# Evaluation and Management of the Patient with Latent Tuberculosis Infection (LTBI)

AAPA 2024

HOUSTON, TX

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# Learning objectives

At the conclusion of this session, participants should be able to:

Recognize the benefits to both the community and individuals of appropriate management of LTBI

Identify the proper screening test for LTBI

Select the appropriate pharmacological therapy for the individual management of LTBI

# Disclosures

No financial disclosures

# Terms

**Tuberculosis (TB) infection**

- Previously: Latent Tuberculosis Infection (LTBI).
- The term *latent* has been removed. Latent implies the TB bacteria are dormant; they are active but contained.
- A state of persistent immune response to *Mycobacterium tuberculosis* without clinical evidence of active TB disease.

**Tuberculosis disease**

- Previously: Active tuberculosis disease or infection
- Progression of an initial exposure, or reactivation of a contained infection.

Behr MA, Kaufmann E, Duffin J, Edelstein PH, Ramakrishnan L. Latent Tuberculosis: Two Centuries of Confusion. Am J Respir Crit Care Med. 2021;204(2):142-148. doi:10.1164/rccm.202011-4239PP

# A typical Monday afternoon at the office

## ANNIE

https://www.flickr.com/photos/kartaba/32433753580/

## ANAYA

https://commons.wikimedia.org/wiki/File:Geethuanna.jpg

# A typical Monday afternoon in the office

<u>One has a positive TB skin test. “But its always positive, I just need an x-ray”.</u>

Which of the following is the next best step?

**A**. Order a chest x-ray and if negative no further follow up is needed.

**B**. Order a chest x-ray and if negative discuss benefits of treatment.

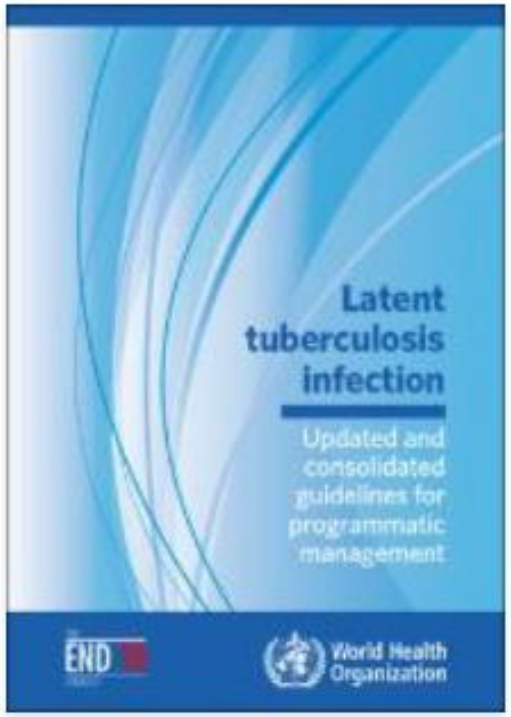
**C**. Repeat the test with an Interferon-gamma release assay.

