Brigham and Women's Hospital
Founding Member, Mass General Brigham

Tuberculosis for the Non-ID Specialist

Dylan Tierney, MD, MPH

Associate Physician
Division of Infectious Diseases
Division of Global Health Equity
Department of Medicine
Brigham and Women's Hospital

Instructor in Medicine
Harvard Medical School

Dylan Tierney, MD, MPH

- Medical School @Virginia Commonwealth
- Internal Medicine Residency @MGH
- Infectious Diseases Fellowship @MGH/BWH
- Instructor in Medicine @HMS
  - Clinical focus: General infectious diseases, TB
  - Research focus: TB transmission, TB care quality improvement
- Associate Medical Director @ Bureau of Infectious Disease and Laboratory Sciences, Massachusetts Department of Public Health

Disclosures

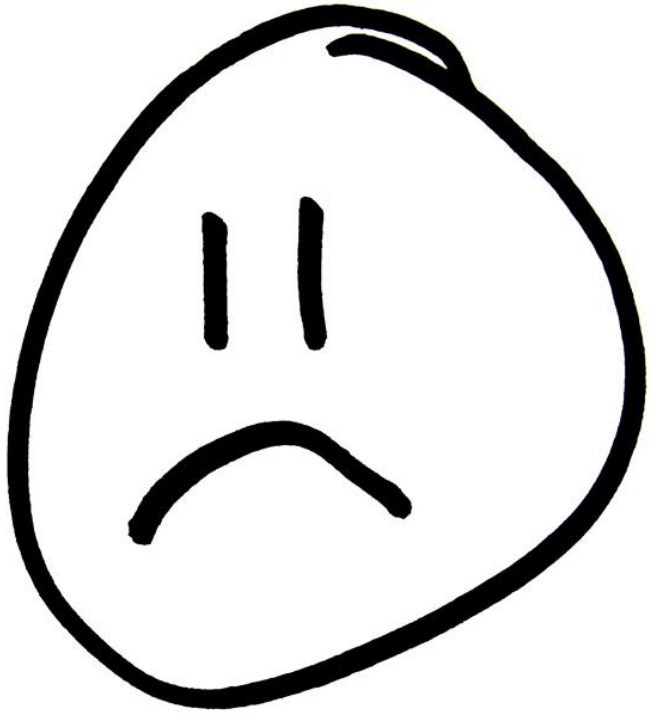
Stockholder

- Seres
- Compugen
- Renovaro

Objectives

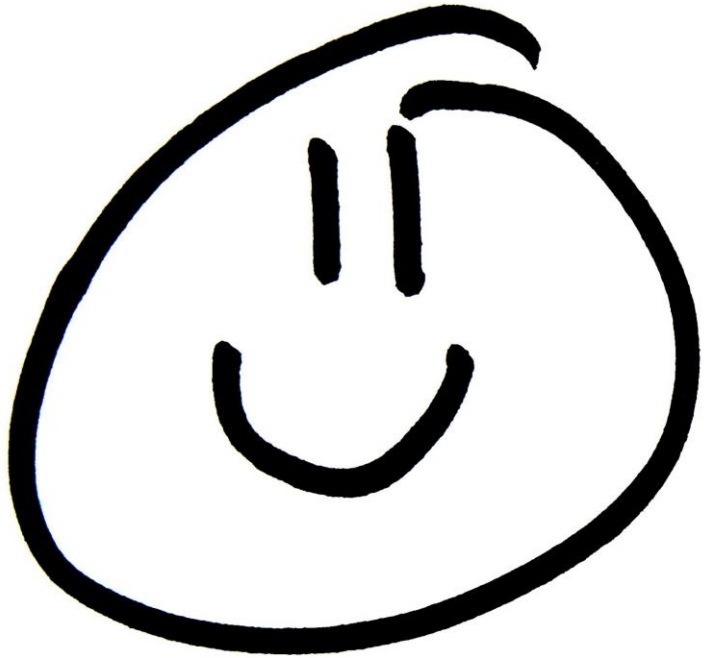
- Understand clinical spectrum of tuberculosis (TB) including latent TB infection (LTBI) and TB disease
- Review diagnostic approaches for LTBI
- Review treatment of LTBI
- Review diagnostic approaches for TB disease
- Review management of TB disease

Tuberculosis Disease



- Sick
- Infectious

Latent Tuberculosis Infection (LTBI)



