MAYO CLINIC

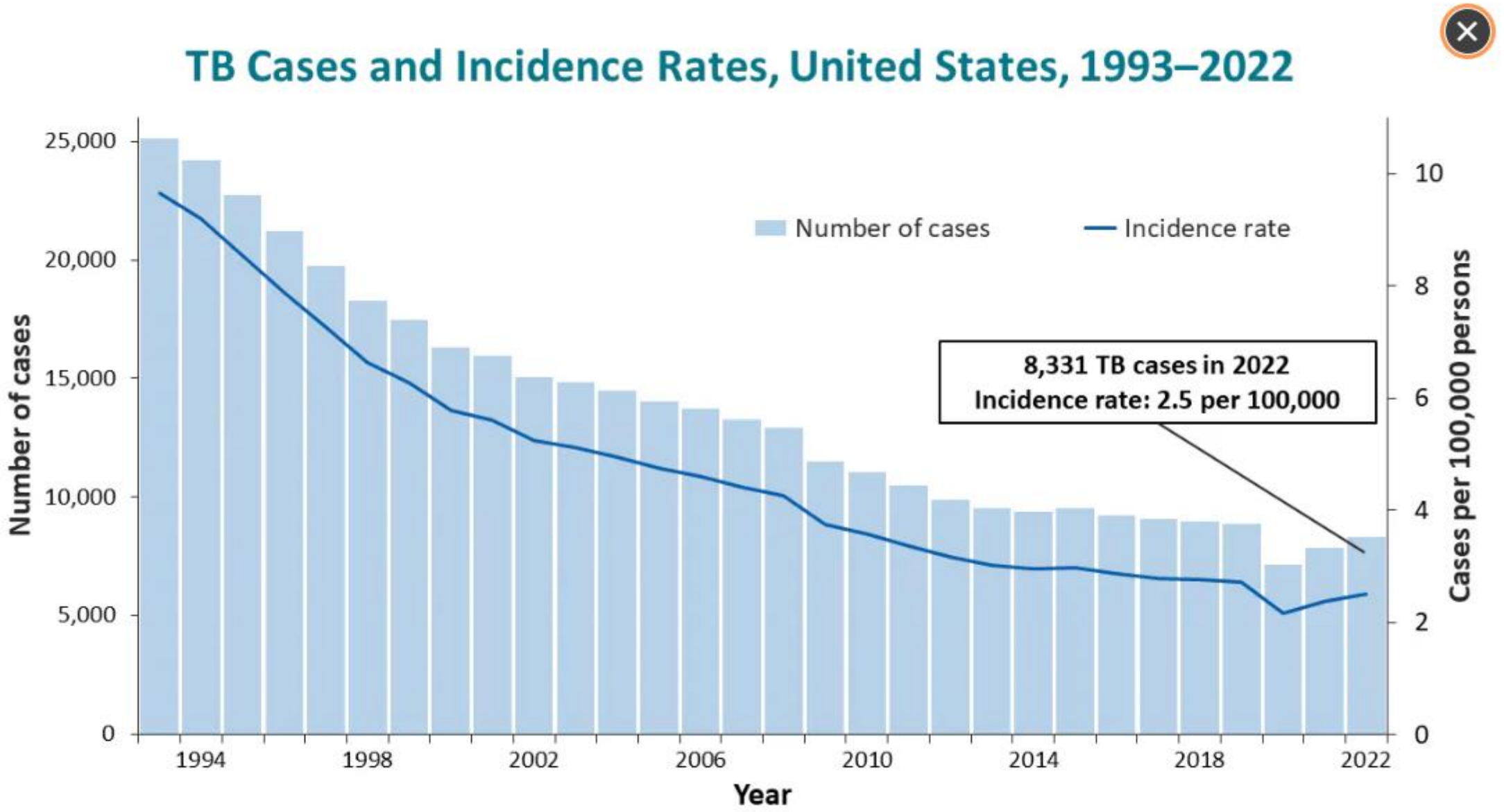
Center for Tuberculosis

# Fundamentals of Tuberculosis

**James Gaensbauer, MD MScPH**
Associate Professor of Pediatric and Adolescent Medicine
Medical Director of Education and Training, Mayo Clinic Center for Tuberculosis

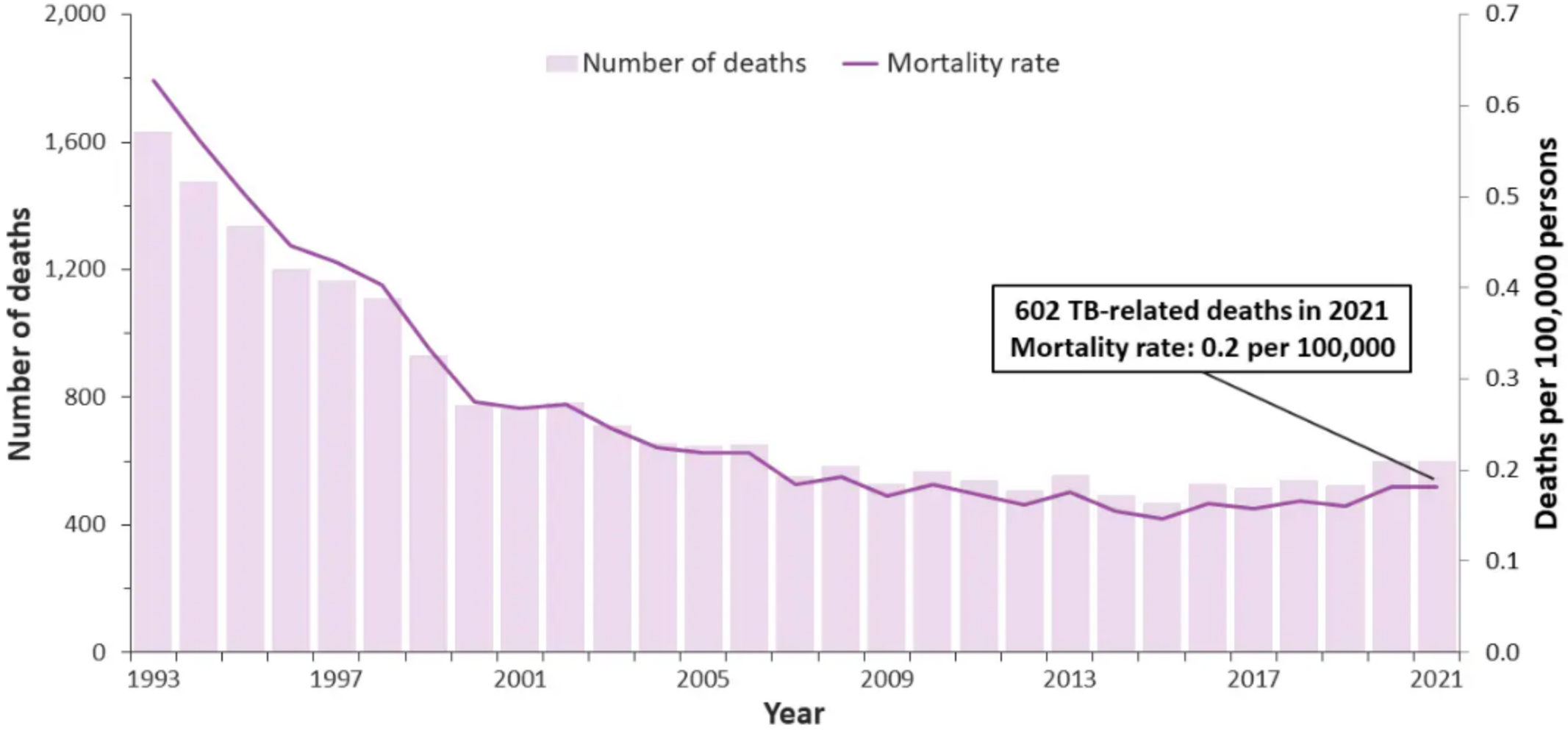
# Learning Objectives

- Describe the burden of tuberculosis in the United States
- Recognize Tb in the right clinical setting
- Describe the organization of TB services in the United States




