TB Targeted Testing in Low Incidence Areas
2015 West Virginia Public Health Symposium

Connie A. Haley, MD MPH
Southeast National TB Center
Division of Infectious Diseases and Global Medicine
University of Florida
Case

• 19 year old woman from Nigeria, arrived in SE U.S. August 30, 2013 to begin freshman year at a local university on scholarship

• Shortly thereafter, she developed intermittently productive cough for which she visited student health services three times
  – Minimally relieved with OTC cough medicine and course of antibiotic (amoxicillin)

• Denied fever, chills, night sweats, hemoptysis, admits to some slight weight loss
At 3rd health center visit on 10/7/13 a CXR is obtained (5 weeks after arrival in US):
Initial course

- Referred to and evaluated at local HD next day 10/8/13
- Sputum AFB Smear: **Numerous AFB organisms seen**
- Patient begun on standard 4 drug anti-TB therapy on 10/8/13:
  - Isoniazid, Rifampin, Pyrazinamide, Ethambutol (IRZE)
- GeneXpert result: M. TB complex with rifampin resistance (rpoB mutation)
- Patient removed from dorm, placed in hotel under isolation (quarantine) awaiting transfer, cont. IRZE
- Sample sent to CDC for molecular susceptibilities: Resistant to INH, RIF, EMB, Moxifloxacin, sensitive to PZA and aminoglycoside
Initial course

- Admitted 10/16/13 for multidrug resistant tuberculosis (MDR-TB)
  - Resistance to at least INH and Rifampin
- Extensively drug resistant (XDR)-TB is defined as MDR-TB plus additional resistance to a fluoroquinolone and a 2nd line injectable (e.g., steptomycin, amikacin or capreomycin)
- Since she has one of the two XDR-TB criteria, she would be classified as “pre-XDR-TB”
Pre-XDR treatment (7 Drugs)

- Capreomycin 750mg 5 days/wk
- Moxifloxacin 400mg/daily
- PZA 1500mg/daily
- Ethionamide 750mg/daily (after ramp up)
- Cycloserine 250mg/daily
- **PAS** 8 grams daily (after ramp up)
- **Linezolid** 600mg daily
  - Vit B6 200mg/daily
- Received 4 ½ mo. AG, TB meds d/c’d after completed **16 months** total therapy, having **15 months** of negative cultures
Subsequent course

• One month after completing TB meds she complained of cough and chest pain
  - “Can you put me back on the TB meds again?”
• Reassured patient that TB relapse was unlikely, gave Z-pack and robitussin-DM
• Repeat CXR and sputum AFB x 3 requested (including GeneXpert)
• Culture confirmed relapse of pre-XDR TB, additional resistance to PZA likely
• Treatment restarted
Re-treatment for “pre-XDR TB”

- Imipenem 1gm IV BID
- Capreomycin 1gm three times a week Mon, Wed and Friday.
- Cycloserine 250mg through G tube daily
- Linezolid 600mg through G tube daily
- Bedaquiline 400mg po daily until 5/26/2015 and then 200mg po three times a week (patient needs to swallow this medicine)
- Ethionamide 250mg through G tube in the morning and 500mg through the G tube at night
- PAS 4 gms twice a day through the G tube
- Vit B6 200mg po daily through G tube
- Give 500ml NS over 60 minutes after Capreomycin infusion
Re-treatment course

• Required transfer to U of FL given
  – Specialized expertise to manage relapsed pre-XDR TB
  – Intensive and specialized monitoring and management of complex multi-drug regimen
  – Multiple complications, side effects, IV access, therapeutic drug monitoring, etc.

• After 3 mos of negative cx’s, she underwent left upper lobectomy 7/29/2015 at NJMC, Denver, CO.

