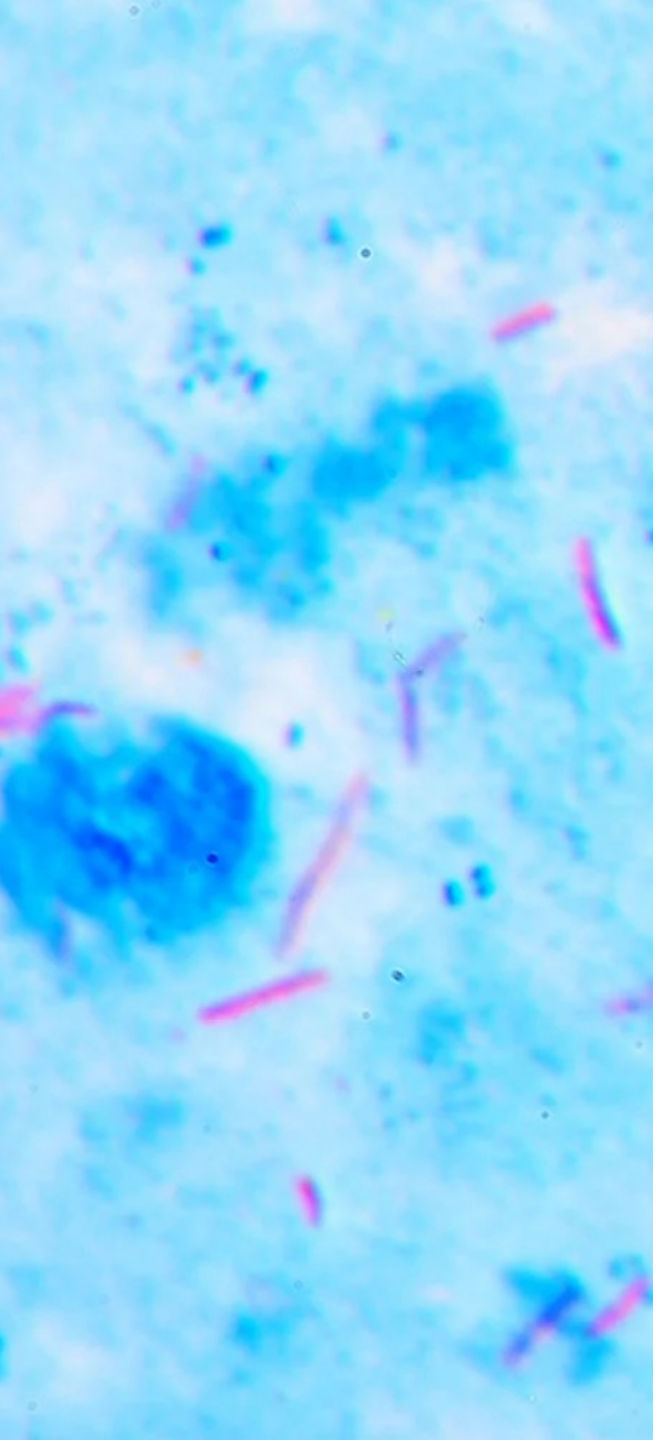


Treatment of latent TB

John Szumowski MD, MPH
Curry Center / UCSF
1-2026

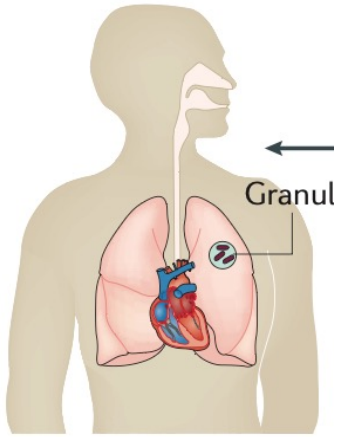
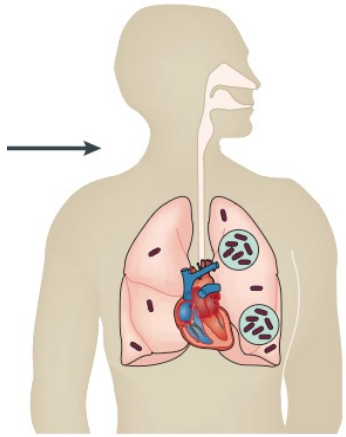
Disclosures

- I am a federal employee (VA). However, I am presenting today in an individual capacity.

Objectives

- What do we mean by latent TB?
- Testing methods: TST & IGRA
- Evaluating a positive result
- LTBI treatment regimens and common challenges

Latent vs Active TB

	Latent TB infection	Active TB disease
		
TST	Positive	Usually positive
IGRA	Positive	Usually positive
Culture	Negative	Positive
Sputum smear	Negative	Positive or negative
Infectious	No	Yes
Symptoms	None	Mild to severe
Preferred treatment	Preventive therapy	Multidrug therapy

Pai et al. Nat Rev Dis Prim 2016

Regulations

California Assembly Bill 2132 was recently passed into law (took effect January 1, 2025):

- Requires an adult patient receiving primary care services to be offered risk assessment and testing if indicated (if covered by insurance)
- Must also provide or refer for follow-up care (CXR, treatment, etc)
- Prohibits health care providers that fail to comply from disciplinary action on license/certification, or any liability, for that failure

California TB Risk Assessment

California Adult Tuberculosis Risk Assessment

- Use this tool to identify asymptomatic **adults** for latent TB infection (LTBI) testing.

LTBI testing is recommended if any of the boxes below are checked.
Only repeat TB testing if there is a new risk factor since last screening

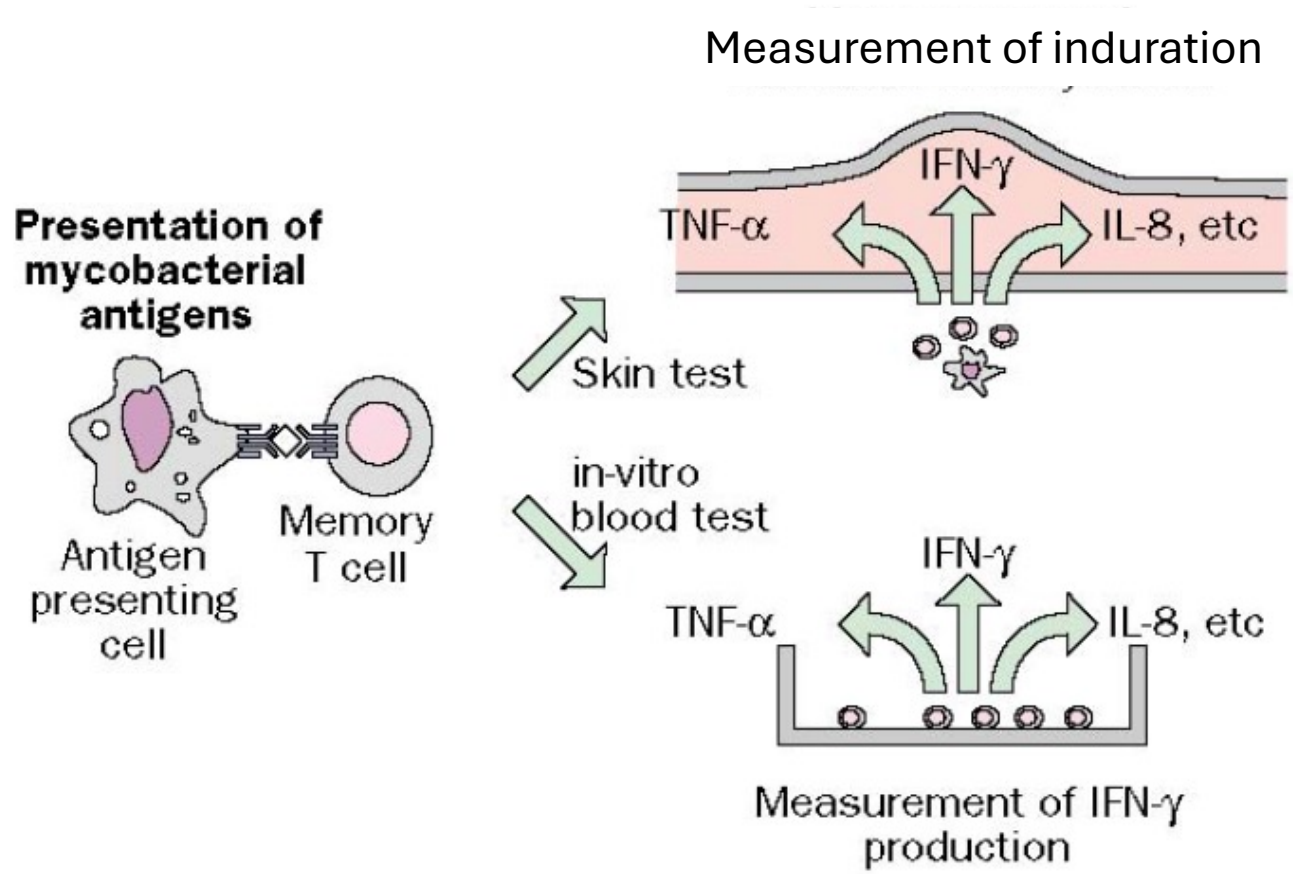
- ☐ **Birth, travel, or residence** for at least 1 month, or frequent border crossing in a country with an elevated TB rate*
  Interferon Gamma Release Assay (IGRA) is preferred over Tuberculin Skin Test (TST), especially for non-U.S.-born persons
- ☐ **Immunosuppression**, current or planned
  HIV infection, organ transplant recipient, congenital or acquired immune deficiency, or treated with biologic agents including TNF-alpha antagonist (e.g., infliximab, adalimumab, etanercept, others), steroids (equivalent of prednisone ≥2 mg/kg/day, or ≥15 mg/day for ≥2 weeks) or other immunosuppressive medication
- ☐ **Close contact** to someone with infectious TB disease during lifetime

Treat for LTBI if LTBI test result is positive and active TB disease is excluded.

