TUBERCULOSIS: TRANSMISSION AND PATHOGENESIS

FARAH PARVEZ, MD, MPH
DIRECTOR, TRAINING AND OUTREACH
BUREAU OF TUBERCULOSIS CONTROL
NEW YORK CITY DEPARTMENT OF HEALTH

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1

Objectives

- Describe the history of tuberculosis (TB)
- Explain how TB is spread (*transmission*)
- Explain the difference between latent TB infection (LTBI) and TB disease
- Explain how LTBI and TB disease develop (*pathogenesis*)
- Describe the classification system for TB

Disclosures: Nothing to disclose

2

History of TB

3

History of TB

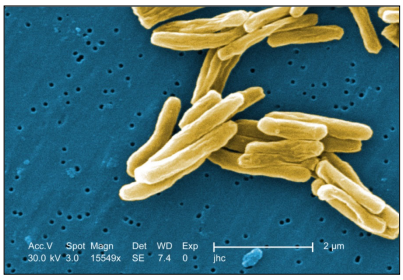
- TB has affected humans for millennia
- Historically known as:
  - "Consumption"
  - "Wasting disease"
  - "White plague"
- Each year
  - ~10 million people develop TB
  - 1.6 million die
- Leading infectious disease killer worldwide (pre-COVID-19)

Vintage image circa 1919
Image credit: National Library of Medicine

4

History of TB: Scientific Discoveries in 1800s

- Until mid-1800s, many believed TB was hereditary
- 1865: Jean Antoine-Villemin showed TB was contagious
- 1882: Robert Koch discovered *M. tuberculosis,* the bacterium that causes TB



Mycobacterium tuberculosis
Image credit: Janice Haney Carr

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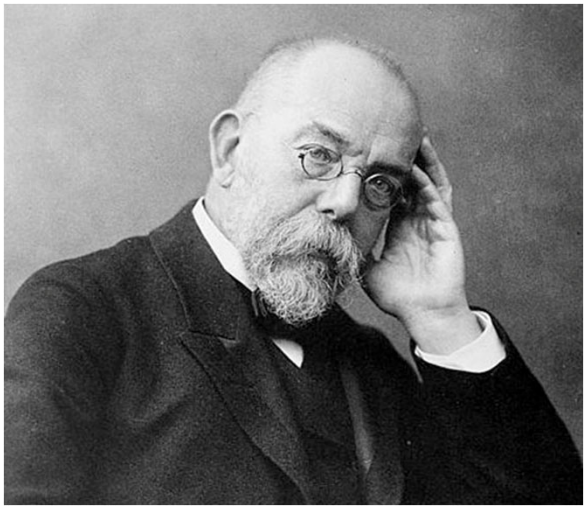
Mycobacterium tuberculosis (*M. tb*) = bacteria Announced by Robert Koch on March 24, 1882 to the German Physiological Society



BERLINER
KLINISCHE WOCHENSCHRIFT.
Organ für practische Aerzte.

Montag, den 10. April 1882. № 15. Neunzehnter Jahrgang.

6

History of TB - Sanatoriums

- Before TB antibiotics, many patients were sent to sanatoriums
- Patients followed a regimen of bed rest, open air, good diet, and sunshine
- TB patients who could not afford sanatoriums often died at home

Sanatorium patients resting outside

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TB History Timeline

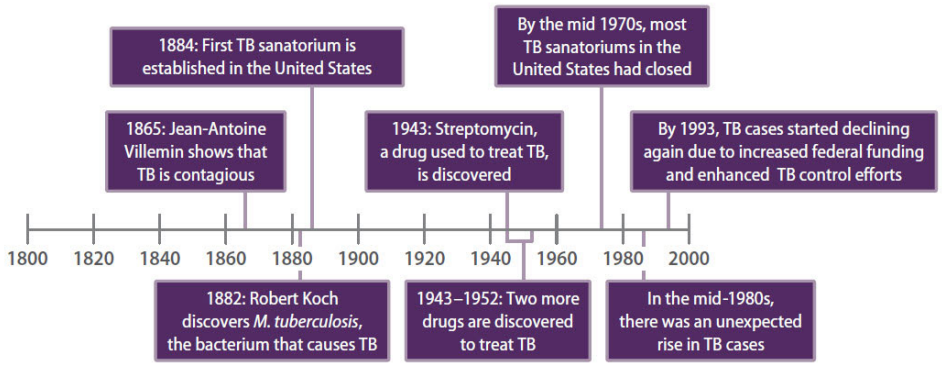

Figure 1.1 Timeline of major events in the history of TB.