https://www.cdc.gov/tb/statistics/reports/2022/national_data.htm

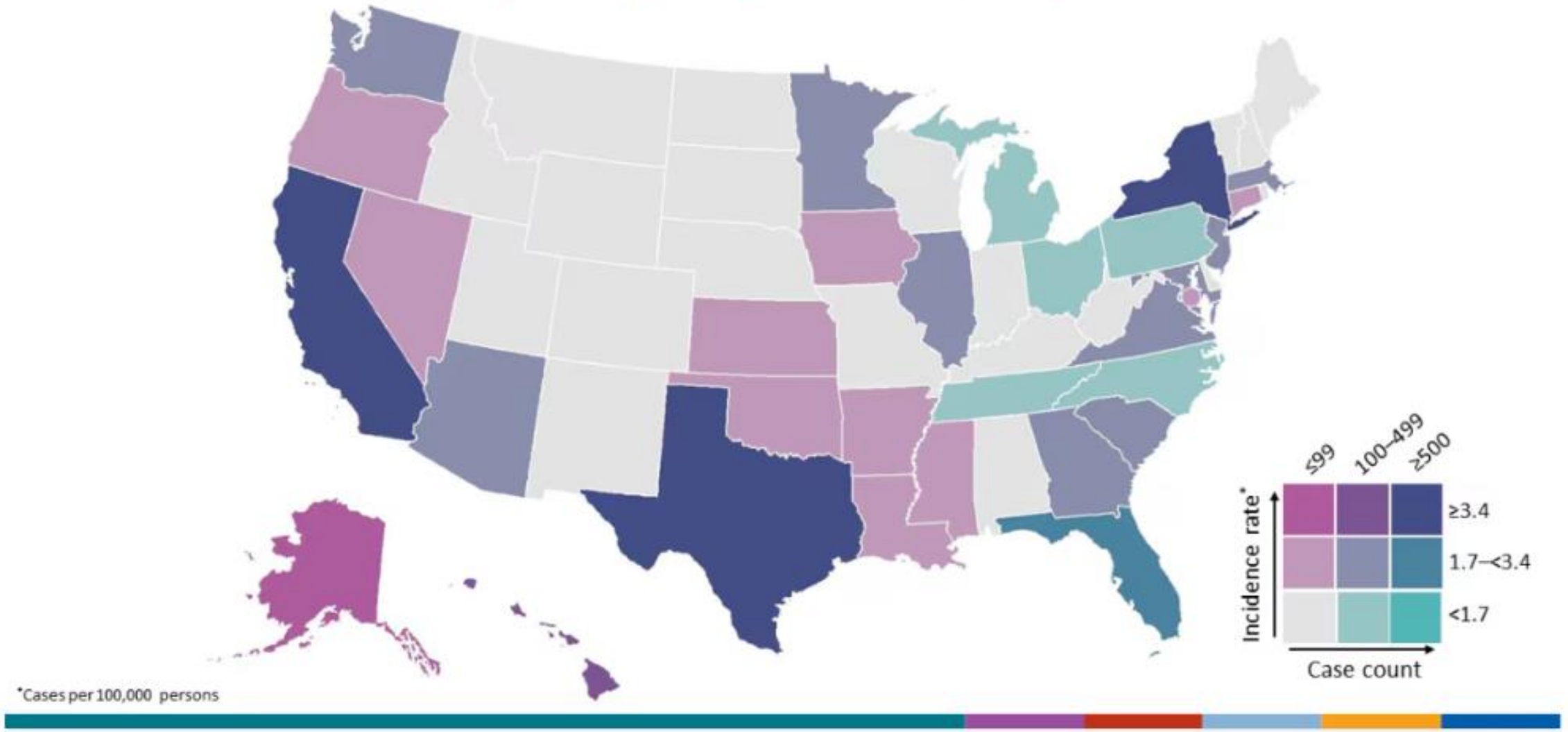
# TB-Related Deaths* and Mortality Rates, United States, 1993–2021




*National Vital Statistics System Underlying Cause of Death (based on deaths reported through 2021)

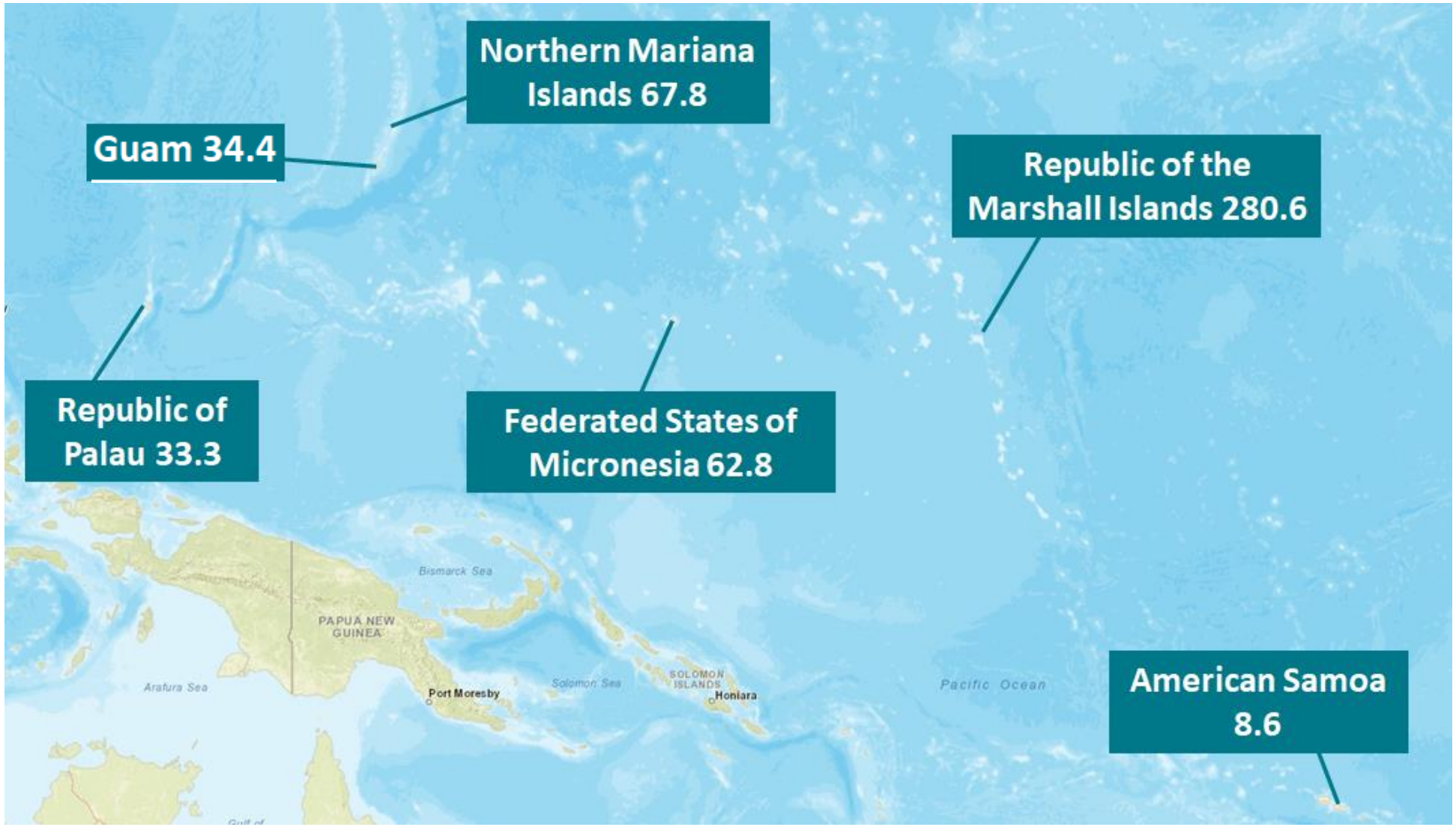
https://www.cdc.gov/tb/statistics/reports/2022/national_data.htm