- Asymptomatic
- Non-infectious

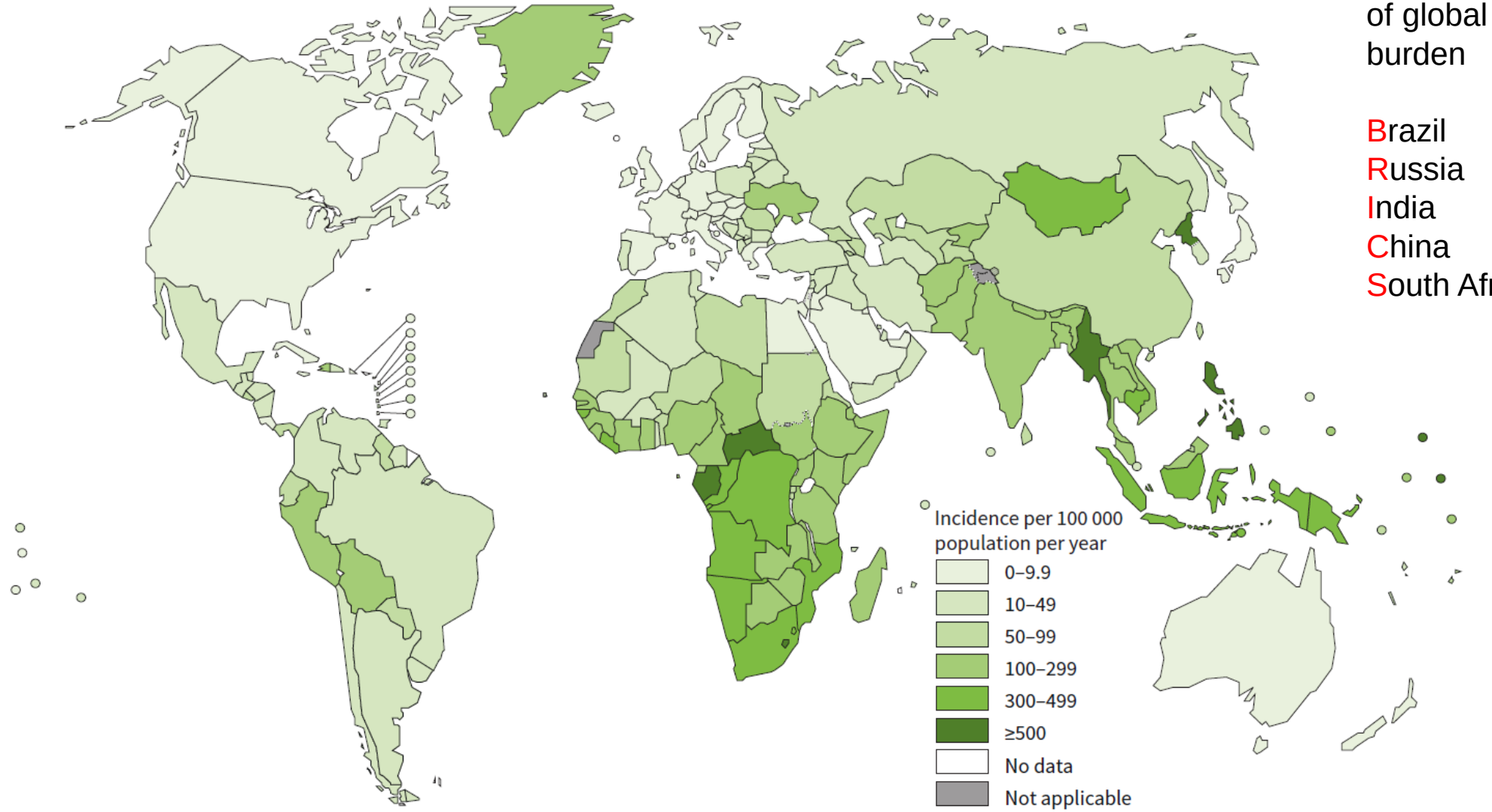
TB – world's leading infectious disease killer

