MAYO CLINIC

Center for Tuberculosis

Latent Tuberculosis Infection (LTBI)

Some Considerations on Diagnosis and Management

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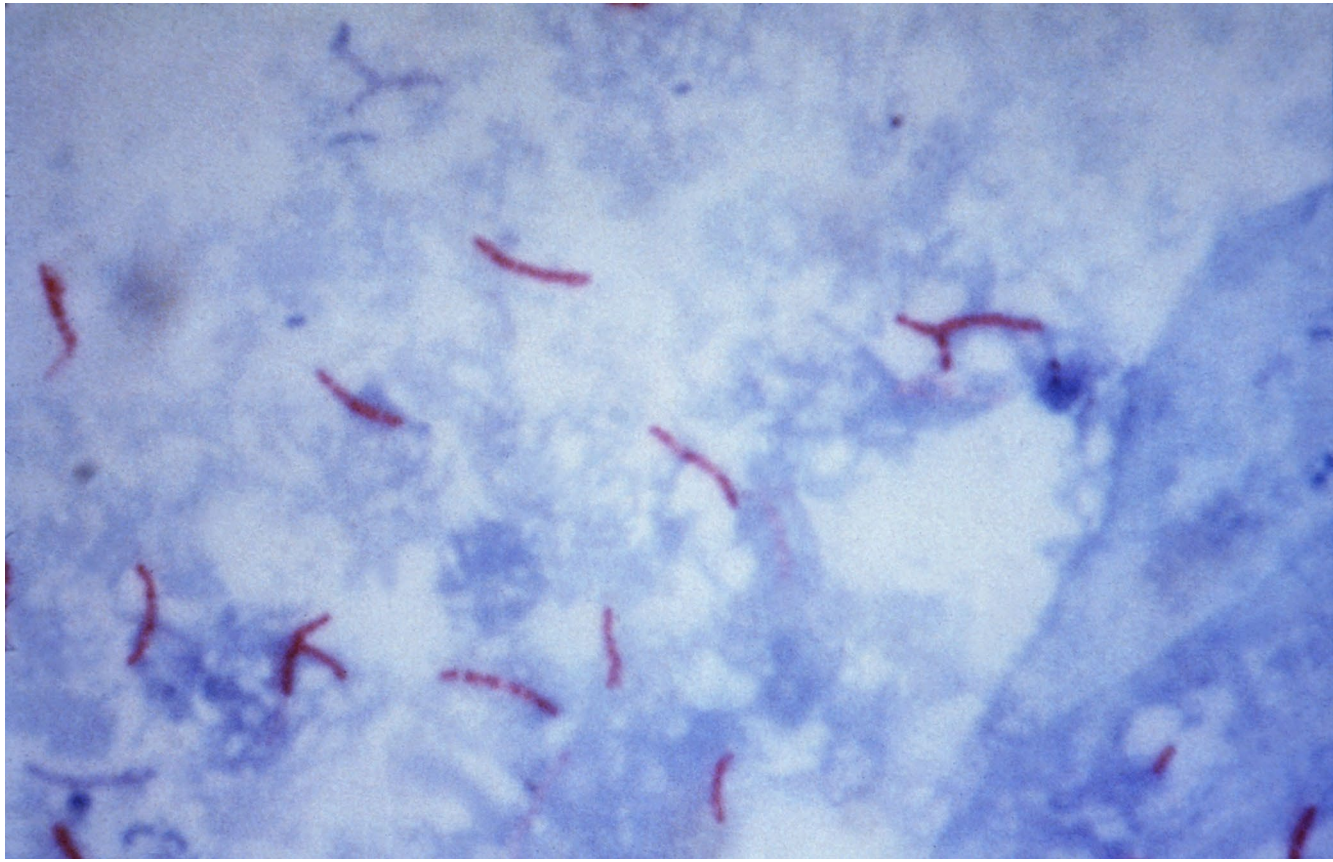
Learning Objectives

- Review diagnosis of Latent Tuberculosis Infection (LTBI)
- Describe management of LTBI
- Recall LTBI medications, common adverse effects and drug interactions

Definitions and Numbers

WHAT IS LTBI?

