

TB Infection: Identify! Report! Treat!

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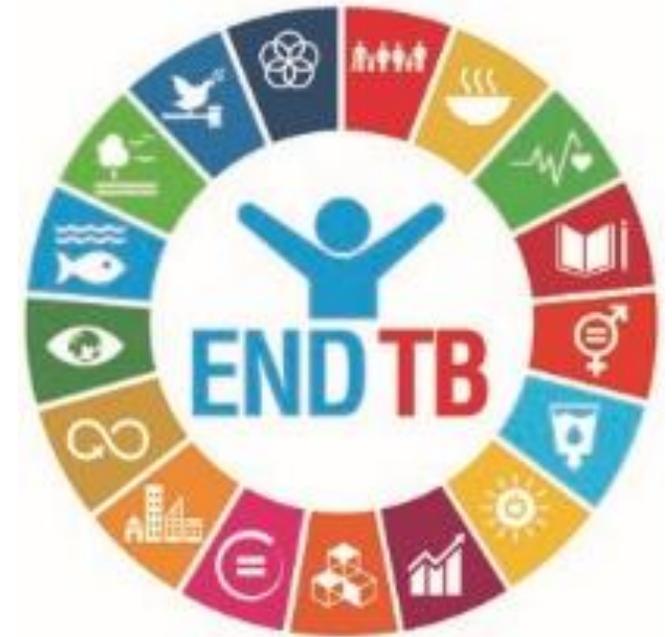
University of Florida

Goals:

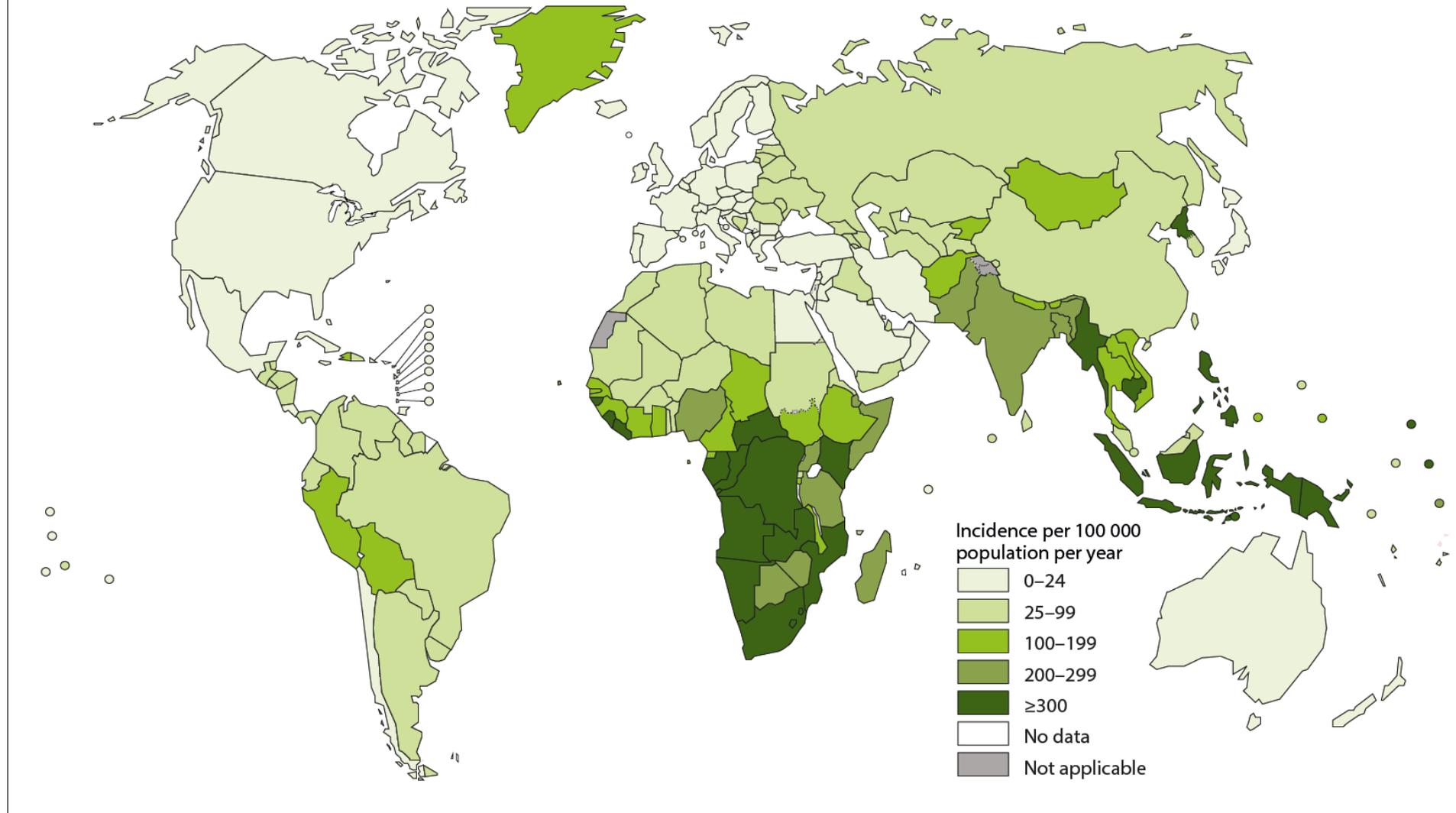
- Recognize why and whom to screen for TB infection
- Review the indications for treating TB infection
- Identify high priority groups for LTBI treatment
- Develop an LTBI treatment plan

Tuberculosis (Mtb)

- Tuberculosis (TB) is one of the top 10 causes of death worldwide
- In 2017, 10 million people fell ill with TB, and 1.6 million died from the disease (including 0.3 million among people with HIV)
- In 2017, an estimated 1 million children became ill with TB and 230 000 children died of TB (including children with HIV associated TB)
- Globally, TB incidence is falling at about 2% per year
- An estimated 54 million lives were saved through TB diagnosis and treatment between 2000 and 2017



Estimated TB incidence rates, 2017



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: *Global Tuberculosis Report 2018*. WHO, 2018.

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**TB ANYWHERE IS
EVERYWHERE**

TAKE ON TB

Too many people
in our country
still suffer from
tuberculosis (TB).

9,105 TB CASES REPORTED IN THE U.S. IN 2017

528

TB Deaths
in 2016

A Typical TB Case Requires:



PLUS

- X-rays
- Lab tests
- Follow-up & testing of contacts



Total cost to U.S.
for TB cases in 2017.

