Diagnosis and treatment of *Mtb* infection

(also known as latent tuberculosis infection - LTBI)

TASP
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D

Disclosures

- Received funding from Merck as a clinical trial investigator

Acronyms Ahead!

- **TB**: tuberculosis
- **MTbI**: *Mycobacterium tuberculosis (Mtb)* infection
- **LTBI**: Latent TB infection
- **TPT**: TB preventive therapy
- **TST/PPD**: tuberculin skin test (purified protein derivative)
- **MDR**: multi-drug resistant
- **XDR**: extensively drug resistant
- **IGRA**: interferon-gamma release assay
- **QFT**: Quantiferon

- **RIF**: rifampicin (R)
- **INH**: isoniazid (H)
- **RPT**: rifapentine (P)

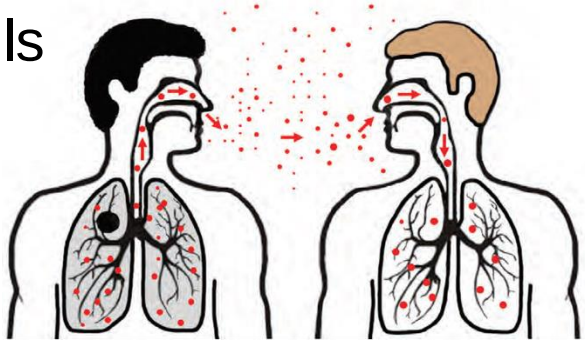
TB pathophysiology

- Caused by *Mycobacterium tuberculosis*
  - Acid-fast, intracellular mycobacterium

- Transmission:

