

Tuberculosis for the Non-ID Specialist

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Disclosures

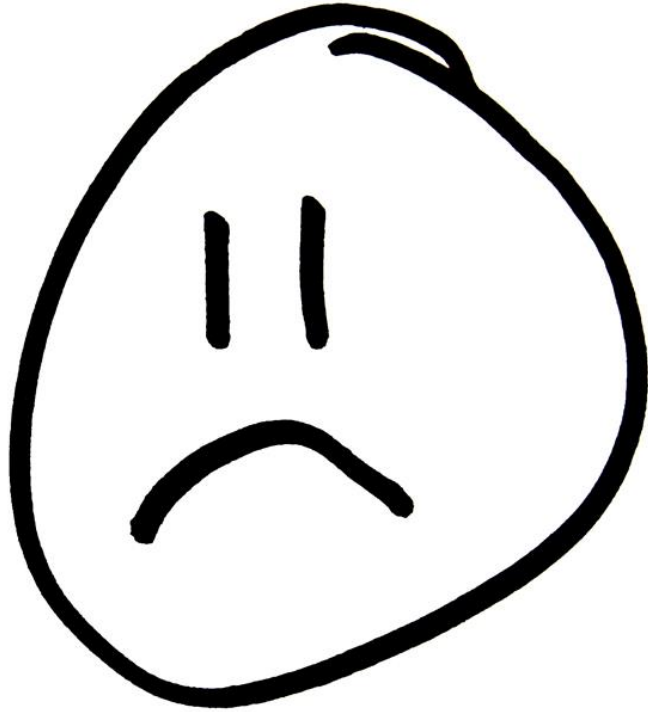
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Objectives

- Understand clinical spectrum of tuberculosis (TB) including latent TB infection (LTBI) and TB disease
- Review diagnostic approaches for LTBI
- Review treatment of LTBI
- Review diagnostic approaches for TB disease
- Review management of TB disease

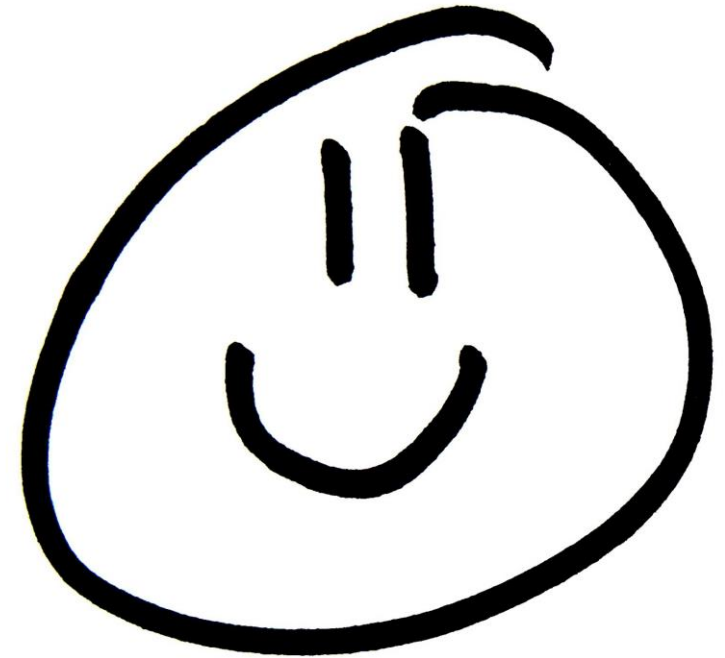
Tuberculosis Disease



- Sick
- Infectious



Latent Tuberculosis Infection (LTBI)