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



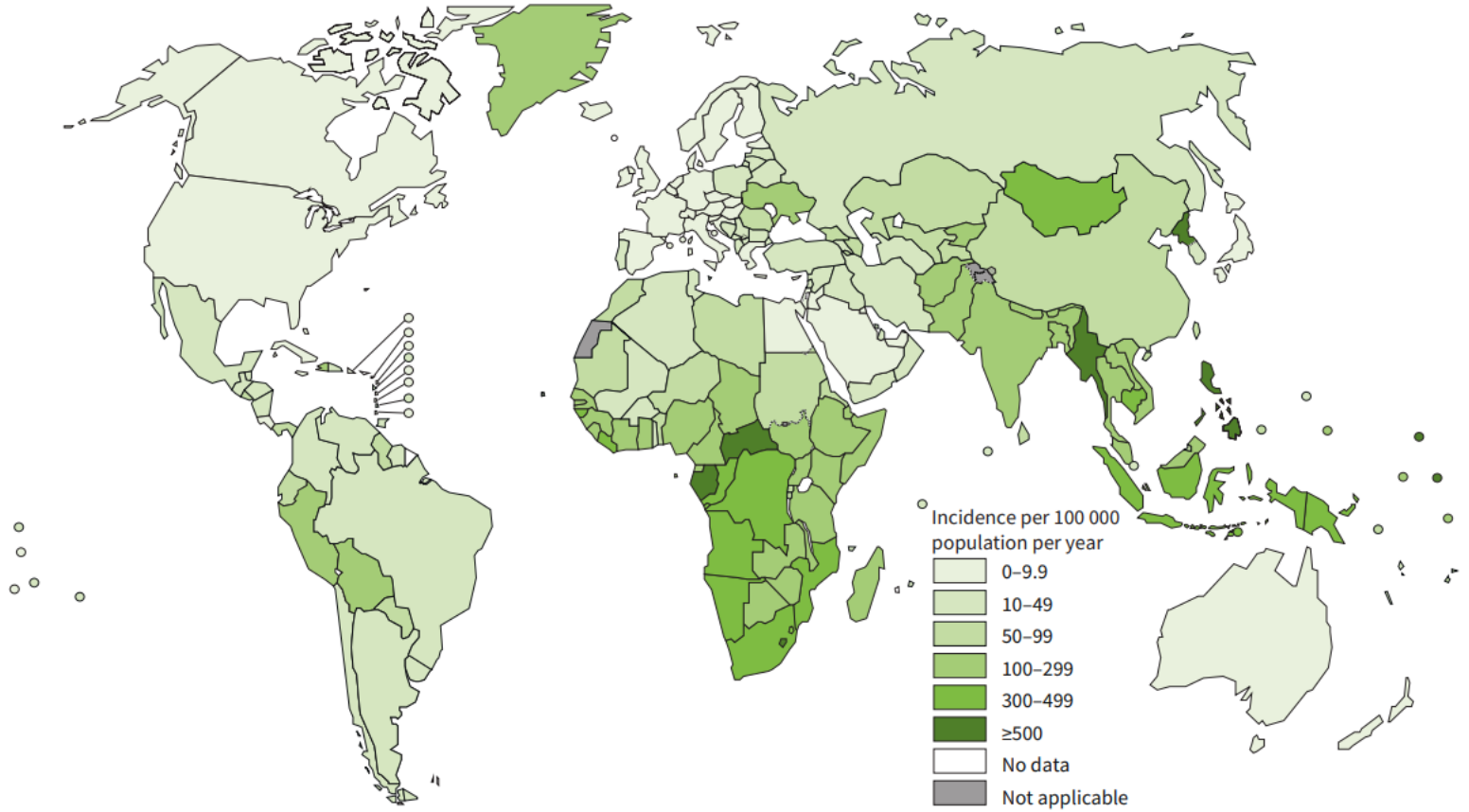
Sputum stained by Ziehl Neelsen stain

Tuberculosis (TB) Disease vs LTBI

TB Disease	LTBI
Symptoms present	No symptoms
Abnormal chest x-ray (unless extrapulmonary disease)	Chest x-ray normal
Specimens smear and/or culture positive	Smear and culture negative
Can spread to others	Cannot spread disease
Needs treatment for TB disease	Should consider treatment to prevent TB disease
TST or TB blood test usually positive	**TST or TB blood test usually positive**