California TB Risk Assessment: Adult, Pediatric, School Staff/Volunteers and College/University Students

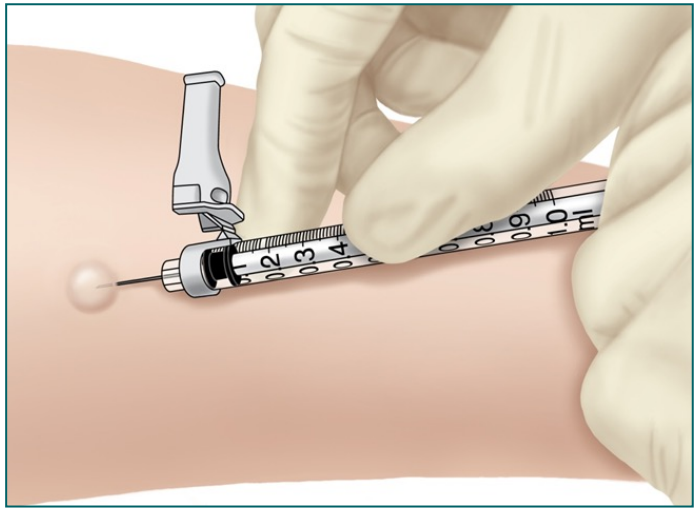
Tests for identifying TB infection

- **No gold standard** for diagnosing LTBI
- <u>All</u> tests assess T-cells for prior exposure to TB antigens



Tuberculin skin testing (TST)

- In use since 1912
- Intradermal injection of tuberculin (Mantoux technique). Protein mixture derived from heat-killed MTB
- Type IV hypersensitivity skin reaction

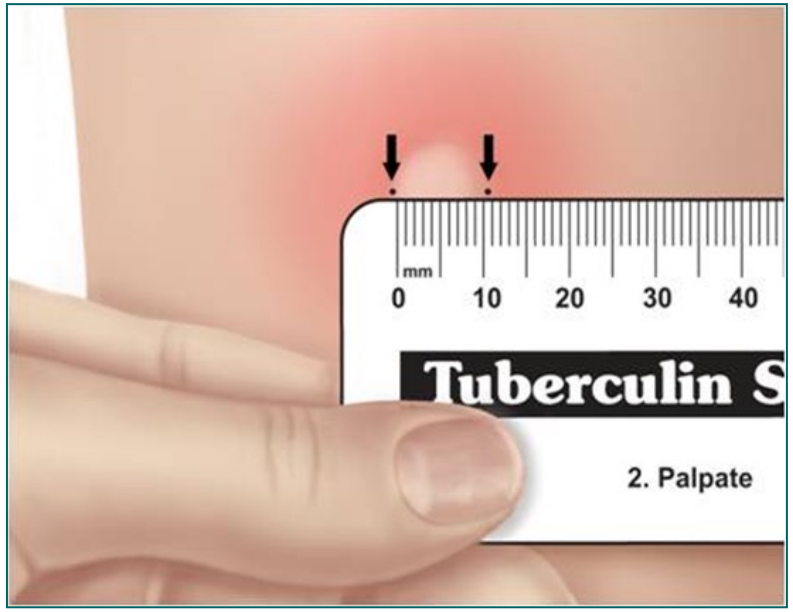


https://www.cdc.gov/tb/hcp/testing-diagnosis/tuberculin-skin-test.html

https://www.cdc.gov/tb/education/mantoux/pdf/Mantoux_TB_Skin_Test.pdf

Horne, D.

Reading the TST



- Read reaction in 48 to 72 hours
- Measure **induration**, not erythema
- Record reaction in mm, not “negative” or “positive”
- Negative reactions can be read accurately for only 72 hours
- Ensure trained health care professional measures and interprets the TST

TST: Thresholds Based on Risk (National guidance)

≥5 mm	≥10 mm	≥15 mm
• HIV • Close contact of infectious TB • Fibrotic changes on CXR consistent with old TB • Severely immunosuppressed (e.g., organ transplant, TNFα blockade)	• Recent immigrants (<5 yrs) from high prevalence countries • Residents/employees of high-risk congregate settings • TB lab personnel • Medical conditions at elevated risk* • IVDU • Children < 4 years of age	• all others

DM
Silicosis
ESRD
Head/neck cancer
Leukemia/lymphoma
Intestinal bypass/Gastrectomy
BMI<=20/ more than 10% below IBW

Risk Factors for Developing Active TB

Risk Factor	Estimated risk for TB relative to persons with no known risk factor
HIV/AIDS	50-170
Transplantation and on immunosuppressant therapy	20-74
Silicosis	30
Chronic renal failure on hemodialysis	10-25
Carcinoma of head and neck	16
Recent TB infection (<2 years)	15
Abnormal CXR with upper lobe fibronodular disease consistent with old TB	6-19
TNF-alpha inhibitor therapy	1.9-9
Treatment with glucocorticoids	4.9
Diabetes mellitus	2-3.6
Young age when infected (0-4 years)	2.2-5
Underweight (BMI ≤ 20)	2-3
Cigarette smoker (1 pack/day)	2-3
Abnormal CXR- granuloma	2
Latent TB infection, normal CXR, no known risk factor	1

*Adapted from: Lobue P, Menzies D. Treatment of latent TB infection: An update. Respirology. 2010 May;15(4):603-22.

California TST interpretation guidelines

> 5 mm of induration	> 10 mm of induration*
Considered positive in: • Persons with HIV or immunosuppression • Recent contacts to an active case of pulmonary or laryngeal TB • Persons with fibrotic changes on chest X-ray consistent with old TB	Considered positive in all other persons recommended for TB screening

Justification: higher sensitivity to identify and treat latent TB infection given California is a high-incidence state

TST pro/con

Challenges of TST

False positive results	False negative results
• Prior BCG vaccination, especially if recent or multiple • NTM • “Boosting” (motivates 2 step testing)	• Immunosuppression • Poor technique • Reagent issue • Inaccurate measurement

- Need trained staff to administer and read test
- Patient needs to return in 48 – 72h for read

Strengths of TST

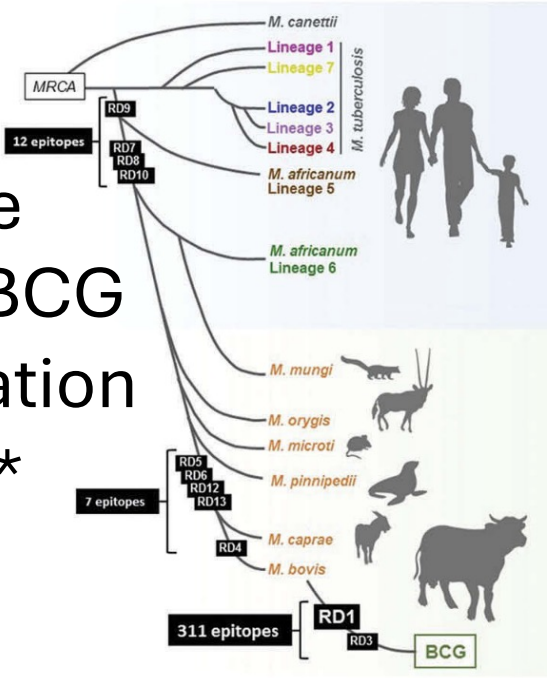
- Well characterized risk for active TB
- Less costly than IGRA

Boosting (TST)

