LTBI Testing:
Areas of Concern and Gray Zones

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Outline

- Positive Predictive Value
- LTBI testing in the general population
- Reproducibility
- Boosting

Positive Predictive Value

- The proportion of true positive among the positive results
- For example, if the prevalence of LTBI is 1%, and the specificity of the test of 97% (and the sensitivity 100%), 100 people are tested…
**Systematic Review**  
*Ann Intern Med.* 2008;149:177-184

- Patients with active TB
  - QFT-GIT: Pooled sensitivity 0.70
  - T-SPOT.TB: Pooled sensitivity 0.90
- Very low risk for TB
  - QFT-GIT: Pooled specificity 0.96
  - T-SPOT.TB: Pooled specificity 0.93
- TST
  - Pooled sensitivity: 0.77
  - Pooled specificity: 0.97 in non-BCG and 0.59 in BCG vaccinated

**Positive Predictive Value:**  
Non-BCG vaccinated → US born

<table>
<thead>
<tr>
<th>LTBI prevalence</th>
<th>TST</th>
<th>QFT Gold</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>20%</td>
<td>44%</td>
</tr>
<tr>
<td>3%</td>
<td>44%</td>
<td>70%</td>
</tr>
<tr>
<td>5%</td>
<td>57%</td>
<td>80%</td>
</tr>
<tr>
<td>10%</td>
<td>74%</td>
<td>90%</td>
</tr>
</tbody>
</table>

**Positive Predictive Value:**  
BCG vaccinated → Foreign born

<table>
<thead>
<tr>
<th>LTBI prevalence</th>
<th>TST</th>
<th>QFT Gold</th>
<th>TSpot</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%</td>
<td>9%</td>
<td>51%</td>
<td>40%</td>
</tr>
<tr>
<td>10%</td>
<td>17%</td>
<td>68%</td>
<td>59%</td>
</tr>
<tr>
<td>20%</td>
<td>32%</td>
<td>83%</td>
<td>76%</td>
</tr>
<tr>
<td>30%</td>
<td>45%</td>
<td>89%</td>
<td>85%</td>
</tr>
</tbody>
</table>
LTBI testing among the general population

Serial TB testing of 2563 Healthcare workers in the U.S.  
*Am J Respir Crit Care Med 2014;189:77–87*

- Methods: QFT Gold In-Tube (QFT-GIT), T-SPOT.TB, and TST at baseline and every 6 mo for 18 mo
- Baseline Positive: 15% from countries where BCG is given as an infant and/or a child
  - QFT-GIT 4.9%, T-SPOT 6.0%, TST 5.2%
- Conversions from negative to positive during the study
  - QFT-GIT 6.1%, T-SPOT 8.3%, TST 0.9%
- The reversion rates of the converters
  - QFT-GIT 76%, T-SPOT 77%
  - TST: 57% refused repeat testing; 91% reversion among those re-tested.

QFT vs. TST in a US Collage Population

- 15,936 tests
- 9,483 students: at least one risk factor (e.g., volunteer at a hospital, diabetes) or healthcare students
- They chose either TST or QFT
- 46% from TB high incidence countries

*Clin Infect Dis 2014;58:1260–6*
Results of TST and QFT by student risk of TB exposure

<table>
<thead>
<tr>
<th>TST</th>
<th>QFT-GIT</th>
<th>TST</th>
<th>QFT-GIT</th>
<th>TST</th>
<th>QFT-GIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td>18.8</td>
<td>16.5</td>
<td>18.4</td>
<td>16.7</td>
<td>18.2</td>
</tr>
<tr>
<td>Low Risk</td>
<td>13</td>
<td>6.6</td>
<td>11.3</td>
<td>5.7</td>
<td>11.2</td>
</tr>
<tr>
<td>No Risk</td>
<td>8.4</td>
<td>5.3</td>
<td>8.1</td>
<td>5.2</td>
<td>8.0</td>
</tr>
</tbody>
</table>

Repeted TST

- Repeated TST can result in larger reaction sizes.
  - Non-specific variation (< 6 mm in 95% of all those tested)
  - True conversion
  - Boosting
- BCG vs. remote infection

Impact of TST on subsequent LTBI testing
Boosting

- Maximal if the interval between the first and second test is 1 – 5 weeks
- Significantly less if the interval is 48 hours or more than 60 days
- But, boosting can be seen up to one - two years
- Boosting can be seen after a third or fourth TST especially among the malnourished.

