MAYO CLINIC

Center for Tuberculosis

Asymptomatic TB or Subclinical TB

Avish Nagpal MD, MPH
Infectious Diseases Consultant, Sanford Health, Fargo
Medical Director for Infection Prevention, Sanford Health, Fargo
Vice Chair for Research, Internal Medicine, University of North Dakota School of Medicine and Health Sciences

Accreditation Statement

Accreditation Statement
In support of improving patient care, Mayo Clinic College of Medicine and Science is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC) to provide continuing education for the healthcare team.

Credit Statement(s):

AMA
Mayo Clinic College of Medicine and Science designates this live activity for a maximum of 1.00 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

ACPE
Mayo Clinic College of Medicine and Science designates this educational activity for a maximum of 1.00 ACPE Knowledge-based contact hours. Participants should claim only the credit commensurate with the extent of their participation in the activity.
UAN Number:
7 AM Session: JA0000238-0000-24-150-L01-P
12 PM Session: JA0000238-0000-24-153-L01-P

ANCC
Mayo Clinic College of Medicine and Science designates this activity for a maximum of 1.00 ANCC contact hours. Nurses should claim only the credit commensurate with the extent of their participation in the activity.

Other Healthcare Professionals:
A record of attendance will be provided to all registrants for requesting credits in accordance with state nursing boards, specialty societies or other professional associations.

For disclosure information regarding Mayo Clinic School of Continuous Professional Development accreditation review committee member(s) and staff, please go to the course accreditation page.

Available Credit
- **1.00** *AMA PRA Category 1 Credit*™
- **1.00** Attendance

Accreditation Statement

Accreditation Statement
In support of improving patient care, Mayo Clinic College of Medicine and Science is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC) to provide continuing education for the healthcare team.

Credit Statement(s):

AMA
Mayo Clinic College of Medicine and Science designates this live activity for a maximum of 1.00 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

ACPE
Mayo Clinic College of Medicine and Science designates this educational activity for a maximum of 1.00 ACPE Knowledge-based contact hours. Participants should claim only the credit commensurate with the extent of their participation in the activity.
UAN Number: JA0000238-0000-26-039-L99-P

ANCC
Mayo Clinic College of Medicine and Science designates this activity for a maximum of 1.00 ANCC contact hours. Nurses should claim only the credit commensurate with the extent of their participation in the activity.

This activity was planned by and for the healthcare team, and learners will receive 1.0 Interprofessional Continuing Education (IPCE) credit for learning and change.

Other Healthcare Professionals:
A record of attendance will be provided to all registrants for requesting credits in accordance with state nursing boards, specialty societies or other professional associations.

For disclosure information regarding Mayo Clinic School of Continuous Professional Development accreditation review committee member(s) and staff, please go here to the course accreditation page.

Available Credit
- 1.00 ACPE,
- 1.00 *AMA PRA Category 1 Credit*™
- 1.00 ANCC
- 1.00 Attendance
- 1.00 IPCE

Disclosure:

No relevant financial disclosures to report and no mention of off-label use of any medications or products

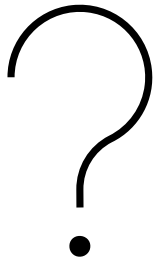
Learning Objectives

- Define latent TB infection (LTBI)
- Describe screening protocols
- Explain treatment options for LTBI

Learning Objectives

- Define latent TB infection (LTBI)
- Describe screening protocols
- Explain treatment options for LTBI

Polling Question



- A 36-year-old woman undergoes screening for TB as part of contact tracing as her son was recently diagnosed with pulmonary TB. Her QuantiFERON ® Gold+ (QFT-Plus) testis positive.
- You see her in the clinic for further evaluation. What is your recommendation to the patient?