# TB Cases and Incidence Rates*
# by Reporting Area, United States, 2022



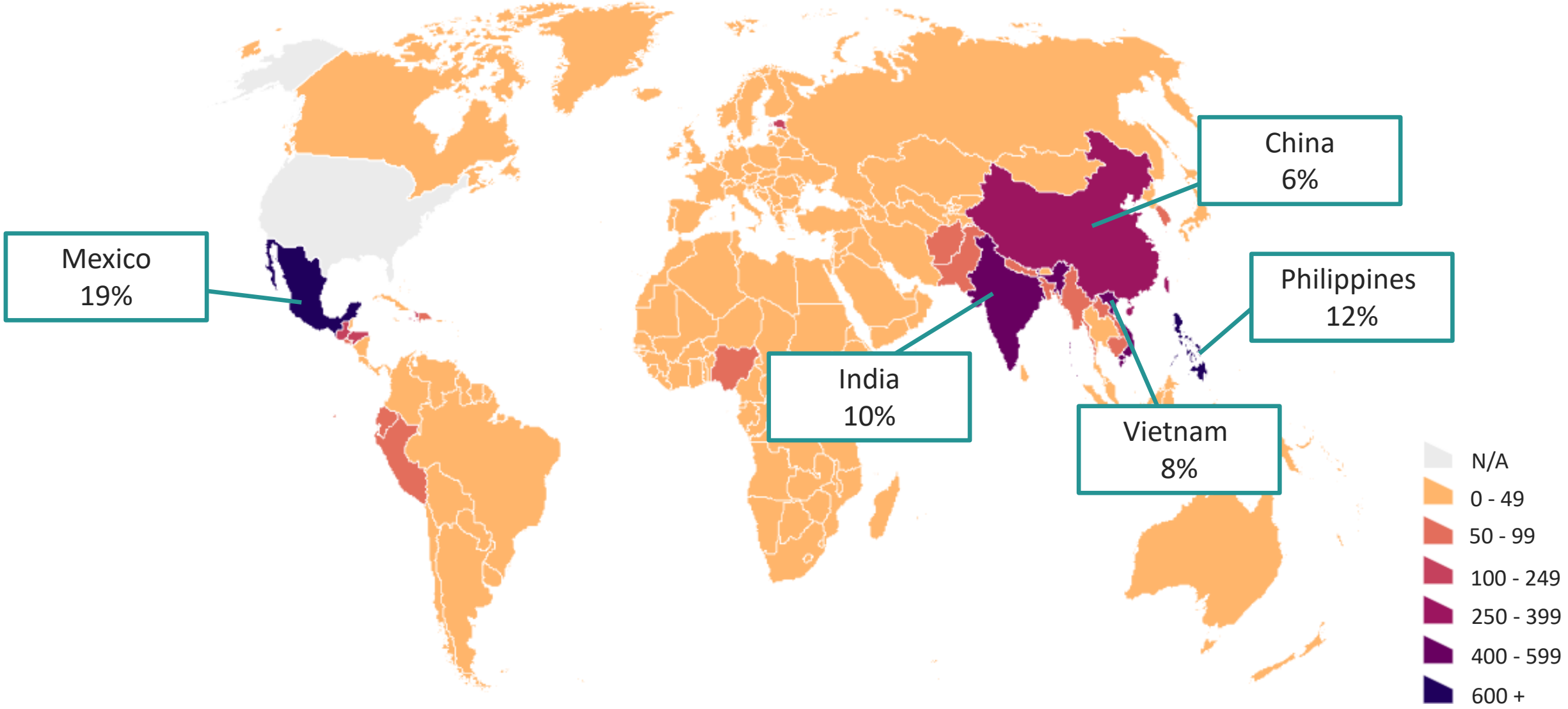

https://www.cdc.gov/tb/statistics/reports/2022/national_data.htm

# TB Incidence Rates* by U.S.-Affiliated Pacific Islands, 2021



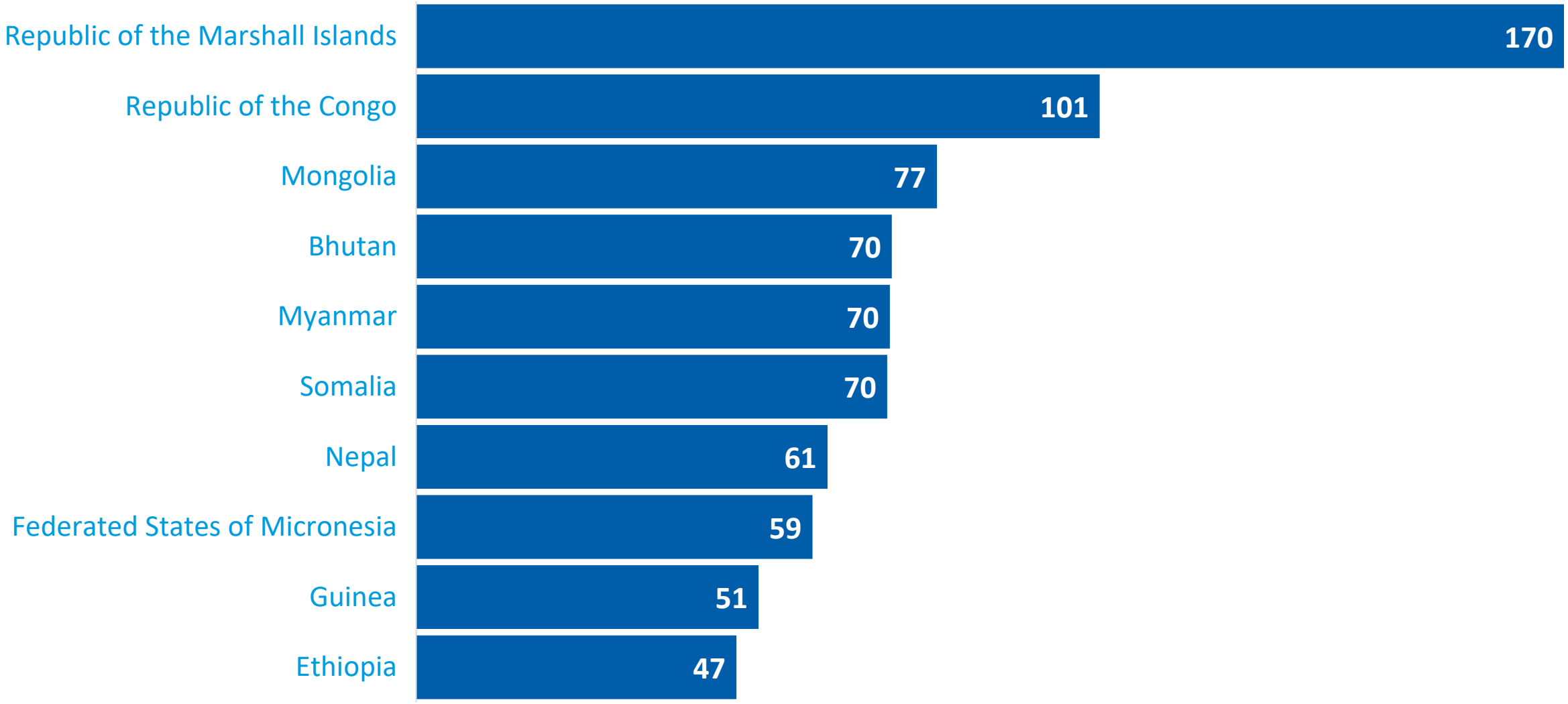

*Cases per 100,000 persons

# TB Cases by Countries of Birth Among Non-U.S.–Born* Persons with TB, United States, 2021 (N=5,626)



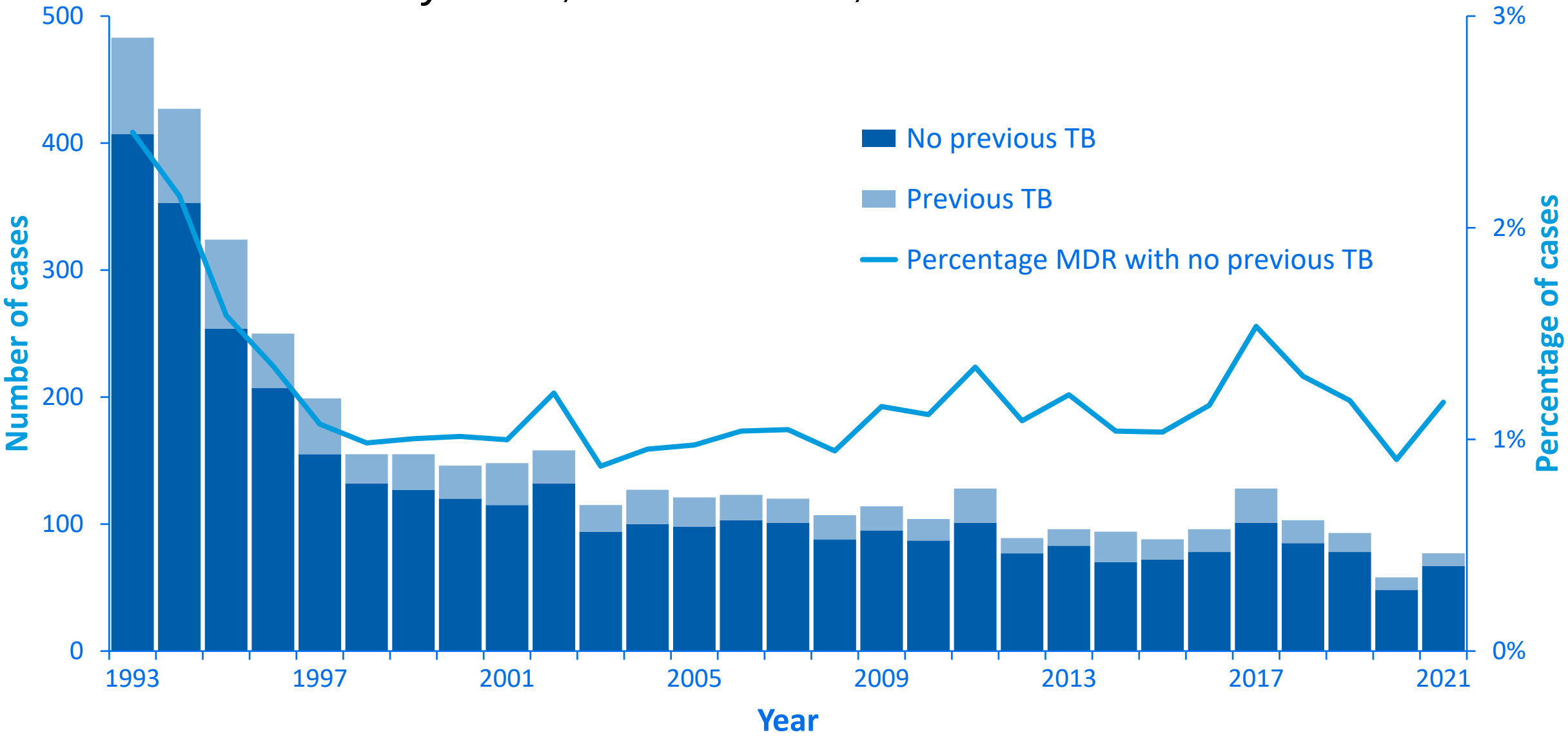

*Persons born in the United States, certain U.S. territories, or elsewhere to at least one U.S. citizen parent are categorized as U.S.-born. All other persons are categorized as non-U.S.–born.

# Top 10 TB Incidence Rates* by Country of Birth, United States, 2017–2021




* Cases per 100,000 persons

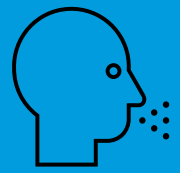
# Number and Percentage of Multidrug-Resistant (MDR)* TB Cases by History of TB, United States, 1993–2021



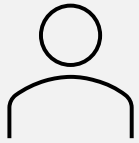

*Resistant to at least isoniazid and rifampin.