• Completed 24 months of therapy for 2\textsuperscript{nd} course in home state.
Major Challenges

- Staff required to do BID IV infusions, close monitoring
- State incurred significant expense
- Competing priorities for patient with school and BID regimen
  - Social issues
  - Cosmetic issues with PICC
  - Severe tape allergies
  - Continuing stress over scholarship status
  - Disabling mental and physical fatigue for 1 ½ - 2 hours following each BID dose - causes significant disruption to her college class and studying schedule
Contact Investigation

- TSPOTS done on classmates, professors, social group, church, and airline contacts
- 592 contacts tested for infection, 12 positive
- Nine foreign born
  - Two faculty
  - One American born student with documented negative TST upon enrollment
Objectives

1. Identify populations in your area at high risk for TB infection
2. Describe populations most likely to progress from LTBI to TB disease
3. Identify the proper use and recommendations for using tuberculin skins tests (TSTs) and interferon-gamma release assays (IGRA)
4. Describe current regimens for the treatment of LTBI
Worldwide Burden of TB

• In 2014, 9.6 million people fell ill with TB globally, and 1.5 million people died from TB
• 6M reported, 3.5M (37%) were missed by national notification systems
  ➢ Global incidence rate of 122/100,000 population
• Estimated 480 000 people with MDR-TB in 2014; only 1 in 4 were diagnosed, virtually all countries surveyed by WHO
WHO. Global TB Report, 2015
Reported TB Cases
United States, 1982–2014*

No. of Cases

Year

*Updated as of June 5, 2015.

TB Case Rates,* United States, 2014

*Cases per 100,000.

≤ 3.0 (2014 national average)
> 3.0

*Cases per 100,000.

Trends in TB Cases in Foreign-born Persons, United States, 1993 – 2014*

No. of Cases

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td></td>
</tr>
<tr>
<td>1994</td>
<td></td>
</tr>
<tr>
<td>1995</td>
<td></td>
</tr>
<tr>
<td>1996</td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td></td>
</tr>
</tbody>
</table>

*Updated as of June 5, 2015.

Annual Estimate of Migrants Entering the U.S.*

Refugees: 70,000-80,000**

Immigrants: ~1.1 million

Non-immigrant Visitors$: 36 million
Border Commuters: 127 million

Total: ~ 163 million

*Source: U.S. Department of Homeland Security (DHS)

**2011 Refugee Admissions: 56,422

*Non-immigrants include students, temporary workers and trainees, and fiancé(e)s of U.S. citizens.
Percent of Foreign-born with TB by Time of Residence in U.S. Prior to Diagnosis, 2013

*Foreign-born TB patients for whom information on length of residence in the U.S. prior to diagnosis is unknown or missing.

Reported TB Cases by Origin and Race/Ethnicity, United States, 2014

**U.S.-born***

- Black or African American 37%
- Hispanic or Latino 21%
- White 30%
- Multiple Race 2%
- American Indian or Alaska Native 4%
- Native Hawaiian or Pacific Islander 3%

**Foreign-born**

- Hispanic or Latino 34%
- Black or African American 13%
- American Indian or Alaska Native 4%
- Asian 4%
- Multiple Race 2%
- White 4%

*All races are non-Hispanic. Persons reporting ≥2 races accounted for 1% of all cases for U.S. born cases and are not shown.

** American Indian or Alaska Native and Native Hawaiian or Other Pacific Islander accounted for less than 1% of foreign-born cases and are not shown. Multiple Race indicates two or more races reported for a person. Does not include persons of Hispanic or Latino origin.

WV Tuberculosis Cases by County 2010-2014 (n=13)

Note: Each county may have one or multiple cases for the period 2010-2014. This map is intended to show the geographic area of the cases only.
WEST VIRGINIA TB PROFILE ANNUAL REPORT 2014
WV Department of Health and Human Resources, Division of TB Elimination
Number of WV TB Cases: Foreign-Born vs. Hispanic, 2008-2014

- **Cases**
  - Foreign-Born: 7, 9, 3, 5, 2, 3, 3
  - Hispanic: 3, 2, 1, 1, 0, 3, 1

WEST VIRGINIA TB PROFILE ANNUAL REPORT 2014
WV Department of Health and Human Resources, Division of TB Elimination
Race of WV TB Cases by Diagnosis Year, 2008-2014