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8

TB Resurgence- Increase in TB cases in the mid-1980s

- Infrastructure
  - Decline of public health funding
- Inappropriate TB care
  - Poor treatment practices
  - Few drug susceptibility results
  - Inappropriate regimens
- Immunosuppression
  - HIV/AIDS epidemic
- Infection control
  - Poor infection control practices & spread in hospitals and congregate setting (shelters & prisons)
  - Increase incidence of multidrug-resistant TB (MDR-TB)
- Immigration
  - Changing patterns in 1970s & 1980s
  - Immigration from high prevalence countries

The outbreak got a lot of media attention which helped to mobilize increased resources for TB control

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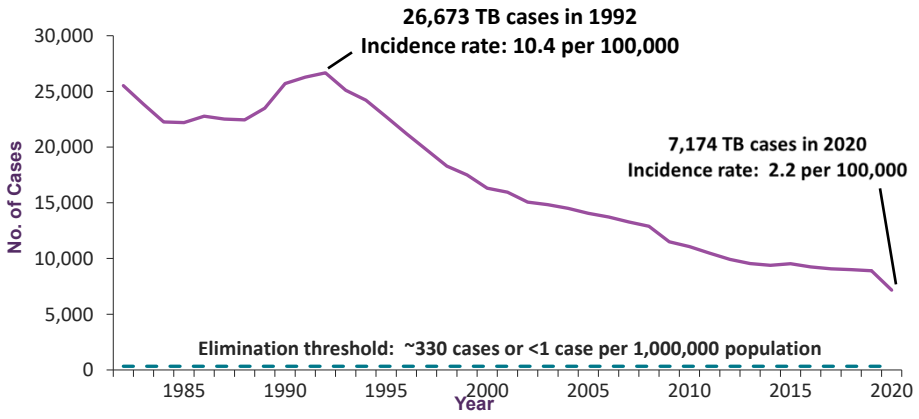
TB Prevention and Control Efforts in the U.S.

- Increased governmental funding for TB control programs began in 1992
- Number of TB cases declined from 1993 to 2014, plateaued, returning to pre-pandemic levels
- Prevention and control efforts must be maintained since TB continues to be reported in the U.S.



Reported TB Cases, U.S., 1982-2020

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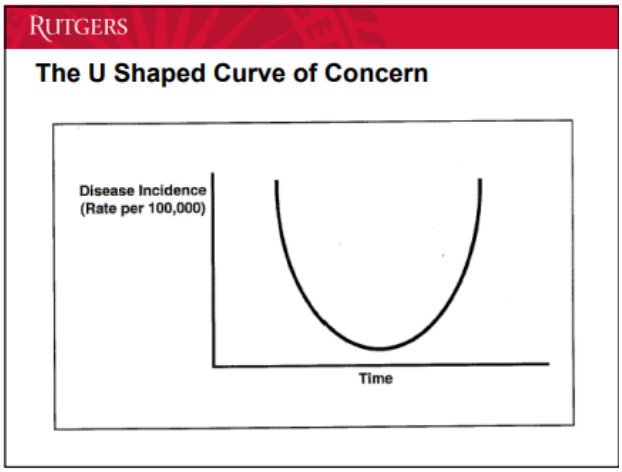
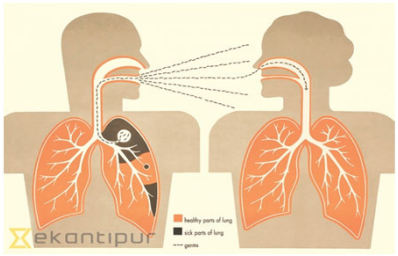
The U-Shaped Curve of Concern

- Described by Dr. Lee Reichman- *Am Rev Respir Dis,1991;144:741-742*
- Disease rates decline → Funding decline → Disease rates increase



