Latent tuberculosis (TB) infection

Jonathan M Wortham MD

April 6, 2023

Agenda

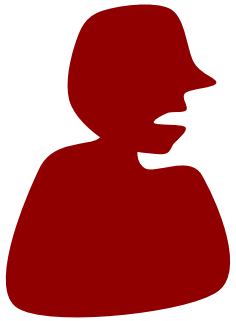
- Goals/objectives
- Discuss basics of clinical TB (“TB 101”)
- Discuss epidemiology of TB disease and LTBI
- Discuss how, why, and in whom LTBI should be tested for and treated
- Summary

Objectives + corresponding goals

- **Briefly discuss the epidemiology of TB in the United States**
- **Briefly discuss the epidemiology of latent TB infection (LTBI)**
  - Name 2 epidemiologic risk factors for TB and LTBI in the United States
  - Discern between risk factors for acquisition of *M. tuberculosis* infection and progression to TB disease
- **Briefly discuss recommendations for LTBI testing and treatment**
  - Name 2 reasons why targeted testing for LTBI is important
  - Name 3 groups for whom LTBI testing is indicated
  - Discuss 2 advantages of interferon gamma release assays (IGRAs)

TB 101

M. tuberculosis transmission and pathogenesis



M. tuberculosis transmission and pathogenesis

Patient with TB disease

Symptoms

- Cough (especially ≥2 weeks)
- Fever
- Weight loss
- Can be nonspecific

Tests (TB skin test or Interferon gamma release assay)

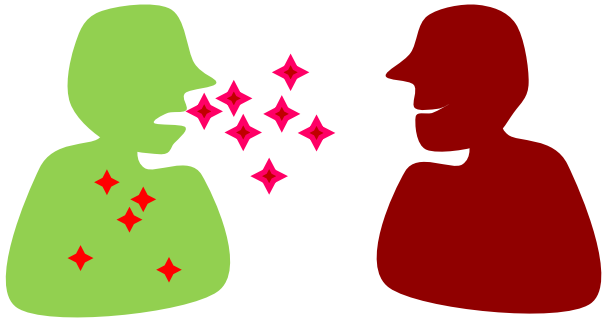
- Usually positive (but might not be)
- A negative test NEVER rules out TB

Chest radiograph

- Usually abnormal

Always need treatment for ≥4 months with ≥3 medicines initially

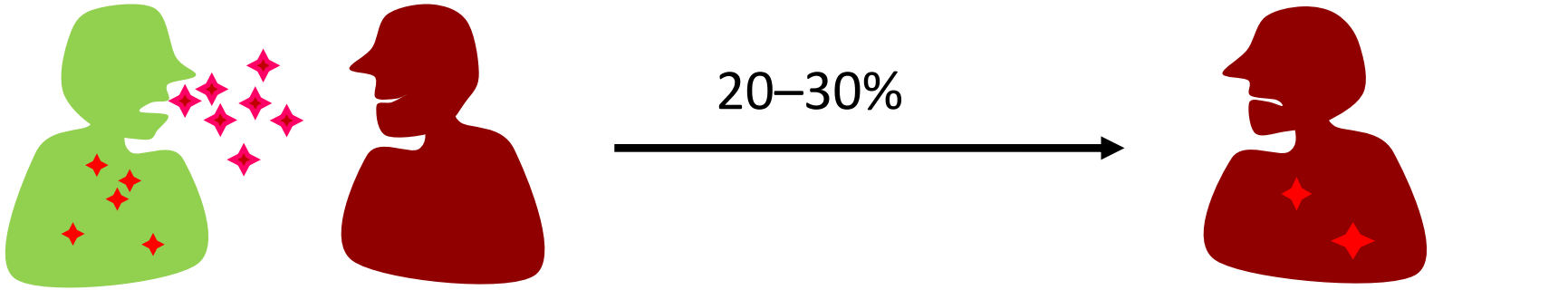
M. tuberculosis transmission and pathogenesis



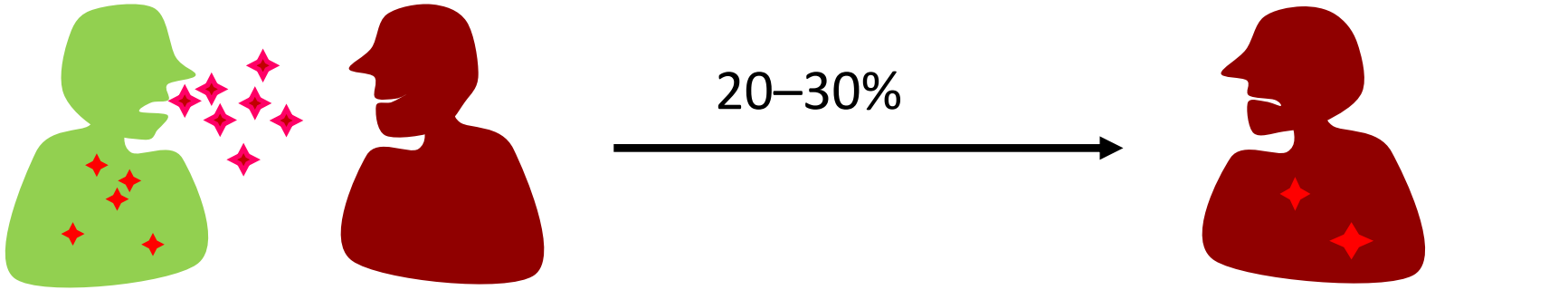
Patient with TB disease

Contact

M. tuberculosis transmission and pathogenesis



M. tuberculosis transmission and pathogenesis



Symptoms

- None

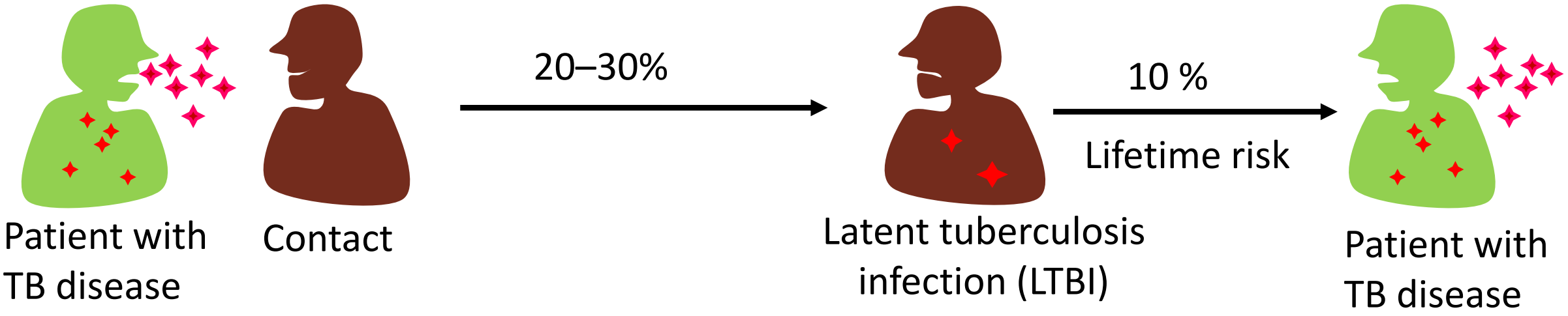
Tests

- Usually Have positive test for TB infection (TB skin test or interferon-gamma release assay)

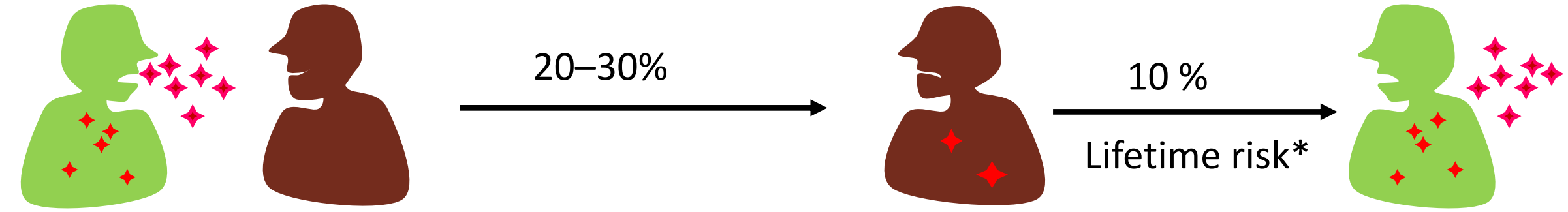
Chest radiograph

- Normal

M. tuberculosis transmission and pathogenesis



M. tuberculosis transmission and pathogenesis

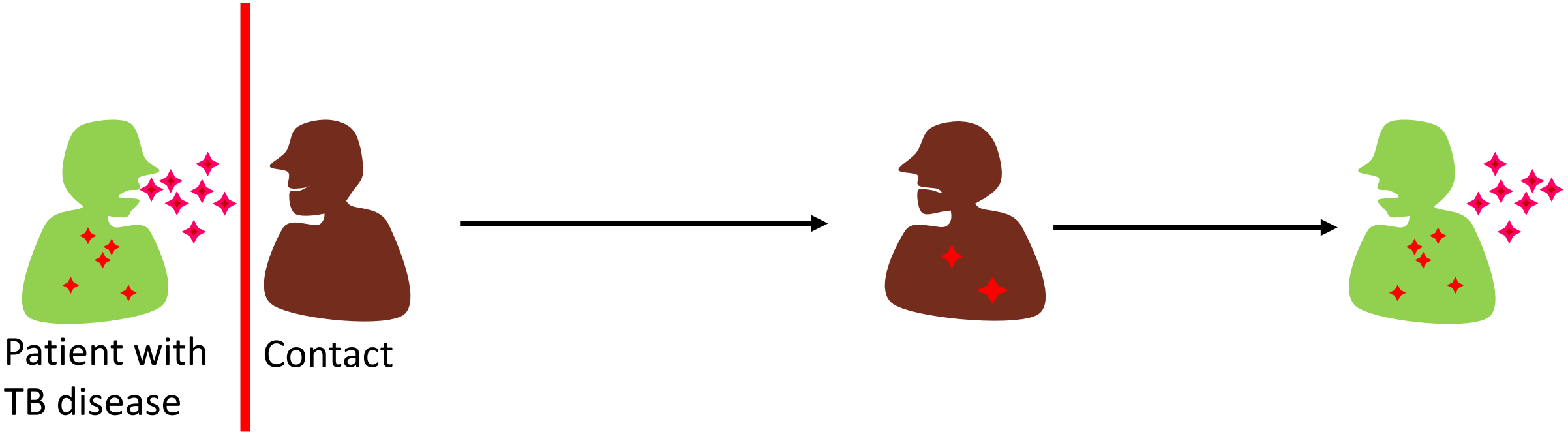


* Higher among persons with

HIV, Age<5 years

Diabetes, immune suppression,
Certain medications (e.g., TNF-α inhibitors)

How do we stop *M. tuberculosis* transmission?



