Tuberculosis: Where Are We Now?

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Global TB Institute
Learning Objectives

• Understand the current epidemiologic state of TB globally and in the United States
• Discuss current diagnostics and treatment options for persons with TB infection
• Understand the basics of TB disease
Outline

• Epidemiology
  – Global
  – Domestic
• Tuberculosis infection versus disease
• Diagnosing TB infection
• Treatment of TB infection
• Basics of TB disease
• Resources
Estimated TB incidence rates, 2015

Source: WHO Global Tuberculosis Report 2016
Top causes of death worldwide in 2012. Deaths from TB among HIV-positive people are shown in grey.

- Ischaemic heart disease
- Stroke
- Lower respiratory infections
- Chronic obstructive pulmonary disease
- TB
- Tracheal, bronchus, lung cancer
- Diarrheal diseases
- Diabetes mellitus
- HIV/AIDS
- Road injury

Estimated number of deaths from HIV/AIDS and TB in 2015. Deaths from TB among HIV-positive people are shown in grey.

- TB
- HIV/AIDS

Source: WHO Global Tuberculosis Report 2016

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a Estimates of causes of death will be updated by WHO before the end of 2016.

b This is the latest year for which estimates for all causes are currently available. See WHO Global Health Observatory data repository, available at http://apps.who.int/gho/data/node.main.GHECOD (accessed 28 July 2016).

c For HIV/AIDS, the latest estimates of the number of deaths in 2012 that have been published by UNAIDS are available at www.unaids.org/en/resources/documents/2016/HIV_estimates_with_uncertainty_bounds_1990-2015. For TB, the estimates for 2012 are those published in this report.

d Deaths from TB among HIV-positive people are officially classified as deaths caused by HIV/AIDS in the International Classification of Diseases.
1/3 of world’s population has latent TB infection
Global strategy and targets for tuberculosis prevention, care and control after 2015

Current global trend: -1.5%/year

-17%/year

-5%/year

-10%/year by 2025

Optimize use of current & new tools emerging from pipeline, pursue universal health coverage and social protection

Introduce new tools: a vaccine, new drugs & treatment regimens for treatment of active TB disease and latent TB infection, and a point-of-care test

Rate per 100,000/year

2015

2020

2025

2030

2035
Reported Tuberculosis (TB) Cases
United States, 1982–2015*

<table>
<thead>
<tr>
<th>Year</th>
<th>No.</th>
<th>Rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>11,159</td>
<td>3.6</td>
</tr>
<tr>
<td>2011</td>
<td>10,510</td>
<td>3.4</td>
</tr>
<tr>
<td>2012</td>
<td>9,942</td>
<td>3.2</td>
</tr>
<tr>
<td>2013</td>
<td>9,550</td>
<td>3.0</td>
</tr>
<tr>
<td>2014</td>
<td>9,406</td>
<td>2.9</td>
</tr>
<tr>
<td>2015</td>
<td>9,557</td>
<td>3.0</td>
</tr>
<tr>
<td>2016</td>
<td>9,287</td>
<td>2.9</td>
</tr>
</tbody>
</table>

*As of June 9, 2016.

TB Case Rates,* United States, 2015

*Cases per 100,000 population; as of June 9, 2016.
TB Case Rates by Race/Ethnicity,* United States, 2003–2015†

* All races are non-Hispanic.
† As of June 9, 2016.
TB Case Rates, by Age Group and Race/Ethnicity,* United States, 2015†

* All races are non-Hispanic; multiple race indicates two or more races reported for a person, but does not include persons of Hispanic/Latino origin.