11

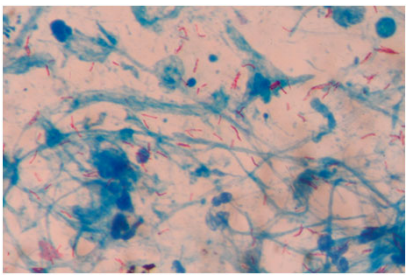
TB Transmission

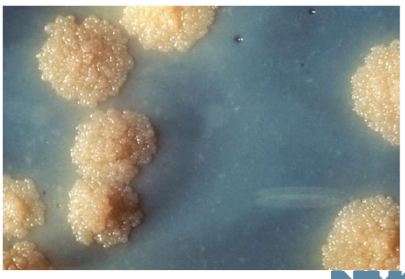


12

Mycobacterium tuberculosis (*M. tb*) Complex

- The majority of TB cases in US are caused by *M. tuberculosis*
- *M. tb* complex – made of:
  - *M. tuberculosis*
  - *M. africanum*
  - *M. bovis*
  - *M. microti*
  - *M. canettii*
  - *M. caprae*
  - *M. pinnipedii*
  - *M. mungi*
  - *M. dassie*
  - *M. orygis*
  - *M. suricattae* (Meerkats)
    - Not typically seen in the US
- Mycobacteria that do not cause TB
  - e.g., *M. avium*-complex





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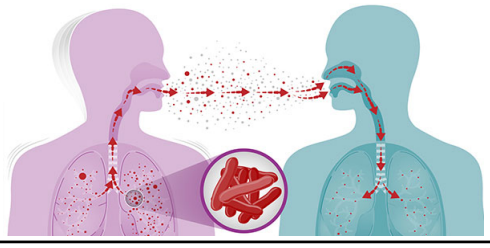
13

TB Transmission

- Defined as the spread of an organism, such as *M. tb*, from one person to another
- *M. tb* is carried in airborne particles of 1–5 microns in diameter called droplet nuclei
- Transmission is not by surface contact
- TB is transmitted from an infectious person to another through the air when the infectious person:
  - Coughs
  - Speaks
  - Sings
  - Laughs
- Transmission occurs when the other person inhales droplet nuclei which traverse the respiratory tract to reach the alveoli of the lungs
  - Droplet nuclei can remain suspended in air for several hours
- Primarily infects the lungs, but can spread to other parts of the body



14

Probability TB Will Be Transmitted

- Not everyone who is exposed to a person with infectious TB becomes infected
- Probability that TB will be transmitted depends on:
  - Infectiousness: number of bacilli TB patient expels into the air
  - Environmental factors: where the exposure occurred that affect the concentration of *M. tb* organisms (concentration of organisms, enclosed vs open space, ventilation)
  - Proximity, frequency and duration of the exposure (close contacts)
  - Susceptibility (immune status) of the exposed individual
- Can be transmitted from children, though less likely
  - TB is often paucibacillary
  - Young children do not often cough with enough force to expel organisms
- The best way to stop transmission is to:
  - Isolate infectious persons
  - Provide treatment to infectious persons as soon as possible

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15

Pathogenesis of LTBI & TB Disease

Defined as the way an infection or disease develops in the body

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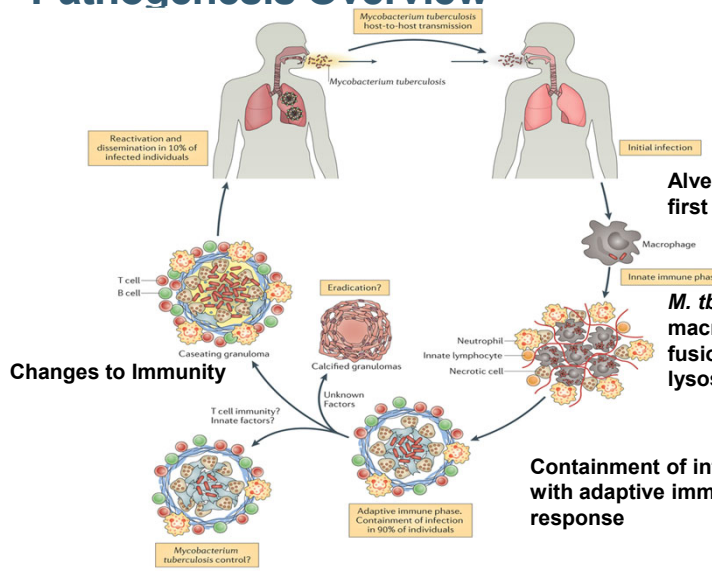
16