A. Cancel the appointment and ask her to isolate

B. Obtain PPD

C. Obtain CXR

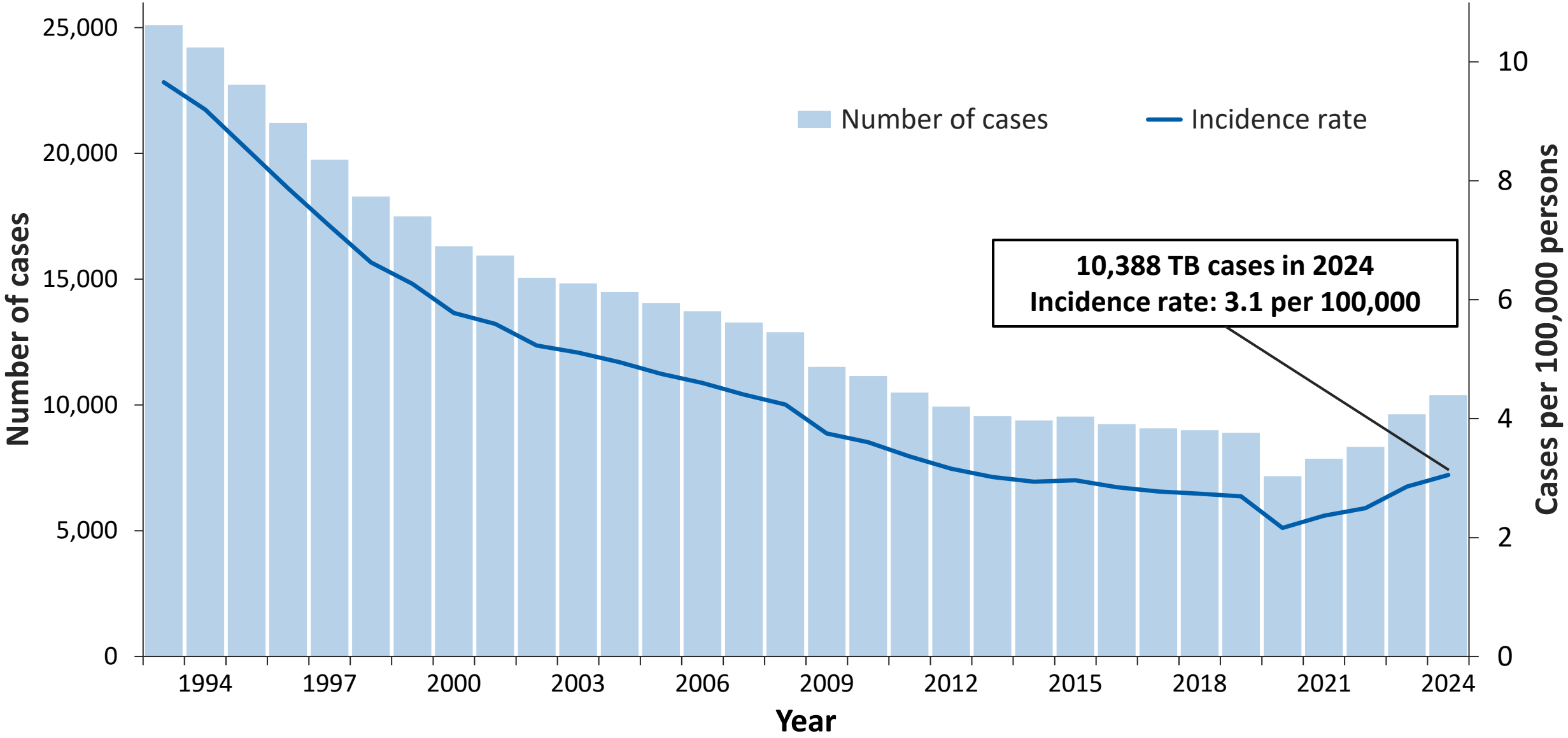
D. Ask about symptoms suggestive of TB

Tuberculosis

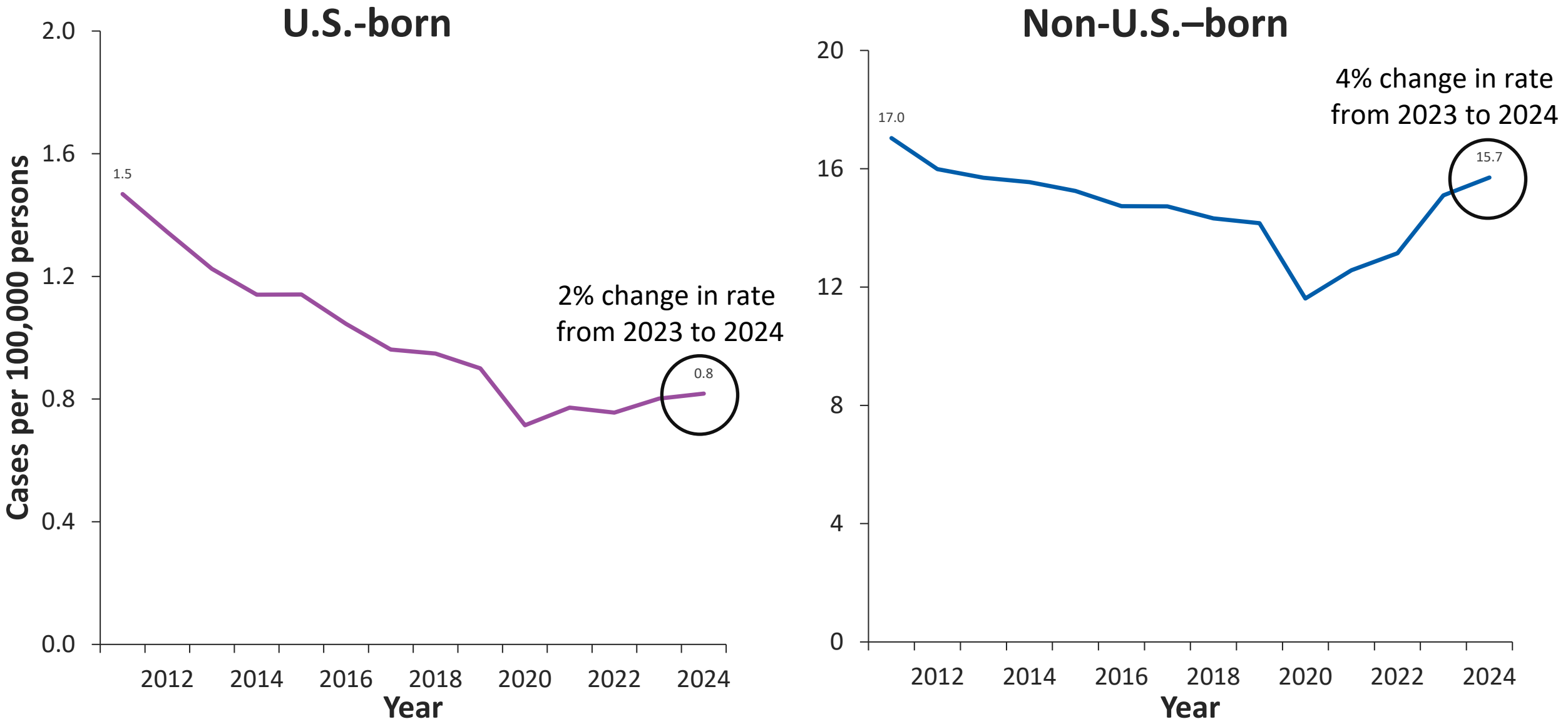
- *aka* ‘Consumption’, ‘Plague’, ‘White Plague’
- 1/3rd of World’s population infected
- 200 million deaths every year
- Growing threat of antimicrobial resistance