***Our current strategies are not enough to
achieve TB elimination in this century.***

Figure 1: Tuberculosis rates, Virginia and the United States, 1987-2017

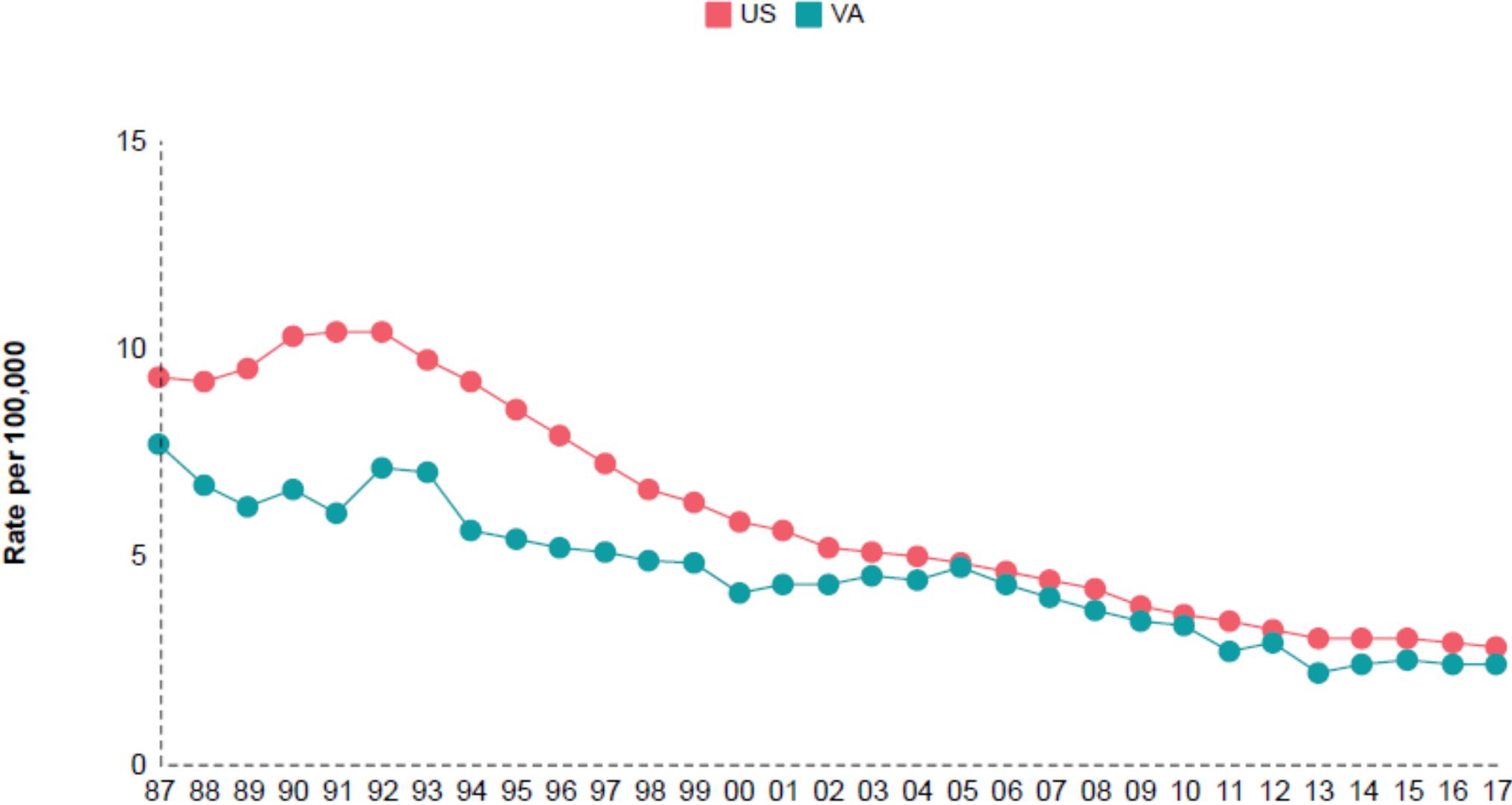
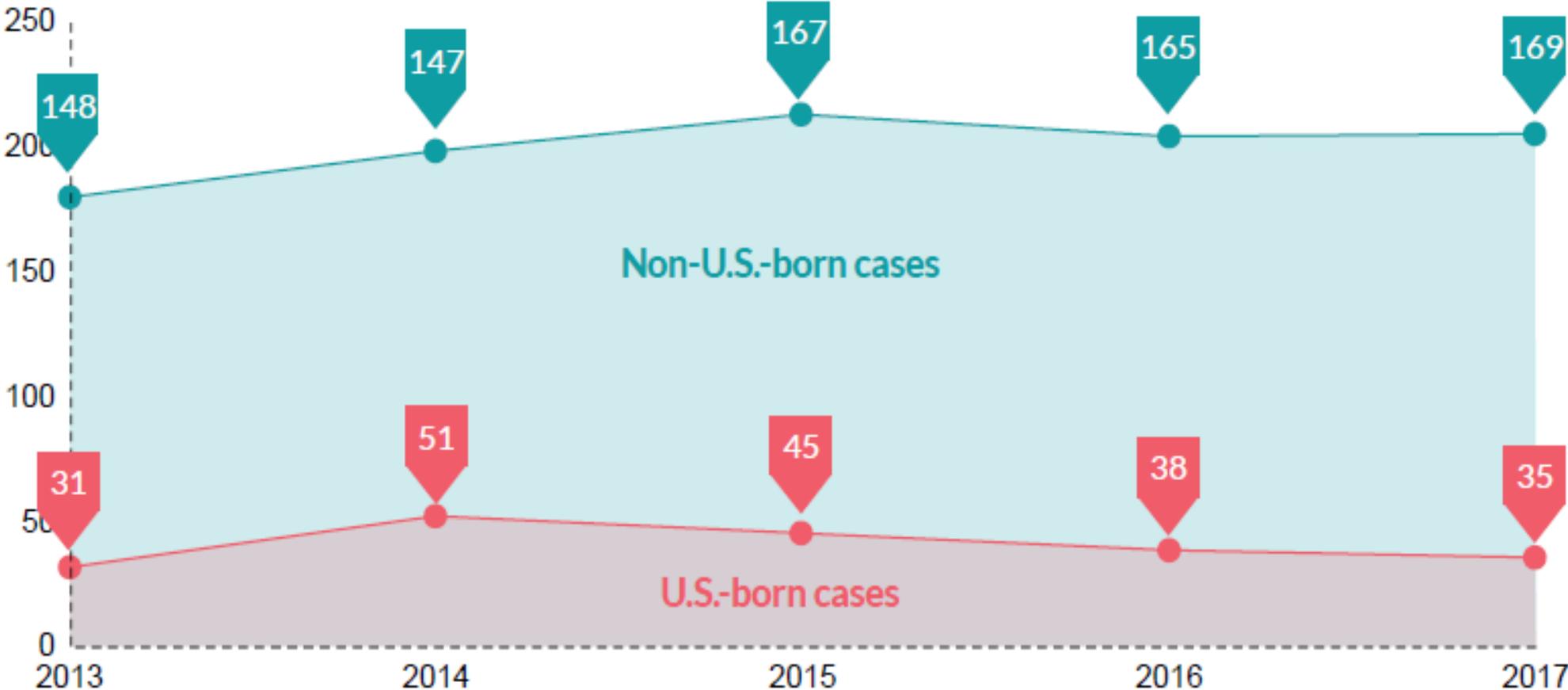


Figure 5: Non-U.S.-born and U.S.-born* Tuberculosis Cases, Virginia, 2013-2017



<http://www.vdh.virginia.gov/content/uploads/sites/112/2019/01/2017-VA-TB-Annual-Report.pdf>