Pathogenesis Overview



Alveolar macrophages are first line of defense

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

Containment of infection with adaptive immune response

Changes to Immunity

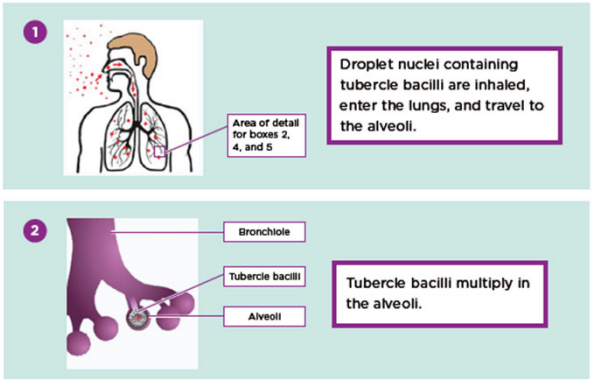
Nature Reviews | Microbiology

Barry, Nat Rev Microbiol, 2009

17

Pathogenesis (1)

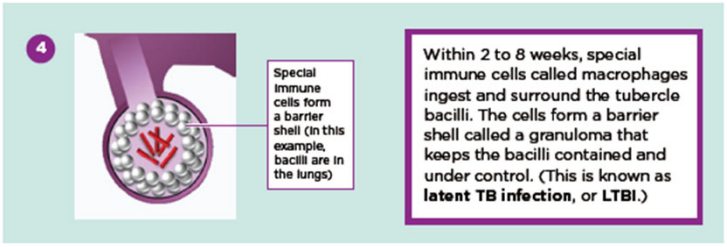
- TB infection occurs when the inhaled droplet nuclei containing tubercle bacilli reach the alveoli of the lungs



18

Pathogenesis (2) - Development of LTBI

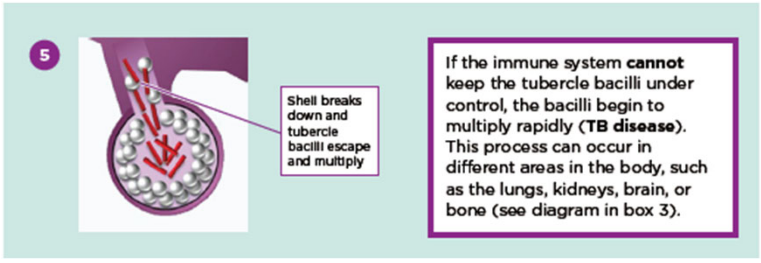
- Alveolar macrophages surround and ingest the tubercle bacilli
- Within 2-8 weeks: T cells and B cells are recruited
- The immune system is usually able to stop the multiplication of bacilli
- A granuloma (barrier shell) is formed
  - If the bacilli are contained and under control, it is Latent TB infection (LTBI)
  - LTBI would be detected via TST or interferon-gamma release assay (IGRA)
  - Persons with LTBI are not infectious and do not spread organisms to others



19

Pathogenesis (3) - Development of TB Disease

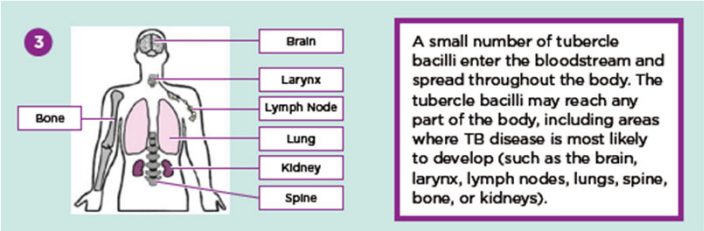
- Most bacilli are destroyed or inhibited, but a small number may multiply intracellularly and be released when the macrophages die.
  - These bacilli enter bloodstream and spread throughout body
- If the immune system CANNOT keep tubercle bacilli under control, bacilli begin to multiply rapidly and cause TB disease
  - If the granuloma breaks down, it produces TB disease
  - This process can occur in different places in the body



20

Pathogenesis (4)

- The bacilli that are still alive may spread by way of lymphatic channels or through the bloodstream to more distant tissues and organs (including areas of the body in which TB disease is most likely to develop; regional lymph nodes, apex of the lung, kidneys, brain, and bone)
- This process of dissemination primes the immune system for a systemic response