Epidemiology

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

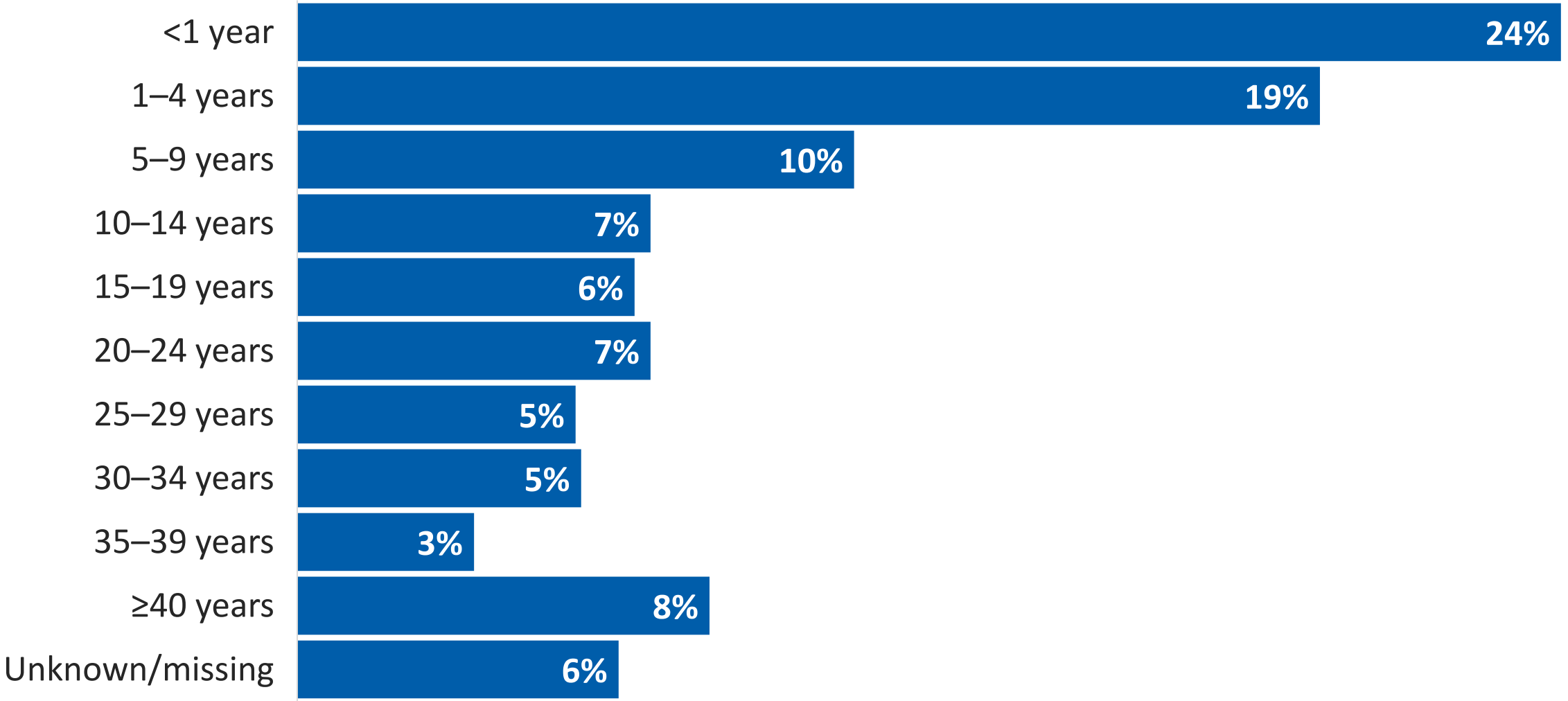


TB Incidence Rates by Origin of Birth,* United States, 2011–2024



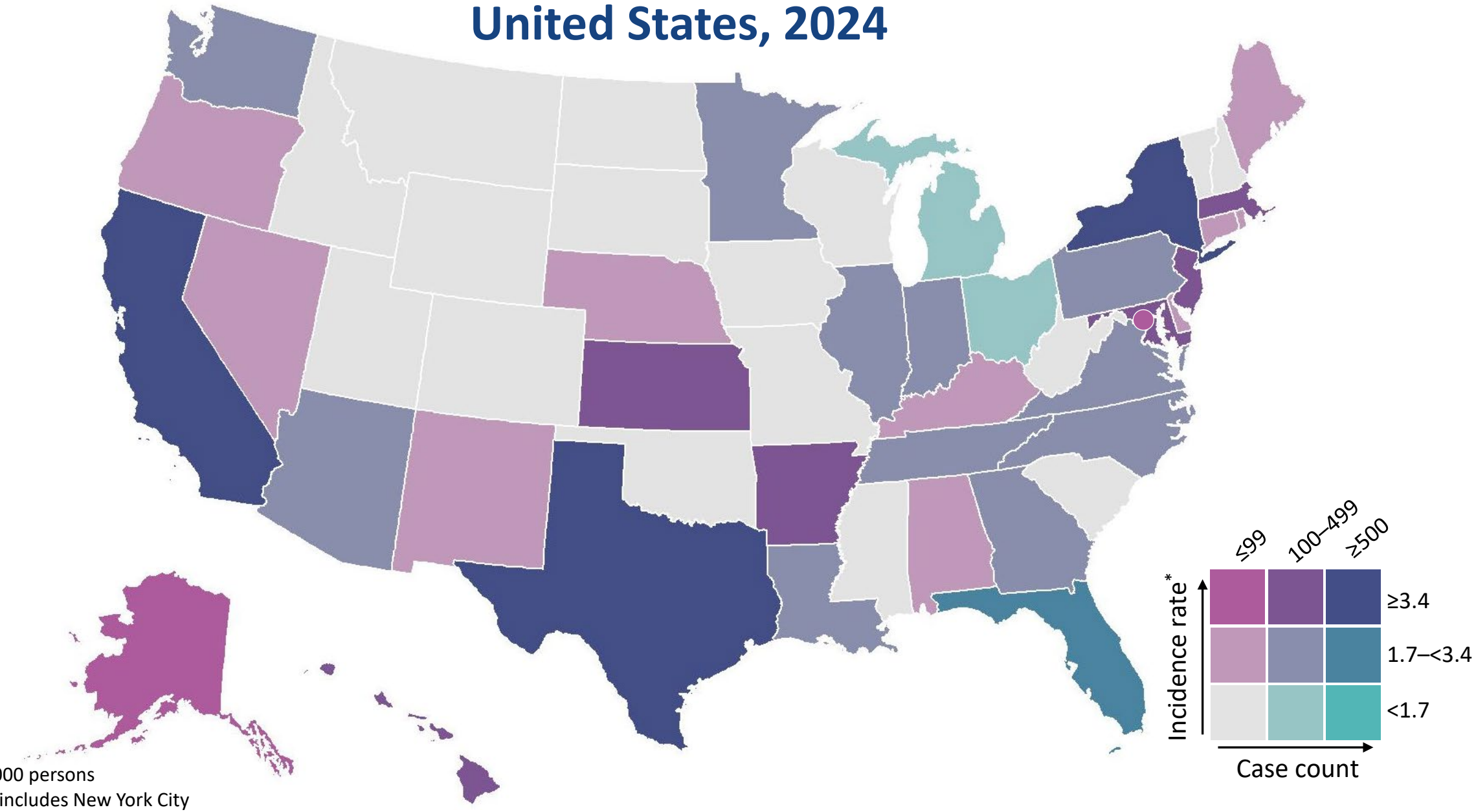
*Persons born in the United States, certain U.S. territories, or elsewhere to at least one U.S. citizen parent are categorized as U.S.-born. All other persons are categorized as non-U.S.–born.

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)



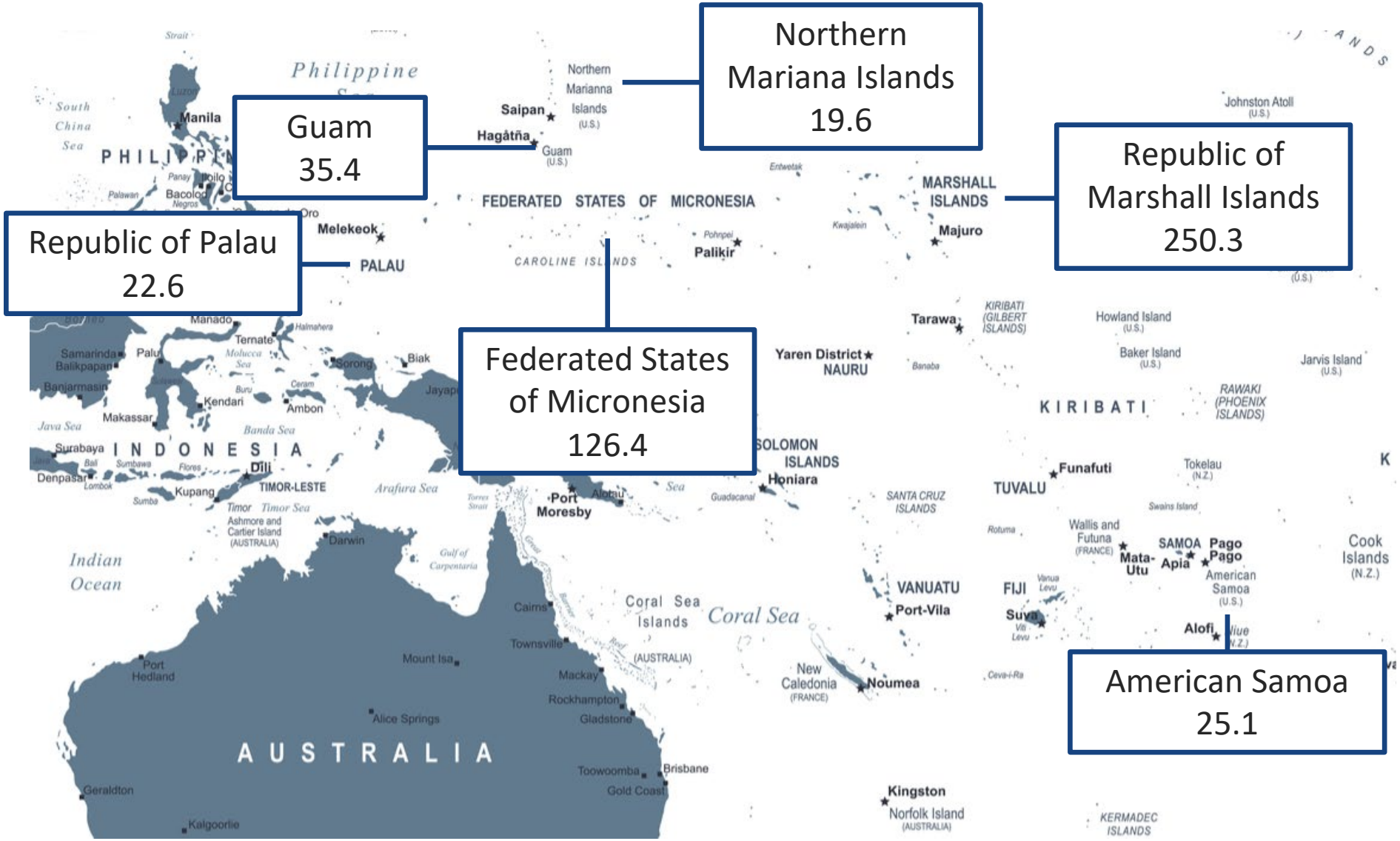
*Persons born in the United States, certain U.S. territories, or elsewhere to at least one U.S. citizen parent are categorized as U.S.-born. All other persons are categorized as non-U.S.–born.