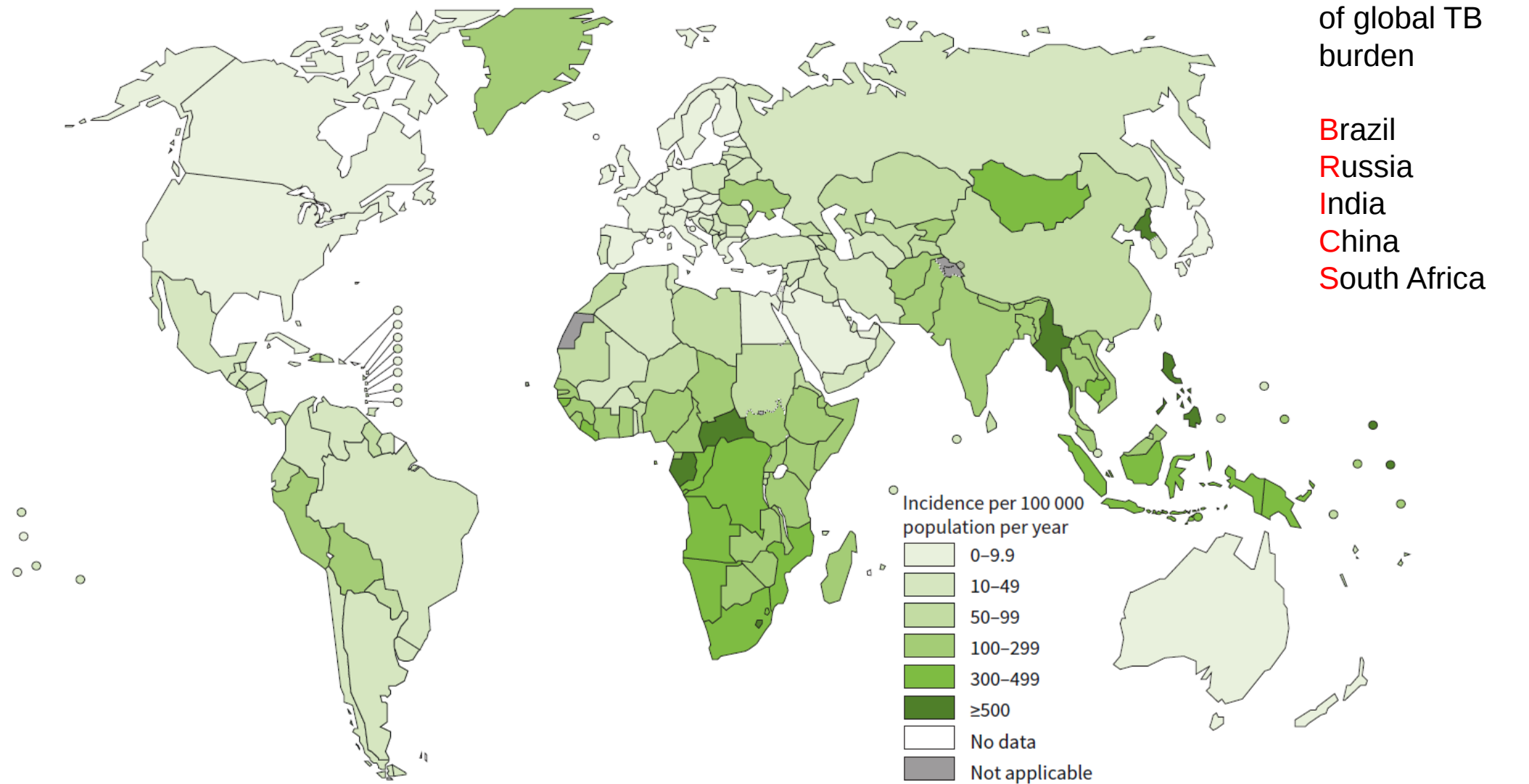


- Asymptomatic
- Non-infectious

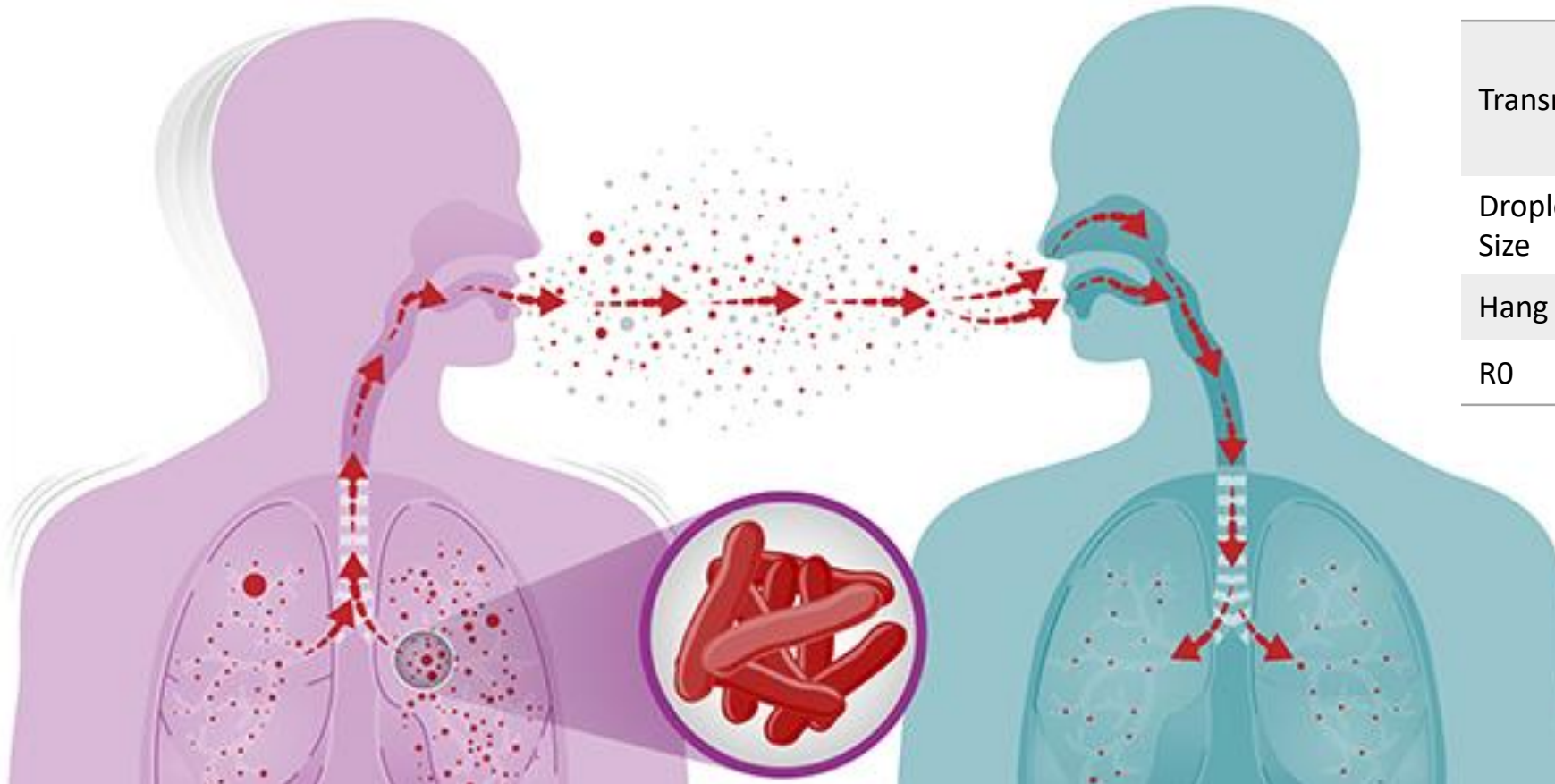
TB – world's leading infectious disease killer

- ~1.09 million deaths due to TB in 2023 (plus 0.16 million deaths due to TB-HIV)
- Leading cause of death among people living with HIV
- 8.2 million people newly diagnosed with TB disease in 2023
- One quarter of the world's population is infected with *Mtb*

Estimated TB disease incidence rates, 2023



Mycobacterium tuberculosis is an airborne pathogen



	SARS-CoV2	MTB
Transmission	Droplet > airborne	Airborne (droplet nuclei)
Droplet Size	>5-10 μm	<5 μm
Hang time	3 hours ?	6 hours
R0	2.2	<1 -4

<https://www.cdc.gov/tb/topic/basics/howtbspreads.htm>

<https://theunion.org/our-work/covid-19/covid-19-and-tb-frequently-asked-questions>

Likelihood of TB transmission increases with exposure time in an enclosed space



Who should undergo screening for LTBI?