- **2008**: 78.6%
- **2009**: 67.9%
- **2010**: 73.3%
- **2011**: 76.9%
- **2012**: 62.5%
- **2013**: 69.2%
- **2014**: 84.6%

**Legend**:
- Asian
- Black
- White
- Native Hawaiian/Pacific Islander
Note: in 2014, 0 patients reported IVDU; 2 reported Non-injection DU.
Cases of TB Disease Reported in WV, 2014

**HOMELESS WITHIN PAST YEAR**

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>NUMBER OF RECORDS</th>
<th>PERCENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>13</td>
<td>100.00%</td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td>Unknown/Missing</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>13</td>
<td>100.00%</td>
</tr>
</tbody>
</table>

**RESIDENT OF A CORRECTIONAL FACILITY AT TIME OF DIAGNOSIS**

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>NUMBER OF RECORDS</th>
<th>PERCENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>12</td>
<td>92.31%</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>7.69%</td>
</tr>
<tr>
<td>Unknown/Missing</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>13</td>
<td>100.00%</td>
</tr>
</tbody>
</table>
TB Control Priorities in the U.S.

1. Detection and treatment of persons with active tuberculosis
2. Investigation of infectious cases to detect contacts with active TB or contacts who are infected at risk of future TB
3. Prevent future TB through screening high risk groups and providing LTBI treatment to persons with *M. tuberculosis* infection (and no active disease)
Figure: Population-level control strategies for tuberculosis elimination.
Arrows show the dynamics of M tuberculosis in the world’s population, with flow from latent infection to active disease, transmission to new hosts, followed by either rapid progression to disease and ongoing transmission or entry into the pool of latent infections. Bars show how different control measures affect these dynamics, interrupting the chain of events. Even if diagnosis and treatment of active tuberculosis is maximised and a new effective vaccine is developed, reactivation from the billions of latently infected will result in new cases for decades to come.
Stages of TB with and without HIV

HIV -
- TB EXPOSED
  - NOT TB INFECTED 70%
  - NOT TB EXPOSED
  - TB INFECTED 30%

HIV +
- TB EXPOSED
  - NOT TB INFECTED 70%
  - NOT TB EXPOSED
  - TB INFECTED 30%

**Latent TB Infection vs. TB Disease**

<table>
<thead>
<tr>
<th>Latent TB Infection (LTBI)</th>
<th>TB Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive, contained tubercle bacilli in the body</td>
<td>Active, multiplying tubercle bacilli in the body</td>
</tr>
<tr>
<td>TST or IGRA blood test results usually positive</td>
<td>TST or IGRA blood test results usually positive</td>
</tr>
<tr>
<td>Chest x-ray usually normal</td>
<td>Chest x-ray usually abnormal</td>
</tr>
<tr>
<td>Sputum smears and cultures negative</td>
<td>Sputum smears and cultures may be positive</td>
</tr>
<tr>
<td>No symptoms</td>
<td>Symptoms such as cough, fever, weight loss</td>
</tr>
<tr>
<td>Not infectious</td>
<td>Often infectious before treatment</td>
</tr>
<tr>
<td>Not a “case of TB”</td>
<td>A “case of TB”</td>
</tr>
</tbody>
</table>

*HIV+ persons may have false-negative TST and IGRA, atypical symptoms or CXR pattern, etc.*
Latent TB Infection

• Accurate diagnosis of LTBI is critical in TB control and for long-term elimination efforts
• No definitive test to diagnose LTBI is available.
• Thus, screening for LTBI relies on combination of:
  – Assessment of individual risk factors and exposures
  – Clinical evaluation for signs/symptoms of active TB
  – Laboratory testing (TST, IGRA, HIV, +/- sputum smear and culture)
  – Radiographic studies
Targeted TB Testing and Treatment of Latent TB Infection