TB Cases and Incidence Rates* by Reporting Area, United States, 2024



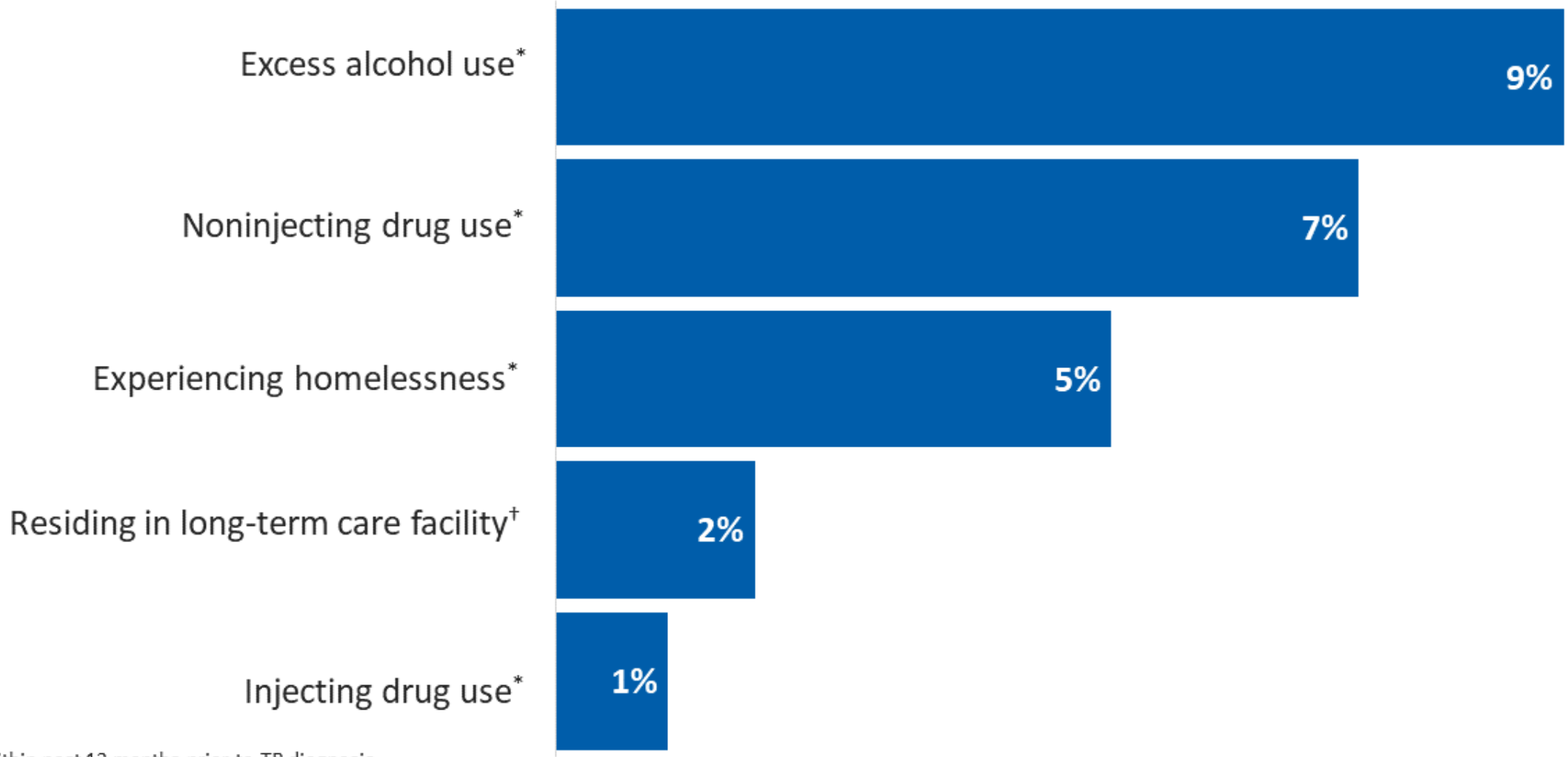
*Cases per 100,000 persons
Note: New York includes New York City

TB Incidence Rates* by U.S.-Affiliated Pacific Islands, 2024



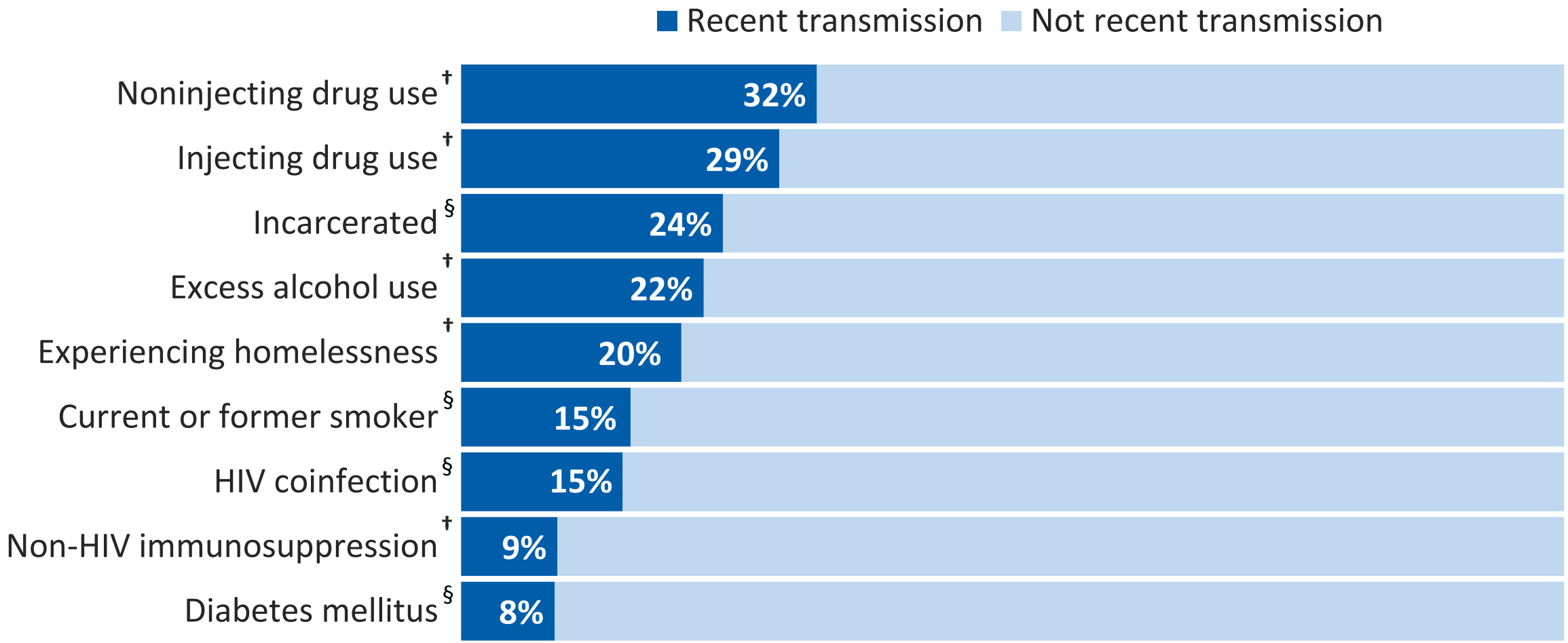
*Cases per 100,000 persons

Percentage of Social and Behavioral Risk Factors Among Persons Aged ≥15 Years with TB, United States, 2022



*Within past 12 months prior to TB diagnosis
†At the time of TB diagnosis

Percentage of TB Cases Attributed to Recent Transmission* by Selected Risk Factors, United States, 2023–2024



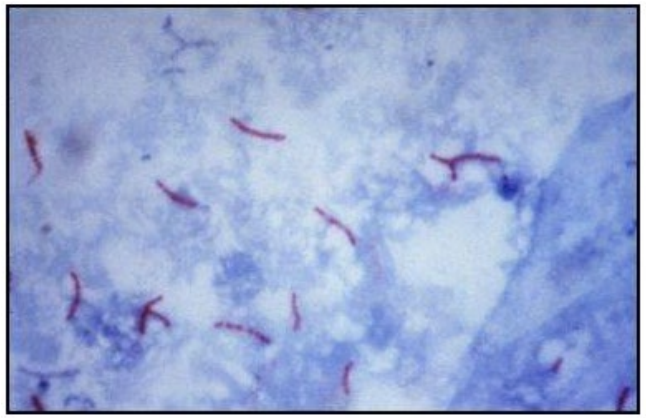
* A case is attributed to recent transmission if a plausible source case can be identified in a person who had an *M. tuberculosis* isolate with the same wgMLSType that differed by ≤5 single nucleotide polymorphisms, had an infectious form of TB, was 10 years of age or older, resided within 100 miles of the case, and was diagnosed within 2 years before the case.