† As of June 9, 2016.
Number of TB Cases Among U.S.-Born versus Foreign-Born Persons, United States, 1993–2015*

- As of June 9, 2016.
- 85% of cases are in minorities
- 68% of all cases are in foreign-born
- Case rate in foreign-born is 14x higher than US-born
Reported TB Cases, by Origin and Race/Ethnicity†, United States, 2015*

U.S.-born persons

- Hispanic/Latino 21%
- White 31%
- Native Hawaiian/Pacific Islander 3%
- American Indian/Alaska Native 4%
- Asian 4%
- Multiple race 1%

Foreign-born persons§

- Hispanic/Latino 32%
- Asian 48%
- Black/African American 13%
- White 4%
- Multiple race 2%

† All races are non-Hispanic; multiple race indicates two or more races reported for a person, but does not include persons of Hispanic/Latino origin.
* As of June 9, 2016.
§ American Indian/Alaska Native and Native Hawaiian/Other Pacific Islander accounted for <1% of cases among foreign-born persons and are not shown.
Percentage of Foreign-Born Persons Among TB Cases, United States,* 2005 and 2015

* As of June 9, 2016.

- 2005
- 2015

Legend:
- ≥50%
- 25%–49%
- ≤24%
- No cases

* Denotes county with no cases.
Percentage of Foreign-Born Persons with TB, by Time of Residence in U.S. Before Diagnosis, 2015*

- **Mexico**: Percentage of foreign-born persons with TB by time of residence in the U.S.
- **Philippines**: Percentage of foreign-born persons with TB by time of residence in the U.S.
- **India**: Percentage of foreign-born persons with TB by time of residence in the U.S.
- **All Other Foreign-Born**: Percentage of foreign-born persons with TB by time of residence in the U.S.

* As of June 9, 2016.
† Foreign-born TB patients for whom information on length of residence in the United States before diagnosis is unknown or missing.
Number of tuberculosis cases diagnosed among foreign-born persons <10 years and ≥10 years after arrival in the United States, 1993–2015

TB in Pennsylvania

TB Cases by Race/Ethnicity, Pennsylvania, 2013

- Other, 50%
- Hispanic/Latino, 6.3%
- Asian, 20.8%
- White, 9.3%
- Black, 13.6%

*AI/AN, American Indian/Alaska Native; Black, Black/African American; Hisp/Lat, Hispanic/Latino; MultRace, Multiple races; NHOP, Native Hawaiian/Other Pacific Islander; Unk, Unknown

2015 200 cases
2016 174 cases
2016 Case rate 1.4
Summary of Trends in US

• Number of cases increased in 2015, but down in 2016; case rate similar
• 2/3 of all cases are in people born outside the US, the majority of whom have been residing in US > 5 years
• HIV coinfection has decreased to < 6%
• TB cases among homeless individuals has also declined (<5%)
• Resuming and intensifying progress to TB elimination (≤ 1 case/million) requires
  – Existing priorities - case identification, early treatment, contact tracing – needed to prevent resurgence
  – Tb elimination requires new strategies especially to detect and treat latent TB infection in at-risk groups
TB Infection (LTBI) in the US

- Up to 13 million people in US infected; ~ 4.5%
- 5-10% may go on to have active TB if untreated
- ~ 70% of LTBI in foreign born individuals
- 19% of US born with LTBI treated; 10% of foreign born
- Treatment 90% effective
- 80% active cases arise from prior infection
- No significant decline in TST or IGRA positivity over past decade

Mancuso et al, AJRCCM, 2016
TB Infection in US

Mancuso et al, AJRCCM, 2016
TB Infection in the US

- Up to 13 million people in US infected; ~ 4.5%
- 5-10% may go on to have active TB if untreated
- 80% active cases arise from prior infection
- ~ 70% of LTBI in foreign born individuals
- No significant decline in TST or IGRA positivity over past decade

- A large reservoir of LTBI remains, and continues to be a barrier to TB elimination
- Ramping up targeted testing and treatment is the path to TB elimination
- Clinicians, health care agencies, community organizations, esp those serving at-risk patients, are critical to success
**Targeted testing and treatment**

- CDC and USPSTF recommend testing in those at increased risk

  **USPSTF**
  - Those from countries with increased TB prevalence, regardless of time in US
  - Those in high risk congregate settings
  - Consult with L/SHD about populations at risk