<u>Find and treat people with TB disease</u>

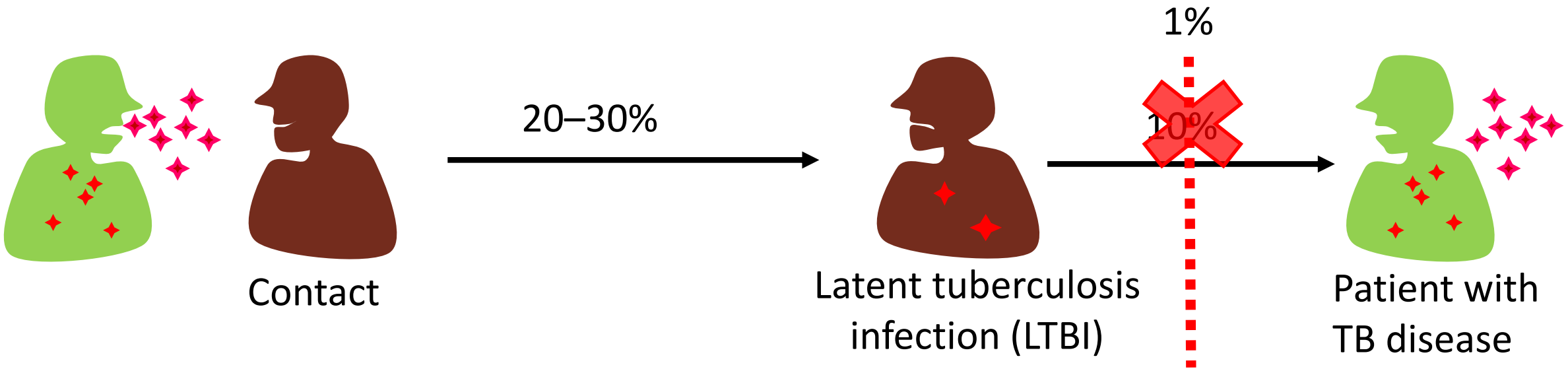
In the United States, directly observed therapy

Find contacts and evaluate them for TB disease

<u>Administer infection control precautions</u>

Limit exposure to persons with TB disease
(i.e. limit number of contacts)

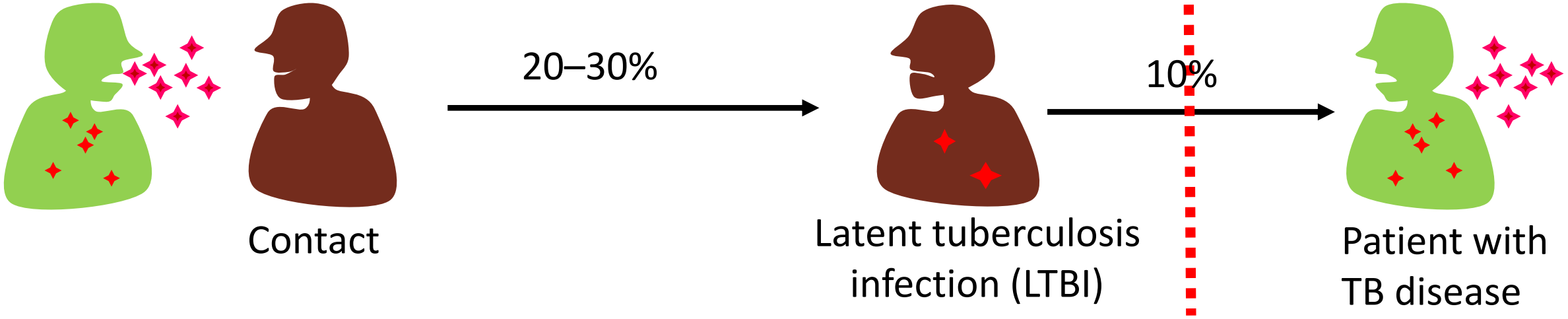
How do we stop *M. tuberculosis* transmission?



<u>Find and treat people with LTBI</u>

Finding and treating persons with LTBI can reduce progression to TB disease by as much as 90%

How do we stop *M. tuberculosis* transmission?



<u>Give BCG vaccine (not in the United States)</u>

BCG vaccine can reduce the risk for severe, disseminated form of TB, including TB meningitis.

Does not prevent pulmonary TB

Epidemiology

TB disease

Patient with TB disease

Symptoms

- Cough (especially ≥2 weeks)
- Fever
- Weight loss
- Can be non-specific

Tests (TB skin test or Interferon gamma release assay)

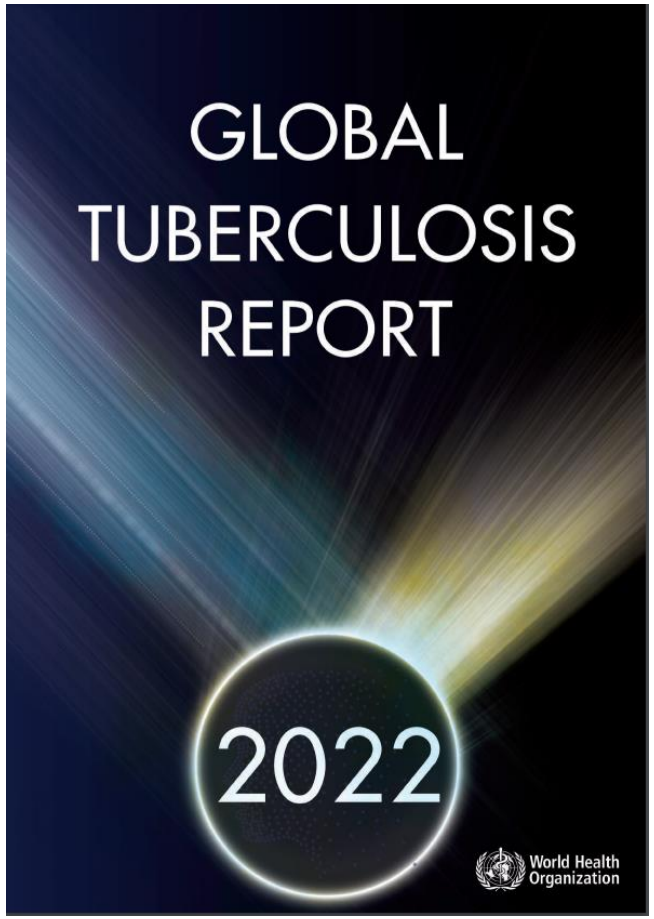
- Usually positive (but might not be)
- A negative test NEVER rules out TB

Chest radiograph

- Usually abnormal

Always needs treatment for ≥4 months with ≥3 medicines initially

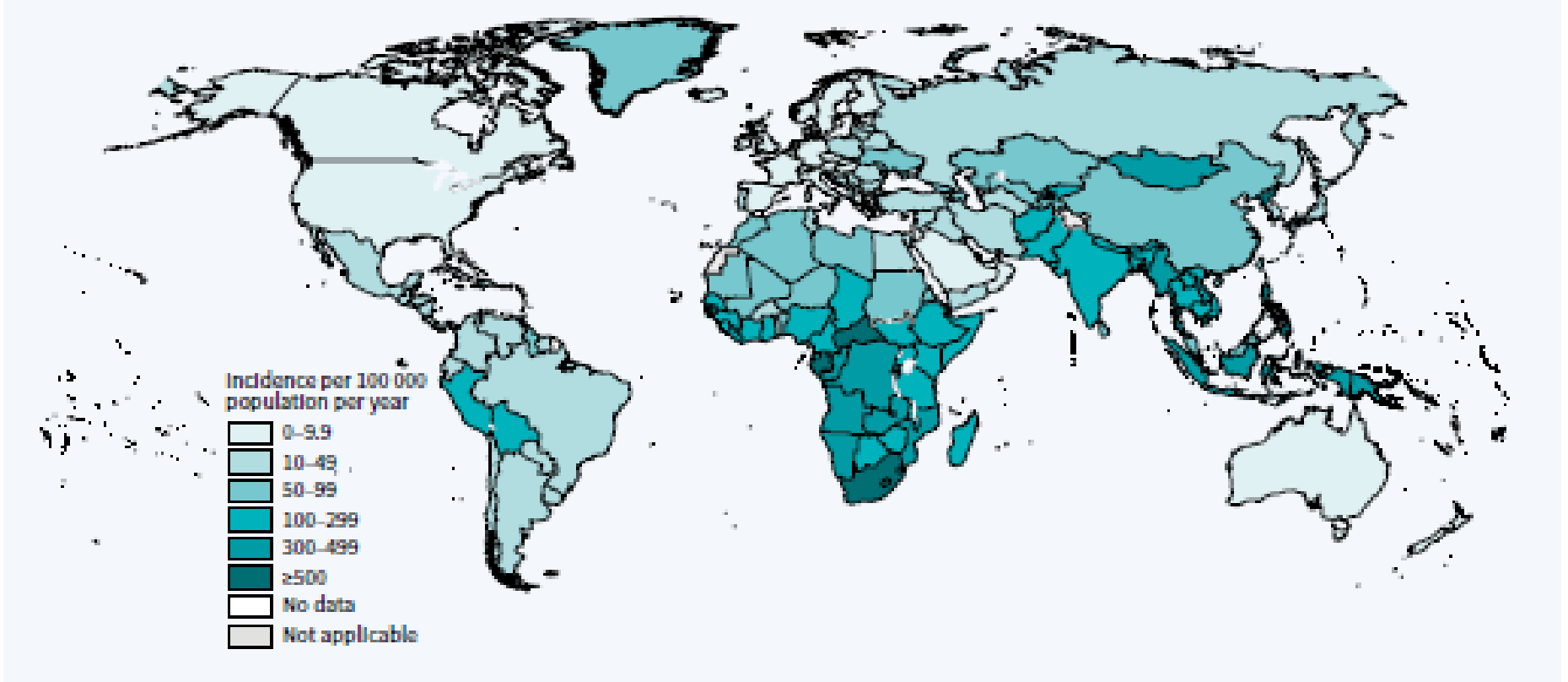
TB is an important cause of morbidity worldwide



- **Estimated 10.6 million cases in 2021**
  - An increase of 4.5% from 2020
- **~2 billion people have LTBI**
  - Approximately ¼ of the world population
- **Estimated 1.6 million deaths in 2021**
  - Leading cause of death due to single infectious agent
- **Most illness, deaths in persons <u>without</u> HIV infection**

