Interferon-Gamma Release Assays: Summary of the evidence and practical approaches
TB Clinician’s Meeting, Washington, DC
November 17, 2011

Karen R Steingart, MD, MPH
karenst@uw.edu
Disclosure

• I serve as Coordinator of the Evidence Synthesis & Policy subgroup of Stop TB Partnership’s New Diagnostics Working Group

• I am an Editor with the Cochrane Collaboration’s Infectious Diseases Group

• I have no financial conflict of interest
Session objectives

• Summarize the evidence from systematic reviews on interferon-gamma release assays

• Discuss who should be tested and what test to use for latent TB Infection

• Discuss case examples

“How on earth do you keep up—there’s an IGRA paper published every minute……..?” PhD student
**LTBI versus Pulmonary TB**

<table>
<thead>
<tr>
<th>Latent TB Infection</th>
<th>Pulmonary TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test for TB infection is positive</td>
<td>Test for TB infection usually positive</td>
</tr>
<tr>
<td>CXR is negative</td>
<td>CXR may be abnormal</td>
</tr>
<tr>
<td>No symptoms or physical findings suggestive of TB disease</td>
<td>Symptoms may include: fever, cough, night sweats, weight loss, fatigue, hemoptysis</td>
</tr>
<tr>
<td>Respiratory specimens are negative</td>
<td>Respiratory specimens may be culture or smear positive</td>
</tr>
</tbody>
</table>
The spectrum of latent tuberculosis: rethinking the biology and intervention strategies

Clifton E. Barry 3rd*, Helena I. Boshoff*, Véronique Dartois†, Thomas Dick‡, Sabine Ehrt§, JoAnne Flynn¶, Dirk Schnappinger§, Robert J. Wilkinson¶#**, and Douglas Young#**

Barry et al. Nature Reviews Microbiol 2009
- “Uncertain what proportion of individuals remain infected with *M. tuberculosis* after TST or IGRA conversion”

- “Uncertain how long adaptive immune responses towards mycobacterial antigens persist in the absence of live mycobacteria”
Approved tests for LTBI

QuantiFERON®-TB Gold In-Tube (Cellestis) measures interferon gamma.

T-SPOT®.TB test (Oxford Immunotec) measures peripheral blood mononuclear cells that produce interferon gamma.
TST – Key Points

• Measures cell-mediated immune response
• Uses PPD
• Measure reaction at 48-72 hrs
• Measure induration, not erythema
• Record reaction in millimeters
• Positive TST can be read up to 7 days
• Negative TST can be read up to 72 hrs
QuantiFERON®-TB Gold In Tube

16-24 hour incubation

ESAT-6  CFP-10  TB 7.7

Nil
Negative control

PHA
Positive control

IFN-γ
Measurement of IFN-γ secreted by antigen specific T cells

**T-SPOT.TB®**

**ELISPOT**

- **ESAT-6**
- **CFP-10**
- **Nil**
- **PHA**

**Overnight incubation**
In the absence of a gold standard, a hierarchy of evidence for tests of LTBI
WHO Expert Group on IGRAs

- Efficacy of preventive therapy based on IGRA test results
- Predictive value of IGRA for active TB
- Correlation with exposure gradient
- Sens/spec in active TB
- Concordance with TST
Efficacy of preventive therapy based on IGRA test results

??

No data
Treatment of latent tuberculosis infection in HIV infected persons

• 12 trials (8,578 randomized participants)
• Intervention: preventive therapy (any anti-TB drug)
• Comparison: placebo
• Outcome: active tuberculosis
  - Overall RR 0.68, 95% CI 0.54 to 0.85
  - TST pos RR 0.38, 95% CI 0.25 to 0.57
  - TST neg RR 0.89, 95% CI 0.64 to 1.24

Protection against TB In HIV (+) who are TST (+)

Akolo C. Cochrane Database Syst Rev 2010
Several large scale studies now completed

- Predictive ability of IGRA is better than TST, but not significantly better
- Neither TST nor IGRA accurately predict who should be treated for LTBI
- The decision to choose one test (IGRA or TST) over the other should be based on specificity, logistics, cost, and patient preference

Efficacy of preventive therapy based on IGRA test results

- Predictive value of IGRA for active TB
- Correlation with exposure gradient
- Sens/spec in active TB
- Concordance with TST

Stronger

Weaker
IGRA vs TST, which has greater predictive value for active tuberculosis? 15 studies (26,680 participants)