- Some people with LTBI may have a false negative skin test because of a waning immune response
- If a subsequent TST is administered, there may be immune “recall” which results in a positive reaction
- Use two-step tests at baseline in persons who will be retested repeatedly
  - If 1st test +, consider infected; if negative, give 2nd test 1–3 weeks later
  - If 2nd test +, consider infected; if negative, consider uninfected

TST and BCG history

- BCG is an attenuated ***M bovis*** vaccine given worldwide
- Problem: LTBI is common in many countries that give BCG vaccination, but TST can be reactive after BCG vaccination
- TST should be interpreted independent of BCG history*



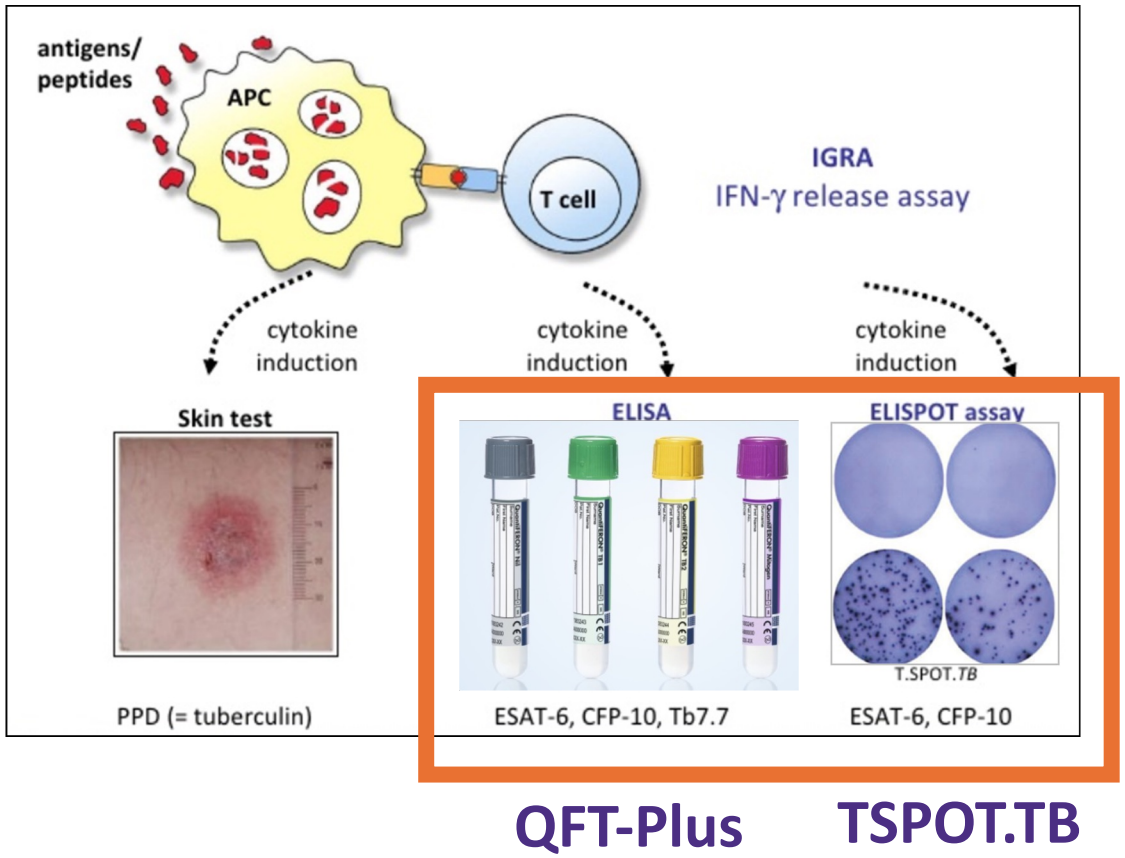
THE BCG WORLD ATLAS 3rd Edition

A DATABASE OF GLOBAL BCG VACCINATION POLICIES AND PRACTICES

Bcgatlas.org

https://www.cdc.gov/tb/hcp/vaccines/index.html

Diagnosing LTBI: Interferon gamma release assays IGRA



IGRAs:

- Available since early 2000s
- Two available tests: QFT-plus and T-SPOT.TB
- Test for TB-specific antigens (ESAT-6, CFP-10)
- No cross-reactivity with BCG
- Less cross-reactivity with NTMs*

Slide modified from Horne, D.
Image credit: Bumbacea D et al 2012

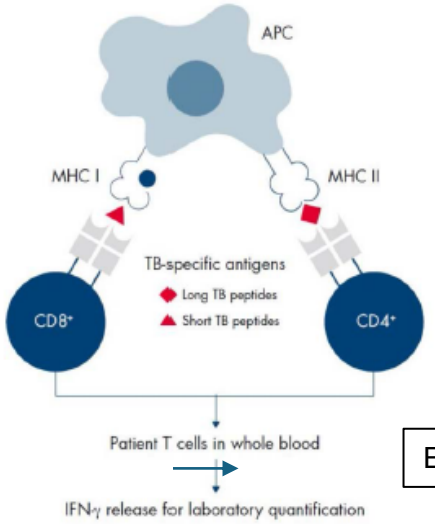
Look at the quantitative results provided in assay report

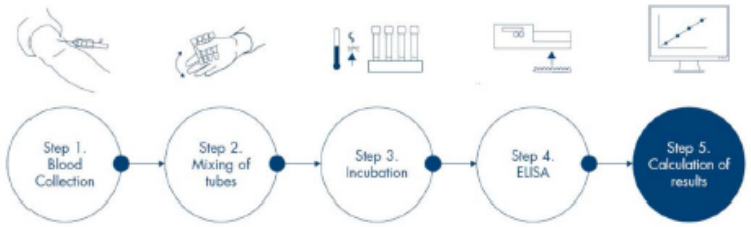
Mitogen – Positive Control
Low response may indicate inability to generate IFN-γ

Nil – Negative Control
Adjusts for background IFN-γ

TB1 – Primarily detects CD4 T cell response

TB2 – Optimized for detection of CD4 and CD8 T cell responses

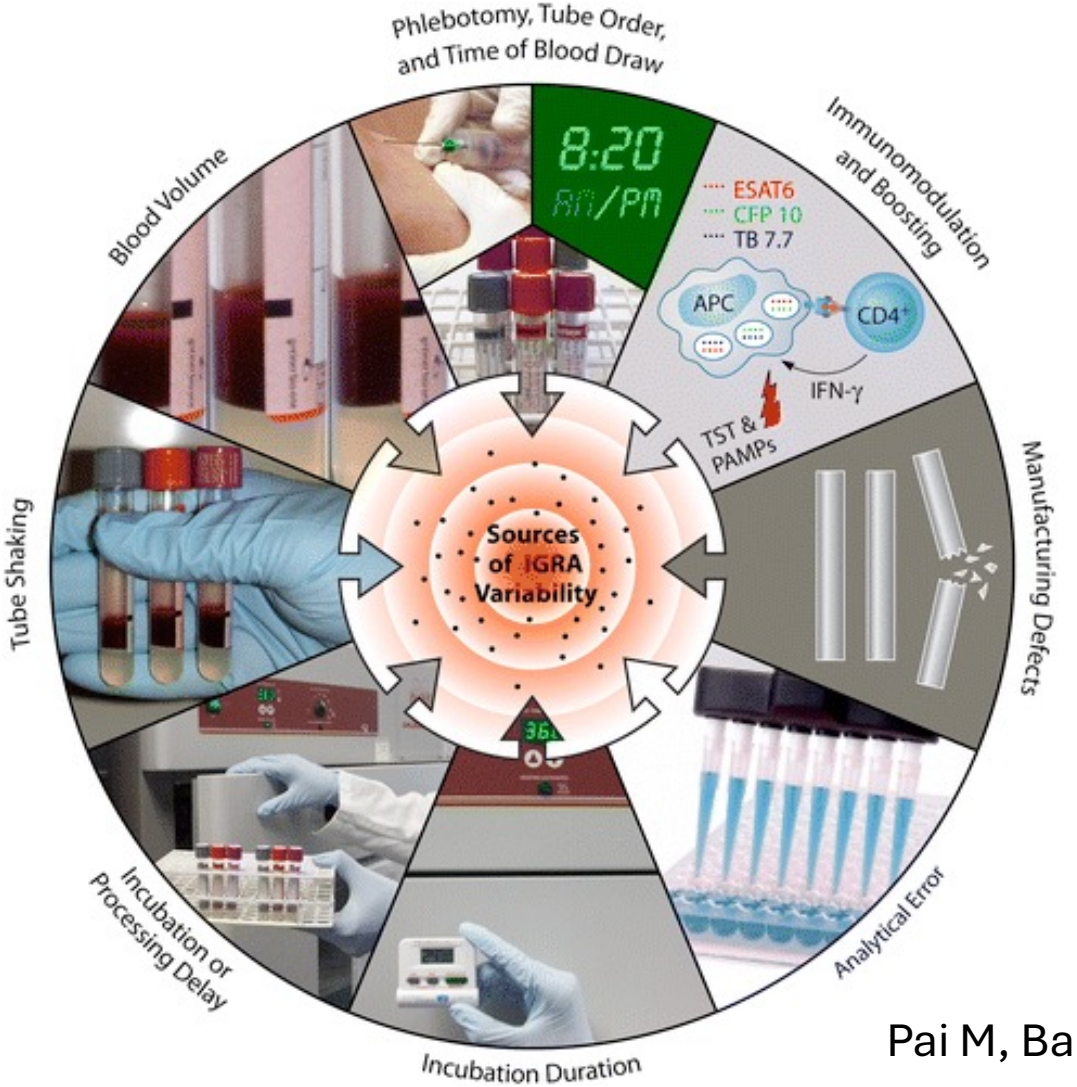




ESAT-6, CFP-10, and proprietary CD8 antigens

QuantiFERON-Gold Plus (QFT-plus)