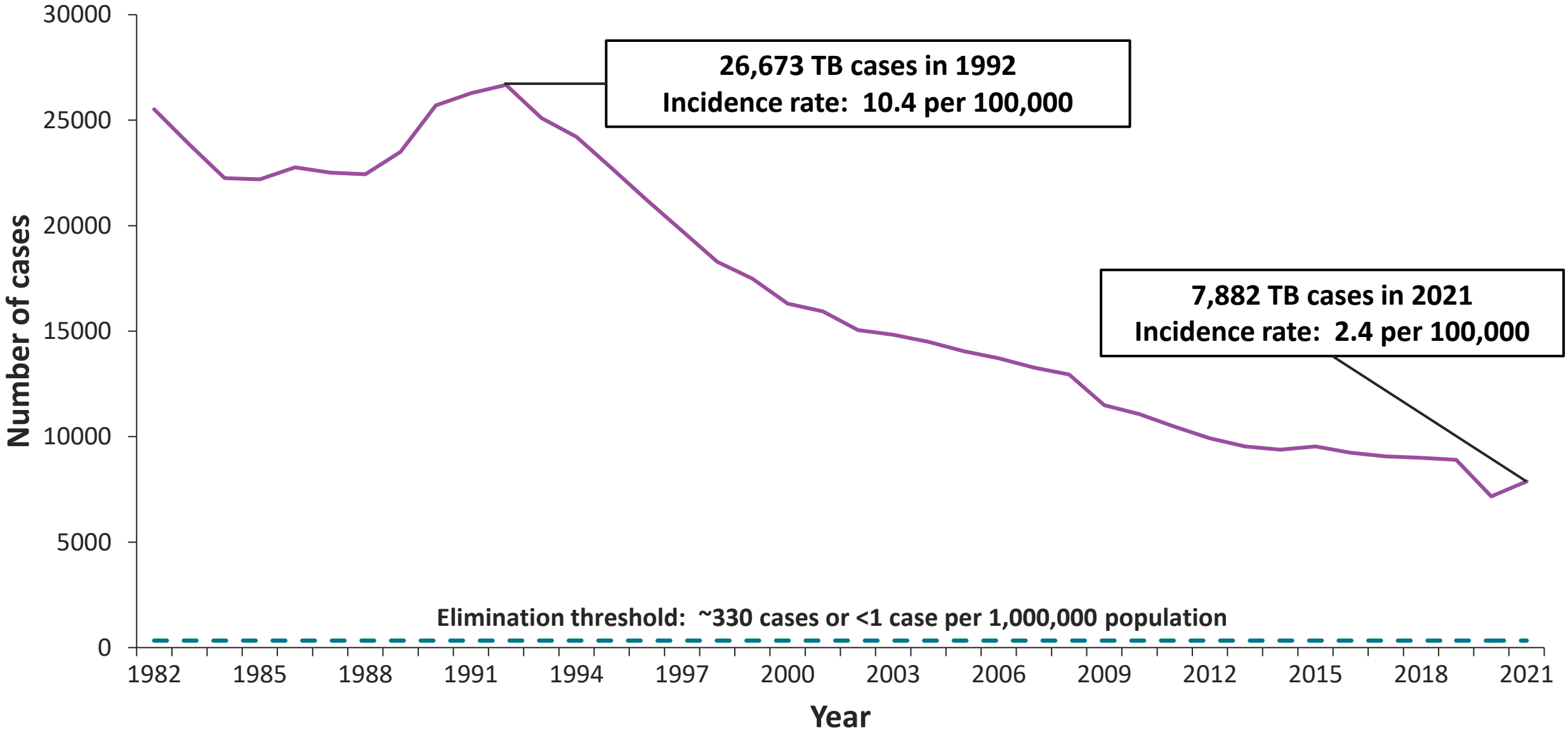
TB prevalence varies

Estimated TB incidence rates, 2021

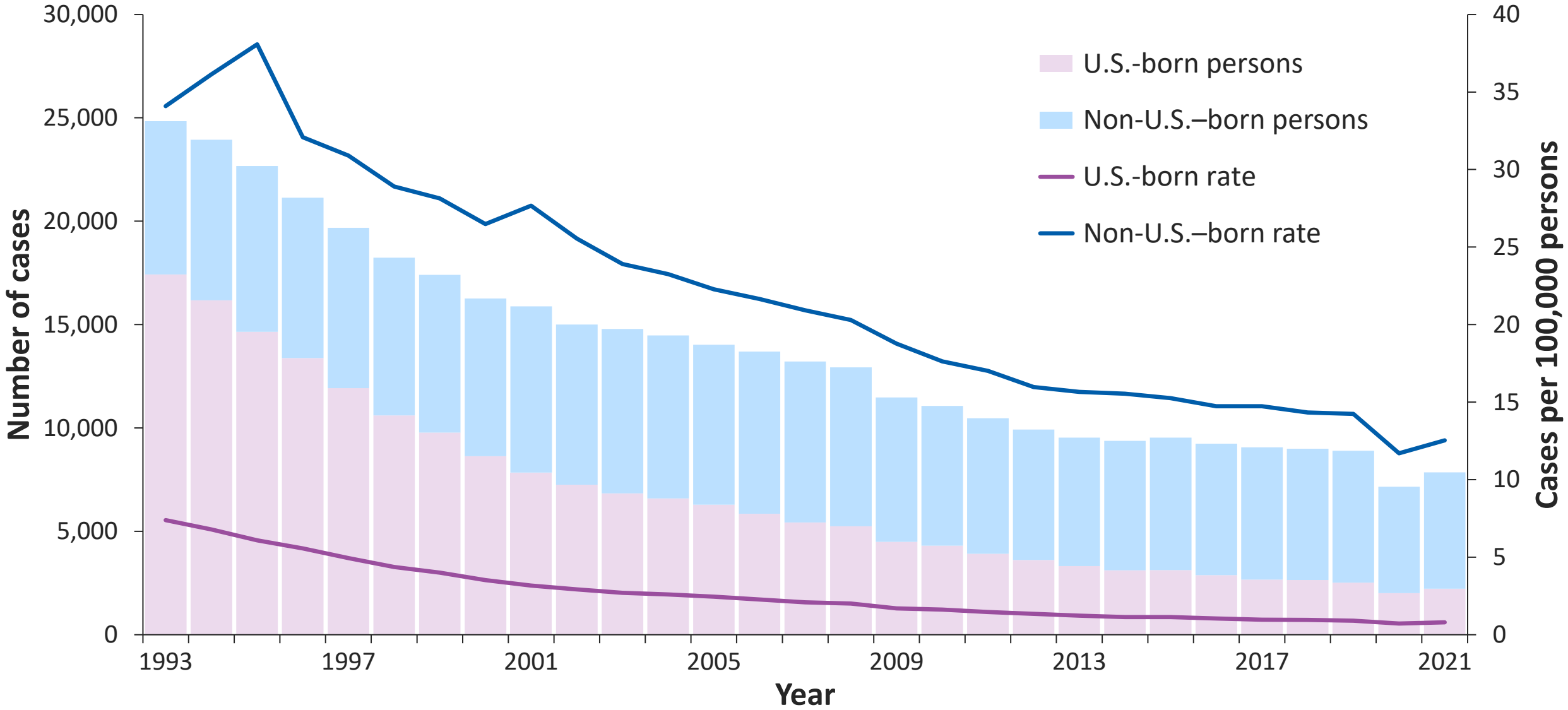


Source: WHO. Global Tuberculosis Report. 2022.