21

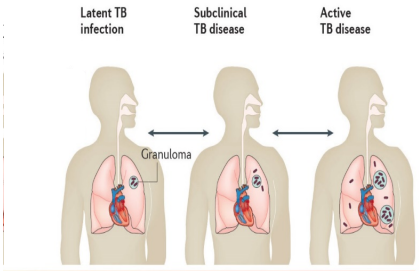
LTBI vs. TB Disease

Person with LTBI (Infected)	Person with TB Disease (Infectious)
Has a small amount of TB bacteria in his/her body that are alive, but inactive	Has a large amount of active TB bacteria in his/her body
Cannot spread TB bacteria to others	May spread TB bacteria to others
Does **not** feel sick, but may become sick if the bacteria become active in his/her body	May feel sick and may have symptoms such as a cough, fever, and/or weight loss
Usually has a TB skin test or TB blood test reaction indicating TB infection	Usually has a TB skin test or TB blood test reaction indicating TB infection **(May be negative)**
Radiograph is typically normal	Radiograph may be abnormal
Sputum smears and cultures are negative	Sputum smears and cultures may be positive
Should consider treatment for LTBI to prevent TB disease	Needs treatment for TB disease
Does **not** require respiratory isolation	May require respiratory isolation
Not a TB case	A TB case

22

Clinical Spectrum of TB

LTBI and Active TB Disease



	Latent TB infection	Subclinical TB disease	Active TB disease
TST	Positive	Positive	Usually positive
IGRA	Positive	Positive	Usually positive
Culture	Negative	Intermittently positive	Positive
Smear	Negative	Usually negative	Positive or negative
Infectious	No	Sporadically	Yes
Symptoms	None	Mild or none	Mild to severe
Treatment	Preventive therapy	Multidrug therapy	Multidrug therapy

- Immune system is activated upon infection
- The term “latent” is a misnomer; the TB bacteria are metabolically active
- Among people with LTBI, there is at least a **10% lifetime risk** for progressing to active TB disease; risk is greater with HIV infection or other immunosuppression
- Progression from LTBI to TB disease may occur at any time, but it is most common **within the first two years** of infection or in the context of certain medical conditions.
- Treatable and preventable

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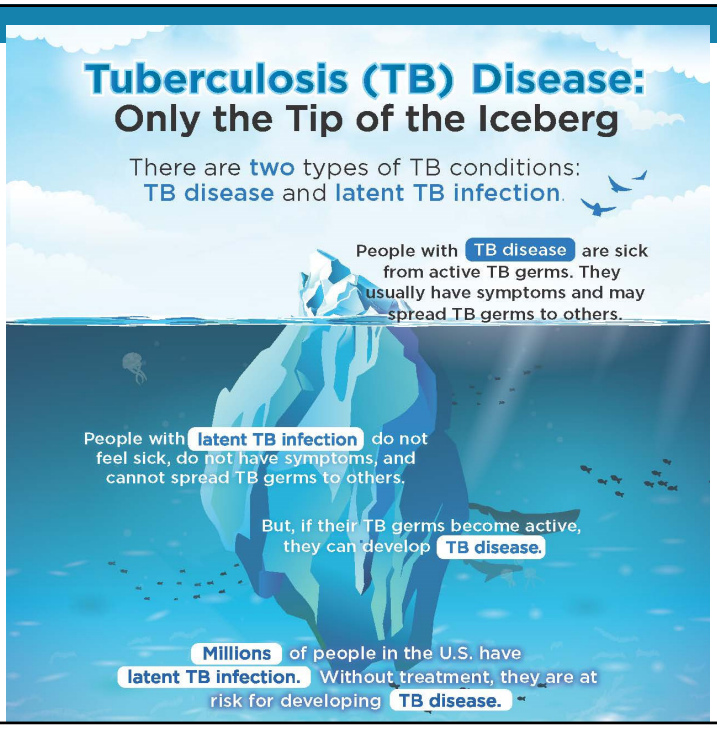
23



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24

Risk of Developing Disease

Normal Immune System

- Untreated, 5% of infected persons will develop TB in first 1–2 years post infection, another 5% later in life
- Thus, about 10% of infected persons with normal immunity will develop TB at some point in life if not treated

Weak Immune System
Increased Risk Progression

- Untreated HIV infection highest risk factor: risk of developing TB disease is 7%–10% *each year*
- Person with both diabetes & TB infection: about a 30% risk of developing TB disease over lifetime
- Children <5 years of age
- Persons with certain medical conditions

25

Advanced HIV

Close contact

CXR evidence of old TB (untreated)