Table 1: Selected Risk Factors of Tuberculosis Cases, Virginia, 2013-2017

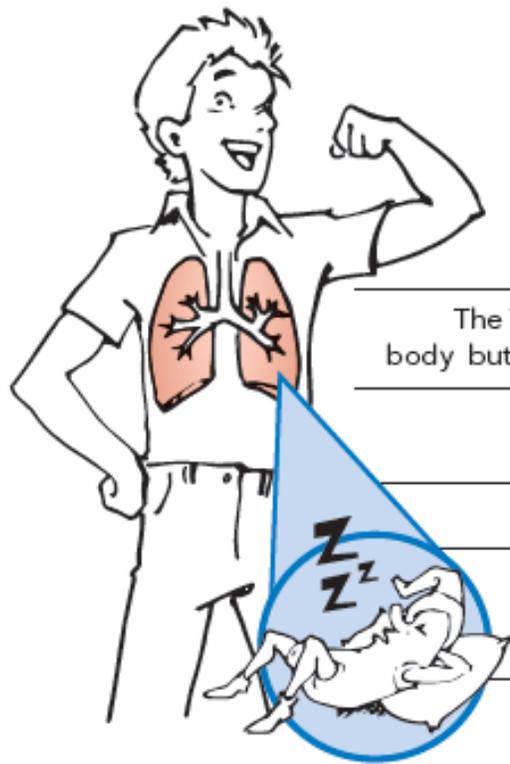
Total Cases	2013		2014		2015		2016		2017	
	No.	%								
Occupation										
Health Care	6	3.4	6	3.0	7	3.3	7	3.4	10	4.9
Migrant	0	0.0	1	0.5	0	0.0	0	0.0	0	0.0
Corrections	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Type of Residence										
Long Term Care	4	2.2	5	2.5	2	0.9	2	1.0	5	2.5
Prison/Jail	0	0.0	0	0.0	1	0.5	2	1.0	2	1.0
Homeless	10	5.6	8	4.0	1	0.5	2	1.0	6	2.9
Co-Morbidity										
Diabetes	26	14.5	33	16.7	45	21.2	32	15.8	33	16.2
HIV	10	5.6	10	5.1	7	3.3	8	3.9	3	1.5
Substance Use										
Alcohol	14	7.8	7	3.5	17	8.0	13	6.4	6	2.9
IDU	2	1.1	0	0.0	2	0.9	4	2.0	2	1.0
Non-IDU	7	3.9	1	0.5	4	1.9	8	3.9	4	2.0

1.5%

Proportion of 2017 TB cases among patients known to be HIV-infected

16.2%

Proportion of 2017 TB cases among patients known to have diabetes



Latent TB Infection

I am healthy.

The TB germs are "sleeping" in my body but could "wake up" in the future.

I have no symptoms.

My chest x-ray is normal.

I am not contagious.

I have a positive result on a TB skin test or blood test.

Active TB Disease

I have a serious illness that could kill me if left untreated.

The TB germs have "woken up".

I may have symptoms – cough, fever, weight loss, night sweats.

My chest x-ray may be abnormal.

I may be contagious and could infect other people when TB germs are spread through the air when I cough, laugh or speak.

I may have a positive result on tests of my phlegm.



Can my **Latent TB Infection** (sleeping germs) wake up and make me sick with **Active TB Disease**?

Yes, and certain factors increase my risk!

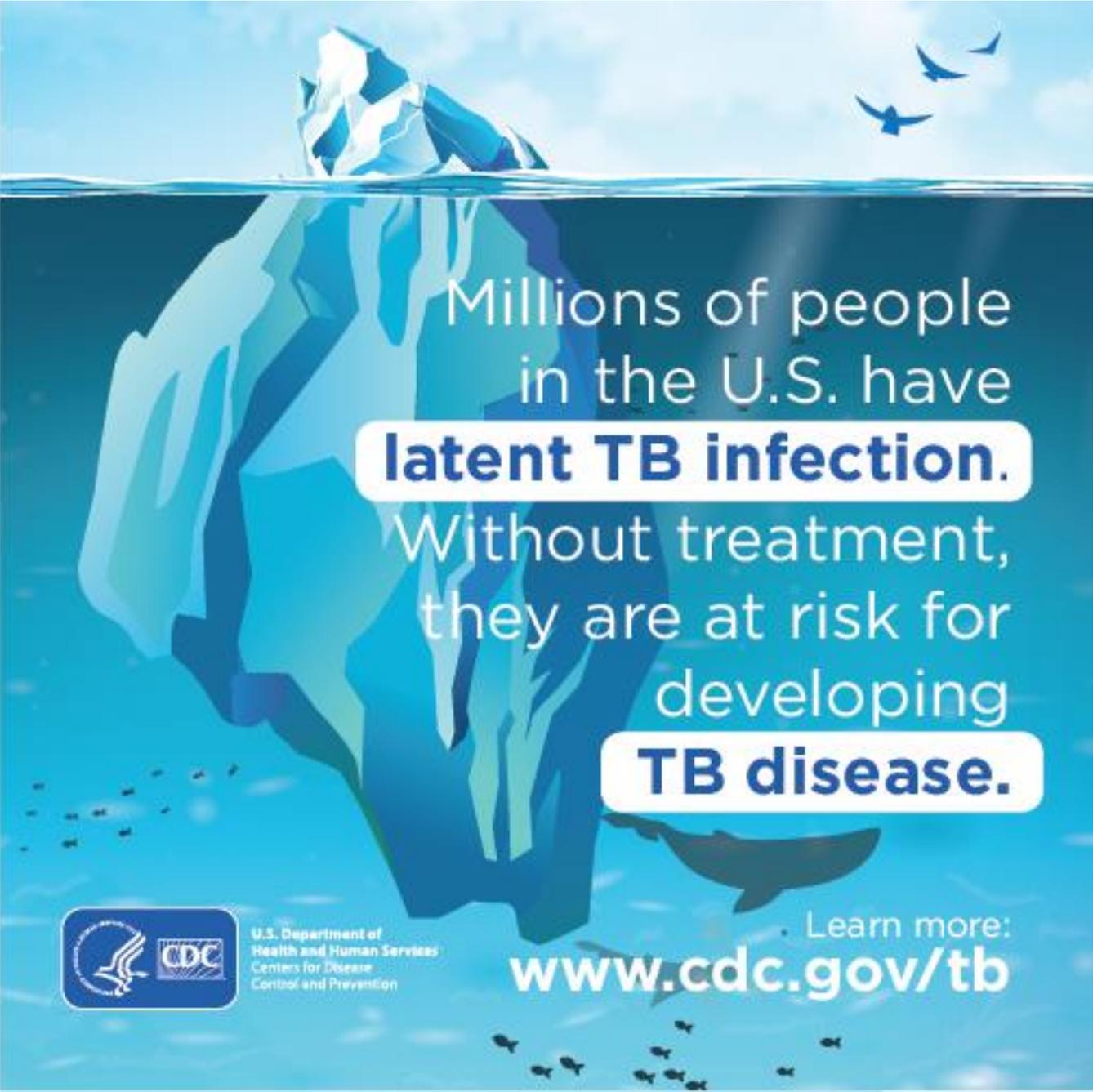
- I arrived recently from another country where TB is common.
- I have HIV.
- I was in close contact with someone with active TB disease.
- I have diabetes, kidney failure, or cancer.
- I had surgery to remove part of my stomach.
- I live or work in a hospital, jail, drug rehab center or shelter.
- I use injection drugs.
- I have received an organ transplant.
- I take certain medications that affect my immune system, like prednisone (steroids) or other pills or injections to treat certain types of skin, joint and gastrointestinal conditions.

