IGRAs in Children

Deborah Anne Lewinsohn, MD
Associate Professor
Infectious Disease, Pediatrics
Disclosure Statement: Deborah Lewinsohn

• I have no significant financial interests in Cellestis or Oxford Immunotech.

• All relevant financial interests are as follows:
  – Cellestis: Honoraria for three Cellestis-sponsored meetings for role as a participant, moderator, or invited speaker.
  – Oxford Immunotech: Sponsored research contract to provide T cells to use for QC for T-spot.TB.
Natural History of *M. tuberculosis* Infection

1° Progressive Disease (<5% vs. 50-80%)

Reactivation Disease (5-10%)

Persistent Infection (90% vs 5-50%)

Adapted from: Henry Boom, TBRU, CWRU
Diagnosis of LTBI using TST

Problems include:
- Inter-reader variability; requires return visit.
- Confusing cutoffs for various risk groups.
- Low positive predictive value in countries with low prevalence
- False negatives
  - Anergy: HIV/ESRD
  - Recent TB
  - Very young
  - Overwhelming disease
- False positives
  - BCG vaccination
  - Nontuberculous mycobacteria
Diagnosis of Mtb infection by TST: TB controllers’ comfort food
T cell based diagnostics for TB: IFN-γ Release Assays (IGRA’s)

• Potent pro-inflammatory cytokine released by T cells and NK cells. Assays reflect adaptive T cell response to TB.

• Two commercially available tests:
  – T-spot®.TB; ELISPOT.
  – QuantiFERON®-TB Gold IT; ELISA.
Antigens Absent from BCG

Gene Map from Sanger Centre; Cole et al., Nature 393, 537-544 (1998).
# TST vs IGRA

<table>
<thead>
<tr>
<th></th>
<th>TST</th>
<th>IFN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cell Types</strong></td>
<td>CD4</td>
<td>CD4 (CD8)</td>
</tr>
<tr>
<td></td>
<td>CD8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Basophils</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DC and Macrophages</td>
<td></td>
</tr>
<tr>
<td><strong>Cytokines</strong></td>
<td>IL-4, IFN-γ, TNF-α, IL-10, IL-12, G-CSF</td>
<td>IFN-γ</td>
</tr>
<tr>
<td><strong>Associated with Protective Immunity</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Timing</strong></td>
<td>2-5 Days</td>
<td>Short Term</td>
</tr>
<tr>
<td><strong>Homing Phenotype</strong></td>
<td>Skin</td>
<td>Polymorphic</td>
</tr>
</tbody>
</table>
QuantiFERON-TB PPD vs. QuantiFERON-TB Gold

QFT-TB PPD (1st)
- PPD
- M. Avium control
- Mitogen Control

QFT-TB Gold (2nd)
- ESAT-6
- CFP10
- Mitogen

Heparinized Blood → Antigen

18-24 Hours

IFN-γ EIA
QuantiFERON®-TB Gold IT: ELISA

1 ml 1 ml 1 ml

Nil TB Antigens Mitogen
CFP-10 ESAT-6 TB7.7

Transport
< 16 hours at room temperature

Incubation at 37°

18-24 Hours

IFN-γ EIA

Adapted from QuantiFERON®-TB Gold IT product insert
### QuantiFERON®-TB Gold IT: ELISA Interpretation of test result

<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><em>M. tuberculosis</em> infection NOT likely</td>
</tr>
<tr>
<td></td>
<td>≥ 0.35 and &lt; 25% of Nil value</td>
<td>≥ 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 0.35 and ≥ 25% of Nil value</td>
<td>Any</td>
<td>Positive²</td>
<td><em>M. tuberculosis</em> infection likely</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 0.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 0.35 and &lt; 25% of Nil value</td>
<td>&lt; 0.5</td>
<td>Indeterminate³</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>

*From: QuantiFERON®-TB Gold IT product insert*
T-spot®.TB: ELISPOT

CPT tubes

Transport < 8 hr at room temperature

ELISPOT assay

- Adults and children 10 years old and over: one 8mL or two 4mL tubes
- Children 2-9 years old: one 4mL tube
- Children up to 2 years old: 2mL paediatric tube

From: T-spot®.TB Visual procedure guide
T-spot®.TB: ELISPOT

Interpretation of test result

• The test result is Positive if (Panel A-Nil) and/or (Panel B-Nil) ≥ 8 spots.
• The test result is Negative if both (Panel A-Nil) and (Panel B-Nil) ≤ 4 spots.
• The test result is Borderline if the highest of the Panel A or Panel B spot count (minus Nil) is 5, 6 or 7.
• The test result is Invalid if:
  – Nil > 10 spots.
  – Mitogen < 20 spots AND both (Panel A-Nil0 and (Panel B-Nil) ≤ 4 spots.