Sources of variability in the results of QuantiFERON-TB Gold In-Tube assay



Pai M, Banaei N et al. Cli Micro Rev 2014

QFT-plus: interpreting the results

Interpretation of results

Cut-off Ag-nil >= 0.35

Table 2

Nil (IU/mL)	TB1 minus nil (IU/mL)	TB2 minus nil (IU/mL)	Mitogen minus nil (IU/mL)	QFT-Plus result
≤8.0	≥0.35 and ≥25% of Nil	Any	Any	Positive
	Any	≥0.35 and ≥25% of Nil		
	<0.35 or ≥0.35 and <25% of Nil	<0.35 or ≥0.35 and <25% of Nil	≥0.50	Negative
	<0.35 or ≥0.35 and <25% of Nil	<0.35 or ≥0.35 and <25% of Nil	<0.50	Indeterminate
>8.0	Any			

Calculation of Positive, Negative, or Indeterminate

Test	Flag	Result	Units	Reference Values	Site*	Report D/T

QuantiFERON-Tb Gold Plus, B

Source: Blood

QuantiFERON-Tb Gold Plus Result	A	Positive		Negative	SDL	FINAL 02/27/18 18:44

Interferon-gamma response to M. tuberculosis antigens detected, suggesting infection with M. tuberculosis. Positive results in patients at low-risk for tuberculosis should be interpreted with caution and repeat testing on a new sample should be considered as recommended by the 2017 ATS/IDSA/CDC Clinical Practice Guidelines for Diagnosis of Tuberculosis in Adults and Children [Lewinsohn DM et. al. Clin. Infect. Dis. 2017;64(2):111-115]. False positive results may occur in patients with prior infection with M. marinum, M. szulgai or M. kansasii.

TB1 Ag minus Nil Result		4.15	IU/mL	SDL	FINAL 02/27/18 18:44
TB2 Ag minus Nil Result		3.43	IU/mL	SDL	FINAL 02/27/18 18:44
Mitogen minus Nil Result		>10.00	IU/mL	SDL	FINAL 02/27/18 18:44
Nil Result		0.04	IU/mL	SDL	FINAL 02/27/18 18:44

QFT-Plus interpretation: Indeterminate test

	NIL	TB1-Nil	TB2-Nil	MIT-Nil
Positive	-	+	+/-	+
Positive	-	+/-	+	+
Negative	-	-	-	+
Indeterminate	↑	-	-	+
Indeterminate	-	-	-	↓

Common in immunocompromised!

Indeterminate result:

- **Low Mitogen response** (weak immune response to a strong stimulant or technical issues)
- **High Nil response** (background level of IFN-gamma)

IGRA Indeterminate results

- Indeterminate result tells you that MTB infection status cannot be obtained from the IGRA test
- Advantage over TST: IGRA tells you if “negative” result reflects a poor immune response (“anergy”) versus true negative result
- Consider:
  - Repeat IGRA test- may see more definitive result (pos/neg) in 68% (Banach IJTLD 2011).
  - Some recommend TST, but concern for non-specificity

IGRA vs. TST

- ***Advantages*** over TST
  - Not affected by BCG vaccination
  - Not affected by most non-tuberculous mycobacteria
  - Interpretation is more objective
  - No return visit needed for interpretation of test
  - Patients and providers may lack confidence in TST results
- **Disadvantages** over TST
  - Blood draw
  - Cost

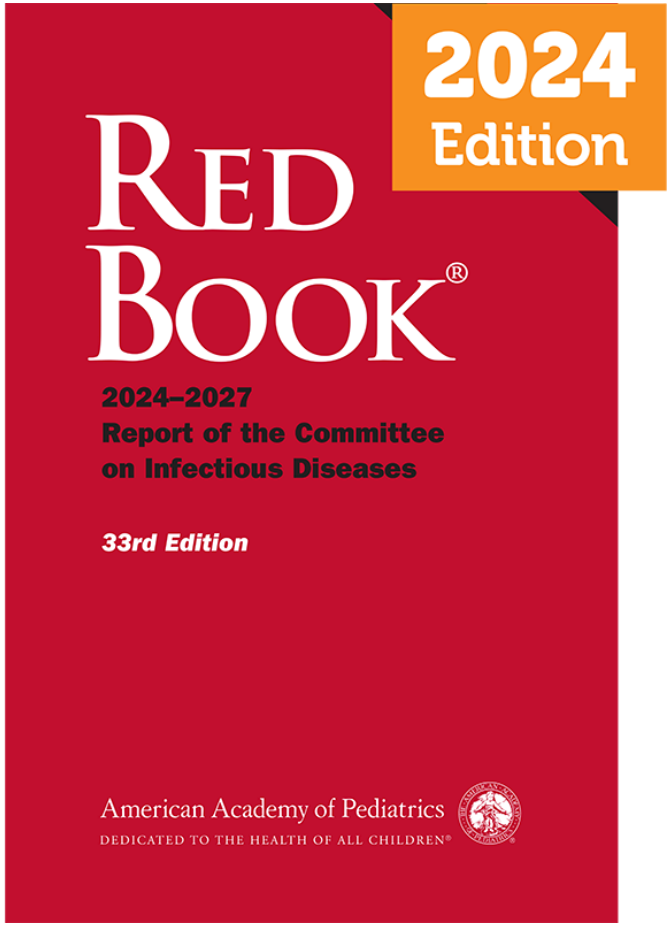
CDC, MMWR, 2010 Pai, Clin Micro Rev 2014

TB testing in immunocompromised patients

- Both TST and IGRA assays depend on functional immune response
- Some consider dual testing with TST and IGRA simultaneously
- Take other risk factors (e.g., contact with an active case, non US born, immunocompromised) into account

Testing in Age Under 5 years

- TST > 3 months
- IGRA can be used in all ages



TST or IGRAs and Vaccinations

- Live virus vaccines might affect test results
- Test on either on the **same day** as vaccination with live-virus vaccine **or 4-6 weeks after** the administration of the live-virus vaccine (e.g. MMR)
- CDC suggests delaying TST 4 weeks after mpox vaccine, though there is guidance available for same day administration if required

https://www.cdc.gov/monkeypox/hcp/vaccine-considerations/intradermal-administration.html

LTBI Case 1

- 55-year-old male born in Chihuahua, Mexico
- Came to the US at age 25
- Reports no medical problems, no history of TB exposure, not taking any medications, no symptoms
- Starting a job as a janitor in a hospital and he is required to get TB clearance
- What LTBI screening test should we use?

LTBI Case 1

A. No testing is needed since he is likely BCG vaccinated
B. Tuberculin skin test (TST)
C. Interferon Gamma Release Assay (IGRA)
D. No testing because not a high-risk group

LTBI Case 2

19-year-old from Korea, received BCG. On college entrance in US, TST is performed, and results is 10 mm. QFT 6 weeks later is negative.

Which of the following statements is true:

A. Given discrepancy, repeat the TST
B. QFT likely false negative, repeat QTF-G
C. No treatment, no additional testing
D. Additional testing, get a CXR

LTBI Case 3

A 35-year-old foreign born physician had a negative TST 0mm before starting her residency program in the US. 12 weeks later TST is 11 mm. She does not have any known exposures to tuberculosis. She denies any symptoms.

What is the most correct statement?

A. The second TST result was unnecessary, and it is a false positive TST result
B. Consider an IGRA to confirm the diagnosis of LTBI
C. The fact that she works in a hospital, and she has a new positive TST means she was recently infected with TB
D. Some people with LTBI may have a false negative TST result when tested years after infection because of a waning response

LTBI Case 4

- 48 year old male works in an office, lives in Grass Valley, CA. US born. No TB exposure
- History of inflammatory myositis triggered by statins x 2 years, has been treated with steroids and methotrexate. Treatment planned with rituximab.
- E-consult question: does patient need LTBI treatment?