If I have **Latent TB Infection**, can I reduce my chances of getting sick with **Active TB Disease**?

Yes, I can prevent tuberculosis!

I can take safe, effective medicines.





Millions of people
in the U.S. have
latent TB infection.

Without treatment,
they are at risk for
developing
TB disease.

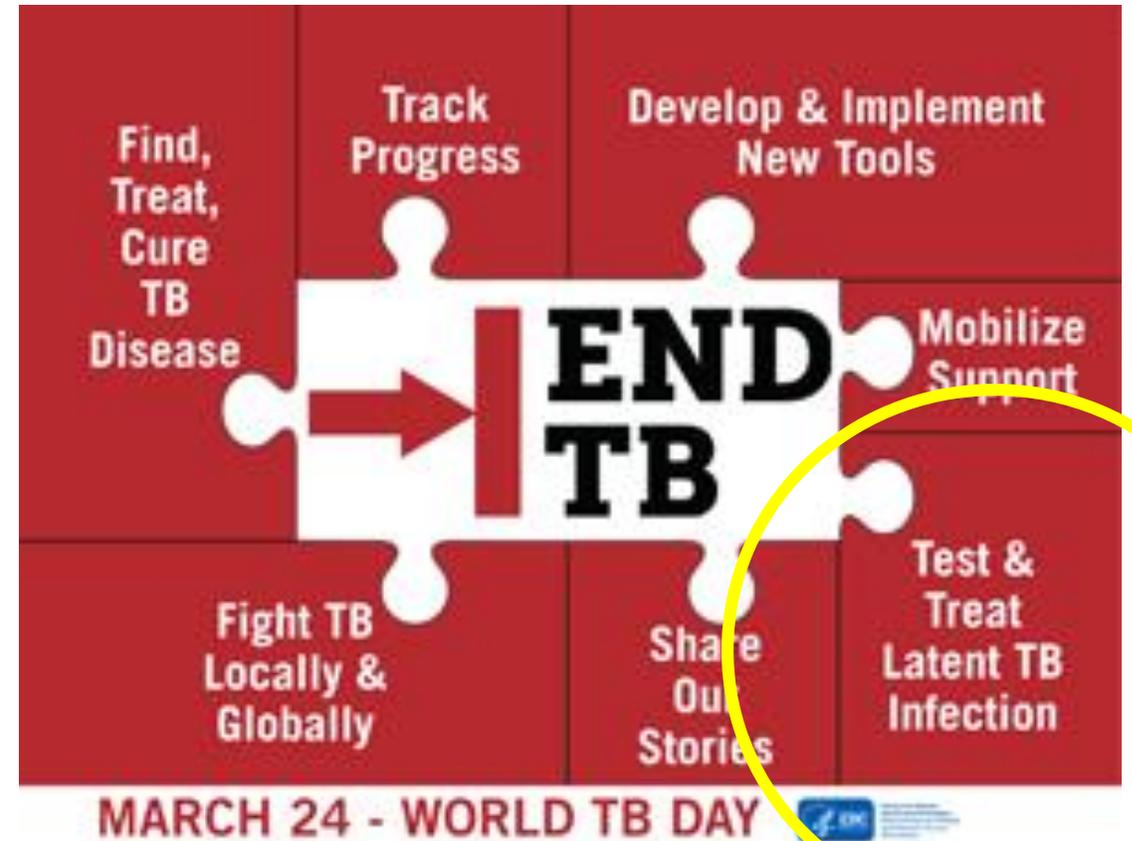


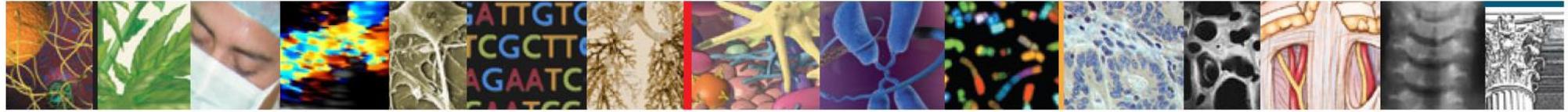
U.S. Department of
Health and Human Services
Centers for Disease
Control and Prevention

Learn more:
www.cdc.gov/tb

LTBI and TB Elimination: TB is a preventable disease

- 13 million people in the US have LTBI
- 4-6% of those infected will go on to develop active TB; half of these occur after recent exposure (~2 years)
- 93% of TB cases in non-US-born persons in the US attributable to reactivation of LTBI
- Proper diagnosis and treatment of LTBI can help significantly reduce the burden of TB disease





The NEW ENGLAND JOURNAL *of* MEDICINE

“From the perspective of an ethics of public health, the lack of action to reduce the rates of latent tuberculosis infection in the United States represents both the government’s failure to protect its people from infectious threats and society’s failure to provide care to its most vulnerable.”

Perspective
SEPTEMBER 21, 2017

Tuberculosis Elimination in the United States — The Need for Renewed Action

Ronald Bayer, Ph.D., and Kenneth G. Castro, M.D.

Screening for Latent Tuberculosis Infection in Adults

US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

- USPSTF recommends screening for LTBI in persons at increased risk for infection
- They found adequate evidence that:
 - 1) Accurate screening tests for LTBI are available,
 - 2) Treatment of LTBI provides a moderate health benefit in preventing progression to active disease
 - 3) Harms of screening and treatment are small

Screening for Latent Tuberculosis Infection in Adults US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

- USPSTF estimated that if a hypothetical cohort of 100,000 asymptomatic, high-risk adults were screened:
 - 52 to 146 active TB cases would be prevented
 - 7 to 67 cases of hepatotoxicity would occur
 - 111 persons would discontinue treatment due to adverse events
- Number needed to treat to prevent 1 case of LTBI from progressing to active TB would range from 111 to 314 (depending on patient risk for progression)

Who is at *increased risk* of infection with *Mtb*?