# When should we suspect TB?

**Symptoms**



**Person**



**Tests**

# Symptoms of Tuberculosis

## Non-specific Constitutional Symptoms

- Loss of appetite
- unexplained weight loss
- Night sweats,
- fever
- Fatigue

## Respiratory Symptoms

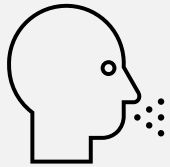
- Prolonged cough (3 weeks or longer)
- Shortness of breath
- Hemoptysis
- Chest pain

## Symptoms Of Possible Extra-pulmonary TB

- Blood in the urine (TB of the kidney)
- Headache/confusion (TB meningitis)
- Back pain (TB of the spine)
- Hoarseness (TB of the larynx)

# When should we suspect TB?

**Symptoms**



**Person**

**Tests**

# Persons at Risk for Developing TB Disease

1

Those who have an increased likelihood of exposure to persons with TB disease

2

Those with clinical conditions that increase their risk of progressing from LTBI to TB disease

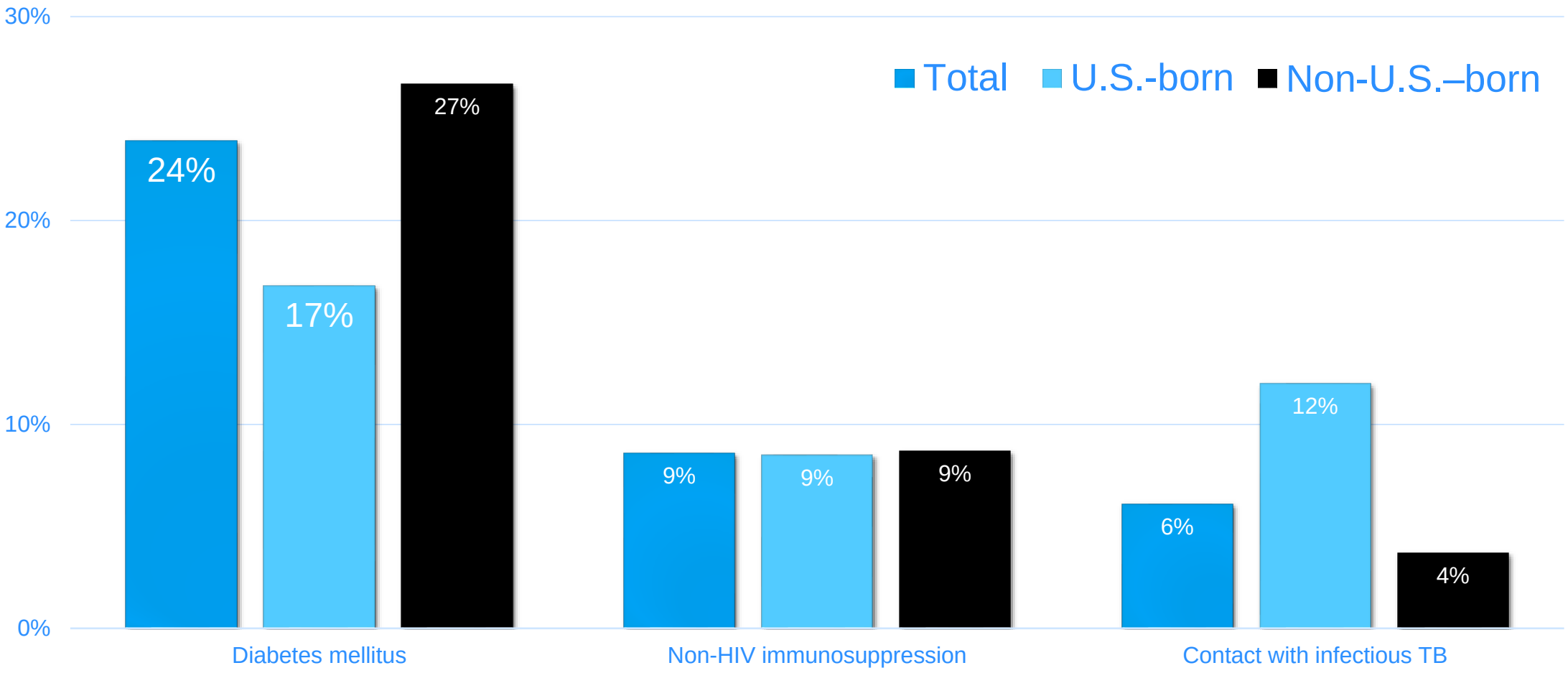
# Increased Likelihood of Exposure to Persons with TB Disease

- Close contacts to person with infectious TB
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, homeless shelters, health care facilities)
- Recent immigrants from TB-endemic regions of the world

# Increased Risk for Progression to TB Disease

- HIV-infected persons
- Those  with a history of prior, untreated TB or fibrotic lesions on chest radiograph
- Children ≤ 5 years with a positive skin test for latent tuberculosis
- Underweight or malnourished persons
- Substance abusers (such as smoking, alcohol abusers, or injection drug use)
- Those receiving biologics
- Those with certain medical conditions
  - Silicosis
  - Diabetes mellitus
  - Chronic renal failure/hemodialysis
  - Solid organ transplantation
  - Carcinoma of head or neck
  - Gastrectomy or jejunoileal bypass

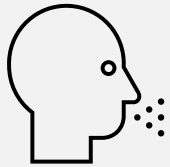
# Percentage of Selected Risk Factors Among Persons with TB by Origin of Birth,* United States, 2021



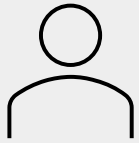

*Persons born in the United States, certain U.S. territories, or elsewhere to at least one U.S. citizen parent are categorized as U.S.-born. All other persons are categorized as non-U.S.–born.

# When should we suspect TB?

**Symptoms**

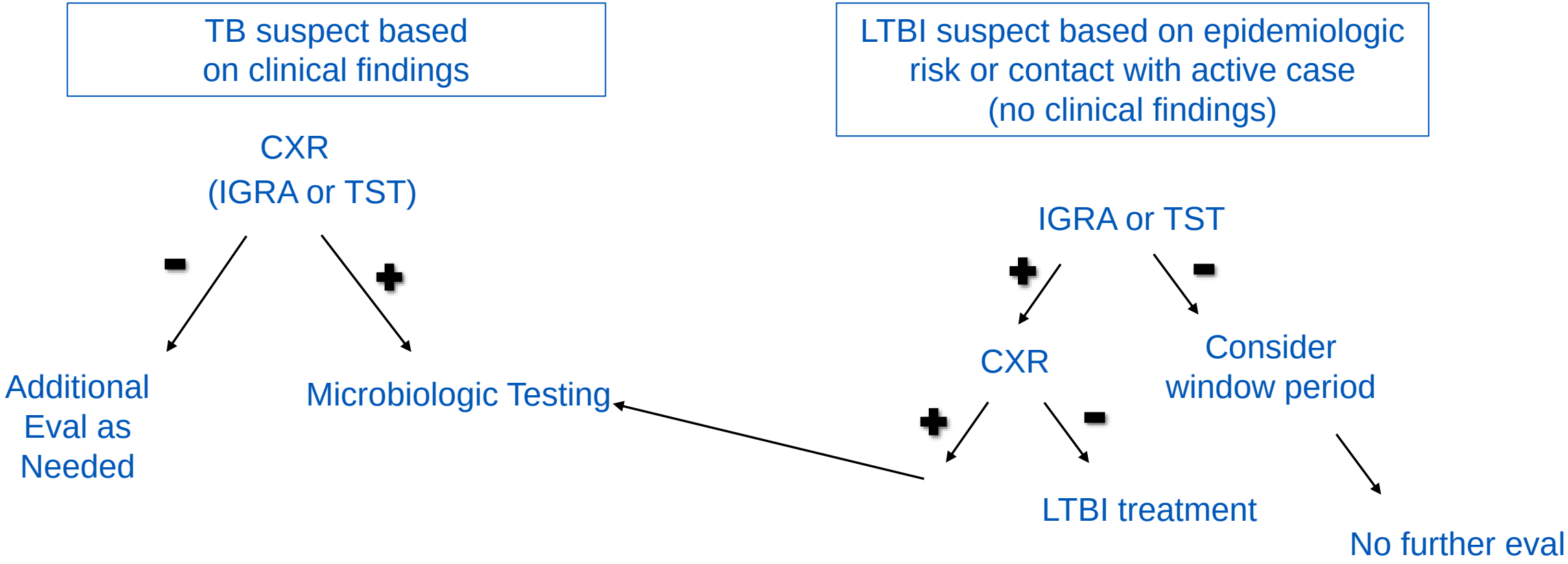


**Person**



**Tests**

# Tubeculosis Tests



# TB infection vs TB disease

## LTBI

- no symptoms
- no abnormal clinical findings
- normal x-ray
- Immunologic evidence of past infection (TST or IGRA)

## TB DISEASE

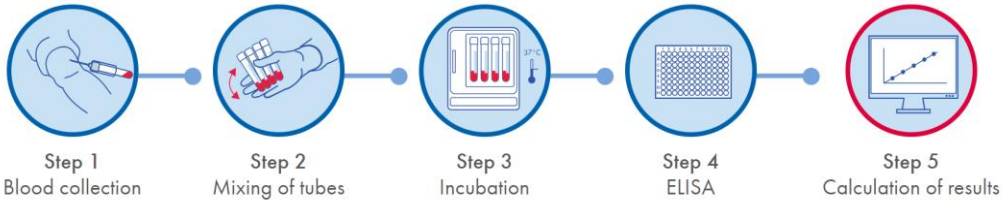
- Clinical signs or symptoms and/or
- Abnormal x-ray
- May or may not have positive immunologic testing
- Possible microbiologic confirmation


