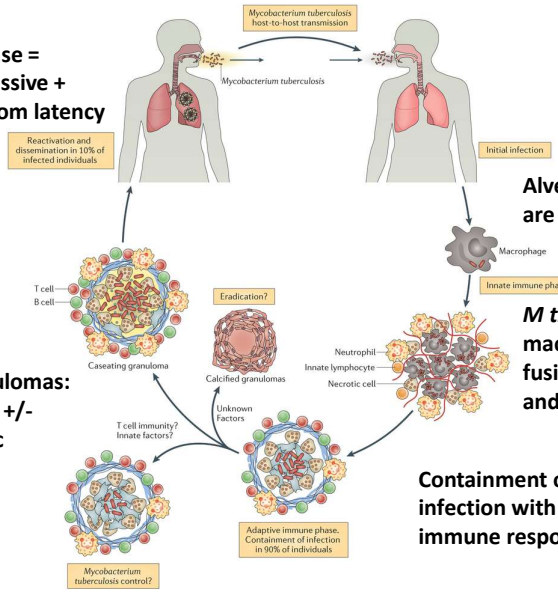
Airborne droplet nuclei up to 6 hours

Active TB disease = Primary progressive + Reactivation from latency



Alveolar macrophages are first line of defense

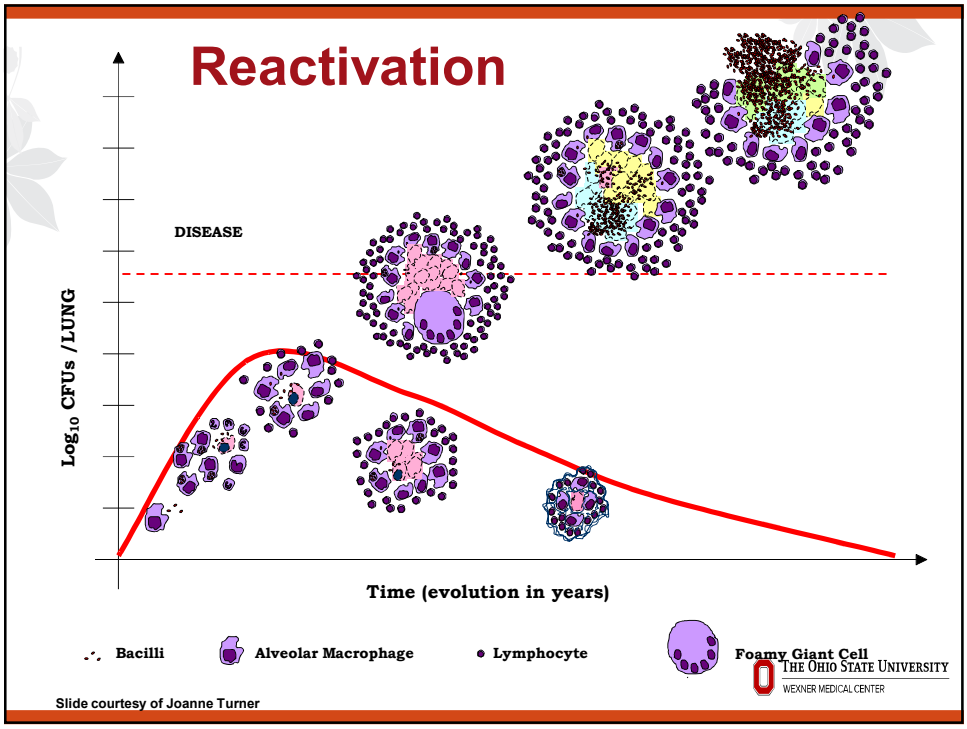
***M tb* survives inside the macrophage- prevents fusion of phagosome and lysosome**

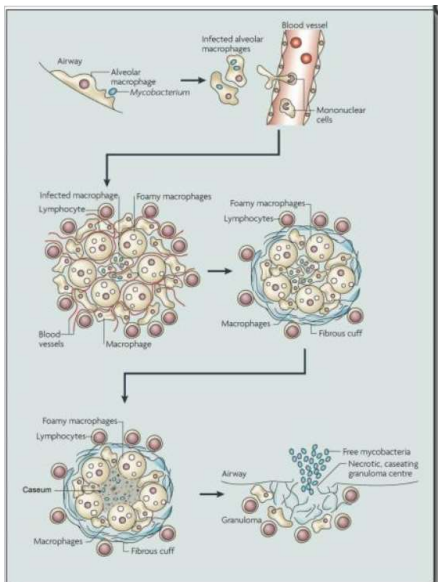
Tissue granulomas: microscopic +/- macroscopic

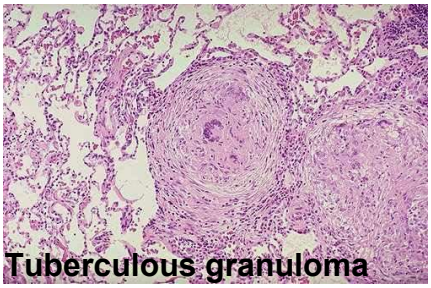
Containment of infection with adaptive immune response