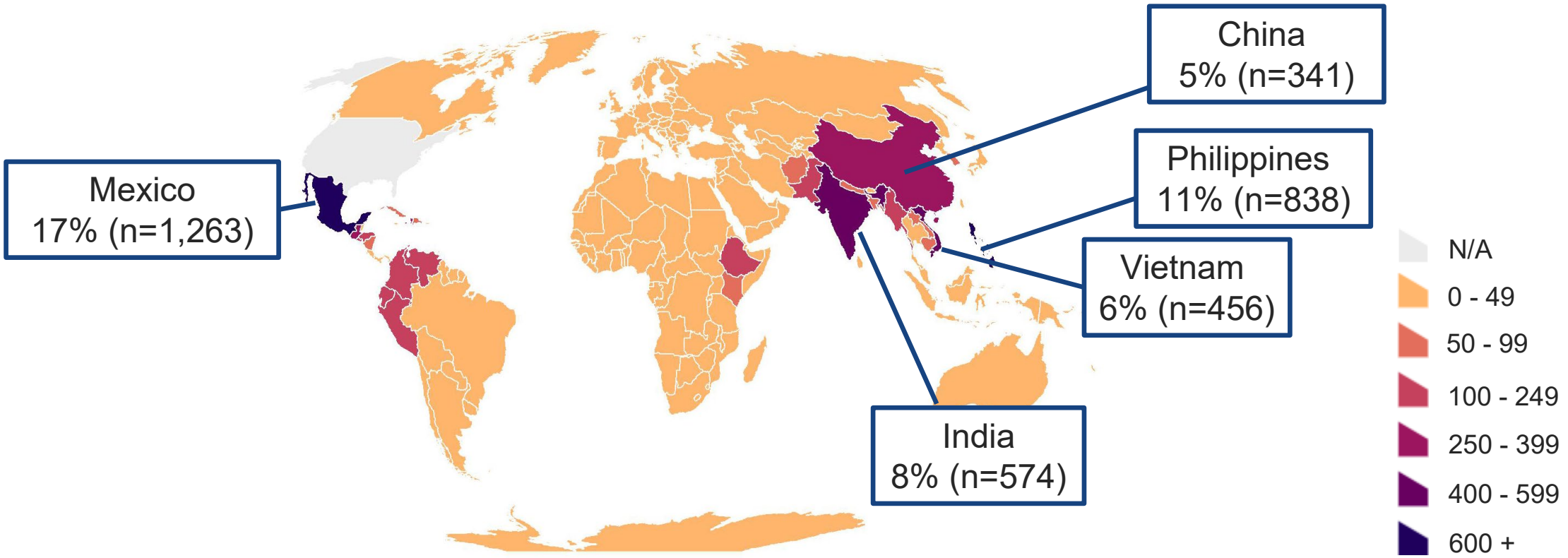
Estimated TB Incidence Rates, 2023

An estimated global total of 10.8 million people fell ill with TB in 2023



World Health Organization. (2023). *Global tuberculosis report 2023*. World Health Organization. https://iris.who.int/handle/10665/373600

TB Cases by Countries of Birth Among Non-U.S.–Born* Persons with TB, United States, 2023 (N=7,299)



*Persons born in the United States, certain U.S. territories, or elsewhere to at least one U.S. citizen parent are categorized as U.S.-born. All other persons are categorized as non-U.S.–born.

