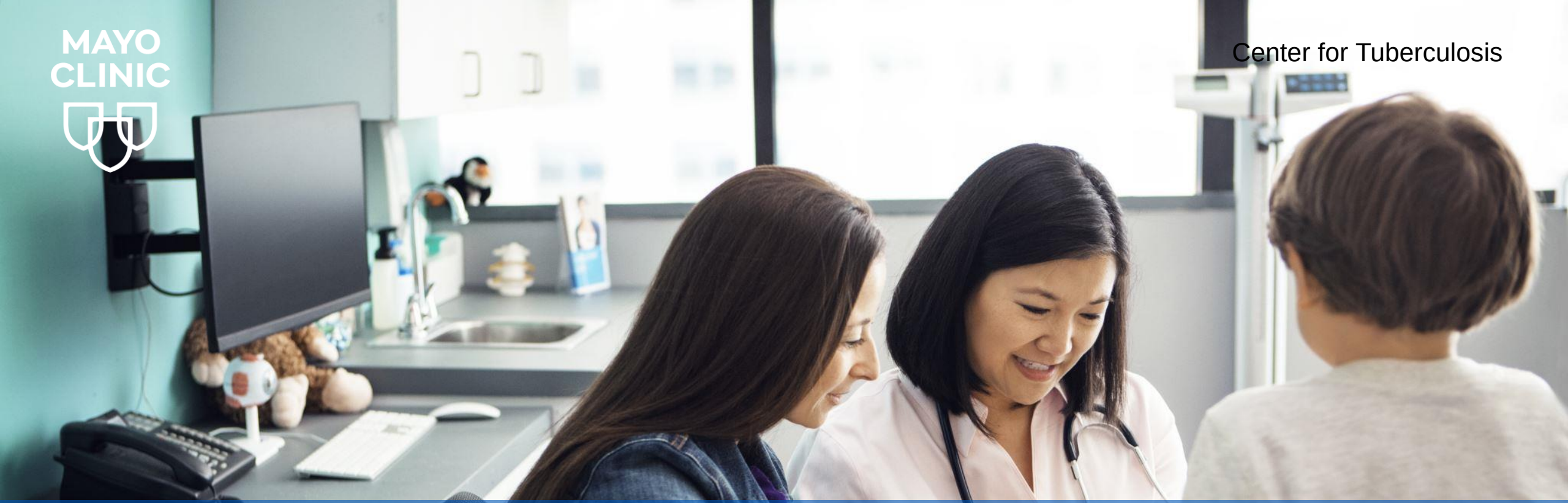

MAYO CLINIC

Center for Tuberculosis

Latent Tuberculosis Infection

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Principal Investigator, Mayo Clinic center for Tuberculosis

Disclosures

NO RELEVANT FINANCIAL CONFLICTS OF INTEREST TO DISCLOSE

Learning Objectives

Define LTBI

Describe the burden of LTBI and its importance

Identify components of nurse case management for LTBI

- Identify individuals who would benefit from testing and treating for latent infection
- Prescribe and interpret diagnostic tests for LTBI and discuss their differences
- Describe the current treatment options
- Monitor patients on LTBI treatment

What is LTBI?

Tuberculosis Terminology

Tuberculosis infection

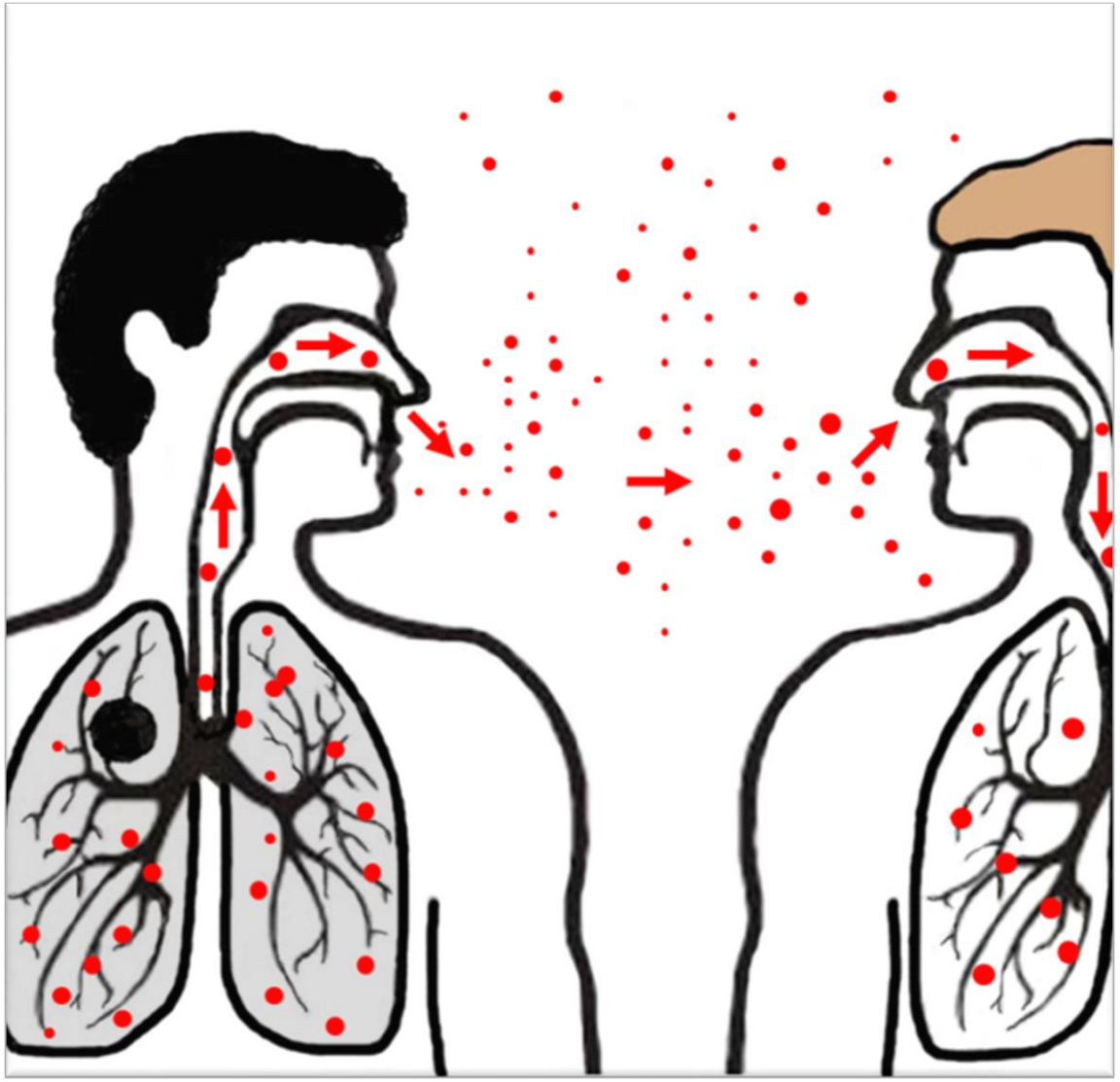
Latent tuberculosis infection

Latent tuberculosis

Am J Respir Crit Care Med. 2021 Mar 30;204(2):142–148.