**D**. Refer to an Infectious disease specialist.

https://www.flickr.com/photos/kartaba/32433753580/

https://commons.wikimedia.org/wiki/File:Geethuanna.jpg

# WHO,CDC,IDSA,ATS,NTCA



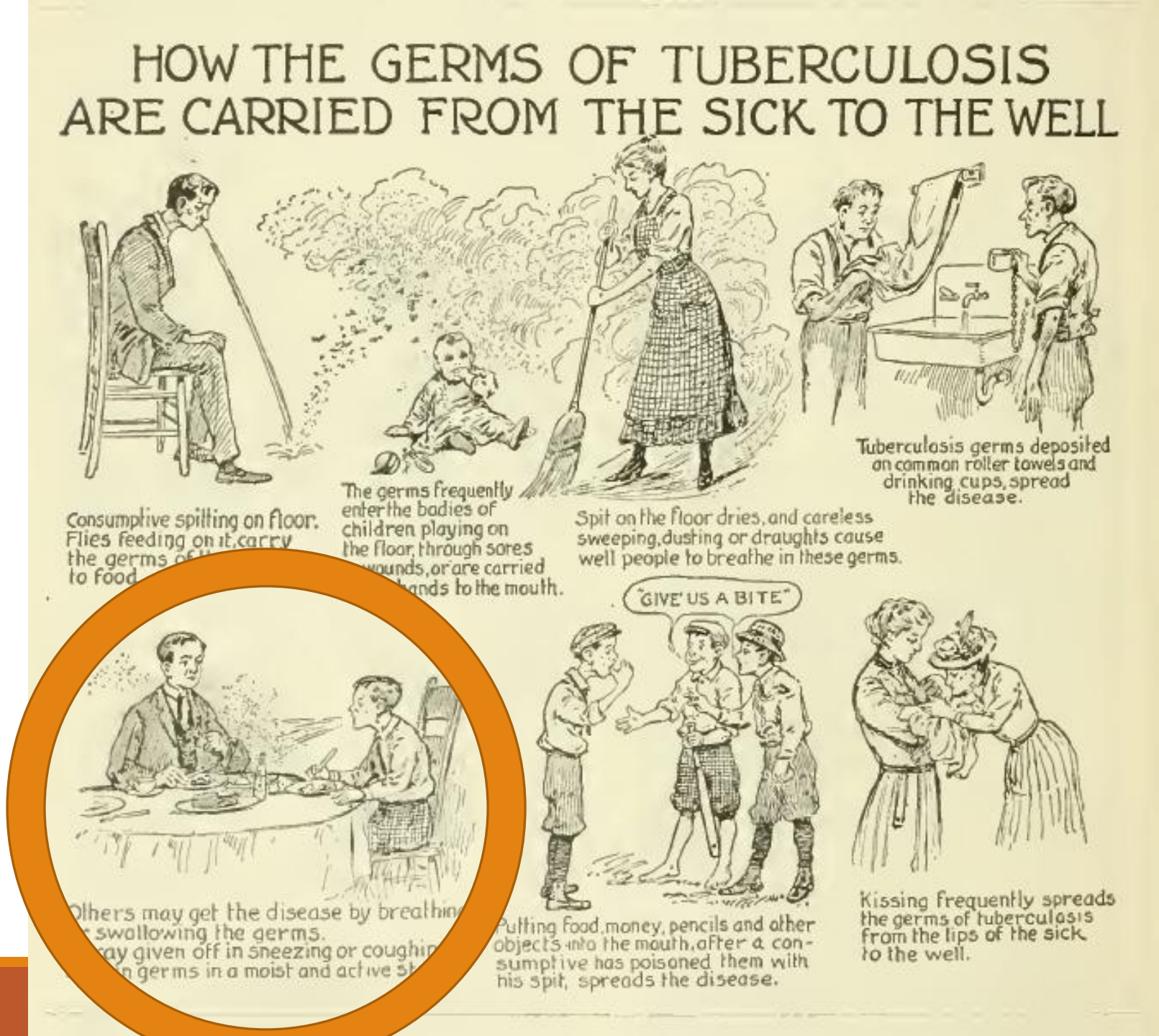

https://www.who.int/publications/i/item/9789241550239http://


https://www.cdc.gov/tb/default.htm

Illustration from the August 1918 issue of North Carolina's Health Bulletin:

Modes of transmission:

- “consumptive spitting” (flies carry it to food)
- “germs on the floor”
- “careless sweeping”
- “common towels and cups”
- “breathing or swallowing”
- “putting things in your mouth”
- “kissing”



# TB transmission and life cycle

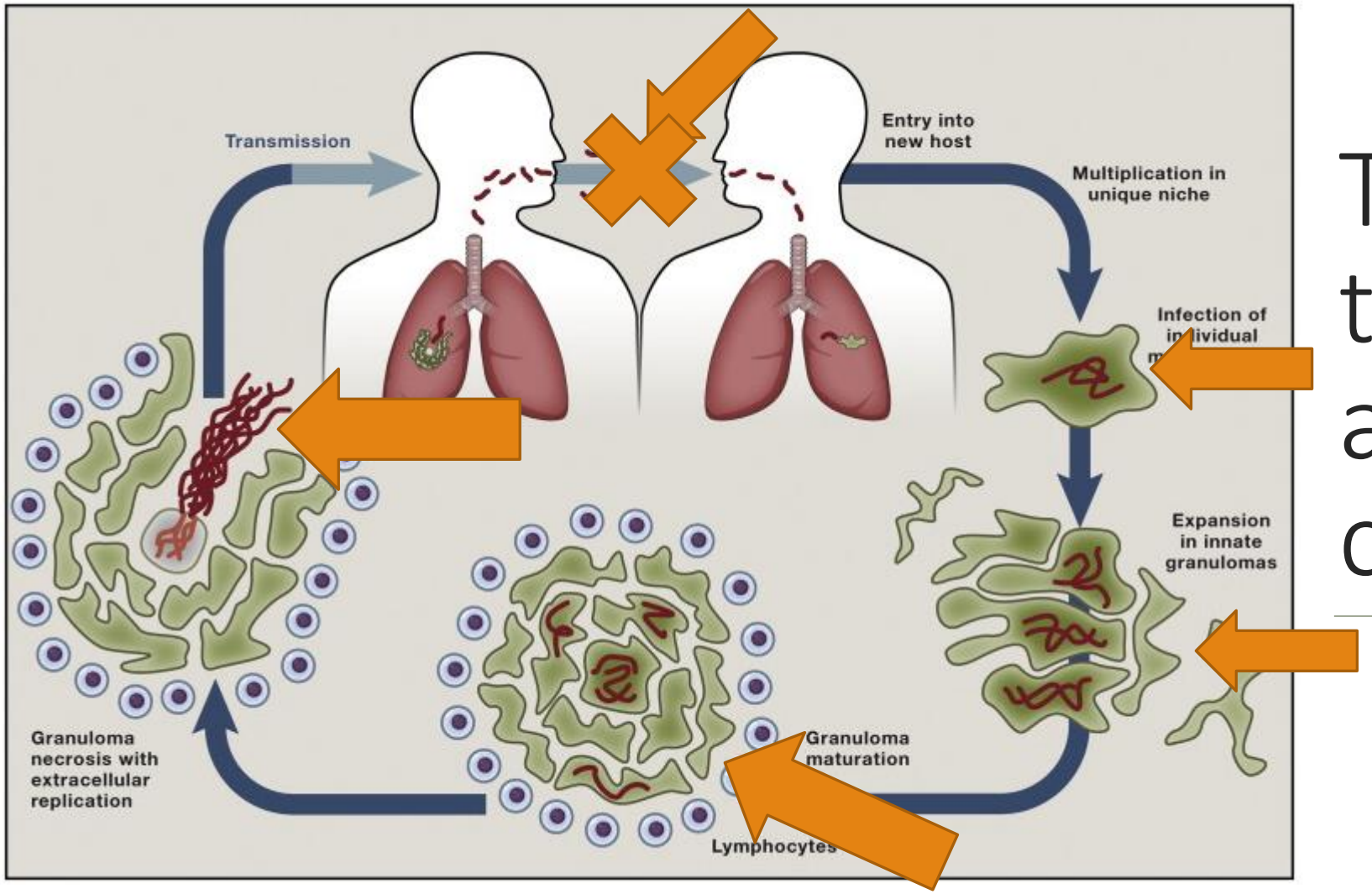



Image: Cambier, C. J., Falkow, S., & Ramakrishnan, L. (2014). Host evasion and exploitation schemes of Mycobacterium tuberculosis. Cell, 159(7), 1497-1509.

Chandra, P., Grigsby, S. J., & Philips, J. A. (2022). Immune evasion and provocation by Mycobacterium tuberculosis. Nature Reviews Microbiology, 20(12), 750-766.

# Mycobacterium Tuberculosis (TB) Worldwide

1/3 of the world is infected.

- i.e., 1/3 of the world's population is acting as a reservoir for TB
- 5-10% lifetime risk of developing active infection.
  - 5% in the first 2 years after infection
  - Another 5% at some point in their lives.

10.6 million new cases of TB in 2022

1.3 million deaths worldwide in 2022

WHO,2023

https://commons.wikimedia.org/wiki/File:Globe.svg

# Mycobacterium Tuberculosis (TB) United States

More than **13 million** people in the United States have LTBI.