June 23, 2023

Nil IU/mL	0.084
TB1 AG-NIL IU/mL	0.634
TB2 AG-NIL IU/mL	0.394
Mitogen-Nil IU/mL	>10

Criteria for Pos

Comment: 1. Nil less than or equal to 8.0 IU/mL AND
2. TB1 Ag-Nil or TB2 Ag-Nil is greater than or equal to 0.35 IU/mL AND greater than or equal to 25% of Nil AND
3. Any Mitogen - Nil

June 28, 2023

Nil IU/mL	0.043
TB1 AG-NIL IU/mL	0.040
TB2 AG-NIL IU/mL	0.005
Mitogen-Nil IU/mL	1.335

Criteria for Neg:

Comment: 1. Nil less than or equal to 8.0 IU/mL AND
2. TB1 Ag-Nil is less than 0.35 IU/mL OR TB1 Ag-Nil is greater than or equal to 0.35 IU/mL and less than 25% of Nil AND
3. TB2 Ag-Nil is less than 0.35 IU/mL OR TB2 Ag-Nil is greater than or equal to 0.35 IU/mL and less than 25% of Nil AND
4. Mitogen-Nil is greater than or equal to 0.5

LTBI Case 4

- Notice in the two tubes how the mitogen-nil is so different only 5 days apart
- This brings up:
  - Were specimens switched?
  - Was one of the tubes not shaken well?
  - Error in the lab including data mis-entry?
- Next steps: Repeat

June 23, 2023

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4. Mitogen-Nil is greater than or equal to 0.5

The TST or IGRA is positive – next steps?

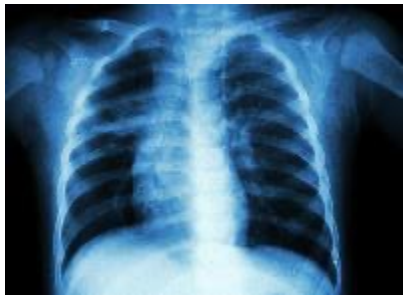
Active TB disease must always be excluded (can be asymptomatic/minimally symptomatic!)

Contact your local health department if you suspect that the patient has active TB disease

Rule out active disease before LTBI treatment

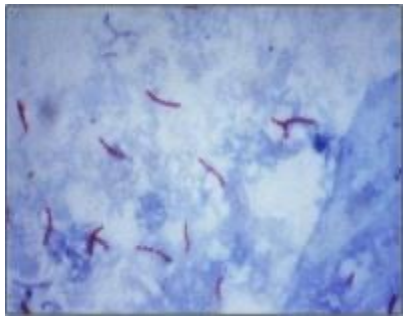
1. Symptom screen

- Cough
- Hemoptysis
- Weight loss
- Fevers/sweats
- Extreme fatigue



2. Chest x-ray

- Infiltrate
- Cavitary lesion
- Nodule
- Effusion
- Hilar LAD

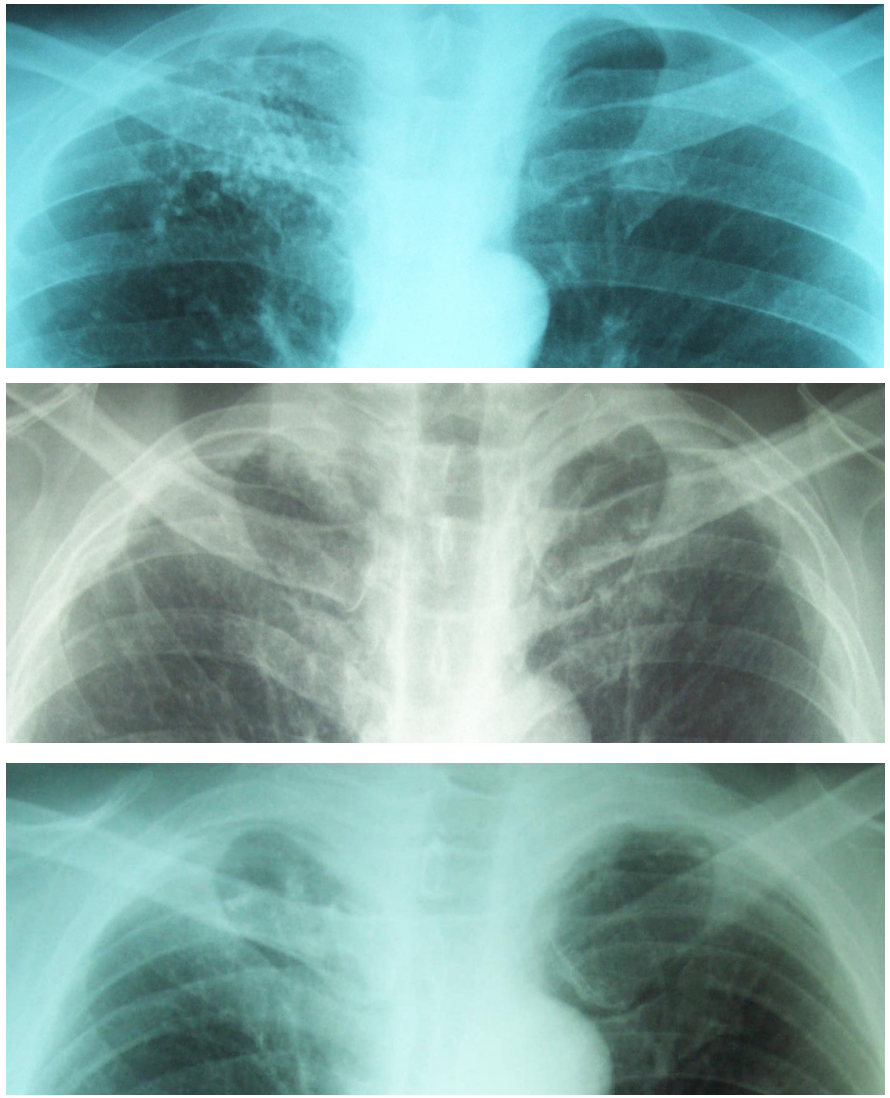


3. Sputum collection
(if +sx or abnormal CXR)

- AFB smear & culture
- MTB PCR

Images: 1. MedlinePlus.gov 2. Adobe Stock Images 3. CDC.gov, TB 101 for Healthcare Workers

3 cases QFN+ with abnormal CXR



A

B

C

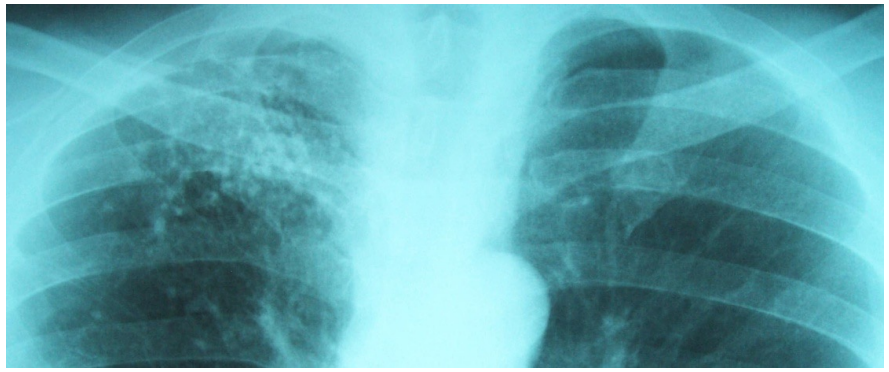
- Non- US born
- Asymptomatic
- QFT+
- CXR report: “BUL nodules, calcified, consistent with old granulomatous disease.”

Check sputa!