TB is spread person to person through the air via droplet nuclei

- Exposure: An infectious person
  - Coughs
  - Sneezes
  - Speaks
  - Sings
- Transmission occurs when another person inhales droplet nuclei



Factors affecting transmission

Susceptibility of exposed person

Infectiousness of patient

- Cavitation
- Smear positive
- Laryngeal

Environment

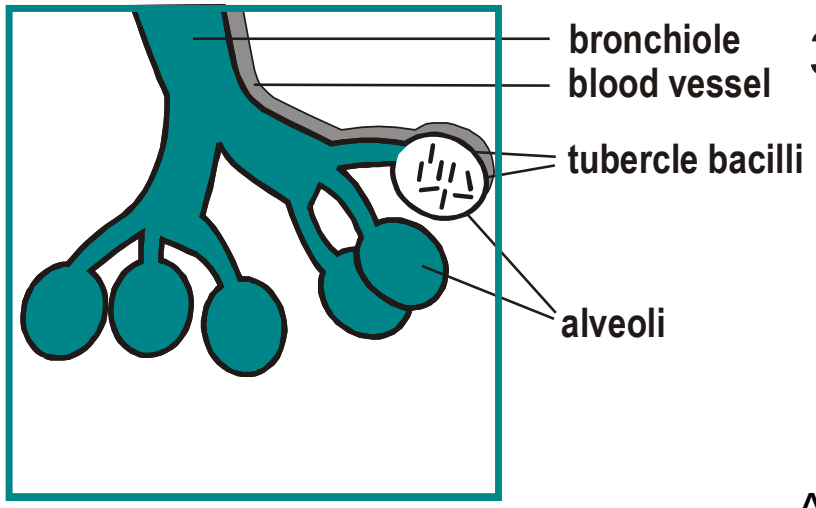
- Small enclosed spaces
- Poor ventilation

Proximity, frequency and duration of exposure

1

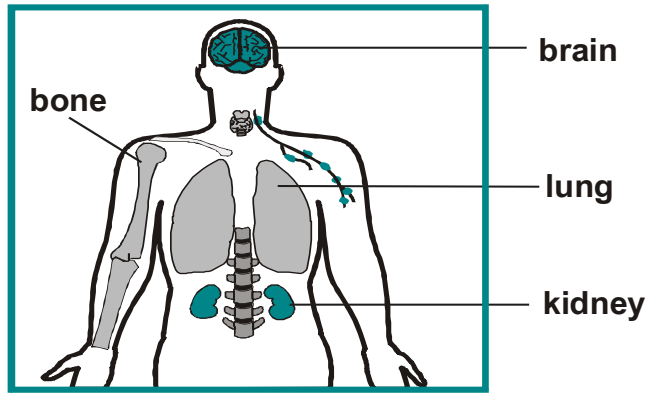
Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to the small alveoli

