Approaches to LTBI Diagnosis

Focus on LTBI
October 8th, 2018

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DISCLOSURES

• I have no disclosures or conflicts of interest to report
Objectives

• By the end of this presentation, participants should be able to:
  • Explain how interferon-gamma release assays (IGRAs) identify true LTBI in individuals who receive BCG vaccination compared to tuberculin skin tests (TSTs)
  • List causes of indeterminate results for IGRAs
  • Describe limitations of using IGRAs to diagnose LTBI in low risk populations
  • Explain why TST and IGRAs cannot rule-out active tuberculosis
Tuberculosis (TB): leading cause of death globally

Top causes of death worldwide in 2016.a,b
Deaths from TB among HIV-positive people are shown in grey.

- Ischaemic heart disease
- Stroke
- Chronic obstructive pulmonary disease
- Lower respiratory infections
- Alzheimer disease and other dementias
- Trachea, bronchus, lung cancers
- Diabetes mellitus
- Road injury
- Diarrhoeal diseases
- Tuberculosis
Latent Tuberculosis Infection: Screening
Release Date: September 2016

Recommendation Summary

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic adults at increased risk for infection</td>
<td>The USPSTF recommends screening for latent tuberculosis infection (LTBI) in populations at increased risk.</td>
<td>B</td>
</tr>
</tbody>
</table>

To read the recommendation statement in JAMA, click here.
To read the evidence summary in JAMA, click here.
Who should get tested?

1. **Close contact to infectious (pulmonary) TB**
   - at any time

2. **Lived (born or travelled > 1 month) to a country where TB is common**
   - Anywhere but United States, Canada, Australia, New Zealand, or Western and North Europe

3. **Immunosuppression or other high risk condition**
   - HIV-positive, TNF-alpha blocker, transplant
   - diabetes, chronic renal failure

Adapted from CA risk assessment  
https://www.cdph.ca.gov
look, a new test for TB infection! Now we can accurately test everyone!
Example TB infection Diagnostic Algorithm

At-risk person

Tuberculin test/IGRA + symptom review

- **Negative**
  - LTBI treatment not indicated

- **Positive (symptoms OR TST/IGRA)**
  - Chest x-ray
    - **Normal**
      - Potential candidate for LTBI treatment if asymptomatic and TST/IGRA was positive
    - **Abnormal**
      - Concerning symptoms?
        - Evaluate for active TB
The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis

Hannah Alsdurf, Philip CHill, Alberto Matteelli, Haileyesus Getahun, Dick Menzies

Lancet Infect Dis 2016

- Large meta-analysis
  - 58 studies, n=748,572
- Completion rates for non-contacts/refugees: 9.7%
  - Reasons for not completing:
    - Toxicity
    - Health systems issues
    - Social situation
- All public health programs, no primary care settings
Of individuals estimated to have LTBI, 1024/7503 or 14% have completed treatment.
Clinical Infectious Diseases

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


1Oregon Health & Science University, Portland, Oregon, 2Emory University School of Medicine and 3Centers for Disease Control and Prevention, Atlanta, Georgia, 4Denver Public Health Department, Denver, Colorado, 5National Jewish Health and the University of Colorado Denver, and 6California Department of Public Health, Richmond; 7St James’s Hospital, Dublin, Ireland; 8Francis J. Curry International TB Center, San Francisco, California; 9Foundation for Innovative New Diagnostics, Geneva, Switzerland; 10McGill University and McGill International TB Centre, Montreal, Canada; 11University of Southampton, United Kingdom; 12National Jewish Health, Denver, Colorado; 13Vanderbilt University School of Medicine, Vanderbilt Institute for Global Health, Nashville, Tennessee, 14Wisconsin State Laboratory of Hygiene, Madison, and 15University of Arkansas for Medical Sciences, Little Rock
Tests for identifying TB infection

- No gold standard for diagnosing LTBI
- All tests assess T-cells for prior exposure to TB antigens
Rationale for testing in selected individuals

<table>
<thead>
<tr>
<th></th>
<th>SENSITIVITY</th>
<th>SPECIFICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>80%</td>
<td>97% (60% if BCG vaccinated)</td>
</tr>
<tr>
<td>Quantiferon</td>
<td>80%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>T-SPOT.TB</td>
<td>90%</td>
<td>&gt;95%</td>
</tr>
</tbody>
</table>

For a US born patient (LTBI prevalence ~3%) with no other risk factors, the PPV of....