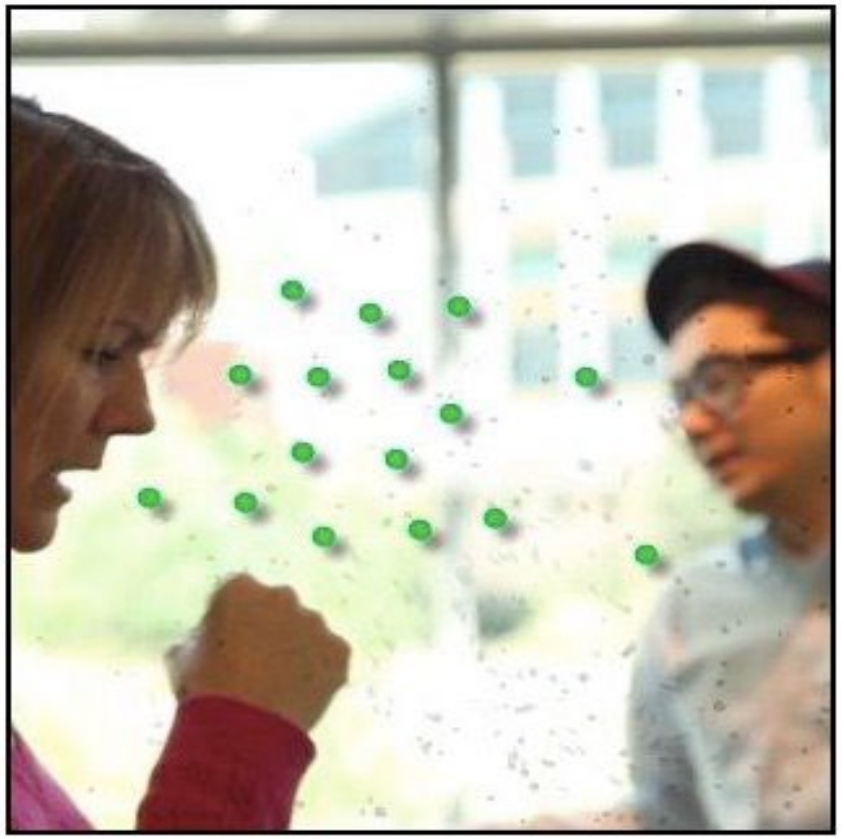
† Within past 12 months prior to TB diagnosis.

§ At the time of TB diagnosis.

Transmission & Pathogenesis

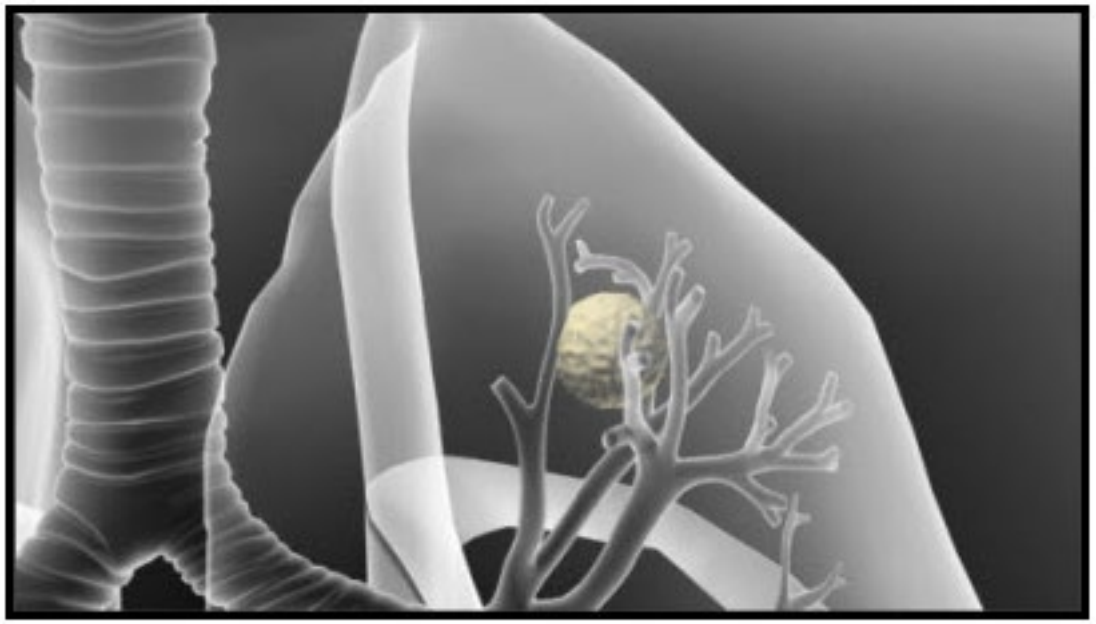
- Airborne disease
- Spread by droplets
- *Mycobacterium tuberculosis*



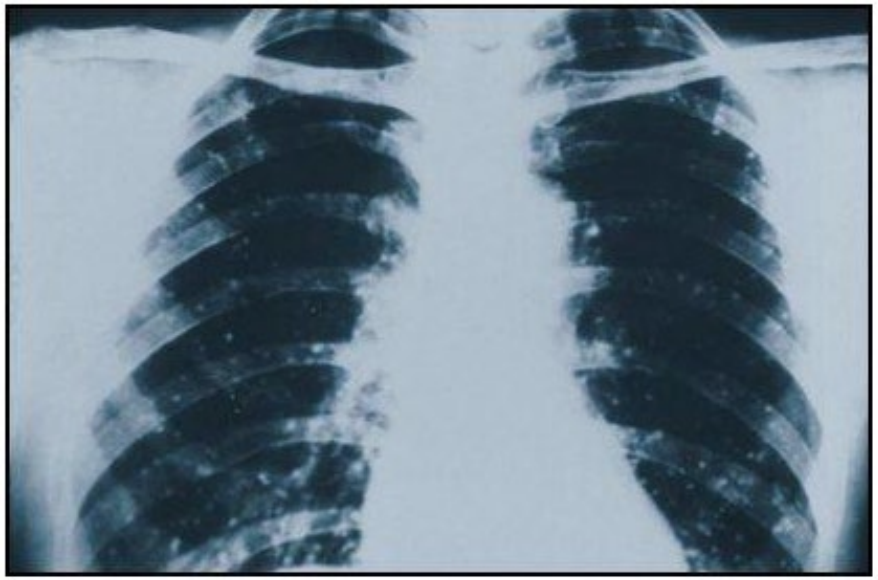


Pathogenesis

- Inhalation of tubercle bacilli
- Entrapment by macrophages
- Formation of Granuloma
- LTBI