- CDC still recommends testing
  - HCW
  - Close contacts
  - Certain medical illnesses (HIV, DM, etc.)
  - Before starting medications such as TNFα blocker

**Clinicians and community organizations critical to TB elimination**

- Many at high risk not seen by HD
- TB disease often missed by today’s clinician
- TB education/outreach needed
Tuberculosis (LTBI)

- Definitions
- Diagnosis
- Treatment
# TB Infection vs. TB Disease

<table>
<thead>
<tr>
<th>A Person with Latent TB Infection</th>
<th>A Person with Active TB Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Has no symptoms</td>
<td>✓ Has symptoms that may include:</td>
</tr>
<tr>
<td>✓ Does not feel sick</td>
<td>• a bad cough that lasts longer than</td>
</tr>
<tr>
<td>✓ Cannot spread TB to others</td>
<td>• 2 weeks</td>
</tr>
<tr>
<td>✓ Usually has a positive skin test or</td>
<td>• pain in the chest</td>
</tr>
<tr>
<td>Interferon Gamma Release Assay</td>
<td>• coughing up blood or sputum</td>
</tr>
<tr>
<td>(IGRA)</td>
<td>• weakness or fatigue</td>
</tr>
<tr>
<td>✓ Has a normal CXR and sputum</td>
<td>• weight loss</td>
</tr>
<tr>
<td>test</td>
<td>• no appetite</td>
</tr>
<tr>
<td></td>
<td>• chills</td>
</tr>
<tr>
<td></td>
<td>• fever</td>
</tr>
<tr>
<td></td>
<td>• night sweats</td>
</tr>
<tr>
<td></td>
<td>✓ May spread TB to others</td>
</tr>
<tr>
<td></td>
<td>✓ Usually has a positive skin test or</td>
</tr>
<tr>
<td></td>
<td>IGRA</td>
</tr>
<tr>
<td></td>
<td>✓ May have an abnormal chest x-ray, or</td>
</tr>
<tr>
<td></td>
<td>positive sputum smear or culture</td>
</tr>
</tbody>
</table>
Who do we test?

- High risk of infection
  - Close contacts
  - Work/live high-risk settings
  - Those from countries where TB is common

- High risk of progression
  - HIV infection
  - Recently infected
  - Young children
  - IDU
  - Immunocompromised
  - Those not properly treated for TB disease in past
Diagnosis of TB Infection

• No definitive or gold standard test
• Tests do not distinguish latent from active TB
• Tuberculin Skin Testing (in use > 100 years)
• Interferon Gamma Release Assays (IGRA)
  – Quanti-FERON® TB Gold In Tube
  – T-SPOT®.TB
• Testing goal is to identify those who will most benefit from treatment
  – Likelihood of infection
  – Risk of progression and morbidity
  – Lower the risk of future transmission
TST Limitations

• Cross reacts with BCG and non-tuberculous mycobacteria
• Limited sensitivity, especially in immunosuppressed
• Poor positive predictive value: Very few will go on to develop TB disease
• Requires technical expertise for administration and test interpretation
• Patient must return for 2nd visit
Interferon Gamma Release Assays (IGRAs)

- In-vitro blood tests
- Measure interferon gamma release from T-cells stimulated by specific antigens
Quanti-FERON® Gold In Tube Method

Tubes: Nil
TB Antigen
Mitogen

Part 1. Blood Incubation
After blood collection, mix QFT tubes thoroughly, by shaking vigorously for 5 seconds.
As soon as possible, and within 16 hours of collection, incubate tubes upright at 37°C for 16–24 hours.
Incubated tubes are stable for up to 3 days at room temperature, enabling shipment to laboratory.
Centrifuge tubes at 2000–3000g (RCF) for 15 minutes.

Part 2. IFN-gamma ELISA
Add 50μL of working conjugate to each well. Add 50μL of plasma or standard. Incubate for 120 minutes at room temperature.
Wash plate ≥6 times. Add 100μL of substrate. Incubate 30 minutes at room temperature.
Add 50μL of stop solution. Read absorbance at 450nm (620–650nm ref).
Calculate results using QuantiFERON-TB Gold In-Tube Analysis Software, or similar.