Primary: Person-to-person

cough
talking →droplets/aerosols
breathing

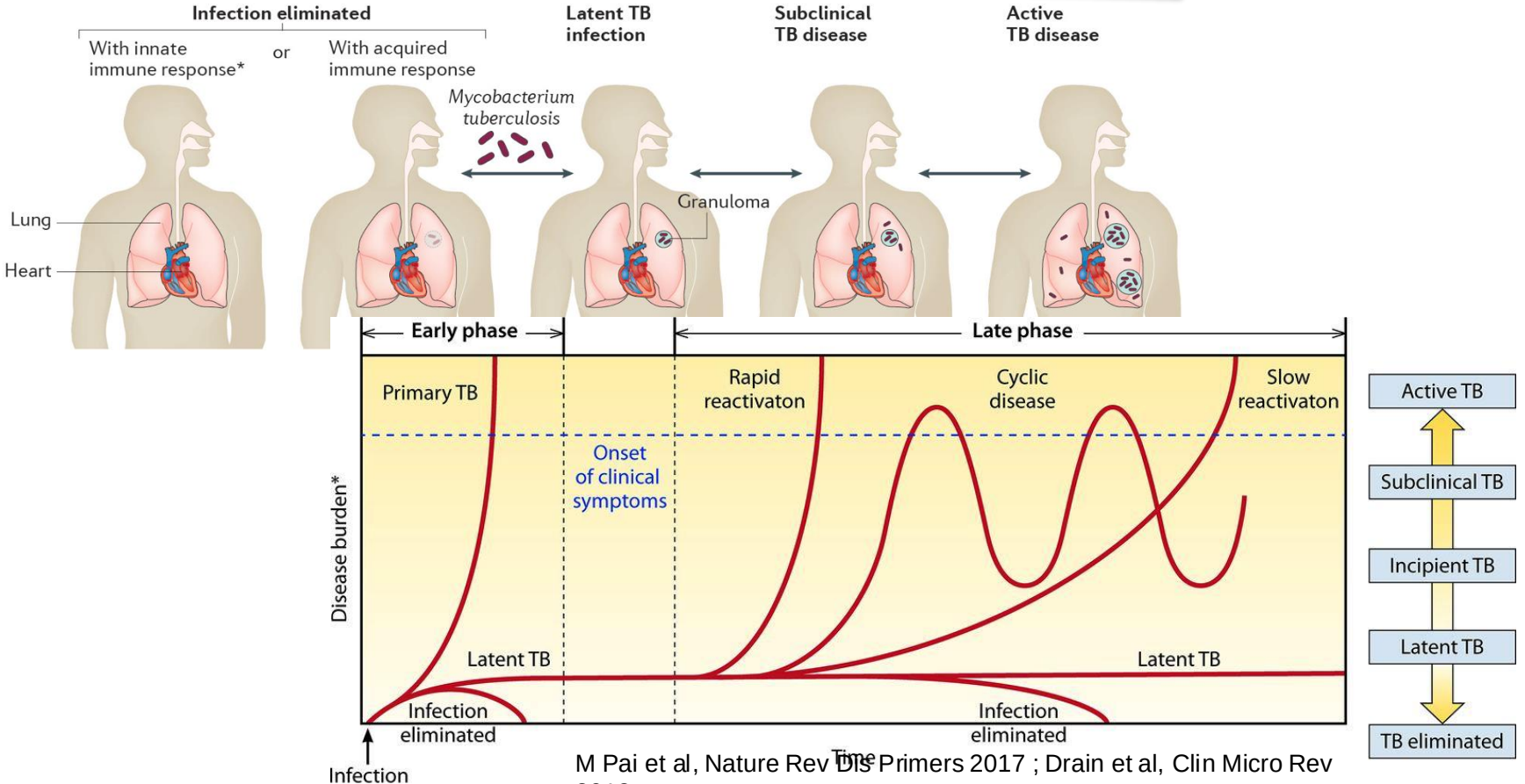


Rare:

- Eating/drinking *M. bovis* infected animal products
- Lab accidents

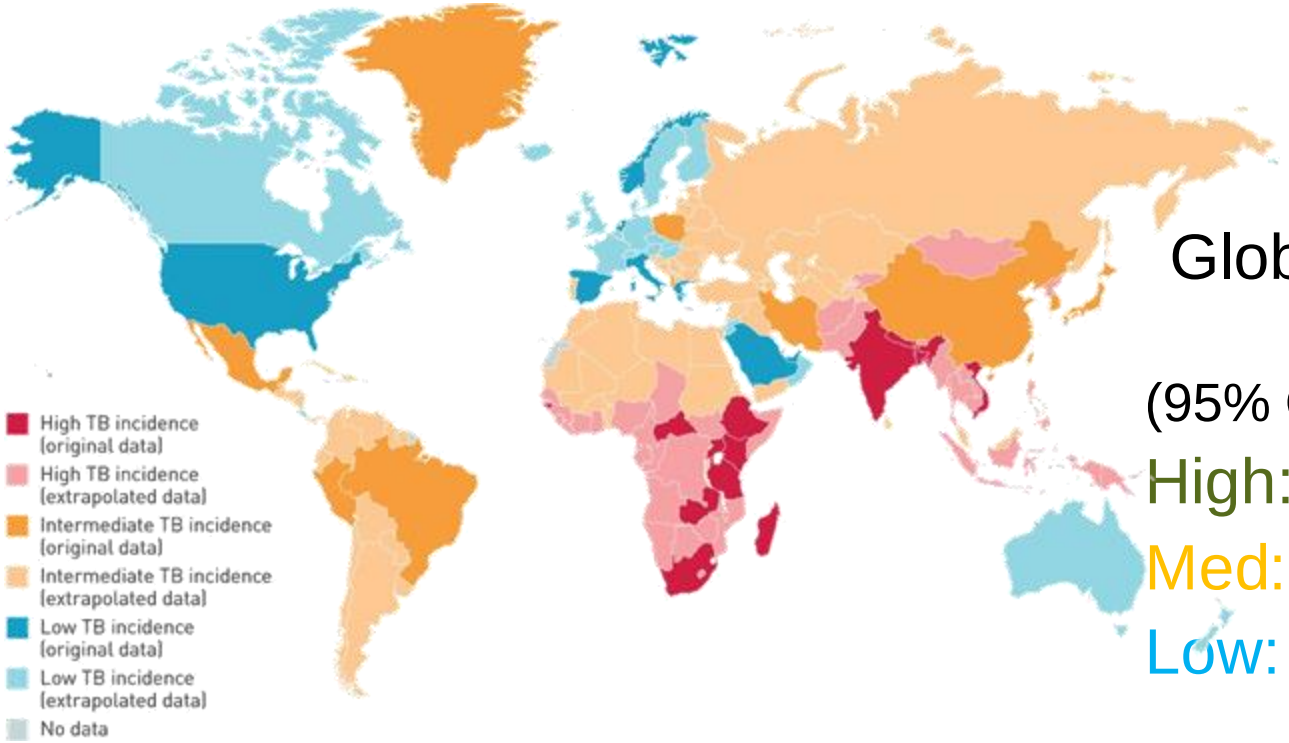
cdc.gov

Spectrum of clinical disease



M Pai et al, Nature Rev Dis Primers 2017 ; Drain et al, Clin Micro Rev

Epidemiology of TB infection



Global prevalence: 24.8%

(95% CI 19.7-29.9%)

