MAYO CLINIC

Center for Tuberculosis

Interpreting the IGRA for Civil Surgeons

- James Gaensbauer, M.D., MScPH
  Medical Director for Education and Training
  Mayo Clinic Center for Tuberculosis

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Accreditation Statement
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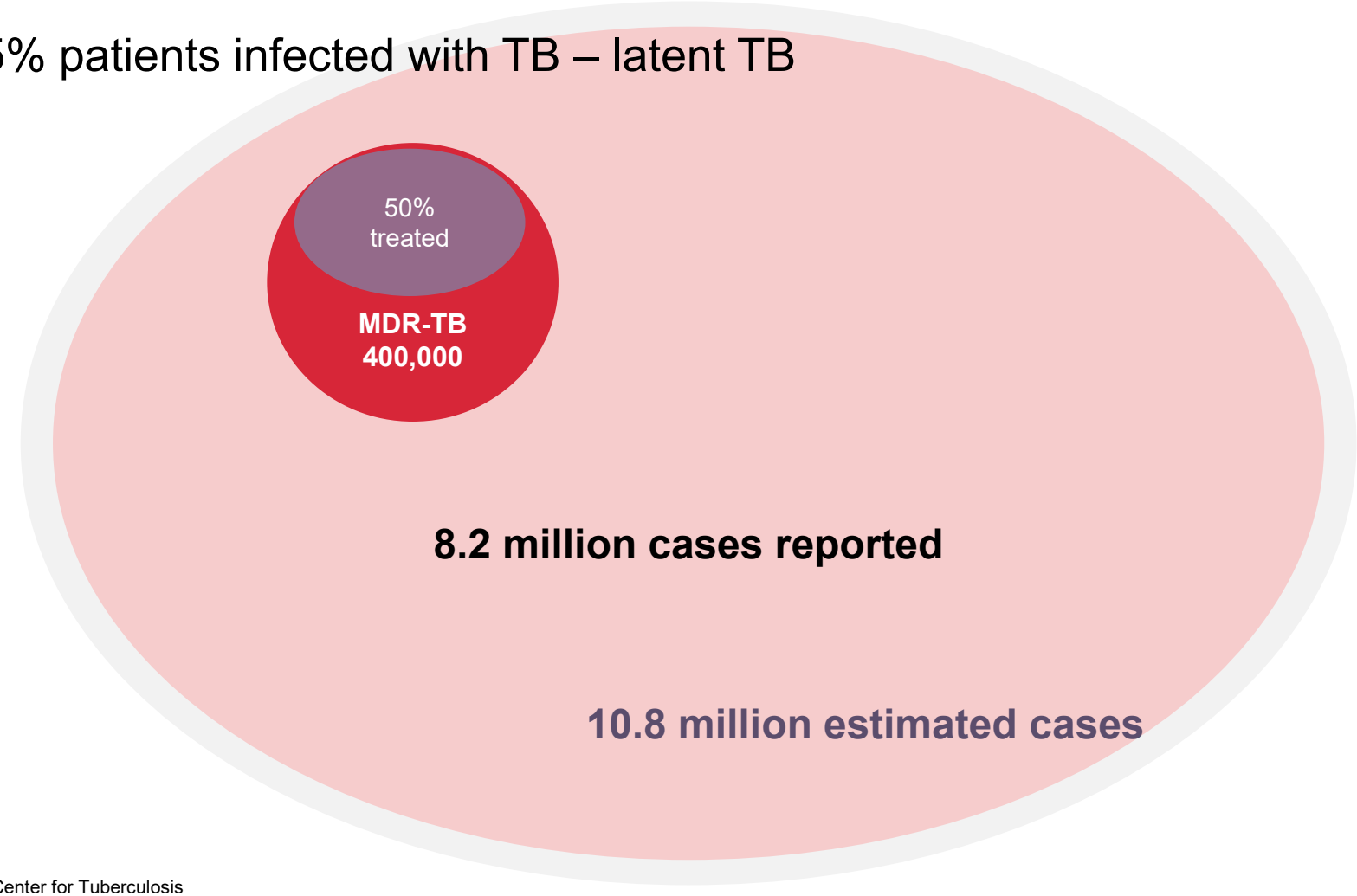
Available Credit
- 1.00 *AMA PRA Category 1 Credit*™
- 1.00 ANCC
- 1.00 Attendance
- 1.00 IPCE

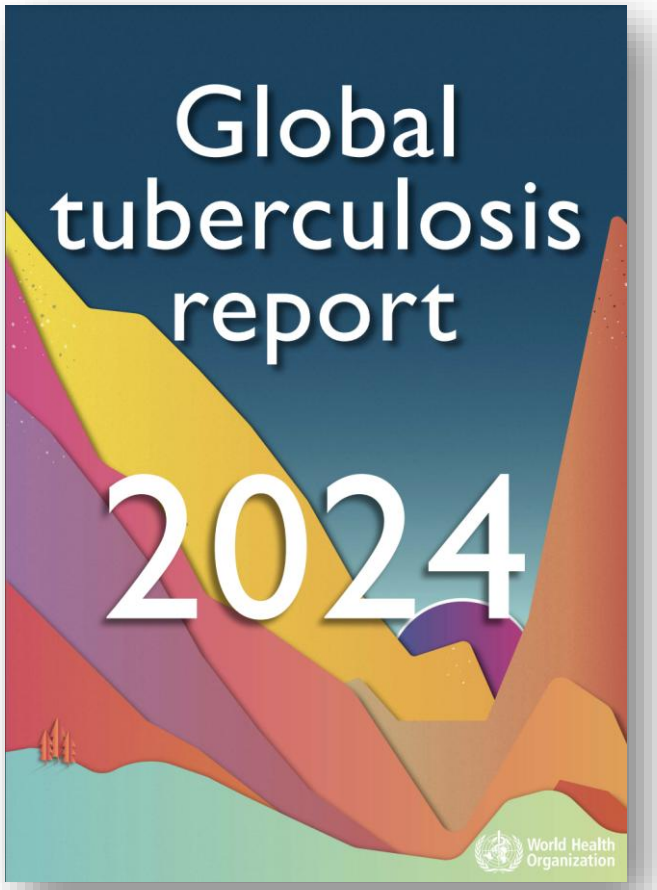
Learning Objectives

- Analyze IGRA test results in the context of TB screening for status adjusters.
- Evaluate IGRA results in clinical situations encountered by civil surgeons.
- Recognize key factors that influence IGRA interpretation.