Figure. Unadjusted incidence rate ratios (IRR) for positive versus negative test result, by test type. Rangaka et al The Lancet Infect Dis 2011

IGRA: IRR 2.11 (1.29, 3.46)

TST: IRR 1.60 (0.94, 2.72)
Several large scale studies now completed

- Predictive ability of IGRA is better than TST, but not significantly better
- Neither TST nor IGRA accurately predict who should be treated for LTBI

The decision to choose one test (IGRA or TST) over the other should be based on specificity, logistics, cost, and patient preference.
Sensitivity Quantiferon-Gold, adults, all settings

16 studies pooled sensitivity = 78%


<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Sensitivity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mori et al., 2004 (7)</td>
<td>0.88 (0.81–0.93)</td>
</tr>
<tr>
<td>Ferrara et al., 2005 (8)</td>
<td>0.55 (0.23–0.93)</td>
</tr>
<tr>
<td>Ravn et al., 2005 (9)</td>
<td>0.85 (0.72–0.94)</td>
</tr>
<tr>
<td>Kang et al., 2005 (10)</td>
<td>0.76 (0.63–0.86)</td>
</tr>
<tr>
<td>Lee et al., 2006 (11)</td>
<td>0.70 (0.59–0.79)</td>
</tr>
<tr>
<td>Ferrara et al., 2006 (12)</td>
<td>0.71 (0.49–0.87)</td>
</tr>
<tr>
<td>Goletti et al., 2006 (13)</td>
<td>0.83 (0.61–0.95)</td>
</tr>
<tr>
<td>Dewan et al., 2007 (14)</td>
<td>0.56 (0.40–0.70)</td>
</tr>
<tr>
<td>Kobashi et al., 2006 (15)</td>
<td>0.86 (0.73–0.94)</td>
</tr>
<tr>
<td>Mazurek et al., 2007 (16)</td>
<td>0.65 (0.54–0.74)</td>
</tr>
<tr>
<td>Kang et al., 2007 (17)</td>
<td>0.87 (0.76–0.94)</td>
</tr>
<tr>
<td>Bua et al., 2007 (18)</td>
<td>0.77 (0.58–0.90)</td>
</tr>
<tr>
<td>Soysal et al., 2008 (19)</td>
<td>0.77 (0.68–0.85)</td>
</tr>
<tr>
<td>Kobashi et al., 2008 (26)</td>
<td>0.85 (0.77–0.90)</td>
</tr>
<tr>
<td>Nishimura et al., 2008 (27)</td>
<td>0.77 (0.66–0.86)</td>
</tr>
<tr>
<td>Kobashi et al., 2008 (28)</td>
<td>0.79 (0.59–0.92)</td>
</tr>
</tbody>
</table>

Pooled sensitivity = 0.78 (0.73–0.82)
Chi-square = 46.23; P < 0.001
Inconsistency $I^2 = 67.6\%$

Sensitivity Quantiferon-Gold, adults, all settings

16 studies pooled sensitivity = 78%

Sensitivity TSPOT.TB, adults, all settings

13 studies pooled sensitivity = 90%

Sensitivity TST, adults, all settings

Pooled Sensitivity = 0.77 (0.71 to 0.82)
Chi-square = 92.77; df = 19 (p = 0.0000)
Inconsistency (I-square) = 79.5%

20 studies pooled sensitivity = 77%

Interferon-Gamma Release Assays for Active Pulmonary TB Diagnosis in Adults in Low- and Middle-Income Countries: Systematic Review and Meta-Analysis, Metcalfe J et al, J of Infection, 2011

### QFT-GIT

<table>
<thead>
<tr>
<th>authoryear</th>
<th>country</th>
<th>Sensitivity (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aabye 2009</td>
<td>Tanzania</td>
<td>81 (71, 88)</td>
<td>15.15</td>
</tr>
<tr>
<td>Chegou 2009</td>
<td>South Africa</td>
<td>96 (78, 100)</td>
<td>12.81</td>
</tr>
<tr>
<td>Chen (a) 2009</td>
<td>China</td>
<td>85 (71, 94)</td>
<td>12.02</td>
</tr>
<tr>
<td>Dheda (d) 2009</td>
<td>South Africa</td>
<td>73 (45, 92)</td>
<td>5.26</td>
</tr>
<tr>
<td>Katiyar 2008</td>
<td>India</td>
<td>96 (87, 99)</td>
<td>17.83</td>
</tr>
<tr>
<td>Pai 2007</td>
<td>India</td>
<td>74 (60, 84)</td>
<td>11.80</td>
</tr>
<tr>
<td>Raby 2008</td>
<td>Zambia</td>
<td>84 (68, 94)</td>
<td>11.09</td>
</tr>
<tr>
<td>Tahereh 2010</td>
<td>Iran</td>
<td>77 (59, 90)</td>
<td>9.02</td>
</tr>
<tr>
<td>Tsiouris 2006</td>
<td>South Africa</td>
<td>77 (46, 95)</td>
<td>5.02</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
<td>100.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(I-squared = 59.8%, p = 0.011)</td>
<td></td>
</tr>
</tbody>
</table>