- 4% of the total population

In 2022, a total of **8331** new active TB cases were reported in the United States.

- 80% were related to untreated LTBI

**602** TB-related deaths reported in 2021

https://commons.wikimedia.org/wiki/File:United_States_on_the_globe_(North_America_centered).svg

Division of Tuberculosis Elimination, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention. Last Reviewed: November 15, 2023. Accessed 2/25/24

# Mycobacterium Tuberculosis (TB) California

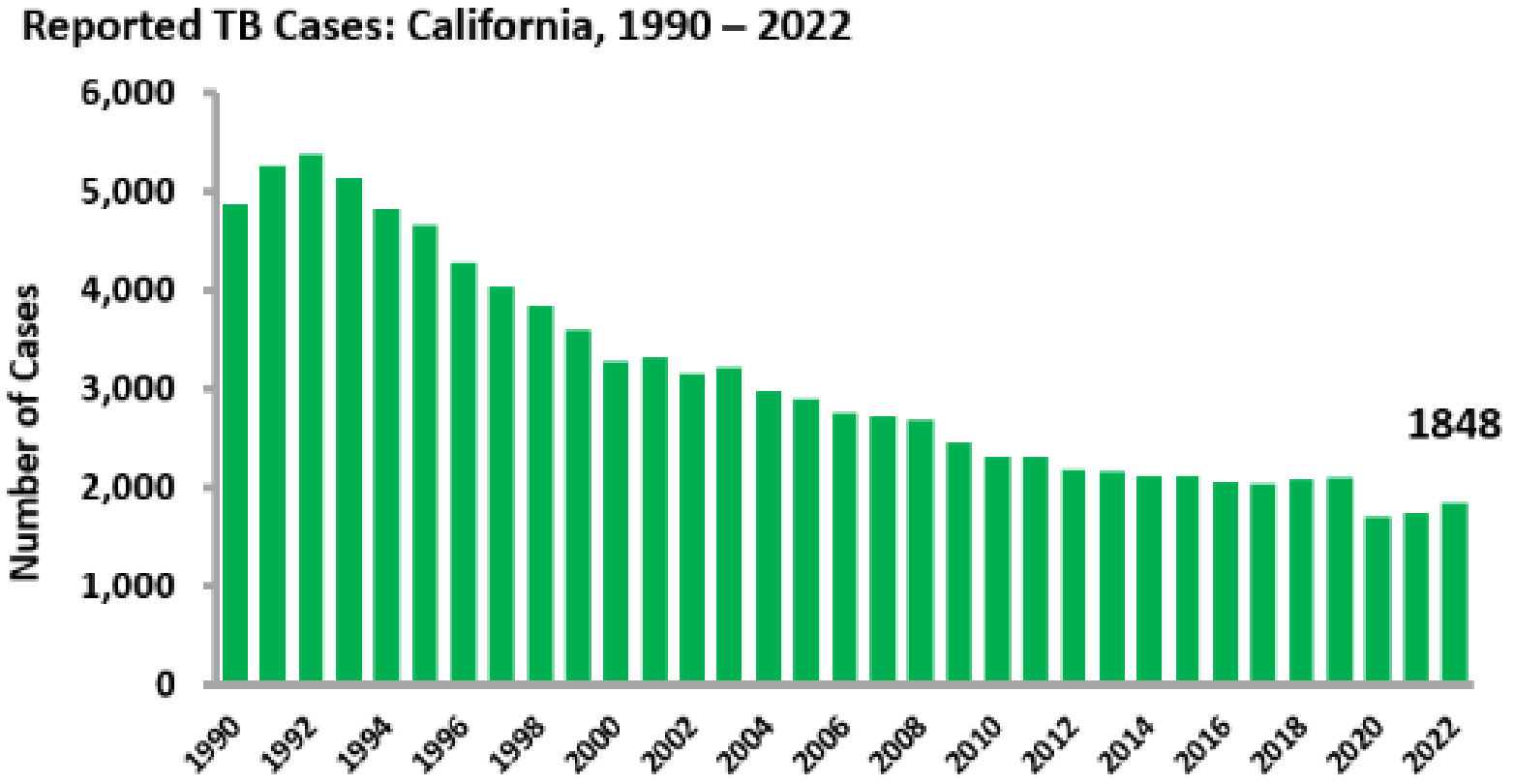
In 2022, California reported **1,848** new active TB cases.

- **Double** the national incidence rate.
- 80% were due to reactivation of LTBI
  - *LTBI is not a reportable condition in CA*.
- 13% resulted from recent transmission.
- 7% were imported from outside the United States.

http://www.erasepoverty.org/taxonomy/term/261/all

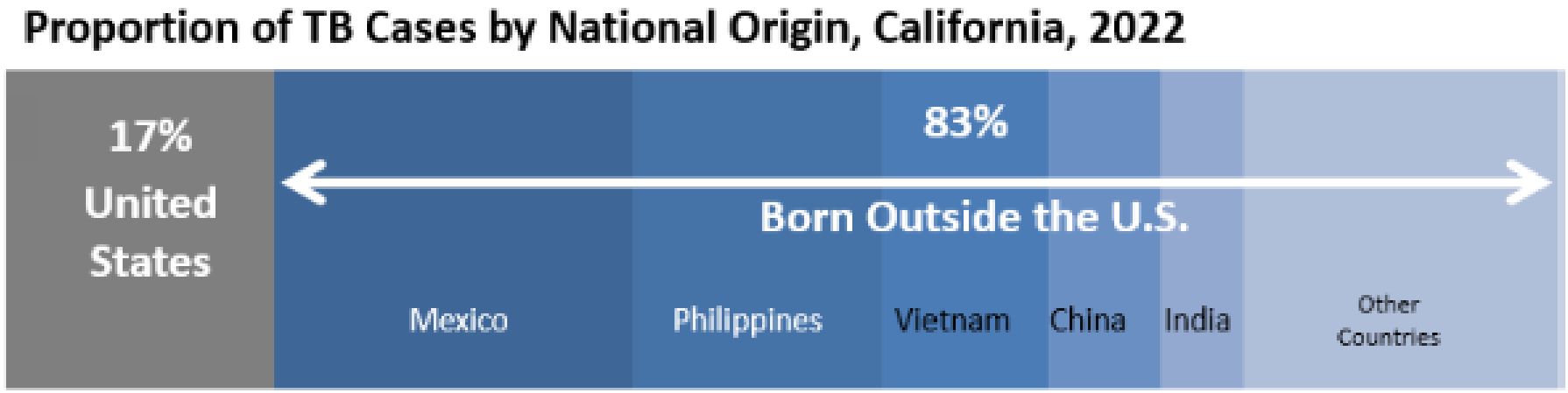
Tuberculosis Control Branch, Report on Tuberculosis in California, 2022. California Department of Public Health, Richmond, CA. Last accessed 1/23/2024
www.cdph.ca.gov/Programs/CID/DCDC/CDPH Document Library/TBCB-TB-Snapshot-2022.pdf