- As TB disease rates in the U.S. decrease, prevention of new cases has become a priority
- LTBI treatment substantially reduces the risk that persons infected with *M. tuberculosis* will progress to TB disease
  - Reduce individual’s morbidity & mortality
  - Decrease community transmission
- Targeted testing = essential TB prevention & control strategy
  - Purpose: To identify persons at high risk for TB who would benefit by treatment of LTBI
  - Screening of low-risk persons not recommended (reduce waste of resources, prevent inappropriate therapy)

The Scope and Impact of Treatment of LTBI in the United States and Canada

- Tuberculosis Epidemiologic Studies Consortium (TBESC) Task Order 13
- Conducted survey of clinics in the U.S. (n=19) and Canada (n=2) that initiated LTBI treatment for ≥10 patients in 2002.
- Extrapolated study data to the entire U.S. population
  - Used an estimated 20-60% treatment effectiveness (9 months INH) and 5% lifetime risk of active TB without treatment.
- Results: Targeted screening and treatment of LTBI likely prevented 4,000 - 11,000 active TB cases in the U.S.

Who should be tested?

- Persons with Risk for Recent TB Infection (Exposure Risk)
- Persons with Risk of Progression to Active TB if Infected with *M. tuberculosi*s
Incidence of Active TB and Prevalence of LTBI in Selected High-Risk Groups, According to Published Studies


<table>
<thead>
<tr>
<th>High-Risk Group</th>
<th>Incidence of Active Tuberculosis</th>
<th>Prevalence of Latent Tuberculosis Infection†</th>
<th>Tuberculin Skin Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>median rate per 1000 population (range)</td>
<td>median percentage (range)</td>
<td></td>
</tr>
<tr>
<td>Persons with HIV infection</td>
<td>16.2 (12.4–28.0)</td>
<td>14.5 (2.7–21.5)</td>
<td>11.3 (4.3–67.6)</td>
</tr>
<tr>
<td>Adult contacts of persons with tuberculosis</td>
<td>0.6‡</td>
<td>21.1 (6.6–55.1)</td>
<td>48.0 (29.6–59.6)</td>
</tr>
<tr>
<td>Patients receiving tumor necrosis factor blockers</td>
<td>1.4‡§</td>
<td>11.8 (4.0–22.3)</td>
<td>20.0 (12.9–25.0)</td>
</tr>
<tr>
<td>Patients undergoing hemodialysis</td>
<td>26.6 (1.3–52.0)</td>
<td>33.4 (17.4–44.2)</td>
<td>43.6 (23.3–58.2)</td>
</tr>
<tr>
<td>Patients undergoing organ transplantation</td>
<td>5.1‡</td>
<td>21.9 (16.4–23.5)</td>
<td>29.5 (20.5–38.5)</td>
</tr>
<tr>
<td>Patients with silicosis</td>
<td>32.1‡</td>
<td>46.6‡</td>
<td>61.0‡</td>
</tr>
<tr>
<td>Prisoners</td>
<td>2.6 (0.03–9.8)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Health care workers</td>
<td>1.3 (0.4–4.1)</td>
<td>14.1 (0.9–76.7)</td>
<td>5.2 (3.5–28.7)</td>
</tr>
<tr>
<td>Immigrants from countries with a high tuberculosis burden</td>
<td>3.6 (1.3–41.2)</td>
<td>30.2 (9.8–53.8)</td>
<td>17.0 (9.0–24.9)</td>
</tr>
<tr>
<td>Homeless persons</td>
<td>2.2 (0.1–4.3)</td>
<td>53.8 (18.6–75.9)</td>
<td>—</td>
</tr>
<tr>
<td>Illicit-drug users</td>
<td>6.0‡</td>
<td>63.0 (1.4–66.4)</td>
<td>45.8 (34.1–57.5)</td>
</tr>
<tr>
<td>Elderly persons</td>
<td>—</td>
<td>16.3‡</td>
<td>—</td>
</tr>
</tbody>
</table>

* Data are from studies in countries with a low incidence of tuberculosis (<1 per 1000 population). The search for the incidence of active tuberculosis covered the period from January 1, 2004, to August 30, 2014, and data were restricted to articles published in English. The search for the prevalence of latent tuberculosis covered the period from January 1, 2009, to August 30, 2014, and data were restricted to articles published in English, Spanish, or French. The list of included studies and specific values for each risk group are provided in Tables S1 and S2, respectively, in the Supplementary Appendix. Dashes denote no data.