Measure IFN-gamma
T-SPOT®.TB Test

1. Collect blood sample, centrifuge to separate PBMCs which are washed and counted to maximise sensitivity.

2. Add PBMCs (●) & specific TB antigens (⊗) to wells pre-coated with antibodies to IFN-γ (γ) and incubate overnight (37°C, CO₂).

3. IFN-γ (•) is released from activated T cells. Wash wells, add secondary conjugated antibody (▲). Incubate for 1 hour.

4. Wash wells, add substrate and incubate for 7 minutes. Stop reaction with water. One spot (●) is the footprint of one activated T cell.

Negative Result  Positive Result

Nil Control  ESAT-6 Panel A

CFP 10 Panel B  Positive Control
<table>
<thead>
<tr>
<th>Strain tested</th>
<th>Antigens</th>
<th>ESAT-6</th>
<th>CFP 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis complex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. tuberculosis</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M. africanum</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M. bovis</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>BCG substrain</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- gothenburg</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- moreau</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- tice</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- tokyo</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- danish</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- glaxo</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- montreal</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- pasteur</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Environmental strains</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. abcessus</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M. avium</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M. branderi</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M. celatum</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M. cheloneae</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M. fortuitum</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M. gordonii</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M. intracellulare</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M. kansasii</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M. malmoense</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M. marinum</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M. oenavense</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M. scrofulaceum</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M. smegmatis</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M. szulgai</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M. terrae</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M. vaccae</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M. xenopi</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

= not present in species/strain, + = present in species/strain.

Interferon Gamma Release Assays (IGRAs)
Overall Test Performance → More specific

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity**</th>
<th>Specificity (BCG vaccinated population)</th>
<th>Specificity (non-BCG vaccinated population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>71-82%</td>
<td>*60%</td>
<td>97%</td>
</tr>
<tr>
<td>QFT</td>
<td>81-86%</td>
<td>&gt; 95%</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td>T-SPOT. TB</td>
<td>90-95%</td>
<td></td>
<td>98%</td>
</tr>
</tbody>
</table>

* Variable, depends on when and how often BCG was given
**Sensitivity wanes in HIV or young children

Advantages: one visit, blood test, more specific

Pai, M et al. Clinical Microbiology Reviews, 2014
King et al., AJRCCM, 2015
### IGRA Interpretation

#### QFT-GIT

<table>
<thead>
<tr>
<th>Result</th>
<th>Nil</th>
<th>TB Ag – Nil (IU/ml)</th>
<th>Mitogen – Nil (IU/ml)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>≤ 8.0</td>
<td>≥ 0.35 and ≥ 25% nil</td>
<td>Any</td>
<td><em>M. tb</em> infection likely</td>
</tr>
<tr>
<td>Negative</td>
<td>≤ 8.0</td>
<td>&lt;0.35 or &lt; 25% nil</td>
<td>≥ 0.5</td>
<td><em>M. tb</em> infection unlikely</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>≤ 8.0</td>
<td>&lt;0.35 or &lt; 25% nil</td>
<td>&lt;0.5</td>
<td>Uncertain likelihood of infection</td>
</tr>
<tr>
<td></td>
<td>&gt; 8.0</td>
<td>Any</td>
<td>Any</td>
<td></td>
</tr>
</tbody>
</table>

#### TB-SPOT.TB

<table>
<thead>
<tr>
<th>Result</th>
<th>Nil</th>
<th>TB Response</th>
<th>Mitogen</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>≤ 10 spots</td>
<td>≥ 8 spots</td>
<td>Any</td>
<td><em>M. tb</em> infection likely</td>
</tr>
<tr>
<td>Borderline</td>
<td>≤ 10 spots</td>
<td>5, 6, 7 spots</td>
<td>Any</td>
<td>Uncertain likelihood of infection</td>
</tr>
<tr>
<td>Negative</td>
<td>≤ 10 spots</td>
<td>≤ 4 spots</td>
<td>≥ 20 spots</td>
<td><em>M. tb</em> infection unlikely</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>&gt; 10 spots</td>
<td>Any</td>
<td>Any</td>
<td>&lt; 20 spots</td>
</tr>
</tbody>
</table>
Indeterminate and Borderline Tests