From: Summarized from T-spot®.TB Product insert
Use of IGRA’s in adults

• CDC Recommendations: “QFT-G can be used in all circumstances in which the TST is used, including contact investigations, evaluation of recent immigrants who have had BCG vaccination, and TB screening of health-care workers and others undergoing serial investigation for *Mycobacterium tuberculosis* infection. QFT-G usually can be used in place of (and not in addition to the TST)” (MMWR, Dec. 16, 2005, Vol.54.)

• FDA Approvals:
  – QFT TB (11/28/01); QFT TB Gold (12/2/04); [QFT TB Gold-IT (10/10/07)]
  – T-SPOT.TB (7/25/08)
Evidence-based evaluation of IGRA’s vs TST

Evaluation without reference to a gold standard diagnostic for LTBI:

• Sensitivity in culture positive TB.
• Relationship with exposure risk factors.
• Specificity in low risk populations.
• Prospective prognostic studies.
Evaluation vs TST in children: Promise of IGRA’s

Evaluation without reference to a gold standard diagnostic for LTBI:

- **Sensitivity in culture positive TB.**
- Relationship with exposure risk factors.
- Specificity in low risk populations.
- Prospective prognostic studies.
<table>
<thead>
<tr>
<th>QFT version</th>
<th>Study, year, country</th>
<th>Age range</th>
<th>Young/total</th>
<th>Sensitivity of TST in active TB n/N (%)</th>
<th>Sensitivity of IGRA in active TB n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QFT Gold</td>
<td>Connell, 2006, Australia</td>
<td>0 - 18</td>
<td>NR/101</td>
<td>9/9 (100)</td>
<td>9/9 (100)</td>
</tr>
<tr>
<td>QFT Gold</td>
<td>Okada, 2007, Cambodia</td>
<td>0 - 5</td>
<td>210/210 &lt; 6 yrs</td>
<td>15/19 (79)</td>
<td>10/19 (53)</td>
</tr>
<tr>
<td>QFT Gold IT</td>
<td>Connell, 2008, Australia</td>
<td>1 - 19</td>
<td>NR/100</td>
<td>NR</td>
<td>8/9 (89)</td>
</tr>
<tr>
<td>QFT Gold IT</td>
<td>Detjen, 2007, Germany</td>
<td>0 - 16</td>
<td>54% &lt; 3 yrs; n = 73</td>
<td>28 /28 (100)</td>
<td>26/28 (93)</td>
</tr>
<tr>
<td>QFT Gold IT</td>
<td>Dogra, 2007, India</td>
<td>1 - 12</td>
<td>42/105 (40%) &lt; 5 yrs</td>
<td>5/8 (52) – Cx+</td>
<td>5/8 (52) – Cx+</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9/11 (82)-Rx</td>
<td>9/11 (82) - Rx</td>
</tr>
<tr>
<td>QFT Gold IT</td>
<td>Dominguez, 2007, Spain</td>
<td>0 - 18</td>
<td>15/134 (11%) &lt; 5 yrs</td>
<td>9/9 (100)</td>
<td>6/9 (67)</td>
</tr>
<tr>
<td>QFT Gold IT</td>
<td>Kampmann, 2009, UK</td>
<td>2 - 16</td>
<td>26/91 &lt; 5 years</td>
<td>20/24 (83) Cx+</td>
<td>20/25 (80) Cx+</td>
</tr>
</tbody>
</table>
### T-spot®.TB for Diagnosis of LTBI in active TB