# Mycobacterium Tuberculosis (TB) California




Tuberculosis Control Branch, Report on Tuberculosis in California, 2022. California Department of Public Health, Richmond, CA. Last accessed 2/25/2024
www.cdph.ca.gov/Programs/CID/DCDC/CDPH Document Library/TBCB-TB-Snapshot-2022.pdf

# Mycobacterium Tuberculosis (TB) California




Tuberculosis Control Branch, Report on Tuberculosis in California, 2022. California Department of Public Health, Richmond, CA. Last accessed 1/23/2024
www.cdph.ca.gov/Programs/CID/DCDC/CDPH Document Library/TBCB-TB-Snapshot-2022.pdf

# Mycobacterium Tuberculosis (TB) Texas

Texas is number Two.

In 2022- 1,097 new active TB cases where reported.

Harris County accounted for 24%.

http://www.erasepoverty.org/taxonomy/term/261/all

Texas Health and Human Services. TB Data and Statistics. www.dshs.texas.gov/tuberculosis-tb/tb-data-statistics. Accessed 1/23/2024

# Why screen for LTBI?

Ending the TB epidemic by 2030 is among the health targets of the United Nations Sustainable Development Goals.

To do so requires elimination of TB reservoir.

Screening and treatment of LTBI are critical components.

**90%** efficacy of first line treatments for LTBI

- If taken properly.
- Unfortunately, completion rates vary from 24%-98%.
  - Average of 50-60%

1.Jasmer RM, Saukkonen JJ, Blumberg HM, Daley CL, Bernardo J, Vittinghoff E, King MD, Kawamura LM, Hopewell PC. Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a multicenter clinical trial. Ann Intern Med. 2002;137(8):640–647
2.Horsburgh CR, Goldberg S, Bethel J, Chen S, Colson PW, Hirsch-Moverman Y, Hughes S, Shrestha-Kuwahara R, Sterling TR, Wall K. et al. Latent TB infection treatment acceptance and completion in the United States and Canada. Chest. 2010;137(2):401–409. doi: 10.1378/chest.09-0394

# The screening dilemma

## ANNIE

https://www.flickr.com/photos/kartaba/32433753580/

## ANAYA

https://commons.wikimedia.org/wiki/File:Geethuanna.jpg

# The screening dilemma

**ANAYA**

27-year-old female.

Immigrated from India 5 years ago.

Software engineer who regularly travels to China and India for work.

“I just need a chest x-ray; I am always positive”

She has no concerning symptoms or other medical conditions.

https://commons.wikimedia.org/wiki/File:Geethuanna.jpg

# The screening dilemma

## ANNIE

https://www.flickr.com/photos/kartaba/32433753580/

26-year-old female.

Moved to the area from Utah 5 years ago.

Works part-time staging homes for a real estate agency.

Has never been outside of the country.

She has no concerning symptoms or other medical conditions.

# Screening for LTBI

**Despite recommendations to the contrary, testing is often done to meet administrative or legal requirements.**

- E.g., persons meeting entrance requirements for certain schools and workplaces.

http://www.southfranceamerican.com/2016/02/how-french-bureaucracy-worksreally.html

Lewinsohn, D. M., Leonard, M. K., LoBue, P. A., Cohn, D. L., Daley, C. L., Desmond, E., ... & Woods, G. L. (2017). Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. Clinical Infectious Diseases, 64(2), e1-e33.

# Screening for LTBI

**Ideally** screening would be targeted based on based on:

- The risk of infection
- The risk of progression to tuberculosis disease
- The benefit of therapy.

All testing should be accompanied by a plan for follow-up care.

- E.g., Intention to treat.

Lewinsohn, D. M., Leonard, M. K., LoBue, P. A., Cohn, D. L., Daley, C. L., Desmond, E., ... & Woods, G. L. (2017). Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. Clinical Infectious Diseases, 64(2), e1-e33.

# Screening for LTBI

**Individuals at risk for new infection due to tuberculosis exposure:**

- Close contact with known active TB.
  - Test initial, and then repeat 8-12 weeks after exposure has ended.
- Healthcare workers who care for patients at increased risk for TB.
  - Baseline 2 step, and then annually.

Center for Disease Control and Prevention. Tuberculosis, Who Should be Tested for TB Infection. Page last reviewed: April 14, 2016 https://www.cdc.gov/tb/topic/testing/whobetested.htm. Accessed 01/23/24

# Screening for LTBI

- **Individuals with an increased risk of progression to active disease due to underlying conditions.**
  - Those on immunosuppressive medications.
  - HIV
    - Progression from LTBI to TB disease is 7-10% per year with untreated HIV.
    - Antiretroviral therapy reduces the risk of progression.
  - IV drug users.
  - Diabetes

Center for Disease Control and Prevention. Tuberculosis, Who Should be Tested for TB Infection. Page last reviewed: April 14, 2016 https://www.cdc.gov/tb/topic/testing/whobetested.htm. Accessed 01/23/24

# Screening for LTBI

- **Infants, children and adolescents exposed to adults who are at increased risk.**
- **People who live or work in high-risk settings.**
  - For example: correctional facilities, long-term care facilities or nursing homes, and homeless shelters.
- **People from a country where TB disease is common**
  - Most countries in Latin America, the Caribbean, Africa, Asia, Eastern Europe, and Russia.