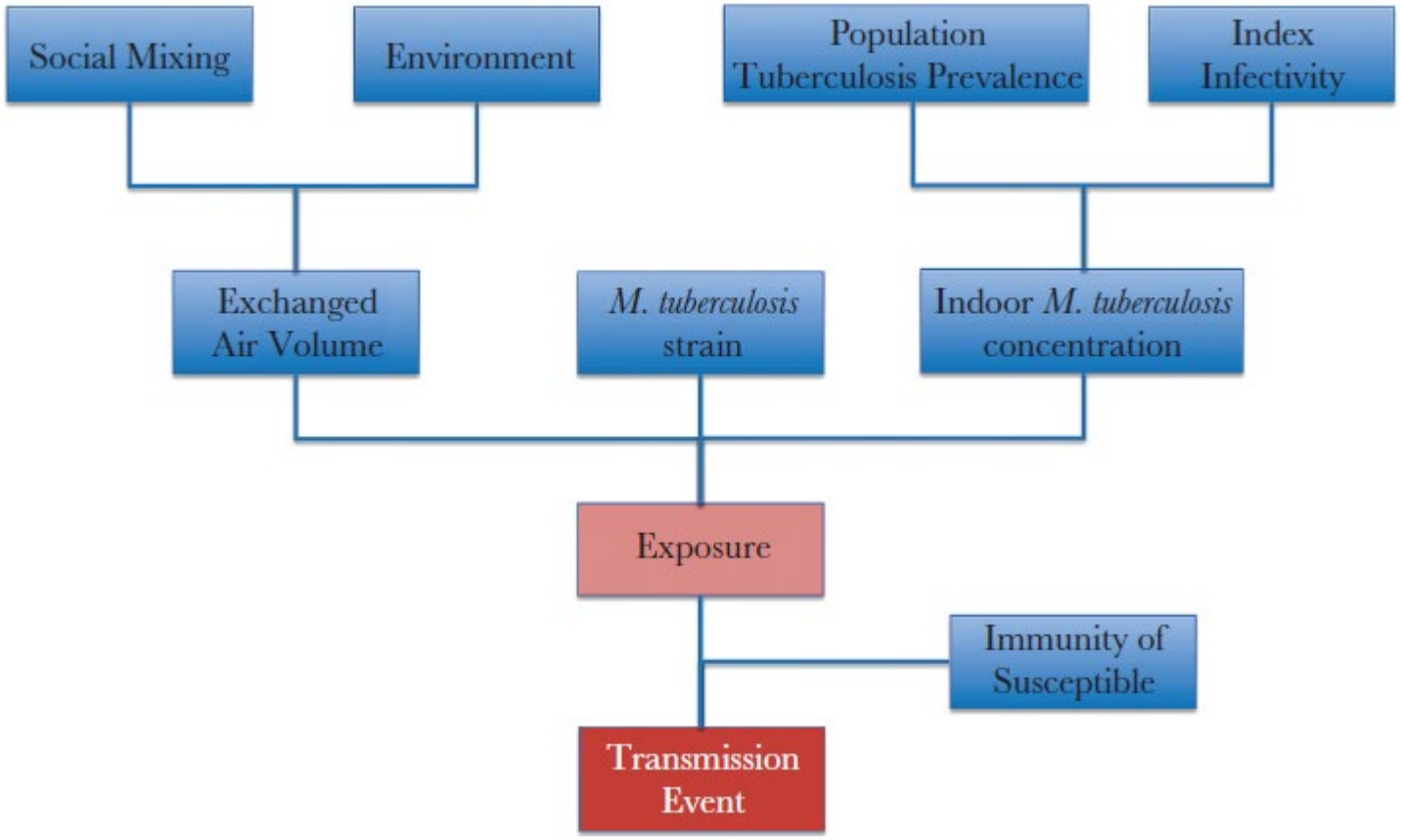


Progression to TB



- Primary TB
- Reactivation
- 10% lifetime risk
- 5% within first 2 years
- Extra pulmonary – Laryngeal, lymph nodes, pleura, brain, kidney, bones & joints
- Miliary disease

Factors Influencing Transmission



Mathema B. J Infect Dis 2017;218(Suppl 6):S644-53 DOI: https://10.1093/infdis/jix354

Risk Factors for TB Transmission

- Environmental
  - Prisons
  - Homeless Shelters
  - Nursing Homes
  - Hospitals

- Biological
  - Alcohol dependence
  - IVDU
  - HIV Infection
  - Diabetes
  - ESRD
  - Silicosis
  - Gastrectomy
  - Steroids
  - Malnutrition

Higher Risk of Transmission

- Cavitary Disease
- AFB Smear Positivity
- Laryngeal TB
- Closed spaces
- HIV negative status
- Delayed Diagnosis
- MDR-TB
- Cough inducing or Aerosol Generating procedures

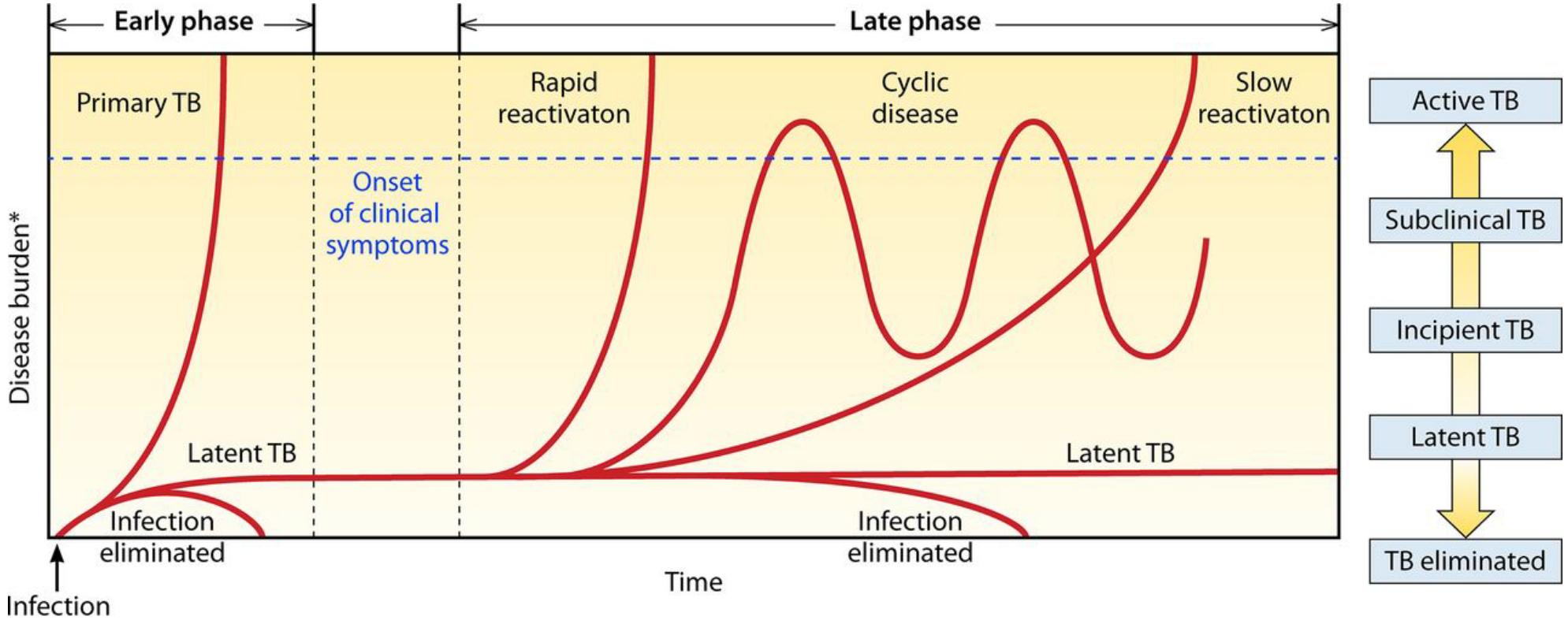
Risk Factor	Relative risk for TB	Weighted Prevalence in total population	Proportion of cases in Population Attributable to Risk Factor
HIV	8.3	1.1%	7.3%
Malnutrition	4.0	17.2%	34.1%
Diabetes	3.0	3.4%	6.3%
Heavy Alcohol Use (>40 g/day)	2.9	7.9%	13.1%
Smoking	2.6	18.2%	22.7%
Indoor Pollution	1.5	71.1%	26.2%

Adapted from: Lönnroth K et al. Soc Sci Med. 2009 Jun;68(12):2240-6. DOI: https://10.1016/j.socscimed.2009.03.041