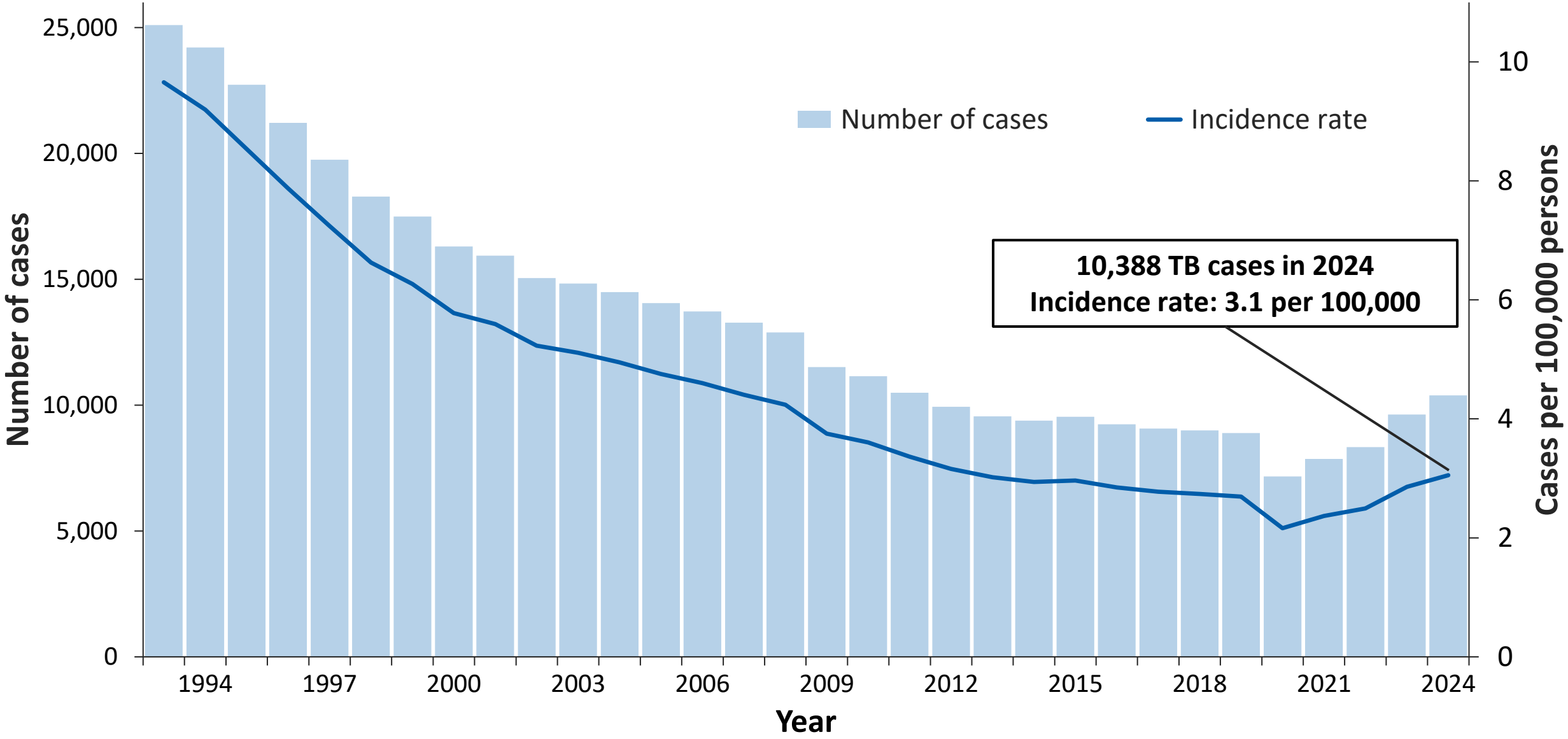
Global Impact of *M. tuberculosis*

- Leading cause of death from a single infectious agent in 2023 (more than COVID in 2023)
- 1.23 million deaths
- 25% patients infected with TB – latent TB

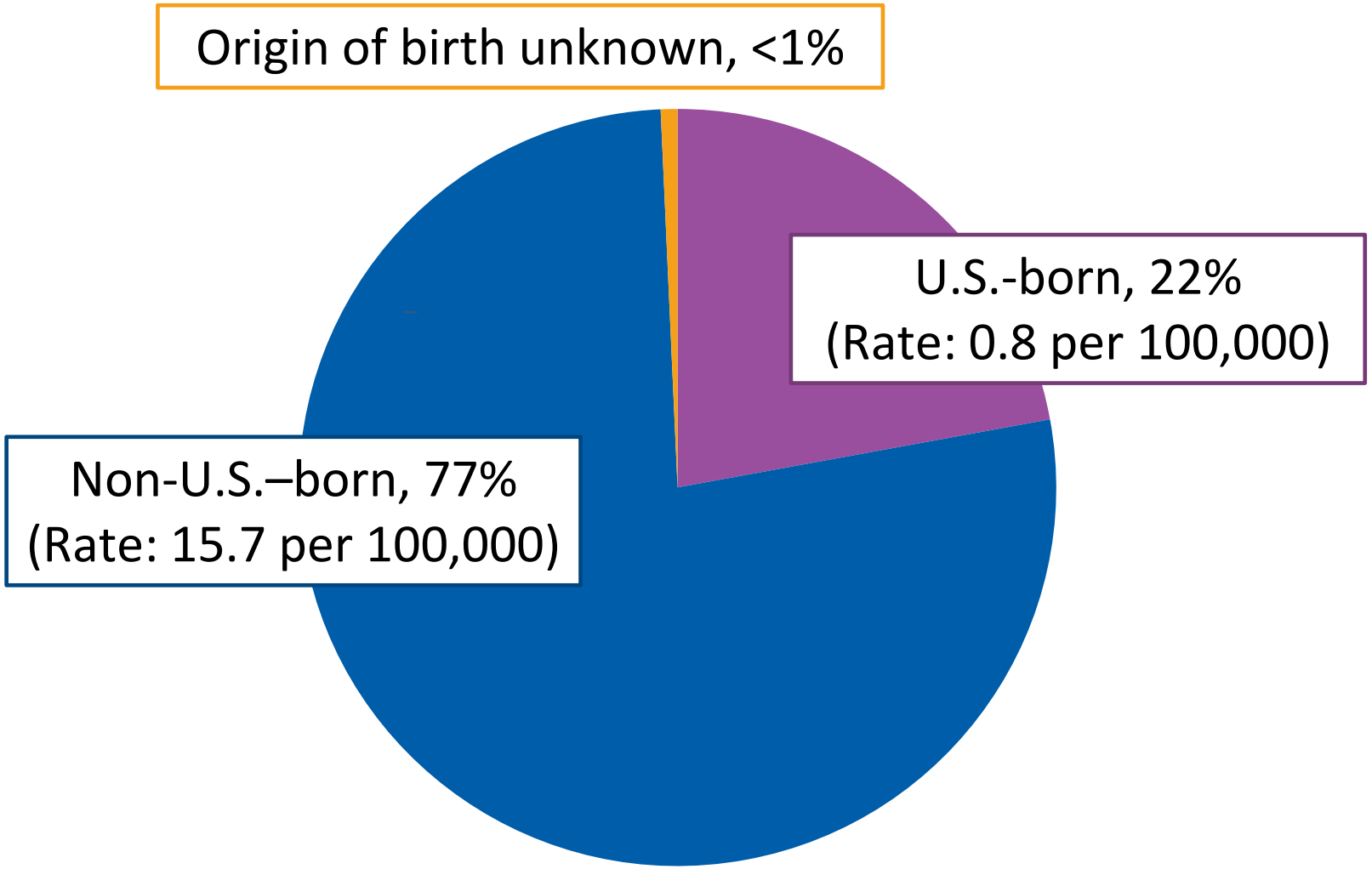




TB Cases and Incidence Rates, United States, 1993–2024

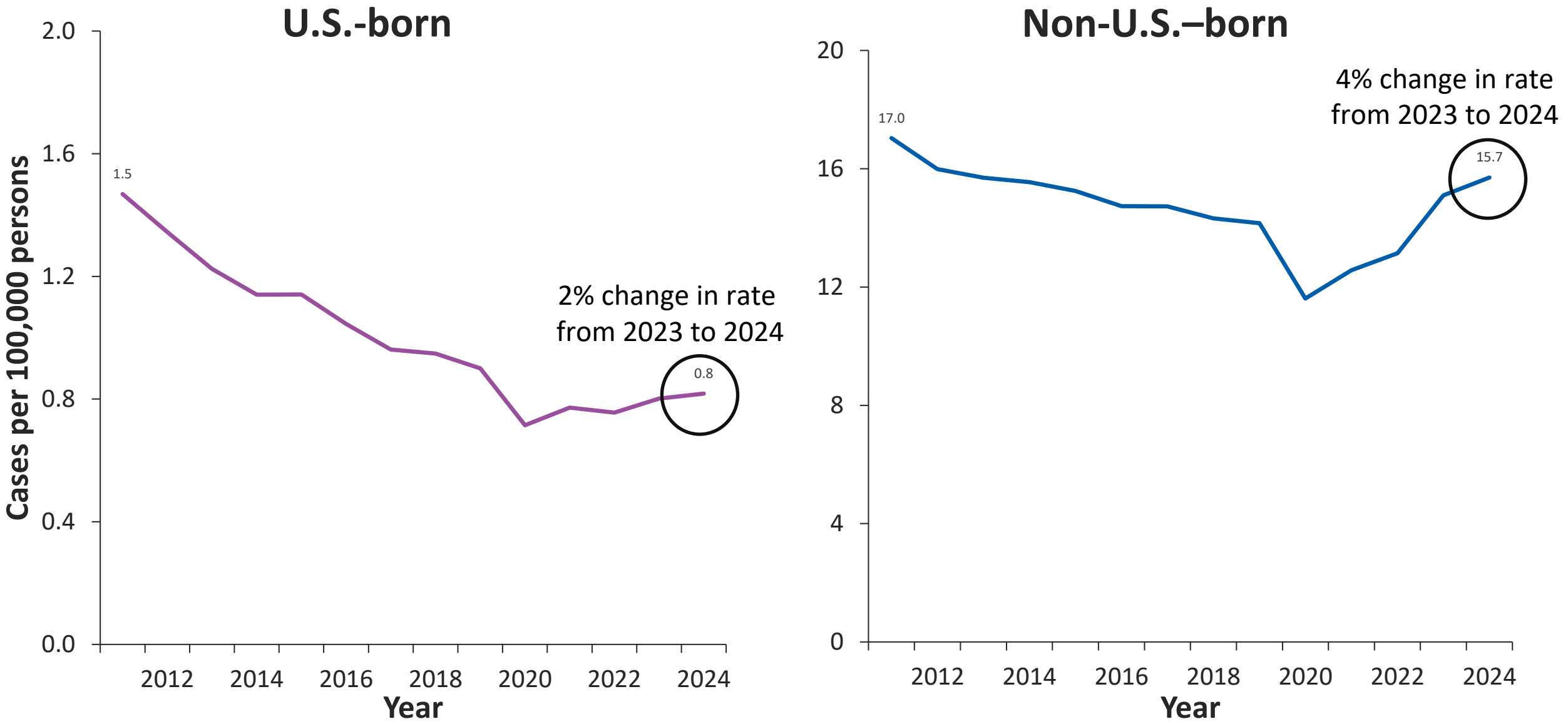


TB Incidence Rates and Percentages by Origin of Birth,* United States, 2024 (N=10,388)