- + TST is 45%
- + QFT is 55%
- + T.SPOT. TB is 58%
TST—how it works

Presentation of mycobacterial antigens

Antigen-presenting cell

Memory T cell

Skin test

in-vitro blood test

Measurement of induration and erythema

IFN-γ

TNF-α

IL-8, etc

Measurement of IFN-γ production

IFN-γ

TNF-α

IL-8, etc
Tuberculin Skin Testing
Mantoux Method

5 TU of PPD
48 to 72 hours

Interpretation depends on person’s risk factors
### Tuberculin Skin Test
Criteria for a Positive Reaction

<table>
<thead>
<tr>
<th>&gt;=5mm</th>
<th>&gt;=10mm</th>
<th>&gt;=15 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-positive</td>
<td>prior BCG vaccination</td>
<td>no risk</td>
</tr>
<tr>
<td>contacts</td>
<td>prior residence in a TB endemic area</td>
<td></td>
</tr>
<tr>
<td>Abnormal chest radiograph</td>
<td>injection drug use</td>
<td></td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>children</td>
<td></td>
</tr>
<tr>
<td></td>
<td>congregate settings such as correctional facilities, nursing facilities, hospitals</td>
<td></td>
</tr>
</tbody>
</table>

Note: Skin test conversion is an increase of ≥10 mm to ≥ 10 mm within a 2-year period
Interval From Primary Infection to TST Conversion

N = 172

Menzies D. AJRCCM 1999;159:15
Tuberculin Skin Testing
“Boosting”

- Induration (mm)
  - 0
  - 5
  - 10
  - 15
  - 20
- Years
  - 0
  - 5
  - 10
  - 15
  - 20
  - 30
  - 31

- Infection
- TST
- TST
- TST
- TST

- 14 mm
- 11 mm
- 12 mm
Tuberculin Skin Testing
Two-step Testing

Place TST
Read at 48-72 hrs

Positive

Negative
Place 2nd TST at one week
Read at 48-72 hours

Positive (True positive)
Negative (True negative)

Follow-up for positive TST and evaluation for TB infection
Stability of Reactions and Inter-reader Variability

• Biologic variation from test to test in the same patient is very small, approximately 1mm.
  • Chaparas et al. ARRD 1985;132:175

• Same reader - Standard deviations of 1.3-1.9 mm
  • Erdtmann, et al. JAMA 1974;228:479

• Different readers - Standard deviations of 2.3-2.5 mm
  • Furcolow et al. ARRD 1967;96:1009.
Tuberculin skin test interpretation: False-**negative** results

- **Host factors**
  - Immunosuppression
  - Recent TB infection (<3 months)
  - Age (newborn, elderly)
  - Infections (viral, fungal, bacterial)
  - Live virus vaccination
  - Overwhelming tuberculosis
  - ESRD
  - Other illness affecting lymphoid organs

- **Technical factors**
  - Tuberculin product (improper storage, contamination)
  - Improper method of administration, reading and/or recording of results

Slide courtesy of Dr. Neha Shah

## TST Specificity

<table>
<thead>
<tr>
<th>Test</th>
<th>Specificity</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST without BCG</td>
<td>97</td>
<td>95–99</td>
</tr>
<tr>
<td>TST with BCG</td>
<td>59</td>
<td>46–73</td>
</tr>
<tr>
<td>QFT</td>
<td>96</td>
<td>94–98</td>
</tr>
</tbody>
</table>


Slide courtesy of Dr. Neha Shah
Tuberculin skin test interpretation:
False-positive results

• Cross-reactions from atypical mycobacterial infections

• Recent or multiple BCG vaccination

• Misinterpretation of immediate hypersensitivity to tuberculin

• Switching tuberculin products (aplisol > tubersol)

Slide courtesy of Dr. Neha Shah

This interactive website provides detailed information on current and past BCG policies and practices for over 100 countries. The Atlas is designed to be a useful resource for clinicians, policymakers and researchers alike, providing information that may be helpful for better interpretation of TB diagnostics as well as design of new TB vaccines.

The rationale and methodology for this Atlas is described in a paper in PLoS Medicine.

