The Tip of the Iceberg: Expanding Latent Tuberculosis Infection Testing and Treatment to Accelerate Tuberculosis Elimination

Philip LoBue, MD
Disclosure

- I have no relevant financial disclosures
Learning objectives

- At the conclusion of this presentation, participants should be able to
  1. Explain why LTBI testing and treatment is an important component of the national strategy for TB elimination
  2. List new opportunities for expanding LTBI testing and treatment
  3. List key components of medical provider and community engagement in expanding LTBI testing and treatment
Outline

- Role of latent tuberculosis infection (LTBI) testing and treatment in USTB elimination strategy
- Modeling of LTBI testing and treatment
- New opportunities
- Challenges
- What is needed to address LTBI
  - Engagement of private providers and affected communities
  - Role of health department
Elements of National Elimination Strategy

- Ending Neglect: The Elimination of Tuberculosis in the U.S.
- Institute of Medicine Report published in 2000
- CDC response includes 6 goals that are elements of elimination strategy in United States
6 Goals

- Main control of TB
- **Accelerate the decline**
- Develop new tools
- Reduce the global TB burden
- Mobilize and sustain support
- Track Progress
Goal II: Accelerate the decline

Advance toward TB elimination through targeted testing and treatment of persons with latent TB infection, appropriate regionalization of TB control activities, rapid recognition of TB transmission using DNA fingerprinting methods, and rapid outbreak response.
Why Focus on Latent TB Infection?

- Modeling
- New Opportunities
Reaching TB Elimination (<1 case per 1 million population)
Hill et al. Modelling tuberculosis trends in the USA

2 x = doubling rate of LTBI treatment; 4 x = quadrupling rate of LTBI treatment
Decrease LTBI Among Foreign-Born Persons to 25% of Current Level

2 x = doubling rate of LTBI treatment; 4 x = quadrupling rate of LTBI treatment
Opportunities to Better Address LTBI

- Relatively low burden of TB disease in the US
- Very high treatment completion rates; not much room for improvement
  - Can we reduce diagnostic delays? No easy answer
- Most TB cases in the US result from reactivation of LTBI
- Newer tests that have advantages in key populations
- Newer and better treatment regimens
- Increased insurance coverage through Affordable Care Act
  - Recommendation by US Preventive Services Task Force
Where are we? Where do we have to go?

Reported TB Cases, United States, 1982–2015

- Elimination threshold: ~300 cases
- 9,563 cases in 2015
Completion of TB Therapy, United States, 1993 – 2011*

* Updated as of June 11, 2014. Data available through 2011 only.

Note: Includes persons alive at diagnosis, with initial drug regimen of one or more drugs prescribed, who did not die during therapy. Excludes persons with initial isolate rifampin resistant, or patient with meningeal disease, or pediatric patient (aged <15) with miliary disease or positive blood culture.
Updated Estimate of Recent TB Transmission


- Used a field-validated plausible source-case method to estimate cases likely resulting from recent transmission during January 2011–September 2014

- Of 26,586 genotyped cases, 14% were attributable to recent transmission

- Remaining 86% likely result from reactivation of LTBI
Key Risk Groups for TB in the United States

- **Foreign-born**: 67% of cases; case rate 13 times higher than US-born
  - Mexico, Philippines, Vietnam, China, India top 5 countries
- **Racial/ethnic minorities**: ~85% of cases; case rates 7-28 times higher than whites
- **HIV infected**: ~7% of cases
- **Homeless**: ~6% of cases
- **Incarcerated**: ~4% of cases
- **Substance abuse**: 7-12% of cases
LTBI Testing: Advantages of Interferon-gamma Release Assays (IGRAs) in Key Populations

- **Foreign-born persons with BCG vaccination**
  - No cross-reaction with BCG so no false positive tests due to BCG

- **One visit for blood draw**
  - Do not have to re-test persons who miss TST reading
  - Advantage in groups that are particularly unlikely to follow up for second visit (e.g., homeless)
  - Only have to track down persons with positive test results
Better Treatment for LTBI

- 12-dose, once-weekly isoniazid and rifapentine (3HP)
- 4 months of daily rifampin (4R)
- Both regimens have better completion rates and less hepatotoxicity than 9 months of isoniazid (9H)
The Affordable Care Act (ACA) and Insurance Coverage

- More people are insured since implementation of ACA
- Increases in coverage are greater in low-income groups and in racial/ethnic minorities
  - Groups at higher risk for TB
Quarterly estimates of the Uninsured Rate
Gallup-Healthways Well-Being Index, 2012-2015