• Indeterminate
  – Poor response to mitogen (+ control), may improve with repeat test
    • Delay in processing
    • Technical errors
    • Patient factors: immunocompromised
  – High background IFN gamma in nil (- control)

• Borderline (T-SPOT®)
  – In borderline zone close to cut point

• If result borderline, invalid or indeterminate still exists, can repeat test
Sources of variability in IGRAs

Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children


Clinical Infectious Diseases (2017): Vol 64

# LTBI Diagnostic Approach

<table>
<thead>
<tr>
<th>Groups with Increased Likelihood of Infection with Mtb</th>
<th>Benefit of Therapy</th>
<th>LTBI Testing Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Household contact or recent exposure of an active case</td>
<td>Yes</td>
<td>Likely to be Infected Low to Intermediate Risk of Progression (TST $\geq 10$mM)</td>
</tr>
<tr>
<td>Mycobacteriology laboratory personnel</td>
<td>Not demonstrated</td>
<td></td>
</tr>
<tr>
<td>Immigrants from high burden countries (&gt;20 / 100,000)</td>
<td>Not demonstrated</td>
<td>Likely to be Infected High Risk of Progression (TST $\geq 5$mM)</td>
</tr>
<tr>
<td>Residents and employees of high risk congregate settings</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>Not demonstrated</td>
<td>Unlikely to be Infected (TST $&gt; 15$mM)</td>
</tr>
</tbody>
</table>

**Risk of Developing Tuberculosis if Infected**

- **Low**
  - No risk factors
  - Children age less than 5
- **Intermediate (RR 1.3-3)**
  - Clinical predisposition
  - Diabetes
  - Chronic renal failure
  - Intravenous drug use
- **High (RR 3-10)**
  - HIV infection
  - Immunosuppressive therapy
  - Abnormal CXR consistent with prior TB
  - Silicosis

**Benefit of Therapy**

- Not demonstrated
- Yes

---

Lewinsohn et al. ATS/IDSA/CDC: Diagnosis of TB in Adults and Children. CID 2017:64
## LTBI Diagnostic Approach

<table>
<thead>
<tr>
<th>Group</th>
<th>Testing Strategy</th>
<th>Considerations</th>
</tr>
</thead>
</table>
| Likely to be Infected, High Risk of Progression (TST ≥ 5mM) | Adults  
Acceptable: IGRA OR TST  
Consider dual testing where a positive result from either result would be considered **positive**  
Children ≤ 5 years of age  
Preferred: TST  
Acceptable: IGRA OR TST  
Consider dual testing where a positive result from either would be considered **positive**  | Prevalence of BCG vaccination  
Expertise of staff and/or laboratory  
Test availability  
Patient perceptions  
Staff perceptions  
Programmatic concerns |
| Likely to be Infected, Low to Intermediate Risk of Progression (TST ≥ 10mM) | Preferred: IGRA where available  
Acceptable: IGRA or TST | - |
| Unlikely to be Infected (TST > 15mM) | **Testing for LTBI is not recommended**  
If necessary:  
Preferred: IGRA where available.  
Acceptable: Either IGRA OR TST  
For serial testing:  
Acceptable: Either IGRA OR TST  
Consider repeat or dual testing where a negative result from either would be considered **negative** | - |
Testing in Health Care Workers

• Serial testing can result in conversions, reversions, boosting, random variability
• Criteria for conversion and boosting have been established for TST
• Definite criteria for conversions and reversions with IGRA not clear yet
• Some studies show quite a bit of variability around the IGRA cut point with serial testing → true infection/conversion versus false positive
• In one large HCW study, IGRA conversion was seen more frequently then TST conversion
A 45 y.o. health care worker who works in a TB clinic, and is otherwise healthy, has an indeterminate QFT GIT test.