- ~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*

WHO Global Tuberculosis Report 2024

Estimated TB disease incidence rates, 2023

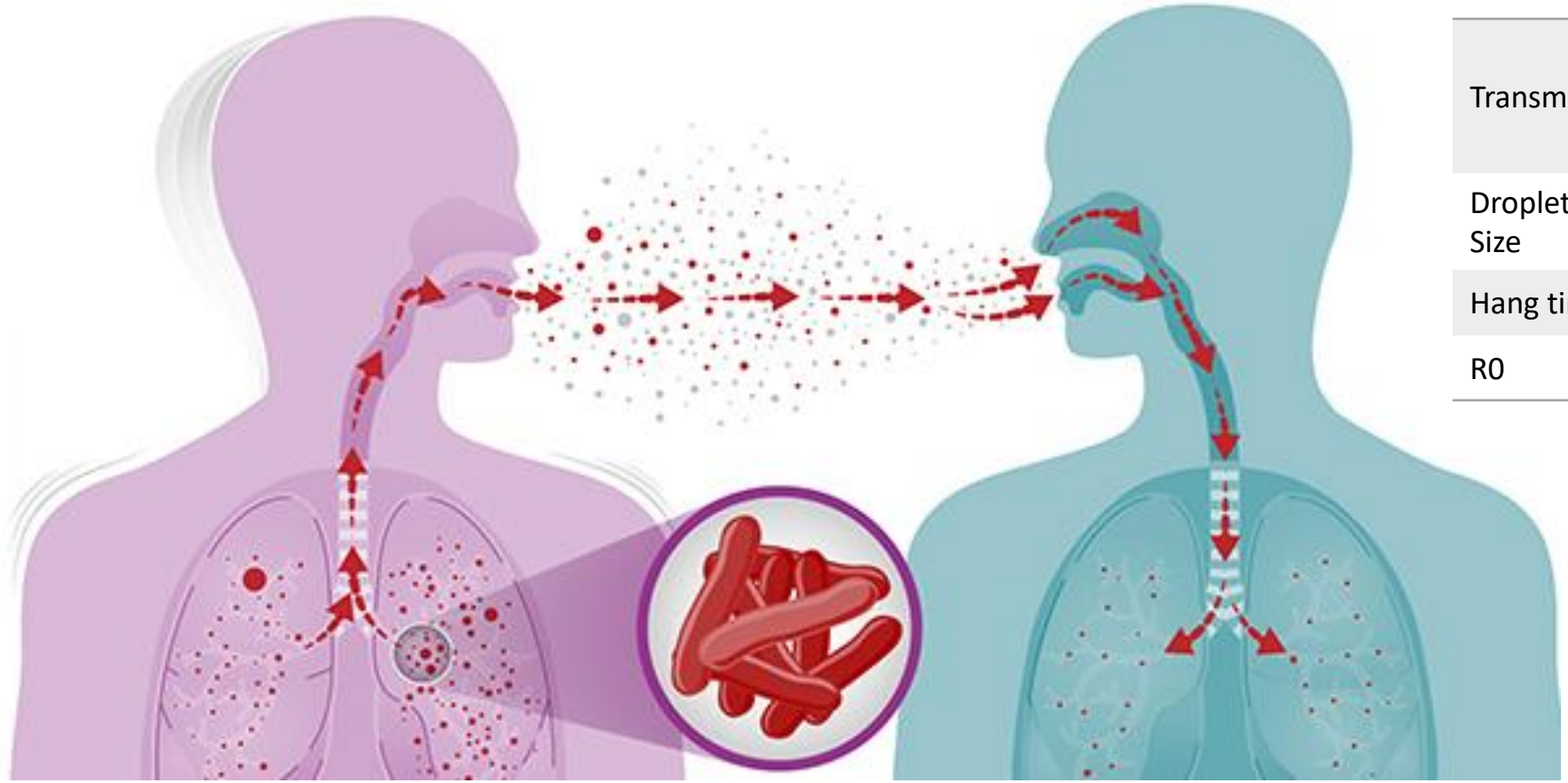


BRICS = 49% of global TB burden

Brazil
Russia
India
China
South Africa

WHO Global Tuberculosis Report 2024

Mycobacterium tuberculosis is an airborne pathogen



	SARS-CoV2	MTB
Transmission	Droplet > airborne	Airborne (droplet nuclei)
Droplet Size	>5-10 µm	<5µm
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

Sosa LE et al. *Morb Mortal Wkly Rep*. 2019;68:439–443

Risk of TB infection progression to TB disease

Condition	Relative Risk %
Untreated HIV infection	9.6 - 9.9
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
Underweight	1.6
Smoking	1.5
Normal host	1.0

High risk
Also includes:
S/p transplant
Leukemia
Head and neck CA
Silicosis

Moderate risk

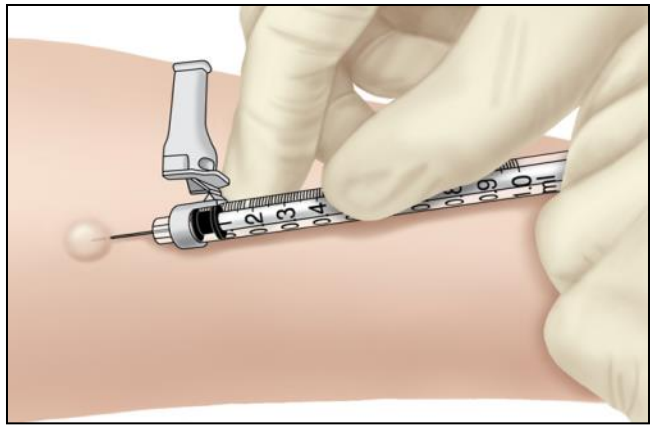
Slight increased risk
Also includes:
Hx calcified granuloma