High: 28–36%

Med: 19–20%

Low: 3–5%

Prior estimates 2016: 23% (95% UI 20.4%-26.4%)

1.7 billion people

Adam Cohen et al. Eur Respir J 2019

Houben & Dodd, PLoS Med 2016

Risk of disease progression

- ~**23%** global pop'n infected with *M. tb*

Risk Factor	Risk of Developing TB	Description
TB infection and no risk factors	 About 10% over a lifetime	For people with TB infection, **no risk factors**, and no treatment, the risk is about 5% in the first 2 years after infection and about 10% over a lifetime.
TB infection and diabetes	 About 30% over a lifetime	For people with TB infection and **diabetes**, and with no treatment, the risk is three times as high, or about 30% over a lifetime.
TB infection and HIV infection	 About 7% to 10% PER YEAR	For people with TB infection and **untreated HIV infection** and with no LTBI treatment, the risk is about 7% to 10% PER YEAR, a very high risk over a lifetime.

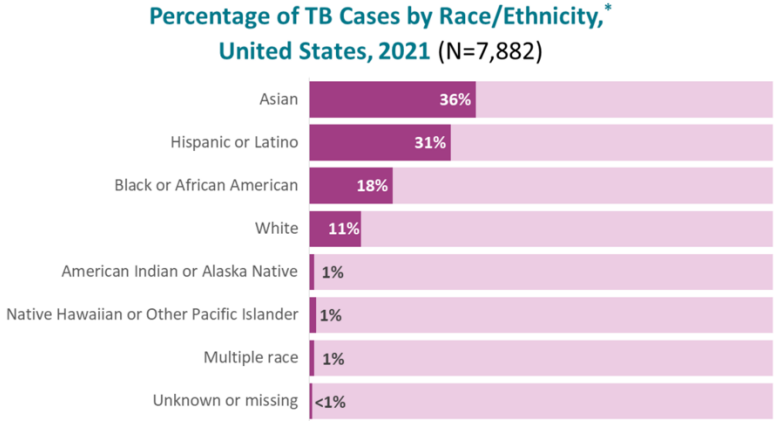
Other risk factors for progression from infection→disease:

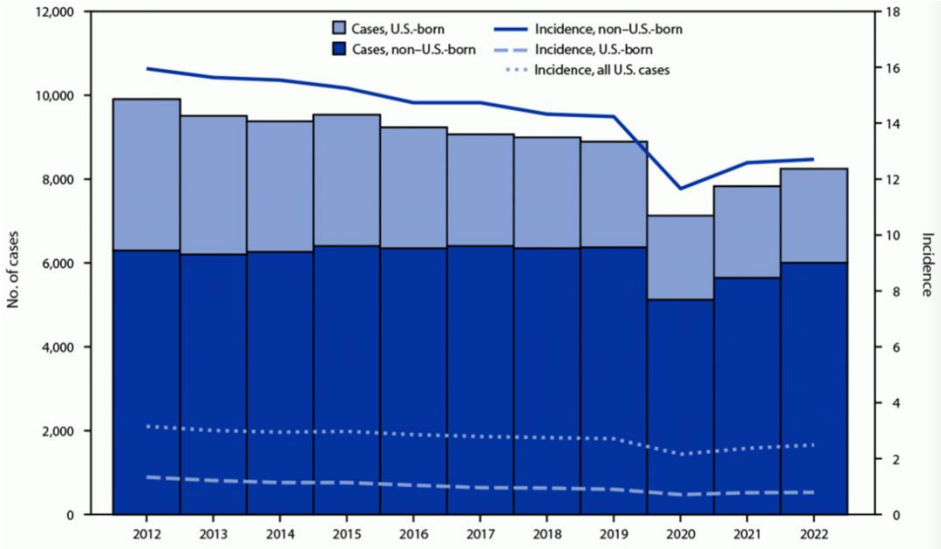
- Recent infection (<2 years) (→ screen close contacts)
- Immunosuppressive comorbidities
- Immunosuppressive medication (TNF-alpha inhibitors; T-cell suppression)