Please select a Country from the drop down box, or use the map to select a country to view all available information concerning that country’s BCG policies and practices.
<table>
<thead>
<tr>
<th>Country</th>
<th>India</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region</td>
<td>South Asia</td>
</tr>
<tr>
<td>TB Incidence (per 100,000 per year) *t</td>
<td>168</td>
</tr>
<tr>
<td>TB Incidence (Count) *t</td>
<td>20,000</td>
</tr>
<tr>
<td>TB Prevalence (per 100,000 per year) *s</td>
<td>420</td>
</tr>
<tr>
<td>TB Prevalence (Count) *s</td>
<td>330,000</td>
</tr>
<tr>
<td>Income group (World Bank)</td>
<td>Low Income</td>
</tr>
<tr>
<td>Current BCG vaccination</td>
<td>Yes</td>
</tr>
<tr>
<td>BCG Recommendation Type</td>
<td>A</td>
</tr>
<tr>
<td>Which year was vaccination introduced</td>
<td>1948</td>
</tr>
<tr>
<td>Year BCG stopped</td>
<td>N/A</td>
</tr>
<tr>
<td>Timing of 1st BCG</td>
<td>At birth</td>
</tr>
<tr>
<td>Multiple BCG?</td>
<td>No</td>
</tr>
<tr>
<td>Timing of BCG #2</td>
<td>N/A</td>
</tr>
<tr>
<td>Timing of BCG #3</td>
<td>N/A</td>
</tr>
<tr>
<td>Multiple BCG in the past?</td>
<td>No</td>
</tr>
<tr>
<td>Timing of old BCG #2</td>
<td>N/A</td>
</tr>
<tr>
<td>Timing of old BCG #3</td>
<td>N/A</td>
</tr>
<tr>
<td>Year booster BCG stopped</td>
<td>N/A</td>
</tr>
<tr>
<td>BCG Strain</td>
<td>BCGV, Chennai strain, BCG, laboratory Gundy, Chennai, India</td>
</tr>
</tbody>
</table>

**BCG Recommendation Types**

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>This country currently recommends BCG vaccination for everyone at a certain age. (Example: BCG at birth or for school-age children, etc.)</td>
</tr>
<tr>
<td>B</td>
<td>This country used to recommend BCG vaccination for everyone, but currently does not.</td>
</tr>
<tr>
<td>C</td>
<td>BCG vaccination was never recommended for everyone in this country. (I.e.: never gave BCG or given only to high-risk groups such as health care workers.)</td>
</tr>
</tbody>
</table>

**Data Availability**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>This entry is not applicable to this country.</td>
</tr>
<tr>
<td>Blank</td>
<td>This data was not available.</td>
</tr>
</tbody>
</table>
IGRA vs. TST

**Advantages over TST**
- Not affected by BCG vaccination
- Not affected by most non-tuberculous mycobacteria
- Interpretation is more objective
- No return visit needed for interpretation of test
- Patients and providers may lack confidence in TST results

**Disadvantages over TST**
- Blood draw
- Cost

Interferon-Gamma Release Assays (IGRAs)

• QuantiFERON®-TB Gold (QFT)
  • Reported as positive, negative, or indeterminate

• T-SPOT.TB (T-Spot)
  • Reported as positive, borderline, negative, or indeterminate

Slide courtesy of Dr. Neha Shah
**IGRAs: how they work**

**Quantiferon®**

- Incubate overnight whole blood with antigens specific for *MTB* (ESAT-6, TB7.7, & CFP-10)
- Measure [IFN$\gamma$] by ELISA

**IFN$\gamma$-release assays**

- Addition of substrate
- Addition of secondary ab
- Wash

**T-SPOT.TB®**

- Each spot = the “footprint” of one IFN$\gamma$-producing cell

**Figure courtesy of Ed Chan**
Antigens used in IGRAs compared to PPD

*M. tuberculosis* antigens shared with NTM, & BCG

Antigens specific to *M. tuberculosis*, e.g., ESAT-6 & CFP-10

*Ganguly et al, 2008: 88, 510-517*

Slide courtesy of Dr. David Horne
QuantiFERON-Gold In Tube

1. Collect 1mL of blood into Nil, Antigen and Mitogen tubes. Shake well. Incubate tubes at 37°C for 16-24 hrs.

2. Centrifuge tubes for 15 minutes.

3. Add conjugate, plasma samples and standards to ELISA. Incubate for 120 minutes at room temperature.

4. Wash and add substrate. Read absorbance after 30 minutes.

5. Software calculates results and prints reports.

3 days

8 weeks at 2 - 8°C

Harvested plasma is stable refrigerated for at least 4 weeks.
## TST and QFT Specificity