Progress Towards TB Elimination, United States, 1982–2021

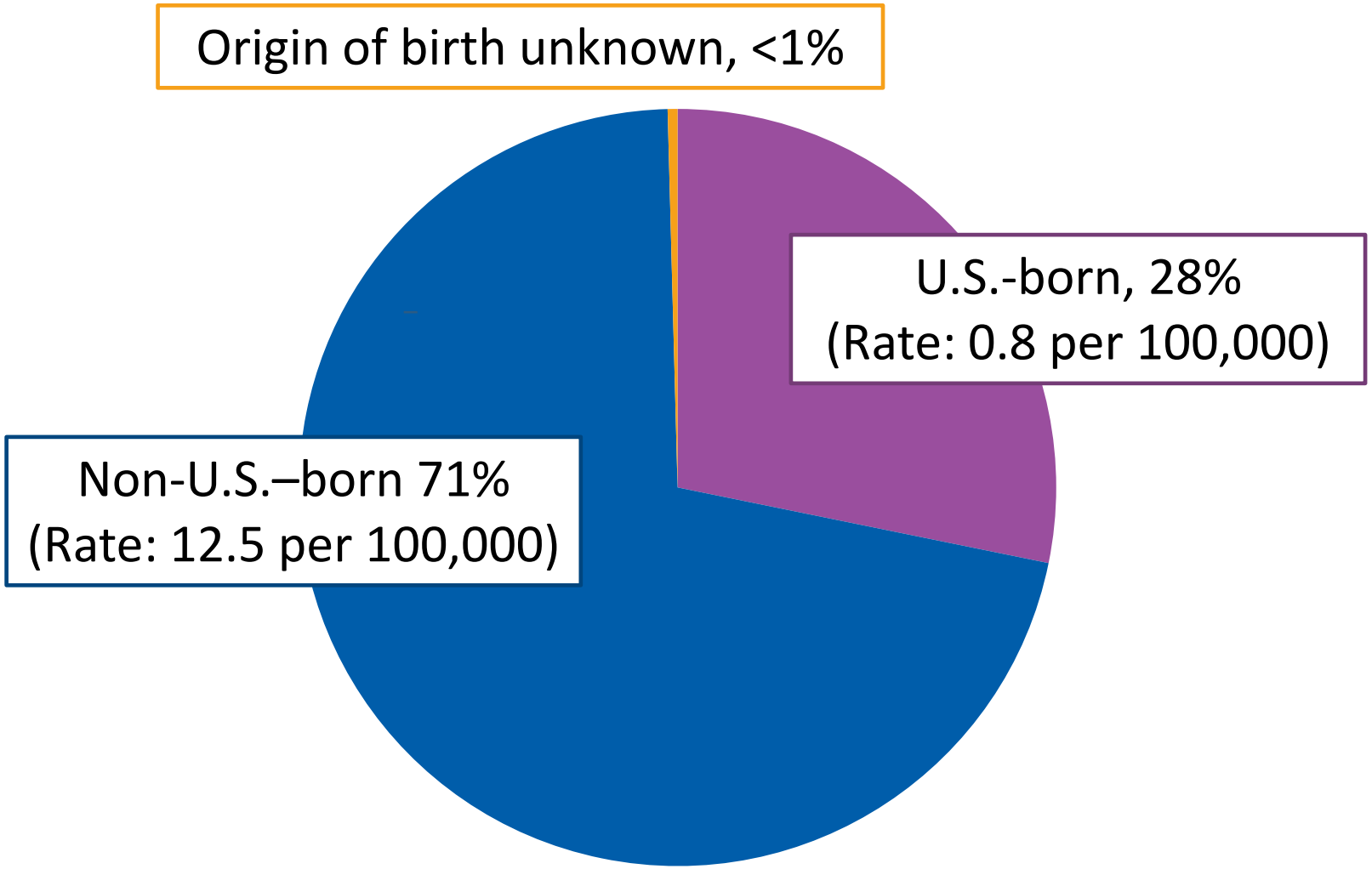


TB Cases and Incidence Rates by Origin of Birth,* United States, 1993–2021



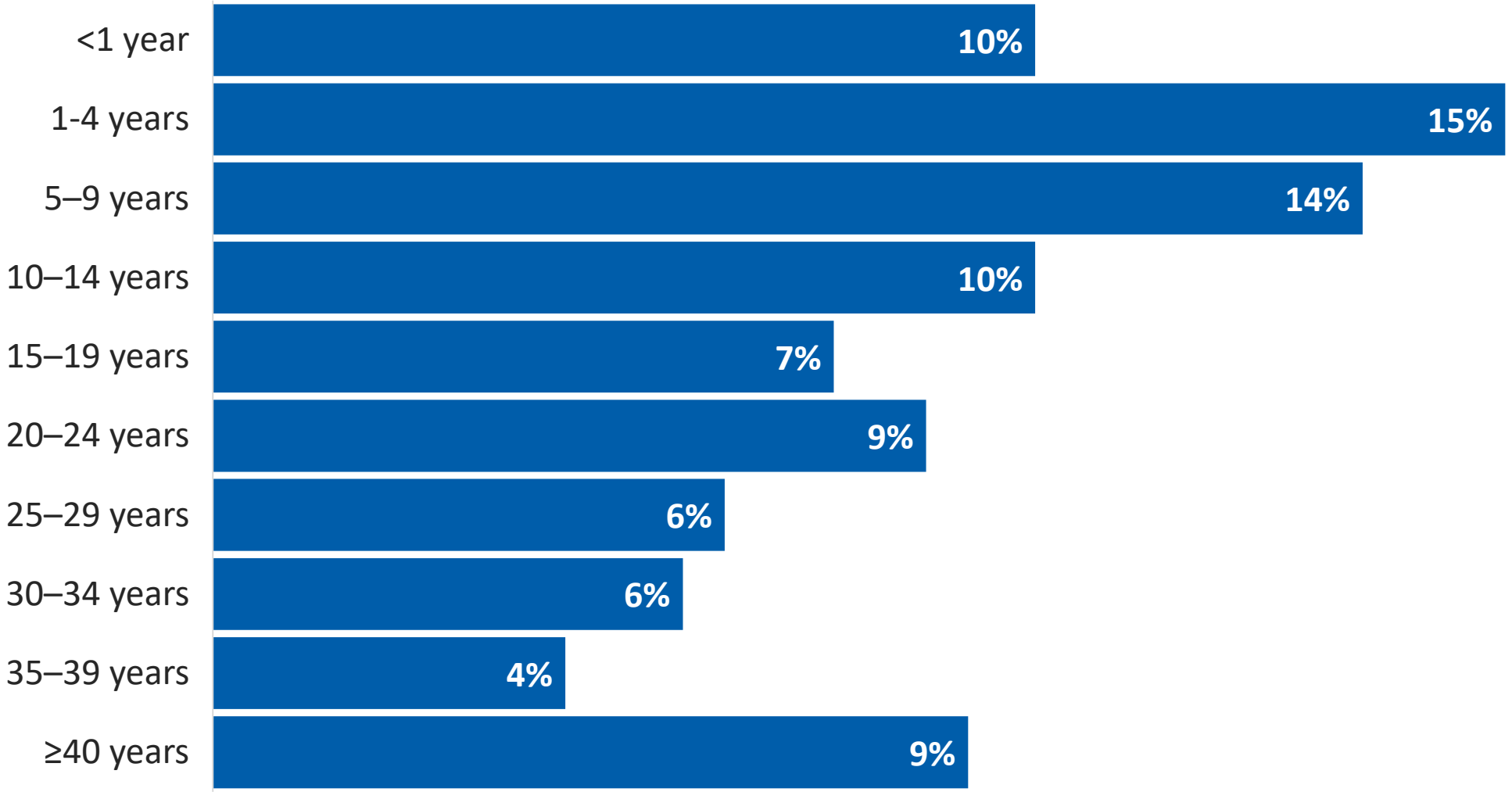
*Persons born in the United States, certain U.S. territories, or elsewhere to at least one U.S. citizen parent are categorized as U.S.-born. All other persons are categorized as non-U.S.–born.

TB Incidence Rates and Percentages by Origin of Birth,* United States, 2021 (N=7,849)



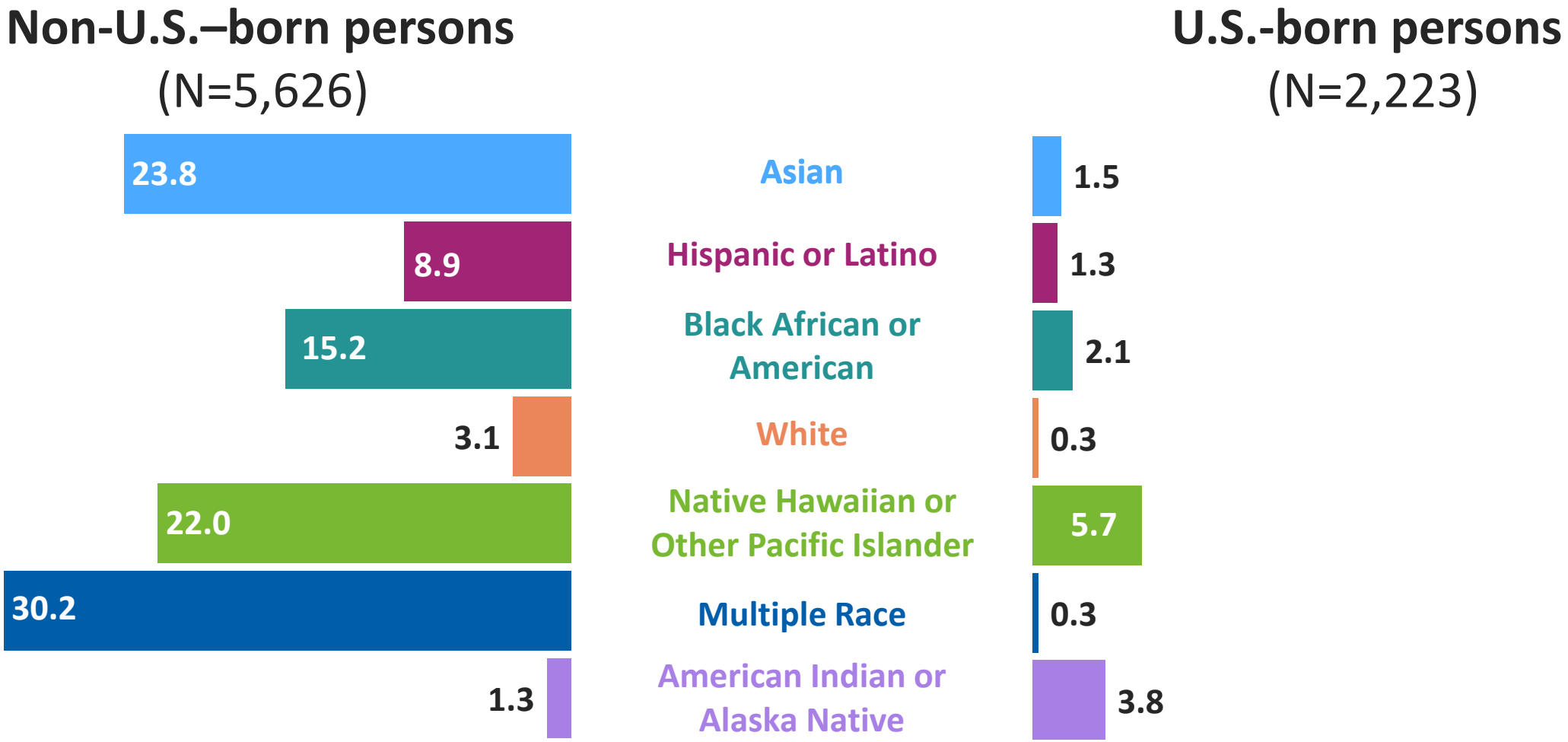
*Persons born in the United States, certain U.S. territories, or elsewhere to at least one U.S. citizen parent are categorized as U.S.-born. All other persons are categorized as non-U.S.–born.

Percentage of TB Cases Among Non-U.S.–Born* Persons by Years Since Initial Arrival in the United States at Diagnosis,† 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.
†The number of years since initial arrival in the United States at diagnosis was unknown or missing for 11% of non-U.S.–born persons. These persons were included in the denominator when calculating percentages.

TB Incidence Rates* by Origin† and Race/Ethnicity,§ United States, 2021

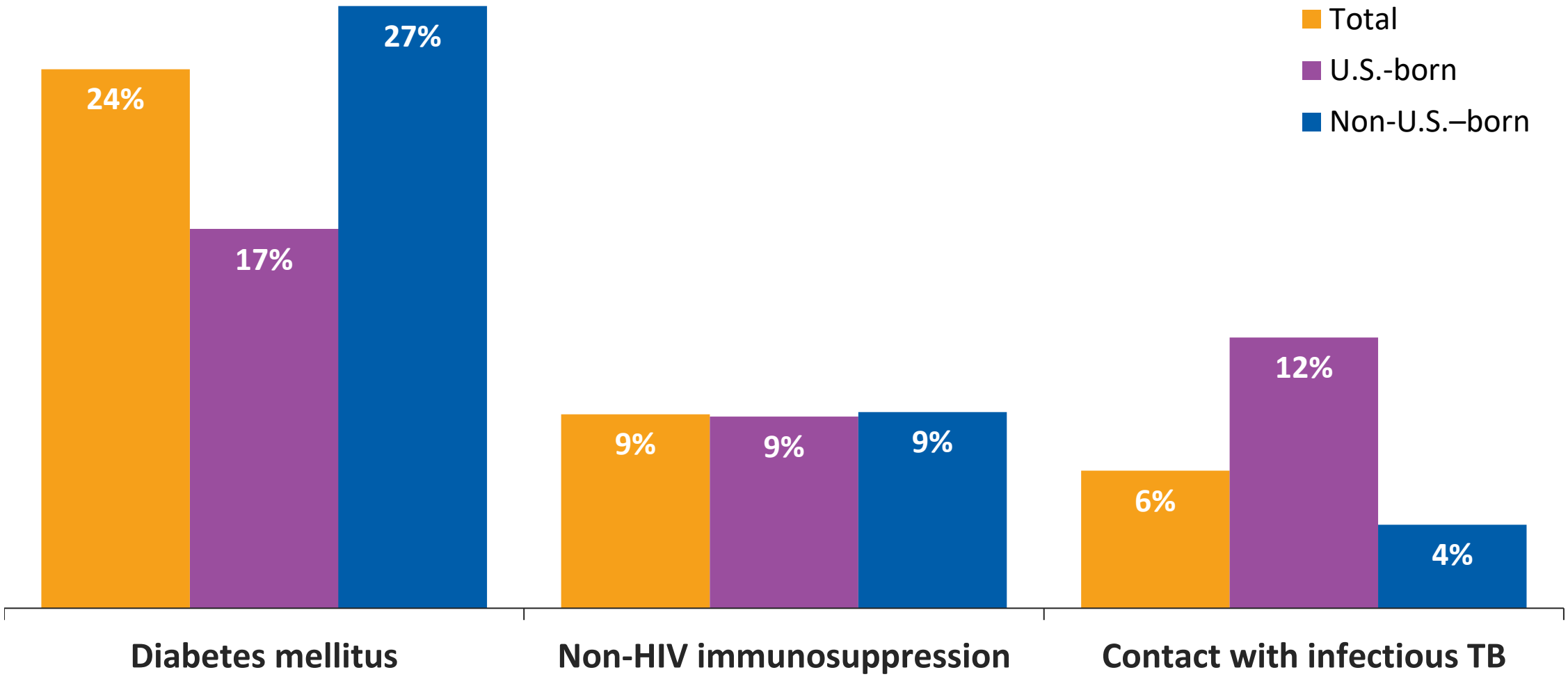


*Cases per 100,000 persons

†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.

§Persons who identified as Hispanic or Latino were categorized as "Hispanic or Latino," regardless of self-reported race. Persons who did not identify as Hispanic or Latino were categorized by self-reported race; if more than one race was reported, the person was categorized as "Multiple race."

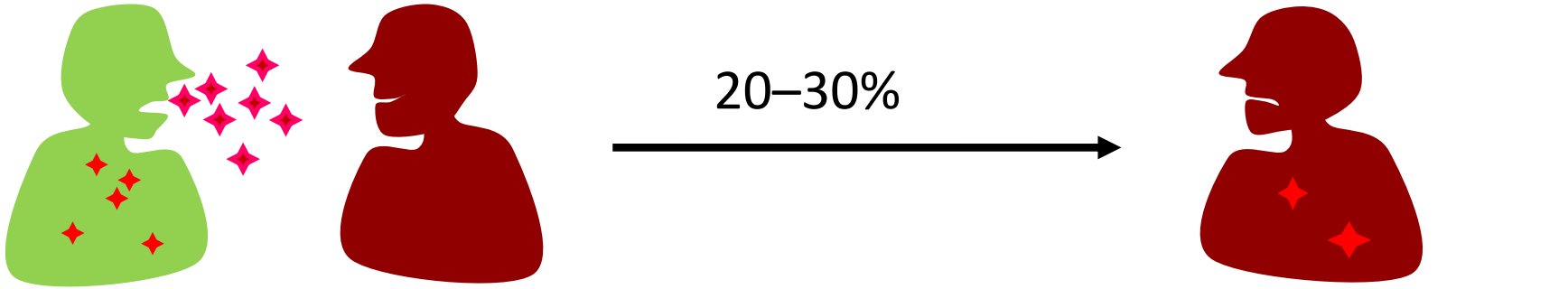
Percentage of Selected Risk Factors Among Persons with TB by Origin of Birth,* United States, 2021



*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.