What should be done next?

Repeat IGRA and try to avoid delays in processing
A college’s student health service is developing a policy on testing for TB infection. In the past, the clinic has had < 50% students return after their initial visit. Some of their students are international exchange students from South Asia and Central America.

If you were asked to choose an IGRA or TST for this clinic’s mode of LTBI diagnosis, which would you choose?

IGRA is the better choice given difficulty getting students back as well as students who have likely had BCG vaccine
Diagnosis of LTBI - Summary

- TST and IGRA are imperfect tests for identifying TB infection; IGRA more specific
- Neither rules out TB Disease
- Neither differentiates TB Disease from TB infection
- Avoid testing in low risk people
- All tests have lower sensitivity in immunocompromised patients
- IGRA is preferred in BCG vaccinated individuals and in those unlikely to return for 2nd visit, who are likely to have *M. tb* infection and have low/intermed risk of progression (2017 guidelines - strong recommendation)
- Both IGRA and TST may be helpful in certain populations (2017 guidelines – conditional recommendations)
- Retesting may be indicated in borderline or indeterminate results
Treatment of TB Infection

• Rule out TB disease
  – History, exam, chest radiograph, bacteriology if needed

• Assess risks and benefits of treatment

• Educate and counsel patient
  – Why treatment is indicated
  – Potential side effects
  – Duration of therapy

• Completion of treatment is low
  – Maximize with shorter regimen, selecting right population
# Treatment Regimens for LTBI

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Months of Duration</th>
<th>Interval</th>
<th>Minimum Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>9*</td>
<td>Daily</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2x wkly**</td>
<td>76</td>
</tr>
<tr>
<td>INH</td>
<td>6</td>
<td>Daily</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2x wkly**</td>
<td>52</td>
</tr>
<tr>
<td>RIF</td>
<td>4</td>
<td>Daily</td>
<td>120</td>
</tr>
<tr>
<td>INH-RPT</td>
<td>3</td>
<td>Weekly**</td>
<td>12</td>
</tr>
</tbody>
</table>

*Preferred  ** Intermittent treatment only with directly observed therapy (DOT)
TB Infection Treatment

• Completion of Isoniazid for 9 months (9H) is variable, but poor even in controlled situations
  – 52%-69% (latter in a controlled study)

• Why?
  – Hepatotoxicity
  – Provider preferences
  – Duration and pill burden
TBTC Study 26: PREVENT TB

Patients with LTBI at high risk for reactivation (mainly close contacts of active cases)

- 9 months of daily INH, self-administered (270 doses)
- 3 months of once weekly INH and rifapentine by DOT (12 doses)

Study endpoint: development of active TB at 33 months
INH and Rifapentine for 12 weeks (3HP)

• Efficacy was similar
• 82% in INH-RPT vs. 69% completion in standard therapy group
• Fewer adverse events in INH-RPT arm
• More hepatotoxicity in INH alone group
• More ‘possible hypersensitivity’ reactions in INH-RPT
INH-RPT Recommendations

- **Equal alternative** to 9 months INH in otherwise healthy individuals ≥ 12 years old + high risk for TB disease:
  - Close contact
  - Converter
  - Fibrotic changes on CXR
  - *HIV not on ART, otherwise healthy*

- Others are considered on an individual basis
- Main limitation: Need for directly observed therapy
INH-RPT NOT Recommended

- Children < 2 years old
- HIV on ART
- Pregnancy, or likely to become pregnant during treatment
- Presumed INH or RIF resistance
- Prior adverse effects with INH or rifamycins
Self Administration or Modified DOT

**iAdhere Study:**
- Directly observed therapy (DOT) v self administered (SAT) v self administered with weekly text reminders (eSAT)
- Completion rates were measured in multiple countries
- SAT in the US was non-inferior to DOT
- Discontinuation due to adverse events was similar among groups