Chronic Prednisone Tx

Chronic Renal Disease

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

26

TB Pathogenesis

Sites of TB Disease

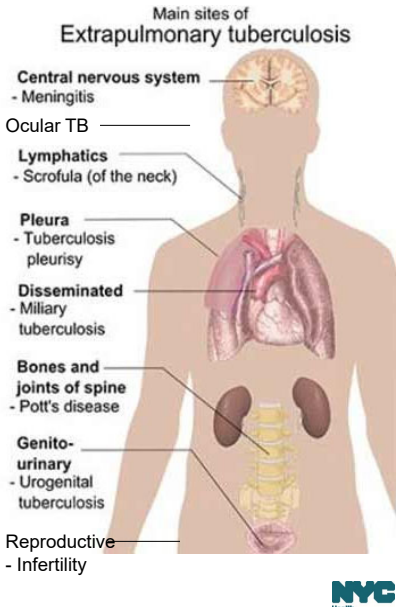
27

Sites & Symptoms of Active TB Disease

PULMONARY

- Most common site; usually infectious
- Symptoms *may* include one or more of the following:
  - Cough (prolonged)
  - Hemoptysis
  - Fever
  - Night sweats
  - Fatigue
  - Decreased appetite
  - Weight loss

Respiratory or other clinical specimens *may* be smear- or culture-positive



28

Sites of TB Disease (2)

	Location	Frequency
Pulmonary TB	**Lungs**	**Most TB cases are pulmonary**
Extrapulmonary TB	**Places other than lungs such as:** ▪ **Larynx** ▪ **Lymph nodes** ▪ **Pleura** ▪ **Brain** ▪ **Kidneys** ▪ **Bones and joints**	**Found more often in:** • **HIV-infected or other immunosuppressed persons** • **Young children**
Disseminated TB	**Carried to all parts of body, through bloodstream**	**Rare; high risk in children < 5 years**

29

Chest X-ray Findings

Common Findings
Consistent with TB Disease

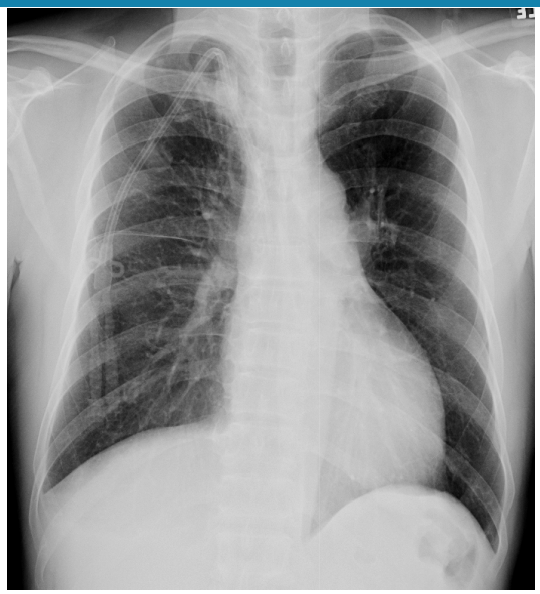
- Cavity formation more common in upper lobes (UL) than lower lobes (LL)
- UL infiltrates (fibronodular changes)
- Pleural effusions/thickening
- Miliary pattern
- Primary TB: middle/LL infiltrates with adenopathy

Atypical Findings
Commonly in Immunocompromised Patients

- Infiltrates in the LLs
- Hilar/mediastinal adenopathy
- Normal chest x-ray

30

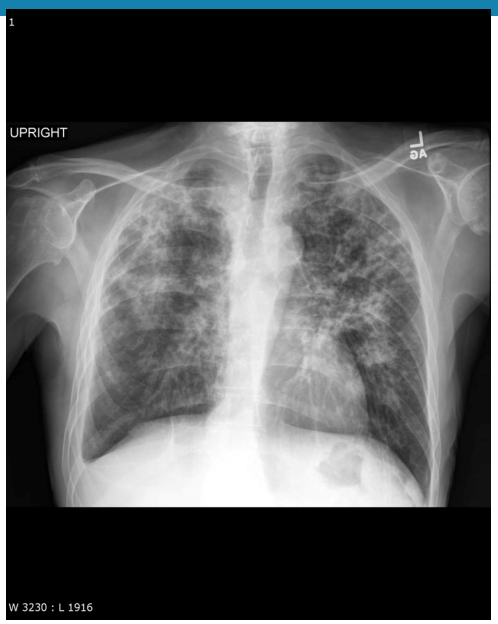
Nodules



Daley CL, Gotway MB, Jasmer RM.
Radiographic Manifestations of Tuberculosis: A Primer for Clinicians, Second Edition (2006), Reprint 2020
San Francisco: Curry International Tuberculosis Center;
December 2020