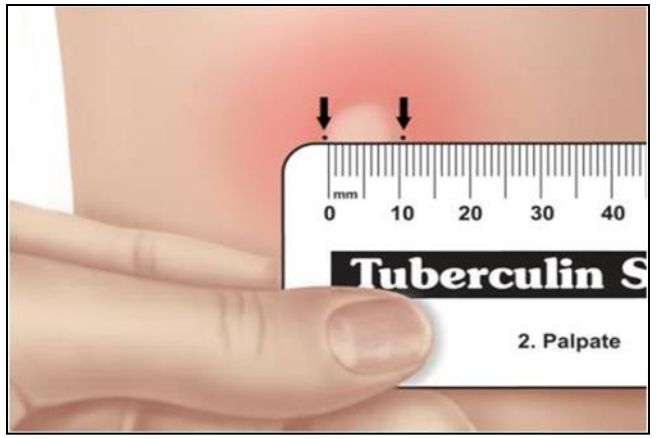
Low risk

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





http://www.cdc.gov/tb/publications/slidesets/LTBI/default.htm

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

Farhat M et al. *IJTLD*. 2006;10(11):1192-204

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

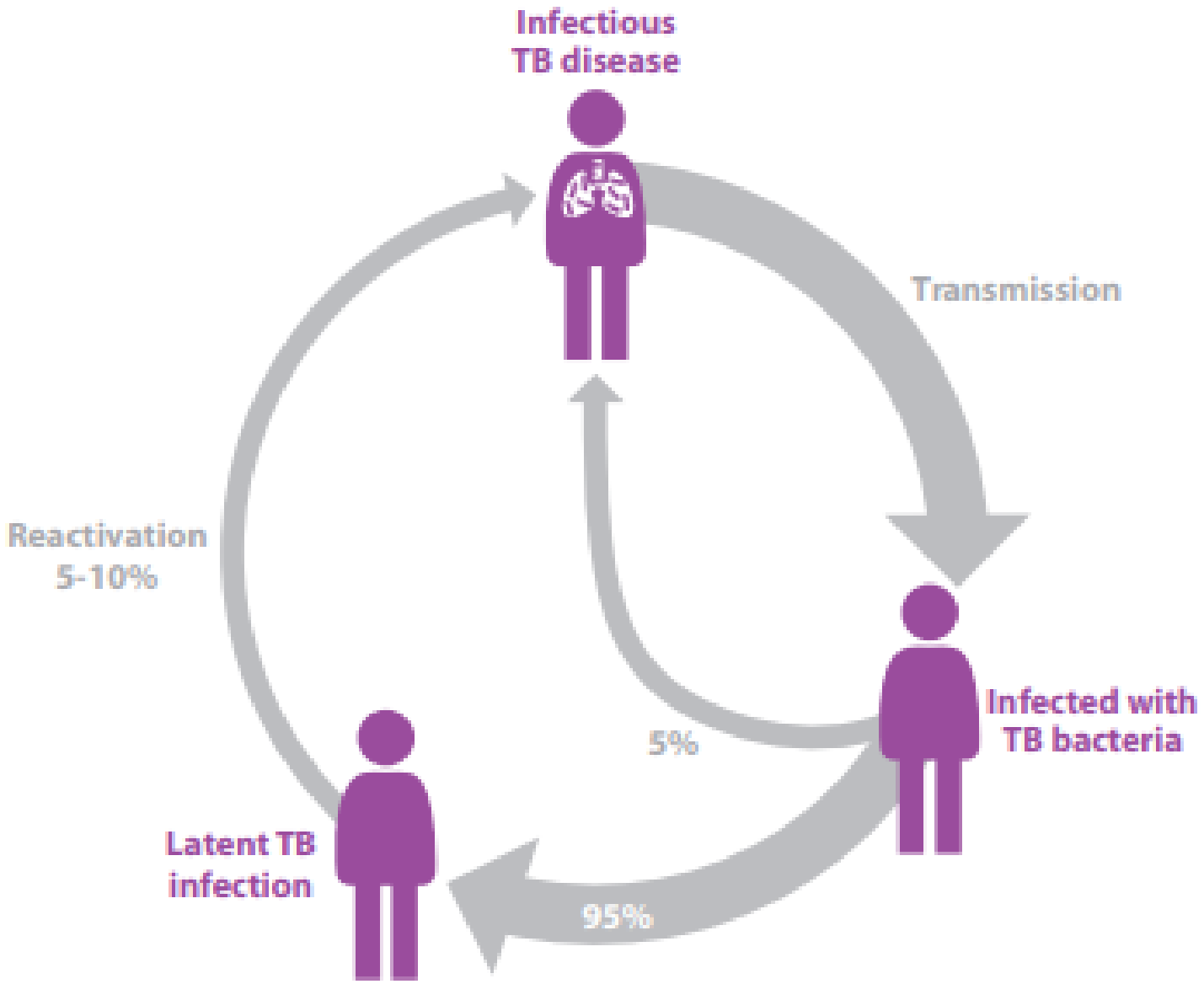
Interferon γ release assays (IGRAs)

- 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


Infectious
TB disease
Transmission
Infected with
TB bacteria
5%
95%
Latent TB
infection
Reactivation
5-10%