- High-risk for **infection**
 - Close contacts of active TB patients
 - Immigrants from TB-endemic countries
 - IV drug use, unhoused
 - Selected healthcare providers (risk-based)
- High-risk for **progression**
 - Immunosuppression (HIV, medications)
 - Silicosis, chest imaging c/w prior TB disease

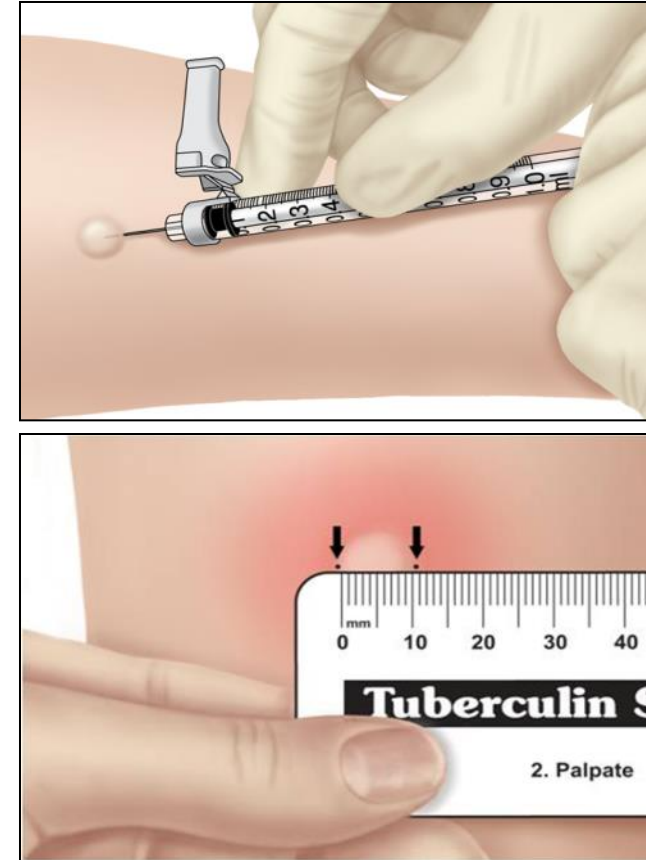
Risk of TB infection progression to TB disease

Condition	Relative Risk %	
Untreated HIV infection	9.6 - 9.9	 High risk Also includes: S/p transplant Leukemia Head and neck CA Silicosis
Close case contact	6.1	
Old TB on chest imaging	5.2	
Daily prednisone (>15mg)	2.8	
Chronic kidney disease	2.4	
Anti-TNF treatment	2.0	
Uncontrolled diabetes	1.7	 Moderate risk
Underweight	1.6	
Smoking	1.5	 Slight increased risk Also includes: Hx calcified granuloma
Normal host	1.0	
		 Low risk

Table adapted from Horsburgh, Rubin. NEJM, 2011 and Lobue, Menzies. Respiriology, 2011

Tuberculin Skin Test (TST)

- Intradermal injection purified protein derivate (PPD) – multiple TB antigens
- Sensitized inflammatory cells migrate to the site causing a delayed-type hypersensitivity reaction
- Read in 48-72 hours
 - Measure in millimeters – transverse diameter



TST positivity depends on probability of infection or progression to TB disease

- 0 mm: Immunocompromised high-risk close contacts
- 5 mm: HIV, close contacts of TB cases
- 10 mm: Other high-risk individuals (health workers)
- 15 mm: Everyone else

Bacillus Calmette-Guerin and TST

- BCG can cause positive TST
- Older age at BCG vaccination → more likely to have persistent positive TST
 - In 240,203 BCG-vaccinated infants, only 56/5639 (1%) were TST-positive if tested > or =10 years after BCG.
- Most positive TSTs represent TB infection even in vaccinated individuals
- Size matters – bigger TST reaction, more likely to be LTBI

Interferon gamma release assays (IGRAs)

- Measures sensitized immune response to TB antigens using stimulation of lymphocytes to produce interferon
- Two formats
 - ELISPOT (T-SPOT.TB)
 - ELISA (QuantiFERON-TB Gold)
- Similar sensitivity to TST
- No cross reaction with BCG so specificity is better



Interferon γ release assays (IGRAs)

- Advantages (over TST)
 - Testing can be completed in a single visit
 - Not subjective
 - No interference from previous BCG vaccination
- Disadvantages
 - Cost
 - Availability
 - Logistics
 - Variable serial test results in low-risk individuals
- Current CDC recommendation is that IGRA can be used in all settings where TST is currently used

What is the clinical definition of latent TB?