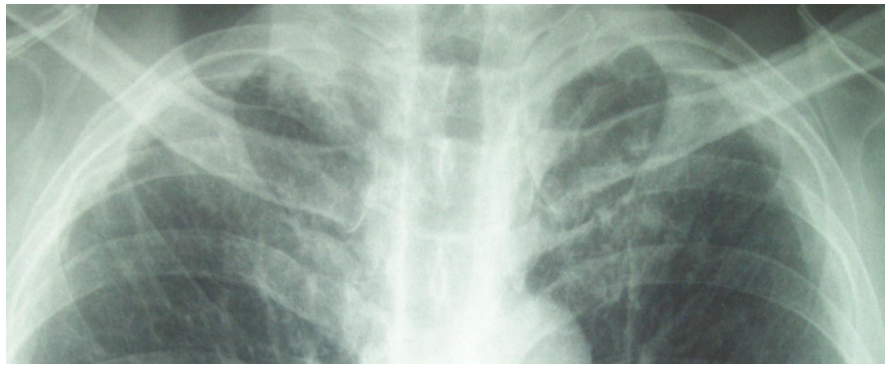
Sputa preliminary results:

- Smear neg x 3, geneXp neg x 1
- Await cultures (8 weeks)

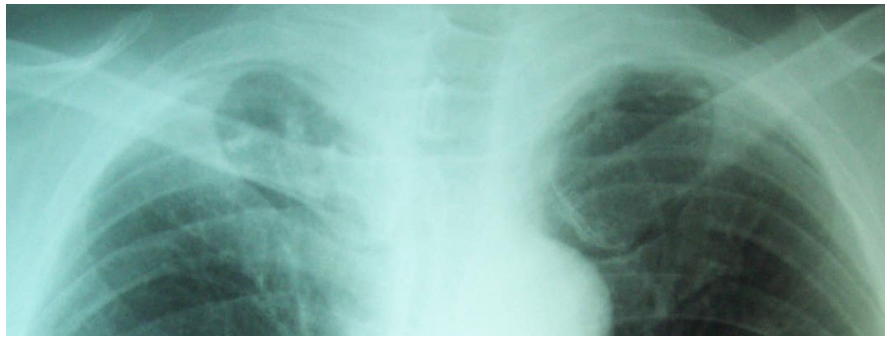
Culture results



A POS, Active TB, pan-sensitive



B NEG, TB 4 (old granulomatous disease, LTBI)



C POS, Active TB, pan-sensitive

LTBI Treatment Options

- Rifampin (4R)
- Isoniazid + Rifapentine (3HP)
- Isoniazid + Rifampin (3HR)
- Isoniazid (6H or 9H)
- FQ x 6mo (MDR)
- Others?

Rifampin (4R, daily x 4 months)
Preferred regimen

- Recommended for most children and adults (all ages, pregnancy included).
  - Alternate option for PLHIV due to limited data and DDI
- **Advantages**:
  - Less hepatotoxicity than INH
  - Greater adherence (78% RIF vs. 60% INH)
  - Cost effective
- **Disadvantages**:
  - Multiple drug interactions (strong CYP3A4 inducer) leading to lower plasma levels of many commonly used medications. ***Essential to assess patient med list.***

Menzies, *N Engl J Med*, 2018

Rifampin- Adverse reactions

- Hepatotoxicity
  - Rare severe hepatitis, more common when combined with other medications
- Asymptomatic hyperbilirubinemia (0.6%)
- Dermatologic: Pruritis, rash (up to 6%)
- Hypersensitivity reaction (0.07-0.3%)
- GI: nausea, anorexia, abdominal pain
- Immune-mediated: thrombocytopenia, TTP, hemolytic anemia (<0.1%)
- Orange discoloration of body fluids

INH + Rifapentine (3HP, weekly x 3 months) Preferred regimen

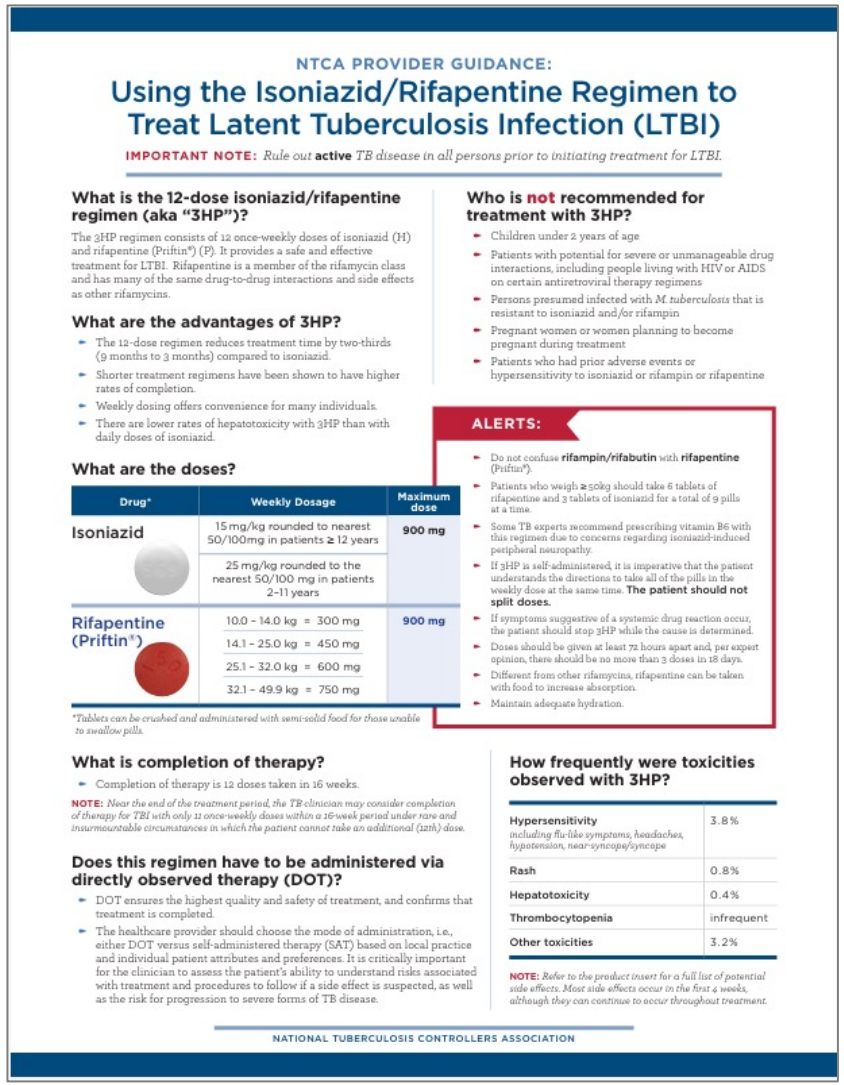
- Recommended for most, EXCEPT for:
  - Children <2yo
  - HIV-infected patients on ART with drug-drug interactions
  - Pregnant or planning to become pregnant
- **Advantages**:
  - Less hepatotoxicity than daily INH
  - Greater adherence (82% INH-RPT vs. 69% INH)
- **Disadvantages**:
  - Multiple drug interactions
  - Pill burden
  - Flu-like / hypersensitivity syndrome (2.2%)
  - Ongoing rifapentine shortage – confirm full course is available when starting

Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection. MMWR 2011;60:1650–1653. MMWR, June 29, 2018 / 67 (25);723-726. Photo credit: San Francisco TB Prevention and Control Program

3HP- Adverse Reactions

- Possible hypersensitivity (3.8%)
- Rash (0.8%)
- Hepatotoxicity (0.4%)
- Thrombocytopenia (rare)
- Other toxicities (3.2%)

- Monitoring similar to INH or RIF
- Rifapentine drug-drug interactions similar to RIF



NTCA PROVIDER GUIDANCE:

Using the Isoniazid/Rifapentine Regimen to Treat Latent Tuberculosis Infection (LTBI)

IMPORTANT NOTE: *Rule out* **active** *TB disease in all persons prior to initiating treatment for LTBI.*

What is the 12-dose isoniazid/rifapentine regimen (aka "3HP")?

The 3HP regimen consists of 12 once-weekly doses of isoniazid (H) and rifapentine (Priftin®) (P). It provides a safe and effective treatment for LTBI. Rifapentine is a member of the rifamycin class and has many of the same drug-to-drug interactions and side effects as other rifamycins.

What are the advantages of 3HP?

- The 12-dose regimen reduces treatment time by two-thirds (9 months to 3 months) compared to isoniazid.
- Shorter treatment regimens have been shown to have higher rates of completion.
- Weekly dosing offers convenience for many individuals.
- There are lower rates of hepatotoxicity with 3HP than with daily doses of isoniazid.

What are the doses?

Drug*	Weekly Dosage	Maximum dose
Isoniazid	15 mg/kg rounded to nearest 50/100mg in patients ≥ 12 years	900 mg
	25 mg/kg rounded to the nearest 50/100 mg in patients 2–11 years	
Rifapentine (Priftin®)	10.0 – 14.0 kg = 300 mg	900 mg
	14.1 – 25.0 kg = 450 mg	
	25.1 – 32.0 kg = 600 mg	
	32.1 – 49.9 kg = 750 mg	

**Tablets can be crushed and administered with semi-solid food for those unable to swallow pills.*

Who is not recommended for treatment with 3HP?