LTBI vs Active TB

Latent TB Infection	Active Disease
No Symptoms or physical findings	Symptomatic with physical exam findings
Not contagious	Usually Contagious
CXR typically normal	Typically abnormal
Sputum smear and culture negative	Usually sputum smear or culture positive unless extra-pulmonary disease
Treatment with 1 or 2 drugs to prevent active TB	Multi drug treatment to cure disease

Pathways of TB Disease Progression



Drain P.K. et al. Clin Microbiol Rev 2018;31(4)::e00021-18 https://doi.org/10.1128/cmr.00021-18

Testing for LTBI

Testing for LTBI

- Targeted testing
  - Persons at higher risk of infection
  - Persons at higher risk of progression to TB disease
- Important for TB control and elimination
- Rx
  - Preventing progression to disease
  - Eliminate secondary cases

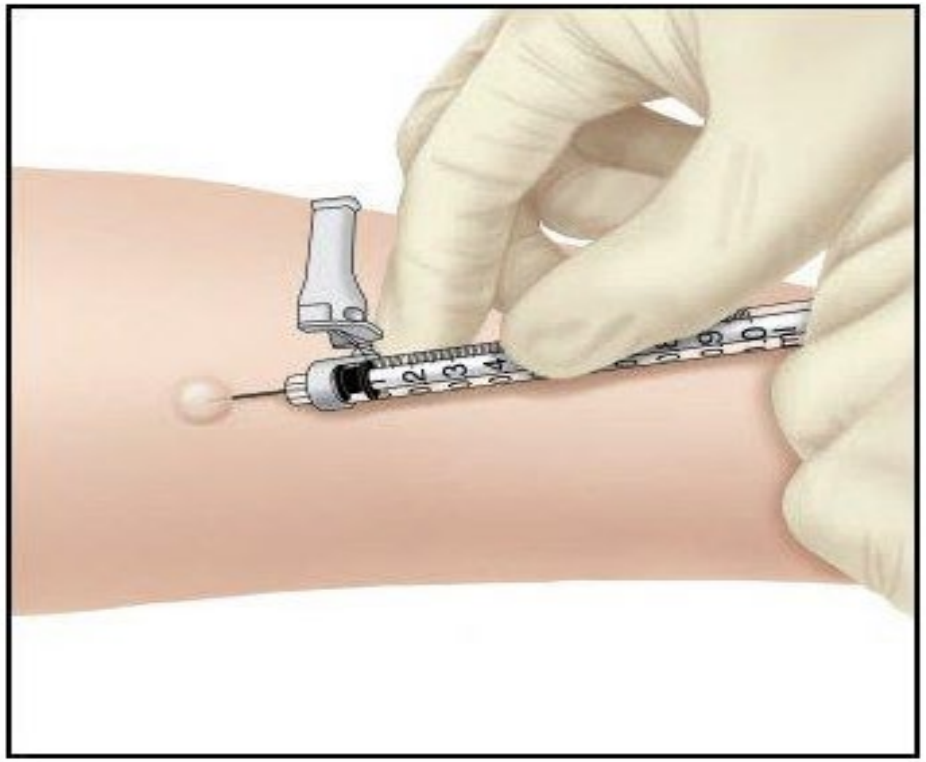
Higher risk of infection

- Close contacts of patients with TB
- Foreign born persons from areas of high TB incidence
- Visitors to TB endemic countries (long or frequent visits)
- Residents and employees of congregate settings
- Health care workers attending to patients at high risk of active TB
- Medically underserved, low-income populations
- Persons who use drugs or alcohol
- Infants, children, and adolescents exposed to adults who are at increased risk for latent *M. tuberculosis* infection or active tuberculosis

Adapted from MMWR 2000;49(RR-6)

Higher Risk of Progression to TB

- HIV
- Age < 5 years
- Recent Exposure (within 2 years)
- Inadequate or Incomplete treatment
- Fibrotic changes on CXR
- Immunosuppression
- Diabetes
- CKD
- Cancer of head and neck or Lung, Leukemia
- Smoking, Alcohol or Drug use
- Malnutrition




0
10
20
30
40
50
60
Tuberculin Skin Tes
2. Palpate
3. Mark

Interpretation of TST

- Dependents on patient characteristics
  - 5 mm
    - HIV
    - Immunosuppression
    - CXR with evidence of prior disease
    - Recent exposure

- 10 mm
  - Foreign born
  - HCWs
  - Mycobacteriology lab personnel
  - IVDU
  - Children and adolescents
  - Medical conditions which increase risk of progression
  - People in high risk congregate settings

- 15 mm
  - People with no history of exposure or risk factors

  - Did they really need to be tested?
  - Was the test interpreted accurately?

Disadvantages of TST

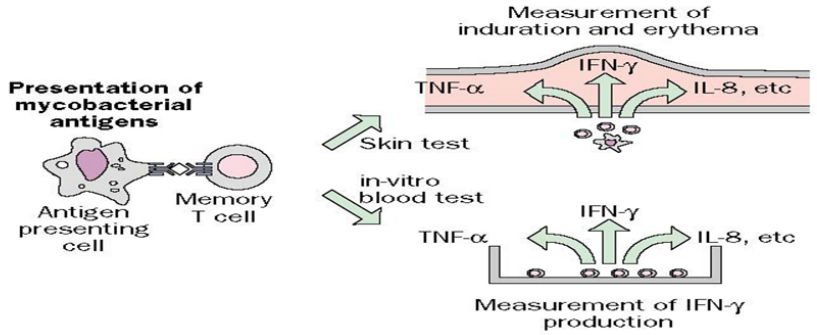
- Operator dependent
- High ‘drop out’ rates
- False positives
  - –BCG vaccination
  - –NTM infection
- False negatives
  - –Immunosuppression
  - –Malnutrition
  - –Children and elderly
  - –Incorrect storage of specimen
  - –recent exposure

IGRA

- Interferon gamma release assay
- QuantiFERON®-TB Gold In-tube test
- T-SPOT. ®*TB*

- Can replace TST in most situations
- Except children < 5 years
- Not affected by prior BCG
- Blood test
- Non operator dependent
- One time test – no need to return for read
- No boosting

Basic Principle of IGRAs



- T-cell lymphocytes release IFN-γ in response to specific antigens
- 3 synthetic TB-specific antigens identified:
  - RD1: ESAT-6, CFP-10
  - RD11: TB7.7
- IFN-γ is stable and measurable in the plasma

QuantiFERON-TB Gold In-tube ®

TB Antigen tube

Assesses IFN-γ response to highly-specific TB antigens.

Mitogen tube (Positive control)