Sure, that’s TB disease, but what about LTBI?

Latent TB infection (LTBI)



Patient with TB disease

Contact

Latent tuberculosis infection (LTBI)

Symptoms

- None

Tests

- Usually Have positive test for TB infection (TB skin test or interferon-gamma release assay)

Chest radiograph

- Normal

PLOS ONE

RESEARCH ARTICLE

Tuberculosis Infection in the United States: Prevalence Estimates from the National Health and Nutrition Examination Survey, 2011-2012

Roque Miramontes*, Andrew N. Hill, Rachel S. Yelk Woodruff, Lauren A. Lambert, Thomas R. Navin, Kenneth G. Castro, Philip A. LoBue

- **CDC estimates that approximately 13 million people in the United States have LTBI**
  - Overall, approximately 1 in 20 (5%) prevalence
- **Non-U.S.–born persons are more likely to have + tests for *M. tuberculosis* infection**

PLOS ONE

RESEARCH ARTICLE

Tuberculosis Infection in the United States: Prevalence Estimates from the National Health and Nutrition Examination Survey, 2011-2012

Roque Miramontes*, Andrew N. Hill, Rachel S. Yelk Woodruff, Lauren A. Lambert, Thomas R. Navin, Kenneth G. Castro, Philip A. LoBue

- **Non-U.S.–born: TST positivity: 20.5%; IGRA positivity: 15.9%**
  - More than 1 in 8 non-U.S.–born are infected with *M. tuberculosis*
- **U.S.–born: TST positivity: 1.5%; IGRA: 2.8%**
  - Distribution in U.S.–born is not uniform either

M. tuberculosis infection prevalence differs according to demographics

Table 4. Interferon Gamma Release Assay Positive Prevalence in the Civilian, Noninstitutionalized U. S. Population, Ages 6+, 2011–2012.

	IGRA Positive Prevalence, % (95% CI)		
Characteristics	**Overall**	**U.S.-born**	**Foreign-born**
Total	5.0 (4.2–5.8)	2.8 (2.0–3.8)	15.9 (13.5–18.7)
Sex			
Female	4.2 (3.3–5.3)	2.3 (1.4–3.6)	14.0 (11.3–17.3)
Male	5.8 (5.0–6.7)	3.3 (2.5–4.4)	17.9 (14.9–21.3)
Age group, yr			
6–14	0.9 (0.4–1.8)§	0.7 (0.3–1.7)§	2.6 (0.7–9.2)*§
15–24	3.0 (1.9–4.5)	2.2 (1.2–4.1)§	7.1 (3.3–14.4)§
25–44	4.4 (3.5–5.5)	1.9 (1.0–3.6)§	12.0 (9.3–15.5)
45–64	6.8 (5.1–8.9)	3.6 (2.3–5.6)	23.5 (18.5–29.4)
≥65	8.3 (6.5–10.5)	5.2 (4.0–6.9)	32.1 (24.4–40.9)
Race/ethnicity			
Non-Hispanic white	2.7 (1.9–3.7)	2.4 (1.6–3.5)	9.4 (4.6–18.5)§
Non-Hispanic black	5.3 (4.0–6.8)	4.4 (3.2–6.0)	15.2 (10.9–20.7)
Hispanic	10.2 (8.7–11.9)	3.7 (2.5–5.4)	15.6 (13.0–18.7)
Non-Hispanic Asian	17.5 (15.0–20.2)	2.9 (1.5–5.4)*§	22.3 (19.6–25.3)
HIV Status[a]			
Negative	4.7 (3.8–5.7)	2.1 (1.3–3.3)	14.6 (12.1–17.4)
Positive	7.6 (3.3–16.7)*§	8.2 (3.3–19.1)*§	. . .

[a] There were no foreign-born study participants with both IGRA positive and HIV positive results

* Estimates and 95% CIs may be unreliable because the number of sample positives is < 10

§ Estimates and 95% CIs may be unreliable because the RSE > 30%

doi:10.1371/journal.pone.0140881.t004

Among non-U.S.–born, *M. tuberculosis* infection prevalence increases with age

Table 4. Interferon Gamma Release Assay Positive Prevalence in the Civilian, Noninstitutionalized U. S. Population, Ages 6+, 2011–2012.

	IGRA Positive Prevalence, % (95% CI)		
Characteristics	**Overall**	**U.S.-born**	**Foreign-born**
Total	5.0 (4.2–5.8)	2.8 (2.0–3.8)	15.9 (13.5–18.7)
Sex			
Female	4.2 (3.3–5.3)	2.3 (1.4–3.6)	14.0 (11.3–17.3)
Male	5.8 (5.0–6.7)	3.3 (2.5–4.4)	17.9 (14.9–21.3)
Age group, yr			
6–14	0.9 (0.4–1.8)§	0.7 (0.3–1.7)§	2.6 (0.7–9.2)*§
15–24	3.0 (1.9–4.5)	2.2 (1.2–4.1)§	7.1 (3.3–14.4)§
25–44	4.4 (3.5–5.5)	1.9 (1.0–3.6)§	12.0 (9.3–15.5)
45–64	6.8 (5.1–8.9)	3.6 (2.3–5.6)	23.5 (18.5–29.4)
≥65	8.3 (6.5–10.5)	5.2 (4.0–6.9)	32.1 (24.4–40.9)
Race/ethnicity			
Non-Hispanic white	2.7 (1.9–3.7)	2.4 (1.6–3.5)	9.4 (4.6–18.5)§
Non-Hispanic black	5.3 (4.0–6.8)	4.4 (3.2–6.0)	15.2 (10.9–20.7)
Hispanic	10.2 (8.7–11.9)	3.7 (2.5–5.4)	15.6 (13.0–18.7)
Non-Hispanic Asian	17.5 (15.0–20.2)	2.9 (1.5–5.4)*§	22.3 (19.6–25.3)
HIV Status[a]			
Negative	4.7 (3.8–5.7)	2.1 (1.3–3.3)	14.6 (12.1–17.4)
Positive	7.6 (3.3–16.7)*§	8.2 (3.3–19.1)*§	…

[a] There were no foreign-born study participants with both IGRA positive and HIV positive results

* Estimates and 95% CIs may be unreliable because the number of sample positives is < 10

§ Estimates and 95% CIs may be unreliable because the RSE > 30%

doi:10.1371/journal.pone.0140881.t004

Among non-U.S.–born, *M. tuberculosis* infection prevalence increases with age

Table 4. Interferon Gamma Release Assay Positive Prevalence in the Civilian, Noninstitutionalized U. S. Population, Ages 6+, 2011–2012.

	IGRA Positive Prevalence, % (95% CI)		
Characteristics	**Overall**	**U.S.-born**	**Foreign-born**
Total	5.0 (4.2–5.8)	2.8 (2.0–3.8)	15.9 (13.5–18.7)
Sex			
Female	4.2 (3.3–5.3)	2.3 (1.4–3.6)	14.0 (11.3–17.3)
Male	5.8 (5.0–6.7)	3.3 (2.5–4.4)	17.9 (14.9–21.3)
Age group, yr			
6–14	0.9 (0.4–1.8)§	0.7 (0.3–1.7)§	2.6 (0.7–9.2)*§
15–24	3.0 (1.9–4.5)	2.2 (1.2–4.1)§	7.1 (3.3–14.4)§
25–44	4.4 (3.5–5.5)	1.9 (1.0–3.6)§	12.0 (9.3–15.5)
45–64	6.8 (5.1–8.9)	3.6 (2.3–5.6)	23.5 (18.5–29.4)
≥65	8.3 (6.5–10.5)	5.2 (4.0–6.9)	32.1 (24.4–40.9)
Race/ethnicity			
Non-Hispanic white	2.7 (1.9–3.7)	2.4 (1.6–3.5)	9.4 (4.6–18.5)§
Non-Hispanic black	5.3 (4.0–6.8)	4.4 (3.2–6.0)	15.2 (10.9–20.7)
Hispanic	10.2 (8.7–11.9)	3.7 (2.5–5.4)	15.6 (13.0–18.7)
Non-Hispanic Asian	17.5 (15.0–20.2)	2.9 (1.5–5.4)*§	22.3 (19.6–25.3)
HIV Status[a]			
Negative	4.7 (3.8–5.7)	2.1 (1.3–3.3)	14.6 (12.1–17.4)
Positive	7.6 (3.3–16.7)*§	8.2 (3.3–19.1)*§	. . .

[a] There were no foreign-born study participants with both IGRA positive and HIV positive results

* Estimates and 95% CIs may be unreliable because the number of sample positives is < 10

§ Estimates and 95% CIs may be unreliable because the RSE > 30%

doi:10.1371/journal.pone.0140881.t004

What could we do about it?

JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Screening for Latent Tuberculosis Infection in Adults

US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

- **Screen + test persons who:**
  - **Were born in, or former residents of, countries with increased tuberculosis prevalence**
  - Have lived in high-risk congregate settings
    - Homeless overnight facilities
    - Correctional facilities
  - Certain other groups
    - Dependent on “local demographic patterns”

Advantages of IGRAs over TST

- Single blood draw; results in 24 hours (TST requires evaluation of results after 48–72 hours)
- Bacille Calmette–Guérin (BCG) vaccine can cause false-positive TST results but **does not affect IGRAs**
- Nontuberculous mycobacteria infections less likely to cause false-positive result for IGRA than TST
- Interpretation is objective (TST interpretation is subjective)

Why not test everyone?

- **Performance characteristics of TST**
  - Sensitivity: 60–90% in some studies
    - *"Overall, 6–9 in 10 people with TB infection will have a positive test"*
  - Specificity: 70–90% in some studies
    - *"Overall, 7–9 in 10 people without TB infection will have a negative test"*
    - Might be lower among BCG-immunized persons
  - Sensitivity increases with lower cutpoint (5mm vs 10mm), but specificity decreases

Why not test everyone?

- **Performance characteristics of IGRA**
  - Sensitivity: similar to TST
  - Specificity: >90% in most studies
    - *"Overall, >9 in 10 people without TB disease will have a negative test"*
    - No differences among BCG-immunized persons
    - High correlation with negative TST

We want people with TB disease and LTBI to test positive

- **Positive predictive value**
  - *"The proportion of positive tests that actually represent persons with the condition"*
  - High prevalence + high sensitivity = more positive tests actually represent persons with TB infections
  - To increase positive predictive value
    - Test groups with higher prevalence
    - Choose tests with higher sensitivity
- **Helps ensure that people who need treatment get it and those who don't will not**

We want people without TB disease and LTBI to test negative

- **Negative predictive value**
  - *"The proportion of negative tests that actually represent persons without the condition"*
  - Low prevalence + high specificity = more negative results represent persons without TB infections
  - To increase negative predictive value
    - Test groups with lower prevalence
    - Choose tests with higher specificity
- **Helps ensure that people who need treatment get it and those who don't will not**

Why not test everyone?

		M. tuberculosis infection		
		Yes	No	Total
IGRA test result	Positive	7	325	332
	Negative	3	15971	15974
	Total	10	16296	16306

Sensitivity: 70%
Specificity: 98%
Prevalence: 0.006 or 0.6%

PPV: 2.0%
325 people with positive tests don't have disease

NPV: 98%
306 people without infection test +

Why not test everyone?