Variability and Boosting of IGRA after TST: South Africa

![Diagram]

<table>
<thead>
<tr>
<th>TST 0.1ml (2TU) 8723 PPD</th>
<th>Visit 1 (Day -21)</th>
<th>Visit 2 (Day -4)</th>
<th>Visit 3 (Day -7)</th>
<th>Visit 4 (Day 0)</th>
<th>Day +3</th>
<th>Day +7</th>
<th>Day +28</th>
<th>Day +84</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>“Reproducibility phase”</td>
<td>“Boosting phase”</td>
<td></td>
<td></td>
<td></td>
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</tr>
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T-SPOT®TB, QuantiFERON®TB-Gold-in-Tube,

Am J Respir Crit Care Med 2009;180:49

Variability and Boosting of IGRA after TST: South Africa

<table>
<thead>
<tr>
<th>TABLE 1. DEMOGRAPHIC DETAILS OF STUDY PARTICIPANTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Number of subjects</td>
</tr>
<tr>
<td>Age, years: mean (SD)</td>
</tr>
<tr>
<td>Racial group, n (%)</td>
</tr>
<tr>
<td>Black African</td>
</tr>
<tr>
<td>Mixed ancestry</td>
</tr>
<tr>
<td>European ancestry</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
</tr>
<tr>
<td>HIV status</td>
</tr>
<tr>
<td>BCG vaccinated</td>
</tr>
<tr>
<td>Previous TB, n</td>
</tr>
</tbody>
</table>

Am J Respir Crit Care Med 2009;180; 49
Variability and Boosting of IGRA after TST: South Africa

- Baseline within-subject variability
  - 7 of the 21 high- or medium risk subjects had conversion or reversion
  - 95% of the variability of “TB response” within 80% of the mean value

Boosting of IGRA after TST: South Africa

- Boosting of IGRA after TST
  - Definition of the boosting for the study: 80% increase in “TB response”
  - Boosting was observed in:
    - 5 of 8 baseline positive IGRA
    - 2 of 16 baseline negative IGRA
    - 1 of 2 borderline IGRA
    - All 3 were TST (+)
  - Remote infection?

Serial TB testing of 2563 Healthcare workers in the U.S.

- Sub-study: 121 subjects had IGRA 7 – 21 days after the baseline TST/IGRAs
  - 8 of 50 (16%) baseline positive TST
  - 3 of 71 (4%) baseline negative TST
### The Case Follow-up

- The patient refused to take LTBI treatment because she was trying to get pregnant.
- ~ a year later, her PCP repeated QFT and it was negative (TB – nil = 0.30)

### Indeterminate Results

- NYC: 28,864 tested
- 522 (2%) indeterminate
  - Low mitogen 264
  - High nil 258
- Repeat QFT: 137 (ASAP after the first test: all within 90 days)
  - 4% positive
  - 64% negative
  - 32% indeterminate (the same type)

### Summary

- IGRAs are not perfect
  - Low positive predictive value in low LTBI prevalence groups.
  - Sensitivity similar to TST
  - Poor reproducibility
  - Uncertain about how to interpret boosting
<table>
<thead>
<tr>
<th>Wisdom</th>
</tr>
</thead>
<tbody>
<tr>
<td>• “TST is preferred for serial testing programs such as those involving health care workers because IGRA has a high false-positive rate in this setting in the United States” <em>(JAMA 2014;312:1460)</em></td>
</tr>
<tr>
<td>• TST/IGRAs are tools to assess the risk of progression to active TB in the future.</td>
</tr>
</tbody>
</table>