2



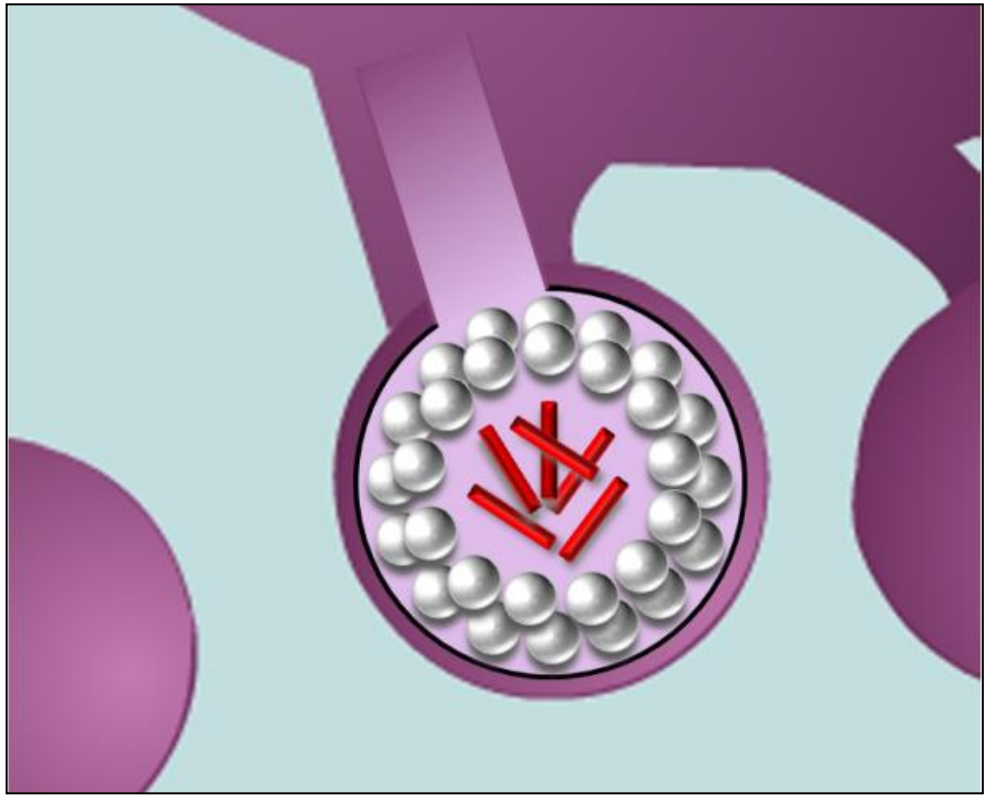
Tubercle bacilli multiply in alveoli

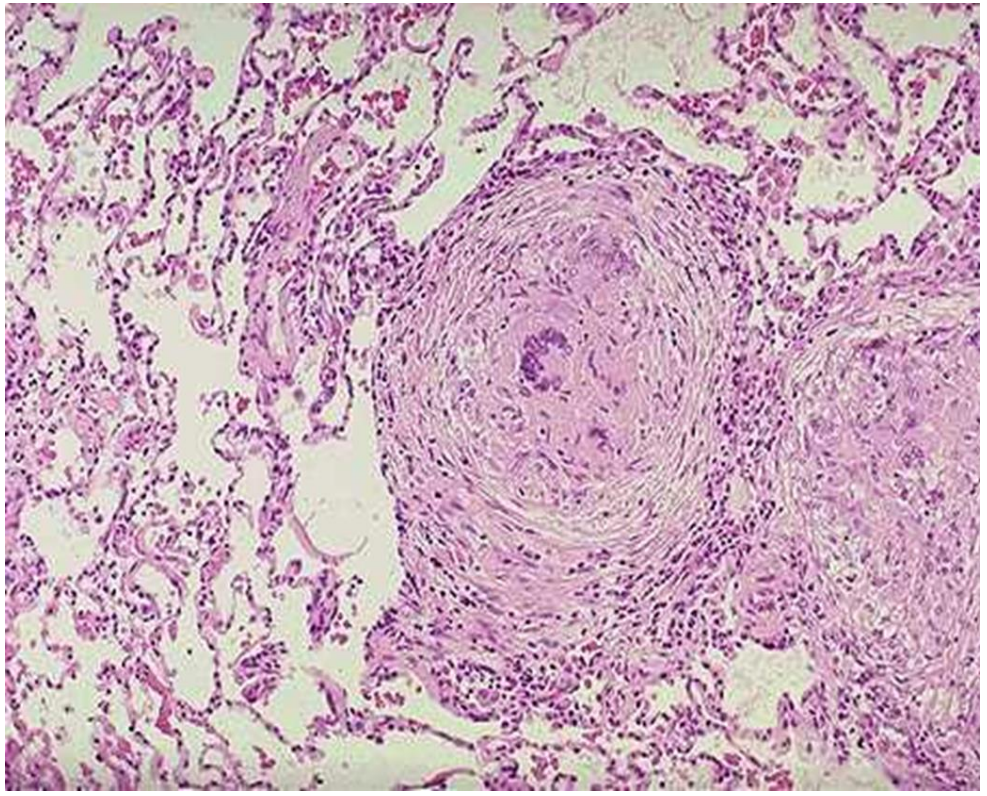
3



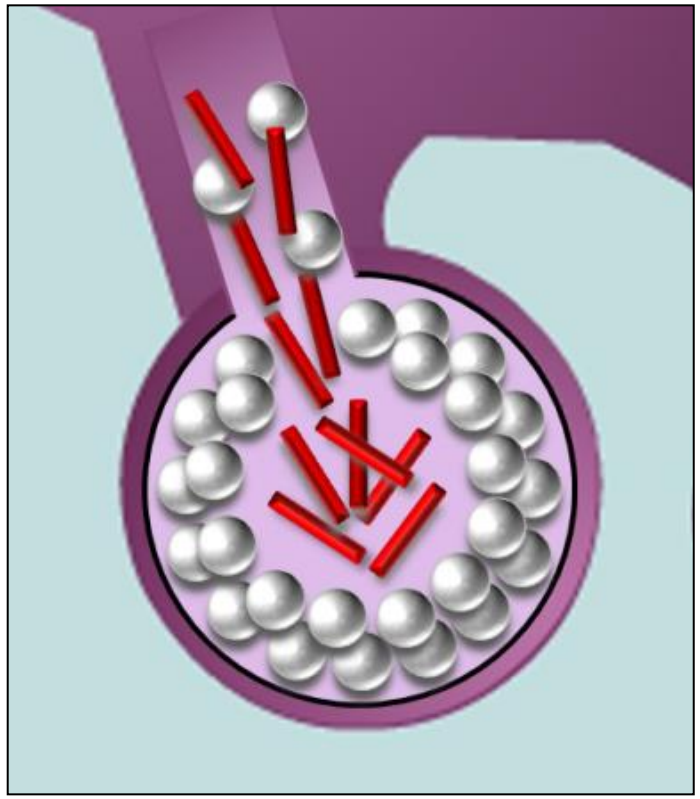
A small number of tubercle bacilli enter bloodstream and spread throughout body

Within 2 to 8 weeks, special immune cells called macrophages ingest and surround the tubercle bacilli. The cells form a barrier shell, called a granuloma, that keeps the bacilli contained and under control.





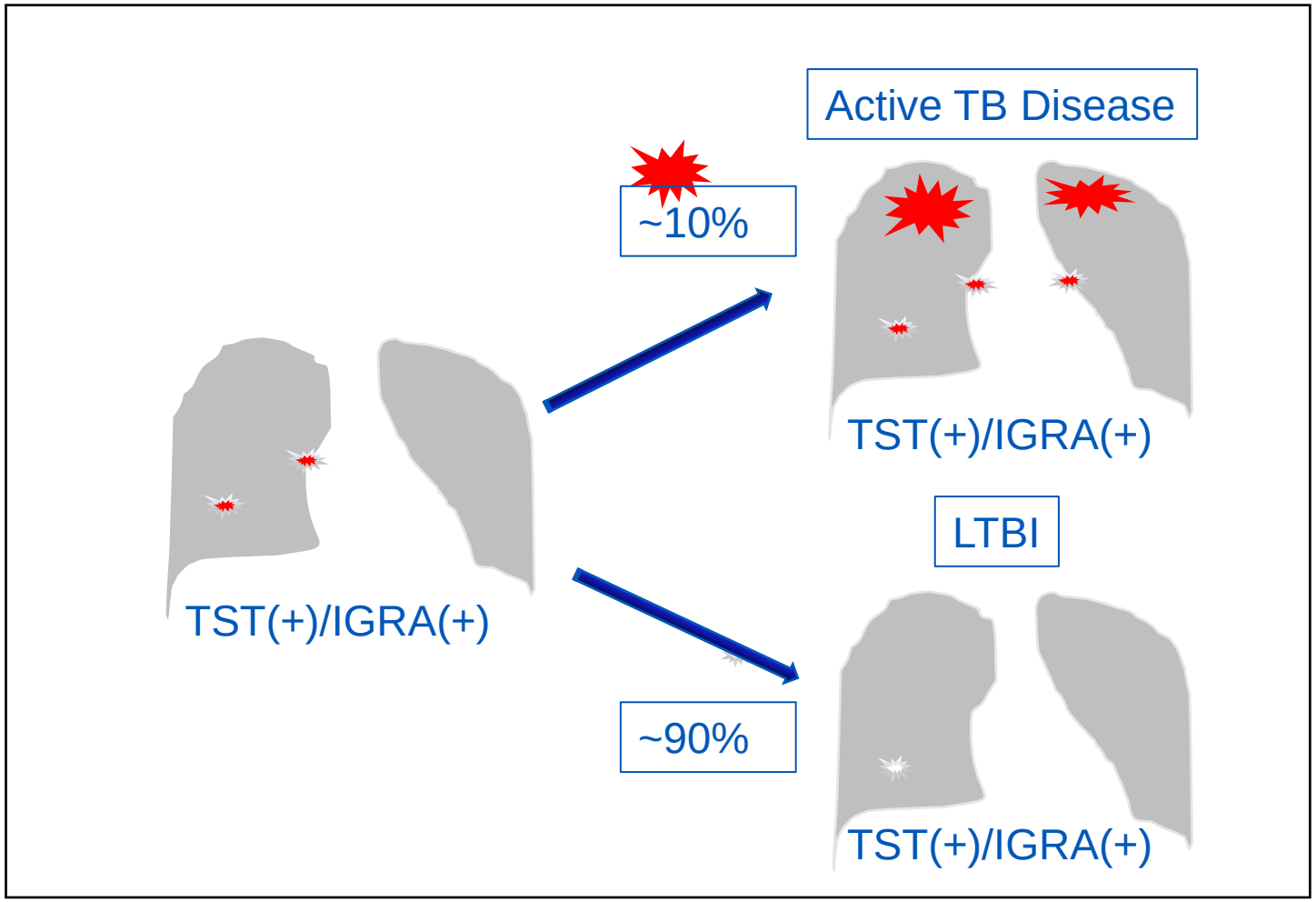
Progression to TB Disease



- Over time, the immune system, for various reasons, may lose the ability to keep the tubercle bacilli under control.
- Thus, the bacilli begin to multiply rapidly = Reactivation
- Reactivation can occur in different areas in the body, such as the lungs, kidneys, brain, or bone.

Natural History of Untreated TB

Approxiamtely 50% of people clear the TB infection before T cell priming and never develop a positive TST or IGRA