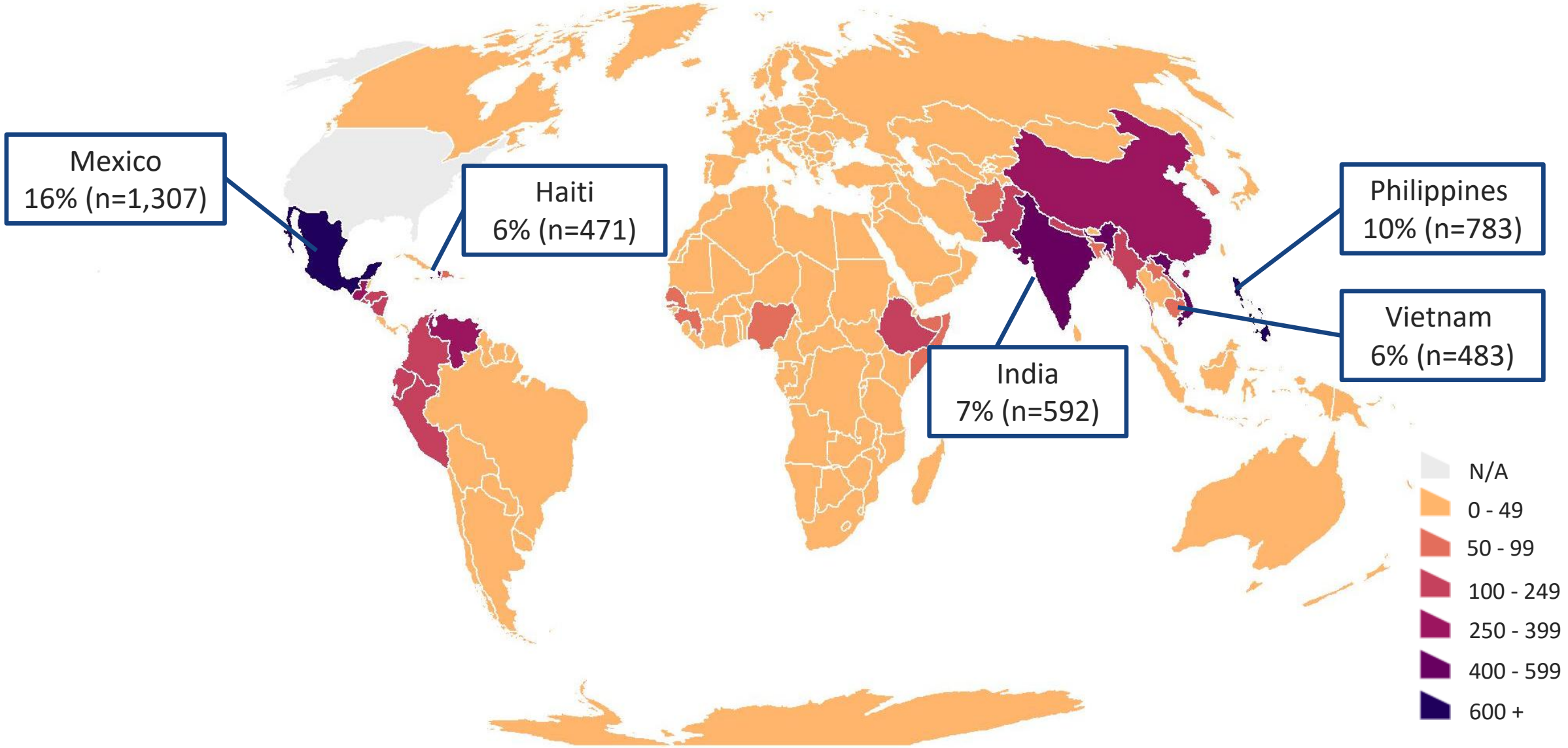
*Persons born in the United States, certain U.S. territories, or elsewhere to at least one U.S. citizen parent are categorized as U.S.-born. All other persons are categorized as non-U.S.–born.

TB Incidence Rates by Origin of Birth,* United States, 2011–2024



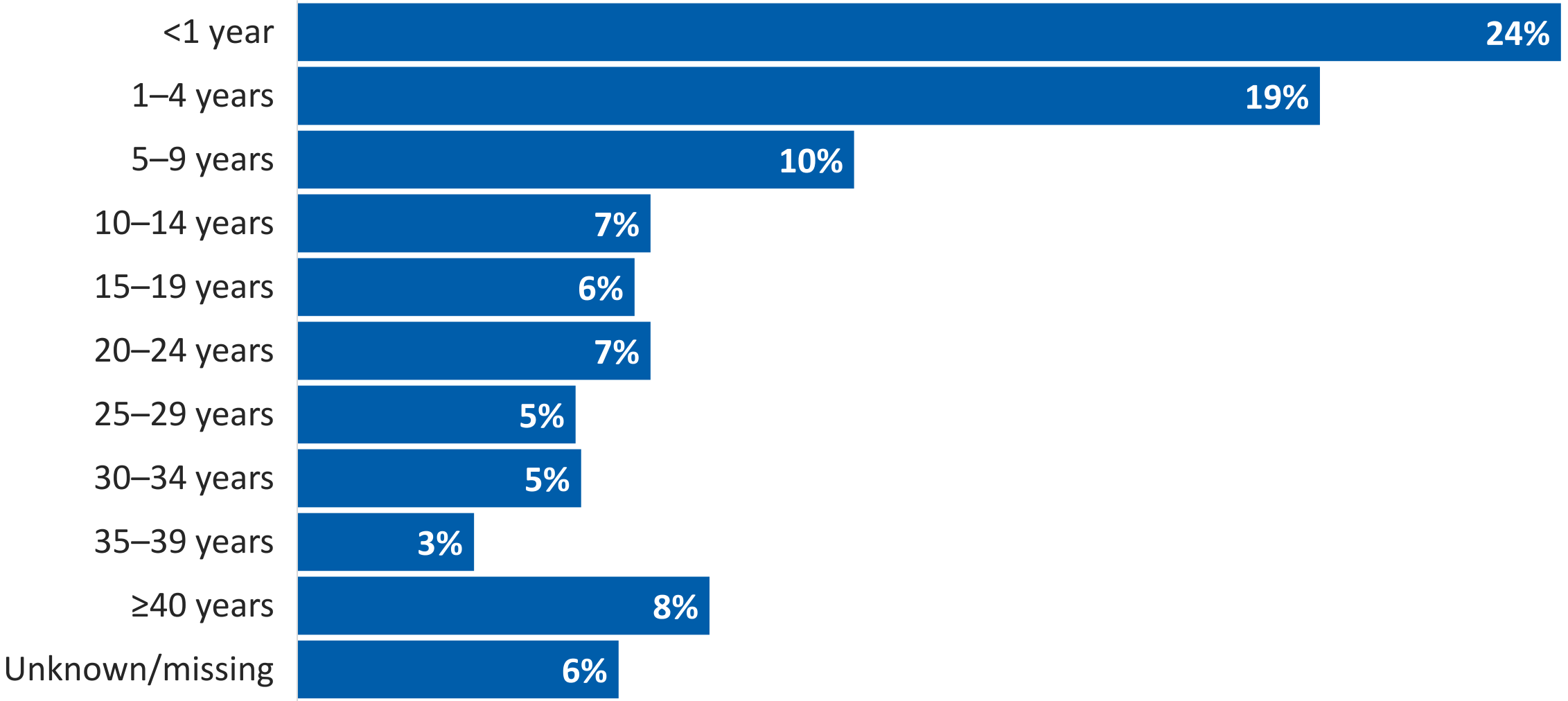
*Persons born in the United States, certain U.S. territories, or elsewhere to at least one U.S. citizen parent are categorized as U.S.-born. All other persons are categorized as non-U.S.–born.

TB Cases by Countries of Birth Among Non-U.S.–Born* Persons, United States, 2024 (N=8,016)



*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.