<table>
<thead>
<tr>
<th>Study, year, country</th>
<th>Age range</th>
<th>Young/total</th>
<th>Sensitivity of TST in active TB n/N (%)</th>
<th>Sensitivity of IGRA in active TB n/N (%)</th>
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<tr>
<td>Connell, 2008, Australia</td>
<td>1 - 19</td>
<td>NR/101</td>
<td>NR</td>
<td>9/9 (89)</td>
</tr>
<tr>
<td>Detjen, 2007, Germany</td>
<td>0 - 16</td>
<td>54% &lt; 3 yrs; n = 73</td>
<td>28 /28 (100)</td>
<td>26/28 (93)</td>
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<td>Dominguez, 2007, Spain</td>
<td>0 - 18</td>
<td>15/134 (11%) &lt; 5 yrs</td>
<td>9/9 (100)</td>
<td>6/9 (67)</td>
</tr>
<tr>
<td>Kampmann, 2009, UK</td>
<td>2 - 16</td>
<td>26/91 &lt; 5 years</td>
<td>20/24 (83)</td>
<td>14/24 (58)</td>
</tr>
<tr>
<td>Nicol, 2009, S. Africa</td>
<td>0 - NR</td>
<td>204/214 &lt; 3 years</td>
<td>30/58 (52)</td>
<td>23/58 (40)</td>
</tr>
<tr>
<td>Warier, 2009 India</td>
<td>0 - 18</td>
<td>NR/15</td>
<td>NR</td>
<td>8/15 (53) – Cx+</td>
</tr>
</tbody>
</table>
Evaluation vs TST in children: Promise of IGRA’s

Evaluation without reference to a gold standard diagnostic for LTBI:

• Sensitivity in culture positive TB.
• **Relationship with exposure risk factors.**
• Specificity in low risk populations.
• Prospective prognostic studies.
## QFT-Gold for LTBI diagnosis

<table>
<thead>
<tr>
<th>QFT version</th>
<th>Study, year, country</th>
<th>Age range</th>
<th>Young/total</th>
<th>TST positivity rate n/N (%)</th>
<th>Concordance TST/IGRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>QFT Gold</td>
<td>Connell, 2006, Australia</td>
<td>0 - 18</td>
<td>NR/101</td>
<td>42/42 (100)</td>
<td>11/42 (26); K = 0.30; TST+/QFT-</td>
</tr>
<tr>
<td>QFT Gold</td>
<td>Hesseling, 2008, S. Africa</td>
<td>0 - 5</td>
<td>29/29</td>
<td>15/28 (54)</td>
<td>NR (88.9); K = 0.78; TST+/QFT-</td>
</tr>
<tr>
<td>QFT Gold</td>
<td>Mandalakas, 2008, S. Africa</td>
<td>NR, X = 4.4</td>
<td>All HIV+; NR/23</td>
<td>6/23 (26)</td>
<td>NR (75) K = .44; TST+/QFT-</td>
</tr>
<tr>
<td>QFT Gold</td>
<td>Okada, 2007, Cambodia</td>
<td>0 - 5</td>
<td>210/210 : &lt; 6 yrs</td>
<td>47/195 (24)</td>
<td>171/195 (88); K = 0.62; TST+/QFT-</td>
</tr>
<tr>
<td>QFT Gold IT</td>
<td>Chun, 2008, Korea</td>
<td>0-13</td>
<td>NR: Med = 1.7 yr</td>
<td>26/42 (62)</td>
<td>24/42 (57); K = 0.19</td>
</tr>
<tr>
<td>QFT Gold IT</td>
<td>Connell, 2008, Australia</td>
<td>1 - 19</td>
<td>NR/100</td>
<td>47/97 (48)</td>
<td>NR; (75); K = .5</td>
</tr>
<tr>
<td>QFT Gold IT</td>
<td>Lighter, 2008, USA</td>
<td>0 - 18</td>
<td>67/207, &lt; 5 yrs</td>
<td>116/204 (56)</td>
<td>112/207 (55); K = .17 TST+/QFT-</td>
</tr>
<tr>
<td>QFT Gold IT</td>
<td>Nakaoka, 2006, Nigeria</td>
<td>0 - 14</td>
<td>NR/207</td>
<td>57/206 (28)</td>
<td>49/66 (74); K = .74; TST-/QFT+</td>
</tr>
<tr>
<td>QFT Gold IT</td>
<td>Dogra, 2007, India</td>
<td>1 - 12</td>
<td>42/105 , &lt; 5 yrs</td>
<td>10/105 (9.5)</td>
<td>100/105; (95); K = .73</td>
</tr>
<tr>
<td>QFT Gold IT</td>
<td>Dominguez, 2007, Spain</td>
<td>0 - 18</td>
<td>15/134 (11%)</td>
<td>115/134 (86)</td>
<td>BCG--;23/40 (58), K=.24</td>
</tr>
<tr>
<td>QFT Gold IT</td>
<td>Kampmann, 2009, UK</td>
<td>0-16</td>
<td>56/118; &lt; 5 yrs</td>
<td>57/114 (50)</td>
<td>NR (77); K = .53</td>
</tr>
<tr>
<td>QFT Gold IT</td>
<td>Tsiouris, 2006, South Africa</td>
<td>5-15</td>
<td>NA/NR</td>
<td>80/184 (44)</td>
<td>145/184 (79); K=.56; TST+/QFT-</td>
</tr>
</tbody>
</table>
Diagnosis of LTBI/household contacts: QFT