**Video DOT**
- Use of recorded or video visits being studied at several sites
- Convenient, well accepted

→ Awaiting CDC recommendation on SAT and modified DOT
→ Such strategies may improve initiation and adherence to therapy

Belknap et al., CROI, 2015
Gold et al., Open Forum Infectious Diseases, 2016
RPT Adverse Effects

• Reddening of secretions
• Uncommon
  – Hepatotoxicity (0.4%)
  – Leukopenia
  – Thrombocytopenia
  – Hypersensitivity seen with other rifamycins (3.8%)
  • Fever, ‘flu-like’, pruritus, hypotension, headache, petechiae
• Hepatic induction of drug metabolism
• Be observant of other potential adverse effects as regimen more widely used
• Report: ltbidruevents@cdc.gov; MedWatch
Other Short-Course Regimens for TB Infection

- RIF daily for 4 months (4R)
  - INH resistant or intolerant
  - Patient unlikely to be adherent for longer treatment period
  - 80-85% treatment completion rates
- In situations where Rifampin cannot be used (e.g., HIV-infected persons receiving protease inhibitors), Rifabutin may be substituted
- Increases completion rate, lessens burden on public health clinic
- Caveats – Be aware of drug interactions
  - Methadone, Prednisone, Protease Inhibitors, Oral contraceptives, Many others
## Treatment of LTBI: Comparison of INH vs. RIF

### Comparison of Regimen Features: 9H and 4R

<table>
<thead>
<tr>
<th>Regimen Feature</th>
<th>9H</th>
<th>4R</th>
</tr>
</thead>
<tbody>
<tr>
<td>High efficacy</td>
<td>X</td>
<td>X*</td>
</tr>
<tr>
<td>Lower hepatotoxicity</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Lower overall cost</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Higher adherence</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>More effective against INH-resistant strains <em>(e.g., among foreign-born persons)</em></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Shorter duration</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Fewer drug-drug interactions</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

* Good evidence that 3R is at least as efficacious as 6H. Inferential reasoning from other evidence suggests that efficacy of 4R may approach that of 9H.
A 47 y.o. household contact to a patient with active TB is found to be QFT GIT positive. She is known to be TST negative in the past. She is on no medications and is otherwise healthy. She works from home and lives with the index case.

Which regimen is best for this patient?

Short – course INH + Rifapentine weekly for 12 weeks via DOT
- No other interfering medications
- Index case also getting home DOT – convenient
- Fits study population
Up to 13 million people in the U.S. have latent tuberculosis (TB) infection.

**Latent TB Infection**
Latent TB infection means TB germs are in the body, but not enough to cause sickness or spread germs to others.

**TB Disease**
If TB germs become active & multiply, latent TB infection can turn into TB disease.

**1 in 10**
Without treatment, 1 in 10 people with latent TB infection will develop TB disease.

**People Who Should be Tested for TB Infection Include:**
- Contacts of people with TB disease.
- People from countries where TB disease is common.
- People with health problems that make it hard to fight TB disease.
- People who spend time in places where TB is more common.

**Treating Latent TB Infection Prevents TB Disease.**
- **TB Skin Test**
  - A skin test or blood test can find TB infection.
- **TB Blood Test**
  - Shorter regimens help patients finish treatment.
- **1 dose**
  - 1 time per week
  - 12 weeks
- **$17,000 TO TREAT TB DISEASE**
- **$500 TO TREAT LATENT TB INFECTION**
  - Treating latent TB infection is less costly than treating disease.

**Eliminating TB Requires Expanding Testing & Treatment of Latent TB Infection. CDC Works To:**
- Engage Affected Communities & Medical Providers.
- Promote Effective Testing & Treatment Options.
- Develop New Guidance & Tools.