# Tuberculin skin test (TST)

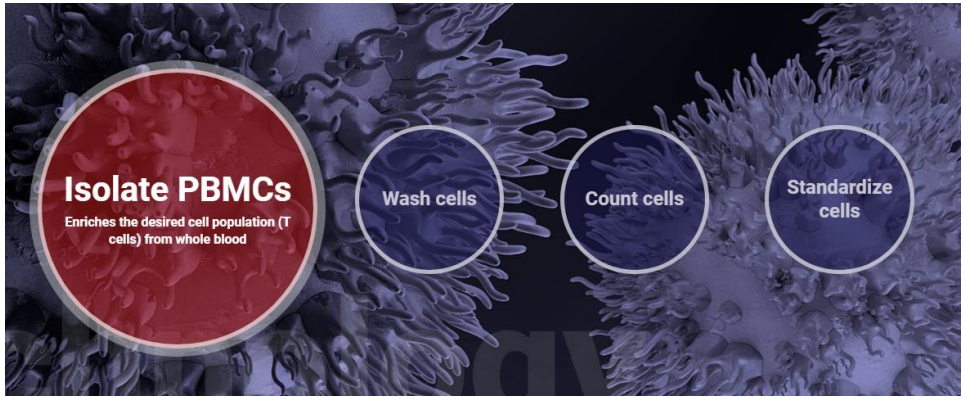
# Interferon-gamma release assays

## The QFT-Plus assay

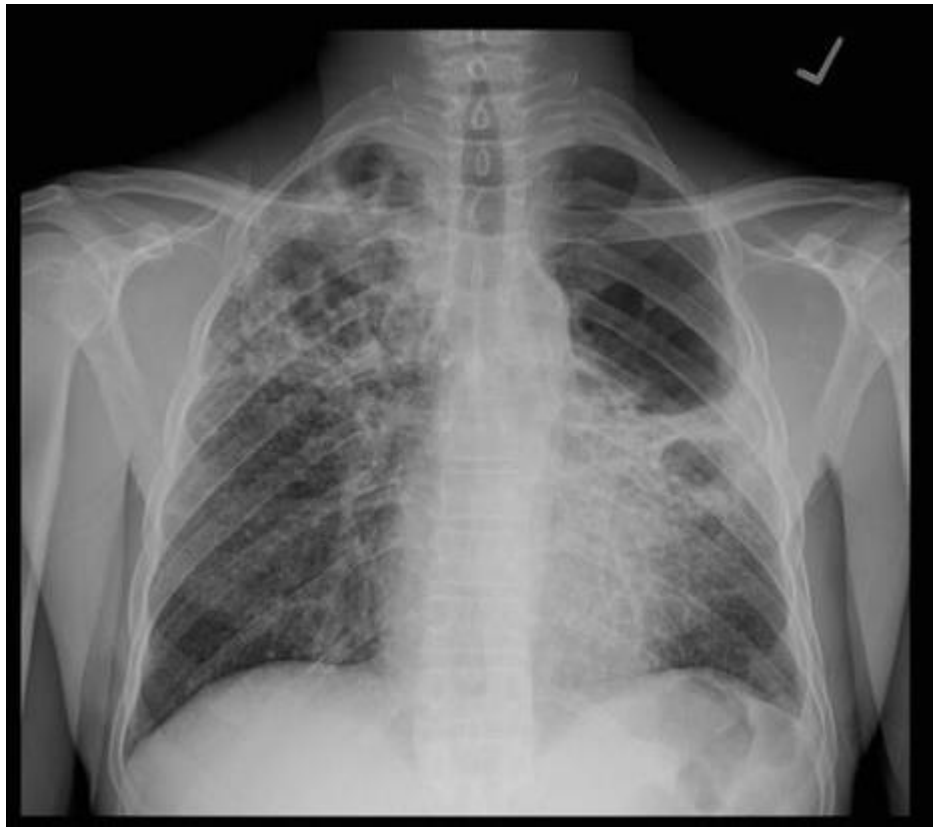
The QFT-Plus assay is an in-vitro diagnostic laboratory test that aids in the indirect detection of infection with MTB. It uses human whole blood, with patented assay technology based on the measurement of Interferon-gamma (IFN-γ) secreted from stimulated T-cells previously exposed to MTB. It is a straightforward laboratory test that involves the following steps:

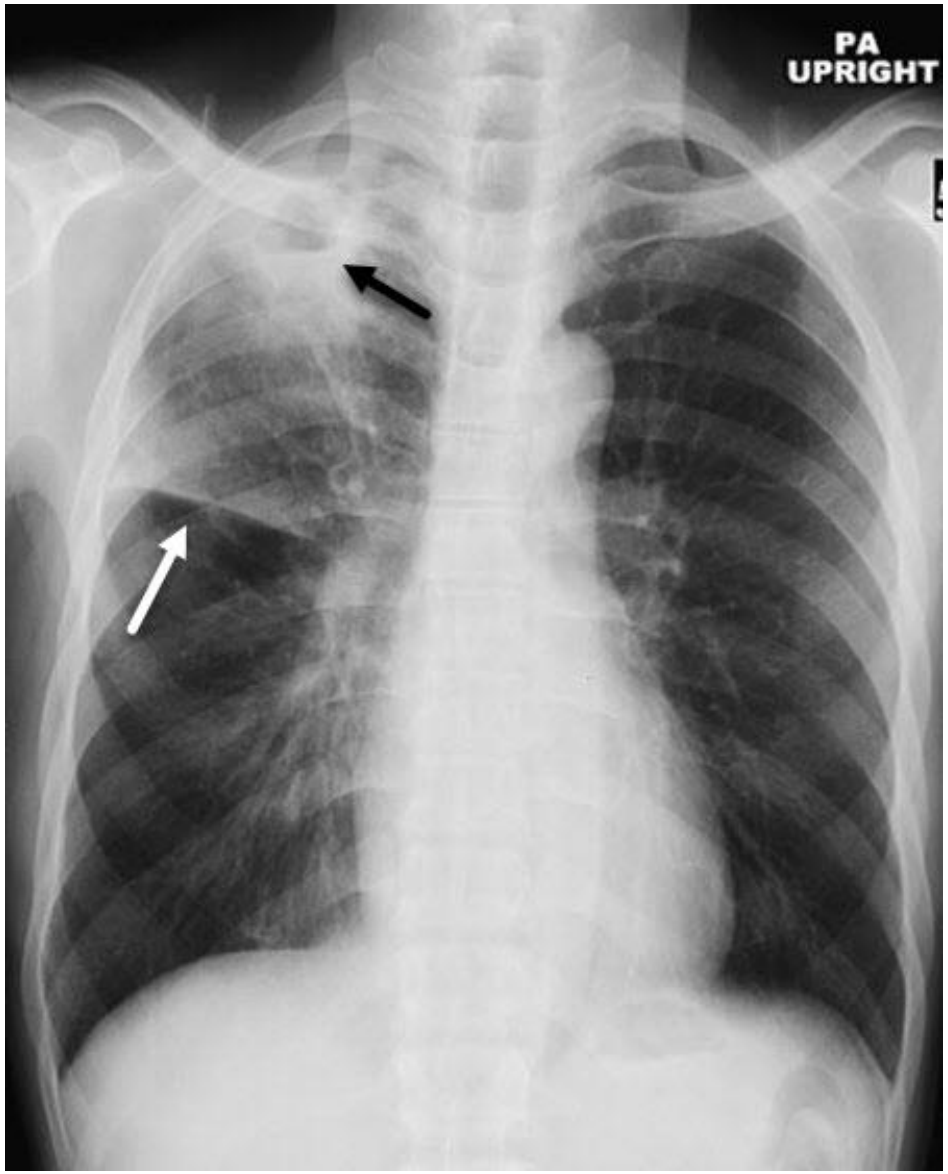



T-SPOT.TB

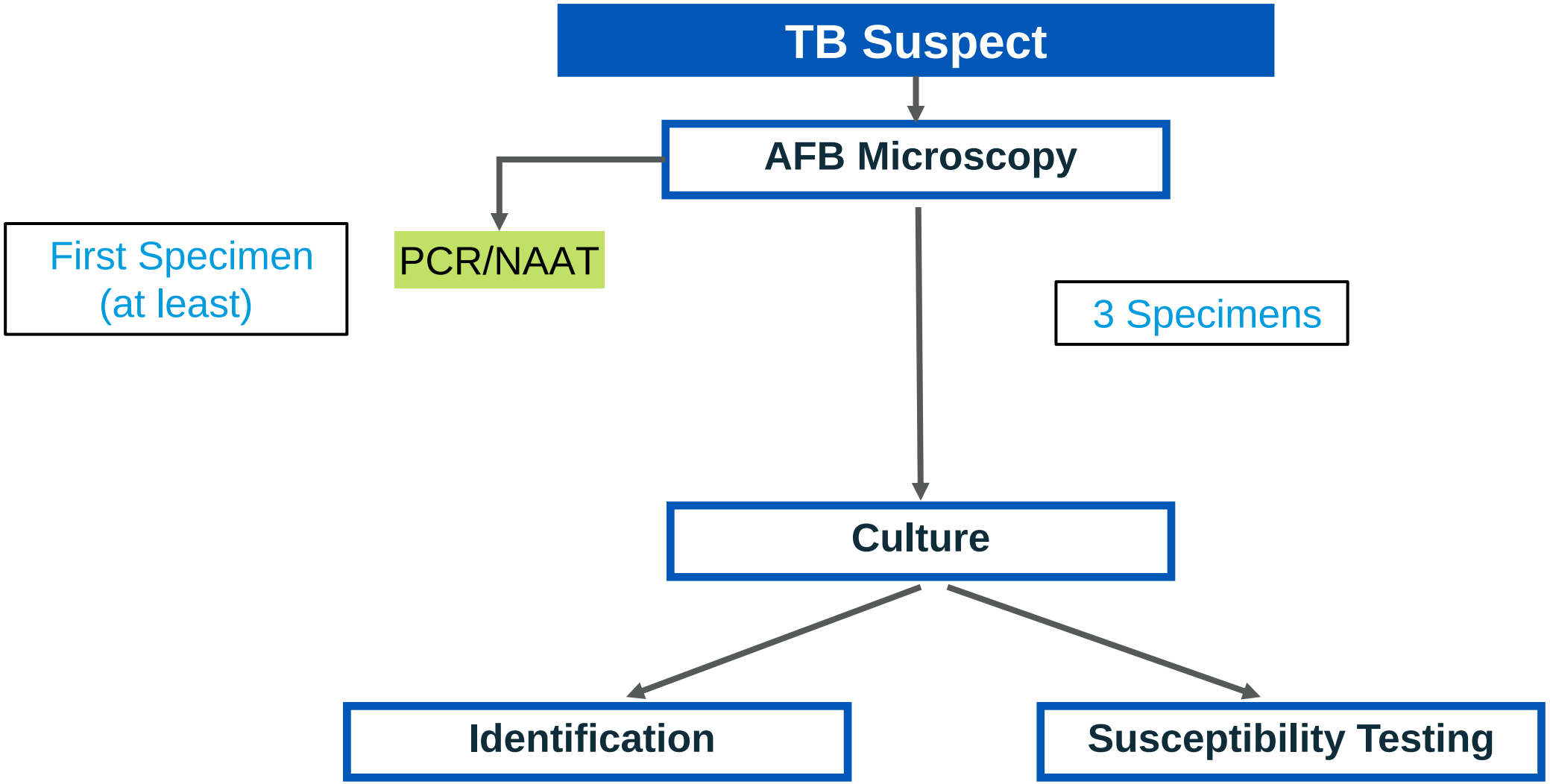


# TB Radiology

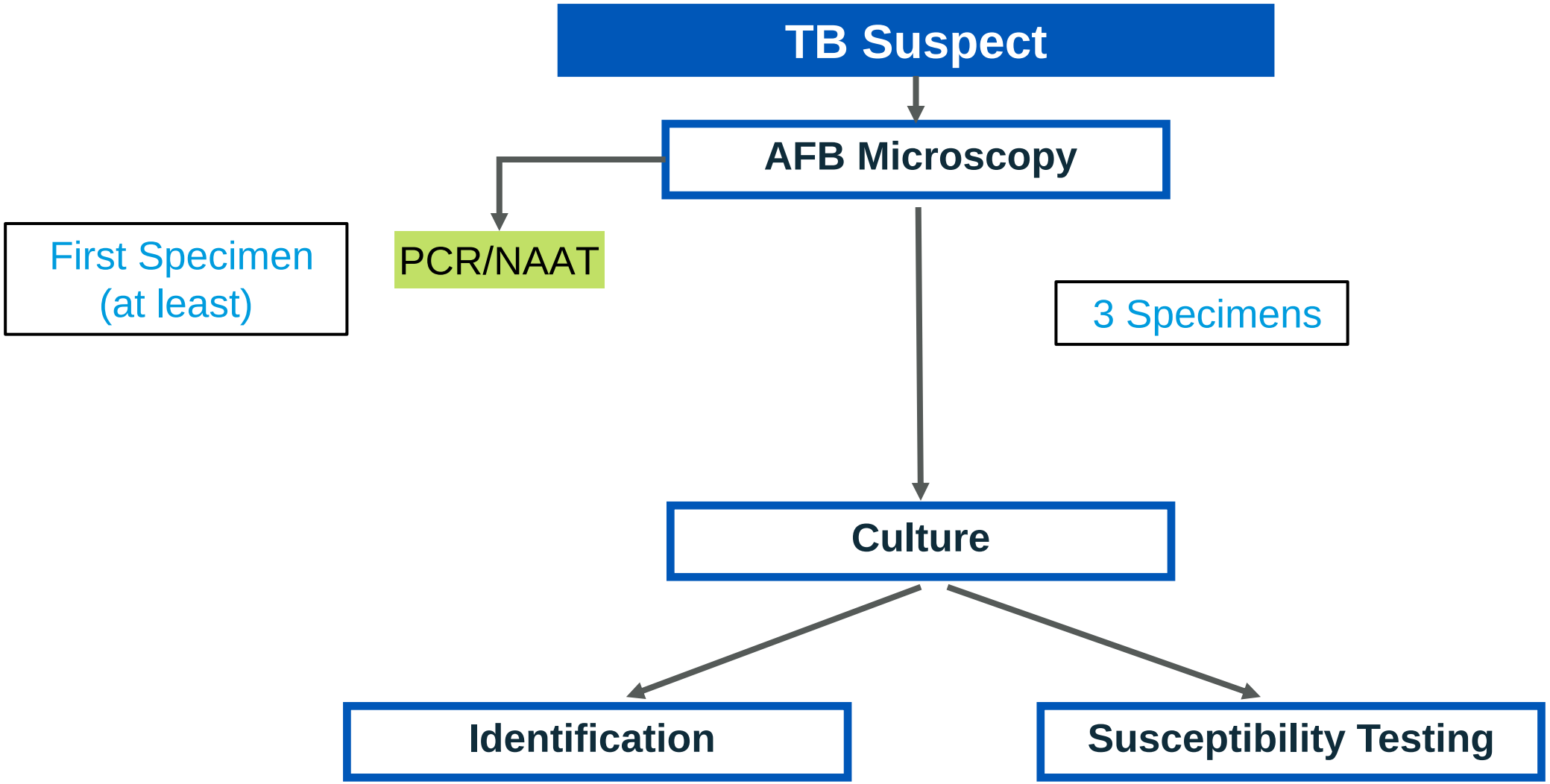




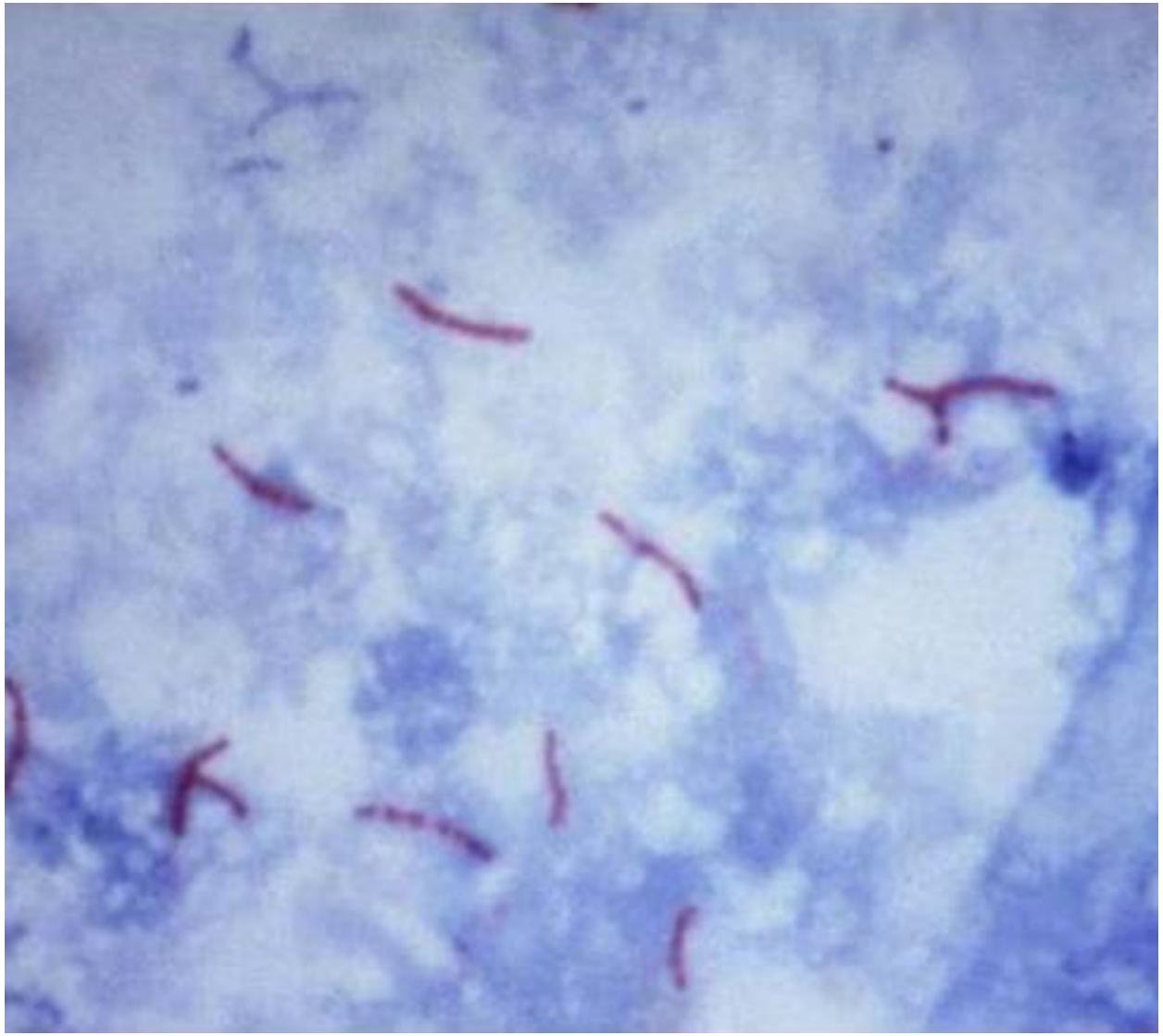
# TB Diagnostic Algorithm



# TB Diagnostic Algorithm



# AFB smear



# Xpert MTB/RIF Assay

A Tool to Diagnose Tuberculosis

KEY POINTS

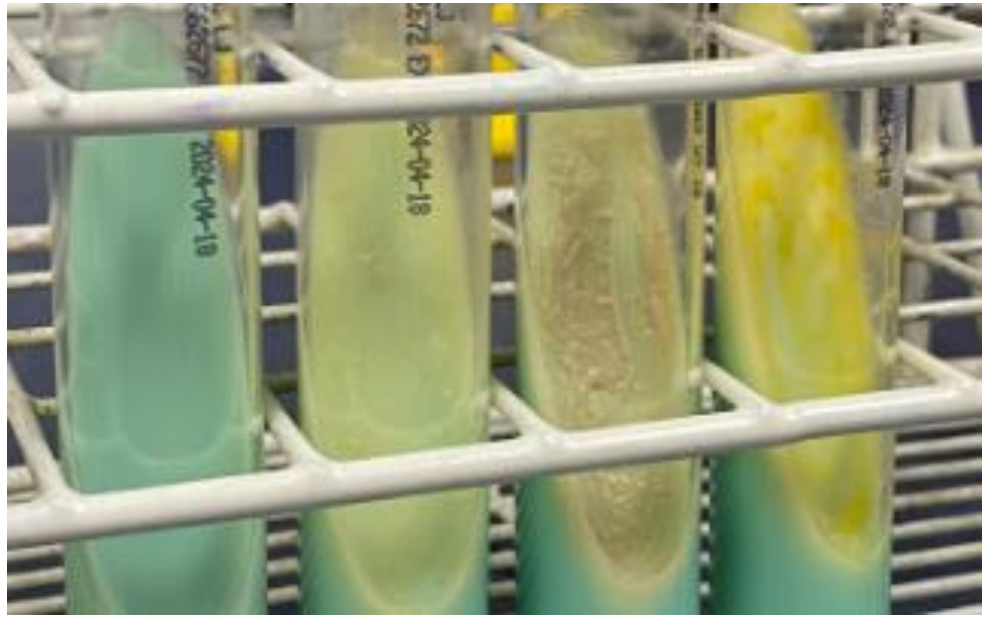
The Xpert MTB/RIF assay is a test that simultaneously detects *Mycobacterium tuberculosis* complex (MTBC) and resistance to rifampin (RIF), one of the most effective drugs used to treat tuberculosis (TB).

https://www.cdc.gov/tb/php/laboratory-information/xpert-mtb-rif-assay.html

# Mycobacterial Culture

## MYCOBACTERIA GROWTH INDICATOR TUBE (MGIT)

## SOLID MEDIA



# Drug resistance and susceptibility testing

## When to suspect drug-resistance?

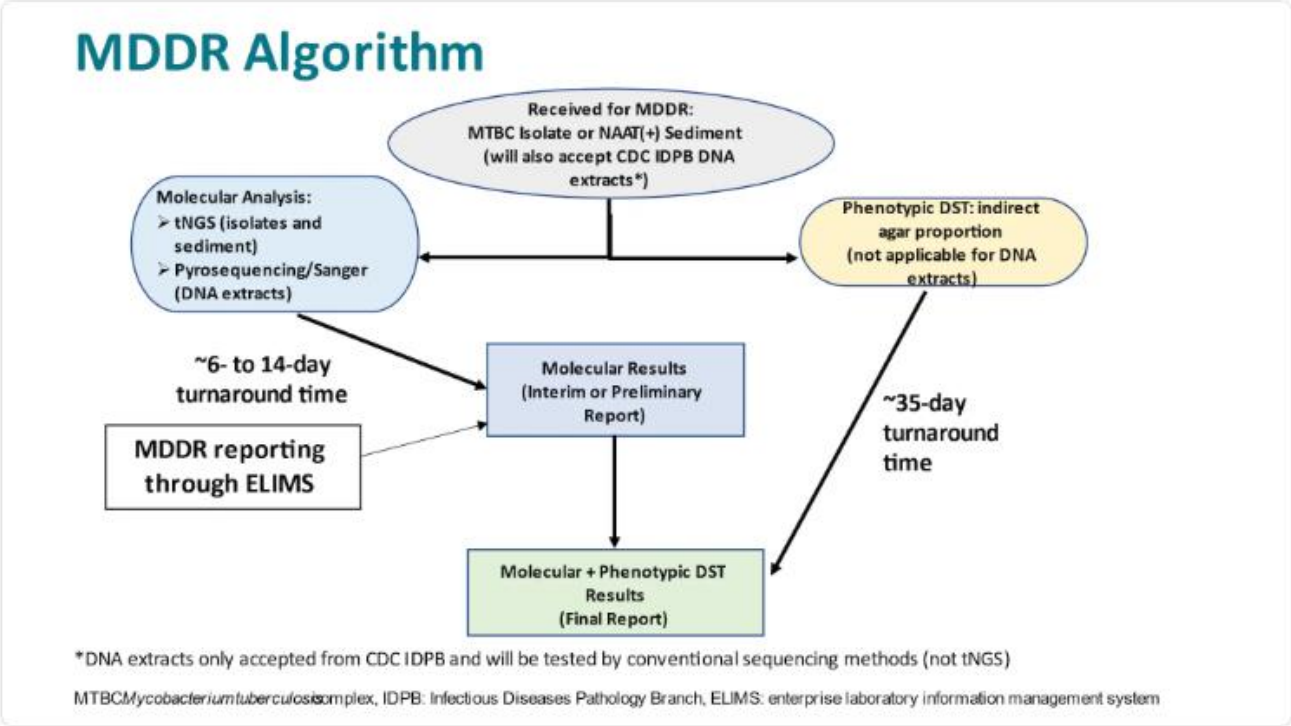
- Rifampin resistance detected on initial NAAT

**The most important predictors of drug-resistant TB are:**

- **Previous episode(s)** of TB treatment
- **Worsening clinical and/or radiographic findings** while on TB therapy
- History of **residence** in, or frequent travel to, a **region or country with a high prevalence of drug-resistant TB** (see **Chapter 1, *Epidemiology***)
- **Exposure to a person with known (or highly suspected) infectious drug-resistant TB,** or exposure to individuals in congregate settings where drug resistance has been documented

HTTPS://WWW.CURRYTBCENTER.UCSF.EDU/PRODUCTS/PAGE/CHAPTER-2-DIAGNOSIS

# Molecular Detection of Drug Resistance (MDDR) in Mycobacterium tuberculosis Complex by DNA Sequencing User Guide




Testing algorithm for the Molecular Detection of Drug Resistance (MDDR) service

tNGS: targeted next generation sequencing assay, NAAT: nucleic acid amplification testing

https://www.cdc.gov/tb/php/laboratory-information/mddr-user-guide.html

# Treatment of TB: RIPE

Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