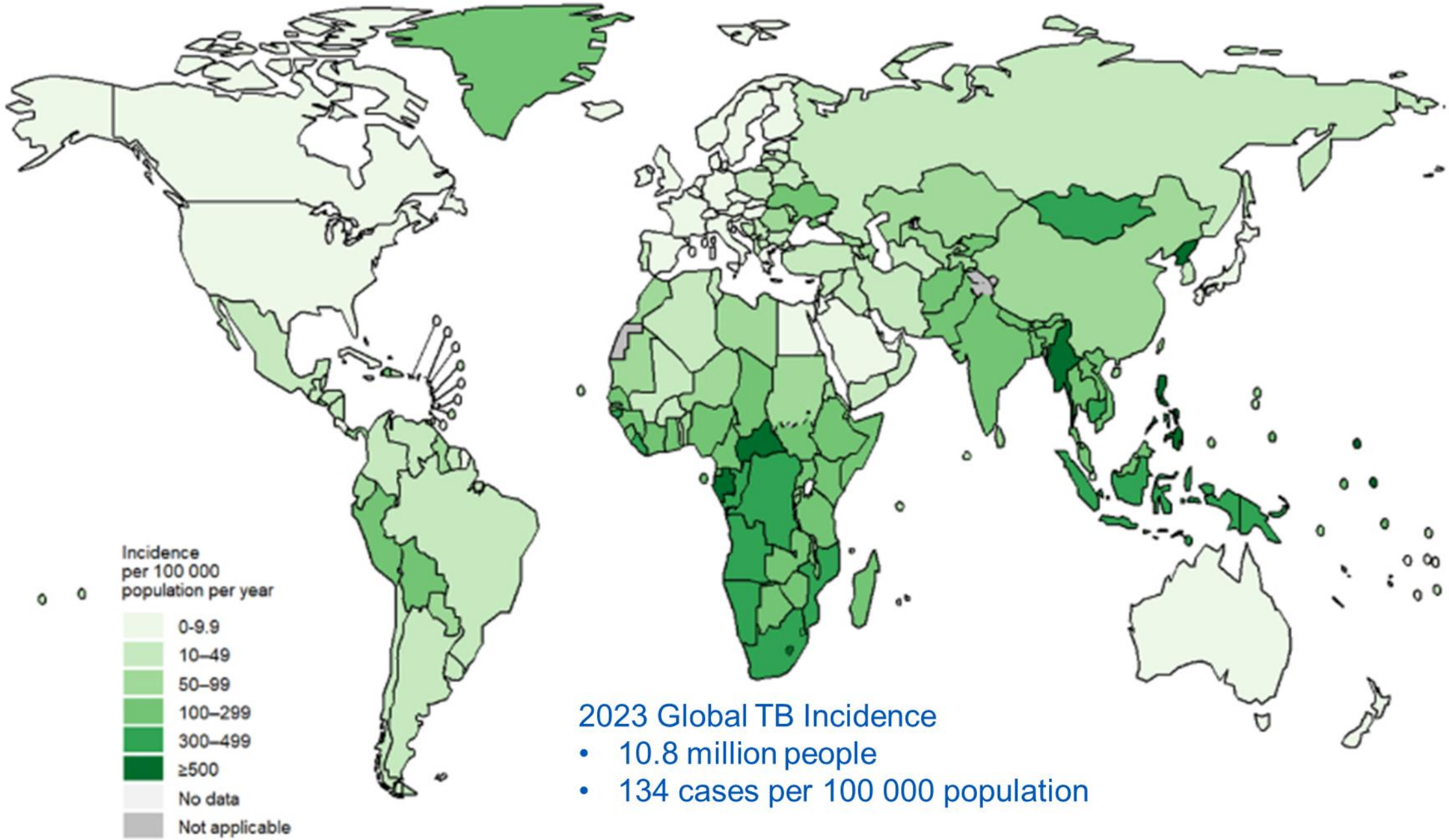


TB Infection (Latent TB, Latent TB Infection)

LTBI is the presence of *M. tuberculosis* organisms (tubercle bacilli) without signs and symptoms or radiographic or bacteriologic evidence of TB disease.

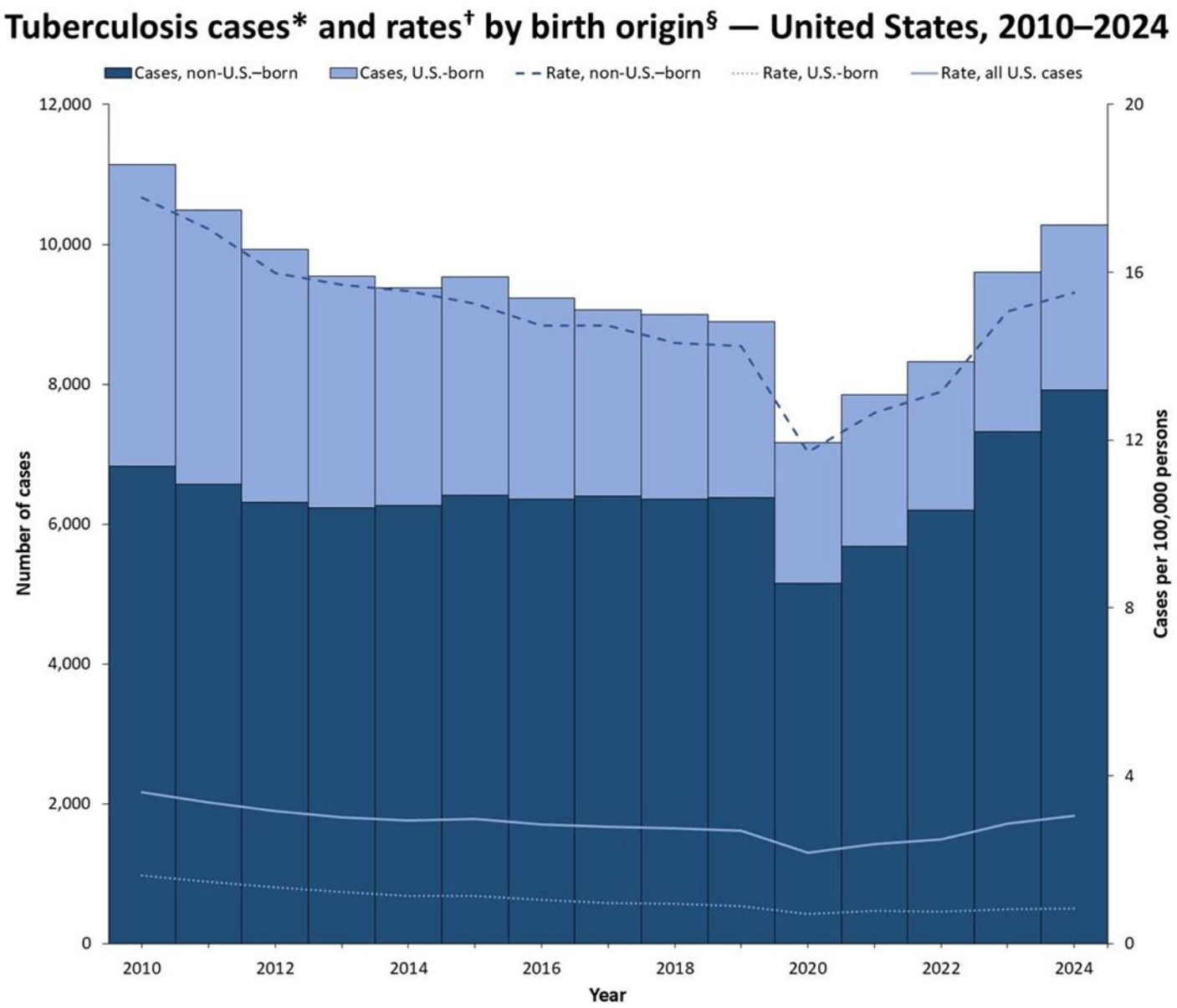
LTBI	TB Disease
No symptoms or physical findings suggestive of TB disease	Has a large amount of active TB bacteria in his/her body
Cannot spread TB bacteria to others	May spread TB bacteria to others
Does not feel sick, but may become sick if the bacteria become active in his/her body	May feel sick and 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
Radiograph is 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

Why is LTBI important?