Figure 2. Proportion of children with positive tuberculin skin test (TST) (>10 mm) and QuantiFERON Gold in Tube (QFT-IT) test results, by adult smear positivity. Error bars show 95% confidence intervals.

QFT-TB Gold-IT, Nigeria
PPD Chiron (5 IU): positive = ≥ 10 mm

Nakaoka, H., Emerg Inf Dis, 2006
# T-spot®.TB for LTBI diagnosis

<table>
<thead>
<tr>
<th>Study, year, country</th>
<th>Age range</th>
<th>Young/total</th>
<th>TST positivity rate n/N (%)</th>
<th>Concordance TST/QFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connell, 2008, Australia</td>
<td>1 - 19</td>
<td>NR/100</td>
<td>47/97 (48)</td>
<td>75% K = .51</td>
</tr>
<tr>
<td>Dominguez, 2007, Spain</td>
<td>0 - 18</td>
<td>15/134 (11%)</td>
<td>115/134 (86)</td>
<td>BCG-:25/40 (62), K=.33</td>
</tr>
<tr>
<td>Hesseling, 2008, South Africa</td>
<td>0-5</td>
<td>29/29</td>
<td>15/28 (54)</td>
<td>NR (46), K=-0.15 TST-/IGRA+</td>
</tr>
<tr>
<td>Kampmann, 2009, UK</td>
<td>0-16</td>
<td>56/118; &lt; 5 yrs</td>
<td>57/114 (50)</td>
<td>NR (75); K = .49</td>
</tr>
<tr>
<td>Mandalakas, 2008, S. Africa</td>
<td>NR, X = 4.4</td>
<td>All HIV+; NR/23</td>
<td>6/23 (26)</td>
<td>NR (67) K = .33; TST-/IGRA+</td>
</tr>
</tbody>
</table>
Evaluation vs TST in children: Promise of IGRA’s

Evaluation without reference to a gold standard diagnostic for LTBI:

- Sensitivity in culture positive TB.
- Relationship with exposure risk factors.
- **Specificity in low risk populations.**
- Prospective prognostic studies.
Specificity of Diagnosis of LTBI in TB suspects: QFT-IT/ T-spot®.TB vs TST

QFT-TB Gold-IT vs T-spot, Germany
PPD Chiron (10 TU), positive ≥ 5 mm

Specificity of Diagnosis of LTBI in TB suspects: QFT-IT/ T-spot®.TB vs TST

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
<th>Positive LR (95% CI)</th>
<th>Negative LR (95% CI)</th>
<th>Positive PV, % (95% CI)</th>
<th>Negative PV, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>100 (88–100)</td>
<td>58 (42–73)</td>
<td>2.4 (1.6–3.4)</td>
<td>0.1a (0.01–0.4)</td>
<td>62 (47–76)</td>
<td>100 (85–100)</td>
</tr>
<tr>
<td>QFT-IT</td>
<td>93 (77–99)</td>
<td>100 (91–100)</td>
<td>37.1b (5.3–258.0)</td>
<td>0.1 (0.02–0.3)</td>
<td>100 (87–100)</td>
<td>95 (84–99)</td>
</tr>
<tr>
<td>T-SPOT</td>
<td>93 (77–99)</td>
<td>98 (87–100)</td>
<td>37.1 (5.3–258.0)</td>
<td>0.1 (0.02–0.3)</td>
<td>96 (81–100)</td>
<td>95 (83–99)</td>
</tr>
<tr>
<td>QFT-IT and T-SPOT (both positive)</td>
<td>89 (72–98)</td>
<td>100 (91–100)</td>
<td>35.7b (5.1–248.4)</td>
<td>0.1 (0.04–0.3)</td>
<td>100 (86–100)</td>
<td>93 (81–99)</td>
</tr>
<tr>
<td>QFT-IT and T-SPOT (1 positive)</td>
<td>96 (82–100)</td>
<td>98 (87–100)</td>
<td>38.6 (5.6–267.5)</td>
<td>0.04 (0.01–0.3)</td>
<td>96 (82–100)</td>
<td>98 (87–100)</td>
</tr>
<tr>
<td>Stepwise approachc</td>
<td>93 (77–99)</td>
<td>100 (91–100)</td>
<td>37.1b (5.3–258.0)</td>
<td>0.1 (0.02–0.3)</td>
<td>100 (87–100)</td>
<td>95 (84–99)</td>
</tr>
</tbody>
</table>