Percentage of TB Cases Among Non-U.S.–Born* Persons by Years Since Arrival in the United States Prior to Diagnosis, 2024 (N=8,016)



*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.

Importance of Identifying Latent TB Infections

~80% of active TB cases in the U.S. stem from untreated LTBI

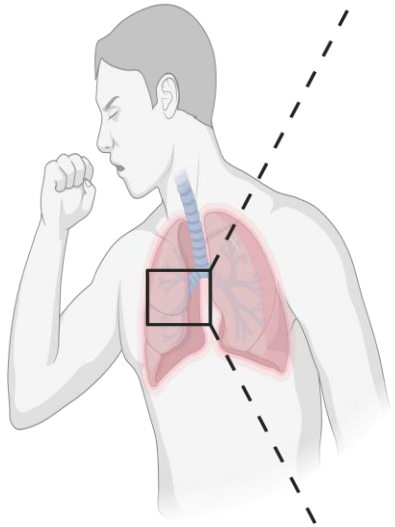
- Identify LTBI in at-risk individuals who would benefit from treatment
  - High risk of acquisition (close contacts, prior residence in high-burden countries)
  - High risk of transmission (congregate settings, shelters)
  - High risk of reactivation (immunosuppression, diabetes, ESRD)

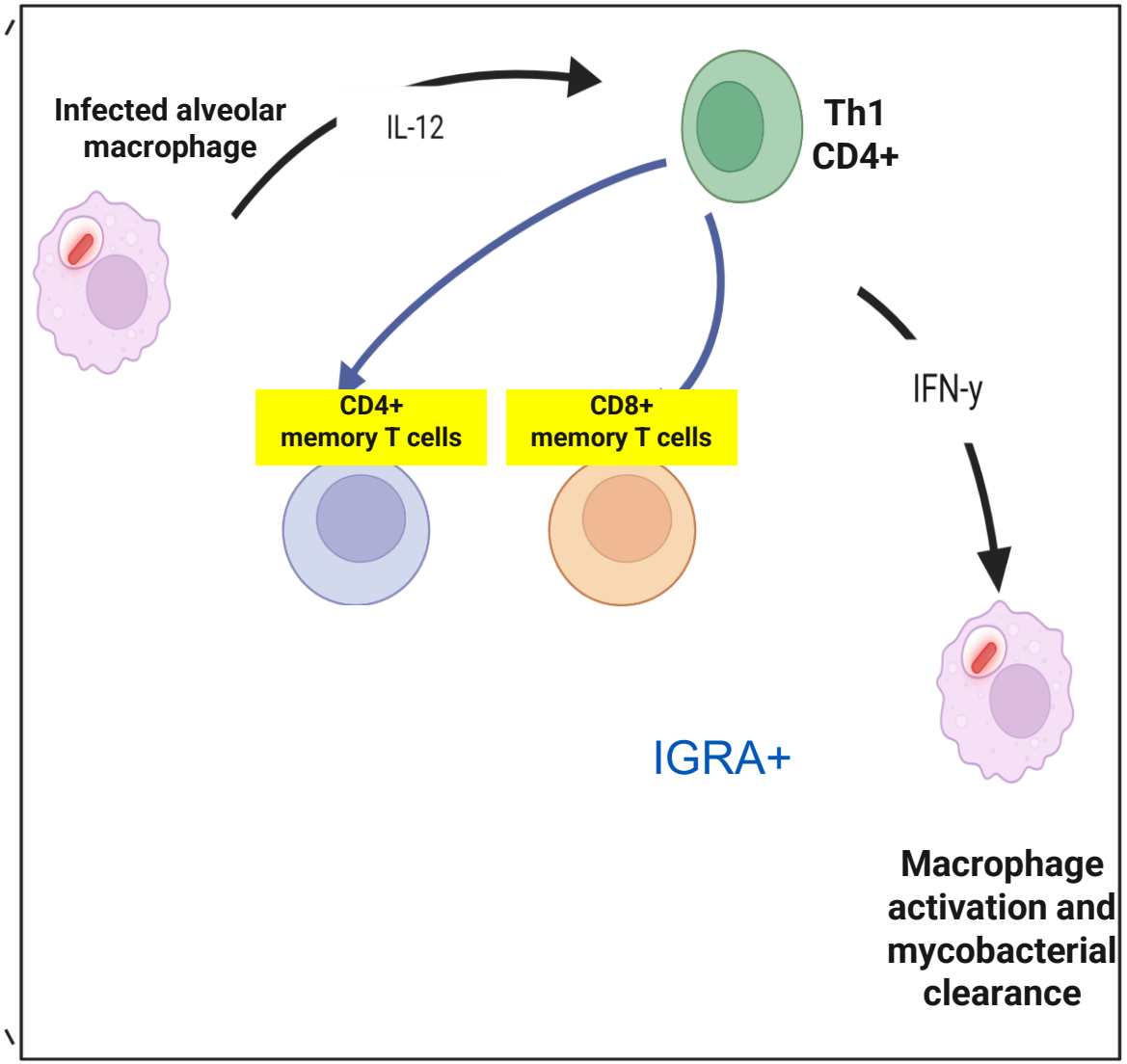
- No ‘gold standard’ method for detection of LTBI
  - All methods are *indirect* approaches detecting host immune response to *M. tuberculosis*

Shea KM, Kammerer JS, Winston CA, Navin TR, Horsburgh CR Jr. 2014. Estimated rate of reactivation of latent tuberculosis infection in the United States, overall and by population subgroup. Am J Epidemiol 179: 216–225