† The QuantiFERON-TB Gold In-Tube assay (Cellestis) and the T-Spot.TB assay (Oxford Immunotec) are interferon-γ release assays. In response to the tuberculin skin test, indurations that measured at least 5 mm in diameter were used to compute prevalence.

‡ Data are from a single study.

§ Patients received treatment with infliximab.
Risk Factors for Recent TB Infection

- Close contact to person with infectious TB
- Skin test conversion (within past 2 y)
- Foreign-born persons from areas with a high incidence of active TB
  - Africa, Asia, Eastern Europe, Latin America
- Persons who visit areas with high prevalence of active TB, esp. if visits are frequent, prolonged
- Residents and employees of congregate settings whose clients are at increased risk for active TB
  - E.g., corrections, long-term care facilities, homeless shelters

Risk Factors for Recent TB Infection

- Health-care workers (HCW) who serve clients who are at increased risk for active TB
  - *Infection Control and Risk Assessment Gloves, MMWR 2005*
- Populations defined locally as having an increased incidence of latent *M. tuberculosis* infection or active TB, possibly including medically underserved, low-income populations, or persons who abuse drugs or alcohol
- Infants, children, and adolescents exposed to adults at increased risk for LTBI or active TB

Risk Factors for Progression from Latent to Active TB Disease

- HIV infection
- Infants and children aged <5 years
- Persons who were recently infected with *M. tuberculosis* (within the past 2 years)
- Persons with a history of untreated or inadequately treated active TB, including persons with fibrotic changes on CXR consistent with prior active TB
- Injection drug use

Risk Factors for Progression from Latent to Active TB Disease

- Certain medical conditions such as
  - Silicosis
  - Diabetes mellitus
  - Chronic renal failure or on hemodialysis
  - Solid organ transplantation (e.g., heart, kidney)
  - Carcinoma of head, neck, or lung
  - Gastrectomy or jejunoilial bypass
  - Other immunosuppressive conditions or therapy (including TNF-α antagonists)
  - <90% of ideal body weight

DIAGNOSIS OF LATENT TB INFECTION
Testing for *M. tuberculosis* Infection

- Two testing methods available for the detection of *M. tuberculosis* infection:
  - Mantoux tuberculin skin test (TST)
  - Interferon-gamma release assays (IGRA)
- These tests *do not* exclude LTBI or TB disease
- Decisions about medical and public health management should include other epidemiologic and clinical information, and not rely only on TST or IGRA results
# Interpreting the Mantoux TST Reaction

<table>
<thead>
<tr>
<th>Induration $&gt;5$ mm</th>
<th>Induration $&gt;10$ mm</th>
<th>Induration $&gt;15$ mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>Recent immigrants, high-incidence areas</td>
<td>No known risk factors for TB</td>
</tr>
<tr>
<td>Recent close contact</td>
<td>Injection drug use</td>
<td></td>
</tr>
<tr>
<td>CXR suggestive of previous TB disease</td>
<td>Live/work congregate settings</td>
<td></td>
</tr>
<tr>
<td>Organ transplants</td>
<td>Mycobacteriology lab workers</td>
<td></td>
</tr>
<tr>
<td>Other immunosuppression</td>
<td>Medical conditions that increase TB risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Children $&lt;5$ y old</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infants, children, adolesc. exposed to high-risk adults</td>
<td></td>
</tr>
</tbody>
</table>
Factors that May Affect the Skin Test Reaction