Center for Disease Control and Prevention. Tuberculosis, Who Should be Tested for TB Infection. Page last reviewed: April 14, 2016
https://www.cdc.gov/tb/topic/testing/whobetested.htm. Accessed 01/23/24

# Screening for LTBI

Estimated TB incidence rates per 100,00:
Latin America
The Caribbean
Africa
Asia
Eastern Europe
Russia


www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023/tb-disease-burden/1-1-tb-incidence

# Risk assessment tool

Diabetes increases lifetime risk of developing active TB by 3-11 x that of non-diabetic.

| Risk Factor | Yes | No |
|---|---|---|
| Recent close or prolonged contact with someone with infectious TB disease | | |
| Foreign-born person from or recent traveler to high-prevalence area | | |
| Chest radiographs with fibrotic changes suggesting inactive or past TB | | |
| HIV infection | | |
| Organ transplant recipient | | |
| Immunosuppression secondary to use of prednisone (equivalent of ≥15 mg/day for ≥1 month) or other immunosuppressive medication such as TNF-α antagonists | | |
| Injection drug user | | |
| Resident or employee of high-risk congregate setting (e.g., prison, long term care facility, hospital, homeless shelter) | | |
| Medical conditions associated with risk of progressing to TB disease if infected (e.g., diabetes mellitus, silicosis, cancer of head or neck, Hodgkin's disease, leukemia, and end-stage renal disease, intestinal bypass or gastrectomy, chronic malabsorption syndrome, low body weight [10% or more below ideal for given population]) | | |
| Signs and symptoms of TB | | |

http://www.cdc.gov/tb/ Adapted from a form developed by Minnesota Department of Health TB Prevention and Control Program

Al-Rifai, R. H., Pearson, F., Critchley, J. A., & Abu-Raddad, L. J. (2017). Association between diabetes mellitus and active tuberculosis: A systematic review and meta-analysis. PloS one, 12(11), e0187967.

# Should they have been screened? If so, how?

**ANNIE**

https://www.flickr.com/photos/kartaba/32433753580/

**ANAYA**

https://commons.wikimedia.org/wiki/File:Geethuanna.jpg

# Screening tests for LTBI

- **Tuberculin skin test (TST) a.k.a "PPD"**
  - Preferred TB test for children under the age of 5.

- **Interferon-gamma release assay (IGRA)**
    - QuantiFERON®-TB Gold-in-Tube test T-SPOT® TB test
  - Preferred test for:
    - Individuals who may have difficulty returning for TST reading.
    - Individuals who have received BCG
      - IGRA does not give false-positive results because of prior BCG vaccination or sensitization to nontuberculous mycobacteria

# Screening tests for LTBI

- **Feel comfortable using either test if it is the only one available.**
- **There is no need to perform both tests.***

- ***Performing a second diagnostic test when the initial test is negative is a strategy to increase sensitivity.**
  - **This should only be used in situations where the consequences of missing LTBI exceed the consequences of inappropriate therapy**

Lewinsohn, D. M., Leonard, M. K., LoBue, P. A., Cohn, D. L., Daley, C. L., Desmond, E., ... & Woods, G. L. (2017). Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. Clinical Infectious Diseases, 64(2), e1-e33.

# Tuberculin Skin Test

Based on a delayed-type hypersensitivity reaction to antigens a.k.a "tuberculins"

Antigens are extracted from *Mycobacterium Bovis*

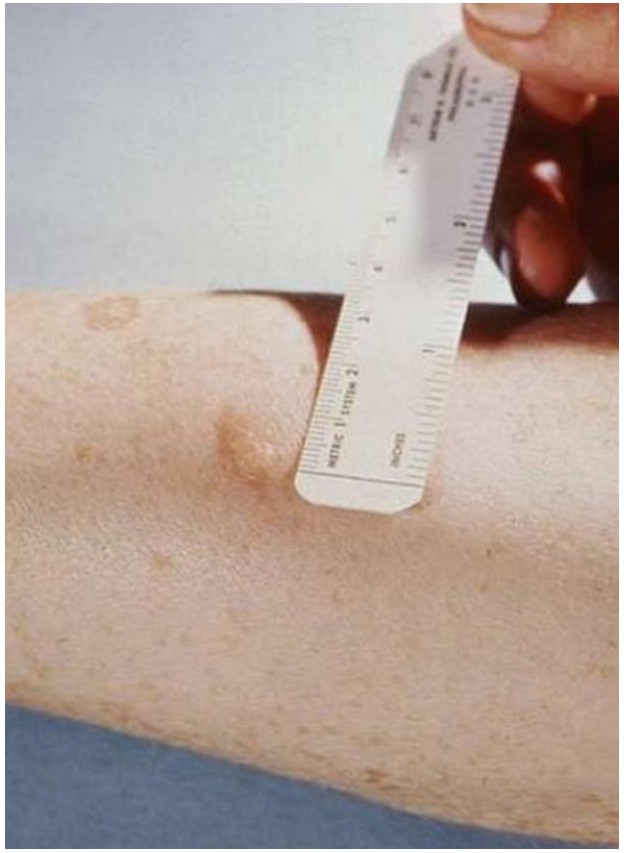
Sensitivity may be affected by:

- HIV
- Malnutrition
- Immunodeficiency

Specificity may be affected by:

- BCG vaccination
- Exposure to non-tuberculosis mycobacteria

# Interpreting skin reaction with TST



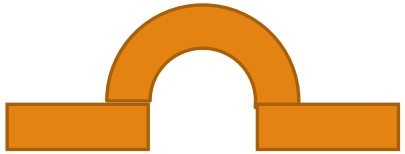
picryl.com/media/mantoux-test-48h-827711

Measurement must be read 48-72 hours after placement to be valid.

Measure and record in millimeters (mm).

Measure the induration.

- Not the amount of erythema.