Traditional concept of TB infection

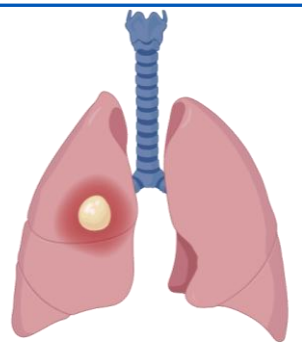
Exposure to MTB



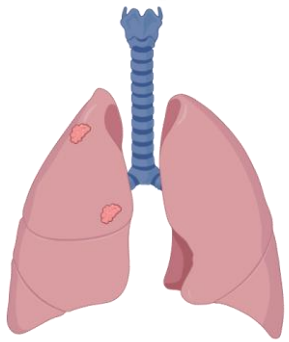


Active TB disease

~10%



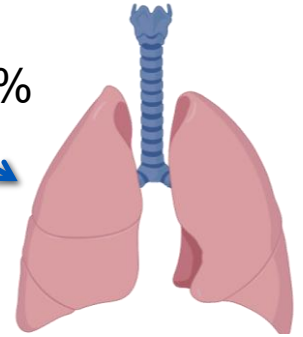
IGRA+/-
Signs/symptoms
Abnormal imaging



Initial TB infection

LTBI

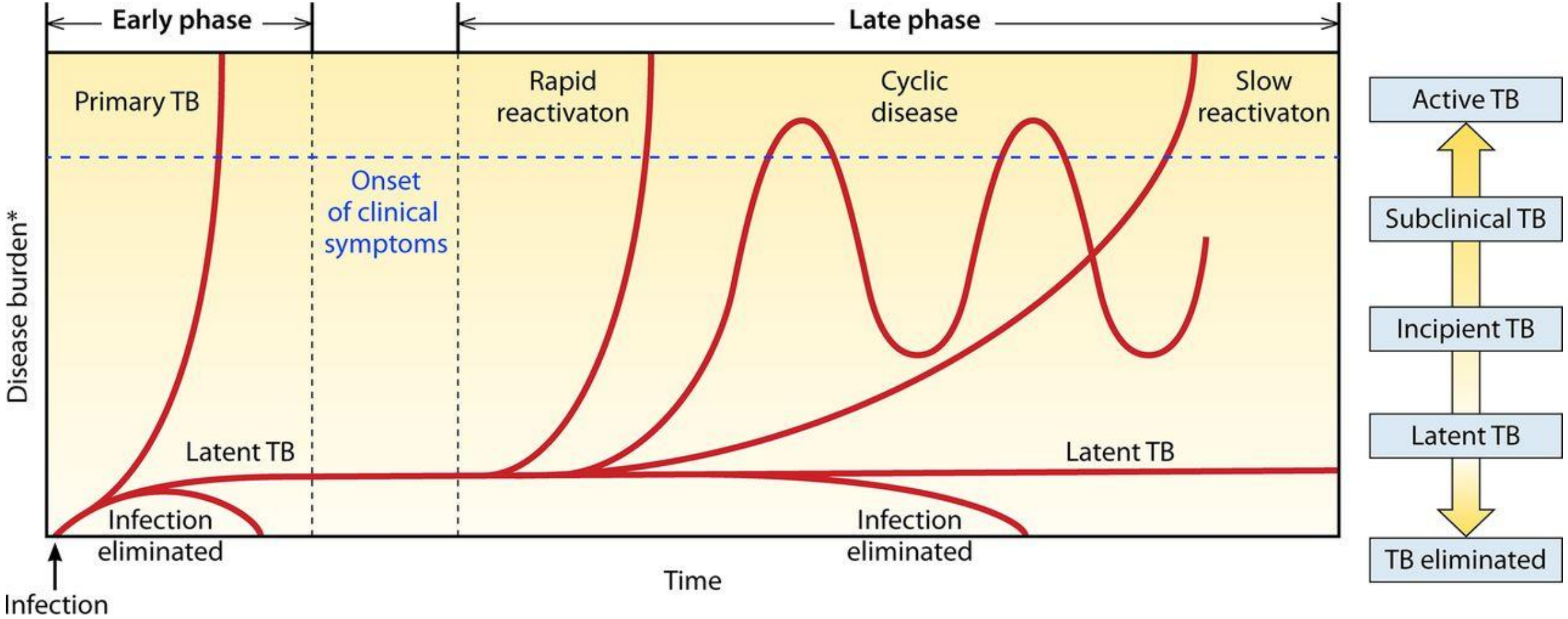
~90 %



IGRA+
Normal x-ray
No signs/symptoms

Modified from Maunank Shah et al, 2021 NEJM

TB infection continuum

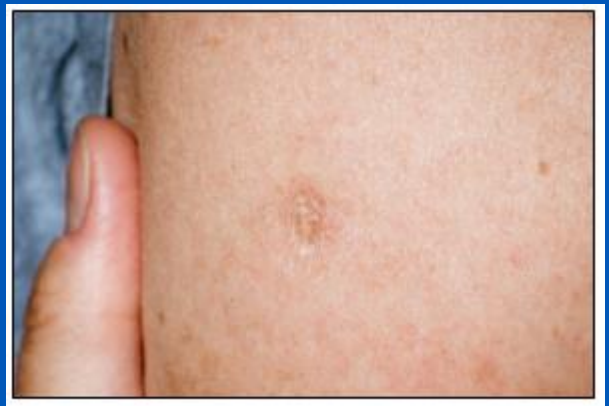


Precipitating factors include HIV, age, uncontrolled diabetes, end-stage renal disease (ESRD), TNF-alpha inhibitors and other immunosuppression, malnutrition, and viral infections.

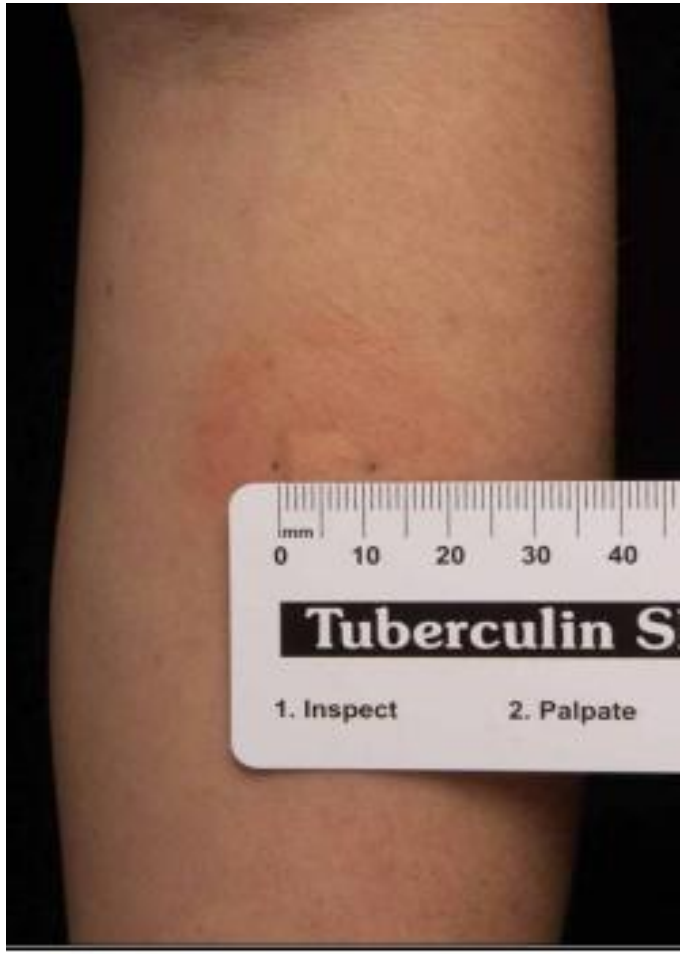
Esmail H et al. *Philos Trans R Soc Lond B biol Sci* 2014
Drain PK, et al. *Clin Microbiol Rev* 2018

TST

Developed in 1921



BCG vaccine scar

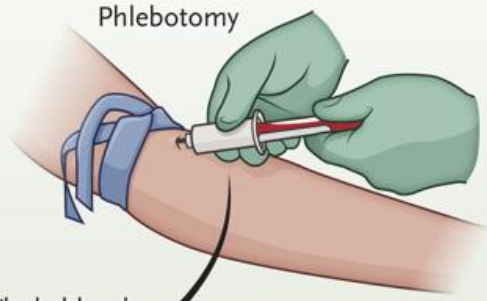


Measuring induration. In this photograph, the induration is 11 mm.

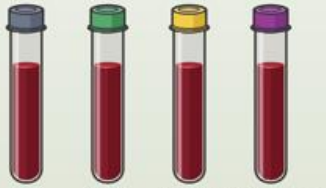
Mayo Clinic Center for Tuberculosis

Source: https://www.cdc.gov/tb/webcourses/tb101/page385.html

QuantiFERON-TB Gold Plus IGRA

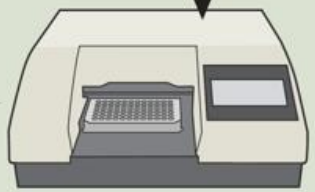


Whole blood

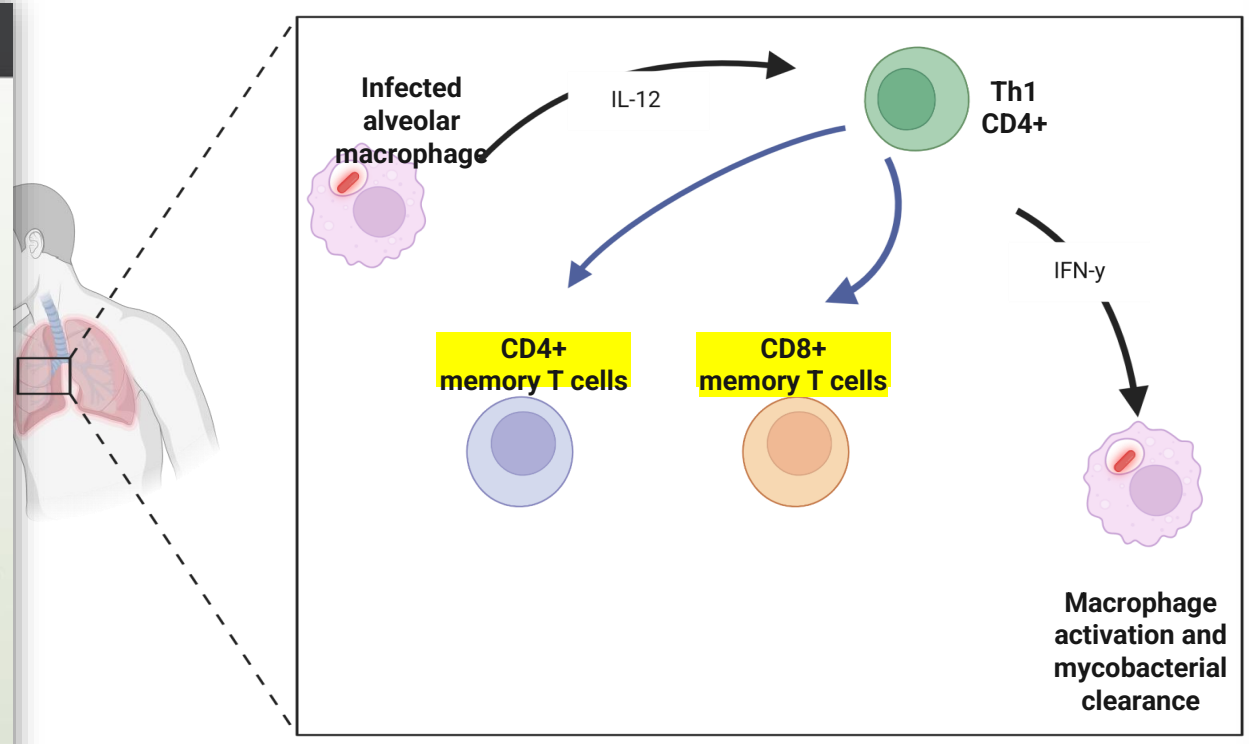


Add blood to tubes precoated with nil control, *M. tuberculosis* antigens (tubes TB1 and TB2), and mitogen positive control.

