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)
M. tuberculosis transmission and pathogenesis
M. tuberculosis transmission and pathogenesis

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
**M. tuberculosis** transmission and pathogenesis

Patient with TB disease → Contact → Latent tuberculosis infection (LTBI) 20–30%
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

Patient with TB disease → Contact → 20–30% → Latent tuberculosis infection (LTBI) → 10% Lifetime risk → Patient with TB disease
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?

Find and treat people with TB disease
In the United States, directly observed therapy
Find contacts and evaluate them for TB disease
Administer infection control precautions
Limit exposure to persons with TB disease
(i.e. limit number of contacts)
How do we stop *M. tuberculosis* transmission?

Find and treat people with LTBI

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

Contact → 20–30% → Latent tuberculosis infection (LTBI) → 10% → Patient with TB disease
How do we stop *M. tuberculosis* transmission?

Give BCG vaccine (not in the United States)

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

Does not prevent pulmonary TB
Epidemiology
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 without HIV infection
TB prevalence varies

Progress Towards TB Elimination, United States, 1982–2021

- 26,673 TB cases in 1992
  - Incidence rate: 10.4 per 100,000

- 7,882 TB cases in 2021
  - Incidence rate: 2.4 per 100,000

Elimination threshold: ~330 cases or <1 case per 1,000,000 population
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)

Origin of birth unknown, <1%

U.S.-born, 28%
(Rate: 0.8 per 100,000)

Non-U.S.–born 71%
(Rate: 12.5 per 100,000)

*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)

- <1 year: 10%
- 1-4 years: 15%
- 5–9 years: 14%
- 10–14 years: 10%
- 15–19 years: 7%
- 20–24 years: 9%
- 25–29 years: 6%
- 30–34 years: 6%
- 35–39 years: 4%
- ≥40 years: 9%

*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

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Non-U.S.–born persons (N=5,626)</th>
<th>U.S.-born persons (N=2,223)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Black African or American</td>
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<tr>
<td>White</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Native Hawaiian or Other Pacific Islander</td>
<td>5.7</td>
<td>5.7</td>
</tr>
<tr>
<td>Multiple Race</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>3.0</td>
<td>3.0</td>
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</table>

*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

- **Diabetes mellitus**
  - Total: 24%
  - U.S.-born: 17%
  - Non-U.S.-born: 27%

- **Non-HIV immunosuppression**
  - Total: 17%
  - U.S.-born: 9%
  - Non-U.S.-born: 9%

- **Contact with infectious TB**
  - Total: 6%
  - U.S.-born: 12%
  - Non-U.S.-born: 4%

*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)

- Symptoms: None
- Tests:
  - Usually have positive test for TB infection (TB skin test or interferon-gamma release assay)
  - Chest radiograph: Normal

Patient with TB disease → Contact → 20–30% → Latent tuberculosis infection (LTBI)
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
▪ 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.
Among non-U.S.–born, *M. tuberculosis* infection prevalence increases with age.
Among non-U.S.–born, *M. tuberculosis* infection prevalence increases with age
What could we do about it?
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?

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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?

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- **Prevalence:** 0.006 or 0.6%
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- **NPV:** 99%
  - 3 people with infection test negative
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**M. tuberculosis infection**

- **Sensitivity:** 70%
- **Specificity:** 98%
- **Prevalence:** 0.06 or 6%
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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 \( \text{M. tuberculosis} \) infection acquired in the remote past
  - More than \( \frac{1}{2} \) 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


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

1. Republic of the Marshall Islands: 170 cases per 100,000 persons
2. Republic of the Congo: 101 cases per 100,000 persons
3. Mongolia: 77 cases per 100,000 persons
4. Bhutan: 70 cases per 100,000 persons
5. Myanmar: 70 cases per 100,000 persons
6. Somalia: 70 cases per 100,000 persons
7. Nepal: 61 cases per 100,000 persons
8. Federated States of Micronesia: 59 cases per 100,000 persons
9. Guinea: 51 cases per 100,000 persons
10. Ethiopia: 47 cases per 100,000 persons

* 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)

~1/3 of cases occurred 20+ years after U.S. arrival

* 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

- Excess alcohol use: 9%
- Noninjection drug use: 7%
- Experiencing homelessness: 4%
- Residing in correctional facility: 3%
- Residing in long-term care facility: 2%
- Injection drug use: 1%
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

Person has a positive test for TB infection

TB disease ruled out

Consider for LTBI treatment

Person accepts and is able to receive treatment of LTBI

Develop a plan of treatment with patient to ensure adherence

If person refuses or is unable to receive treatment for LTBI, follow-up TST or IGRA and serial chest radiographs are unnecessary

Educate patient about the signs and symptoms of TB disease
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
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?