# Interpreting skin reaction with TST

**> 15 mm**: induration in a healthy person > 4 y.o. Or any degree of vesiculation

**> 10 mm:** in the following populations:

- Recent immigrants from high prevalence areas (<5y)
- Risk for infection due to: IV drug use, diabetes, some malignancies, underweight.
- Residents and staff of high-risk settings.
  - Prisons, shelters, mycobacteria labs, and health care facilities
- Children < 4
- Children exposed to high-risk adults

# Interpreting skin reaction with TST

- **>5mm:**
  - Immunosuppression
    - E.g., ESRD, organ transplants, methotrexate use, long term steroid use
  - HIV
  - Recent contact with active TB
  - Abnormal CXR with fibrotic findings consistent with prior TB infection.

# Interferon-gamma release assay (IGRAs)

Measurement of the immune response to TB antigens:

- Whole blood is mixed with antigens derived from *M.Tuberculosis*.
- White blood cells recognize the antigens, and release interferon-gamma (IFN-g).

IGRA interpretations are based on:

- the amount of IFN-g that is released.
- the number of cells that release IFN-g.

Reported as both a qualitative and quantitative.


pxhere.com/en/photo/977887

# Interpreting IGRA

| QUANTIFERON®-TB GOLD IN-TUBE TEST | T-SPOT®TB TEST |
| --- | --- |
| Positive | Positive |
| Negative | Negative |
| Indeterminate | Indeterminate |
| | Borderline |

# The screening dilemma continues…

"But I had BCG as a kid!!!"

"All my family has a positive skin test!!!"

"I just need a chest x-ray"

"Look, I even have the scar!"

ANAYA

# Bacillus Calmette–Guérin (BCG) Vaccine

Produced from *Mycobacterium bovis*

The first use was in 1921 and it is the most used vaccine in the world!

- Typically, in the setting of newborn immunization in high-risk countries.

Efficacy

- BCG is 70 to 80 percent effective against all forms of TB when administered at birth to mycobacteria-naïve infants.
  - Particularly to prevent the most severe forms of TB:
    - TB meningitis and miliary TB.
    - Also protects against Leprosy.

Provides 20-50 years of protection.

von Reyn CF. Correcting the record on BCG before we license new vaccines against tuberculosis. J R Soc Med. 2017 Nov;110(11):428-433. doi: 10.1177/0141076817732965. Epub 2017 Sep 26. PMID: 28949270; PMCID: PMC5728619

# Bacillus Calmette–Guérin (BCG) Vaccine

**Screening with a known history of BCG**

A person with a history of BCG vaccination can be tested with TST and treated for LTBI if they react.

- IGRA is the preferred test

TST reactions should be interpreted based on risk stratification regardless of BCG vaccination history.

A CXR alone is not the appropriate screening recommendation.

https://www.cdc.gov/tb/publications/ltbi/diagnosis.htm. Accessed 2/25/24

# Next steps after a positive test


www.pexels.com/photo/elderly-man-patient-talking-at-his-doctor-8413410/

# Meta-analysis of 58 studies (70 distinct cohorts) including 748,572 people

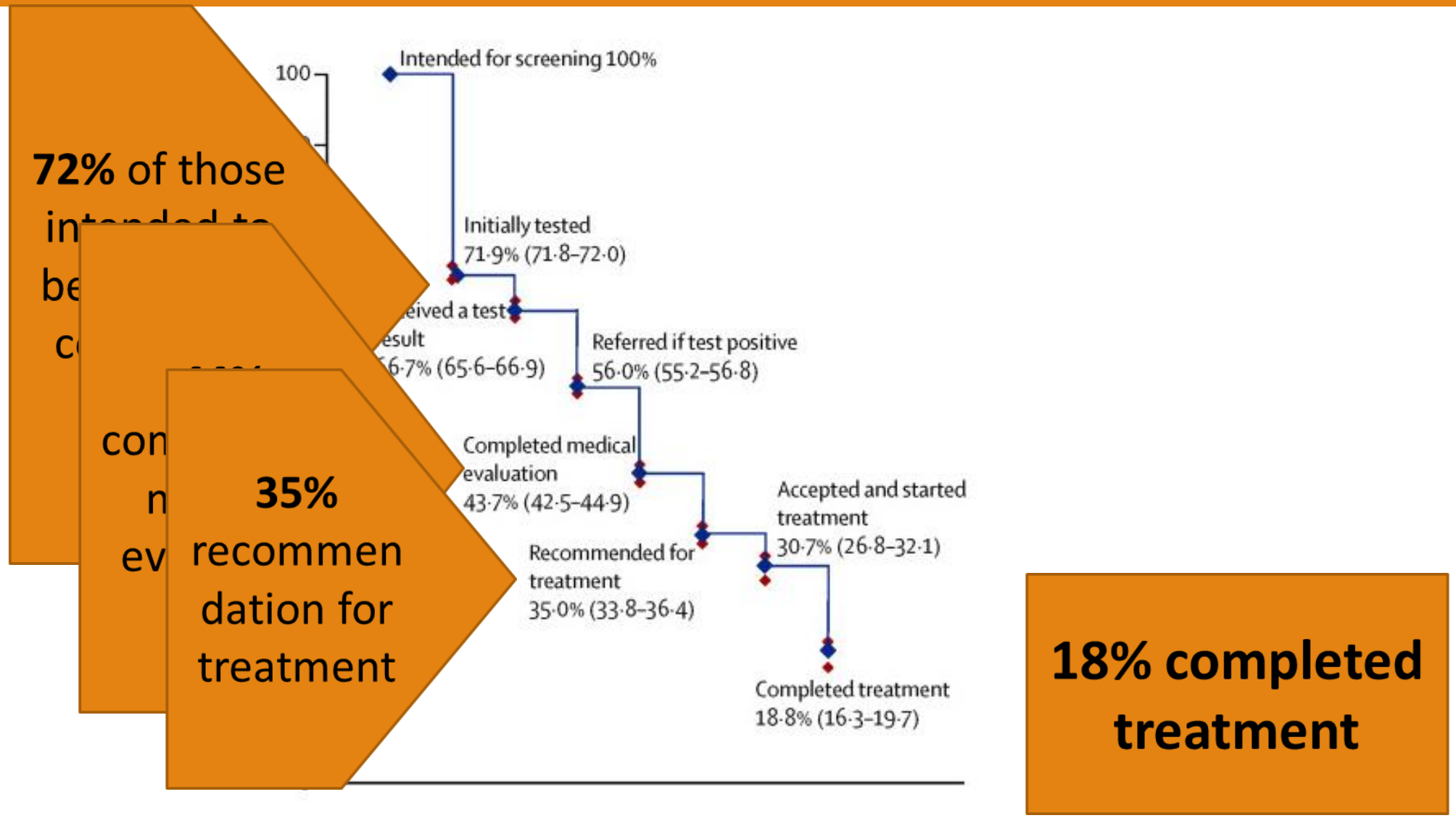



**Figure 2** Losses and drop-outs at each stage of the cascade of care in latent tuberculosis

Alsdurf, H., Hill, P. C., Matteelli, A., Getahun, H., & Menzies, D. (2016). The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. The Lancet Infectious Diseases, 16(11), 1269-1278.