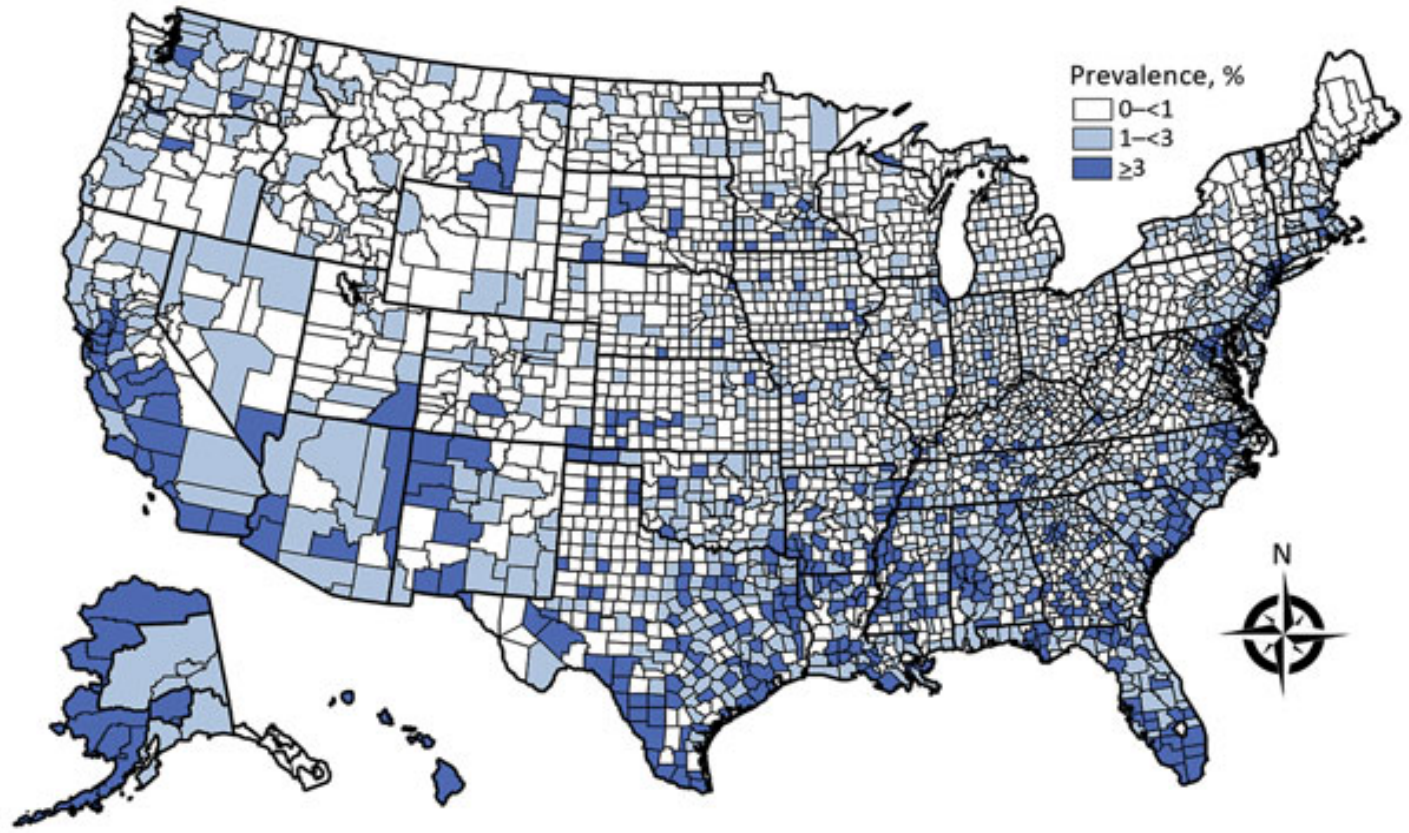
Centers for Disease Control and Prevention. (2024, July 17). *Tuberculosis (TB) disease in the United States, 1993–2023* [Slide set]. Division of Tuberculosis Elimination, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, U.S. Department of Health and Human Services. https://www.cdc.gov/tb-surveillance-report-2023/media/pdfs/2024/10/2023_TB_in_the_United_States_Slide_Set.pdf

LTBI Prevalence

- World: 24.8% and 21.2% based on IGRA and a 10 mm TST cut-off respectively
- United States: CDC estimates that up to 13 million people have latent TB infection (8.6 to 14 million)

Adam Cohen, Victor Dahl Mathiasen, Thomas Schön, Christian Wejse
European Respiratory Journal 2019; **DOI:** 10.1183/13993003.00655-2019

Estimated Prevalence of LTBI, by county, United States, as Derived from Genotyped Cases of Tuberculosis Reported to the US National Tuberculosis Surveillance System, 2011–2015



<1% in 1,981 counties

1%–<3% in 785 counties

≥3% in 377 counties

Haddad MB, Raz KM, Lash TL, Hill AN, Kammerer J, Winston CA, et al. Simple Estimates for Local Prevalence of Latent Tuberculosis Infection, United States, 2011–2015. Emerg Infect Dis. 2018;24(10):1930-1933. https://doi.org/10.3201/eid2410.180716

Diagnosing LTBI

How Patients Present

Patient 1

- 33-year-old female. RN. Healthy. On OCPs
- Born in the Philippines; moved to the U.S. five years ago
- Self-referred to TB Clinic, given recent diagnosis of TB disease in close family members
- Interested in treatment given family member with TB disease
- Positive QuantiFERON