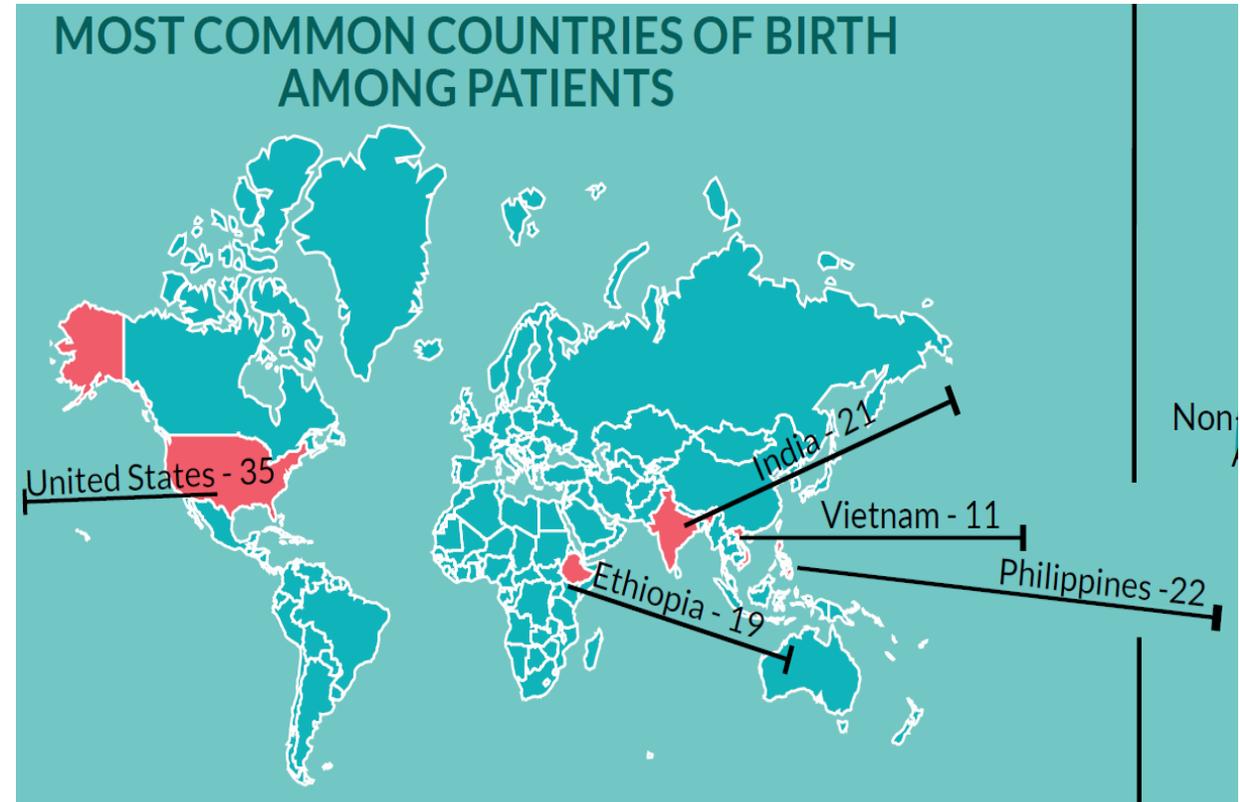
- A. Household contact or recent exposure to an active case
- B. Immigrants from high burden countries (>20/100,000)
- C. Mycobacteriology lab personnel
- D. Residents and employees of high-risk congregate settings
- E. All of the above

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- E. All of the above

Increased risk of *Mtb* infection

- Contacts to active cases
- Non-US-born individuals from Asia, Africa, Caribbean, Latin America, Mexico, South America, Pacific Islands or Eastern Europe
- *Low prevalence countries are USA, Canada, Japan, Australia, Western Europe, and New Zealand*



Increased risk of *Mtb* infection

- Persons who live in, or have lived in, high-risk congregate settings have a higher prevalence of active TB and increased risk of exposure:
- LTBI prevalence:
 - 23.1-87.6% among prisoners
 - 18.6-79.8% among homeless



Who is at *high risk* of progression from latent to active TB?

- A. Children age < 5
- B. HIV infection
- C. Abnormal CXR (fibrotic changes) consistent with prior TB
- D. Silicosis
- E. Immunosuppressive therapy
- F. All of the above

Table 1. Risk of progression to TB disease by age in untreated patients with LTBI ^{1,3}

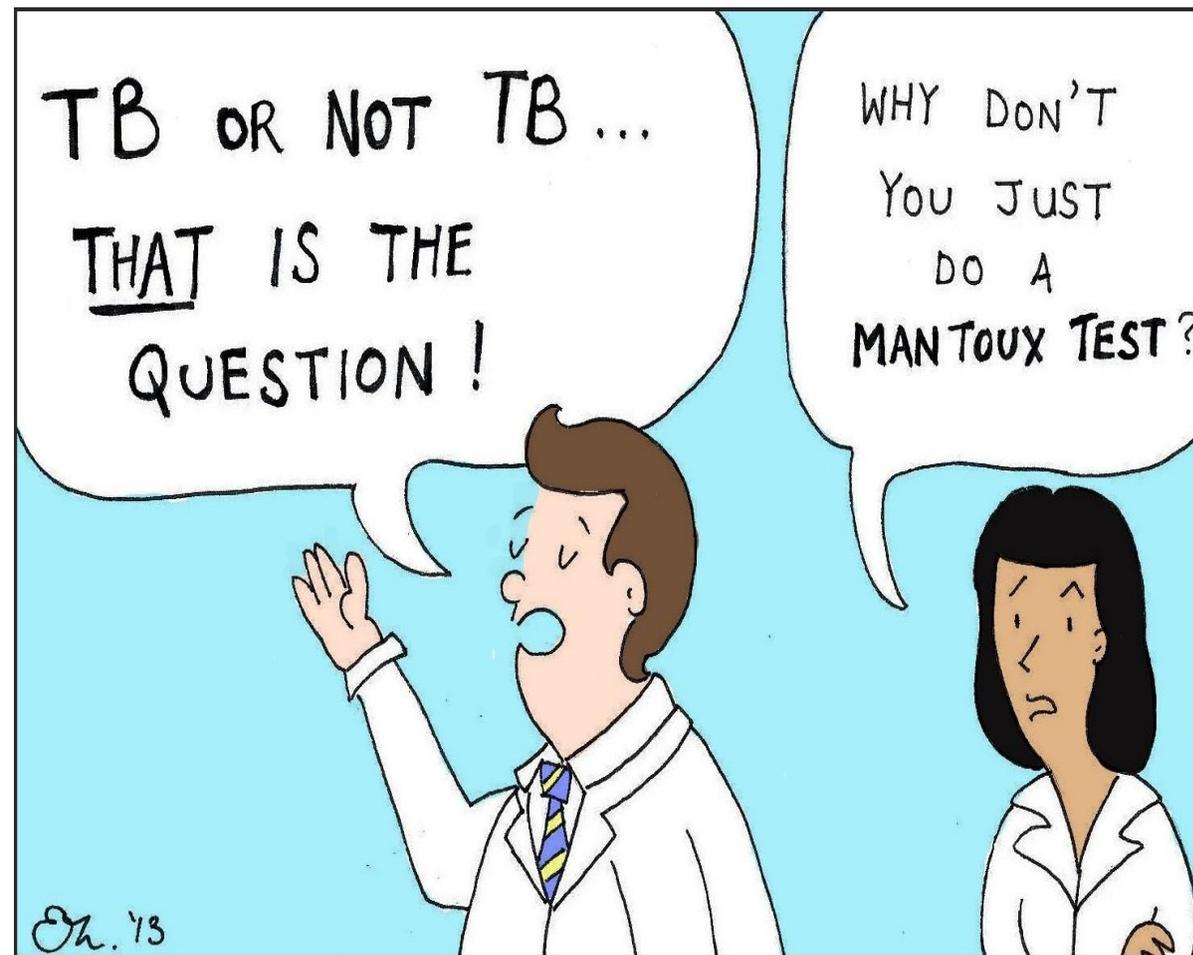
Age at Infection	Risk of TB Disease
Birth-12 months	43-50%
1-5 years	20-25%
6-10 years	2%
11-15 years	16%
Healthy Adults	5-10% lifetime risk
HIV Infected Adults	30-50% lifetime risk