# Barriers to treatment

**Provider Barriers**

- Lack of knowledge.
- Uncomfortable with LTBI management.
- Misconceptions about LTBI testing.
  - E.g., high cost
- High likelihood of referral to specialists.

Szkwarko D, Kim S, Carter EJ, Goldman RE (2022) Primary care providers' and nurses' knowledge, attitudes, and skills regarding latent TB infection testing and treatment: A qualitative study from Rhode Island. PLoS ONE 17(4): e0267029. https://doi.org/10.1371/journal.pone.0267029

# Barriers to treatment

**Patient barriers**

- Fear of adverse effects
- Long duration of treatment
- Financial barriers
- Lack of transportation
- Insufficient ressources for LTBI control

Liu Y, Birch S, Newbold KB, Essue BM. Barriers to treatment adherence for individuals with latent tuberculosis infection: A systematic search and narrative synthesis of the literature. Int J Health Plann Manage. 2018;33(2):e416-e433. doi:10.1002/hpm.2495

# Management of tuberculosis infection

**General principles**:

- Exclude TB disease.
  - Ensure history and physical do not include cough, fevers, weight loss, or night sweats.
  - Chest XRAY is obtained to rule out asymptomatic disease.
    - Up to 50% of TB disease can be asymptomatic.

# Management of tuberculosis infection

**Evaluate comorbid conditions and current medications**.

- Treatment is associated with liver toxicity, but there is no universal recommendation to screen prior to treatment.
- Exceptions:
  - Heavy alcohol use
  - known liver disease or a history of elevated transaminases
  - IV drug use
  - Already on hepatotoxic medications
- Baseline liver transaminase testing > 3 x normal needs further evaluation.

# Management of tuberculosis infection

CDC and the National Tuberculosis Controllers Association (NTCA) **preferentially recommend short-course, rifamycin-based, 3- or 4-month treatment options**.

Medications used to treat TB infection, either on their own or in combination.

- Isoniazid (INH)
- Rifapentine (RPT)
- Rifampin (RIF)

# Management of tuberculosis infection

Three months of once-weekly isoniazid plus rifapentine (3HP)

Four months of daily rifampin (4R)

Three months of daily isoniazid plus rifampin (3HR)

Although effective, 6 month and 9 months of isoniazid have higher toxicity risk and lower completion rates.

| Drug(s) | Duration | Dose | Frequency | Total Doses |
|---|---|---|---|---|
| Isoniazid (INH)* and Rifapentine (RPT)† | 3 months | Adults and Children aged 12 years and older:<br>INH: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum<br>RPT:<br>10–14.0 kg 300 mg<br>14.1–25.0 kg 450 mg<br>25.1–32.0 kg 600 mg<br>32.1–49.9 kg 750 mg<br>≥50.0 kg 900 mg maximum<br>Children aged 2–11 years:<br>INH*: 25 mg/kg; 900 mg maximum<br>RPT†: as above | Once weekly | 12 |
| Rifampin (RIF)§ | 4 months | Adults: 10 mg/kg<br>Children: 15–20 mg/kg‖<br>Maximum dose: 600 mg | Daily | 120 |
| Isoniazid (INH)* and Rifampin)§ | 3 months | Adults:<br>INH*: 5 mg/kg; 300 mg maximum<br>RIF§: 10 mg/kg; 600 mg maximum<br>Children:<br>INH*: 10-20 mg/kg; 300 mg maximum<br>RIF§: 15-20 mg/kg; 600 mg maximum | Daily | 90 |

INH formulated as 100mg and 300mg tablets.

Rifapentine formulated as 150mg tablets.

Rifampin formulated as 150 mg and 300 mg capsules

www.cdc.gov/tb/topic/treatment/ltbi.htm

# Management of tuberculosis infection

## Which one is best?

Choice of treatment should be based on:

- Adherence
- Potential for adverse effects
- Preference (provider, patient, facility)

Sterling TR, Njie G, Zenner D, et al. Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020. MMWR Recomm Rep. 2020;69(1):1-11. Published 2020 Feb 14. doi:10.15585/mmwr.rr6901a1

# What happened to DOT?

| | | | | |
|---|---|---|---|---|
| Isoniazid (INH) | 6 months | Adults: 5 mg/kg<br>Children: 10–20 mg/kg¶<br>Maximum dose: 300 mg | Daily | 180 |
| | | Adults:15 mg/kg<br>Children: 20–40 mg/kg¶<br>Maximum dose: 900 mg | Twice weekly‡ | 52 |
| | 9 months | Adults: 5 mg/kg<br>Children: 10–20 mg/kg¶<br>Maximum dose: 300 mg | Daily | 270 |
| | | Adults: 15 mg/kg<br>Children: 20–40 mg/kg¶<br>Maximum dose: 900 mg | Twice weekly‡ | 76 |

‡Intermittent regimens must be provided via directly observed therapy (DOT), that is, a health care worker observes the ingestion of medication.

Directly observed therapy (DOT) **must** be done for intermittent INH therapies.

https://www.cdc.gov/tb/topic/treatment/ltbi.htm

# Management of tuberculosis infection: Follow up

At LEAST monthly evaluation for:

- Adherence
- Signs and symptoms of TB disease
- Signs and symptoms of adverse effects
  - hepatitis
    - jaundice, loss of appetite, fatigue, and/or muscle and joint aches
  - Peripheral neuropathy
  - Rifamycins may cause rash and thrombocytopenia.
  - Labs?