- Children under 2 years of age
- Patients with potential for severe or unmanageable drug interactions, including people living with HIV or AIDS on certain antiretroviral therapy regimens
- Persons presumed infected with *M. tuberculosis* that is resistant to isoniazid and/or rifampin
- Pregnant women or women planning to become pregnant during treatment
- Patients who had prior adverse events or hypersensitivity to isoniazid or rifampin or rifapentine

ALERTS:

- Do not confuse **rifampin/rifabutin** with **rifapentine** (Priftin®).
- Patients who weigh ≥ 50kg should take 6 tablets of rifapentine and 3 tablets of isoniazid for a total of 9 pills at a time.
- Some TB experts recommend prescribing vitamin B6 with this regimen due to concerns regarding isoniazid-induced peripheral neuropathy.
- If 3HP is self-administered, it is imperative that the patient understands the directions to take all of the pills in the weekly dose at the same time. **The patient should not split doses.**
- If symptoms suggestive of a systemic drug reaction occur, the patient should stop 3HP while the cause is determined.
- Doses should be given at least 72 hours apart and, per expert opinion, there should be no more than 3 doses in 18 days.
- Different from other rifamycins, rifapentine can be taken with food to increase absorption.
- Maintain adequate hydration.

What is completion of therapy?

- Completion of therapy is 12 doses taken in 16 weeks.

NOTE: *Near the end of the treatment period, the TB clinician may consider completion of therapy for TBI with only 11 once-weekly doses within a 16-week period under rare and insurmountable circumstances in which the patient cannot take an additional (12th) dose.*

Does this regimen have to be administered via directly observed therapy (DOT)?

- DOT ensures the highest quality and safety of treatment, and confirms that treatment is completed.
- The healthcare provider should choose the mode of administration, i.e., either DOT versus self-administered therapy (SAT) based on local practice and individual patient attributes and preferences. It is critically important for the clinician to assess the patient's ability to understand risks associated with treatment and procedures to follow if a side effect is suspected, as well as the risk for progression to severe forms of TB disease.

How frequently were toxicities observed with 3HP?

Hypersensitivity *including flu-like symptoms, headaches, hypotension, near-syncope/syncope*	3.8%
Rash	0.8%
Hepatotoxicity	0.4%
Thrombocytopenia	infrequent
Other toxicities	3.2%

NOTE: *Refer to the product insert for a full list of potential side effects. Most side effects occur in the first 4 weeks, although they can continue to occur throughout treatment.*

NATIONAL TUBERCULOSIS CONTROLLERS ASSOCIATION

NTCA 2-page guide with dosing chart (https://tbcontrollers.org/resources/tb-infection/3hp/)

Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection. MMWR 2011;60:1650–1653
https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/TBCB-INH-RIF-LTBI-fact-sheet.pdf

INH + Rifampin (3HR, daily x 3 months)
Preferred regimen (conditional recommendation)

- Recommended for most children and adults (all ages, pregnancy, HIV)
  - Some experts have used this preferentially for TB4 (old granulomatous disease without presence of active TB)
- **Advantages**:
  - Shorter duration, treatment completion better/comparable to INH alone
  - May be more hepatotoxic than 4R, but less than 6-9H
- **Disadvantages**:
  - Multiple drug interactions (see Rifampin)
  - Limited data compared to other preferred regimens

Sterling, et al. MMWR Recomm Rep. 2020 Feb 14;69(1):1-11. Red Book, 2023.

Isoniazid (6H or 9H, 6-9 months daily INH)

Alternative Regimen

- Usually recommended if rifamycin based regimen cannot be used
- **Advantages**:
  - Efficacy is 60%–90%, depending on duration of treatment
  - Fewer drug-drug interactions (inhibits cytochrome P450 enzymes)
- **Disadvantages**:
  - Adherence: Completion rates <50%
  - More hepatotoxic than other regimens
  - Risk for peripheral neuropathy; supplement B6 in groups at risk
  - Clinic time required for 9 monthly visits

Nolan, JAMA, 1999, 2. Smieja, Cochrane Database Syst Rev, 2000, 3. Menzies, Ann Int Med, 2008

Isoniazid- Adverse Reactions

- Clinical hepatotoxicity: Incidence 0.1%, but increases with age (nearly 2% in persons 50-64) and underlying medical conditions
- Asymptomatic hepatic enzyme elevation- seen in 10%-20%
- Peripheral neuropathy (<0.2 %)
- Rash
- Mild neurologic symptoms
- Drug interaction – increases dilantin, carbamazepine and antabuse levels

Clinical Monitoring (monthly)

Evaluate monthly* for:

- Adherence
- Signs and symptoms of TB disease
- Symptoms of hepatitis or other side effects
    - Anorexia, nausea, vomiting, or abdominal pain in right upper quadrant
    - Fatigue or weakness
    - Dark urine
    - Rash
    - Persistent numbness in hands or feet

*Does not have to be in-person visit

Which of the following is routine lab monitoring indicated for LTBI treatment?

A. Person living with HIV
B. Woman who delivered a baby 2 months ago
C. Healthy 9 yo female
D. A and B
E. A, B, and C

Laboratory Monitoring (liver function)

- **Baseline testing** recommended for:
  - History of liver disease, hepatitis, or other liver disorders
  - Regular alcohol or drug use
  - Risk for chronic liver disease
  - HIV infection
  - Pregnancy / Early postpartum (<3mo)
  - Multiple comorbidities/concomitant medications
  - Use of potentially hepatotoxic medications, older age

- **Routine follow-up testing** (e.g., monthly): consider for risk factors above, abnormal baseline testing

Management of side effects: Drug-induced liver injury

- Re-review hepatotoxic meds (tylenol, statins, etc), ETOH use, prior hepatitis risk/screen
- **HOLD Treatment if:**
  - Symptoms of hepatotoxicity and AST/ALT > 3 times the upper limit of normal
  - Asymptomatic but AST/ALT > 5 times the upper limit of normal or bili >3
- If less than parameters above, continue treatment with plan to repeat labs in 1-4 weeks
- Depending on above, consider alternate therapy with close LFT monitoring

Treatment completion / Missed Doses

Based on total number of doses, not just duration

Regimen	# doses	Timeframe to complete within
INH daily x 9 months	270	12 months
INH BIW x 9 months	76	12 months
INH daily x 6 months	180	9 months
INH BIW x 6 months	52	9 months
RIF/RFB daily x 4 months	120	6 months
INH+RFP (3HP)*	12	16 weeks

CDC. Targeted tuberculin testing and treatment of latent TB infection. MMWR 2000.
*In Sterling, et al, NEJM, 2011, 3HP treatment completion was defined as taking at least 11/12 doses within 16 weeks

71 yo M with LTBI develops transaminitis on INH x 4.5 months → plan switch to Rifampin.

What is your recommended treatment length?

A. RIF x 4 mo (full course)
B. RIF x 3 mo (partial credit)
C. RIF x 2 mo (partial credit)

Treatment switches

- Options: start over vs partial credit for time taken
- No guidelines or data and recommend consultation, if needed!
- Consider:
  - Risk of progression
  - How much therapy has been missed (<2 months)
  - Early vs late in therapy

Partial credit example:

– Pt completes 4.5 months of INH (50% of planned regimen). Needs 50% left of RIF regimen (i.e., 2 mo of a 4 mo total RIF regimen)

Pregnancy & lactation

- Risk for increased hepatotoxicity during pregnancy and early partum (especially INH)
- Treatment recommended in those that are at high risk for progression:
  - Recent contact with someone with infectious TB
  - Immunosuppression/HIV
  - Recent TB test conversion
- All others: wait until 2-3 months post-partum (CDC recommendation).
- Options include: 4R, 3HR, 6-9H (not 3HP)
- Breastfeeding is not a contraindication to LTBI treatment

https://www.cdc.gov/tb/about/pregnancy.html, https://www.tbcontrollers.org/resources/tb-infection/clinical-recommendations/

You are evaluating a healthy 4-year-old male. He is U.S. born, but returned 2 weeks ago from the Philippines, where he had a prolonged stay with his grandfather, who was just diagnosed with pulmonary TB.

- The child's TST is negative today; CXR, exam, and symptom screen are normal. What do you do next:

A. Nothing - evaluation is complete
B. Retest him in 8-10 weeks
C. Start 9H immediately, retest him in 8-10 weeks
D. Start 4R immediately, retest him in 8-10 weeks
E. Other

“Window-prophylaxis” for high-risk contacts

Definition: LTBI tx of persons at high-risk for progression with initial *negative* TB testing and active disease ruled out.

Purpose: To abort early TB infection and prevent progression to active TB.

Recommended in the following:

- Children <5 years old
- HIV/immunosuppressed contacts should be fully treated, even if repeat testing remains negative

Follow-up: Repeat TB testing 8-10 weeks after exposure ended or source patient is no longer contagious.