### TSPOT

<table>
<thead>
<tr>
<th>authoryear</th>
<th>country</th>
<th>Sensitivity (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dheda (c) 2009</td>
<td>South Africa</td>
<td>93 (68, 100)</td>
<td>15.47</td>
</tr>
<tr>
<td>Ozekinci (a) 2007</td>
<td>Turkey</td>
<td>93 (76, 99)</td>
<td>26.13</td>
</tr>
<tr>
<td>Shao-ping 2009</td>
<td>China</td>
<td>91 (71, 99)</td>
<td>18.95</td>
</tr>
<tr>
<td>Soysal (a) 2008</td>
<td>Turkey</td>
<td>81 (72, 88)</td>
<td>39.45</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
<td>100.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(I-squared = 27.5%, p = 0.247)</td>
<td></td>
</tr>
</tbody>
</table>

### HIV infected

Pooled sensitivity

- QFT-GIT 65%
- TSPOT 68%

### HIV uninfected

Pooled sensitivity

- QFT-GIT 84%
- TSPOT 88%

HIV infected

- Pooled sensitivity
- QFT-GIT 65%
- TSPOT 68%

Subtotal (I-squared = 76.2%, p = 0.000)
Specificity of QFT-Gold and QFT-GIT and effect of BCG vaccination

BCG-nonvaccinated
Pooled specificity 99%

BCG-vaccinated
Pooled specificity 96%

Specificity of the TST and effect of BCG vaccination

BCG-nonvaccinated
Pooled specificity 97%

BCG-vaccinated
Pooled specificity 59%

How BCG affects TST results

False-positive tuberculin skin tests: what is the absolute effect of BCG and non-tuberculous mycobacteria?

M. Farhat,*† C. Greenaway,** M. Pai,*§ D. Menzies*

* Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, McGill University, Montreal, Quebec, Canada; † Massachusetts General Hospital, Harvard University, Boston, Massachusetts, USA; ‡ Division of Infectious Disease and Microbiology, SMBD Jewish General Hospital, McGill University, Montreal, § Joint Departments of Epidemiology & Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada

24 studies with 240,243 subjects

BCG given in infancy: false-positive TST results due to BCG occurred in only 6% of vaccinated subjects

BCG given after infancy: false-positive TST results due to BCG occurred in 40% of vaccinated subjects
Online Atlas: www.bcgatlas.org
<table>
<thead>
<tr>
<th>Country</th>
<th>Bosnia and Herzegovina</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region</td>
<td>Europe &amp; Central Asia</td>
</tr>
<tr>
<td>TB Incidence (per 100 000 per year) **+</td>
<td>50</td>
</tr>
<tr>
<td>TB Incidence (Count) **+</td>
<td>1900</td>
</tr>
<tr>
<td>TB Prevalence (per 100 000 per year) **+</td>
<td>62</td>
</tr>
<tr>
<td>TB Prevalence (Count) **+</td>
<td>2300</td>
</tr>
<tr>
<td>Income group (World Bank)</td>
<td>Lower middle 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>1950</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>Yes</td>
</tr>
<tr>
<td>Timing of old BCG #2</td>
<td>3 yrs</td>
</tr>
<tr>
<td>Timing of old BCG #3</td>
<td>5, 7, 13 &amp; 19 yrs</td>
</tr>
<tr>
<td>Year booster BCG stopped</td>
<td>1996</td>
</tr>
<tr>
<td>BCG Strain</td>
<td>Pasteur's Institute Paris</td>
</tr>
<tr>
<td>Is TST done post BCG?</td>
<td>No</td>
</tr>
<tr>
<td>Year of BCG coverage estimate</td>
<td>2008</td>
</tr>
<tr>
<td>BCG coverage (%)</td>
<td>97%</td>
</tr>
<tr>
<td>Year of changes to BCG schedule</td>
<td>1996</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>
India, BCG given at birth has limited effect on TST
Japan, BCG given after birth has major effect on TST
Case 1

- 18-month-old adopted male arrived in San Francisco from China
- No known TB exposure
- TST= 15 mm, QFT-GIT indeterminate
- Chest radiograph PA and lateral normal
- Parents are wary of medications and have read on the internet about isoniazid and liver toxicity

- What else would you like to know?
- Could TST be a false positive result?
- How would you manage this child?