Treatment of LTBI

- Studies have shown LTBI treatment reduces subsequent development of TB disease in the following patient groups:
 - Individuals with evidence of healed TB on CXR
 - Household contact of active TB patients
 - Native Alaskan communities
 - Residents of mental health facilities
 - Persons with HIV infection
 - Individuals treated with TNF Inhibitors
- This data is then extrapolated to patients at low (no risk factors) and intermediate risk (Diabetes, Chronic kidney disease) for progression to active disease

Goal of LTBI testing

- To identify those who will benefit from prophylactic therapy
- LTBI completion rates are historically low:
 - In one study, 83% of those diagnosed with LTBI started treatment, only 39% completed treatment
- Better tests, testing strategies and treatment regimens will allow resources to be focused on patients who are most deserving of evaluation and treatment of LTBI and result in increased therapy completions rates



Risk of Infection ↑	Groups with Increased Likelihood of Infection with Mtb	Benefit of Therapy	LTBI Testing Strategy		
			Likely to be Infected Low to Intermediate Risk of Progression (TST ≥ 10mM)	Likely to be Infected High Risk of Progression (TST ≥ 5mM)	
	Household contact or recent exposure of an active case	Yes	Likely to be Infected Low to Intermediate Risk of Progression (TST ≥ 10mM)	Likely to be Infected High Risk of Progression (TST ≥ 5mM)	
	Mycobacteriology laboratory personnel	Not demonstrated			
	Immigrants from high burden countries (>20 / 100,000)	Not demonstrated			
	Residents and employees of high risk congregate settings	Yes	Unlikely to be Infected (TST > 15mM)		
	None	Not demonstrated			
			Risk of Developing Tuberculosis if Infected →		
			Low	Intermediate (RR 1.3 -3)	High (RR 3-10)
			No risk factors	Clinical predisposition Diabetes Chronic renal failure Intravenous drug use	Children age less than 5 HIV infection Immunosuppressive therapy Abnormal CXR consistent with prior TB Silicosis
			Benefit of Therapy		
			Not demonstrated		Yes

LTBI Diagnostic Tools: Which test do you prefer?



- A. Tuberculin Skin Test (TST)
- B. Interferon- γ release assay (IGRA)

Tuberculin Skin Testing

- Inject 0.1 ml of standardized mix of TB proteins (purified protein derivative)
- Given intradermally on volar forearm
- Measure **induration** 48-72 hrs after placement
- Measure in millimeters, not “positive” or “negative”
- Should be interpreted by well-trained health care professional



Picture from: www.info.gov.hk/dh/diseases/CD/TB.htm

Tuberculin Skin Test

- **Pros:**

- Easy to perform
- Low cost
- Well-controlled studies support the use of TST to detect LTBI and guide prophylactic therapy
- Well-established definitions of TST conversion

- **Cons:**

- Requires two visits
- Inter and intra-reader variation
- False positive in prior BCG vaccination and NTM exposure

<https://www.cdc.gov/tb/publications/factsheets/testing.htm>

Classification of the Tuberculin Skin Test Reaction

An **induration of 5 or more millimeters** is considered positive in

- » HIV-infected persons
- » A recent contact of a person with TB disease
- » Persons with fibrotic changes on chest radiograph consistent with prior TB
- » Patients with organ transplants
- » Persons who are immunosuppressed for other reasons (e.g., taking the equivalent of >15 mg/day of prednisone for 1 month or longer, taking TNF- α antagonists)

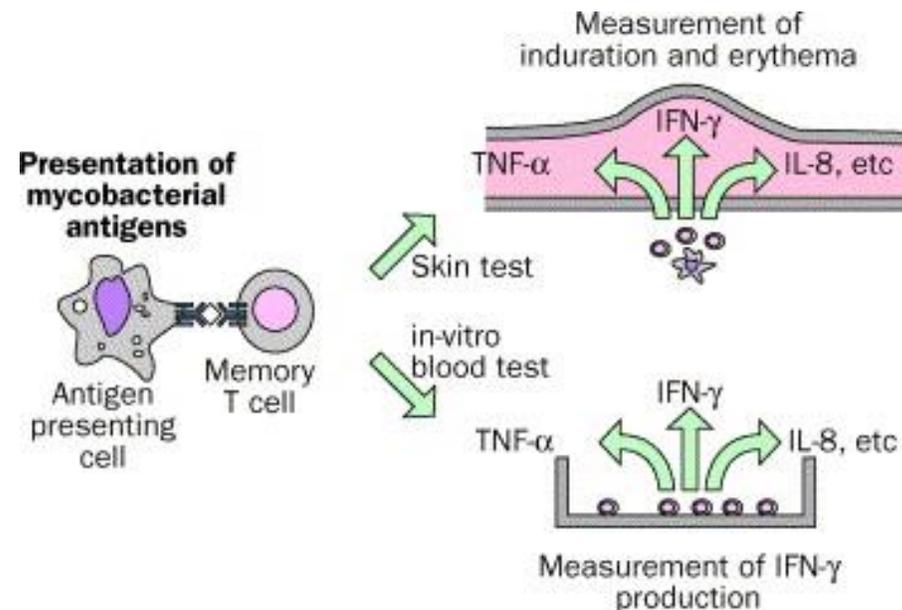
An **induration of 10 or more millimeters** is considered positive in

- » Recent immigrants (< 5 years) from high-prevalence countries
- » Injection drug users
- » Residents and employees of high-risk congregate settings
- » Mycobacteriology laboratory personnel
- » Persons with clinical conditions that place them at high risk
- » Children < 4 years of age
- » Infants, children, and adolescents exposed to adults in high-risk categories

An **induration of 15 or more millimeters** is considered positive in any person, including persons with no known risk factors for TB. However, targeted skin testing programs should only be conducted among high-risk groups.

Blood Tests for TB Infection

- Interferon Gamma Release Assays (IGRA)
- Developed in 2001
- Measures the interferon gamma (IFN- γ) released in response to *M.tuberculosis* antigens



IGRAS:

- T-SPOT®. *TB* (Oxford Immunotec):
 - positive, negative, indeterminate, borderline
- QuantiFERON®-TB Gold Plus (Qiagen)
 - positive, negative, indeterminate

IGRAs

PROS:

- Requires single patient visit
 - “One and done”
- Results can be available within 24 hours
- Does not boost responses measured by subsequent tests
- Prior BCG vaccination does not cause a false-positive result
- Largely unaffected by most environmental nontuberculous mycobacteria (NTM)
- Data suggest not affected by intravesicular BCG

CONS:

- Expensive
- Blood samples must be processed 8-30 hours after collection
- Errors in collecting or transporting blood specimens or in running and interpreting the assay can decrease accuracy
- Inconsistent test reproducibility
- Limited data on effect of IGRA-guided therapy on prevention of TB disease
- False positive can occur in individuals infected with: *M. marinum*, *M. kansasii*
- May be boosted by TST (>3 days to 3 months)

Which LTBI test should be performed?