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

Sterling TR et al. *Morb Mortal Wkly Rep*. 2020 Feb 14;69(1):1–11

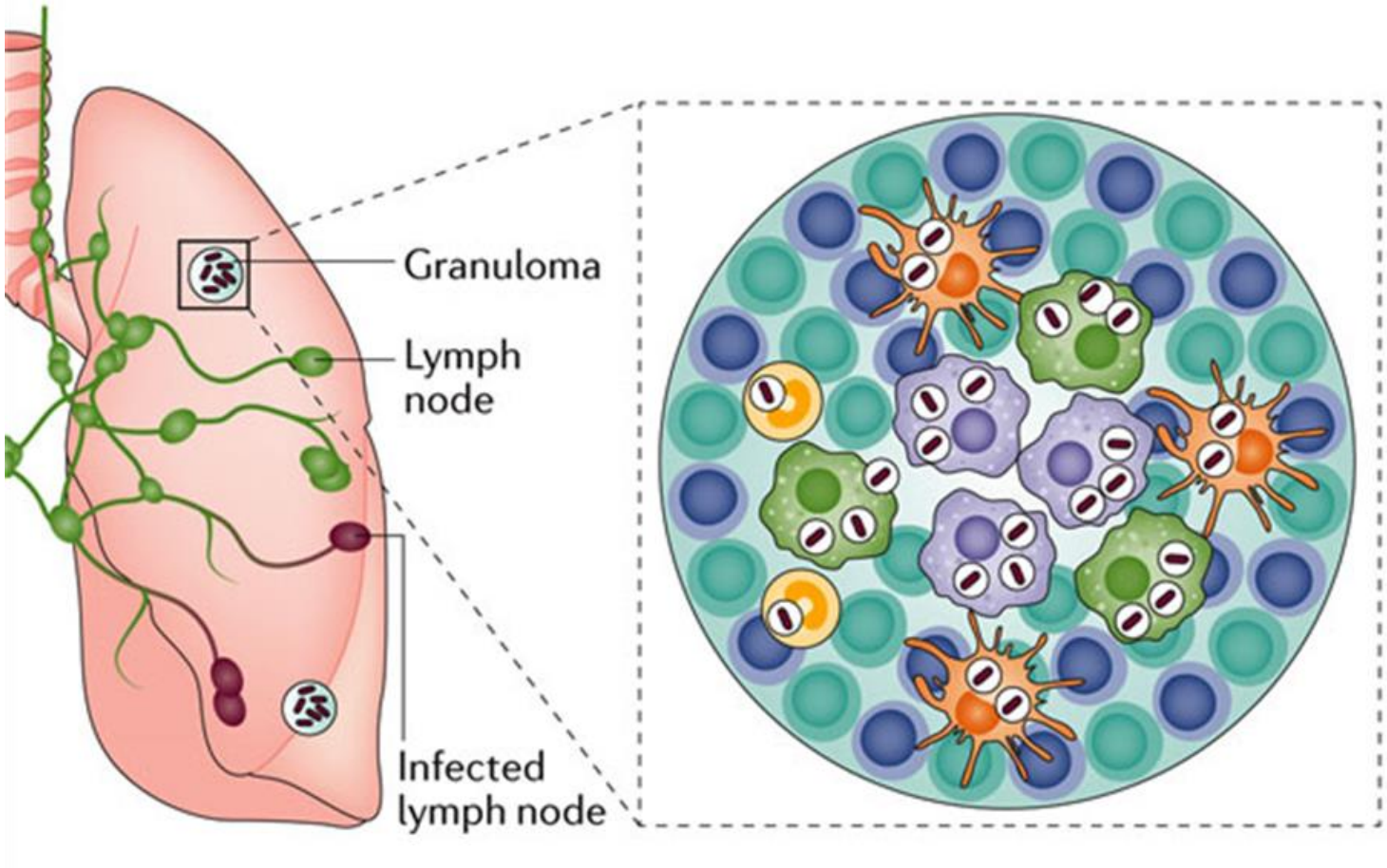
Side effects of LTBI treatment

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

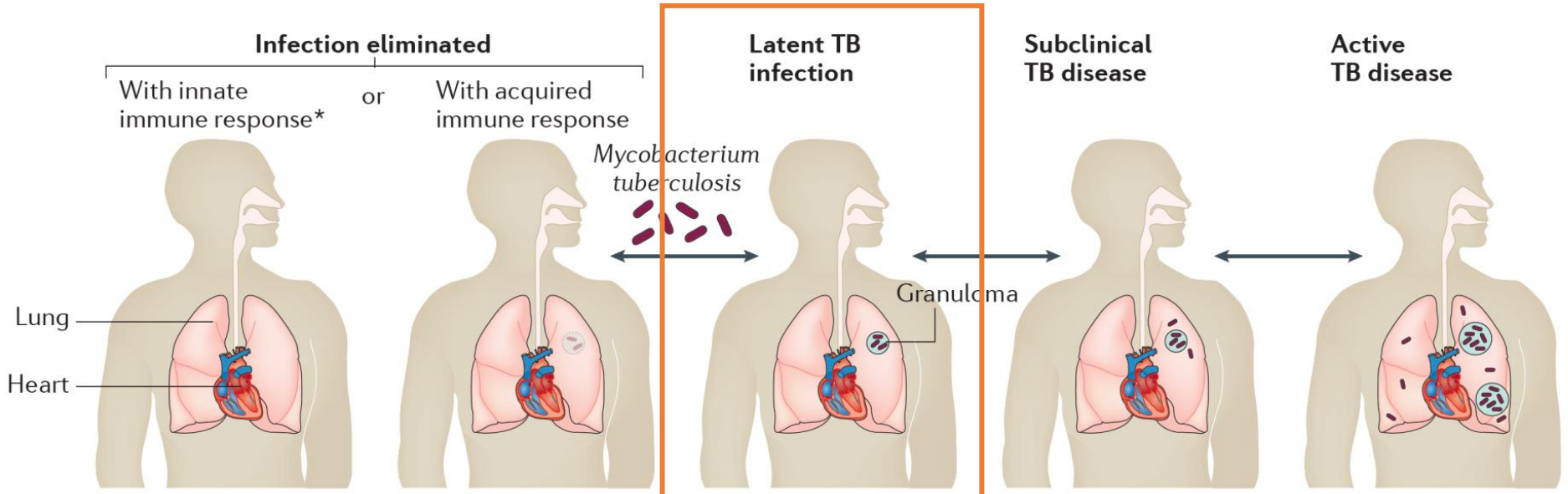
Risk/benefit for LTBI testing and treatment