Patient 2

- 62-year-old man. Retired from 26 years of work as a correction officer
- No foreign travel
- Medical history significant for well-controlled hypertension, atrial fibrillation on warfarin
- Had a positive QuantiFERON, done as part of pre-employment evaluation in home-based patient care

Targeted Testing

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- Generally, groups at high risk fall into two broad categories:
  - People who are at high risk for exposure to or infection with *M. tuberculosis*
  - People who are at high risk for developing TB disease once infected with *M. tuberculosis*

- Targeted testing in the strategy used to identify and treat persons in these categories

At Risk for TB Exposure

- Health care workers who serve patients with TB disease
- Infants, children, and adolescents exposed to adults who are at increased risk for LTBI or TB disease
- Born in or frequently travel to countries where TB disease is common
- Contacts of people with infectious TB disease
- Currently live or used to live in large group settings where TB is more common, such as homeless shelters, prisons, jails, or nursing homes
- Employees of high-risk congregate settings

At Risk of Severe TB Disease

- People living with HIV
- Children < 5 years of age
- Recent M. tuberculosis infection (within the last 2 years)
- History of untreated or inadequately treated TB disease
- On immunosuppressive therapy
- Chronic disease:
  - Silicosis; chronic renal failure; leukemia; or cancer of the head, neck, or lung; diabetes mellitus
- History of gastrectomy or jejunoileal bypass
- Low body weight

At Risk for TB Exposure and Severe Disease

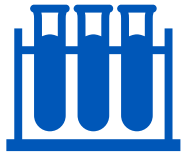
- Populations defined locally as having an increased incidence of LTBI or TB disease
  - medically underserved
  - low-income
  - people who abuse drugs or alcohol

Making a Diagnosis of LTBI

TOOLS

- History
- Physical examination
- Chest x-ray

TESTS SPECIFIC TESTS



- TB skin test
- TB blood tests
- Mycobacterial smear and culture

History and Examination

Symptom Review

- Cough, hemoptysis, fever or chills, night sweats, unintended weight loss, fatigue, chest pain, other symptoms related to site of possible infection

Physical Exam

- Include, head and neck, lymph node exam, lungs, abdomen, skin

TB Skin Test

- 0.1 ml of 5TU PPD tuberculin injected intradermally
- Produce wheal 6 mm to 10 mm in diameter
- The test is read in 48 to 72 hours