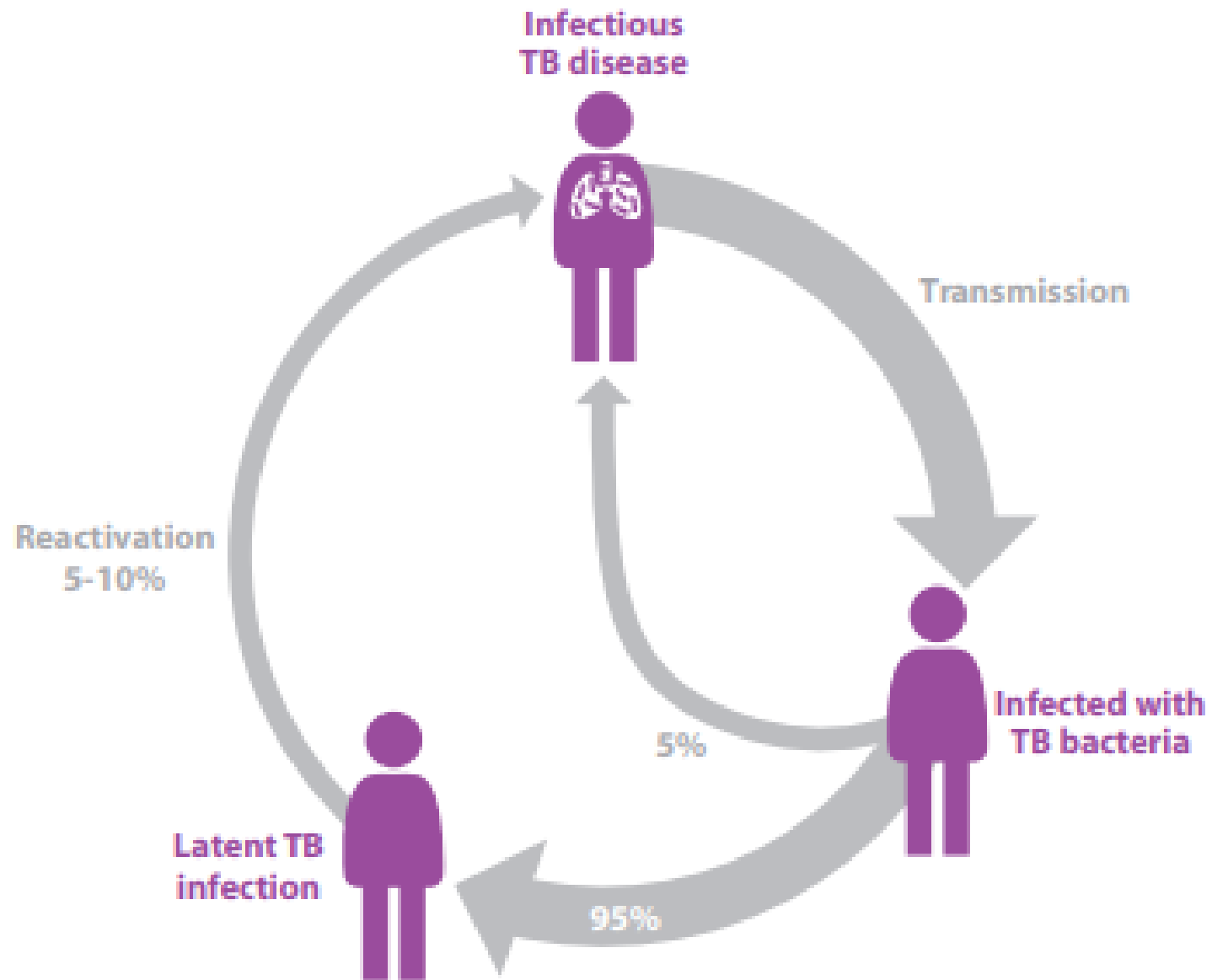
1. Positive TB screening test

- TST or IGRA (T-SPOT or QuantiFERON)

2. Absence of clinical features concerning for TB disease

- No symptoms (fever, cough, weight loss)
- Microbiology without evidence of *Mtb*
- Absence of active inflammatory process in pulmonary parenchyma on chest imaging
 - Calcified granuloma or scarring okay

The TB Cycle



Treatment options for LTBI

Priority Rank	Regimen	Duration	Interval
Preferred	Isoniazid + rifapentine (3HP)	3 months	Once weekly, directly observed
Preferred	Rifampin (4R)	4 months	Daily
Preferred	Isoniazid + rifampin (3HR)	3 months	Daily
Alternative	Isoniazid (9H)	9 months	Daily
Alternative	Isoniazid (6H)	6 months	Daily