		M. tuberculosis infection		
		Yes	No	Total
IGRA test result	Positive	7	325	332
	Negative	3	15971	15974
	Total	10	16296	16306

Sensitivity: 70%
Specificity: 98%
Prevalence: 0.006 or 0.6%

PPV: 2.0%
325 people with positive tests don't have disease

NPV: 98%
306 people without infection test +

Why not test everyone?

		M. tuberculosis infection		
		Yes	No	Total
IGRA test result	Positive	7	325	332
	Negative	3	15971	15974
	Total	10	16296	16306

Sensitivity: 70%

Specificity: 98%

Prevalence: 0.006 or 0.6%

PPV: 2.0%

325 people with positive tests don't have disease

NPV: 98%

306 people without infection test +

Why not test everyone?

		M. tuberculosis infection		
		Yes	No	Total
IGRA test result	Positive	7	325	332
	Negative	3	15971	15974
	Total	10	16296	16306

Sensitivity: 70%

Specificity: 98%

Prevalence: 0.006 or 0.6%

PPV: 2.0%

325 people with positive tests don't have disease

NPV: 98%

306 people without infection test +

Why not test everyone?

		M. tuberculosis infection		
		Yes	No	Total
IGRA test result	Positive	7	325	332
	Negative	3	15971	15974
	Total	10	16296	16306

Sensitivity: 70%
Specificity: 98%
Prevalence: 0.006 or 0.6%

PPV: 2.0%
325 people with positive tests don't have disease

NPV: 98%
306 people without infection test +

Why not test everyone?

		M. tuberculosis infection		
		Yes	No	Total
IGRA test result	Positive	7	325	332
	Negative	3	15971	15974
	Total	10	16296	16306

Sensitivity: 70%
Specificity: 98%
Prevalence: 0.006 or 0.6%

PPV: 2.0%
325 people with positive tests don't have disease

NPV: 99%
3 people with infection test negative

Why not test everyone?

		M. tuberculosis infection		
		Yes	No	Total
IGRA test result	Positive	700	306	1006
	Negative	300	15000	15300
	Total	1000	15306	16306

Sensitivity: 70%

Specificity: 98%

Prevalence: 0.06 or 6%

PPV: 69.5%

306 people with positive tests don't have disease

NPV: 98%

300 people with infection test -

Why not test everyone?

		M. tuberculosis infection		
		Yes	No	Total
IGRA test result	Positive	700	306	1006
	Negative	300	15000	15300
	Total	1000	15306	16306

Sensitivity: 70%
Specificity: 98%
Prevalence: 0.06 or 6%

PPV: 69.5%
306 people with positive tests don't have disease

NPV: 98%
300 people with infection test -

Treat TB disease and LTBI

- **TB disease**
  - Always requires treatment with ≥3 drugs for ≥4 months under directly observed therapy
  - Always requires health department notification
- **LTBI**
  - Must exclude TB disease first!
  - Preferred regimens
    - 12 weekly doses of isoniazid and rifapentine
    - 4 months of daily rifampin
    - 3 months of daily isoniazid and rifampin

Summary: key points

- **Worldwide, TB is a common infection**
  - TB is a leading cause of mortality
  - Approximately ¼ of the world's population is infected with *M. tuberculosis*

- **In the United States, TB incidence is low**
  - Substantial declines since the 1990s
  - However, annual rate of decline is not sufficient to meet elimination goals

Summary: key points

- **In the United States, TB incidence in non-U.S.–born persons is approximately 10x rates in U.S.–born persons**
  - Most of these cases are thought to be the result of *M. tuberculosis* infection acquired in the remote past
  - More than ½ among non-U.S.–born occur >10 years after entry

- **LTBI testing and treatment is effective for preventing TB disease**
  - Reduces morbidity for individuals, reduces incidence for societies

Summary: key points

- **However, current diagnostics have limited performance characteristics**

- **Therefore, in addition to contacts, current guidelines recommend testing for *M. tuberculosis* infection for**
  - **Non-U.S.–born persons (and those who have resided outside United States in countries with relatively high TB incidence)**
  - Persons living in high-risk congregate settings
  - Other groups dependent on “local demographic patterns”

Summary: key points

- **CDC estimates >13 million people have LTBI**
  - Testing and treatment in settings other than public health TB clinics will facilitate broader uptake of this preventive treatment

References

- Yelk Woodruff R, Hill A, Marks S, Navin T, Miramontes R. Estimated Latent Tuberculosis Infection Prevalence and Tuberculosis Reactivation Rates Among Non-U.S.-Born Residents in the United States, from the 2011-2012 National Health and Nutrition Examination Survey. *J Immigr Minor Health*. 2021 Aug;23(4):806-812.
- US Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, Curry SJ, Bauman L, Davidson KW, Epling JW Jr, García FA, Herzstein J, Kemper AR, Krist AH, Kurth AE, Landefeld CS, Mangione CM, Phillips WR, Phipps MG, Pignone MP. Screening for Latent Tuberculosis Infection in Adults: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2016 Sep 6;316(9):962-9.
- Mazurek GH, Jereb J, Vernon A, LoBue P, Goldberg S, Castro K; IGRA Expert Committee; Centers for Disease Control and Prevention (CDC). Updated guidelines for using Interferon Gamma Release Assays to detect *Mycobacterium tuberculosis* infection — United States, 2010. *MMWR Recomm Rep*. 2010 Jun 25;59(RR-5):1-25.

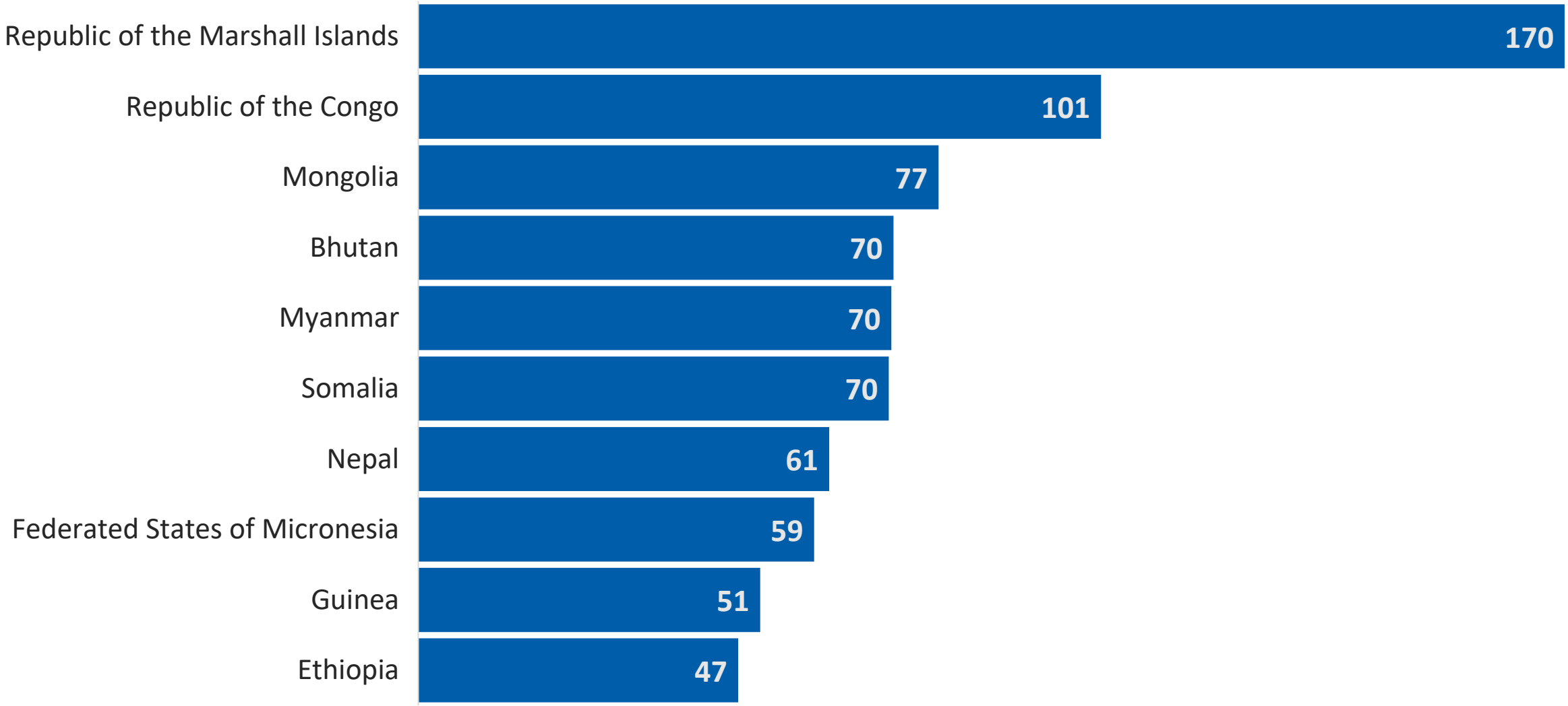
Objectives + corresponding goals

- **Briefly discuss the epidemiology of TB in the United States**
- **Briefly discuss the epidemiology of latent TB infection (LTBI)**
  - Name 2 epidemiologic risk factors for TB and LTBI in the United States
  - Discern between risk factors for acquisition of *M. tuberculosis* infection and progression to TB disease
- **Briefly discuss recommendations for LTBI testing and treatment**
  - Tell a colleague why targeted testing for LTBI is important
  - Name 3 groups for whom LTBI testing is indicated
  - Discuss advantages of interferon gamma release assays (IGRAs)