2023 Global TB Incidence

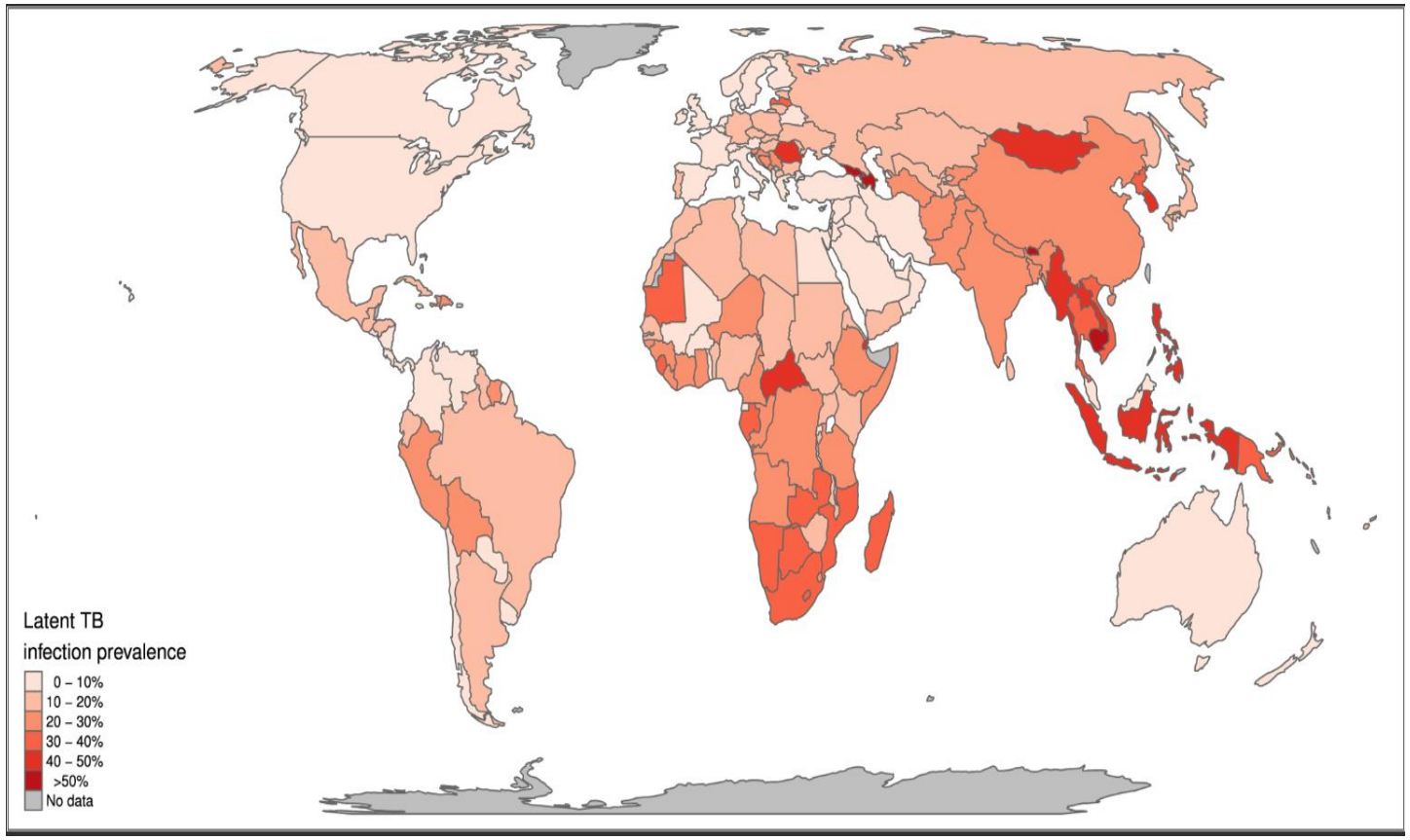
- 10.8 million people
- 134 cases per 100 000 population



9622 TB cases in 2023
Incidence rate: 2.9 per 100,000

10,347 TB cases in 2024
Incidence rate: 3.0 per 100,000

Burden of Latent Tuberculosis



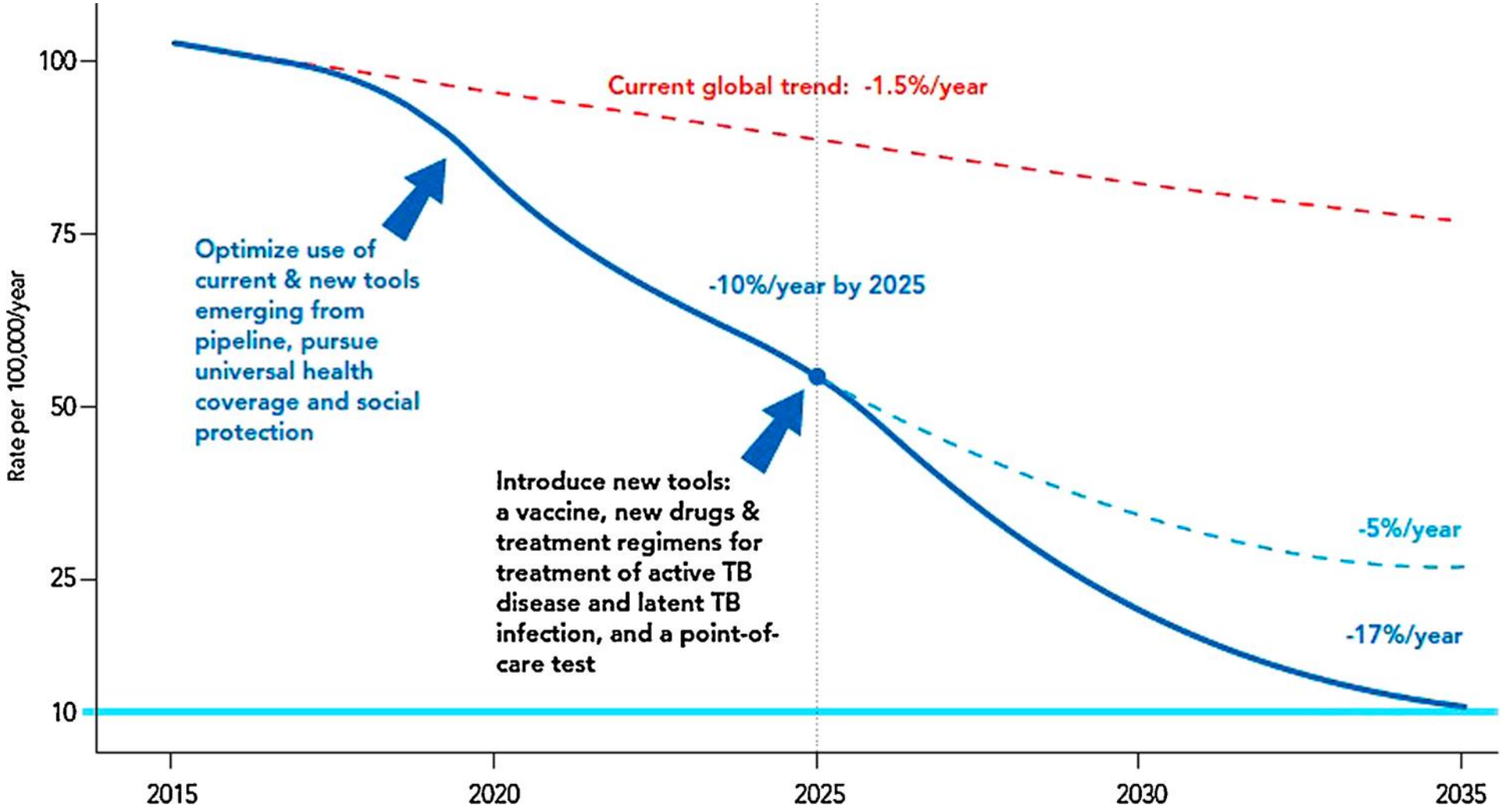
Global burden of LTBI:
23.0%, 1.7 billion people.

United States burden of LTBI:
5%, 13 million people.