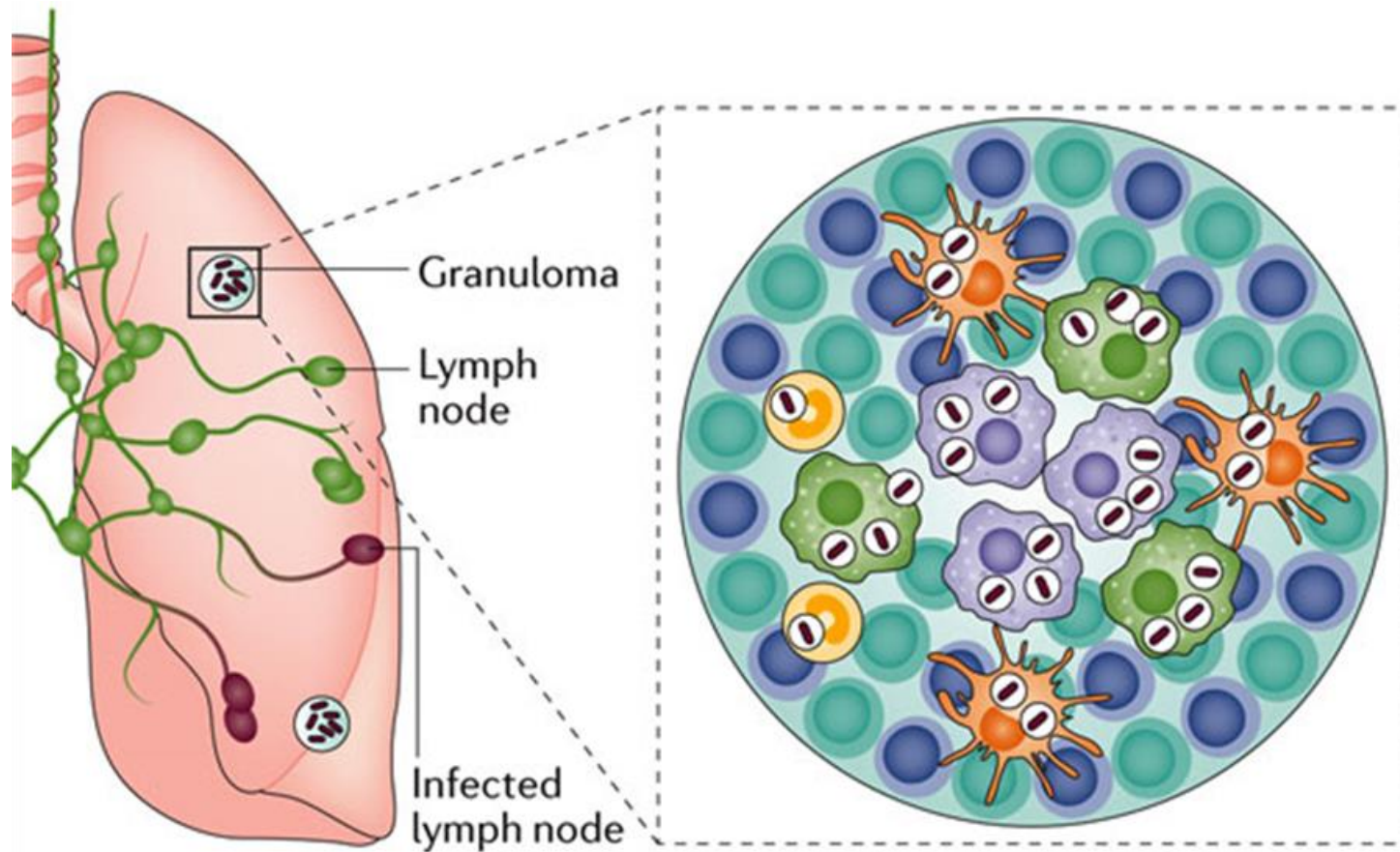
Side effects of LTBI treatment

- Isoniazid
 - Hepatitis (increases with age)
 - Peripheral neuropathy (prevented with vitamin B6)
- Rifampin
 - Orange-colored secretions
 - Gastrointestinal intolerance
 - Drug-drug interactions
 - Nitrosamines

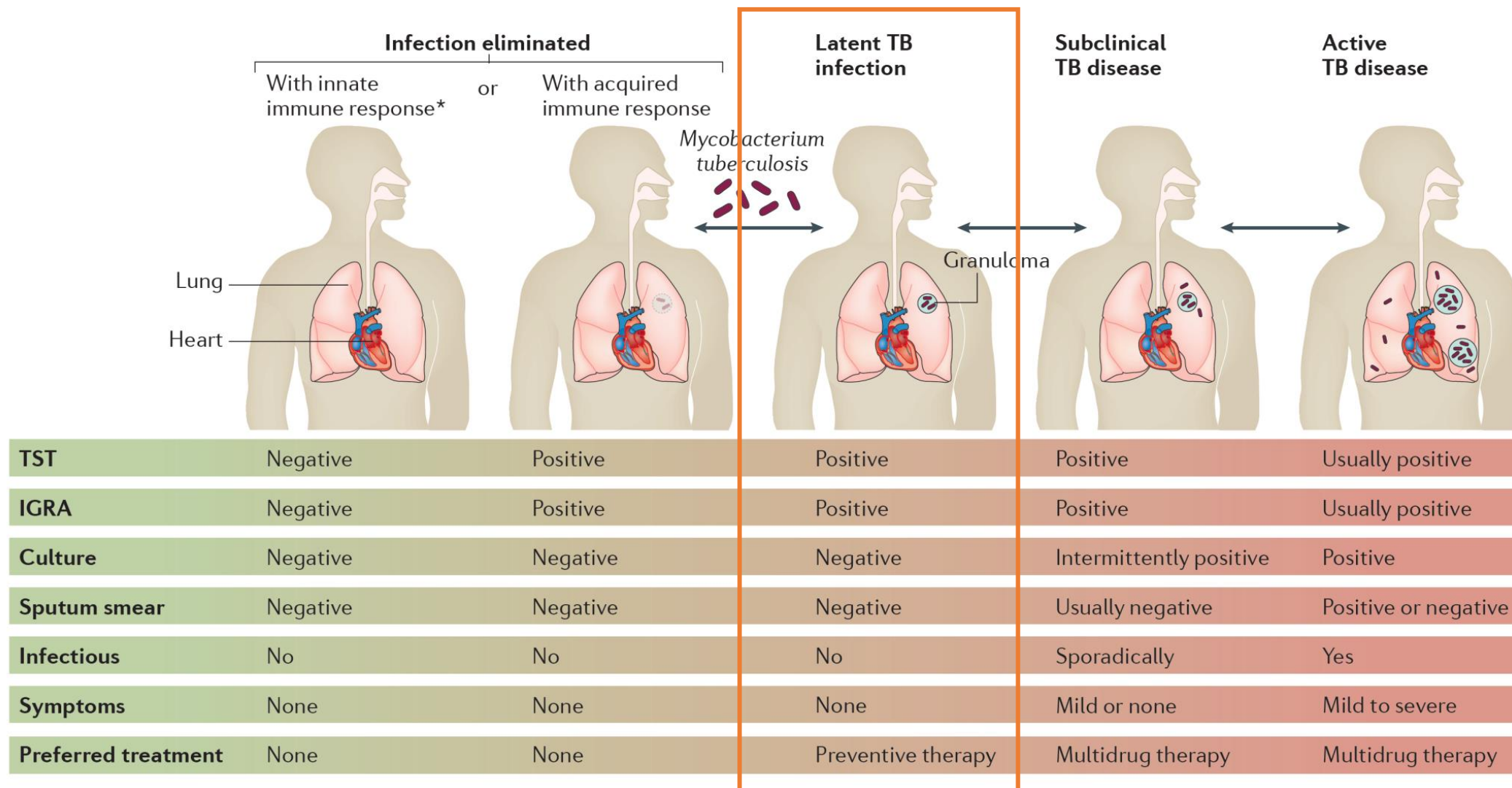
Risk/benefit for LTBI testing and treatment