Can be useful to indicate

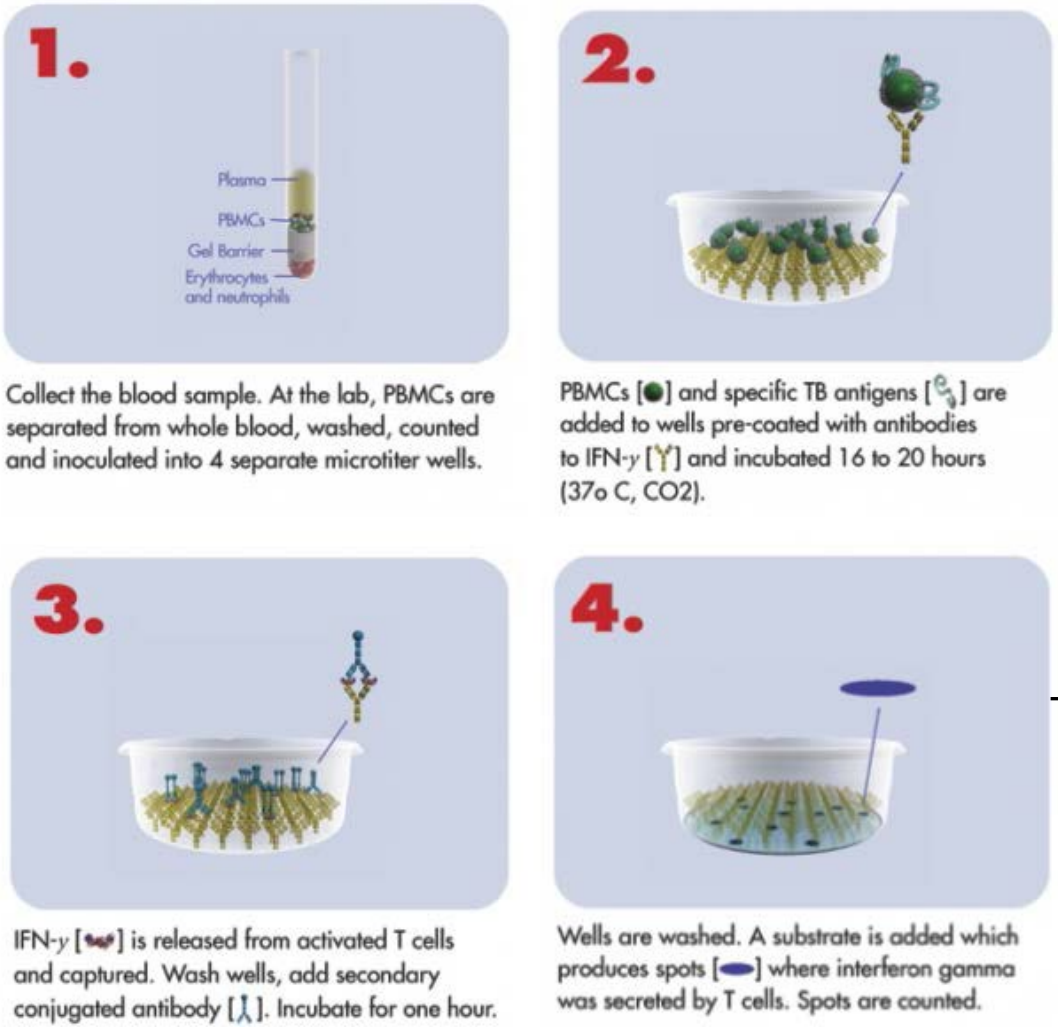
- Patient's immune status
- Correct blood handling and incubation

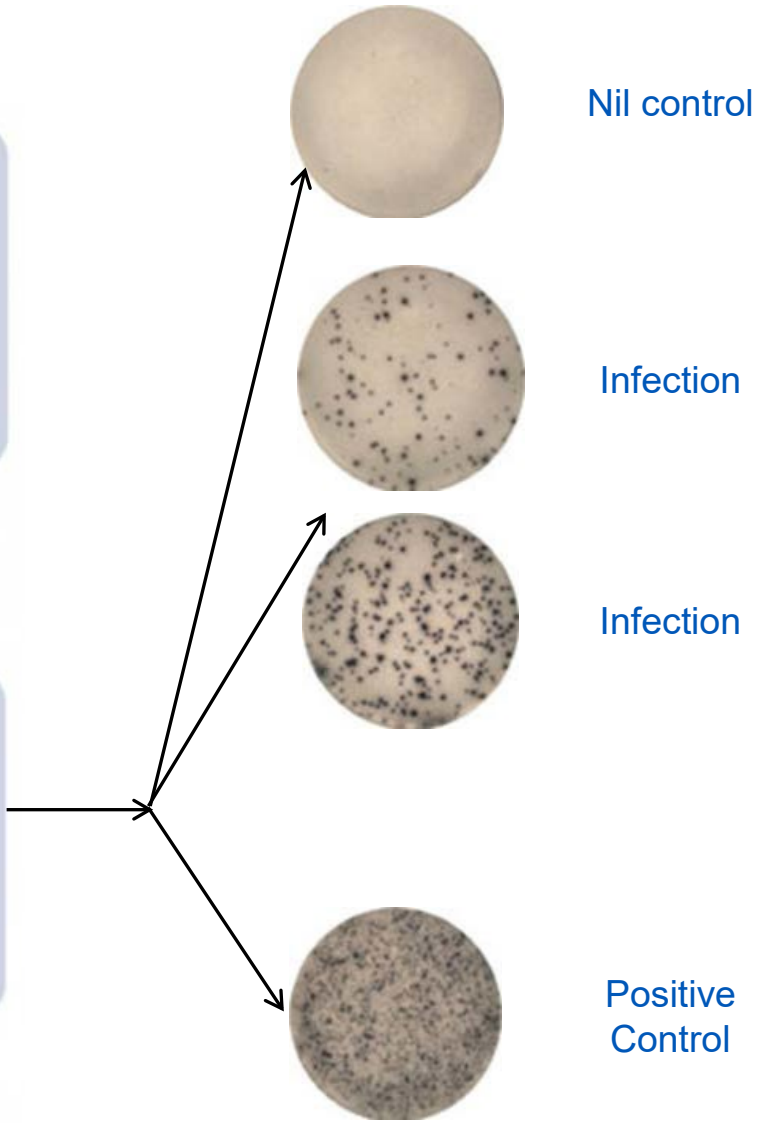
Note: a low-mitogen result, in conjunction with a negative TB result, is classified as an "indeterminate".

Nil tube (Negative control)

Adjusts for background noise.

T-Spot®.*TB* test (T-Spot)





Limitations of IGRAs

- Process within 8-30 hours while white blood cells are still viable.
- Does not predict who will progress to TB disease in the future.
- Limited data on the use of IGRAs for:
  - Children younger than 5 years of age;
  - Persons recently exposed to *M. tuberculosis*;
  - Immunocompromised persons; and
  - Serial testing
- Tests may be expensive.

Treatment

Principles of Management

- Symptom screen
- Prior history of TB or LTBI treatment
- Chest X ray
- Drug interactions
- Risks / Benefits of treatment

LATENT TB INFECTION TREATMENT REGIMENS

	DRUG	DURATION	FREQUENCY
Preferred	ISONIAZID[†] AND RIFAPENTINE[††] (3HP) 	3 months	Once weekly
Preferred	RIFAMPIN[§] (4R) 	4 months	Daily
Preferred	ISONIAZID[†] AND RIFAMPIN[§] (3HR) 	3 months	Daily
Alternative	ISONIAZID[†] (6H/9H)	6 months	Daily
			Twice weekly[¶]
		9 months	Daily
			Twice weekly[¶]

Dosing of LTBI Meds

- INH
  - 15 mg/kg; Max 900 mg if given weekly or twice weekly
  - 5 mg/kg; Max 300 mg if given daily
- RIF
  - 10 mg/kg daily
  - Max 600 mg daily
- RPT
  - 900 mg weekly

Adverse effects of INH

- Hepatotoxicity
  - 10 – 20%
  - May resolve with ongoing Rx
  - Stop if liver enzymes > 5 x ULN and asymptomatic or
  - >3 x ULN with symptoms
  - Evaluate for other conditions – NASH, Alcohol use, Hep B or C

- Peripheral Neuropathy
  - Risk Factors: HIV, Pregnancy, Breast Feeding, Diabetes, Alcohol use, Malnutrtion, Renal Failure
  - Pyridoxine supplementation 25 – 50 mg/day

Adverse Effects of RIF / RPT

- Hepatotoxicity: 0.6%
- Pruritis / Itching
- Hypersensitivity
- Nausea / Anorexia
- Orange discoloration of body fluids
- Drug interactions – Methadone, Contraceptives, Anticoagulants

Monitoring

- Clinical monitoring once a month
  - Adherence
  - Signs and symptoms of TB
  - Adverse reactions
- Baseline testing for at risk patients
- Follow up testing:
  - Underlying liver disease
  - Clinical indication

CDC's LTBI Guide for PCPs

https://www.cdc.gov/tb/media/pdfs/Latent-TB-Infection-A-Guide-for-Primary-Health-Care-Providers.pdf

Questions and Answers

Thank you