# Management of tuberculosis infection: Laboratory Monitoring

Routine laboratory monitoring during treatment of LTBI is recommended only for:

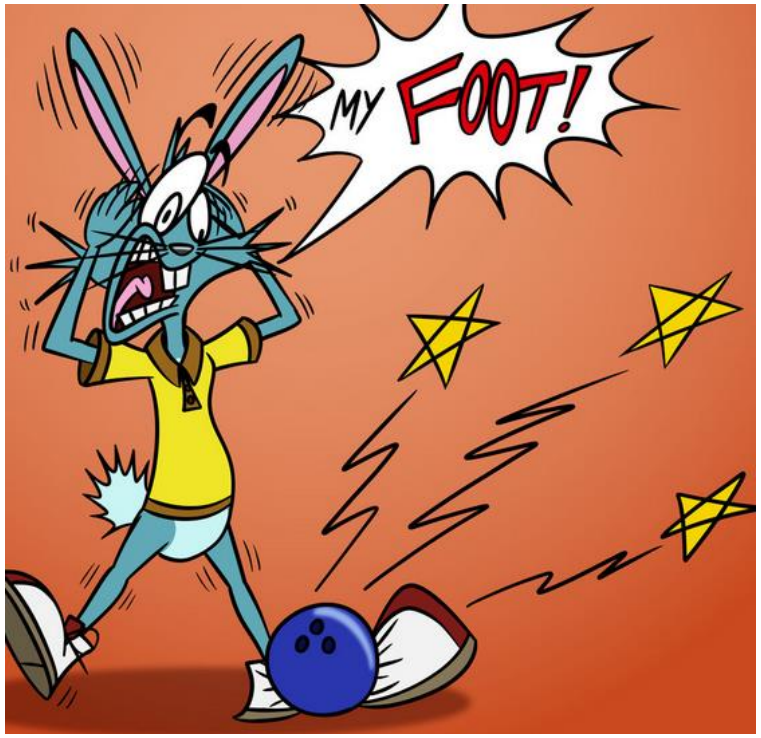
- Abnormal baseline liver function tests.

# Management of tuberculosis infection: INH Neuropathy

Typical presentation is paresthesia.

Pyridoxine/vitamin B-6 is not routinely recommended when using INH.

- Except during pregnancy, or if symptoms of neuropathy develop.
- Neuropathy develops in less than .4%

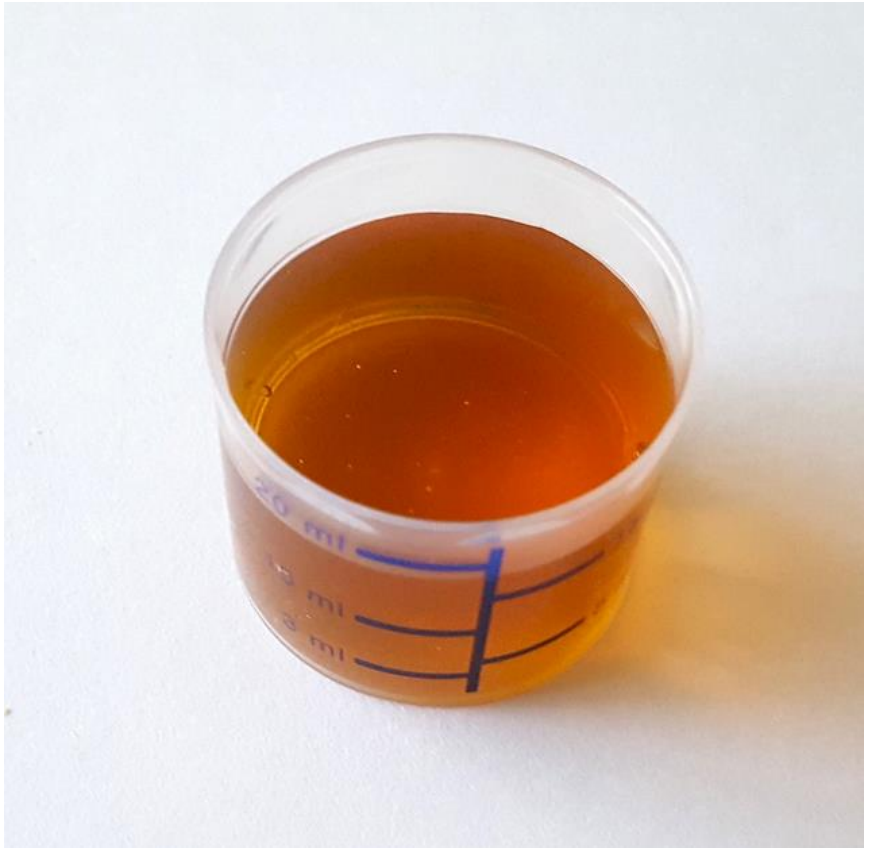



www.deviantart.com/theendertoonist/art/Hayden-Hare-Drop-The-Bowling-Ball-950025929

# Management of tuberculosis infection: Important patient education

RIF or RPT  will cause orange discoloration of body fluids including urine and tears.

- Wearing soft contact lenses while on the medication is not recommended.
  - They may become stained.



www.flickr.com/photos/157786281@N07/46912443664

# Management of tuberculosis infection: Interactions

Notable interactions:

- INH increases blood levels of phenytoin (Dilantin) and disulfiram (Antabuse)
- RIF and RPT decrease blood levels of:
  - oral contraceptives, warfarin, sulfonureas, and methadone

# Management of tuberculosis infection: Treatment Completion

Give documentation of:

- TST or IGRA results
- Medication, duration, and treatment completion dates.

Remind them that treatment reduces the risk of progression to TB disease but does not eliminate it.

Review the signs and symptoms of TB disease:

- Advise to seek medical attention if these occur.

Risk of reinfection.

Future screening (TST or IGRA) is inaccurate.

# Take home points

Identification and treatment of LTBI is the cornerstone of controlling TB in the U.S.

Proper screening is important, but don’t let bureaucratic policies ruin your day ☺

All screening should be done with an intention to treat positive results.

Appropriately test and treat individuals who have had BCG.

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