Age	Risk of INH hepatotoxicity	High risk LTBI	Moderate risk LTBI	Slight increased risk LTBI	Low risk LTBI
>65	>5%	Test and treat	Defer	Defer	Defer
50-65	3-5%	Test and treat	Test and treat	Defer	Defer
<50	<3%	Test and treat	Test and treat	Test and treat	Defer
<35	<1%	Test and treat	Test and treat	Test and treat	Test and treat

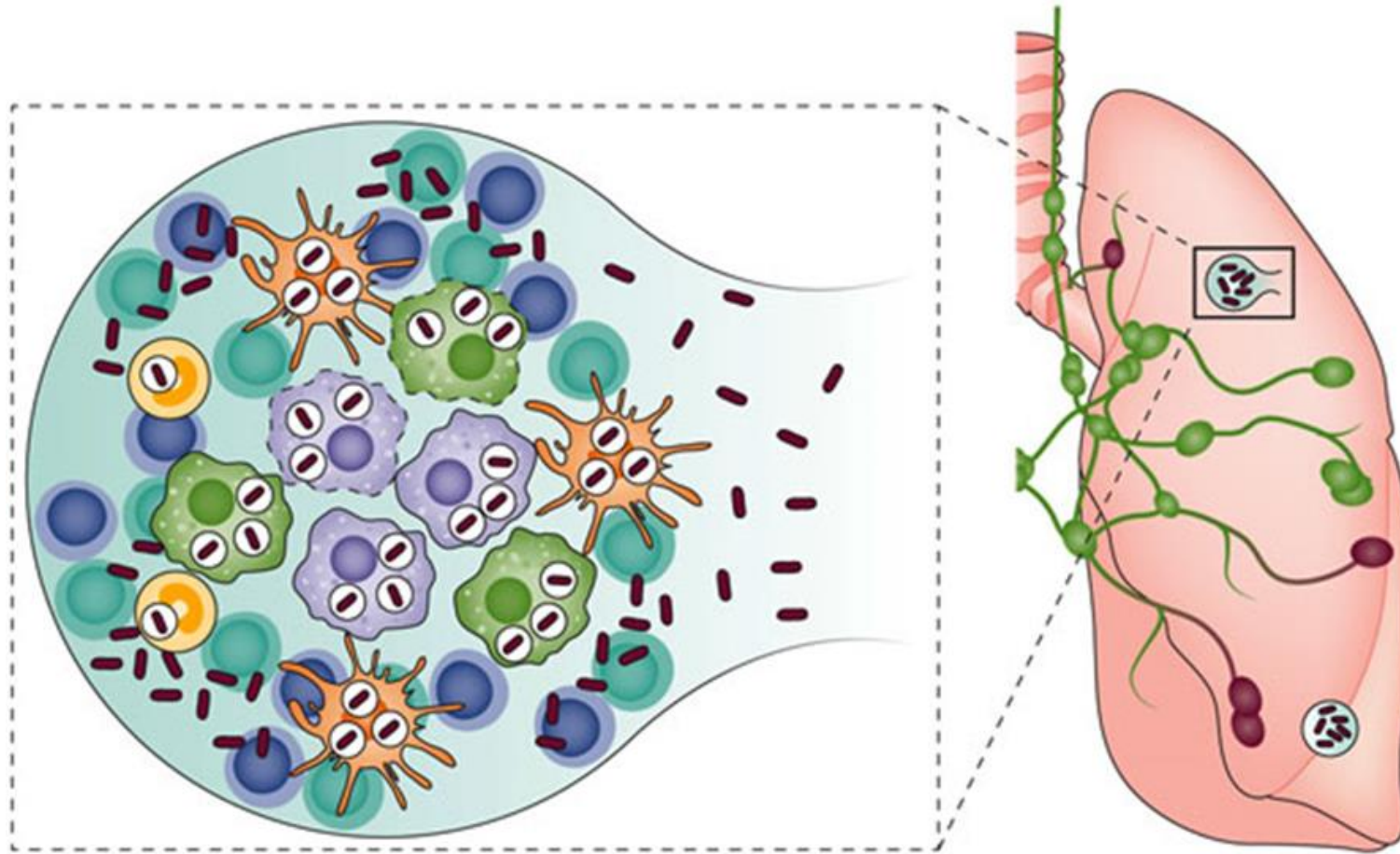
Latent tuberculosis is a dynamic balance between pathogen and host immune system