Interpreting the TST

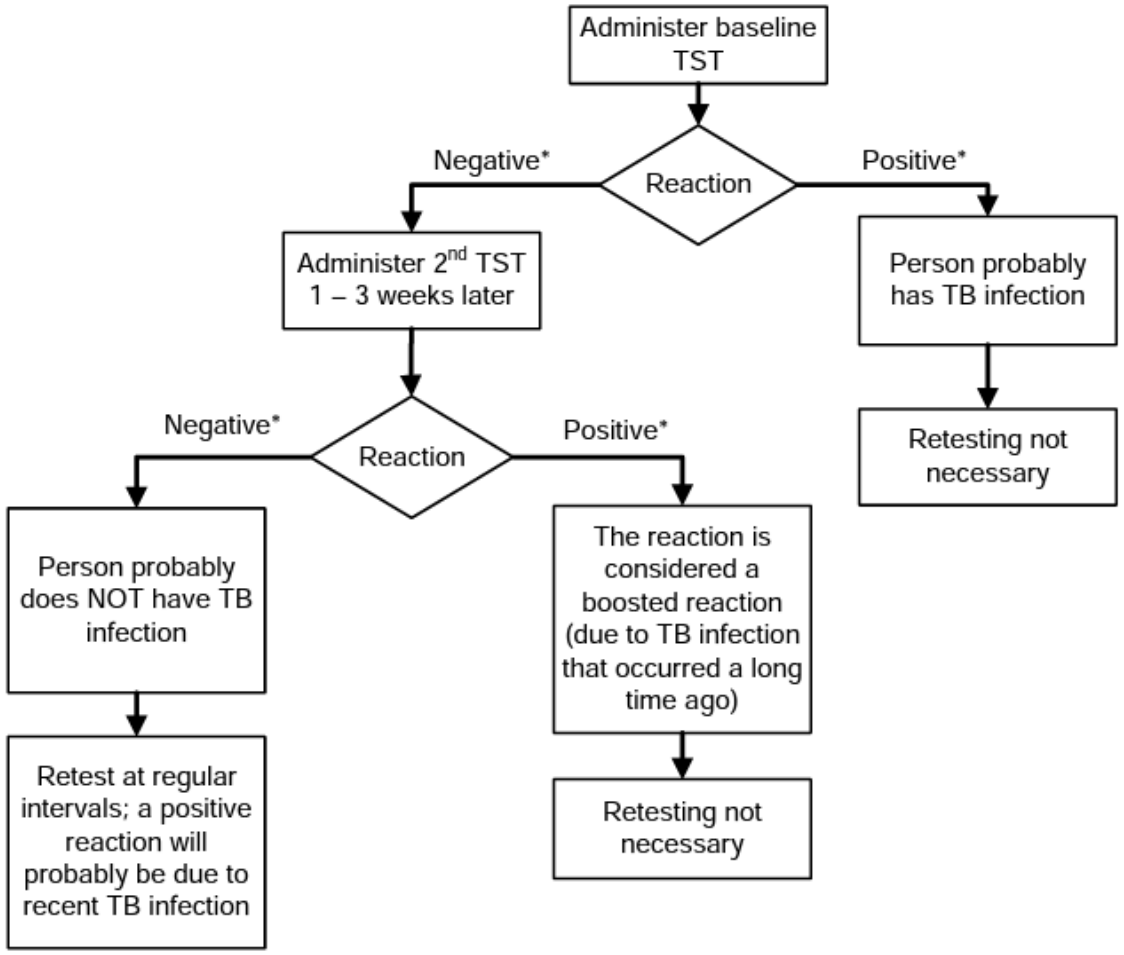
≥5 mm	≥10 mm	≥15 mm
• People living with HIV • Recent contacts of people with infectious TB • CXR suggestive of previous TB disease • With organ transplants • Immunosuppressed patients	• Born in countries where TB disease is common • People who abuse drugs • Mycobacteriology lab workers • Live or work in high-risk congregate settings • Chronic medical conditions • Low body weight • Infants, children, and adolescents exposed to adults in high-risk categories	• No known risk factors for TB

Special Considerations: Boosting

- Some people with LTBI may have negative skin test reaction when tested years after infection
- Initial skin test may stimulate (boost) ability to react to tuberculin
- Implications
  - Positive reactions to subsequent tests may be misinterpreted as a new infection
  - Use two-step testing for initial skin testing of adults who will be retested periodically

Two Step TB Skin Test

Use two-step testing for initial skin testing of adults who will be retested periodically



*using 5, 10, or 15 mm cutoffs, depending on person's risk factors for TB

Minnesota Department of Health (Adapted from CDC); Updated: 10/26/2022

Special Populations and Considerations

Type of Reaction	Possible Causes
False-positive	• Nontuberculous mycobacteria • BCG vaccination (esp. when BCG is given after the first year of life – 60% specificity)
False-negative	• Anergy • Recent TB infection • Very young age (< 6 months old) • Live-virus vaccination • Overwhelming TB disease

TB Blood Tests

- Interferon gamma release assay tests (IGRAs)
- QuantiFERON-TB assay
  - Enzyme-linked immunosorbent assay (ELISA)-based whole-blood test that uses peptides from three TB antigens
- T-SPOT.TB assay
  - Enzyme-linked immunospot assay performed peripheral blood

Mayo Stock Photo

IGRAS: Sensitivity and specificity

- Specificity: >95 percent for diagnosis of TB infection
- Sensitivity: 80-90%
- Sensitivity
  - Decreased by HIV infection
  - Diminished due to the temporary anergy of acute illness

IGRAs: Advantages over TST

- Single visit
- Less variation in application and interpretation
- No cross reactivity with BCG
- Not affected by prior infection with nontuberculous mycobacteria
- No boosting with serial IGRA testing
- No skin blistering and ulceration
- Blood draw versus ID injection –acceptance
- Cost-effectiveness in select populations
  - Contacts
  - HCW