(Houben & Dodd, PLoS Med 2016; cdc.gov)

TB Epidemiology in the US

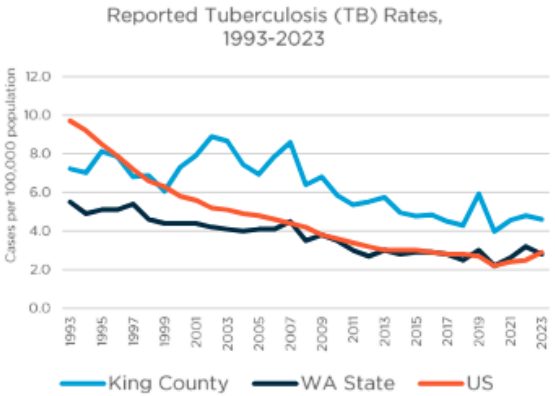
- Disease incidence rebounded after COVID
- >70% cases in nUSb
- Estimated 13 million with Mtb infection in US

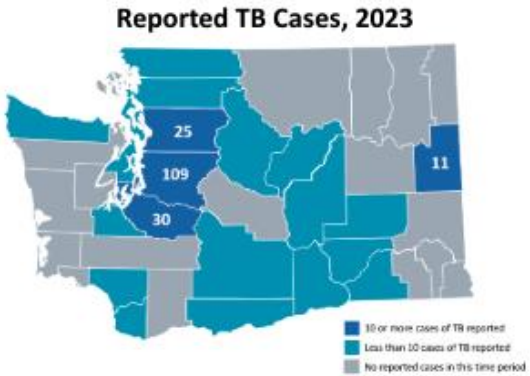




Tuberculosis disease cases* and incidence per 100,000,† by patient U.S. birth origin status§,¶ — National Tuberculosis Surveillance System, United States, 2012–2022
Schildknecht KR, et al. MMWR Morb Mortal Wkly Rep 2023

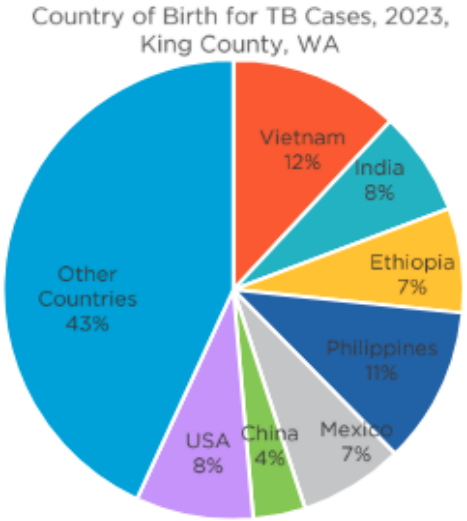
US/WA/King County TB Epidemiology





MDR-TB 2019-23:

- 1-8 cases of MDR-TB in WA per year
- No XDR-TB to date

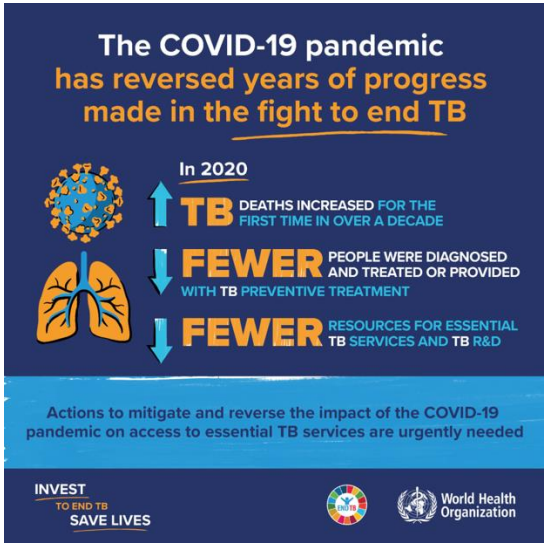


92% of 2021 cases born outside U.S.,
2/3 of these are from 6 countries

https://cdn.kingcounty.gov/-/media/king-county/depts/dph/documents/health-safety/disease-illness/tuberculosis/2023-tb summary.pdf?rev=c6e4d533304641ea84ba7d6f9a974a6e&hash=D1EF6FF9B425351F321FF235437BE259