31

Cavitary TB



Daley CL, Gotway MB, Jasmer RM.
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San Francisco: Curry International Tuberculosis Center;
December 2020

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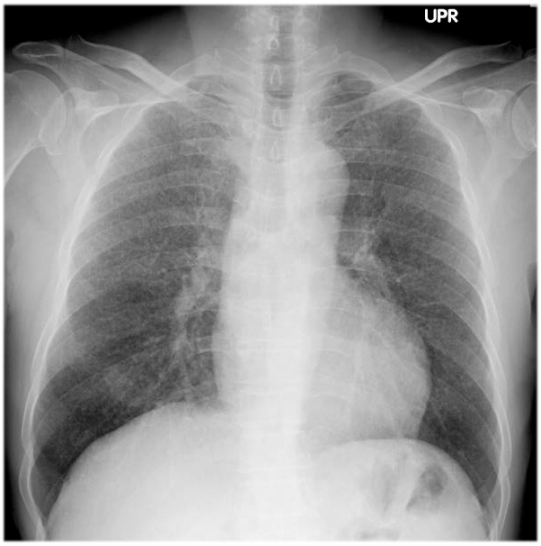
Miliary/Disseminated TB



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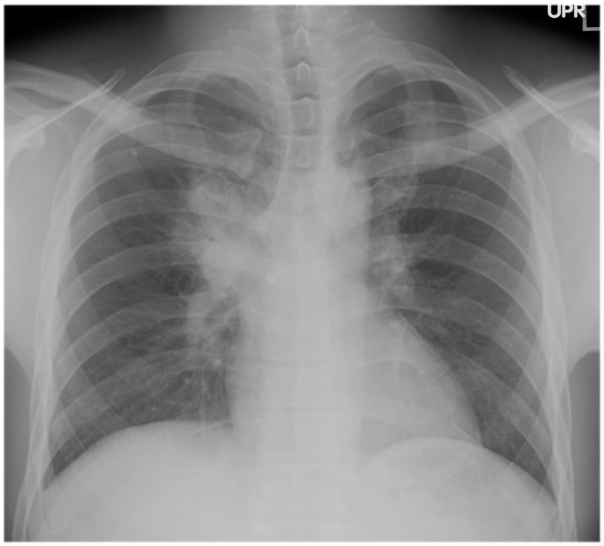
33

Hilar Adenopathy



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December 2020

34

TB Classification System

Class	Type	Description
0	No TB exposure—**Not** infected	• No history of TB exposure and no evidence of *M. tuberculosis* infection or disease • Negative reaction to TST or IGRA
1	TB exposure—No evidence of infection	• History of exposure to *M. tuberculosis* • Negative reaction to TST or IGRA (test given at least 8 to 10 weeks after exposure)
2	TB infection—No TB disease	• Positive reaction to TST or IGRA • Negative bacteriological studies (smear and cultures) • No clinical or radiographic evidence of active TB disease
3	TB disease clinically active	• Positive culture for *M. tuberculosis* **OR** • Positive reaction to TST or IGRA, plus clinical, bacteriological, or radiographic evidence of current active TB disease
4	Previous TB disease (**not** clinically active)	• May have past medical history of TB disease • Abnormal but stable radiographic findings • Positive reaction to the TST or IGRA • Negative bacteriologic studies (smear and cultures) • No clinical or radiographic evidence of current active TB disease
5	TB disease suspected	Signs and symptoms of active TB disease, but medical evaluation **not** complete

35

TB Classification System

- Based on TB risk, signs, and symptoms
- Primarily used by public health programs for surveillance and monitoring
- Class 3 or 5 TB should be reported to health department
  - Class 5 should be resolved by 3 months
- Class II (contacts, kids <5 years) may also be reportable
- Health care providers should comply with state and local laws and regulations requiring the reporting of TB disease

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36

Summary

- TB is a resilient bacteria
- Preventable and curable
- Think, test, and treat TB!

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37

Questions?