Source: Office of the Assistant Secretary for Planning and Evaluation (ASPE) analysis of Gallup-Healthways Well-Being Index survey data through 3/4/15.
### Insurance Coverage Under ACA by Medicaid Expansion and Federal Poverty Level (FPL)

<table>
<thead>
<tr>
<th></th>
<th>Baseline Uninsured Rate</th>
<th>Q1 2014</th>
<th>Q3 2014</th>
<th>Q1 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-expansion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;138% of FPL</td>
<td>61.8</td>
<td>2.7</td>
<td>-0.9</td>
<td>-7</td>
</tr>
<tr>
<td>139-400% of FPL</td>
<td>22.2</td>
<td>-4.7</td>
<td>-7.3</td>
<td>-10.1</td>
</tr>
<tr>
<td>&gt;400% of FPL</td>
<td>1.9</td>
<td>0.4</td>
<td>-0.6</td>
<td>-1.1</td>
</tr>
<tr>
<td><strong>Expansion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;138% of FPL</td>
<td>55.0</td>
<td>-2.7</td>
<td>-5.5</td>
<td>-13</td>
</tr>
<tr>
<td>139-400% of FPL</td>
<td>18.1</td>
<td>-4.1</td>
<td>-8.3</td>
<td>-9.5</td>
</tr>
<tr>
<td>&gt;400% of FPL</td>
<td>1.8</td>
<td>-0.4</td>
<td>-1.3</td>
<td>-1.3</td>
</tr>
</tbody>
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## Insurance Coverage Under ACA by Race/Ethnicity

<table>
<thead>
<tr>
<th></th>
<th>Baseline Uninsured Rate</th>
<th>Q1 2014</th>
<th>Q3 2014</th>
<th>Q1 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Whites</strong></td>
<td>14.3</td>
<td>-1.7</td>
<td>-4.7</td>
<td>-5.3</td>
</tr>
<tr>
<td><strong>African Americans</strong></td>
<td>22.4</td>
<td>-4.5</td>
<td>-7.2</td>
<td>-9.2</td>
</tr>
<tr>
<td><strong>Latinos</strong></td>
<td>41.8</td>
<td>-4.1</td>
<td>-5.9</td>
<td>-12.3</td>
</tr>
</tbody>
</table>

Change in Percentage Points from Baseline Trend
ACA and US Preventive Services Task Force (USPSTF)

- In 2016, USPSTF recommends that LTBI testing should be done with grade B
- ACA mandates that USPSTF recommendations with grade A or B be covered by insurance with no co-pay
<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults who are at increased risk for tuberculosis</td>
<td>The USPSTF recommends screening for latent tuberculosis infection (LTBI) in populations that are at increased risk.</td>
<td>B</td>
</tr>
<tr>
<td>Grade</td>
<td>Definition</td>
<td>Suggestions for Practice</td>
</tr>
<tr>
<td>-------</td>
<td>---------------------------------------------------------------------------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>A</td>
<td>The USPSTF recommends the service. There is high certainty that the net benefit is substantial.</td>
<td>Offer or provide this service.</td>
</tr>
<tr>
<td>B</td>
<td>The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.</td>
<td>Offer or provide this service.</td>
</tr>
<tr>
<td>C</td>
<td>The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.</td>
<td>Offer or provide this service for selected patients depending on individual circumstances.</td>
</tr>
<tr>
<td>D</td>
<td>The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.</td>
<td>Discourage the use of this service.</td>
</tr>
<tr>
<td>I</td>
<td>The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.</td>
<td>Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.</td>
</tr>
</tbody>
</table>
**Patient Population Under Consideration**

This recommendation applies to asymptomatic adults age 18 years and older who are at increased risk for tuberculosis (see the “Assessment of Risk” section for more information). It does not apply to adults with symptoms of tuberculosis or children or adolescents.

**Assessment of Risk**

Populations that are at increased risk for LTBI based on increased prevalence of active disease and increased risk of exposure include persons who were born in, or are former residents of, countries with increased tuberculosis prevalence and persons who live in, or have lived in, high-risk congregate settings (such as homeless shelters and correctional facilities).