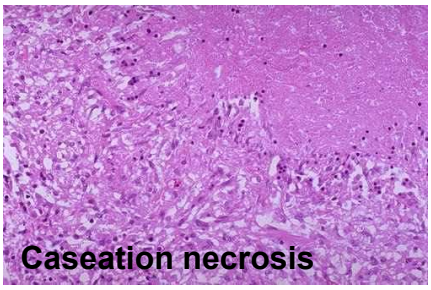
Nature Reviews | Microbiology

Barry, Nat Rev Microbiol, 2009









Russell et. al, Science 2010

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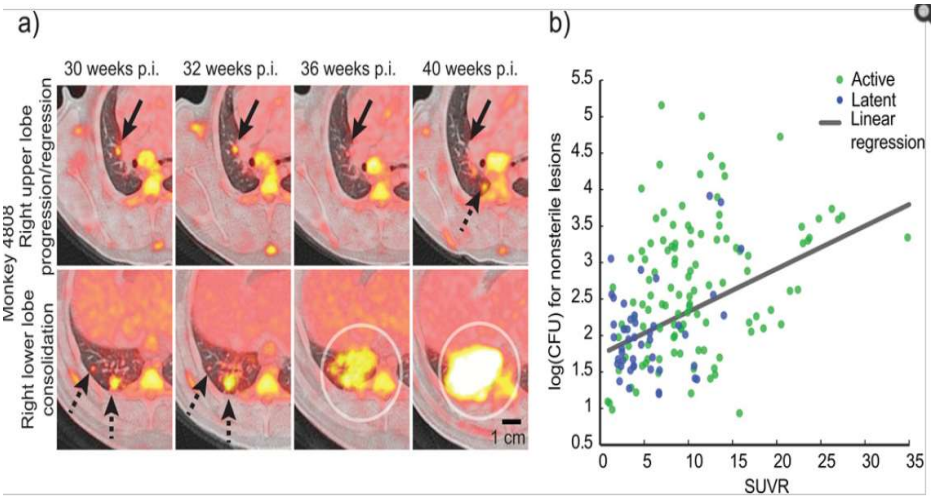
Dynamic Evolution of Lesions in TB



Lin et al., Nat Med 2014

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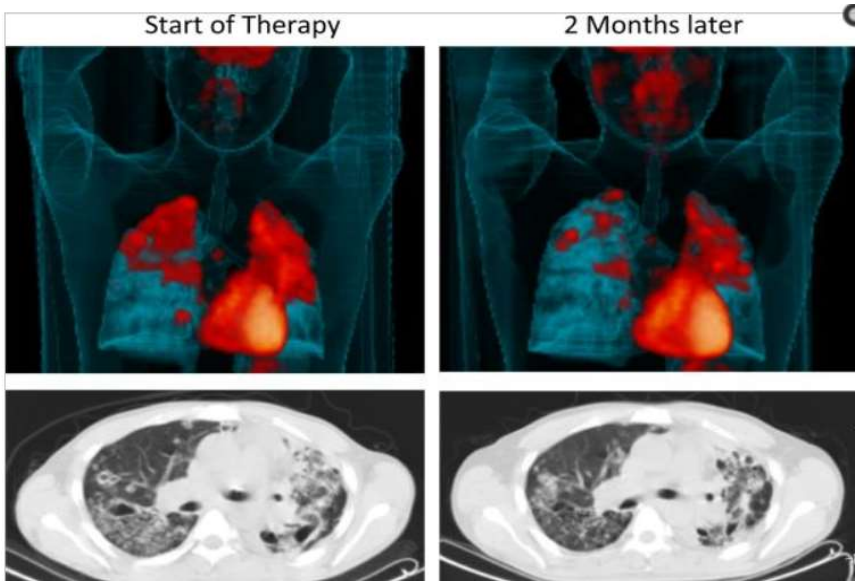
Disease Progression in Humans



Russell et. al, Science 2010

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Risk of Developing TB Disease

TB infection and no risk factors (about 10% over a lifetime)	TB infection and diabetes (about 30% over a lifetime)	TB infection and HIV infection (a very large risk over a lifetime)
		
For people with TB infection and no risk factors, the risk is about 5% in the first 2 years after infection and about 10% over a lifetime.	For people with TB infection and diabetes, the risk is 3 times greater, or about 30% over a lifetime.	For people with TB infection and HIV infection (not on HIV treatment), the risk is about 7% to 10% PER YEAR, a very large risk over a lifetime.