The spectrum of TB



Unbalancing of host/pathogen interaction leads to TB disease



Case

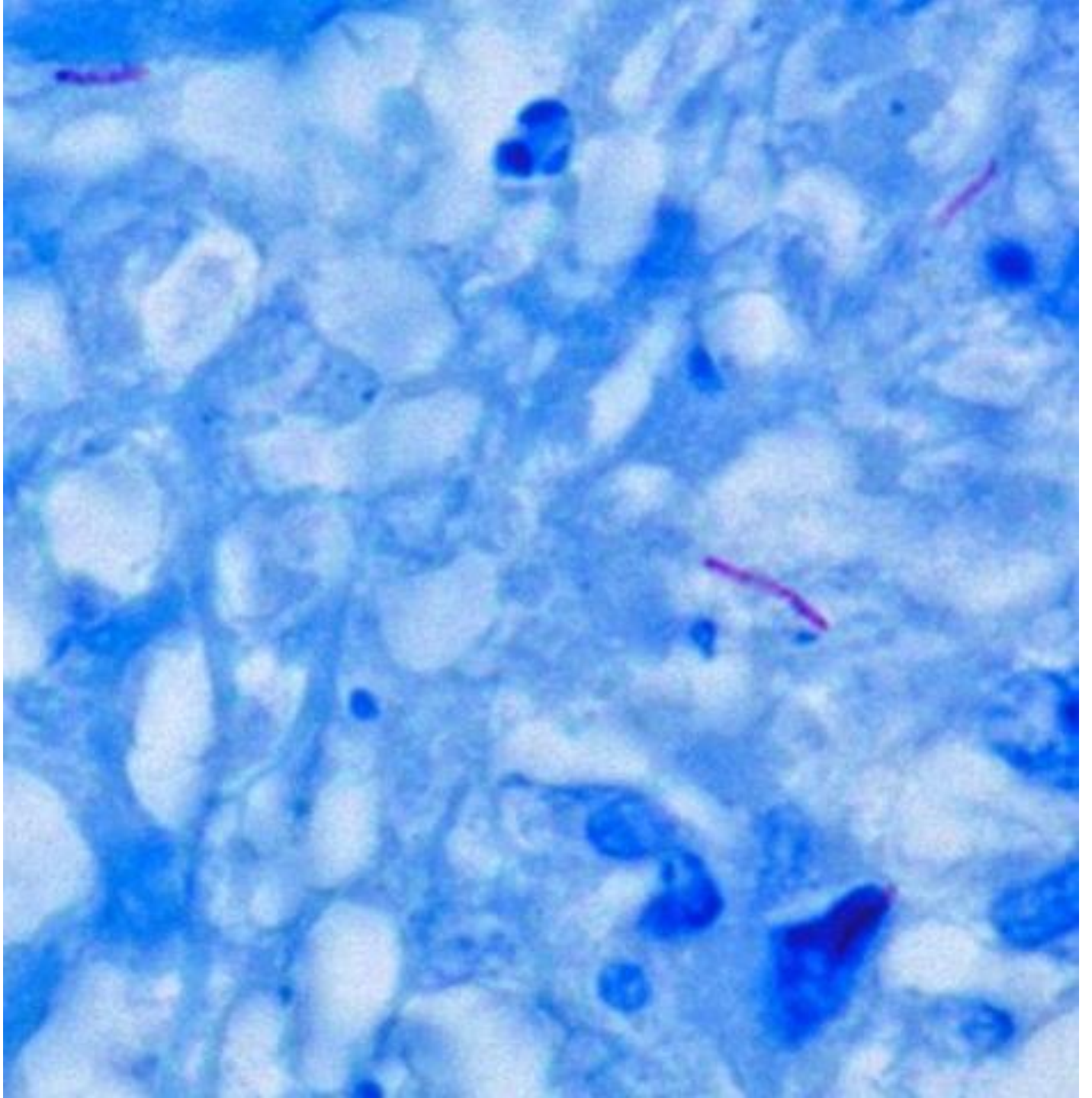
- 29-year-old man who recently immigrated from India, working in biomedical research in Boston
- Healthy
- Non-smoker
- Occupational health screening: IGRA positive
- Chest CT with bilateral nodular opacities

ATS/IDSA/CDC evaluation of TB disease

- If pulmonary TB suspected:
 - Three sputum specimens strongly recommended to improve sensitivity
 - Smear microscopy for acid-fast bacilli (AFB) should be performed
 - Both solid and liquid AFB cultures for every specimen
 - Nucleic acid amplification testing (NAAT) should be done on the initial respiratory specimen

Smear microscopy

- Stain for AFB
- Technology circa 1880
- Widely available
- Positive in advanced TB
- Nonspecific



Mycobacterial culture

- Gold standard
- (but culture-negative TB possible)
- Slow results
 - Liquid: 7-12 days
 - Solid: weeks
- Need sophisticated lab