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38

Drug-Resistant TB

39

Defining Drug Resistance
Multi-drug and Other-Drug Resistance

- MDR TB
  - A specimen of *M. tuberculosis* isolate that is resistant to at least INH and RIF
  - Can be resistant to other drugs as well
- ODR TB
  - Resistant to INH, sensitive to RIF, with or without resistance to other first or second-line drugs
  - Resistant to RIF, sensitive to INH, with or without resistance to other drugs
  - Resistance to any (1 or more) first-line drugs (EMB, PZA, SMN) other than INH or RIF

40

Defining Drug Resistance
Extensively Drug Resistant TB

Previous Definition:

- Resistance to at least INH and RIF from among the 1st -line anti-TB drugs (MDR TB)
- Plus resistance to any fluoroquinolone
- And to at least one of 3 injectable 2nd-line anti-TB drugs used in TB treatment
  - Capreomycin
  - Kanamycin
  - Amikacin

Current Definition (January 2021):

- MDR/RR-TB plus resistance to any fluoroquinolone and other WHO Group A MDR Drug (BDQ, LNZ)

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41

Primary & Secondary Drug Resistance

Primary Drug Resistance	Secondary Drug Resistance
Caused by person-to-person transmission of drug-resistant organisms	Develops during TB treatment

Circumstances that increase a person's risk of infection with drug-resistant TB:
• Exposure to a person who
  • Has known drug-resistant TB
  • Had prior treatment for TB (treatment failure or relapse) and whose susceptibility test results are **unknown**
  • Is from an area in which there is a high prevalence of drug resistance
  • Continues to have positive smears and cultures after 2 months of treatment
• Travel in areas with a high prevalence of drug-resistant TB
	Circumstances that lead to secondary drug resistance:
	• Patient was **not** treated with the appropriate treatment regimen
	• Patient did **not** follow the treatment regimen as prescribed
	  • Took the drugs incorrectly
	  • Took the drugs irregularly
	• Malabsorption of drugs
	• Drug-drug interactions causing low serum levels

42

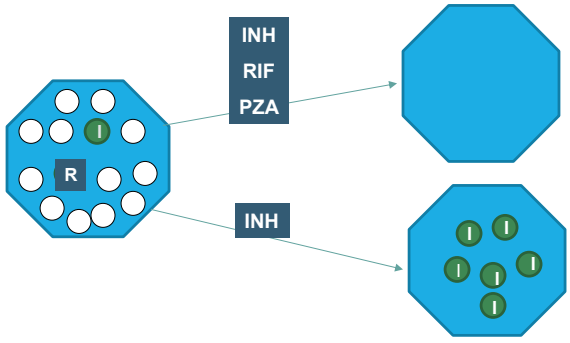
Rates of Natural Resistance in *M. tb*

Isoniazid	1 in 10^6
Rifampin	1 in 10^8
Ethambutol	1 in 10^6
Streptomycin	1 in 10^5
INH & RIF	1 in 10^{14}

Number of organisms in a TB cavity = 10^9-10^{11}

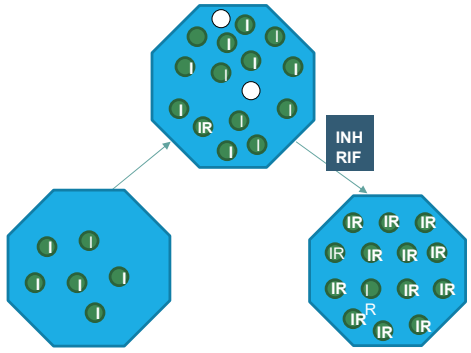
43

Pathogenesis of Drug Resistance – 1



44

Pathogenesis of Drug Resistance – 2



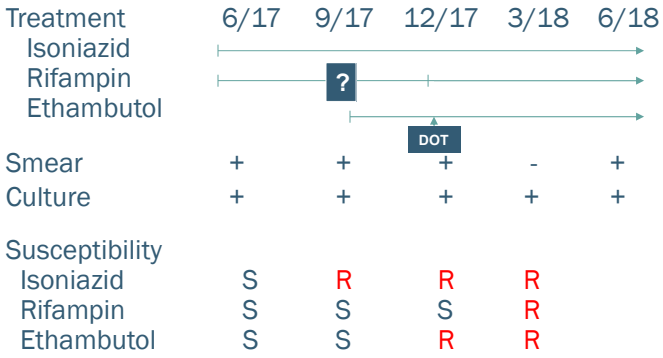
45

Emergence of Resistance: Inappropriate Therapy

Treatment	6/18	9/18	2/19
Isoniazid	→	→	→
Rifampin	→	→	→
Ethambutol		→	→
Smear	+	+	+
Culture	+	+	+
Susceptibility			
Isoniazid	R	R	R
Rifampin	S	R	R
Ethambutol	S	S	R

46

Emergence of Resistance: Inappropriate Therapy and Nonadherence



47