| Regimen | Intensive Phase | | Continuation Phase | | Range of Total Doses | Comments[c,d] | Regimen Effectiveness |
|---|---|---|---|---|---|---|---|
| | Drug[a] | Interval and Dose[b] (Minimum Duration) | Drugs | Interval and Dose[b,c] (Minimum Duration) | | | |
| 1 | INH<br>RIF<br>PZA<br>EMB | 7 d/wk for 56 doses (8 wk), or<br>5 d/wk for 40 doses (8 wk) | INH<br>RIF | 7 d/wk for 126 doses (18 wk), or<br>5 d/wk for 90 doses (18 wk) | 182–130 | This is the preferred regimen for patients with newly diagnosed pulmonary tuberculosis. | Greater |

# Treatment of TB: 4-month rifapentine with moxifloxacin

RESEARCH SUMMARY

## Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

Dorman SE et al. DOI: 10.1056/NEJMoa2033400

CLINICAL PROBLEM

The standard treatment of drug-susceptible pulmonary tuberculosis is a 6-month course of a daily rifamycin-based antimicrobial regimen. A more potent regimen with improved rifamycin exposure might shorten treatment duration, potentially improving adherence and reducing adverse effects and costs.

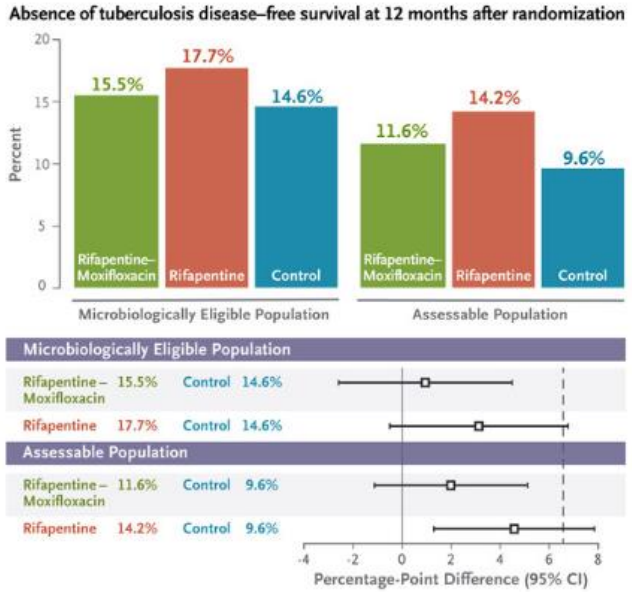
CLINICAL TRIAL

**Design:** A randomized, open-label, noninferiority trial of two 4-month rifapentine-containing regimens, as compared with a standard 6-month rifampin-containing regimen, for the treatment of drug-susceptible tuberculosis.

**Intervention:** 2516 participants 12 years of age or older with newly diagnosed tuberculosis were randomly assigned to a 6-month control regimen, a 4-month regimen in which rifampin was replaced with rifapentine (rifapentine group), or a 4-month regimen in which rifampin was replaced with rifapentine and ethambutol with moxifloxacin (rifapentine–moxifloxacin group). The primary efficacy outcome was survival free of tuberculosis at 12 months after randomization, and safety was assessed through day 14 after the last dose of a trial drug.

RESULTS

**Efficacy:** The rifapentine–moxifloxacin regimen, but not the rifapentine regimen, was shown to be noninferior to the control regimen.