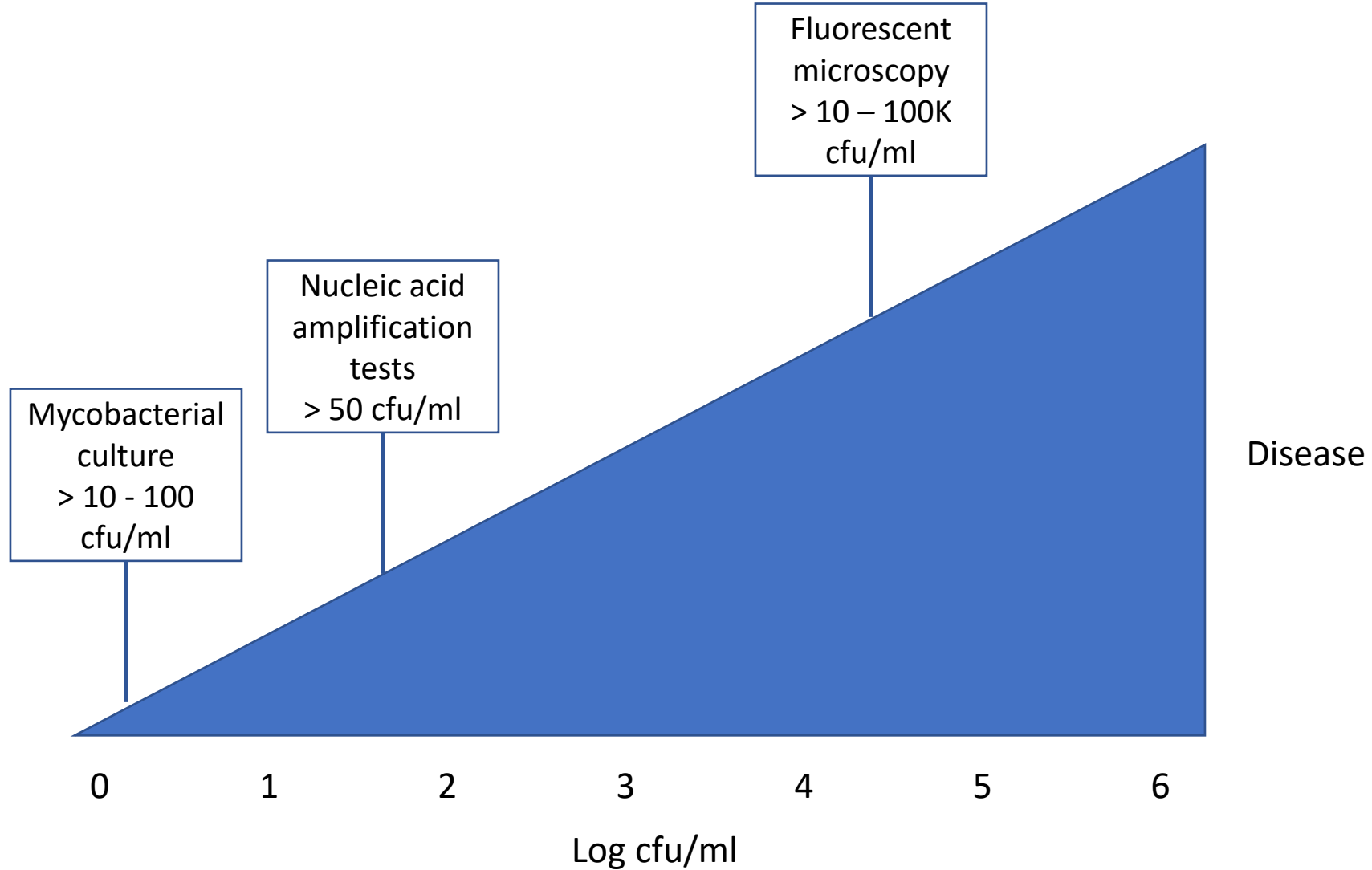


Nucleic acid amplification tests (NAAT)

- Rapid
- Automated
- High sensitivity detection of *Mtb*
- Simultaneous drug susceptibility testing (limited drugs)



Sensitivity (cfu/ml) of TB diagnostics



WHO case definitions - diagnostic confidence

Bacteriologically confirmed - a biological specimen is positive by smear microscopy, mycobacterial culture or WHO-approved rapid nucleic acid amplification test (such as Xpert MTB/RIF)

Clinically diagnosed - does not fulfill the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment

Includes:

- cases diagnosed based on chest radiology abnormalities
- suggestive histology
- extrapulmonary cases without bacteriological confirmation

“Short course” first-line TB therapy

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Isoniazid (H)						
Rifampin (R)						
Pyrazinamide (Z)						
Ethambutol (E)						

2HREZ/4HR

Entirely oral regimen

Cost < \$20

For drug-sensitive disease, cure >95%

Pregnancy category C

Average mutation rate in *M. tuberculosis*

Drug resistance mutation	Mutation Rate
Isoniazid	2.56×10^{-8} mutations per bacterium per generation
Rifampicin	2.25×10^{-10} mutations per bacterium per generation
Ethambutol	1.0×10^{-7} mutations per bacterium per generation
Streptomycin	2.95×10^{-8} mutations per bacterium per generation
Isoniazid + rifampicin	$2.56 \times 10^{-8} \times 2.25 \times 10^{-10} = 5.76 \times 10^{-18}$ mutations per bacterium per generation

Pulmonary cavities contain about 10^7 to 10^9 bacilli; thus, they are likely to contain bacilli resistant to each of the anti-tuberculosis drugs but unlikely to contain bacilli resistant to two drugs simultaneously.

Multidrug resistance

- Defined as resistance to isoniazid and rifampin
- Treatment is arduous; requires expert consultation
 - Regimens composition depends on drug susceptibility testing results and ability to tolerate agents
 - Bedaquiline, pretomanid, linezolid (BPaL) plus/minus moxifloxacin for six to nine months has emerged as an effective regimen

Public health considerations

- Pulmonary TB disease is transmissible
 - Frequency of transmission is roughly proportional to the burden of organisms in expectorated sputum
 - Positive smear microscopy = infectious
- Transmission is largely restricted to contacts of smear positive patients
 - All cases should be reported → contacts screened for TB
- **Effective treatment rapidly decreases infectiousness**
 - Release from community isolation after five days of therapy

Question 1

- Which of the following are acceptable treatments for latent tuberculosis infection
 - a. Isoniazid and vitamin B6 daily for 5 months
 - b. Rifampin daily for 4 months
 - c. Isoniazid and rifapentine and B6 daily for 12 weeks
 - d. All of the above
 - e. None of the above

Question 1

Which of the following are acceptable treatments for latent tuberculosis infection

- a. Isoniazid and vitamin B6 daily for 9 months
- b. Rifampin daily for 4 months**
- c. Isoniazid and rifapentine and B6 weekly for 12 weeks
- d. All of the above
- e. None of the above

Question 2

Which of the following is true of treatment for active tuberculosis

- a. Treatment should be initiated after the results of antibiotic sensitivity tests are available
- b. Pregnant women should not receive isoniazid
- c. Antibiotic choice or duration should be altered in the presence of drug resistance
- d. Antibiotic resistance is found only in those previously treated with drugs
- e. All of the above

Question 2

- Which of the following is true of treatment for active tuberculosis
 - a. Treatment should be initiated before the results of antibiotic sensitivity tests are available
 - b. Pregnant women may receive isoniazid
 - c. **Antibiotic choice or duration should be altered in the presence of drug resistance**
 - d. Antibiotic resistance is found not only in those previously treated with drugs
 - e. All of the above

Take home points

- LTBI is defined as 1) positive TST or IGRA and 2) the absence of TB disease
- Rifampin x four months is the preferred treatment for LTBI
- Pulmonary TB should be evaluated by microscopy, culture and nucleic acid amplification of respiratory secretions
- Treatment of TB disease requires regimens composed of multiple effective antibiotics

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