**NOTE.** Calculations were based on 68 children, including 28 children with confirmed tuberculosis (group A) and 40 unvaccinated children without tuberculosis (19 children with confirmed nontuberculous mycobacterial lymphadenitis [group B] and 21 children with other respiratory tract infections [group C]). LR, likelihood ratio; PV, predictive value; QFT-IT, QuantiFERON-TB Gold In-Tube (Cellestis); T-SPOT, T SPOT-TB (Oxford Immunotec).

a For calculation of this LR, we classified 1 correct diagnosis in a child with tuberculosis as a false-negative result (to avoid division by 0).

b For calculation of this LR, we classified 1 correct diagnosis in a child without tuberculosis as a false-positive result (to avoid division by 0).

c We also calculated diagnostic accuracy in a stepwise approach according to recent National Institute of Health and Clinical Excellence guidelines [15]; only patients with positive TST results were tested with IFN-γ release assays. QFT-IT and T-SPOT showed the same values for all indicators.

QFT-TB Gold-IT vs T-spot, Germany
PPD Chiron (10 TU), positive ≥ 5 mm

*Detjen, et al., CID, 2007.*
Specificity of IGRA in BCG-vaccinated children

- Inclusion: No risk and TST $\geq 5$ mm.
- 62 children age 2 months – 14 years, all BCG vaccinated.
- 0/62 QFT-IT positive

QFT-IT, Korea
PPD RT 23 (2 TU), positive $\geq 5$ mm induration

Chun, et al., Diag Micro Inf Dis, 2008
Evaluation vs TST in children: Promise of IGRA’s

Evaluation without reference to a gold standard diagnostic for LTBI:

• Sensitivity in culture positive TB.
• Relationship with exposure risk factors.
• Specificity in low risk populations.
• Prospective prognostic studies.
Diagnosis of LTBI/school contacts: QFT

- 349 15-16 y/o boys, all BCG vaccinated.
- Tested with TST: 95 of 349 positive.
- 88 TST positive tested with QFT-TB Gold: 4 of 88 positive.
- 3 of 4 in high exposure group – received INH.
- Remaining TST positive students – no INH and no disease with 3+ years follow-up.

QFT-TB Gold, Japan
PPD Nippon (≈ 2.5 TU), positive ≥ 30 mm erythema

Higuchi, K., et al., Respirology, 2007
Limitations of IGRA’s in Children

• Paucity of data in children < 5 years.
• Increased frequency of indeterminate assays in children < 5 years.
• Required blood volumes.
• Lack of longitudinal data.
## Limitations of IGRA’s in young children