<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Possible Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>False-positive</td>
<td>• Nontuberculous mycobacteria</td>
</tr>
<tr>
<td></td>
<td>• BCG vaccination</td>
</tr>
<tr>
<td></td>
<td>• Problems with TST administration</td>
</tr>
<tr>
<td>Type of Reaction</td>
<td>Possible Cause</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>False-negative</td>
<td>• Anergy</td>
</tr>
<tr>
<td></td>
<td>• Viral, bacterial, fungal co-infection</td>
</tr>
<tr>
<td></td>
<td>• Recent TB infection (w/in 8-10 weeks)</td>
</tr>
<tr>
<td></td>
<td>• Very young age (&lt;6m); advanced age</td>
</tr>
<tr>
<td></td>
<td>• Live-virus vaccination</td>
</tr>
<tr>
<td></td>
<td>• Overwhelming TB disease</td>
</tr>
<tr>
<td></td>
<td>• Renal failure/disease</td>
</tr>
<tr>
<td></td>
<td>• Lymphoid disease</td>
</tr>
<tr>
<td></td>
<td>• Low protein states</td>
</tr>
<tr>
<td></td>
<td>• Immunosuppressive drugs</td>
</tr>
<tr>
<td></td>
<td>• Problems with TST administration</td>
</tr>
</tbody>
</table>
Whole Blood Interferon Gamma Release Assay

- IGRAs use purified antigens from MTB to stimulate peripheral-blood lymphocytes to produce gamma interferon
- QuantiFERON tests (QFT) measures gamma interferon (IFN-γ) in the supernatant of the cell suspension
- TSPOT measures cells producing gamma interferon using ELISpot assay
Interferon Gamma Release Assays

• Three IGRAs approved by the U.S. FDA and are commercially available in the U.S.:
  - QuantiFERON®-TB Gold test (QFT-G);
  - QuantiFERON®-TB Gold In-Tube test (QFT-GIT);
  - T-SPOT®.TB test (T-Spot)

<table>
<thead>
<tr>
<th></th>
<th>QFT-Gold</th>
<th>QFT-Gold In Tube (QFT-GIT)</th>
<th>T-Spot</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Format</strong></td>
<td>Process whole blood within 12h</td>
<td>Process whole blood within 16h</td>
<td>Process peripheral blood mononuclear cells (PBMCs)</td>
</tr>
<tr>
<td><strong>M. Tuberculosis antigen</strong></td>
<td>Separate mixtures of synthetic peptides representing ESAT-6 &amp; CFP-10</td>
<td>Single mixture of synthetic peptides representing ESAT-6 &amp; CFP-10, and TB 7.7</td>
<td>Separate mixtures of synthetic peptides representing ESAT-6 &amp; CFP-10</td>
</tr>
<tr>
<td><strong>Measurement</strong></td>
<td>IFN-γ concentration</td>
<td>IFN-γ concentration</td>
<td># of IFN-γ producing cells (spots)</td>
</tr>
<tr>
<td><strong>Possible Results</strong></td>
<td>Positive, negative, indeterminate</td>
<td>Positive, negative, indeterminate</td>
<td>Positive, negative, indeterminate, borderline</td>
</tr>
</tbody>
</table>

Note: CDC guidelines for QFT-GIT and T-SPOT published June 2010
www.cdc.gov/mmwr Vol. 59, No. RR-5
LTBI Testing Summary:
Comparison of Quantiferon and TST

Quantiferon
- In vitro test
- Specific antigens
- No boosting
- 1 patient visit
- Minimal inter-reader variability
- Results in 1 day
- Requires blood test
- Not affected by BCG, most atypical mycobacteria
- May increase acceptance of LTBI therapy if positive

TST
- In vivo test
- Single antigen
- Boosting phenomenon
- 2 patient visits
- Inter-reader variability
- Results in 2-3 days
- No phlebotomy
- Cross-reacts with BCG, atypical mycobacteria
IGRA: General Points

• IGRAs are highly specific (~95%)
  - Both QFT and T-SPOT TB substantially more specific than the PPD since they contain antigens not found in BCG
  - Distinguish most NTM (except *M. Kansasii*, *M. marinum*, *M. szulgai*, *M. flavescens*)
  - PPD contains large number of mycobacterial proteins not specific to *M. tuberculosis*