COVID-19 pandemic impact on TB

- TB neglected, but did not disappear during COVID pandemic
  - TB prevention & care set back a decade
  - TB deaths increased for the 1st time in 10 years
- 31% decrease in case detection – King County

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ACCEPTED MANUSCRIPT

Delayed Tuberculosis Diagnoses During the COVID-19 Pandemic in 2020 — King County, Washington FREE

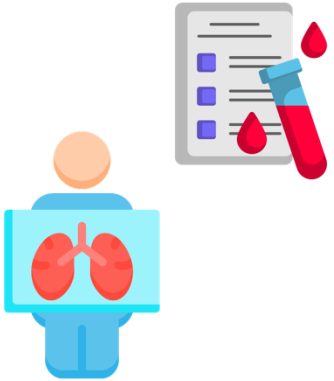
Masahiro Narita, MD ✉, Grace Hatt, MPH, Katelynne Gardner Toren, MPH, Kim Vuong, RN BSN, Monica Pecha, MPH, John A Jereb, MD, Neela D Goswami, MD

Clinical Infectious Diseases, ciab387, https://doi.org/10.1093/cid/ciab387

Published: 06 May 2021 **Article history**

Algorithm for screening and treatment of Mtb infection

- Screen for Mtb infection
  - IGRA or TST
  - Consider HIV test
- Exclude TB disease → *why?*
  - Symptom screen, CXR
- Initiate TPT/treatment of Mtb infection
  - Review labs, concurrent medications
  - Select treatment regimen
- Monitor, complete TPT
  - Labs prn
  - Document completion of TPT



CDC/IDSA/ATS Guidelines:

Who to screen for M**TB infection (LTBI)** in primary care?

At elevated risk for having LTBI

At elevated risk for progression to TB disease

Someone you would treat if screen+

Do NOT screen:

People with signs/symptoms of active TB→ get sputum to test for active TB

U.S. Preventive Services TASK FORCE

Recommendation Summary

Population	Recommendation	Grade
Asymptomatic adults at increased risk of latent tuberculosis infection (LTBI)	The USPSTF recommends screening for LTBI in populations at increased risk. See the "Assessment of Risk" section for additional information on adults at increased risk.	B

Pathway to Benefit

To achieve the benefit of screening, it is important that persons who screen positive for LTBI receive followup and treatment.

https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/latent-tuberculosis-infection-screening

USPSTF Clinician Summary of USPSTF Recommendation

Screening for Latent Tuberculosis Infection in Adults

April 2023

What does the USPSTF recommend?

B Grade

For asymptomatic adults at increased risk of latent tuberculosis infection (LTBI):
Screen for LTBI in populations at increased risk.
See "How to implement this recommendation" for additional information on adults at increased risk.

To whom does this recommendation apply?

This recommendation applies to asymptomatic adults 18 years or older at increased risk for tuberculosis (TB). It does not apply to adults with symptoms of TB or to children and adolescents.

What's new?

- This recommendation replaces and is consistent with the 2016 USPSTF recommendation on LTBI screening.
- In 2016, the USPSTF recommended screening for LTBI in populations at increased risk (B recommendation).

How to implement this recommendation?

- **Populations at increased risk for LTBI,** based on increased prevalence of active disease and increased risk of exposure, include persons who were born in, or are former residents of, countries with high TB prevalence and persons who live in, or have lived in, high-risk congregate settings (eg, homeless shelters or correctional facilities).

https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/latent-tuberculosis-infection-screening

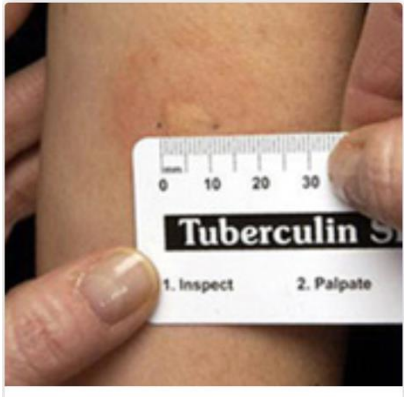
US Priority populations for outreach→ screening→TPT