<table>
<thead>
<tr>
<th></th>
<th>Specificity</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST without BCG</td>
<td>97</td>
<td>95–99</td>
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</tr>
<tr>
<td>QFT</td>
<td>96</td>
<td>94–98</td>
</tr>
</tbody>
</table>

• Menzies, Ann Intern Med, 2007
Testing Individuals with prior BCG-vaccination

• Using a test with poor specificity will result in many false-positive results

<table>
<thead>
<tr>
<th>Test</th>
<th>Specificity</th>
<th>False-positive rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>QFT</td>
<td>94 – 98</td>
<td>12%</td>
</tr>
<tr>
<td>TST</td>
<td>46 – 73</td>
<td>73%</td>
</tr>
</tbody>
</table>

BCG vaccinated population

• Pai, Clin Micro Rev, 2014
• Miramontes, PLOS One, 2015
Interpreting Quantiferon-Gold

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 8.0</td>
<td>&lt; 0.35</td>
<td>≥ 0.5</td>
<td>Negative</td>
<td>M. tuberculosis infection NOT likely</td>
</tr>
<tr>
<td></td>
<td>≥ 0.35 and &lt; 25% of Nil value</td>
<td>≥ 0.5</td>
<td>Positive</td>
<td>M. tuberculosis infection likely</td>
</tr>
<tr>
<td></td>
<td>≥ 0.35 and ≥ 25% of Nil value</td>
<td>Any</td>
<td>Indeterminate</td>
<td>Results are indeterminate for TB Antigen responsiveness</td>
</tr>
<tr>
<td>&gt; 8.0</td>
<td>Any</td>
<td>Any</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Valid ELISA test run.

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Nil</th>
<th>TB Ag</th>
<th>Mitogen</th>
<th>TB Ag-Nil</th>
<th>Mitogen-Nil</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.86</td>
<td>2.18</td>
<td>&gt; 10</td>
<td>1.32</td>
<td>&gt; 10</td>
<td>POSITIVE</td>
</tr>
</tbody>
</table>
# QuantiFERON®-TB Gold Test
## Report of Results

<table>
<thead>
<tr>
<th>Result</th>
<th>Report/Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>TB infection <em>likely</em></td>
</tr>
<tr>
<td>Negative</td>
<td>TB infection <em>unlikely, BUT</em> cannot be excluded especially if patient has TB signs and symptoms</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>Test inconclusive about the likelihood of TB infection. Either: 1. Repeat QFT-G 2. Administer a TST 3. Evaluate quantitative QFT result</td>
</tr>
</tbody>
</table>
Mitogen – Positive Control
Low response may indicate inability to generate IFN-γ

Nil – Negative Control
Adjusts for background IFN-γ

TB1 – Primarily detects CD4 T cell response

TB2 – Optimized for detection of CD4 and CD8 T cell responses

QuantiFERON-Gold Plus (QFT-plus)
QFT-TB Gold Plus

- Goal - Improved Sensitivity
- CD4 and CD8 tubes

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>QFT-Plus result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Indeterminate</td>
<td>Negative##</td>
</tr>
<tr>
<td>Low-risk controls</td>
<td>106</td>
<td>0</td>
</tr>
<tr>
<td>Active TB</td>
<td>119</td>
<td>3</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>72</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>47</td>
<td>2</td>
</tr>
<tr>
<td>Smear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>65</td>
<td>1</td>
</tr>
<tr>
<td>Positive</td>
<td>54</td>
<td>2</td>
</tr>
<tr>
<td>Localisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTB</td>
<td>79</td>
<td>3</td>
</tr>
<tr>
<td>EPTB</td>
<td>40</td>
<td>0</td>
</tr>
</tbody>
</table>

Barcellini, Eur Resp J Feb 11, 2016
Interpretation of results

Results of the QFT-Plus assay are interpreted objectively using QuantiFERON-TB Gold Plus analysis software.