36 yo Filipino lady presents to Civil Surgeon for medical evaluation to pursue permanent US resident status:

-She reports history of BCG as a child in the Philippines

-She moved to the US 5 years ago but returns to visit family in Manila for several weeks each year

- A. IGRA
- B. TST
- C. Both
- D. Neither test
- E. Either test

IGRA*

- IGRA preferred test in individuals 2 years or older who meet the following criteria:
 - 1) likely to be infected with *Mtb*,
 - 2) have a low to intermediate risk of disease progression,
 - 3) it has been determined that LTBI testing is warranted,
 - 4) either have a history of BCG vaccination or are unlikely to have their TST read

*A TST is an acceptable alternative, especially in situations where an IGRA is not available, too costly or too burdensome

LTBI Testing in BCG vaccination

- IGRAS are more specific and equally or more sensitive than TST in individuals who have received the BCG vaccination
- Therefore, false positive results are less likely than TST and unnecessary treatment and its accompanying risks can be avoided

Which LTBI test should be performed?

47 yo employee of local homeless shelter who was a contact to an infectious pulmonary TB case:

-no medical conditions

- A. IGRA
- B. TST
- C. Both
- D. Neither test
- E. Either test

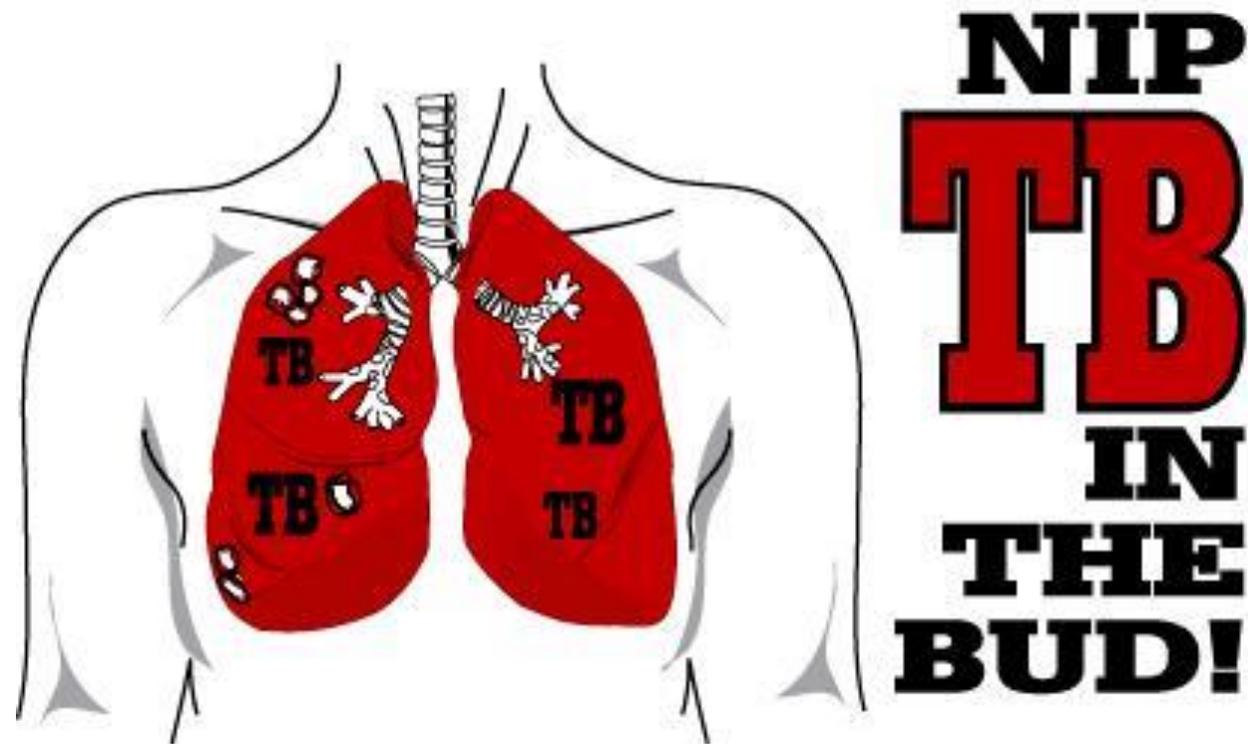
IGRA*

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 - 1) likely to be infected with *Mtb*,
 - 2) have a low to intermediate risk of disease progression,
 - 3) it has been determined that LTBI testing is warranted

*TST may be appropriate in a sizeable minority due to availability, feasibility cost or burden

Group	Testing Strategy	Considerations
<p>Likely to be Infected High Risk of Progression (TST \geq 5mM)</p>	<p>Adults Acceptable: IGRA OR TST Consider dual testing where a positive result from either result would be considered positive</p> <p>Children \leq 2 years of age Preferred: TST Acceptable: IGRA OR TST</p> <p>Consider dual testing where a positive result from either would be considered positive¹</p>	<p>Prevalence of BCG vaccination Expertise of staff and/or laboratory Test availability Patient perceptions Staff perceptions Programmatic concerns</p>
<p>Likely to be Infected Low to Intermediate Risk of Progression (TST \geq 10mM)</p>	<p>Preferred: IGRA where available Acceptable: IGRA or TST</p>	
<p>Unlikely to be Infected (TST $>$ 15mM)</p>	<p>Testing for LTBI is not recommended If necessary: Preferred: IGRA where available. Acceptable: Either IGRA OR TST</p> <p>For serial testing: Acceptable: Either IGRA OR TST</p> <p>Consider repeat or dual testing where a negative result from either would be considered negative²</p>	

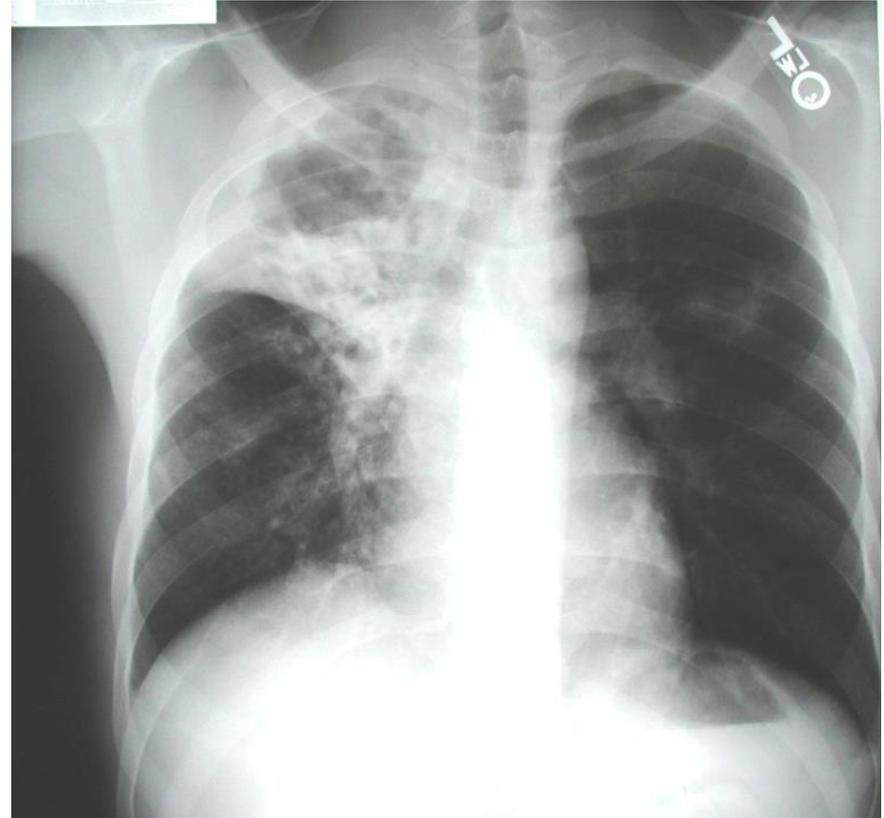
1. Performing a second diagnostic test when the initial test is negative is a strategy to increase sensitivity. This may reduce specificity, but the panel decided that this is an acceptable tradeoff in situations in which the consequences of missing LTBI (i.e., not treating individuals who may benefit from therapy) exceed the consequences of inappropriate therapy (i.e., hepatotoxicity).
2. Performing a confirmatory test following an initial positive result is based upon both the evidence that false-positive results are common among individuals who are unlikely to be infected with Mtb and the committee's presumption that performing a second test on those whose initial test was positive will help identify initial false-positive results.