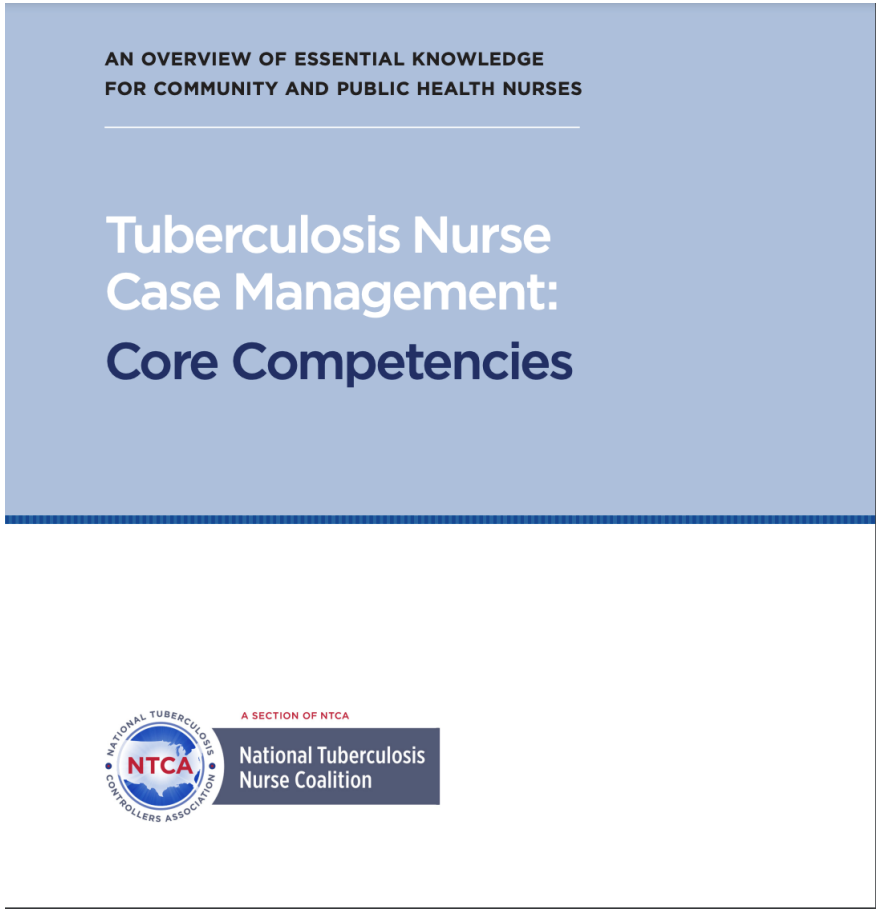
Houben RMGJ, Dodd PJ (2016) The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. PLoS Med 13(10): e1002152. https://doi.org/10.1371/journal.pmed.1002152

https://www.cdc.gov/tb/statistics/ltbi.htm

Projected Acceleration in the Decline of Global Tuberculosis Incidence Rates



WHO, Geneva (2015). http://www.who.int/tb/strategy/End_TB_Strategy.pdf



https://www.tbcontrollers.org/resources/core-competencies/tb-nurse-case-manager/

Nurse Case Management for LTBI

Who should be tested for LTBI?

Persons at Risk for Developing TB Disease

1

Those who have an increased likelihood of exposure to persons with TB disease

2

Those with clinical conditions that increase their risk of progressing from LTBI to TB disease

Increased Likelihood of Exposure to Persons with TB Disease

Close contacts to person with infectious TB

Residents and employees of high-risk congregate settings (e.g., correctional facilities, homeless shelters, health care facilities)

Individuals from TB-endemic regions of the world

Increased Risk for Progression to TB Disease

HIV-infected persons

Diabetes mellitus

Biologics

Transplantation

Those with a history of prior, untreated TB or fibrotic lesions on chest radiograph

Children ≤ 5 years with a positive skin test for latent tuberculosis

Underweight or malnourished persons

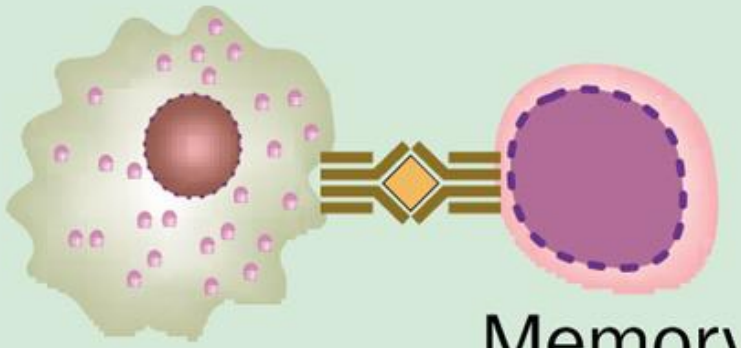
Substance users (such as smoking, alcohol, or injection drug use)

Certain medical conditions

- Silicosis
- Chronic renal failure/hemodialysis
- Carcinoma of head or neck
- Gastrectomy or jejunoileal bypass

How do we test for LTBI?