Age	Risk of INH hepatotoxity	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



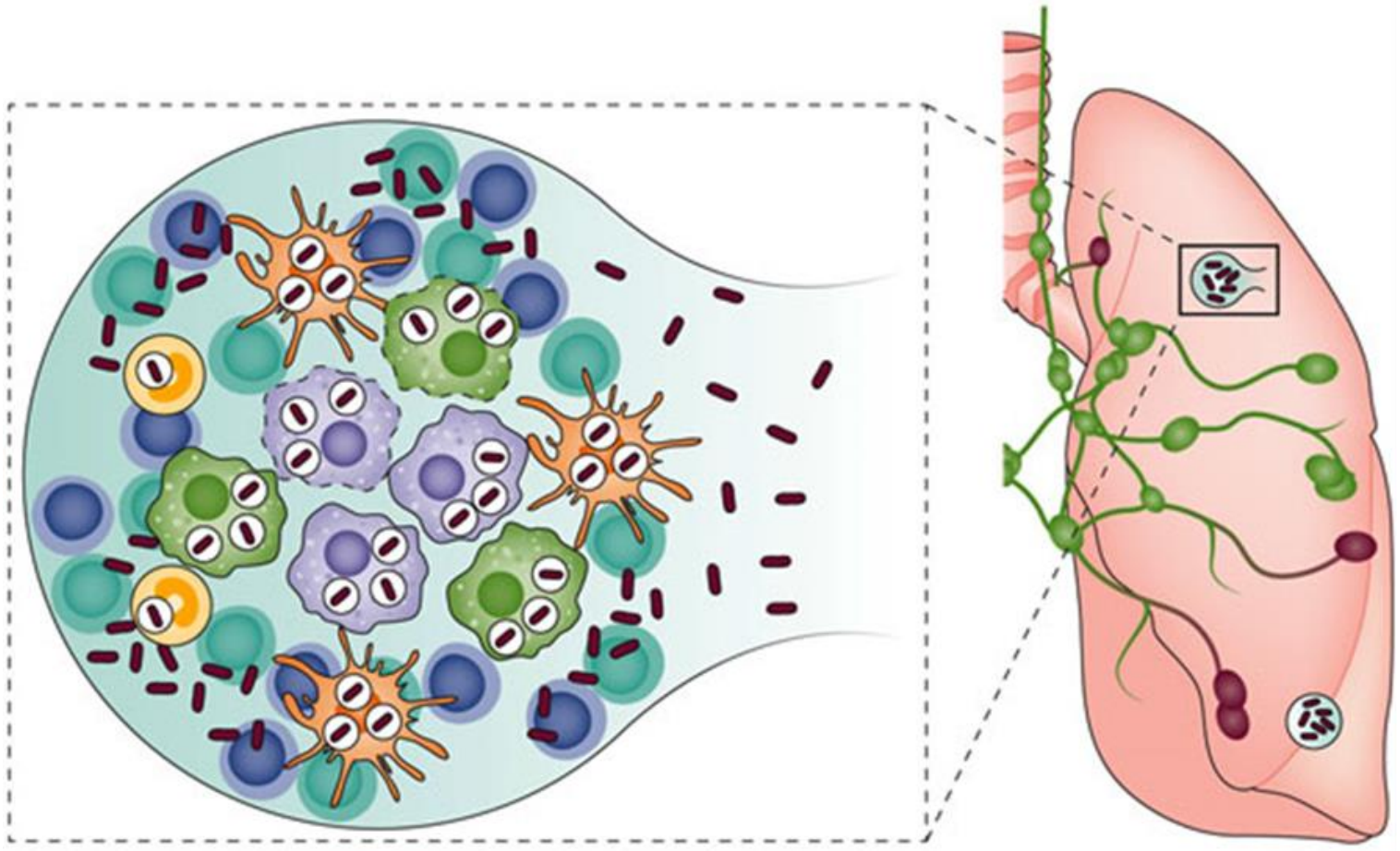
The spectrum of TB



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 et al. Nature Rev, 2016

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

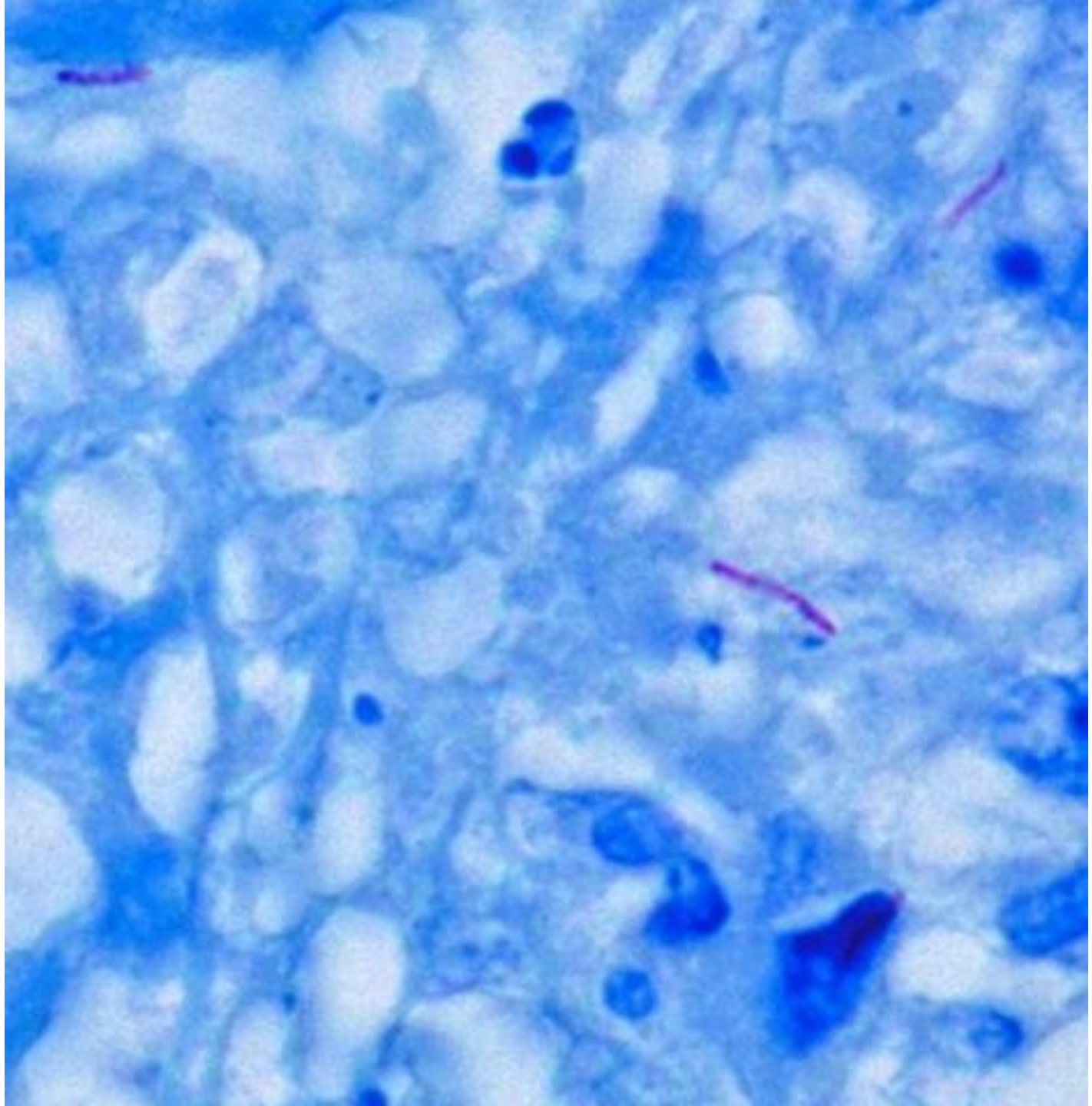
ATS/IDSA/CDC evaluation of TB disease

- 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