High income: sensitivity 81%
Low/middle: sensitivity 78%

High income: sensitivity 86%
Low/middle: sensitivity 84%
Mandalakas

- Pooled specificities were similar among the 3 tests (~90%)
- Decreased sensitivity of TST, QFT-Gold/QFT-GIT and T-SPOT.TB when
  - average age was < 5 years,
  - all children were HIV-infected
  - > 50% were BCG-vaccinated
“IGRAs cannot be recommended routinely for use in children younger than 5 years of age or for immunocompromised children of any age because of a lack of published data about their utility with these groups”

http://www.cps.ca/english/statements/id/tuberculosis.htm
Summing up: IGRAs versus TST sensitivity

• QFT = TST (~80%) in immunocompetent
• TSPOT (~90%) > TST or QFT
• Lower in HIV infection
• Lower in high-incidence countries
• Similar sensitivity for detection of LTBI in children
Summing up: IGRAs versus TST specificity

• TST specificity is high in BCG non-vaccinated, but low and variable in BCG vaccinated
• IGRAs have high specificity (>95%) in low-incidence settings
  – IGRA > TST
  – IGRAs are not affected by BCG vaccination
  – IGRAs may be helpful in settings that give BCG after infancy or give multiple vaccinations
Case 2

- 35-year-old Bosnian female arrived in the US 2 yrs ago
- Diabetes mellitus treated with oral medication
- Received BCG vaccine as child, does not recall when
- TST = 12 mm
- No signs or symptoms of TB, CXR normal
- No known contact with a TB patient
- Bosnia TB incidence = 51 per 100,000 per year
- Could TST be a false positive result?
- What are this patient’s risk factors for TB?
- How would you manage this patient?
Diabetes Mellitus Increases the Risk of Active Tuberculosis: A Systematic Review of 13 Observational Studies

Christie Y. Jeon*, Megan B. Murray
Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, United States of America

Funding: CYJ is supported by a departmental grant from the Department of Epidemiology at Harvard School of Public Health. The department had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

Academic Editor: Brian Williams, World Health Organization, Switzerland

Citation: Jeon CY, Murray MB (2008) Diabetes mellitus increases the risk of active tuberculosis: A systematic review of 13 observational studies.

ABSTRACT

Background

Several studies have suggested that diabetes mellitus (DM) increases the risk of active tuberculosis (TB). The rising prevalence of DM in TB-endemic areas may adversely affect TB control. We conducted a systematic review and a meta-analysis of observational studies assessing the association of DM and TB in order to summarize the existing evidence and to assess methodological quality of the studies.

Methods and Findings

We searched the PubMed and EMBASE databases to identify observational studies that had reported an age-adjusted quantitative estimate of the association between DM and active TB disease. The search yielded 13 observational studies (n = 1,786,212 participants) with 17,698 TB
Diabetes and LTBI

After a short stay in the US, Michelangelo’s David returns to Italy.
Case 3

• Patient is referred for possible LTBI
• 55-year-old female emigrated from El Salvador to Texas in 1985
• Employed at a poultry processing plant for 15 years
• Diagnosed with rheumatoid arthritis
• Prescribed prednisone 20 mg twice daily, methotrexate and Humira [adalimumab-a tumor necrosis factor alpha antagonist]

• How would you evaluate this patient?

Case courtesy of Heartland National TB Center
• Individuals with immune-mediated inflammatory disorders (IMIDs) are at increased risk of developing active TB

• Current evidence does not suggest that IGRAs > TST in identifying patients with IMID who could benefit from LTBI treatment

• Tendency for guidelines to prefer IGRA over TST in IMIDs or to recommend both tests

• If high index of suspicion for LTBI, perform both tests
Two strategies to detect LTBI in patients with immune-mediated inflammatory disease, Smith, Current Opinion Rheumatol 2011

Strategy 1: either test positive to maximize sensitivity; best used in areas that have not used BCG vaccine. Benefit: fewer false negatives. Drawback: in areas that do use BCG vaccine, some patients with discordant TST+/IGRA- will be incorrectly classified as LTBI.