- **QFT-Plus Positive**
  - *M. tuberculosis* infection is likely
  - Nil ≤ 8.0; and
  - TB1 and/or TB2 minus Nil ≥ 0.35 and ≥ 25% of Nil

- **QFT-Plus Negative**
  - *M. tuberculosis* infection is NOT likely
  - Nil ≤ 8.0, Mitogen minus Nil ≥ 0.5; and
  - TB1 and TB2 minus Nil < 0.35 or ≥ 0.35 and < 25% of Nil

- **QFT-Plus Indeterminate**
  - Likelihood of *M. tuberculosis* infection cannot be determined
  - Nil > 8.0
  - Nil ≤ 8.0 and TB1 and TB2 < 0.35 or ≥ 0.35 and < 25% of Nil and Mitogen minus Nil < 0.5
T-SPOT.TB

Collect peripheral venous blood

Centrifuge

8 hours

Plasma
PBMCs
Red cells

Remove PBMCs, wash and count

Incubate overnight

Add PBMCs and antigens to 4 wells

Wash, develop and dry plate

Pre-coated wells

Count the coloured spots in each well

First 24 hours

T-Cell Xtend – 32 hours
## T-SPOT Interpretation

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Negative</th>
<th>Borderline</th>
<th>Indeterminate</th>
</tr>
</thead>
<tbody>
<tr>
<td>T Spot TB</td>
<td>≥ 8 spots*</td>
<td>≤ 4 spots*</td>
<td>5-7 spots*</td>
<td>Controls fail:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- High Nil</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Poor Mitogen</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>response</td>
</tr>
</tbody>
</table>

* (TB Ag - Nil) and assumes appropriate control responses
# T-Spot Test

## Report of Results

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<td>TB infection <em>likely</em></td>
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<td>Negative</td>
<td>TB infection unlikely, BUT cannot be excluded especially if patient has TB signs and symptoms</td>
</tr>
</tbody>
</table>
| Borderline or Indeterminate | Test inconclusive about the likelihood of TB infection. 
Either: 
1. Repeat T-Spot 
2. Administer a TST |
IGRAs – Basic similarities

- Single blood draw
- Incubate blood cells with antigens from the region of difference 1 (RD1)
  - not contained in BCG but present in *M. bovis*
  - Antigens present in *M. marinum, kansasii, szulgai, and flavescens*
- Results available in 1 day
Indeterminate/borderline results

- Cannot determine whether someone has TB infection
  - Low lymphocyte count
  - Low lymphocyte activation potential
  - Specimen collection errors

- Repeat test with valid result (pos/neg) in 68% (Banach IJTL 2011)
  - Repeating the test is often the next step
Sources of variability and indeterminate results

• IFN-γ may vary by +0.24 IU/ml when result between 0.25-0.80 (Metcalfe AJRCCM 2013)

• S. Africa study of serial QFTs – “converters” who had levels < 0.7 IU/ml had same TB risk as those with levels <0.2 IU/ml (Nemes AJRCCM 2017)
Patient at risk for TB infection:

• 20 year old man with prior residence in India:
  • Required to undergo TB testing for college
  • 11 mm TST, normal CXR
    “It’s due to my BCG”
  • QFT positive (TB-nil = 1.15)
    “It’s boosting from the TST. I would like to be tested again.”

*What would you do next?*
Discordant results? Testing for TB infection more than once and dealing with the outcome
Repeat testing after the first test result

• You don’t like the first test result so you repeat it to get the one you like

• Positive result in low risk individual (healthcare worker who is required to undergo testing)

• High risk individual who has a negative result
  • Repeating in person with HIV whose CD4 has risen above 200
Patient at risk for TB infection:

• 20 year old man with prior residence in India:
  • Required to undergo TB testing for college
  • 11 mm TST, normal CXR
    “It’s due to my BCG”
  • QFT positive (TB-nil = 1.15)
    “It’s boosting from the TST. I would like to be tested again.”
  • Repeat QFT negative (TB-nil = 0.34)
    “Finally we agree”
TST and IGRA agreement

<table>
<thead>
<tr>
<th></th>
<th>US-born</th>
<th>Lived in TB endemic area</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>QFT 0.35 IU</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TST 10 mm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>+</strong></td>
<td>0.6%</td>
<td>2.2% (0.3-1.0%)</td>
</tr>
<tr>
<td></td>
<td>(0.6-1.0%)</td>
<td>(1.5-3.2%)</td>
</tr>
<tr>
<td><strong>-</strong></td>
<td>0.8%</td>
<td>96.4% (95.0-97.4%)</td>
</tr>
<tr>
<td></td>
<td>(0.4-1.6%)</td>
<td>(95.0-97.4%)</td>
</tr>
<tr>
<td><strong>TST 10 mm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>+</strong></td>
<td>9.1%</td>
<td>7.2% (5.5-9.4%)</td>
</tr>
<tr>
<td></td>
<td>(7.0-11.6%)</td>
<td>(5.5-9.4%)</td>
</tr>
<tr>
<td><strong>-</strong></td>
<td>11.2%</td>
<td>72.5% (66.5-77.8%)</td>
</tr>
<tr>
<td></td>
<td>(0.8-15.3%)</td>
<td>(66.5-77.8%)</td>
</tr>
</tbody>
</table>