To learn more about latent TB infection: www.cdc.gov/tb

March 1, 2016
TB Infection: Future Directions

• Emphasize use of short-course rifamycin containing regimens

• Ongoing trials
  – 9H v 4R
  – 9H v 1 month daily INH and Rifapentine
  – Self-administered weekly INH and Rifapentine with text messaging reminders (iAdhere)

• Role of Rifabutin
Advances in TB Disease

• Diagnosis
  – GeneXpert
  – Line probe assays
  – Urine LAM

• Treatment
  – New uses for known drugs
  – New drugs
  – Short course and novel regimens
TB Disease

- Maintain a high index of suspicion especially in high-risk groups
  - Transplant, patients on TNF blockers, patients receiving chemotherapy, dialysis patients
  - Consult with local health department to understand who is at-risk in your community
- Diagnostic tools are only useful if disease is suspected
- New diagnostics allow for more rapid identification AND treatment of TB → preventing transmission
- Prevention (by identifying and treating LTBI) is the key
Think TB!

Recognize possible signs and symptoms of Tuberculosis. Early diagnosis and treatment reduces spread. Contact your Health Department or physician for more information.
9,557 TB CASES REPORTED IN THE U.S. IN 2015

A Typical TB Case Requires:

493 TB Deaths in 2014

PLUS

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

$450 MILLION

Total cost to U.S. for TB cases in 2015.

Our progress towards elimination is slowing - the U.S. saw the first increase in cases in over 20 years!

TB CAN HAPPEN ANYWHERE & TO ANYONE!

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

TB case rates are:

29x Higher for Asians than whites.

8x Higher for African Americans than whites.

8x Higher for Hispanics/Latinos than whites.

2 out of every 3 TB cases occur among foreign-born persons.

DRUG-RESISTANT TB IS COMPLEX & COSTLY.

Drug-resistance threatens our ability to treat & control TB.

TOTAL 2015 CASES

1 Extensively Drug-Resistant TB

88 Multidrug-Resistant TB

9,468 Tuberculosis (Drug-Susceptible)

DIRECT TREATMENT COST PER CASE

$494,000

$154,000

$18,000

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

To learn more about TB, visit: www.cdc.gov/tb

NOVEMBER, 2016
Summary – “Unite to End TB”

• Demographics of TB in US are changing
• USPSTF policy + advances in diagnosing (IGRA) + treating (3HP and other short course regimens) TB infection will help get us to TB elimination
• New strategies and partnerships between public health and other health care providers key
• Newer, faster diagnostics for TB disease, but need to “think TB”
• There are many resources available in different formats; know your local and regional experts
Diagnosis and Treatment of Latent Tuberculosis Infection (LTBI)

Based on: the Official Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC), Morbidity and Mortality Weekly Report (MMWR) 2000, 49 (RR-6); MMWR 2010, 59 (RR-5); MMWR 2011, 60 (RR-3); the American Academy of Pediatrics (AAP) 2015 Red Book: Report of the Cor

Global Tuberculosis Institute
New Jersey Medical School

TB INFOLINE: 1-800-4TB-DCCS  http://globaltb.njms.rutgers.edu

Supportive Adjustment to a New Life Makes TB Care Possible

This article highlights the story of a refugee family from Burma, which is affected by TB. The story was shared by a local health department in the Northern United States. Names and some details of the case have been altered to protect the identity of the patient.

Our patient, Thida, Begam, was born in Burma, also known as Myanmar, and arrived in the United States (US) in June 2012 with her children, including a 13-year-old daughter and her younger siblings. Prior to arrival in the US, Thida and her children lived in a refugee camp. Thida's oldest daughter, Sara, was pregnant when she arrived in the US, and had a baby a few months after her arrival. The family also lived in part of the Kachin ethnic group.

Soon after arriving in the Northern Plains, Thida became ill and was admitted to the hospital where she was diagnosed with TB. As a result of her illness, she missed many of the cultural education classes that were offered through the local refugee resettlement agency. These classes typically provide practical information such as learning how to take public transportation, managing medical appointments, learning how to access shopping facilities, registering children in school, and connecting refugees with needed social support services. Many resettlement agencies also offer community classes, English for Speakers of Other Languages (ESOL) classes, job training, interpretation and translation services, and driving lessons.