Presentation of mycobacterial antigens

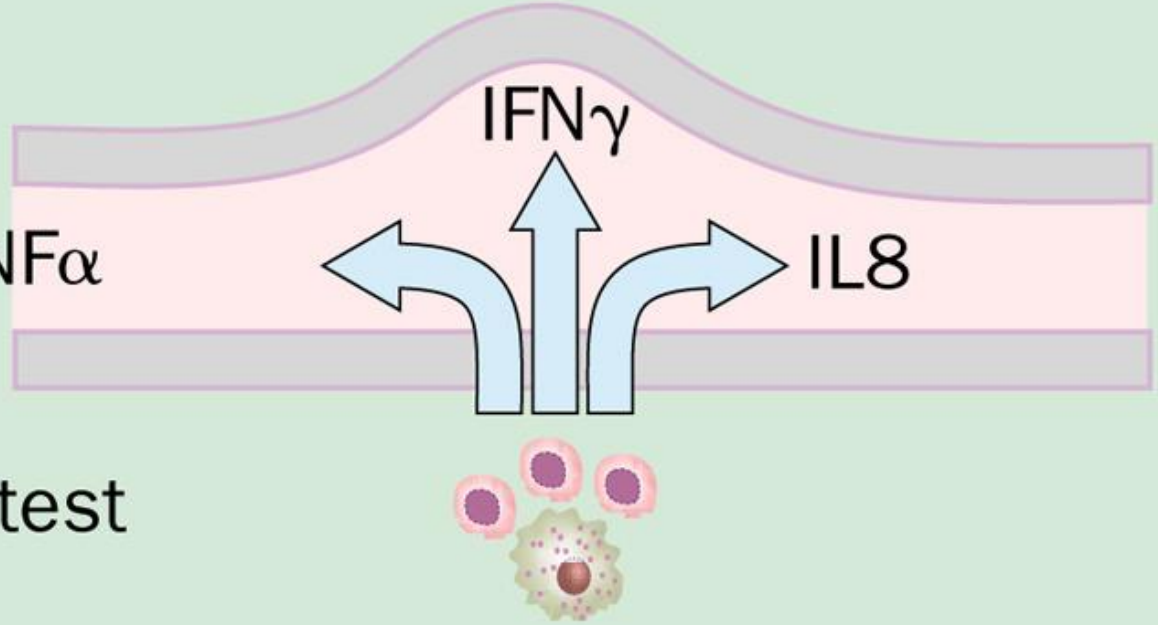


Antigen presenting cell

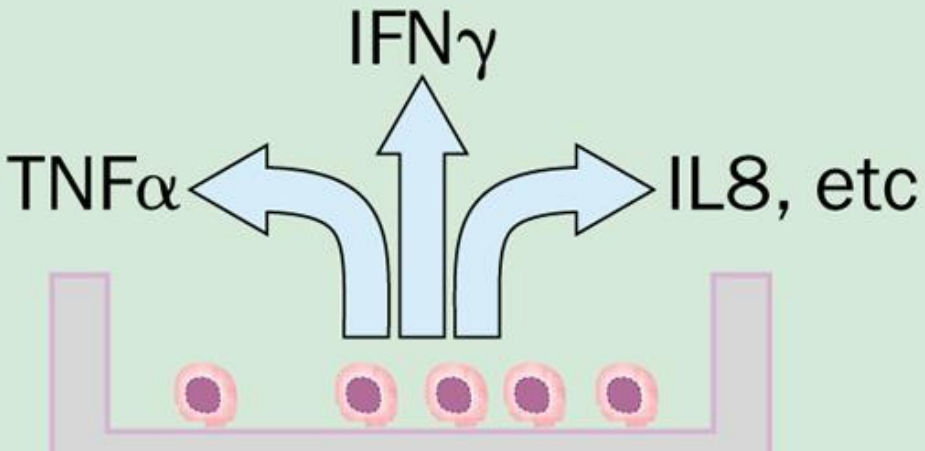
Memory T cell

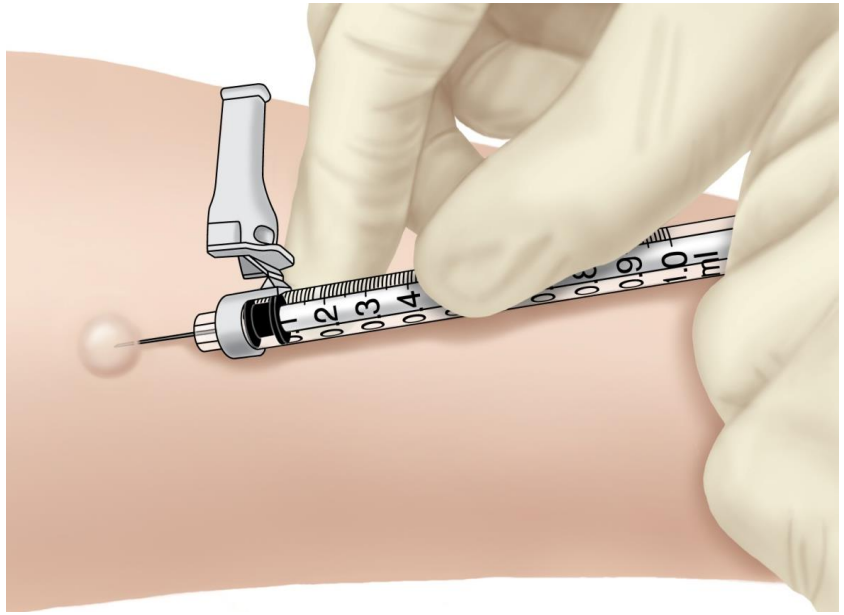
Skin test

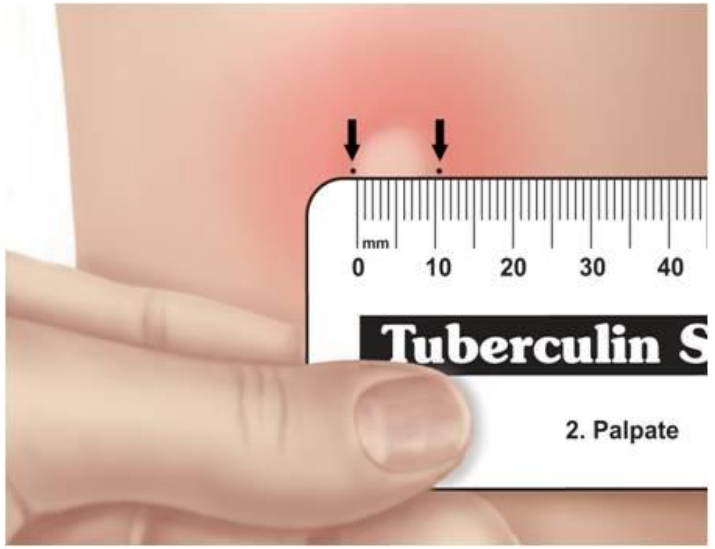
Measurement of induration and erythema



In vitro blood test



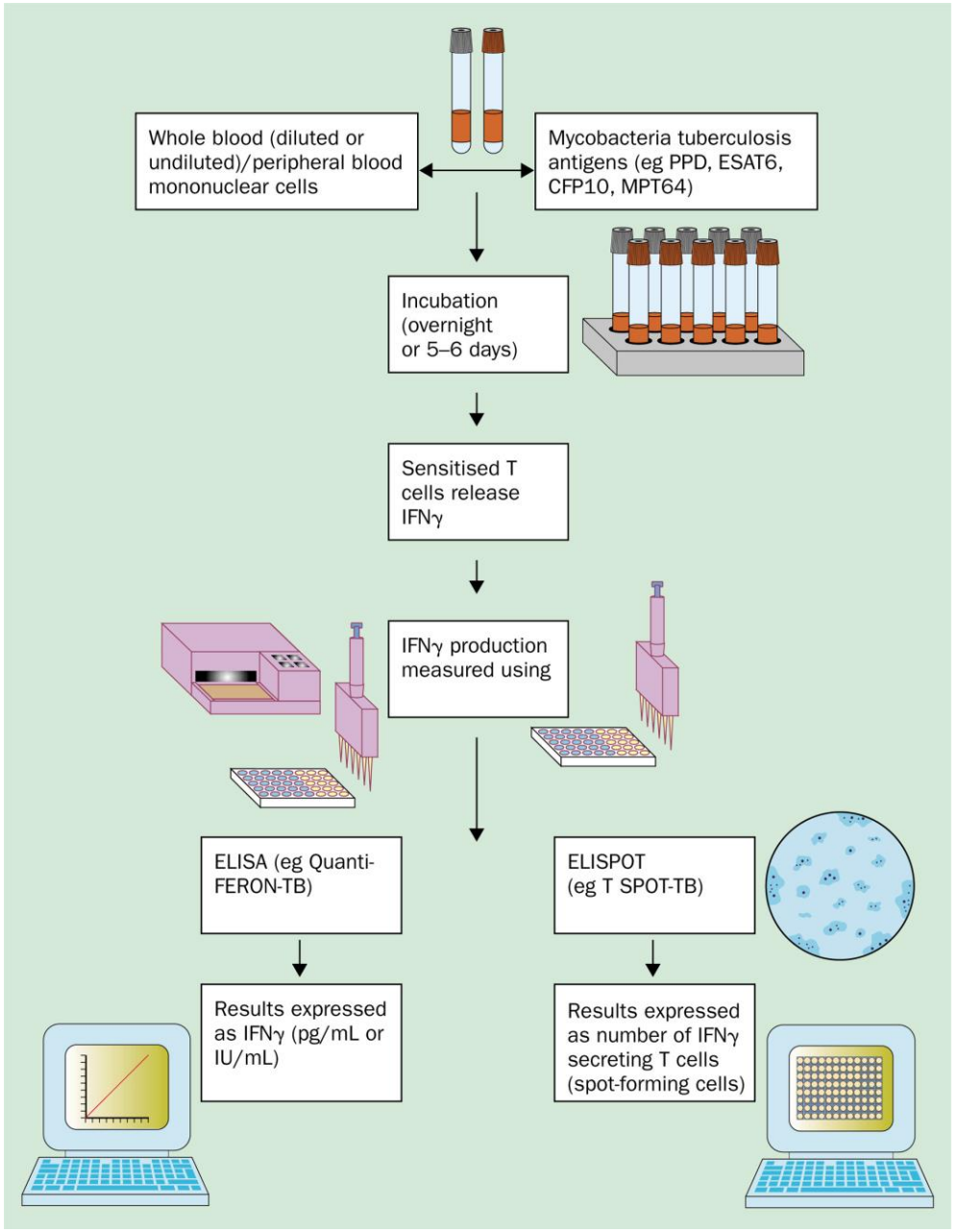




≥ 5 mm	≥ 10 mm	> 15 mm
• HIV positive persons • Recent contacts of persons with active tuberculosis • Fibrotic changes on chest radiograph, consistent with tuberculosis • Patients with organ transplants and other immunosuppressed patients	• Immigrants from high-prevalence areas • Injection drug users • Residents and employees* of high-risk congregate settings • Personnel in mycobacteriology laboratories • Persons with clinical conditions that place them at high risk • Children: <4 years of age; all exposed to adults at high-risk	• No known risk factors