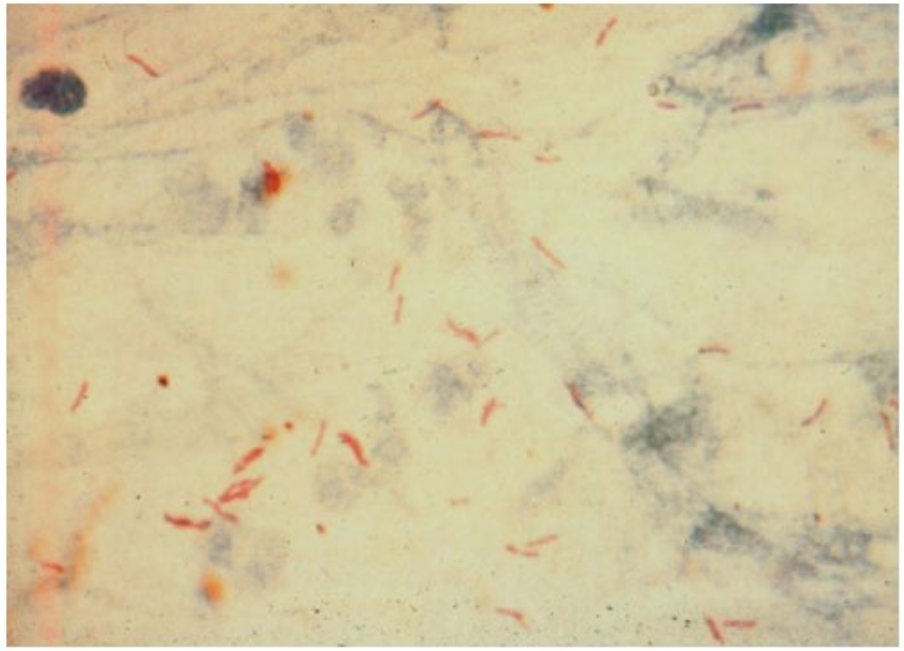
Chest X-ray

- Indicated
  - When TB skin test or blood test is positive
  - When there has been close contacts with a person with infectious TB
- In request for x-ray, let radiologist know that you would like to exclude TB
- Valid if within three months of treatment initiation
- If pregnant and in first trimester, postpone chest x-ray unless in extenuating circumstances

Mayo Stock Photo

Sputum Tests

- AAFB smear and mycobacteria culture indicated:
  1. When chest x-ray is abnormal
  2. When respiratory symptoms are present
- 2 to 3 sputa, including at least 1 early morning specimen
- Sputum induction, if needed
- Wait for culture results before initiating treatment for LTBI



Sputum, decontaminated and concentrated, and stained using the Ziehl-Neelsen method.

Rodríguez, et al. South Health and Policy. 4. 343.

Treatment of LTBI

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Why Treat LTBI?

- >80% of TB cases in the US result from longstanding, untreated LTBI
- Risk of developing TB:

1. Approximately 10% of immunocompetent people with LTBI will develop active TB disease in their lifetime
2. At risk populations:

High Risk

X6 higher risk

- Major immunosuppression
- HIV infection
- CXR with fibronodular changes typical of healed TB

Moderate Risk

X3 to X6 higher risk

- Diabetes mellitus
- On corticosteroid therapy

Slightly Higher Risk

X1.5 to X3 higher risk

- Underweight
- Smokers
- Small granulomas on CXR

Before Initiating LTBI Treatment

- Rule out TB disease: clinical history, physical examination, chest x-ray and sputum study when indicated
- Determine prior history of treatment for LTBI or TB disease
- Assess risks and benefits of treatment
- Review history of previous drug therapy
- If history of TB disease contact, review, if available, drug susceptibility
- Medication history

Baseline Lab Tests

- Test for hepatitis A, B, and C antibodies, as indicated
- HIV testing for all patients who do not know their HIV status
- Liver enzymes, complete blood counts for
  - All patients with HIV infection
  - Daily or heavy alcohol use, liver disease, or chronic hepatitis
  - Pregnant and postpartum patients
  - IVDU
  - On other potentially hepatotoxic medications
  - Prior abnormal liver enzymes
  - Patients with hematologic conditions
  - Based on clinical discretion

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Medication Regimens

- 3 months of isoniazid and rifapentine, once weekly (3HP)
- 3 months of isoniazid and rifampin, daily (3HR)
- 4 months of rifampin, daily (4R)
- 6 months of isoniazid, daily or twice weekly (6H)
- 9 months of isoniazid, daily or twice weekly (9H)