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

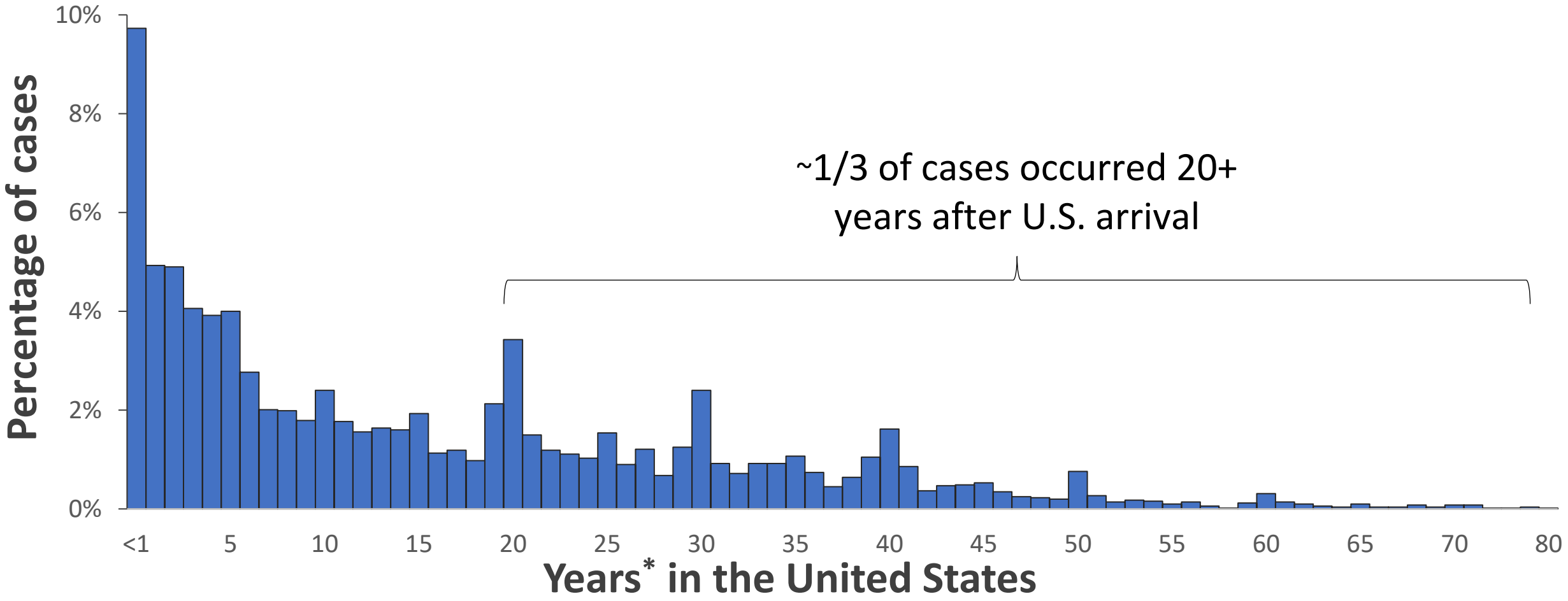
Extra Slides

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



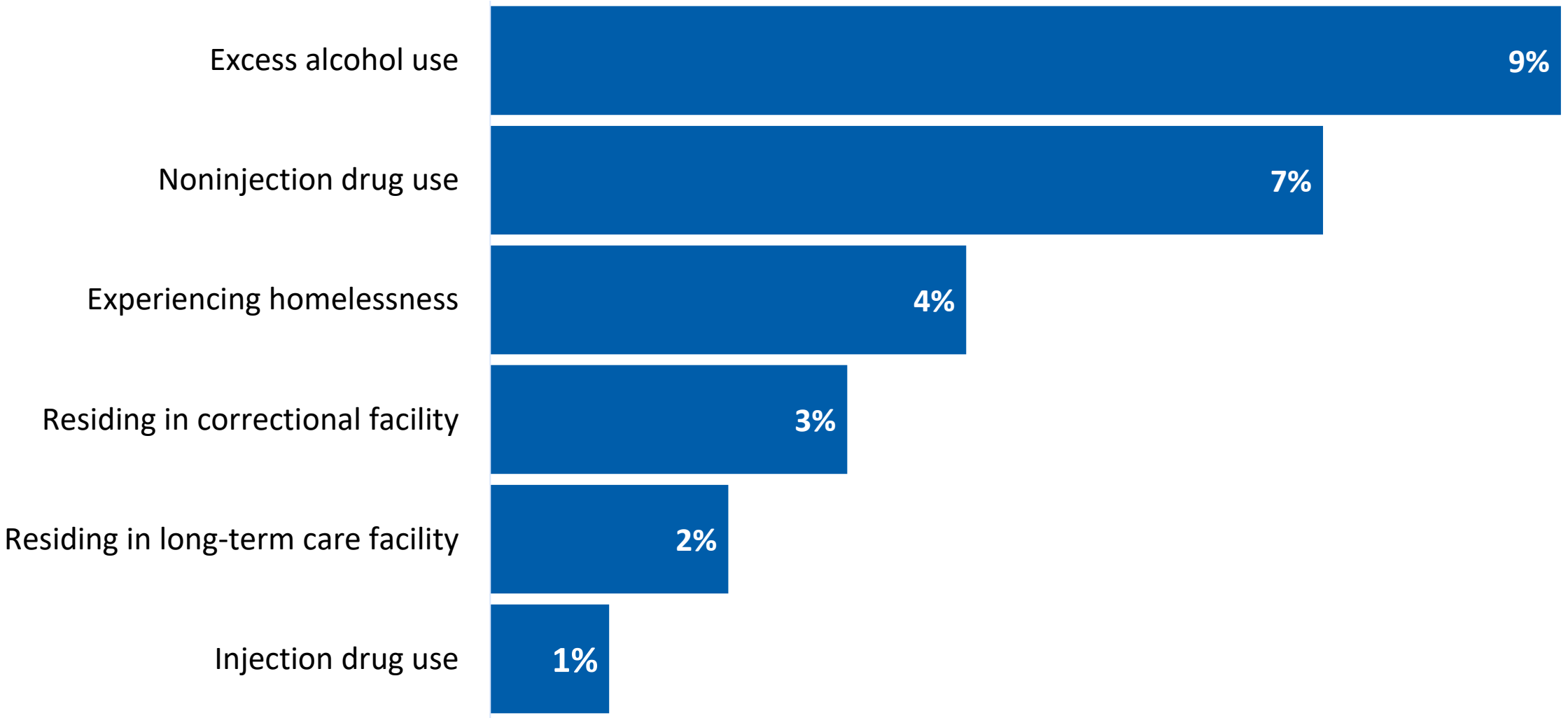
* Cases per 100,000 persons

Percentage of TB Cases Among Non-U.S.–born Persons by Year Since Initial Arrival in the United States at Diagnosis, 2020 (N=5,127)



* Years since arrival was missing/unknown for 585 cases (11.4%).

Percentage of Social Risk Factor Among Persons Aged ≥15 Years with TB, United States, 2020



TB Test Selection

Selecting a Test to Detect TB Infection - 1

- **IGRAs are preferred method of testing for**
  - Groups of people who have poor rates of returning to have TST read
  - Persons who have received BCG vaccine

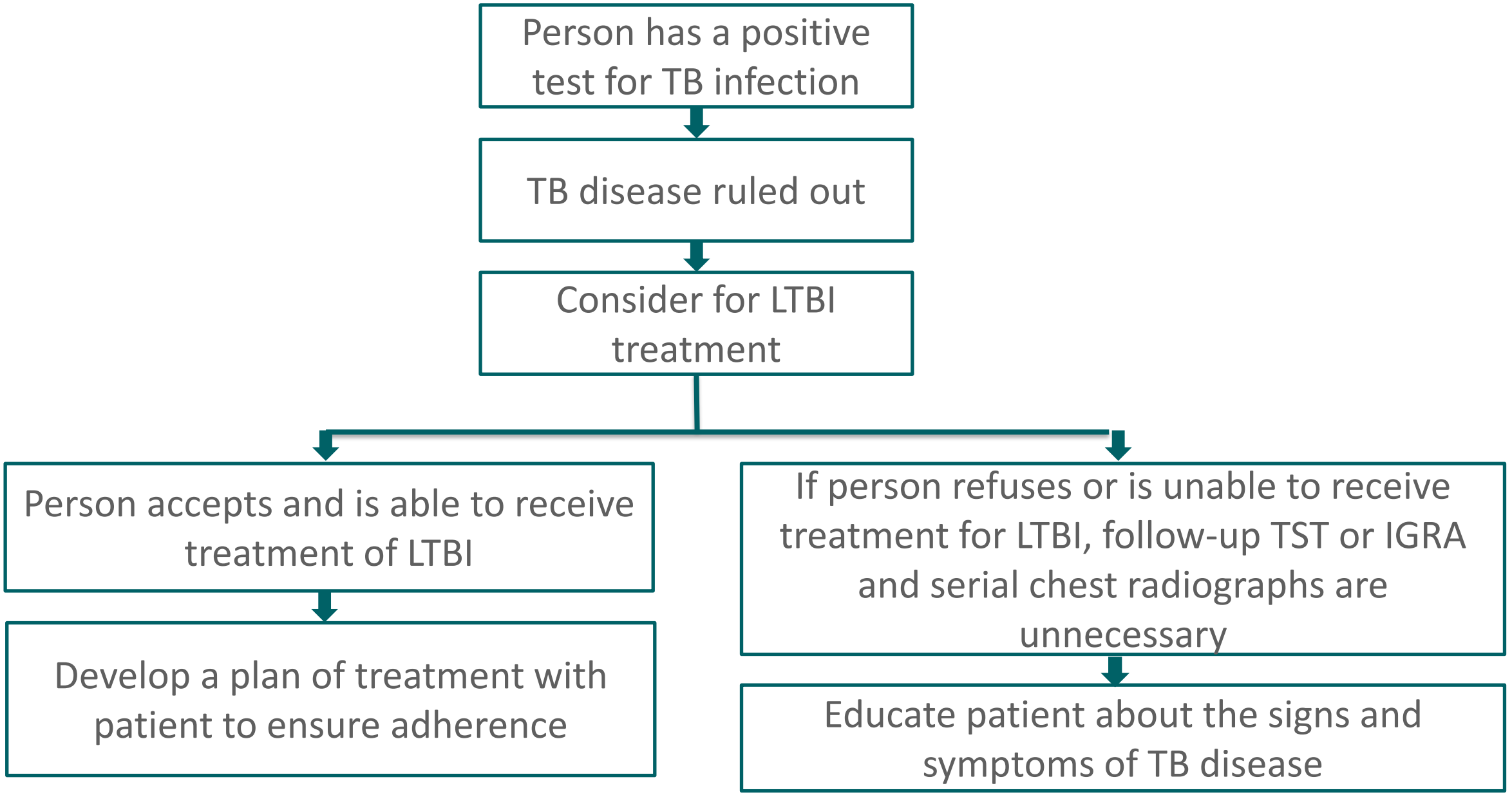
- **TST is the preferred method of testing for**
  - Children under the age of 5

Selecting a Test to Detect TB Infection - 2

Before initiating treatment for LTBI

- Either TST or IGRA can be used without preference for other groups that are tested for LTBI
- Routine testing with TST and IGRA is *NOT* recommended

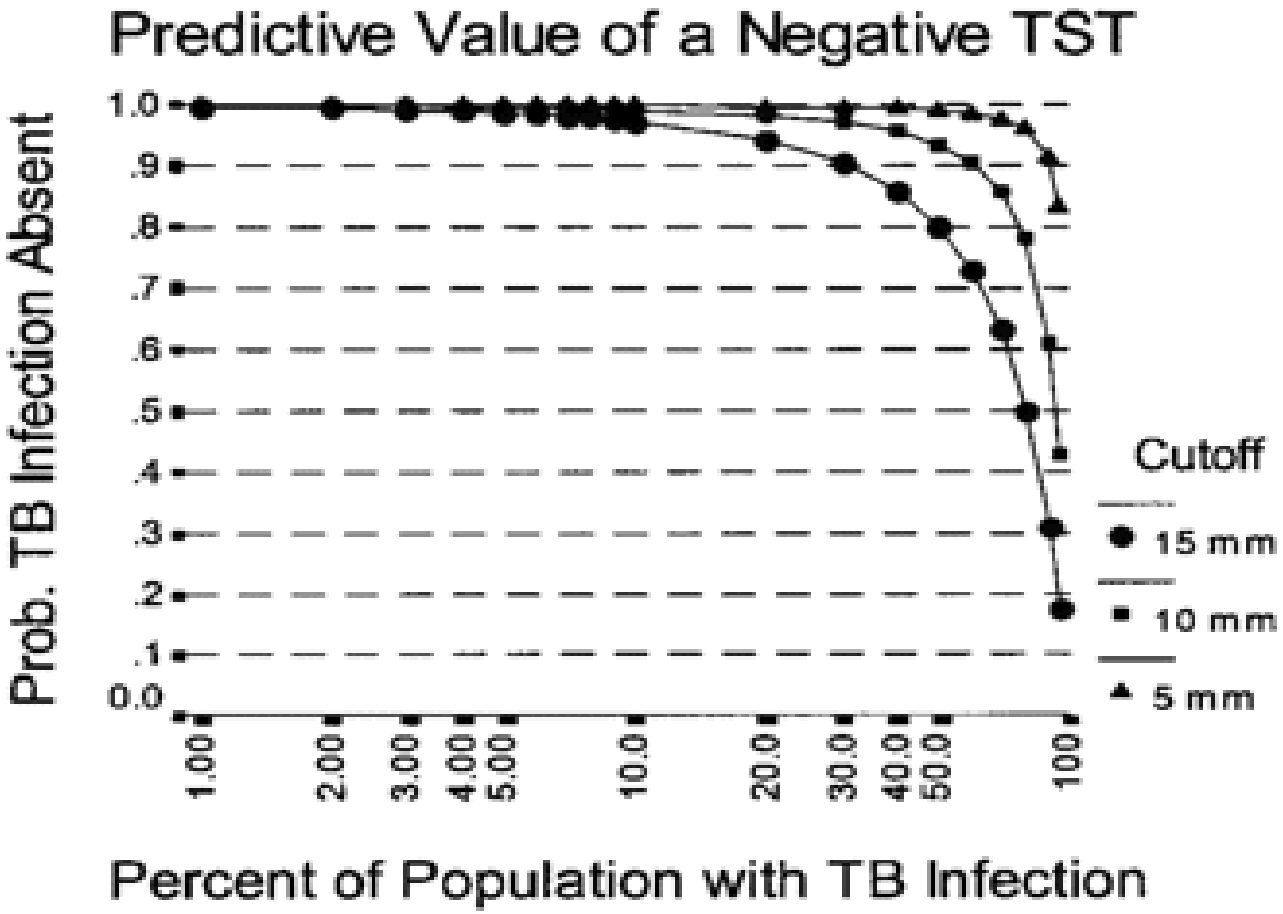
Evaluation of Persons with Positive TB Test Results