- **Non–U.S.-born persons**: 71.5% of TB patients in 2020;
  - Mexico, Philippines, India, Vietnam, and China are the leading countries of origin among non–U.S.-born persons diagnosed with TB in the United States.
  - Among non–U.S.-born persons diagnosed with TB, **48.7% have lived in the United States for ≥ 10 years.**
- Racial/ethnic minority groups: 89% of overall TB patients; 71.8% of cases among U.S.-born persons; case rates 7–32 times higher than White persons;
- Persons living with **HIV**: ~4.8% of TB patients;
- Persons with **diabetes**: ~22.5% of TB patients;
- Persons experiencing homelessness: ~4.3% of TB patients;
- Persons who are incarcerated: ~2.6% of TB patients;
- Persons who use drugs or alcohol: ~1–9% of TB patients

CDC Division of TB Elimination
https://www.cdc.gov/tb/about/strategic-plan-background.htm

TB skin test (TST)

Administering the TB skin test



Reading the result of a TB skin test

Interferon-gamma release assay (IGRA)

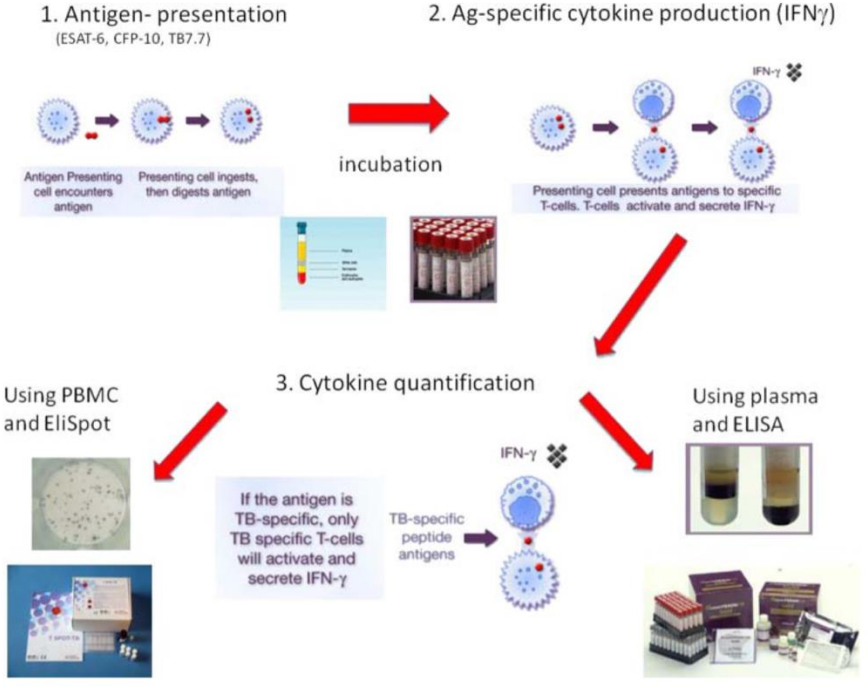


Figure 1 Immunological principles of commercially available interferon γ release assays.

How to screen for Mtb infection/LTBI

	Pros	Cons
IGRA QFT-Gold (thru 2017) QFT-PLUS (2017-present) T.Spot (send-out)	Specific* to *M. tb* complex (does not cross-react w/ BCG)	$$$
	single-visit blood test	timing of sample to lab
	lab result appears in chart for permanent documentation	user dependence: sample handling (lab tech)
		4 x 8ml tubes of blood
PPD **tuberculin skin test (TST)**	$ (direct cost of materials)	requires 2 pt visits: one for placement, one for reading @48hrs
		False-positives with BCG & env. mycobacteria
		User variability in interpretation of induration
		Documentation challenging (not a lab result)

What does a Quantiferon (IGRA) measure?

A. Interferon-gamma secreted by active *M. tuberculosis* bacteria

B. Interferon-gamma secreted by latent *M. tuberculosis* bacteria

C. Interferon-gamma produced by CD4+/CD8+ T cells after stimulation with *M. tuberculosis* antigens

D. Antibodies to *M. tuberculosis*

Requirements for a valid positive QFT result:

1. A functioning immune system (T-cell immunity)
2. That has encountered Mtb antigens before (regardless of whether they are currently present)

Indirect test of infection

EVER/NEVER infected*

Interpreting IGRA Results

Positive	Negative	Indeterminate	
True positive: immune system has seen TB	**True negative:** never infected	Inadequate immune response to mitogen (positive control)	Inadequate immune response
False positive: Cross-reaction with NTM species *M. marinum* *M. kansasii* *M. szulgai*	Uninformative negative: waning of positive response over time (reversion)	Too high response to negative control relative to TB antigen	
	False negative: Inadequate immune response	Sample handling error	

Consider repeating with immune reconstitution if possible

Repeat

What do you expect IGRA to show?