Strategy 2: maximize specificity; best used in areas that have used BCG vaccine. Benefit: fewer false positives. Drawback: false negative IGRA results are possible and more likely in IMID patients.
Case 4

- 40-year-old male living with HIV
- CD4 count of 337 cells/mm³
- On antiretroviral therapy with undetectable HIV RNA level
- Presents for routine follow-up, asymptomatic
- States that his partner was recently diagnosed with active pulmonary TB and is currently receiving TB treatment
- How would you evaluate this patient? Would you do anything different if CD4 count were 100 cells/mm³?

Case courtesy of Ingrid A. Binswanger, MD, MPH
Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America

- All persons should be tested for LTBI at time of HIV diagnosis
- Persons with negative tests for LTBI and CD4+ count <200 cells/µL should be re-tested once they start ART and attain CD4+ count >200 cells/µL
- Annual testing for LTBI is recommended for HIV-infected persons at high risk (jail, congregate settings, IDU, etc)
- All HIV-infected persons with a positive test for LTBI should receive CXR and clinical evaluation to rule out active TB
“Although desirable, a substantially improved test to better define individuals at risk of future tuberculosis does not seem imminent. It is thus all the more important that only individuals are tested who are at a high risk of tuberculosis in the future and who are fully appraised of the treatment consequences.”

Lange C and Rieder H, AJRCCM 2011
### Who should be tested?

**Risk factors for the development of active tuberculosis among persons infected with *Mycobacterium tuberculosis***

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Estimated risk for TB relative to persons with no known risk factor</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acquired immunodeficiency syndrome (AIDS)</td>
<td>110-170</td>
<td>1,2</td>
</tr>
<tr>
<td>Human immunodeficiency virus infection (HIV)</td>
<td>50-110</td>
<td>3,4</td>
</tr>
<tr>
<td>Transplantation (related to immune-suppressant therapy)</td>
<td>20-74</td>
<td>5-8</td>
</tr>
<tr>
<td>Silicosis</td>
<td>30</td>
<td>9,10</td>
</tr>
<tr>
<td>Chronic renal failure requiring hemodialysis</td>
<td>10-25</td>
<td>11-14</td>
</tr>
<tr>
<td>Carcinoma of head and neck</td>
<td>15.0</td>
<td>15</td>
</tr>
<tr>
<td>Recent TB infection (≤2 years)</td>
<td>15.0</td>
<td>16,17</td>
</tr>
<tr>
<td>Abnormal chest x-ray with apical fibronodular changes typical of healed TB (not granuloma)</td>
<td>6-19</td>
<td>18-20</td>
</tr>
<tr>
<td>Tumor necrosis factor (TNF)-alpha inhibitors</td>
<td>1.7-9</td>
<td>21,22,35,36</td>
</tr>
<tr>
<td><strong>Moderate risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment with glucocorticoids</td>
<td>4.9</td>
<td>23</td>
</tr>
<tr>
<td>Diabetes mellitus (all types)</td>
<td>2-3.6</td>
<td>24-27</td>
</tr>
<tr>
<td>Young age when infected (≤4 years)</td>
<td>2.2-5</td>
<td>28</td>
</tr>
<tr>
<td><strong>Slightly increased risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight (&lt;85 percent of ideal body weight); for most individuals this is equivalent to body mass index (BMI) ≤20.</td>
<td>2.3</td>
<td>29</td>
</tr>
<tr>
<td>Cigarette smoker (1 pack/day)</td>
<td>2.3</td>
<td>30,31</td>
</tr>
<tr>
<td>Chest x-ray with solitary granuloma</td>
<td>2</td>
<td>20,32</td>
</tr>
<tr>
<td><strong>Low risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infected person, no known risk factor, normal chest x-ray (&quot;low risk reactor&quot;)</td>
<td>1</td>
<td>33</td>
</tr>
<tr>
<td><strong>Very low risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive booster (two step test) with no other known risk factor and normal chest x-ray</td>
<td>0.5</td>
<td>Extrapolated from 33 and 34</td>
</tr>
</tbody>
</table>
CDC Updated Guidelines for Using IGRAs – Key Points

• TST, QFT-GIT, TSPOT measure different aspects of the immune response
  - use different antigens
  - use different interpretation criteria
• Different tests can yield different results
• IGRA may be used in place of (not in addition to) TST in all situations in which CDC recommends TST as an aid in diagnosing *M. tuberculosis* infection