Neither an IGRA nor TST can distinguish LTBI from active tuberculosis!

Evaluation of LTBI

- Assess for symptoms: fever, night sweats, weight loss, cough of *any* duration, lymphadenopathy
- CXR
- Assess for extrapulmonary TB:
 - more common in HIV
 - more common when $CD4 < 200$



36 yo Filipino lady presented to Civil Surgeon for evaluation for permanent US residency, positive IGRA.

- Her symptom screen and CXR are negative
 - You discuss the diagnosis of LTBI with her and the risk of developing active TB
 - She would like to take LTBI treatment to reduce her risk of developing active TB
 - Which LTBI treatment regimen do you recommend?
- A. 3 months of once-weekly Isoniazid and Rifapentine via directly-observed therapy
 - B. 9 months of Isoniazid
 - C. 4 months of Rifampin
 - D. No treatment → she has a low likelihood of having latent TB

LTBI Treatment Options

- 3HP: Isoniazid/Rifapentine once a week for three months via directly observed therapy
- 4R: 4 months of Rifampin
- 9H: 9 months of Isoniazid

3HP: Three months of isoniazid/rifapentine once weekly

- “The 12-week regimen”
- Recommended for LTBI treatment since 2011
- Short course regimens like 3HP are preferred for convenience and higher rates of treatment completions
- Systemic review performed to show that this regimen is effective, safe and has high treatment completion rates
- Given via directly observed therapy

3HP: LTBI Treatment Recommendations

- Individuals with LTBI, including those aged 2-17
- Individuals with LTBI, living with HIV, who are taking efavirenz or raltegravir antiretrovirals
- Given via directly observed therapy

Isoniazid

15 mg/kg rounded up to the nearest 50 or 100 mg;
900 mg maximum

Rifapentine

10.0–14.0 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

Isoniazid (INH) is formulated as 100 mg and 300 mg tablets. Rifapentine (RPT) is formulated as 150 mg tablets packed in blister packs that should be kept sealed until usage. New formulations with larger dosage per tablet and fixed-dose INH-RPT combinations are in development.

Source: Three months of weekly rifapentine and isoniazid for *Mycobacterium tuberculosis* infection (PREVENT TB). Information available at <http://clinicaltrials.gov/ct2/show/nct00023452?term=rifapentine&rank=9>.

3HP: Monitoring and side effects

- Consider a baseline hepatic chemistry blood test for older patients on an individual basis, especially for those taking medications for chronic medical conditions
- Order baseline hepatic chemistry blood tests (at least aspartate aminotransferase (AST)) for patients with specific conditions:
 - human immunodeficiency virus infection,
 - liver disorders, including viral hepatitis,
 - postpartum period (≤ 3 months after delivery),
 - regular alcohol usage,
 - intravenous (IV) drug usage

SYMPTOM CHECKLIST

The 12-Dose Regimen for Latent Tuberculosis (TB) Infection

Patient Name: _____



Normal Side Effects

Most people can take their TB medicines without any problems. The rifapentine medicine may cause your urine (pee), saliva, tears, or sweat to appear an orange-red color. This is normal and the color may fade over time.



STOP taking your medicine and **CALL** your TB doctor or nurse right away if you have any of the problems below:

- | | |
|---|---|
| <input type="checkbox"/> Dizzy or lightheaded when sitting or standing | <input type="checkbox"/> Skin or whites of your eyes appear yellow |
| <input type="checkbox"/> Less appetite, or no appetite for food | <input type="checkbox"/> Skin rash or itching |
| <input type="checkbox"/> Stomach upset, nausea, or vomiting | <input type="checkbox"/> Bruises, or red or purple spots on your skin that you cannot explain |
| <input type="checkbox"/> Stomach pain or stomach cramps | <input type="checkbox"/> Nosebleeds, or bleeding from your gums or around your teeth |
| <input type="checkbox"/> Pain in your lower chest or heartburn | <input type="checkbox"/> Shortness of breath |
| <input type="checkbox"/> Flu-like symptoms with or without fever | <input type="checkbox"/> Pain or tingling in your hands, arms, or legs |
| <input type="checkbox"/> Severe tiredness or weakness | <input type="checkbox"/> Feelings of sadness or depression |
| <input type="checkbox"/> Fevers or chills | |
| <input type="checkbox"/> Severe diarrhea or light colored stools (poop) | |
| <input type="checkbox"/> Brown, tea-colored, or cola-colored urine | |



Please talk to your doctor or nurse if you have any questions or concerns about treatment for latent TB infection.

Doctor/Clinic Contact Information

Name of the staff caring for you: _____

Phone number: _____

Address: _____

Hours: _____



Centers for Disease
Control and Prevention
National Center for HIV/AIDS,
Viral Hepatitis, STD, and
TB Prevention

www.cdc.gov/tb

Other LTBI Treatment Options:

Rifampin (10 mg/kg [max. 600 mg]) daily for 4 months

Pros:

- High completion rates due to short course
- Well-tolerated
- Effective

Cons:

- Drug interactions: warfarin, oral contraceptives, methadone

Other LTBI Treatment Options:

Isoniazid (5 mg/kg [max. 300 mg]) daily for 9 months

Pros:

- Few drug interactions
- Effective (60-90%)

Cons:

- Lower rates of completion due to duration
- Risk of hepatitis (incidence of 1/1000 persons)
- Peripheral neuropathy in 2% of patients → give B6

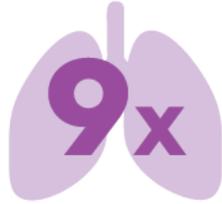
TB CAN HAPPEN ANYWHERE & TO ANYONE!

To eliminate TB, we must reach the hardest hit populations.

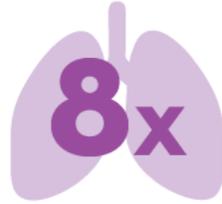
TB case rates are:



Higher for
Asians
than whites.



Higher for
African Americans
than whites.



Higher for
Hispanics/Latinos
than whites.



7 out of every 10
TB cases occur among non-U.S. -born persons.

ELIMINATING TB REQUIRES A COMPREHENSIVE APPROACH.

CDC is committed to fighting TB whenever & wherever it occurs through:



Vigilant Surveillance



Better Diagnostics
& Treatments



Testing & Treatment of
High-Risk Populations



Education of
Health Care Providers

Thank you!