Other populations that are at increased risk for LTBI or progression to active disease include persons who are immunosuppressed (including persons living with HIV; patients receiving immunosuppressive medications, such as chemotherapy or tumor necrosis factor-alpha inhibitors; and persons receiving an organ transplant) and patients with silicosis (a lung disease). However, given that screening in these populations may be considered standard care as part of disease management or indicated prior to the use of certain medications, the USPSTF did not review evidence on screening in these populations. Persons who are contacts of persons with active tuberculosis, as well as health care workers and workers in high-risk congregate settings, may also be at increased risk of exposure. Since screening in these populations is conducted as part of public health\(^{10}\) or employee health\(^{11,12}\) surveillance, the USPSTF also did not review the evidence in these populations. Clinicians seeking further information on testing for tuberculosis in these populations can refer to the “Useful Resources” section.
**Screening Tests**

Two types of screening tests for LTBI are currently available in the United States—TST and IGRA. TST requires intradermal placement of purified protein derivative and interpretation of response 48 to 72 hours later. IGRA requires a single venous blood sample and laboratory processing within 8 to 30 hours after collection. Two types of IGRA are currently approved by the U.S. Food and Drug Administration: T-SPOT. TB (Oxford Immunotec Global PLC, Marlborough, MA) and QuantiFERON®-TB Gold In-Tube (Qiagen, Germantown, MD). Numerous patient and systems factors may influence the selection of a screening test. The CDC recommends screening with either TST or IGRA. IGRA tests may be preferred for persons who have received a Bacillus Calmette–Guérin vaccination or persons who may be unlikely to return for TST interpretation. Additional information on the use and interpretation of TST and IGRA is available at www.cdc.gov/tb/publications/factsheets/testing/tb_testing.htm.

**Screening Intervals**

The USPSTF found no evidence on the optimal frequency of screening for LTBI. Depending on specific risk factors, screening frequency could range from one-time only screening in persons who are at low risk for future exposure to annual screening in those who are at continued risk of exposure.

**Treatment**

Currently, the CDC recommends four different treatment regimens for LTBI (www.cdc.gov/tb/topic/treatment/ltdi.htm). Medications include rifampin, isoniazid, or isoniazid plus rifapentine, and treatment duration ranges from 3 to 9 months. If a nondaily dosing regimen is offered, the CDC recommends directly observed therapy.
Children: Bright Futures

- National health promotion and prevention initiative, led by the American Academy of Pediatrics and supported by the Maternal and Child Health Bureau, Health Resources and Services Administration
- Bright Futures Guidelines provide theory-based and evidence-driven guidance for all preventive care screenings and well-child visits
- ACA coverage requirements also apply to recommendations made in Bright Futures Project
<table>
<thead>
<tr>
<th>Selective Screening</th>
<th>Medical History Risk Factors</th>
<th>Risk Assessment&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Action if Risk Assessment Is Positive</th>
</tr>
</thead>
</table>
| **Hearing**         | Risk indicators that are marked with an asterisk (*) are of greater concern for delayed-onset hearing loss.  
  - Caregiver concern about hearing, speech, language, or developmental delay*  
  - Family history of permanent childhood hearing loss*  
  - Neonatal intensive care of more than 5 days  
  - In utero infections  
  - Craniofacial anomalies  
  - Physical findings such as white forelock  
  - Syndromes associated with hearing loss or progressive or late-onset hearing loss*  
  - Neurodegenerative disorders*  
  - Culture-positive postnatal infections associated with sensorineural hearing loss*  
  - Head trauma, especially basal skull or temporal bone fracture*  
  - Chemotherapy* |  
  - Do you have concerns about how your child hears?  
  - Do you have concerns about how your child speaks? | Referral for diagnostic audiologic assessment |
| **Lead<sup>a</sup>**  
  (Low prevalence area and not on Medicaid) |  |  
  - If no previous screen or change in risk  
    - Does your child live in or regularly visit a house or child care facility built before 1950?  
    - Does your child live in or regularly visit a house or child care facility built before 1978 that is being or has recently been (within the last 6 months) renovated or remodeled?  
    - Does your child have siblings or playmates who have lived with lead-paint-damaged housing? | Lead screen |
| **Tuberculosis**     |  |  
  - Was your child born in a country at high risk for tuberculosis (countries other than the United States, Canada, Australia, New Zealand, or Western Europe)?  
  - Has your child traveled (had contact with resident populations) for longer than 1 week to a country at high risk for tuberculosis?  
  - Has a family member or contact had tuberculosis or a positive tuberculin skin test?  
  - Is your child infected with HIV? | Tuberculin skin test |
Main Challenges to TB Elimination

- **Political commitment**
  - As cases continue to decrease, seems less of a priority to general public and policymakers
  - Resources at risk

- **Loss of expertise and experience**
  - Clinical, laboratory, program

- **Drug and biologic shortages because of lack of market**
  - Regulatory requirements limit access to GDF or other mechanisms that can access larger global market

- **Concentration of remaining cases and outbreaks in more difficult-to-reach populations**
  - Foreign-born, homeless, etc.