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Advanced HIV

Close contact

CXR evidence of old TB (untreated)

Chronic renal dz

TNF-alpha inhibitor

Poorly controlled DM

Underweight

Smoking

Risk Factor and Study	Relative Risk (95% CI) %
Advanced, untreated HIV infection	
Moss et al.[10]	9.9 (8.7–11)
Pablos-Méndez et al.[16]	9.5 (3.6–25)
Close contact with a person with infectious tuberculosis†	
Ferebee[17]	6.1 (5.5–6.8)
Radiographic evidence of old, healed tuberculosis that was not treated	
Ferebee[17]	5.2 (3.4–8.0)
Treatment with ≥15 mg of prednisone per day‡	
Jick et al.[18]	2.8 (1.7–4.6)
Chronic renal failure	
Pablos-Méndez et al.[16]	2.4 (2.1–2.8)
Treatment with TNF-α inhibitor	
Askling et al.[19]	2.0 (1.1–3.5)
Poorly controlled diabetes	
Pablos-Méndez et al.[16]	1.7 (1.5–2.2)
Weight ≥10% below normal	
Palmer et al.[20]	1.6 (1.1–2.2)
Smoking	
Bates et al.[21]	1.5 (1.1–2.2)

NEJM 2011; 364(15): 1441-8

TB and HIV

In an HIV-infected person, TB can develop in one of two ways:

- **Person with LTBI becomes infected with HIV and then develops TB disease as the immune system is weakened**
- **Person with HIV infection becomes infected with *M. tuberculosis* and then rapidly develops TB disease**

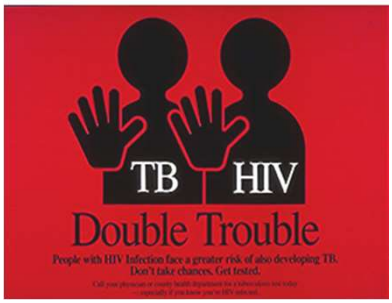

Image credit: Mississippi State Department of Health

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TB Infection vs. TB Disease

A Person with Latent TB Infection	A Person with Active TB Disease
✓ Has no symptoms ✓ Does not feel sick ✓ Cannot spread TB to others ✓ Usually has a positive skin test ✓ Has a normal CXR and sputum test	✓ Has symptoms that may include: • a bad cough that lasts longer than 2 weeks • pain in the chest • coughing up blood or sputum • weakness or fatigue • weight loss • no appetite • chills • fever • night sweats ✓ May spread TB to others ✓ Usually has a positive skin ✓ May have an abnormal chest x-ray, or positive sputum smear or culture

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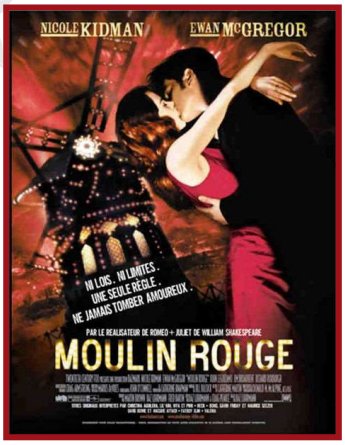
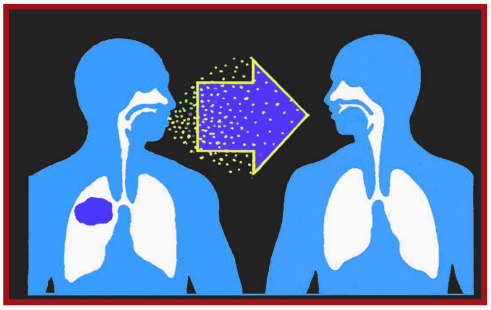
Role of Public Health



All TB Cases Began As TB Contacts



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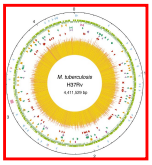
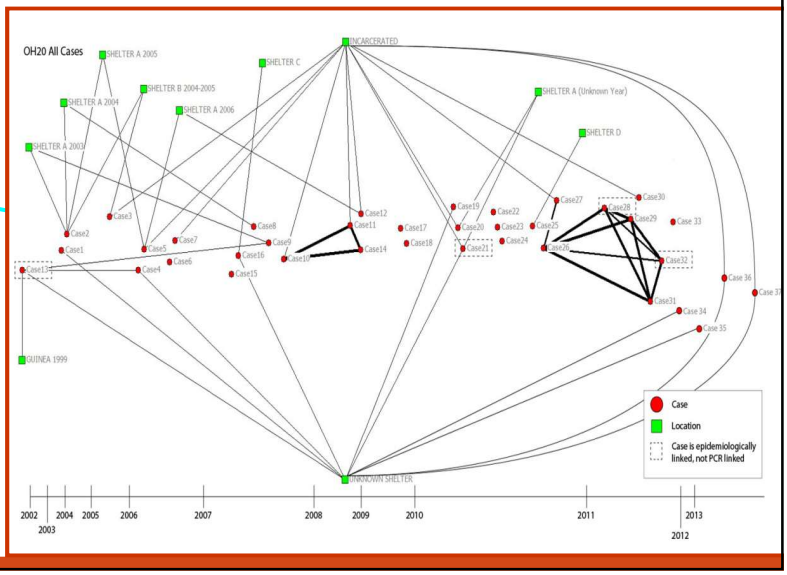
Social Network Analysis and Molecular Genotyping

Ted





Acknowledgements

- Stacey Rizza
- James Sunstrum
- Christopher Vinnard