Incubate 16–24 hr. Add aliquot of stimulated plasma to wells of ELISA plate that contains interferon-γ antibodies.



A secondary enzyme-linked antibody is added and binds to interferon-γ. A detection reagent is added, and absorbance at 450 nm is measured. Concentration of interferon-γ is calculated on the basis of a standard curve.



IGRAs are **indirect** tests for infection with MTB

Patients infected with MTb have primed T-cells

Exposure of primed T-cells to MTb antigens induces IFN-γ production

IFN-γ detected by EIA/CIA or ELISPOT methods

2 FDA-cleared assays :

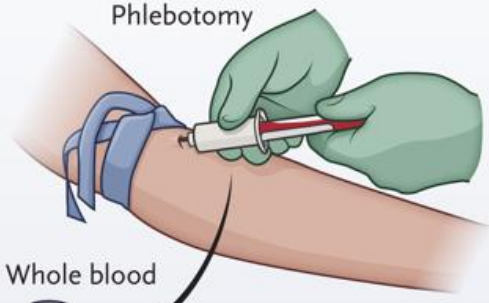
T.SPOT ®-TB (Oxford Immunotec)

QuantiFERON® TB-Gold Plus (QFT-Plus; Qiagen)

Both stimulate $CD4^+$ and $CD8^+$ T-cells

Modified from Maunank Shah et al, 2021 NEJM

T-SPOT.*TB* IGRA



Whole blood

PBMCs

Centrifugation

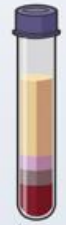
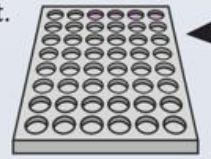
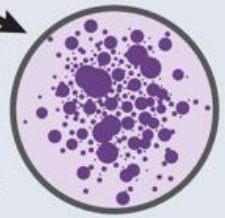


Plate 250,000 cells into each of four wells per patient.

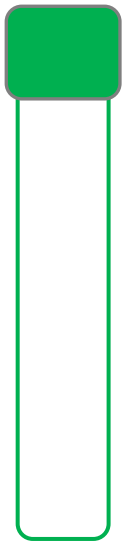


Add nil control, *M. tuberculosis* antigens (×2), and mitogen positive control. Incubate for 16–20 hr.



Interferon-γ antibodies capture interferon-γ as it is released from cells. A secondary enzyme-labeled antibody is added and binds to captured interferon-γ. A detection reagent is added, resulting in spots that are a footprint of the location where the interferon-γ was released by a cell. Spots are counted.

QFT-Plus Assay

	Nil Control	Mitogen Control	Tb 1 Antigens	Tb 2 Antigens
				
Antigens:	None	PHA*	**ESAT-6 CFP-10**	**ESAT-6 CFP-10 other peptides**
T-Cells Stimulated:	N/A	Universal T-cell stimulus	**TB-specific CD4+**	**TB-specific CD4+/ CD8+**
Purpose:	Determine baseline IFN-γ levels	Determine ability to generate IFN-γ		

Negative Result:
IFN-γ levels < 0.35 IU/mL in *both* Tb antigen tubes

Positive Result:
IFN-γ levels ≥ 0.35 IU/mL in *either one or both* Tb antigen tubes

Indeterminate Result:
1. High IFN-γ level (≥ 8.0 IU/mL) in **Nil** Control tube
2. Low IFN-γ level (<0.50 IU/mL) in **Mitogen** Control tube

*PHA, phythaemagglutinin-P

QuantiFeron-Tb Gold Plus

	Nil Control	Tb 1 Antigens	Tb 2 Antigens	Mitogen Control
				
Antigens	None			PHA phythaemagglutinin-P
T cell stimulated	N/A			Universal T-cell stimulant
Purpose	Adjusts for background IFN-γ levels			Low response may indicate inability to generate IFN-

QuantiFeron-Tb Gold Plus

	Nil Control	Tb 1 Antigens	Tb 2 Antigens	Mitogen Control
				
Antigens	None	**ESAT-6 CFP-10**	**ESAT-6 CFP-10**	PHA phythaemagglutinin-P
T cell stimulated	N/A	**CD4+**	**CD4+/ CD8+**	Universal T-cell stimulant
Purpose	Adjusts for background IFN-γ levels			Low response may indicate inability to generate IFN-

QuantiFeron-Tb Gold Plus

	Nil Control	Tb 1 Antigens	Tb 2 Antigens	Mitogen Control
				
Antigens	None	**ESAT-6 CFP-10**	**ESAT-6 CFP-10**	PHA phythaemagglutinin-P
T cell stimulated	N/A	**CD4+**	**CD4+/ CD8+**	Universal T-cell
Purpose	Adjusts for background IFN-γ levels			Low response may indicate inability to generate IFN-

Negative Result:
IFN-γ levels <0.35 IU/mL in ***both*** Tb antigen tubes and <25% of Nil

Positive Result:
IFN-γ levels ≥ 0.35 IU/mL in ***either one or both*** Tb antigen tubes

Example 1

QuantiFERON-TB Gold Plus, B

QuantiFERON-TB Gold Plus Result	Negative

The reference range for the 'TB1 Ag minus Nil Result' and 'TB2 Ag minus Nil Result' is an Interferon-gamma level <0.35 IU/mL.

TB1 Ag minus Nil Result	-0.01	IU/mL
TB2 Ag minus Nil Result	-0.01	IU/mL
Positive Control(Mitogen minus Nil)	5.20	IU/mL
Negative Control (Nil Result)	0.06	IU/mL

Example 2

QuantiFERON-Tb Gold Plus, B

QuantiFERON-Tb Gold Plus Result	Positive

The reference range for the 'TB1 Ag minus Nil Result' and 'TB2 Ag minus Nil Result' is an Interferon-gamma level <0.35 IU/mL.

TB1 Ag minus Nil Result	5.81	IU/mL
TB2 Ag minus Nil Result	6.26	IU/mL
Positive Control(Mitogen minus Nil)	9.92	IU/mL
Negative Control (Nil Result)	0.08	IU/mL

QuantiFERON-Tb Gold Plus

	Nil Control	Tb 1 Antigens	Tb 2 Antigens	Mitogen Control
				
Antigens	None	**ESAT-6 CFP-10**	**ESAT-6 CFP-10**	PHA phythaemagglutinin
T cell stimulated	N/A	**CD4+**	**CD4+/ CD8+**	Universal T-cell stimulant
Purpose	Adjusts for background IFN-γ levels			Low response may indicate inability to generate IFN-

Mitogen not reacting

Indeterminate results due to poor mitogen response

Low IFN-γ level (<0.50 IU/mL) in **Mitogen** Control tube

Immunosuppressed patients
Technical issues

What to do?

Consider getting T spot test

QuantiFERON-Tb Gold Plus

	Nil Control	Tb 1 Antigens	Tb 2 Antigens	Mitogen Control
				
Antigens	None	**ESAT-6 CFP-10**	**ESAT-6 CFP-10**	PHA phythaemagglutinin-P
T cell stimulated	N/A	**CD4+**	**CD4+/ CD8+**	Universal T-cell stimulant
Purpose	Adjusts for background IFN-γ levels			Low response may indicate inability to generate IFN-

Nil reacting

Indeterminate results due to Nil reacting

High IFN-γ level (≥ 8.0 IU/mL) in **Nil** Control tube

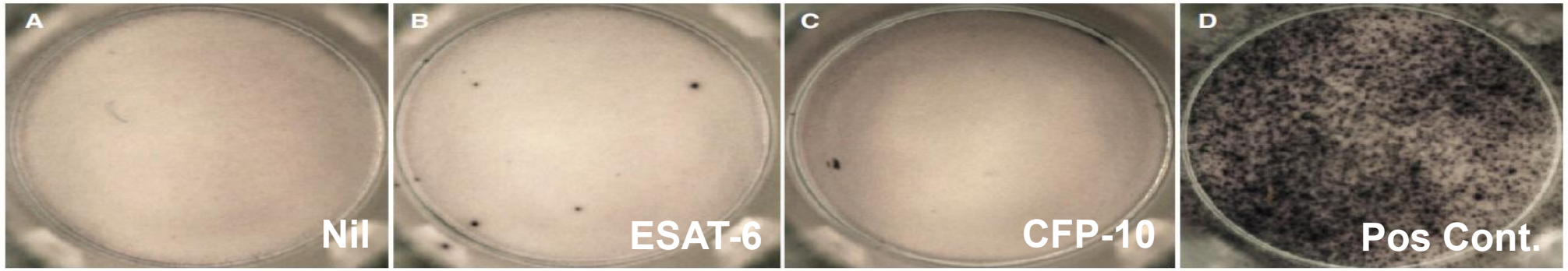
Elevated baseline IFN-γ levels, such as certain infections, autoimmune diseases, or other inflammatory conditions

What to do?