*MMWR. June 25, 2010 / Vol. 59 / No. RR-5*
IGRA Preferred but TST Acceptable for:

• Persons from groups that historically have low rates of returning to have TSTs read (homeless persons)

• Persons who have received BCG as a vaccine or for cancer therapy
TST *Preferred* but IGRA Acceptable for:

- Children younger than 5 years

Note: Some experts recommend both IGRA and TST to increase sensitivity in this age group
Either TST or IGRA Used for:

- Recent contacts of persons known/suspected with active TB
  - Confirm negative results obtained *before* 8 weeks after end of exposure by repeat testing 8-10 weeks after end of exposure

- Surveillance programs for health-care workers
  - IGRAs do not boost subsequent test results
Both IGRA and TST Used for

- Persons with increased risk for infection, progression, and poor outcome (HIV infected, children <5)
- Suspected active TB (symptoms, signs, and/or radiographic evidence)

- Remember: Even multiple negative results from any combination of these tests CANNOT exclude TB
Discordant Results
What do they mean? What should one do?

- Discordant results = IGRA+/TST- or IGRA-/TST+
- Consider positive result of *either* IGRA or TST as evidence of TB infection when
  - Clinically suspect active TB
  - Risks for infection, progression, and poor outcome are increased (HIV infection, children <5 yrs)
- In BCG-vaccinated persons (not at risk for poor outcome), can discount TST result <15 mm when IGRA is negative
• High week-to-week variability
Guidelines on interferon-γ release assays for tuberculosis infection: concordance, discordance or confusion?

C. M. Denkinger¹, K. Dheda²,³ and M. Pai⁴,⁵
1) Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA, 2) Lung Infection and Immunity Unit, Division of Pulmonology and UCT Lung Institute, Department of Medicine, University of Cape Town, Cape Town, South Africa, 3) Department of Infection, University College London Medical School, London, UK, 4) Department of Epidemiology, Biostatistics, and Occupational Health, McGill University and 5) Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, Montreal, QC, Canada

Abstract

Identification of latent tuberculosis (TB) infection and preventive therapy is important for TB control, especially in high-risk populations. Since the advent of interferon-γ release assays (IGRAs), many studies have evaluated their role in the diagnosis of active and latent TB. With the growing evidence base, many guidelines now include IGRAs. We surveyed the literature and contacted experts to identify 33 guidelines and position papers from 25 countries and two supranational organizations. The results show considerable diversity in the recommendations on IGRAs, with four approaches commonly proposed: (i) two-step approach of tuberculin skin test (TST) first, followed by IGRA either when the TST is negative (to increase sensitivity, mainly in immunocompromised individuals), or when the TST is positive (to increase specificity, mainly in bacillus Calmette-Guérin-vaccinated individuals); (ii) Either TST or IGRA, but not both; (iii) IGRA and TST together (to increase sensitivity); and (iv) IGRA only, replacing the TST. Overall, the use of IGRAs is increasingly recommended, but most of the current guidelines do not use objective, transparent methods to grade evidence and recommendations, and do not disclose conflicts of interests. Future IGRA guidelines must aim to be transparent, evidence-based, periodically updated, and free of financial conflicts and industry involvement.

Keywords: Diagnosis, guidelines, immunodiagnostics, interferon-γ release assays, tuberculosis

Article published online: 25 April 2011

Clin Microbiol Infect 2011; 17: 806–814
TST and IGRAs are similar in some ways

• Do not distinguish latent infection from active disease
• Do not provide any direct evidence of the presence of viable bacilli
• Determine that infection has at some point led to an acquired immune response that is detectable following re-challenge with antigen
• Are both affected by HIV infection
TST and IGRAs are dissimilar in some ways

- IGRAs are specific in all settings
- TST is specific in BCG unvaccinated or those who get BCG in infancy
- IGRAs have operational characteristics that are more advantageous
- IGRAs require more resources
References

- Systematic reviews on IGRAs and other TB diagnostics are available at Evidence-based tuberculosis diagnosis, www.tbevidence.org
- Barry C et al. Nature Reviews Microbiology | AoP, published online 26 October 2009; doi:10.1038/nrmicro2236
- ATS/CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. MMWR Recomm Rep 2000 ;49(RR-6)
Are we going to see THE END OF TB in our lifetimes?

Thank you!