Scenario	IGRA result	
1. 45 yo woman from Philippines. Treated for active TB at age 26. Took 6M TB treatment, told she was cured. Asymptomatic.	+	Treated TB
2. 50 yo man from Ethiopia. Worked as a nurse on a TB ward for 20 years. Asymptomatic. Has never had TB or any TB treatment.	+	Untreated LTBI
3. 57 yo man. Had a positive PPD 10 years ago, received 2M INH, but did not tolerate treatment so stopped.	+	Incompletely treated LTBI
4. 26 yo woman. Had a positive QFT 3 years ago, received 9M INH.	+	Treated LTBI
5. 28 yo graduate student. Returned to Seattle 2M ago after winter break at home overseas with his family. Learned that his grandmother was diagnosed with TB right shortly after he left. Presents with 4 wks progressive cough, night sweats, fevers, weight loss.	?-	Early TB disease

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Recommendations and Reports / Vol. 69 / No. 1
February 14, 2020

TB Preventive Therapy (TPT)

Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020

Regimen	Medication (s)	Duration	Dosing
3HR	Isoniazid & Rifampicin	3 months	Daily
3HP	Isoniazid & RifaPENtine	3 months	Weekly
4R	Rifampicin	4 months	Daily
*1HP	Isoniazid & RifaPENtine	1 month	Daily
6H	Isoniazid	6 months	Daily
9H	Isoniazid	9 months	Daily

*1HP is alternate for people with HIV; accumulating experience in populations where rapid treatment important (e.g. pre-transplant)


ORIGINAL ARTICLE

One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis

Susan Swindells, M.B., B.S., Ritesh Ramchandani, Ph.D., Amita Gupta, M.D., Constance A. Benson, M.D., Jorge Leon-Cruz, M.S., Noluthando Mwelase, M.B., Ch.B., Marc A. Jean Juste, M.D., Javier R. Lama, M.D., M.P.H., Javier Valencia, M.D., Ayotunde Omoz-Oarhe, M.D., Khuanchai Supparatpinyo, M.D., Gaerolwe Masheto, M.D., et al., for the BRIEF TB/A5279 Study Team*

March 14, 2019
N Engl J Med 2019; 380:1001-1011
DOI: 10.1056/NEJMoa1806808

https://www.cdc.gov/mmwr/volumes/69/rr/rr6901a1.htm?s_cid=rr6901a1_w

	DRUG	DURATION	FREQUENCY	TOTAL DOSES	DOSE AND AGE GROUP
Preferred	**ISONIAZID† AND RIFAPENTINE†† (3HP)** 	3 months	Once weekly	12	**Adults and children aged ≥12 yrs** INH: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum RPT: 10–14.0 kg; 300 mg 14.1–25.0 kg; 450 mg 25.1–32.0 kg; 600 mg 32.1–49.9 kg; 750 mg ≥50.0 kg; 900 mg maximum
					Children aged 2–11 yrs INH†: 25 mg/kg; 900 mg maximum RPT††: See above
	RIFAMPIN§ (4R) 	4 months	Daily	120	**Adults:** 10 mg/kg; 600 mg maximum
					Children: 15–20 mg/kg‖; 600 mg maximum
	ISONIAZID† AND RIFAMPIN§ (3HR) 	3 months	Daily	90	**Adults** INH†: 5 mg/kg; 300 mg maximum RIF§: 10 mg/kg; 600 mg maximum
					Children INH†: 10-20 mg/kg#; 300 mg maximum RIF§: 15-20 mg/kg; 600 mg maximum
Alternative	**ISONIAZID† (6H/9H)**	6 months	Daily	180	**Adults** Daily: 5 mg/kg; 300 mg maximum Twice weekly: 15 mg/kg; 900 mg maximum
			Twice weekly¶	52	
		9 months	Daily	270	**Children** Daily: 10-20 mg/kg#; 300 mg maximum Twice weekly: 20–40 mg/kg#; 900 mg maximum
			Twice weekly¶	76	