- Consider repeating QuantiFERON
- Get T-spot test

IGRA by ELISpot Method (T-Spot)

- Standardized number of peripheral blood monocytes incubated in wells containing:
  - Anti-IFN gamma
  - TB-specific antigens
- Detection with enzyme-linked antibodies



Interpretation	No. of Spots
Positive	ESAT-6 and/or CFP-10 minus Nil = ≥ 8 spots
Negative	ESAT-6 and CFP-10 minus Nil = < 4 spots
Borderline	5, 6 or 7 spots

IGRA in HIV

- In active TB and HIV(+), in low-middle income countries
  - **Sensitivity:**
    - QFT= 61% (95%CI, 47 to 75%)
    - TSPOT= 72% (95%CI, 62 to 81%)
    - Neither IGRA was consistently more sensitive than TST
  - **Indeterminate results**
    - QFT= 8.2%
    - TSPOT= 5.9%
    - ↑ indeterminate results with CD4 < 200 (11.6% QFT vs. 11.4% TSPOT)
    - ↓ with CD4 > 200 (3.1% QFT vs. 7.9% TSPOT)
- In suspected LTBI and HIV(+), IGRAs perform similarly to TST
- Both TST and IGRAs have suboptimal sensitivity, suggesting potential role for using both tests, especially in severely immunosuppressed individuals

Cattamanchi A. et al. *J AIDS* 2011
Santin M. et al. *PLoS One* 2012
Chen J. et al. *PLoS One* 2011
Pai M, et al. *Clin Microbiol Rev* 2014
Lewinsohn DM, et al. *Clin Infect Dis* 2016

Variability for the QFT Assays

With-in subject variability:

Overall ± 0.60 IU/mL

Borderline ± 0.24 IU/mL

Assay cut-off for positive: ≥ 0.35 IU/mL

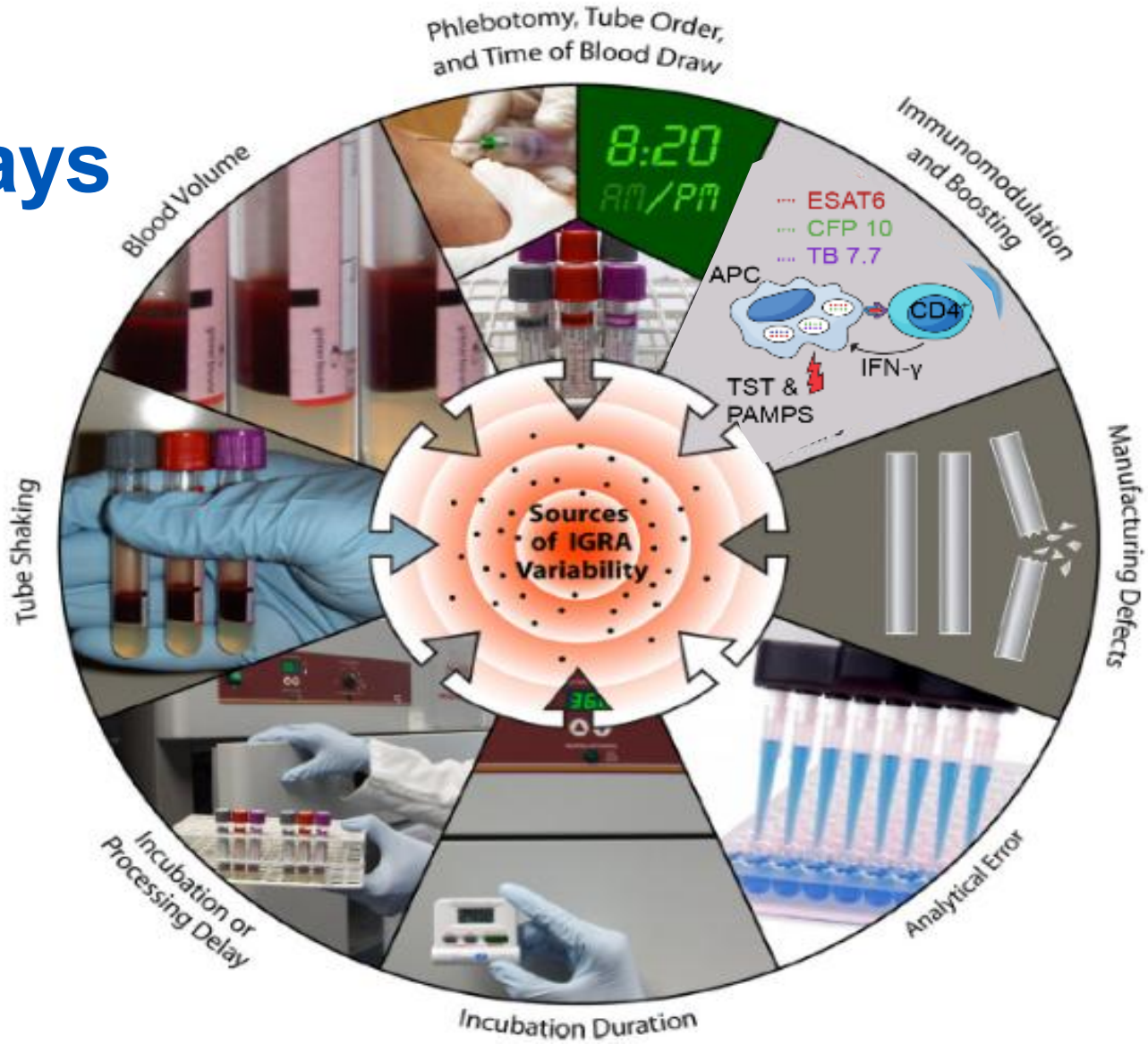
Interpret positive QFT values between

0.35 - 0.95 IU/mL with caution!

High rates of spontaneous conversion/reversion:

QFT-Plus: 22/196 **(11%)**

QFT-Gold: 16/188 **(8.5%)**



Sources of variability for the QFT Assays

Pai M. et. al. Clin Micro Rev. 2014;27(1):3-39, Oh CE, et al. *Clin Infect Dis*. 2021;73:e116-e1125
Metcalfe JZ et. al. Am J Respir Crit Care Med. 2013;187(2): 206-211

Detection of Latent TB Infection via IGRAs

- **False Positives:**
  - *M. marinum, M. kansasii, M. szulgai, M. flavescens*
  - Pre-analytic processing errors
- **False Negatives:**
  - Immunosuppression
  - Pre-analytic processing errors

- **Persistence of positive results**

- **Can IGRAs be used to monitor response to therapy?**
  - "…monitoring IGRA changes over time seems to have a speculative value only." (Chiappini, Clin. Therapy 2012)
- **Do IGRAs have a predictive value for progression to active TB?**
  - Predictive value of IGRAs is low.

IGRA Considerations for the Civil Surgeon

Melanie Swift, MD, MPH
Professor of Medicine
Division of Public Health, Infectious Diseases and Occupational Medicine
Mayo Clinic, Rochester, MN
Civil Surgeon since 2017

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- 1.00 IPCE

Technical Instructions for Civil Surgeons

updated
May 15, 2024

Tuberculosis

Technical Instructions for Civil Surgeons

AT A GLANCE

These instructions are in accordance with CDC regulations and are for the use of civil surgeons evaluating persons applying for adjustment of status for U.S. permanent residence and others required to have a medical examination.

Background

The CDC Division of Global Migration Health (DGMH) developed these instructions in consultation with U.S. tuberculosis subject matter experts. One of the goals of the status adjustment medical examination is to diagnose and treat certain infectious diseases, thus these instructions define the specific responsibilities of civil surgeons in terms of testing for infectious tuberculosis disease among applicants and referral for treatment. For the purposes of these instructions, the term infectious tuberculosis disease refers to disease of the lung parenchyma, pleura, larynx, or intrathoracic lymph nodes. Other forms of extrapulmonary tuberculosis and latent tuberculosis infection (LTBI) are not included in the definition of infectious tuberculosis disease and are defined separately.