Interpretation Criteria for T-Spot. TB Test (T-Spot)			
Interpretation	**Nil***	**TB Response†**	**Mitogen§ (Positive Control)**
Positive¶	≤10 spots	≥8 spots	Any number of spots
Borderline**	≤10 spots	5, 6, or 7 spots	Any number of spots
Negative††	≤10 spots	≤4 spots	≥ 20 spots
Indeterminate**	>10 spots	Any	Any number of spots
	≤10 spots	<5 spots	< 20 spots

Interpretation Criteria for QuantiFERON-TB Gold in-Tube Test (QFT-GIT)			
Interpretation	**Nil***	**TB Response†**	**Mitogen Response§**
Positive¶	≤8.0	≥0.35 IU/ml and ≥25% of Nil	Any
Negative**	≤8.0	<0.35 IU/ml or <25% of Nil	≥0.5
Indeterminate††	≤8.0	<0.35 IU/ml or <25% of Nil	<0.5
	>8.0	Any	Any



The Lancet Infectious Diseases, Volume 4, Issue 12, 761 - 776

IGRA	TST
Requires only one patient visit to conduct the test	Requires 2 visits to conduct the test
Not subject to the biases and errors associated with TST placement and reading	Subject to the biases and errors associated with TST placement and reading
Results can be available within 24 hours	Results available 48-72 hours later
Unaffected by the bacille Calmette Guérin (BCG) vaccine and most nontuberculous mycobacteria	BCG vaccination can cause a false-positive result
A negative test result does not fully exclude the diagnosis of LTBI or TB disease	A negative test result does not fully exclude the diagnosis of LTBI or TB disease

IGRA vs. TST

Using either IGRA or TST is acceptable medical and public health practice.

How do we treat LTBI?

Positive TST or IGRA
Principles of Management

Prior history of TB or LTBI treatment

Medical History

- comorbidities

Physical examination

Rule out active TB

- Symptom screen
  - Do not forget extra-pulmonary TB
- Chest X ray
- May need microbiology studies

Recommendations for regimens to treat latent tuberculosis infection

Priority rank*	Regimen
Preferred	3 mos isoniazid plus rifapentine given once weekly
Preferred	4 mos rifampin given daily
Preferred	3 mos isoniazid plus rifampin given daily
Alternative	6 mos isoniazid given daily
Alternative	9 mos isoniazid given daily

MMWR Recomm Rep. 2020 Feb 14;69(1):1–11. doi: 10.15585/mmwr.rr6901a1

Three Months of Weekly Isoniazid Plus Rifapentine

3HP

ADVANTAGES

- Equivalent effectiveness to 9 months of daily isoniazid
- Less hepatotoxicity than 9 months of daily isoniazid
- Higher treatment completion rates

DISADVANTAGES

- Cost
- Pill burden
- Cumulative safety and drug interaction issues from 2 drugs
- Influenza like syndrome
- Availability
- DOT*

N Engl J Med 2011;365:2155–66. 10.1056/NEJMoa1104875
Ann Intern Med 2017;167:689–97. 10.7326/M17-1150

Four Months of Daily Rifampin

ADVANTAGES

- Equivalent effectiveness to 9 months of daily isoniazid
- Less hepatotoxicity than 9 months of daily isoniazid
- Less treatment discontinuation due t adverse events
- Higher treatment completion rates

DISADVANTAGES

- Drug interactions

N Engl J Med 2018;379:454–63. 10.1056/NEJMoa1714284
N Engl J Med 2018;379:440–53. 10.1056/NEJMoa1714283
Am J Respir Crit Care Med 2004;170:445–9. 10.1164/rccm.200404-478OC
Ann Intern Med 2008;149:689–97. 10.7326/0003-4819-149-10-200811180-00003

Three Months of Daily Isoniazid Plus Rifampin

ADVANTAGES

- Equivalent effectiveness to ≥6 months of daily isoniazid
- Equivalent safety to ≥6 months of daily isoniazid
- Higher treatment completion rates

DISADVANTAGES

- Cumulative safety and drug interaction issues from 2 drugs

Enferm Infecc Microbiol Clin 2007;25:300–4.
Int J Tuberc Lung Dis 2013;17:326–32. 10.5588/ijtld.12.0510

Six or Nine Months of Daily Isoniazid

ADVANTAGES

- Long track record
- 6 months of isoniazid an alternative for those persons unable to take a shorter preferred regimen
- Higher treatment completion rates

DISADVANTAGES

- Hepatotoxicity
- Duration adversely impacts treatment completion

Am Rev Respir Dis 1967;95:935–43.
Int J Epidemiol 1973;2:153–60. 10.1093/ije/2.2.153
Bull World Health Organ 1982;60:555–64.
Am Rev Respir Dis 1992;145:36–41. 10.1164/ajrccm/145.1.36

Monitoring of LTBI Treatment

Monthly Clinical Assessment

- In person or virtually
- Adherence
- Symptoms review
  - Adverse drug reactions
  - Progression of TB
- Laboratory evaluation when indicated
- Provide medications sufficient to last until the next assessment
- Directed physical examinations as needed to evaluate those symptoms.

Symptoms Review

Flu-like symptoms (fever, chills, myalgias) Headaches
Syncope or near-syncope
Rash
Easy bruising
Anorexia, nausea, vomiting, weight loss
Abdominal pain (especially in the right upper quadrant)
Jaundice, dark urine
Paresthesia of the hands or feet
Persistent fatigue and weakness

Management of Treatment Interruption: General Principles

When the specified number of doses cannot be administered within the target period, decision should be made

- Continuing the same regimen for the remaining duration of time
  - In general, if less than two months were missed
- Restarting treatment from the beginning.
  - The earlier the interruption in the course of treatment
  - The longer the duration of the interruption
    - if more than two months were missed

Latent TB Infection Treatment Completion Criteria

 4R Rifampin Four months/once daily total 120 doses.	Complete doses within six consecutive months.
 3HP Isoniazid and Rifapentine Three months once weekly total 12 doses.	A minimum of 11 doses must be taken within 16 consecutive weeks.
 3HR Isoniazid and Rifampin Three months/once daily total 90 doses.	Complete doses within four consecutive months.
 6H Isoniazid Six months/once daily total 180 doses.	Complete doses within nine consecutive months.
 9H Isoniazid Nine months/once daily total 270 doses.	Complete doses within 12 consecutive months.

- A 28-year-old man with TB infection was prescribed the 4 month daily oral rifampin regimen.
He tolerated the medication well and completed 3 months of treatment but discontinued 3 months ago, when he got a new job in a new state. He remains asymptomatic.
What would you recommend?

1. Restart daily Rifampin for another 4-month treatment
2. Prescribe daily INH for 6 months
3. Prescribe daily rifampin for 1 more month
4. Consider LTBI treatment completed

1. Restart daily Rifampin for another 4-month treatment
2. Prescribe daily INH for 6 months
3. Prescribe daily rifampin for 1 more month
4. Consider LTBI treatment completed

- A 28-year-old man with TB infection was prescribed the 4 month daily oral rifampin regimen.

He tolerated the medication well and completed 3 months of treatment but discontinued 1 month ago, when he got a new job in a new state. He remains asymptomatic.

What would you recommend?

Questions and Answers

Thank you