Slide courtesy of Dr. David Horne
**IGRA Screening & Low LTBI Risk**

- IGRA responses may change over time
  - 2400 U.S. HCW, serial TST, QFT, T-SPOT (Dorman AJRCCM 2014)
  - Conversions occurred: TST 0.9% QFT 6.1% T-SPOT 8.3%

<table>
<thead>
<tr>
<th>Baseline TB-nil</th>
<th>Participants with Result [n (% of Total)]</th>
<th>Participants with Reversion among Those with at Least One Follow-up Result after Baseline [n/Subtotal (%)]</th>
<th>Participants with Conversion among Those with at Least One Follow-up Result after Baseline [n/Subtotal (%)]</th>
<th>Percentage of All Conversions [n/Subtotal (%)]</th>
<th>Participants Whose Conversion was “Transient,” among Those with at Least One Follow-up Visit after Conversion [n/Subtotal (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>QFT-GIT (n = 2,418)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.01</td>
<td>1,176 (48.6)</td>
<td>52/1,129 (4.5)*</td>
<td>52/138 (37.7)</td>
<td>35/43 (61.4)*</td>
<td></td>
</tr>
<tr>
<td>0.01–0.19</td>
<td>1,024 (42.3)</td>
<td></td>
<td>65/972 (6.7)*</td>
<td>35/46 (76.1)*</td>
<td></td>
</tr>
<tr>
<td>0.20–0.35</td>
<td>63 (2.6)</td>
<td></td>
<td>21/62 (33.9)*</td>
<td>11/17 (64.7)*</td>
<td></td>
</tr>
<tr>
<td>0.36–0.49</td>
<td>29 (1.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.50–0.69</td>
<td>23 (1.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.70–0.99</td>
<td>13 (0.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.00–2.99</td>
<td>23 (1.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.00+</td>
<td>30 (1.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indeterminate</td>
<td>37 (1.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-SPOT (n = 2,418)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>1,309 (54.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–4</td>
<td>754 (31.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–7</td>
<td>74 (3.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>17 (0.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>19 (0.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>8 (0.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>100 (4.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invalid or failed</td>
<td>137 (5.7)</td>
<td></td>
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</tr>
</tbody>
</table>
Diagnosing Latent TB Infection

• TSTs and IGRAs cannot distinguish between latent TB infection and active TB disease

• Always evaluate for underlying active TB

• IGRAs and TSTs can be falsely negative in up to 25% of individuals with active TB

Slide courtesy of Dr. Neha Shah
Can IGRAs be used to monitor a response to treatment?

- 15 studies that evaluated LTBI responses
- No consistent pattern using reversions or quantitative IFN-gamma levels
## Pros and Cons

<table>
<thead>
<tr>
<th><strong>IGRA</strong></th>
<th><strong>TST</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>in vitro</em></td>
<td><em>in vivo</em></td>
</tr>
<tr>
<td>Specific Mtb antigens</td>
<td>PPD</td>
</tr>
<tr>
<td>1 patient visit</td>
<td>2 patient visits</td>
</tr>
<tr>
<td>phlebotomy</td>
<td>intracutaneous injection</td>
</tr>
<tr>
<td>stimulate within hours</td>
<td>injected = done</td>
</tr>
<tr>
<td>results possible in 1 day</td>
<td>results in 2–3 days</td>
</tr>
<tr>
<td>complex laboratory test</td>
<td>point-of-care test</td>
</tr>
<tr>
<td>Much that is not understood</td>
<td>data storage—varies</td>
</tr>
</tbody>
</table>
Summary

• Neither an IGRA or TST can distinguish between latent TB infection and active TB
  • A negative test does not exclude active TB

• Test people at risk for infection
  – 1⁰ people born or lived in a high-burden country
  – Prioritize those with risk for exposure AND progression (HIV, DM, ESRD etc.) on a programmatic level or clinic level to allow for scaling up of TB testing

• Prefer IGRA if available
  – Better in BCG-vaccinated people
  – Results are easily retrieved

• Repeat all (+) IGRA in lower risk people
  – healthcare workers
  – Consider for those with risk of progression (HIV, DM etc.) but no risk for exposure
Questions?