*For persons with HIV/AIDS, see Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV available at: https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/367/overview.
†Isoniazid is formulated as 100-mg and 300-mg tablets.
††Rifapentine is formulated as 150-mg tablets in blister packs that should be kept sealed until use.
¶Intermittent regimens must be provided via directly observed therapy (i.e., a health care worker observes the ingestion of medication).
§Rifampin (rifampicin) is formulated as 150-mg and 300-mg capsules.
‖The American Academy of Pediatrics acknowledges that some experts use rifampin at 20–30 mg/kg for the daily regimen when prescribing for infants and toddlers (**Source**: American Academy of Pediatrics. Tuberculosis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book: 2018 Report of the Committee on Infectious Diseases. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:829–53).
#The American Academy of Pediatrics recommends an INH dosage of 10–15 mg/kg for the daily regimen and 20–30 mg/kg for the twice weekly regimen.

CDC
CDC and the National TB Controllers Association
LTBI Treatment Guidelines

https://www.cdc.gov/tb/topic/treatment/pdf/LTBITreatmentRegimens.pdf

TPT cont'd

- Rifamycin-containing regimens preferred if possible
- Short-course→Better treatment-completion rates
  - (12 weeks, 3M, 4M)
- Rifampicin and rifapentine induce CYP450→ Drug-drug interactions can be limiting
  - Warfarin
  - Hormonal contraceptives
  - Antiepileptic drugs
  - Glucocorticoids (steroids)
  - Opioids including MOUD
  - Antiretrovirals (HIV medication)

Rifabutin has fewer interactions

- INH-only: 9M higher treatment success than 6M; 6M lower risk of hepatotoxicity. Current recommendations (2020):
  - 6M>9M

Considerations for choosing TPT

- National shortage of rifapentine (Priftin) → 3HP/1HP options limited.

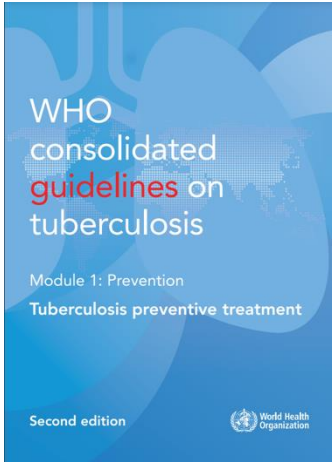
fda.gov 17-MAR-25

- **Drug-drug interactions** with current medications: most can be managed with dosing adjustments
  - Curry Center resource: https://www.currytbcenter.ucsf.edu/products/rifamycin-drugdrug-interactions-a-guide-for-primary-care-providers-treating-latent-tuberculosis
- Lab monitoring: CMP at baseline, consider LFTs periodically, LFTs with any GI/liver sx
- **Adherence support**:
  - can consider DOT/VOT for 3HP, but no longer mandatory.
  - Shared decisionmaking with patients
- Side effects: May limit adherence.
  - Prescribe vitamin B6/pyridoxine 25-50mg po to prevent peripheral neuropathy.
  - Anticipatory counseling: GI upset, rash, hepatotoxicity, (INH>RIF), flu-like syndrome with 3HP (<2%)

https://dps.fda.gov/drugshortages/searchresult?type=rifapentine

TPT for Multi-Drug Resistant TB

- Levofloxacin daily for 6 months



2024

status: a 1-month regimen of daily rifapentine plus isoniazid or 4 months of daily rifampicin.

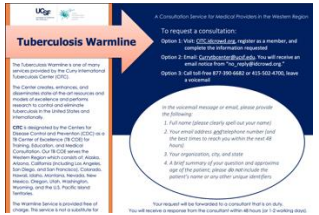
TB preventive treatment with levofloxacin
21. In contacts exposed to multidrug- or rifampicin-resistant tuberculosis, 6 months of daily levofloxacin should be used as TB preventive treatment.

[a] The recommendations in the current update are compared with those in the 2020 guidelines in Annex 1.

Additional Resources

CDC: LTBI treatment guidelines & information
https://www.cdc.gov/tb/topic/treatment/ltbi.htm

Curry Center: https://www.currytbcenter.ucsf.edu/
-online resources
-warmline consultation services



TB ECHO: https://doh.wa.gov/you-and-your-family/illness-and-disease-z/tuberculosis-tb/public-health-professionals/tb-echo

UW: eConsult to Infectious Diseases (Epic order)