Lewinsohn DM et al. *Clin Infect Dis*. 2017;64(2):e1–e33

Smear microscopy

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



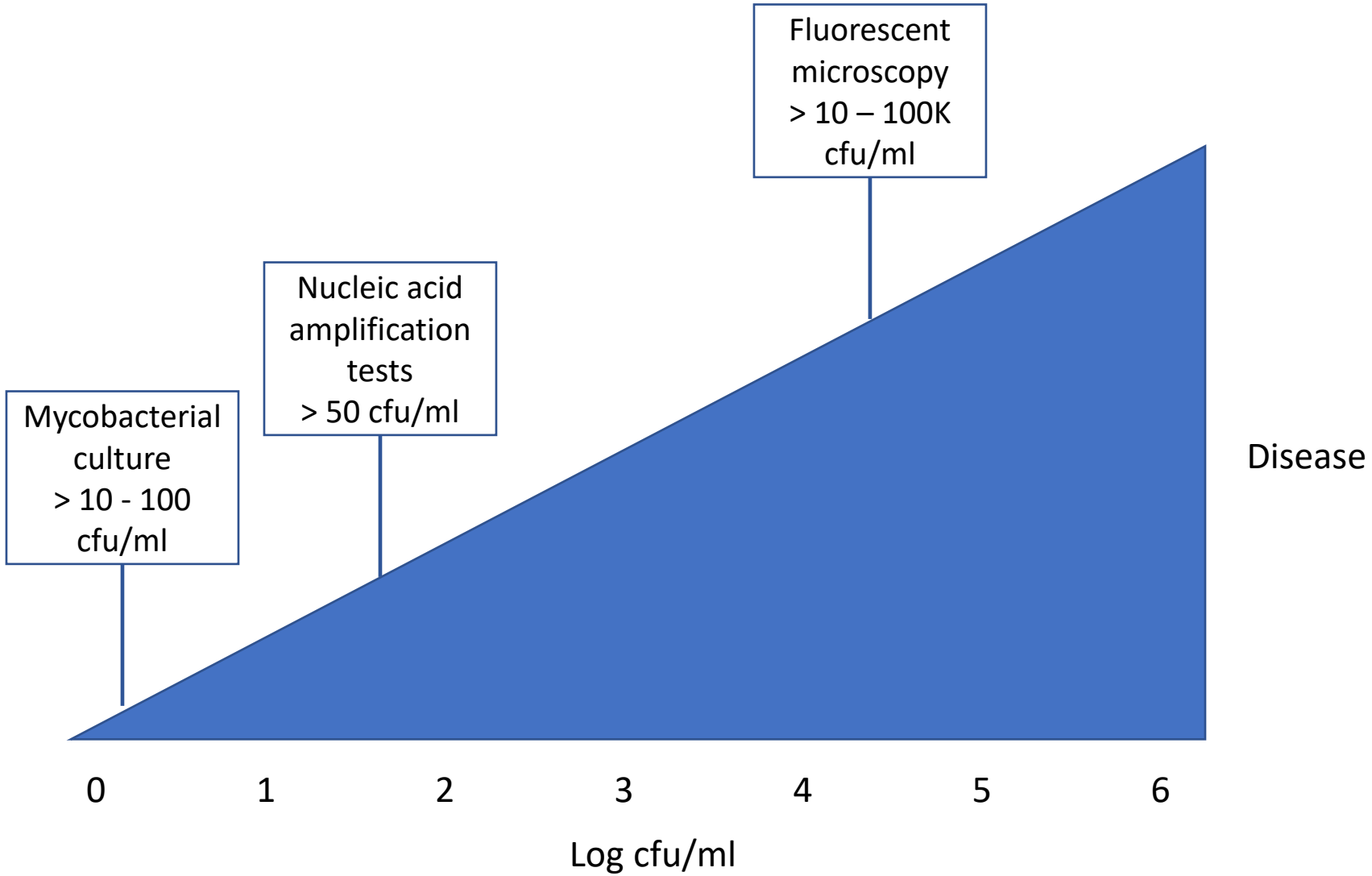
Mycobacterial culture

- 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

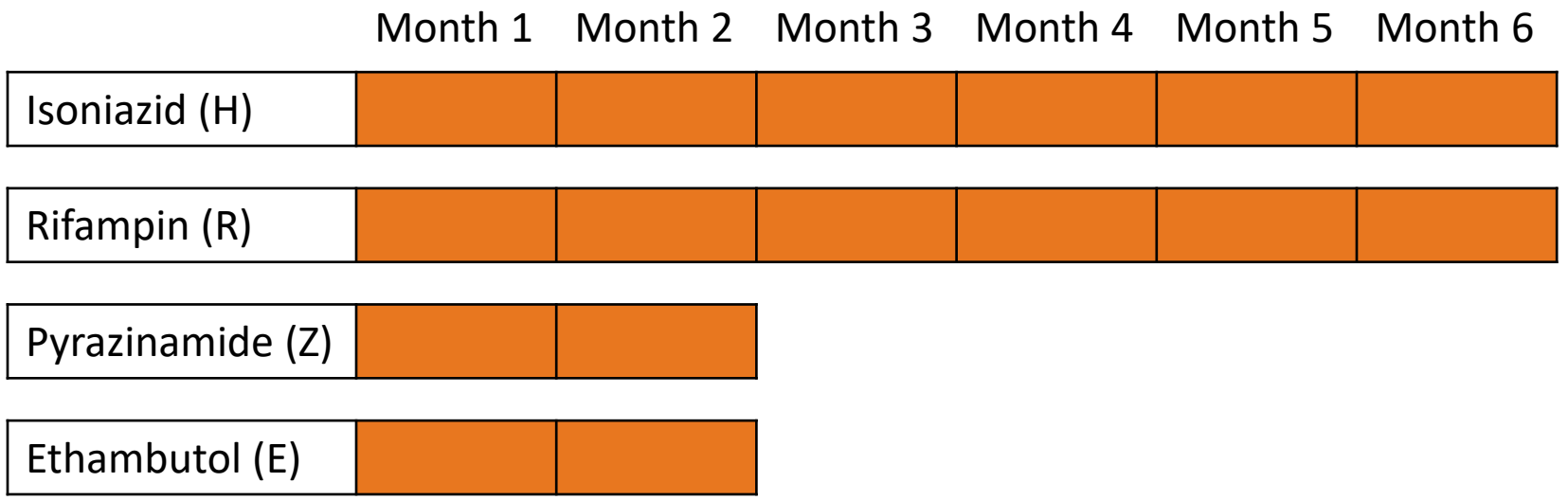
Bacteriologically confirmed - a biological specimen is positive by smear microscopy, mycobacterial culture or WHO-approved rapid nucleic acid amplification test (such as Xpert MTB/RIF)

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



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	$2.56*10^{-8}$ X $2.25*10^{-10}$ = **$5.76*10^{-18}$ 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

Shah M et al. *Clin Infect Dis*. 2024; Apr 18:ciae199. doi: 10.1093/cid/ciae199

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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