- **How to address the large pool of persons with latent tuberculosis infection (LTBI)**
  - <10 thousand TB cases; millions of persons with LTBI
Tuberculosis (TB) Disease:
Only the Tip of the Iceberg

There are two types of TB conditions: TB disease and latent TB infection.

People with TB disease are sick from active TB germs. They usually have symptoms and may spread TB germs to others.

People with latent TB infection do not feel sick, do not have symptoms, and cannot spread TB germs to others.

But, if their TB germs become active, they can develop TB disease.

Millions of people in the U.S. have latent TB infection. Without treatment, they are at risk for developing TB disease.

To learn more about TB, visit www.cdc.gov/tb
**Estimating LTBI: NHANES**

- NHANES is a series of sequentially run cross-sectional studies, implemented in 2-year cycles that assess the health of the civilian, non-institutionalized U.S. population.
- To obtain a nationally representative sample of the civilian, non-institutionalized U.S. population, NHANES employs a complex, stratified, multistage probability cluster sampling design.
- Approximately 5,000 persons participate in the survey in approximately 15 counties per year.
- In 2011-2012, NHANES included a TB component with TST and Quantiferon testing.
# How Much LTBI Is There in the United States?

<table>
<thead>
<tr>
<th></th>
<th>Prevalence</th>
<th>Number of people</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TST positive</strong></td>
<td>4.7%</td>
<td>13.1 million</td>
</tr>
<tr>
<td><strong>Quantiferon positive</strong></td>
<td>5.0%</td>
<td>13.9 million</td>
</tr>
<tr>
<td><strong>Both positive</strong></td>
<td>2.1%</td>
<td>5.9 million</td>
</tr>
</tbody>
</table>

Estimates from National Health and Nutrition Examination Survey, 2011-2012, manuscript submitted
How Much LTBI Is There in the United States in Foreign-born Persons?

<table>
<thead>
<tr>
<th></th>
<th>Prevalence</th>
<th>Number of people</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST positive</td>
<td>20.5%</td>
<td>8.2 million</td>
</tr>
<tr>
<td>Quantiferon positive</td>
<td>15.9%</td>
<td>6.4 million</td>
</tr>
<tr>
<td>Both positive</td>
<td>9.3%</td>
<td>3.7 million</td>
</tr>
</tbody>
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Targeted Testing and Treatment of Latent Tuberculosis

- Primary focus on foreign-born from medium- and high-incidence countries
- Highest priority to foreign-born with conditions that increase risk of progression (e.g., HIV, smoking, diabetes, TNF-a antagonists)
- IGRA have an advantage in BCG-vaccinated persons
- Short-course regimens can increase completion
- Expansion of testing and treatment beyond health department
LTBI: What Needs to Be Done Using Existing Tools?

- Major initiative with 5 parts
  - Requires substantial additional resources
- 1) Registry/surveillance system
- 2) Scale up of testing to targeted populations
- 3) Scale up of short course LTBI treatment
- 4) Communication, outreach
- 5) Increased public health staffing for implementation and oversight
Expansion of Testing and Treatment Beyond Health Department

- How can we leverage Affordable Care Act?
  - In particular, USPSTF draft recommendation for LTBI testing
- Who serves targeted populations in the community and how can we engage them?
- Effective engagement of affected communities and their medical providers
Medical Provider and Community Engagement

- Provider education
- Outreach to primary care professional societies
- Toolkits for providers
  - Easy to use apps and brochures
- Integration of clinical decision support tools for LTBI testing and treatment into electronic health records
- Outreach to community leaders at all levels
- Community education
Role of Health Department

- Lead community and provider engagement
- Consultation and oversight
- Require increased staff and resources
What New Tools Are Needed?

- A test that is much more predictive of progression from LTBI to TB disease than TST or IGRAs
  - IGRAs are better in BCG vaccinated persons, but are still poor
- Even shorter LTBI treatment
  - Next aim should be for 4-6 weeks
Thank You!
Questions?