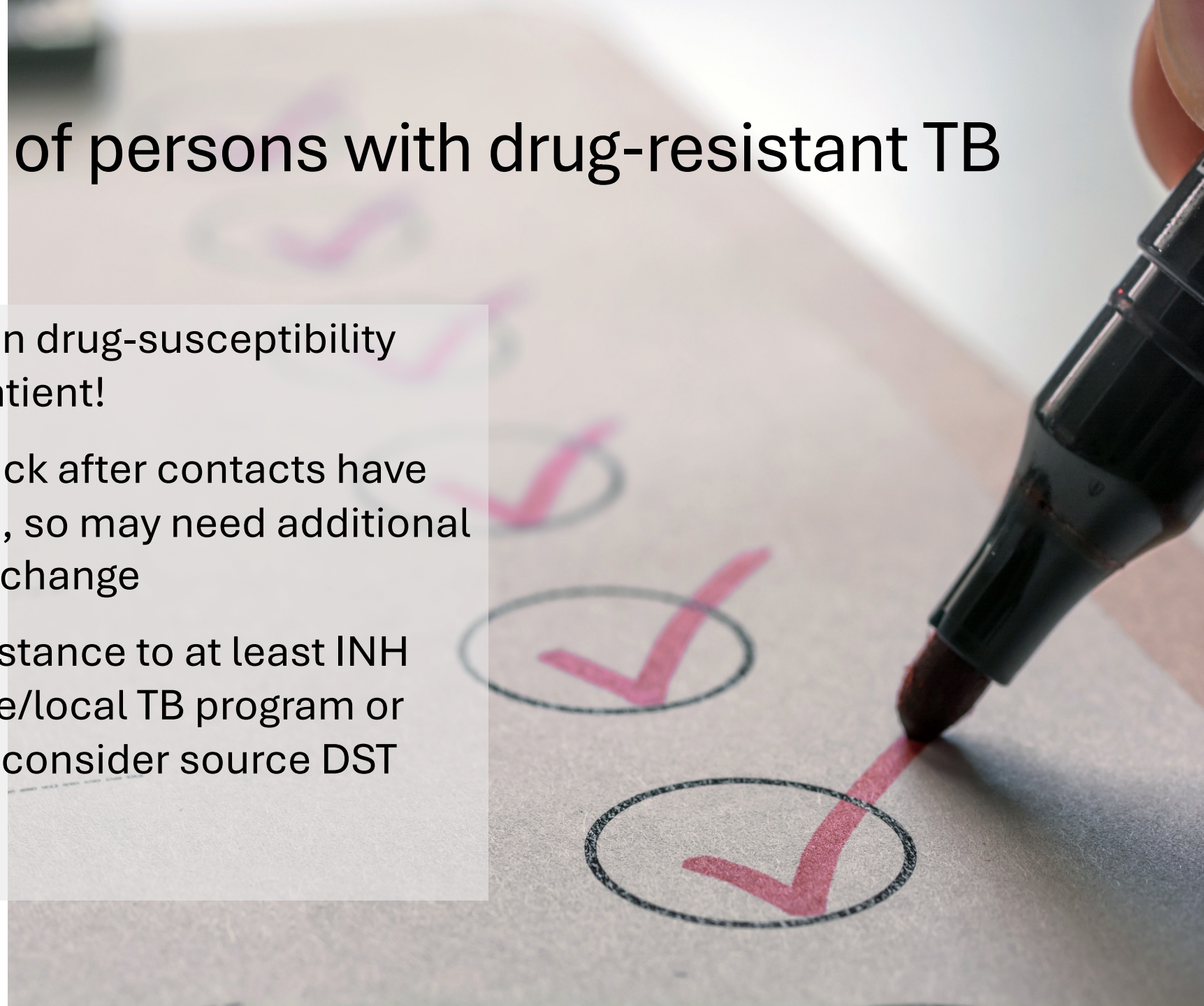
Additional resources: Parent handout and Fact sheet for pediatric primary care

Re-treatment for LTBI

- What is the probability of acquiring new infection? What was the likelihood that the person took adequate treatment in the past?
- Consider transmission and infectiousness of source case.
- Recommended in:
  - Those at risk for rapid progression: HIV infected or other immune suppression, prior to severe immune suppression (e.g. transplant, anti-TNF), < 5 years old
  - Contact to MDR or drug-resistant case

Treating contacts of persons with drug-resistant TB

- Adjust treatment based on drug-susceptibility testing (DST) of source patient!
- DST results may come back after contacts have started on LTBI treatment, so may need additional counseling on reason for change
- Exposure to MDR TB (resistance to at least INH and RIF): Check with state/local TB program or seek expert help → must consider source DST



Key points

- Identification and treatment of LTBI remains an important health need.
- IGRA generally preferred over TST especially in BCG-vaccinated populations, but test interpretation questions remain common
- Encourage shorter regimens to optimize treatment completion, but caution with rifamycin drug-drug interactions!

Acknowledgements

- Slides compiled by prior presenters including Lisa Chen MD, David Horne MD, Janice Louie MD, CDPH TB Control Branch and others

Additional slides

IGRA is the preferred test if BCG vaccinated

TST and QFT Specificity

	Specificity	95% confidence interval
TST without BCG	97	95–99
TST with BCG	59	46–73
QFT	96	94–98

73% false positive rate

12% false positive rate

- Menzies, Ann Intern Med, 2007
- Pai, Ann Intern Med, 2008

Slide courtesy of Dr. Neha Shah

Rationale for testing in selected individuals

	SENSITIVITY	SPECIFICITY
TST	80%	97% (60% if BCG vaccinated)
Quantiferon	80%	>95%
T-SPOT.TB	90%	>95%

$$\text{PPV} = \frac{\text{sensitivity} \times \text{prevalence}}{\text{sensitivity} \times \text{prevalence} + (1 - \text{specificity}) \times (1 - \text{prevalence})}$$

For a US born patient (LTBI prevalence ~3%) with no other risk factors, the PPV of....

- + TST is 45%
- + QFT is 55%
- + T.SPOT. TB is 58%

Risk of false positives is high in a low incidence population

Prioritize persons with risks for progression

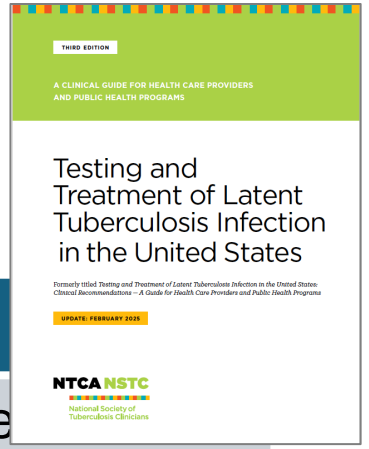
If health system resources do not allow for testing of all non-U.S. born persons from a country with an elevated TB rate, prioritize patients with at least one of the following medical risks for progression:

- diabetes mellitus
- smoker within past 1 year
- end stage renal disease
- leukemia or lymphoma
- silicosis
- cancer of head or neck
- intestinal bypass/gastrectomy
- chronic malabsorption
- body mass index ≤20
- History of chest x-ray findings suggestive of previous or inactive TB (no prior treatment). Includes fibrosis or non-calcified nodules, but does not include solitary calcified nodule or isolated pleural thickening. In addition to LTBI testing, evaluate for active TB disease.

LTBI guidance/recs (specific populations)

Guidelines/Recommendation	
Pediatrics: Red Book Report of the Committee of Infectious Diseases, American Academy of Pediatrics	Revised frequently
HIV/AIDS: DHHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents With HIV • https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/tuberculosishiv-coinfection?view=full (TB/HIV coinfection) • https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/mycobacterium?view=full (TB/OI)	Revised frequently
Persons exposed to MDR-TB: Treatment of Drug-Resistant Tuberculosis. An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline, 2019 **Persons exposed to Drug-Resistant TB:** Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 3rd edition (2022) https://www.currytbcenter.ucsf.edu/products/cover-pages/drug-resistant-tuberculosis-survival-guide-clinicians-3rd-edition ➢ **Consultation with state/local TB program and CDC Centers of Excellence (Curry) recommended!**	Update covering BPaL/M 10/2024 Based on evidence and expert opinion. Covers treatment selection, monitoring, duration, follow-up, and more….

LTBI guidance/recommendations



Guidelines/Recommendation	
Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, MMWR 2020 (CDC/NTCA) https://www.cdc.gov/mmwr/volumes/69/rr/rr6901a1.htm	Based on GRADE evidence, provide recommendations on LTBI regimens, dosing charts Does not cover cost effectiveness, programmatic implementation, management of side effects
Testing and Treatment of Latent Tuberculosis Infection in the United States: A Clinical Guide for Health Care Providers and Public Health Programs, last update Feb 2025 (NTCA/NSTC) https://www.tbcontrollers.org/resources/tb-infection/clinical-recommendations/	Based on evidence in literature and expert opinion. Expansive coverage on **practical topics**: e.g., choosing a regimen, monitoring, special populations, nurse case management, treatment interruptions