<table>
<thead>
<tr>
<th>QFT version</th>
<th>Study, year, country</th>
<th>Age range</th>
<th>Young/total</th>
<th>Indeterminate n/N (%)</th>
<th>QNS Blood n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QFT Gold</td>
<td>Mandalakas, 2008, S. Africa</td>
<td>NR, X = 4.4</td>
<td>All HIV+; NR/23</td>
<td>0/12 (0)</td>
<td>11/23 (47)</td>
</tr>
<tr>
<td>QFT Gold</td>
<td>Okada, 2007, Cambodia</td>
<td>0 - 5</td>
<td>210/210 : &lt; 6 yrs</td>
<td>9/208 (6)</td>
<td>13/217 (6)</td>
</tr>
<tr>
<td>QFT Gold IT</td>
<td>Bruzzese, 2009, Italy</td>
<td>2 - 24</td>
<td>NR; all HIV neg, immunocomp</td>
<td>16/80 (20)</td>
<td>NR</td>
</tr>
<tr>
<td>QFT Gold IT</td>
<td>Chun, 2008, Korea</td>
<td>0-13</td>
<td>NR; Med = 1.7 yr</td>
<td>17/227 (7.5)</td>
<td>NR</td>
</tr>
<tr>
<td>QFT Gold IT</td>
<td>Connell, 2008, Australia</td>
<td>1 - 19</td>
<td>NR/100</td>
<td>0/38 (0)</td>
<td>5/101 (5)</td>
</tr>
<tr>
<td>QFT Gold IT</td>
<td>Lighter, 2008, USA</td>
<td>0 - 18</td>
<td>67/207, &lt; 5 yrs</td>
<td>3/207 (1)</td>
<td>0/207 (0)</td>
</tr>
<tr>
<td>QFT Gold IT</td>
<td>Nakaoka, 2006, Nigeria</td>
<td>0 - 14</td>
<td>NR/207</td>
<td>33/207 (16)</td>
<td>NR</td>
</tr>
<tr>
<td>QFT Gold IT</td>
<td>Dogra, 2007, India</td>
<td>1 - 12</td>
<td>42/105, &lt; 5 yrs</td>
<td>0/105 (0)</td>
<td>0/105 (0)</td>
</tr>
<tr>
<td>QFT Gold IT</td>
<td>Dominguez, 2007, Spain</td>
<td>0 - 18</td>
<td>15/134 (11%)</td>
<td>3/134 (2)</td>
<td>NR</td>
</tr>
<tr>
<td>QFT Gold IT</td>
<td>Kampmann, 2009, UK</td>
<td>0-16</td>
<td>56/118; &lt; 5 yrs</td>
<td>14/209 (7)</td>
<td>0/209 (0)</td>
</tr>
<tr>
<td>QFT Gold IT</td>
<td>Tsiouris, 2006, South Africa</td>
<td>5-15</td>
<td>NA/NR</td>
<td>NR</td>
<td>37/221 (17)</td>
</tr>
</tbody>
</table>
Indeterminate rates of IGRA’s


QFT-TB Gold vs QFT-IT vs T-spot, Italy
Longitudinal IGRA data in children

Longitudinal IGRA data in children

QFT vs T-SPOT.TB

Specificity: QFT
• BCG-vaccinees

Sensitivity: T-SPOT.TB
• Immunocompromised
• Young children
What would we like in a test?

Specificity and Sensitivity: The DiCaprinator

With permission: Photoshop by David Lewinsohn
QFT vs T-SPOT.\textit{TB} in children

- QFT more available than T-SPOT.\textit{TB}
- More published data in children for QFT than for T-SPOT.\textit{TB}.
- Less indeterminate results for T-SPOT.\textit{TB} compared to QFT.
- Less blood required for T-SPOT.\textit{TB} than for QFT.
- Specificity equivalent in one study.
- Sensitivity of T-SPOT.\textit{TB} increased, equal, decreased when compared with QFT-IT.
- Increase positive tests with T-SPOT.\textit{TB}
Indications for IGRA’s and TST in children (My opinion)

- Close contacts of active TB cases:
- Immigrants from endemic countries:
- Significant travel history:
  - IGRA preferred to TST in children $\geq 5$ years.
  - TST preferred to IGRA in children $< 5$ years.
Indications for IGRA’s and TST in children
(My opinion - continued)

• TB suspects:
• HIV infection:
• Increased risk of progression of LTBI:
  – Consider both IGRA and TST and take either positive as evidence of infection.
Upcoming recommendations

- ATS/CDC/IDSA (AAP) guidelines:
- CDC guidelines – updated for QFT-Gold-IT and T-SPOT.TB.
- AAP – 2009 RedBook
Future research needs for IGRA’s in children

• High risk young children in low incidence setting (Household contact study in young children).

• Longitudinal data in young children (Data to inform “window prophylaxis”).

• Young immunosuppressed and HIV-infected children.
New assays for TB diagnosis in children

- IP-10 assays (ELISA/CD4)
- IFN-γ, IL-2, TNF-α (Flow cytometry)
- CD8+ T cells (ELISPOT)
- Antibodies in lymphocyte supernatant (ALS)
Slides Credits:
Henry Boom
Chuck Daley
David Lewinsohn
Madhu Pai