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

# A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis

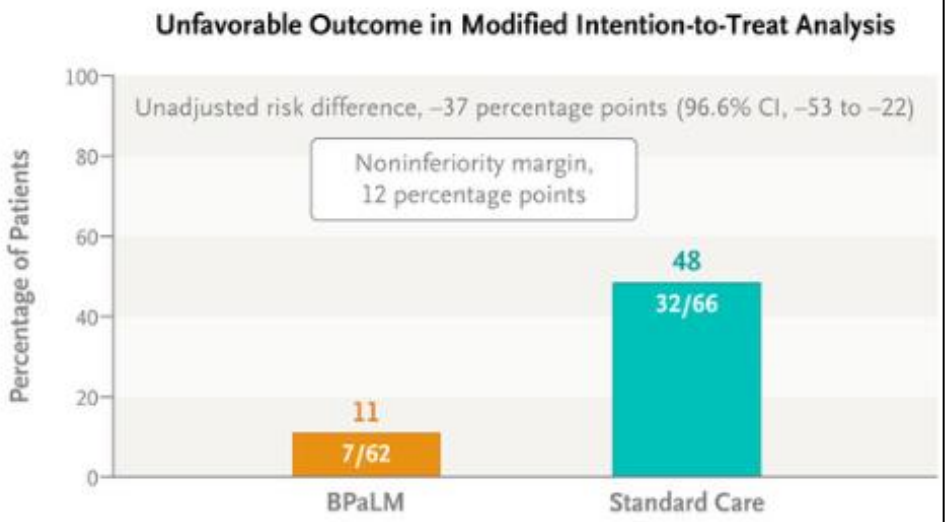
Nyang'wa B-T et al. DOI: 10.1056/NEJMoa2117166

## CLINICAL PROBLEM

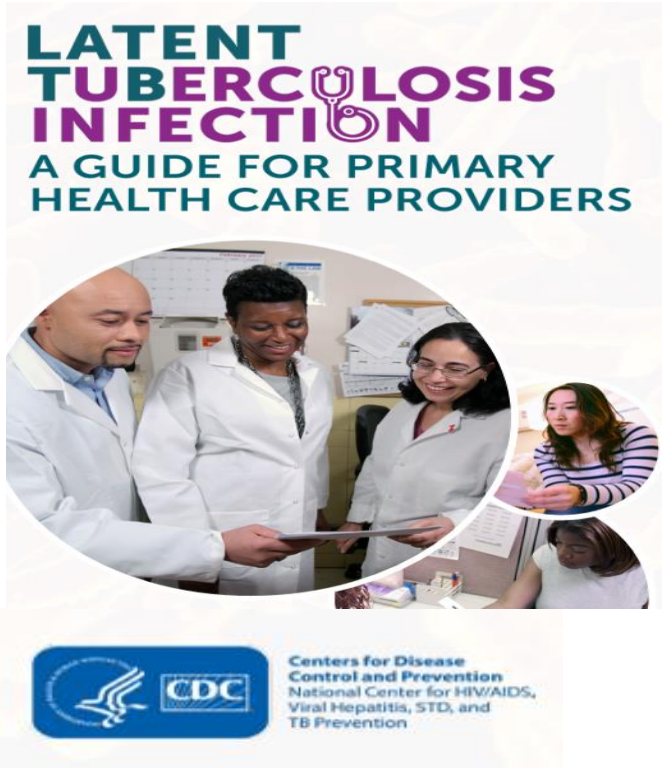
The currently recommended duration of treatment for rifampin-resistant tuberculosis is 9 to 20 months, and treatment involves up to 20 tablets per day; unfavorable outcomes are common. Effective treatments of shorter duration are needed.

## CLINICAL TRIAL

**Design:** In the second stage of a phase 2–3, multicenter, open-label, randomized, controlled, noninferiority trial, the efficacy and safety of a 24-week, all-oral regimen containing bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) in patients with rifampin-resistant tu-



# LTBI and importance of public health/healthcare partnership




## Treatment Regimens

- **Three Months of Once-weekly Isoniazid (INH) plus Rifapentine (RPT) Regimen (3HP)**
- **Four Months of Daily Rifampin (RIF) Regimen (4R)**
- **Six or Nine Months of Daily Isoniazid (INH) Regimens (6H or 9H)**

# Organization of TB Services in the United States

# National TB Program

- Most core activities of the National TB Program are administered by or at CDC
- Develops national policies and guidelines
- Serves as the national reference laboratory
- Maintains national TB registry
- Is responsible for overseas screening of immigrants and refugees
- Provides resources for training and education
- Conducts epidemiologic, operational, and clinical research

# U.S. National TB Program jurisdictions

- TB services exist at federal, state, and local levels
- 50 States
- 5 territories
- 3 sovereign freely-associated nations
- 10 large cities that receive direct federal funding
- 100+ metropolitan areas with pops. >500,000
- 3,143 counties

# National TB Program

- Division of Tuberculosis Elimination provides categorical funding for 67 programs through cooperative agreements with
- All 50 states
- 9 large cities (including Washington DC)
- 5 U.S. territories (Guam, AS, CNMI, PR, USVI)
- 3 freely-associated nations (FSM, RMI, Palau)

# National TB Program

- State TB Control Functions
- Support, oversight, and evaluation
- Develop policies and guidelines
- Funding
- Training and technical assistance
- Public Health Laboratory
- Surveillance
- Public health authority

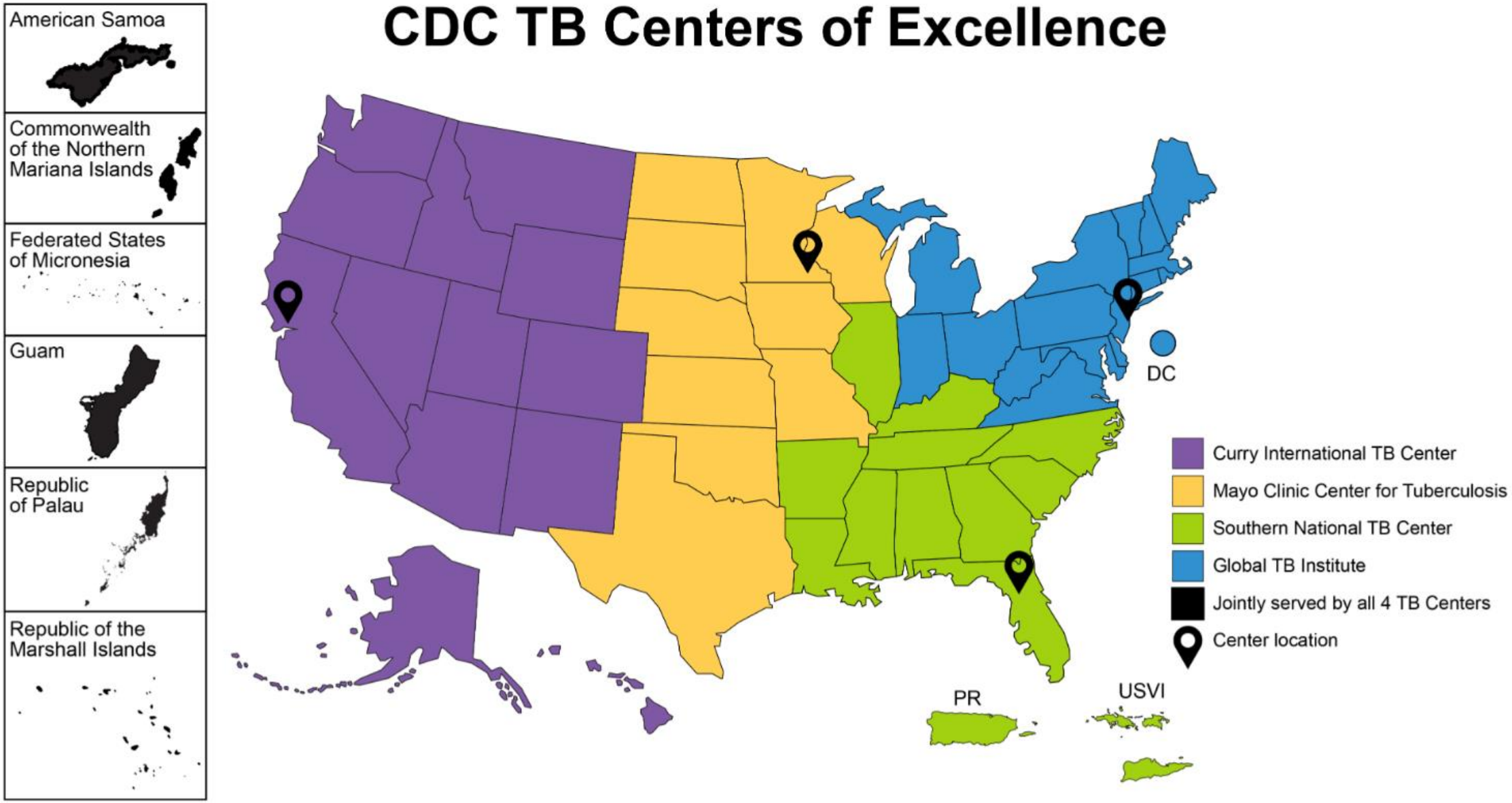
# National TB Program

- Local TB Control Functions
- Case management
- Contact investigations
- Collaboration with private medical providers
- Direct medical care, at many sites
- Program evaluation
- TB surveillance

# Public VS Private Sector

- 55% of TB patients receive some TB care in private sector
- Certain services are always in the public sector:
- Provision of DOT
- Contact tracing
- Surveillance
- Outbreak investigations and management

# CDC TB Centers of Excellence



# TB Support

CDC and its domestic and international partners are working together to eliminate this deadly disease.

- National TB Controllers Association
- Stop TB USA, We Are TB
- TB Elimination Alliance
- Stop TB Partnership

# Questions and Answers


# Thank you