3HP: 3 Months of Isoniazid and Rifapentine Once Weekly

Advantages	Disadvantages	Contraindications
• Shortest currently approved treatment regimen • Fewest number of doses and total pills • Lower hepatotoxicity than with daily isoniazid monotherapy • Better treatment completion than with isoniazid regimens	• Higher drug cost • Drug-drug interactions • Large pill burden for single dose • Rare hypotension and syncope	• Aged <2 years • Pregnancy • Exposure to a patient with an isolate resistant to isoniazid or rifampin Relative CI: • HIV-positive status and taking an ART regimen with serious drug-drug interactions

Completion of treatment

12 doses within 16 weeks (or minimum 11 doses are within 16 weeks)

3HR: 3 Months of Isoniazid and Rifampin Daily

Advantages	Disadvantages	Contraindications
• Potentially effective treatment of infection with an unsuspected isoniazid-resistant organism • Shorter duration of therapy compared to 4R and isoniazid regimens	• Less experience with this regimen for the treatment of LTBI in the United States than with the other regimens • Potential additive hepatotoxicity	• HIV-positive status and presence of significant drug-drug interactions with ART • History of allergic or other significant adverse effect to rifamycins

Completion of treatment
90 doses taken within 4 months

4R: 4 Months of Rifampin Daily

Advantages	Disadvantages	Contraindications
• Lower hepatotoxicity than isoniazid • Better adherence to treatment than with isoniazid regimens • Treatment option after exposure to isoniazid-resistant but rifampin-susceptible TB • Treatment option for persons unable to use isoniazid	• Many drug-drug interactions	• HIV-positive status and presence of significant drug-drug interactions with ART • History of allergic or other significant adverse effect to rifamycins

Completion of treatment
120 doses within 6 months

6H/9H: 6 or 9 Months of Isoniazid Daily or Twice Weekly

Advantages	Disadvantages	Contraindications
• Low cost • Few drug-drug interactions	• Hepatotoxicity, more commonly in adults than in children, which can be serious and lead to liver failure and death • Long duration of treatment leading • Poor completion rates	• Acute active hepatitis • Chronic hepatitis with liver enzyme elevation • Prior significant AE related to isoniazid • Heavy or daily alcohol use

Completion of treatment

Daily: is 270 doses pr 180 doses within 12 months.

Twice weekly by DOT: Completion of treatment is 76 doses or 52 doses within 12 months

Adverse Events: Rifamycins

- Orange-red discoloration of body fluids
- Flu-like symptoms
- Rash
- GI symports (nausea, vomiting, dyspepsia, diarrhea)
- Low blood counts
- Hypersensitivity reactions

Medication Interactions: Rifamycins

- Cytochrome P-450 enzymes inducers
- (+) metabolism and (-) serum levels and therefore the effectiveness of many drugs
- Examples
  - Anticoagulants, including warfarin
  - Anticonvulsants
  - Cyclosporine
  - Dapsone
  - Digitalis
  - Estrogens
  - Glucocorticoids
  - Hormonal contraceptives,
  - Ketoconazole
  - Levothyroxine
  - Opioids
  - Oral hypoglycemic agents
  - Theophylline

Adverse Events: Isoniazid

- Rash, hair loss
- Gynecomastia, hyperglycemia, metabolic acidosis,
- GI side effects (nausea, vomiting, abdominal discomfort, pancreatitis
- Low blood counts
- Liver: Drug-induced liver injury or hepatitis; mild and transient elevation of transaminases; severe hepatitis
- Optic neuritis
- Monoamine poisoning (avoid food containing tyramine and histamine)
- Pyridoxine deficiency →Peripheral neuropathy
  - Give 25 mg/day of pyridoxine for patients with symptoms of, or at increased risk of, peripheral neuropathy

Medication Interactions: Isoniazid

Increases Concentrations

- Carbamazepine
- Disulfiram
- Dofetilide
- Fosphenytoin
- phenytoin
- Nimodipine
- Tacrolimus
- Theophylline
- Triazolam
- Ubrogepant
- Valproic acid
- Warfarin

Decreases Concentrations

- Itraconazole
- Ketoconazole

Affected by

- Systemic corticosteroids
- Aluminum-containing antacids

Monitoring Treatment

- Ongoing education
- Ongoing monitoring: adherence, symptoms, exam, lab tests
- Education regarding any future TB testing
- Partnership with patients and families

Useful Resources

- Testing and Treatment of Latent Tuberculosis Infection in the United States NSTC/NTCA Clinical Recommendations | February 2025
- https://tbcontrollers.org/resources/tb-infection/clinical-recommendations/

THANK YOU