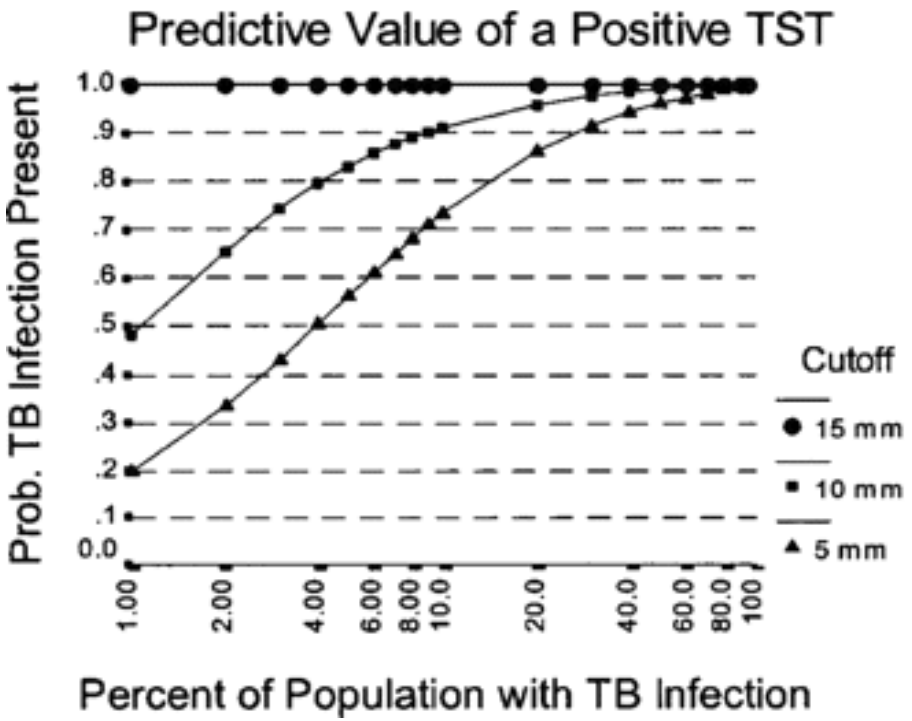
How to test for *M. tuberculosis* infection? TST vs. IGRA

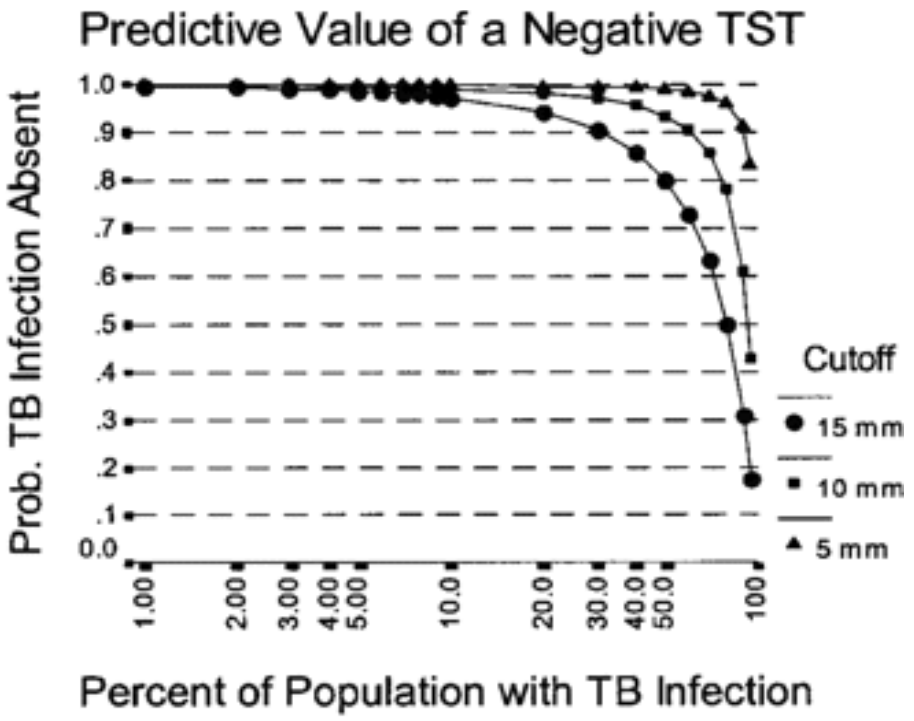
- **IGRA**
  - Results in one visit
  - **No cross reaction with BCG**
  - Limited time from blood draw to incubation in lab
  - Less subjective interpretation of results
  - More expensive
  - CDC: preferred for: **non-US–born**, those unlikely to return for follow-up care
- **TST**
  - Results in ≥2 visits
  - Can cross react with BCG; potential for false positives
  - Limited time for reading after placement
  - Might require more personnel time
  - CDC: preferred for children <5 years old

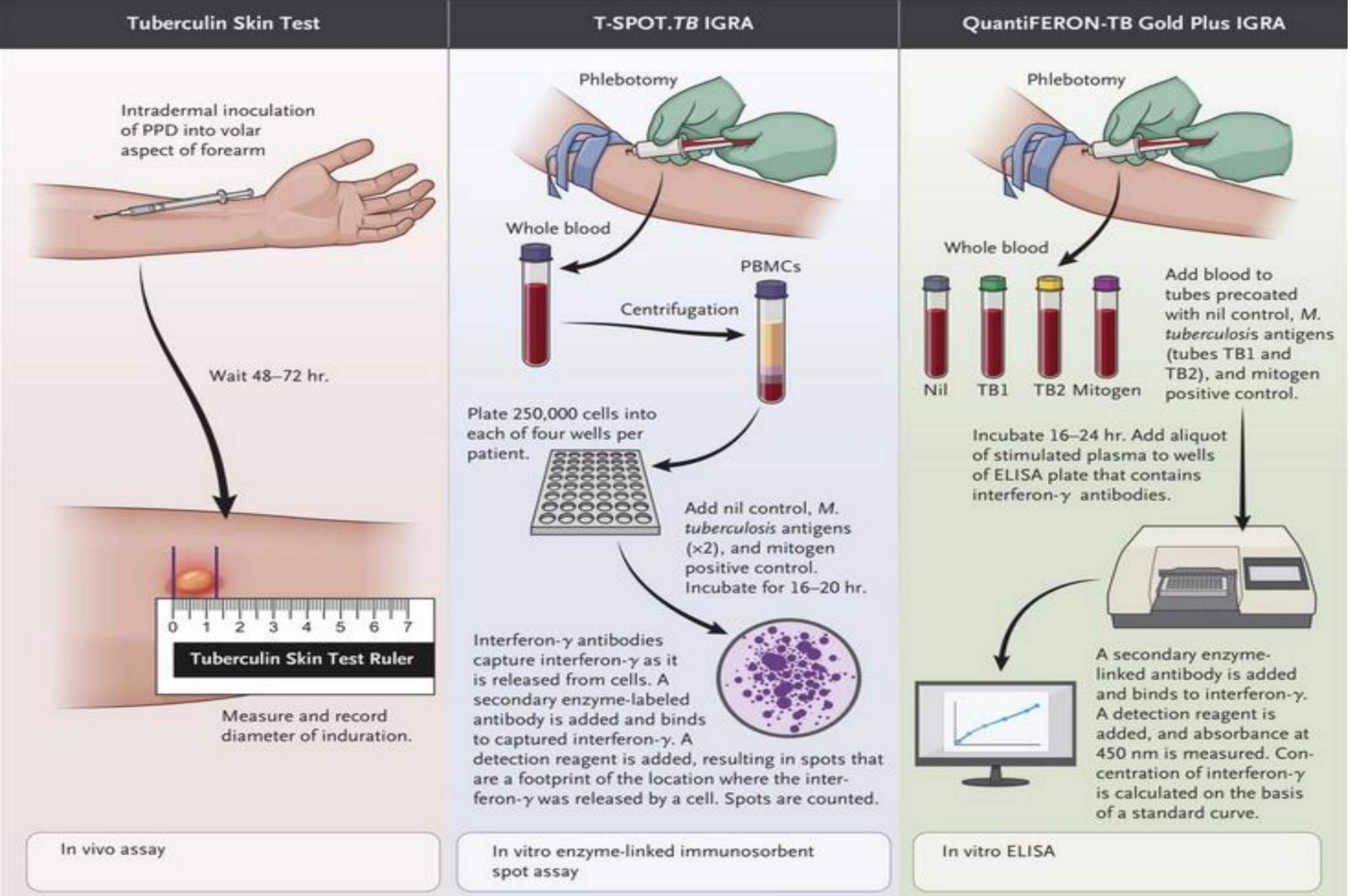
Why not just test everyone



Why not just test everyone







The NEW ENGLAND JOURNAL of MEDICINE

M Shah, SE Dorman. *N Engl J Med.* 2021;385:2271-2280.

Cases

Case 1

- **32-year-old woman born in high prevalence TB country presents to clinic for annual examination**
- **She's excited because she just got married, but does not want to have children for another 3–4 years**
- **She's taking oral contraceptives**
- **She has a + IGRA**
- **You're considering treatment for LTBI**
  - What are some considerations?

Case 2

- **50-year-old man from high prevalence TB country presents to clinic for annual examination**
- **He drinks 10 beers per day**
- **He has a positive IGRA**
- **You're considering treatment for LTBI**
  - What are some considerations?
  - When do you want to see him back in clinic?

Case 2

- **50-year-old man from high prevalence TB country presents to clinic for annual examination**
- **He drinks 10 beers per day**
- **He has a positive IGRA**
- **You're considering treatment for LTBI**
  - What are some considerations?
- **He starts vomiting after his 25th dose of rifampin**
  - Also has loss of appetite and is "itching a lot"

Case 3

- 40-year-old man from high incidence TB country is on LTBI regimen (12 weekly doses of isoniazid and rifapentine)
- After the 3rd dose, develops fever, flu-like symptoms, headache, and nausea
- What do you want to do?