• IGRAs have moderate to high sensitivity
  - QFT being as sensitive as PPD (70-80%) in immunocompetent
  - T-SPOT TB more sensitive (~90%) than QFT and PPD in immunocompromised
Considerations for IGRA

• No gold standard for TB infection
• Studies of serial testing in health care workers and other groups have shown unexpectedly high rates of:
  - IGRA positivity
  - Conversion (change from a negative to positive)
  - Reversion (change from positive to negative)
• Boosting has been reported 7-21d after a baseline TST (9.1% for QFT-GIT and 11.3% TSPOT.TB)
• “Wobble Effect”- small changes occurring around fixed cut point that could result in changes from (-) to (+)

Dorman et al. Am J Respir Crit Care Med Vol 189, Iss 1, pp 77–87, Jan 1, 2014
Considerations for IGRA

• Limited data on use of IGRAs to predict who will progress to TB disease in the future
• Limited data on the use of IGRAs for:
  - Children younger than 5 years of age
  - Persons recently exposed to *M. tuberculosis*
  - Immunocompromised persons
  - Serial testing
• Discordant test results and test-retest variability
• Tests may be expensive
  – NOTE: some cost-effectiveness studies indicate that health system costs associated with IGRA use may make them attractive overall)
William Osler

“Medicine is a science of uncertainty and an art of probability.”

“It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has.”
## Recommended LTBI Treatment Regimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>Frequency</th>
<th>Duration</th>
<th>Issues</th>
<th>Abbrev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Daily</td>
<td>9 months (6 months)</td>
<td>Long duration, poor adherence</td>
<td>9H</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Twice weekly</td>
<td>9 months (6 months)</td>
<td>Directly-observed, long duration</td>
<td>9H-DOT</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Daily</td>
<td>4 months</td>
<td>Drug interactions</td>
<td>4R</td>
</tr>
<tr>
<td>Isoniazid + rifapentine</td>
<td>Once weekly</td>
<td>3 months</td>
<td>DOT</td>
<td>3HP</td>
</tr>
</tbody>
</table>

### Other regimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>Frequency</th>
<th>Duration</th>
<th>Issues</th>
<th>Abbrev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid + rifampin</td>
<td>Daily</td>
<td>3 months</td>
<td>Not in U.S. recommendations</td>
<td>3HR</td>
</tr>
<tr>
<td>Rifampin + pyrazinamide</td>
<td>Daily or 2x/week</td>
<td>2 months</td>
<td>Potentially fatal: NOT RECOMMENDED</td>
<td>2RZ</td>
</tr>
</tbody>
</table>
Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection


N Engl J Med
Volume 365(23):2155-2166
December 8, 2011
Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection
TBTC Study 26 (PREVENT-TB)

- 8,053 “high-risk” patients in U.S., Brazil, Spain
  - Contacts, converters; HIV+ (few); Children ≥2y
- Compared self-administered 9H vs. 12 wk INH/Rifapentine weekly for by DOT (3HP-DOT)
  - Rifapentine 900mg + INH 15-25mg/kg; 900mg max
- Both arms similar efficacy: (3HP=0.19%; 9H=0.43%)
- Completion much higher with 3HP (80%)
- Toxicity slightly higher with 3HP (5% vs. 3% in 9H)
  - Hepatotoxicity the same
  - “Excess” toxicity was hypersensitivity (over-reported?)