These instructions are specific to the status adjustment medical examination and should not be used as guidance to test for or treat tuberculosis disease in other settings or as a clinical manual that defines detailed laboratory procedures or specific treatment regimens. Treatment of applicants for drug-susceptible tuberculosis disease must be consistent with current CDC guidance: Treatment for TB Disease.

U.S. Citizenship and Immigration Services (USCIS) in the U.S. Department of Homeland Security (DHS) designates civil surgeons. Civil surgeons must perform the medical examination according to the procedures prescribed in these Technical Instructions. Civil

ON THIS PAGE

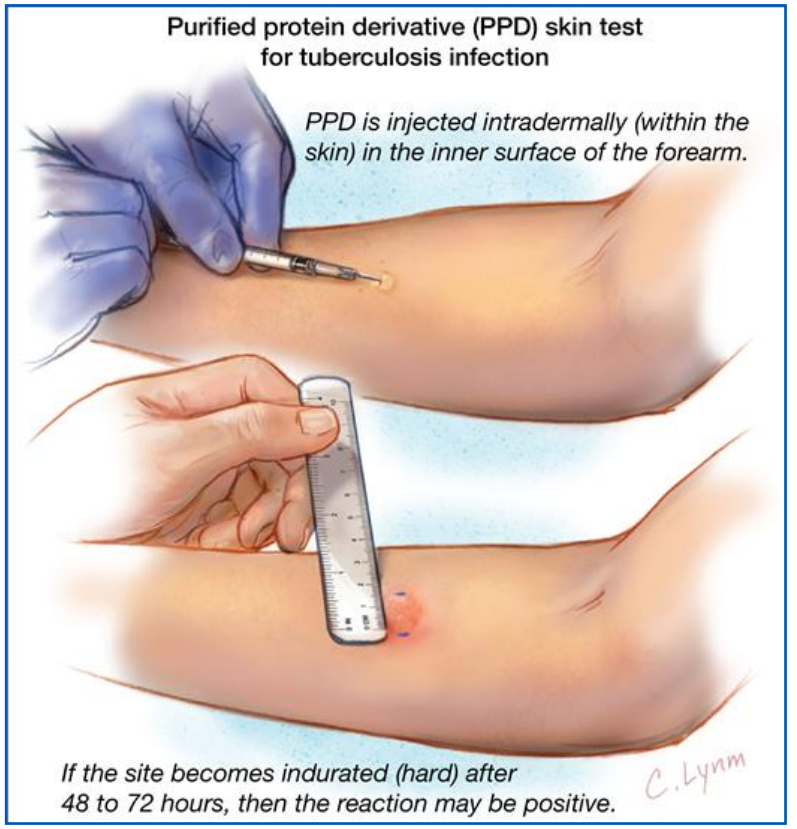
https://www.cdc.gov/immigrant-refugee-health/hcp/civil-surgeons/tuberculosis.html

Changes to TB testing rules in 2018

- Blood tests (IGRAs) must be used instead of the tuberculin skin test (TST)
- TST cannot be substituted for IGRA
- Applicants with **untreated** LTBI must be reported to their local health department
  - November 1, 2023 – must also be entered in eMedical
- Civil surgeons must not refer applicants to a health department for their required IGRA or chest X-ray

Limited use of TST

- Only in children under age 2, as directed by health department
  - Child is HIV positive
  - Child is close contact of person with communicable TB disease



When may IGRA testing be exempted for status adjusters >2 years of age?

A. Documented completion of treatment for LTBI

B. Documentation of a prior positive IGRA

C. Documentation of a prior positive TST

D. Any of the above

IGRA Exemption

- Written documentation of previous **positive** IGRA
  - Test date
  - Type of IGRA
  - Results in standard units of measurement
  - Interpretation
  - Testing physician’s name, signature, and office information

Not eligible for IGRA exemption

Civil Surgeon must obtain IGRA

- Prior positive TB skin test
- Documentation of treatment for LTBI
- Recent Negative IGRA

No testing required for certain applicants

- Age < 2 years (no HIV or symptoms)
- Refugees (and spouse/dependent)
- K visa (fiancé of a US citizen)

4. Immigration Medical Examination Requirement

A. ☐ I am eligible for completion of the vaccination record portion only, because I previously completed an overseas immigration medical examination, signed by a panel physician (refugee or derivative asylee adjustment of status applicants under Immigration and Nationality Act (INA) section 209 and K nonimmigrant visa holders applying for adjustment of status).

NOTE: If you selected this box for Item A. in Item Number 4., you, the applicant, and the civil surgeon are responsible for completing Parts 1. - 5., Part 7., and Part 10.

In the context of interpreting IGRA results, what distinguishes the approach for a civil surgeon from a general medical practice?

A. Civil surgeons must treat an indeterminate result as though it were positive.

B. Civil surgeons may not repeat a positive IGRA on a low-risk individual.

C. Civil surgeons must repeat a negative IGRA on high-risk individuals.

D. There is no difference in IGRA interpretation for civil surgeons.

Civil Surgeon actions based on IGRA result

IGRA Result	**Civil Surgeon Exam requirement**	**Personal counseling**
Negative	No further testing	
Positive	Obtain chest X-ray Do not repeat IGRA	Consider repeating IGRA in **low-risk** individuals
Indeterminate, borderline or equivocal	Document as indeterminate No further testing	Consider repeating IGRA

A. Tuberculosis (TB): An initial screening test, an interferon gamma release assay (IGRA), is required for all applicants 2 years of age and older; for children under 2 years of age, see the *Technical Instructions for Civil Surgeons*. The civil surgeon will perform further evaluation if needed (chest X-ray).

(1) Interferon Gamma Release Assay (for acceptable IGRAs, consult the *Technical Instructions for Civil Surgeons* and any updates posted on the CDC's website):

☐ Not Administered (IGRA exception; please explain in Remarks section below)

Select **only one** box.

☐ QuantiFERON

Date Blood Sample Drawn (mm/dd/yyyy)

☐ T-Spot

Date Blood Sample Drawn (mm/dd/yyyy)

Result:

☐ Negative (no chest X-ray required)

☐ Positive (chest X-ray required)

☐ Indeterminate (including borderline/equivocal) (no chest X-ray required)

Documented treatment for LTBI

- **Order IGRA** unless documentation of prior positive IGRA
  - Prior positive TST does not meet IGRA exemption
  - Prior treatment does not meet IGRA exemption
- **Order** an updated CXR
- **Ask** about TB symptoms
- **Verify** treatment completion
- **Classify as "No Class A or Class B TB" if:**
  - No symptoms
  - No known HIV infection
  - No concern for active disease on CXR
  - Documentation of complete course of treatment for latent TB infection
  - Does NOT require reporting to public health or eMedical

Criteria for LTBI treatment completion

www.health.state.mn.us/diseases/tb/meds/ltbicompcrit.pdf

DEPARTMENT OF HEALTH

Minnesota provider guide: Latent TB infection (LTBI) treatment completion criteria

This document contains guidance to Minnesota providers who are monitoring patients during treatment of LTBI. It outlines how to manage patient missed doses and completion criteria.

4R Rifampin (RIF) regimen

Four months/once daily totaling 120 doses.

Monitor monthly. Complete doses within six consecutive months.

3HP Isoniazid (INH) and Rifapentine (RPT) regimen

Three months/once weekly totaling 12 doses.

Monitor weekly if by DOT* or monthly if by SAT**. A minimum of 11 doses must be taken within 16 consecutive weeks.

3HR Isoniazid (INH) and Rifampin (RIF) regimen

Three months/once daily totaling 90 doses.

Monitor monthly. Complete doses within four consecutive months.

6H Isoniazid (INH) regimen

Six months/once daily totaling 180 doses.

Monitor monthly. Complete doses within nine consecutive months. If gap(s) are ≥two months, patient should be re-evaluated for signs and symptoms before resuming treatment.

9H Isoniazid (INH) regimen

Nine months/once daily totaling 270 doses.

Monitor monthly. Complete doses within 12 consecutive months. If gap(s) are ≥two months, patients should be re-evaluated for signs and symptoms before resuming treatment.

6H or 9H Isoniazid (INH) regimens

Six months/twice weekly totaling 52 doses; or **nine** months/twice weekly totaling 76 doses.

When must the Civil Surgeon refer an HIV-positive applicant to the Health Department for sputum smear and culture?

A. Only if they report TB symptoms

B. Only if they have a positive IGRA

C. If they have an abnormal X-ray OR report TB symptoms

D. All HIV positive patients must be referred, regardless of symptoms, IGRA result, or X-ray findings

Questions and Answers

Thank you