3HP CDC Recommendations (2011)

• 3HP: Rifapentine 900 mg plus INH 900 mg once per week for 12 doses
• 3HP is an equal alternative to 9H for the following:
  - Contacts
  - Recent converters
  - Old, healed (Class IV) TB *(rule out active TB)
• Adults and children ≥12 years
  - Can be used in children 2-11y on a “case by case” basis
• HIV+ if healthy and on no ARVs

*MMWR. Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat LTBI, 2011.
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w
3HP CDC Recommendations (2011)

- Choice between 9INH and 3HP depends on:
  - Feasibility of DOT
  - Ability to obtain drugs
  - Ability to monitor side effects
  - Ability to complete treatment
  - Preference of patient and physician

- Practical advantages: corrections, shelters, clinics for recent immigrants

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cidmm6048a3_w
3HP CDC Recommendations (2011)

- INH-RPT NOT recommended for:
  - Children under 2y
  - HIV patients on ART
  - Pregnant women or women wanting to become pregnant
  - Contacts to INH or Rif-resistant TB

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w
Identifying Barriers to Initiation and Adherence

- Physician perceptions
- LTBI patient has no symptoms, low perceived risk of TB
- Appointment hours that conflict with patient’s schedule; inconvenient clinic locations
- Misinformation about TB or HIV
- Health beliefs and practices
- Limited financial resources
- Co-existing medical conditions
- Medication side effects (or fear of side effects)
- Cultural and language barriers
- Real or perceived stigma related to LTBI diagnosis or tx
- Other fears (doctors, government, loss of confidentiality)
CDC Treatment Cascade - HIV

- Diagnosed: 82%
- Linked to Care: 66%
- Retained in Care: 37%
- Prescribed ART: 33%
- Virally Suppressed: 25%
CDC Cascade, 2011

- HIV-infected*: 1,178,350
- HIV-diagnosed*: 941,950
- Linked to HIV care†: 725,302
- Retained in HIV care$: 480,395
- On ART*: 426,590
- Suppressed viral load (≤200 copies/mL)**: 328,475

MMWR, December 2, 2011;60(47);1618-23.
Questions?

TUBERCULOSIS IS CURABLE AND PREVENTABLE

If you are rundown or have a cough, get a medical examination.

Maritime Tuberculosis Educational Committee.
Additional Resources

- Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection  *MMWR* 2000; 49 (No. RR-6)  
  [http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm)

- Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent *Mycobacterium tuberculosis* Infection  
  [http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w)

  [http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5905a1.htm?s_cid=rr5905a1_e](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5905a1.htm?s_cid=rr5905a1_e)
Additional Resources

  [http://ajrccm.atsjournals.org/content/174/8/935.full.pdf+html](http://ajrccm.atsjournals.org/content/174/8/935.full.pdf+html)

  [http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5908a3.htm?s_cid=mm5908a3_e](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5908a3.htm?s_cid=mm5908a3_e)

- Latent Tuberculosis Infection: A Guide for Primary Health Care Providers  
Additional Resources

- Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis
- CDC TB Website  http://www.cdc.gov/tb
- Southeastern National TB Center
  http://sntc.medicine.ufl.edu/
- National TB Controllers Association  www.ntca-tb.org/
- CDC’s Morbidity and Mortality Weekly Report
  http://www.cdc.gov/tb/publications/reportsarticles/mmwr/default.htm
Latent TB Infection and LTBI Incidence/100,000 population in West Virginia

<table>
<thead>
<tr>
<th></th>
<th>CENSUS</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTBI</td>
<td>1,852,994</td>
<td></td>
<td></td>
<td>388</td>
<td>288</td>
<td>249</td>
<td>182</td>
<td>182</td>
</tr>
</tbody>
</table>
Reactivation of Latent TB Infection among the Foreign-born in the U.S.

- Studies of TB genotypes in U.S. suggest that TB among foreign-born individuals is more attributable to reactivation of LTBI acquired before arrival to U.S. instead of recent TB transmission (Geng, NEJM 2002; Jasmer Ann Int Med 1999; Ricks, PLoS ONE 2011)

- TB case rates declined with increasing time since US entry, but remained higher than among US-born persons—even more than 20 years after arrival. (Cain, JAMA. 2008)

- 50% of foreign-born TB cases occurred among persons who had been in the U.S. for >5 years and, thus, would not qualify as being at high risk for TB according to current guidelines (Cain AJRCCM 2007)