LTBI: Screening & Testing
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October 14, 2013

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has the following disclosures to make:

• No conflict of interests
• No relevant financial relationships with any commercial companies pertaining to this educational activity
Roadmap for this talk....

- Current concepts, policies, and priorities regarding *M. tb* infection in children
- What have we recently learned that is relevant to children in North America?
  - Screening
  - Testing
- Practical considerations to improve outcomes in TB affected children.

Traditional Model of Tuberculosis Pathogenesis

*Exposed* → *Infected* → *Diseased*
Key Transitions in the Transmission of Tuberculosis

_A New_er Conceptual Model_

Susceptible → Exposed → Infected → Diseased → Infectious → Sick → Accessed care → Recognized → Diagnosed → Treated → Completed → Cured

ORIGINS: Don Enarson

Screening and testing relationship

Screening  Testing  Testing
Sensitivity = Specificity = 95%

90% prevalence
PPV = 99% (1% false+)

1% prevalence
PPV = 15% (85% false+)

Criterion Standard
<table>
<thead>
<tr>
<th>Disease</th>
<th>No disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive test results</td>
<td>a</td>
</tr>
<tr>
<td>Negative test results</td>
<td>c</td>
</tr>
</tbody>
</table>

Sensitivity = \( \frac{a}{a + c} \)
Specificity = \( \frac{d}{b + d} \)

Positive predictive value = \( \frac{a}{a + b} \)
Negative predictive value = \( \frac{d}{c + d} \)

Likelihood ratio for disease if test positive = \( \frac{\text{sensitivity}}{1 - \text{specificity}} \)
Likelihood ratio for disease if test negative = \( \frac{1 - \text{sensitivity}}{\text{specificity}} \)
INDURATION SIZE —
Positive Tuberculin Skin Test

≥ 5 mm
✓ HIV co-infection
✓ Immune compromise
✓ Recent contact to TB
✓ Suspected disease

≥ 10 mm
✓ Foreign-born from a HR country
✓ Drug users
✓ Living in HR congregate setting
✓ Specific HR groups
✓ Children < 4 yrs old (AAP)

>15 mm
✓ No risk factors

http://www.tstin3d.com/
Foreign born: stratified assessment of TB risk

- Region of origin: SSAfrica and Asia
- Immigration category: refugees have RR = 2 (lo-intermediate risk)
- Comorbidities:
  - *infected in past 2 years* → RR=15 (high risk category)
  - *1-4 years of age @ infection* → RR= 2.2 – 5 (intermediate risk category)
- Time since arrival: greatest in first year
- 2011 Canadian Guidelines for Immigrant Health

**Table 1: Incidence of tuberculosis/100 000 population for immigrants and refugees after arrival in high-income countries**

<table>
<thead>
<tr>
<th>Country of origin</th>
<th>Overall rate (incidence per 100 000 population)</th>
<th>Time since migration: ≤ 1 yr</th>
<th>&gt; 1–5 yr</th>
<th>≥ 5 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>All world regions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All foreign-born*†‡¶</td>
<td>35</td>
<td>128</td>
<td>37</td>
<td>17</td>
</tr>
<tr>
<td>Refugees received by US*§</td>
<td>504</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TB Epidemiology US Children:**

1994-2007

- Foreign born contribute to 31% of notified TB among those <18 years of age
- Foreign born adolescents have a 20fold increased risk of TB vs US born adolescents
- Among FB children and adolescents with TB, 20% are diagnosed within 3 months of entry
- Enhance pre- and post-immigration screening

Pre-emigration screening

- **Canada**
  - Residents, refugees, and studying/working > 6 months
  - CXR (excludes kids <11 yrs)
    - sputum if CXR ABNormal
    - TB – treated before entry
  - Old or Inactive TB (LTBI)
    - begin monitoring within 30 days of entry at *Post Landing – Surveillance Programs*

- **United States**
  - Age and burden stratified
  - Applicants >15 years of age
    - History, PE, and CXR
    - If CXR positive \(\rightarrow\) Smear, Ctx, speciation and DST
  - DOTS required
  - Revised in 2007 & 2009
  - Complete roll-out by Oct 2013

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US Pre-emigration screening in kids

originating in countries with TB incidence rate ≥ 20/100,000 pop

- For applicants 2–14 years of age
  - Medical history
  - Physical examination
  - T-Accord skin test or IGRA
  - TST ≥15 mm or IGRA positive
  - Chest radiograph
  - Medical history, examination, or chest radiograph suggestive of tuberculosis or HIV infection
  - Three sputum smears and cultures for *Mycobacterium tuberculosis*
  - Drug susceptibility testing of positive cultures

- For applicants ≥15 years of age
  - Medical history
  - Physical examination

NB: <2 years, country incidence ≥ 20/100K OR >15 years, incidence < 20/100K
  \(\rightarrow\) history and PE \(\rightarrow\) TST or IGRA if screen positive
Special considerations for kids

- IGRA use acceptable for all ages
  - Indeterminate IGRA considered negative
  - Need to repeat in US
- Children ≤ 10 years may travel before culture results are back if they seem “not infectious”
- DOPT in US unless known PTB contact in a child <4 years of age or with immune compromised
  - DOPT provided regardless of TST or IGRA results
  - repeat TST/IGRA 8 weeks after contact ends
    - if repeat NEG, discontinue DOPT
  - Provide with 30 day supply of preventive meds
  - Categorize as “Class B3 TB, Contact Evaluation”

What is a post-landing surveillance program???

- School-based screening
- Immigrant & refugee clinics
- Migrant worker services
- Targeted screening of high risk and undocumented migrants
- Contact investigations

Frame 352 from the Patterson-Gimlin film alleged to show a Sasquatch in the Pacific Northwest.
TB Epidemiology US Children: 2008-2010

- Among pediatric TB cases
  - 31% are FB
  - 75% FB or residence outside of US
- Among FB TB cases,
  - 52% age 13-17 years in US >3 years
- Among US born cases,
  - 66% >= 1 FB parent
  - 3 fold >> general population


Effectiveness of Canadian screening programs

- Pre-immigration screening
  - <1% identified with active TB
  - 3-5% identified with inactive TB
  - accounts for a small proportion of TB in foreign born
- Foreign born pool includes 1 million arriving annually and 4 million from high TB burden countries already living in Canada
- Ongoing exposure in those already resident from high mobility including visits to and from country of origin

Canadian Guidelines for Immigrant Health

Tuberculosis: evidence review for newly arriving immigrants and refugees
NYCDOH QUESTIONNAIRE
RISK ASSESSMENT

- Has your child had any contact with a case of TB?
- Was any household member including your child born in or has traveled to areas where TB is common?
- Does your child have regular contact with adults at high risk for TB?
- Does your child have HIV infection?


NYCDOH QUESTIONNAIRE FOR LTBI - RESULTS

- 23/413 (5.6%) of children with at least one risk factor had a reactive TST
- 4/2507 (0.16%) of children with no risk factors had a reactive TST
- ¾ children not identified were > 11 years old

TARGETED TST TESTING
KAISER PERMANENTE GROUP

- 33,553 children in 18 offices

Validated Risk Factors: Any Child Who...

- was born outside the United States
- received a BCG vaccine
- lived outside the United States
- lives with someone with TB history


TX DSHS: TB Questionnaire for Children
(EF12-11494 in English)

<table>
<thead>
<tr>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB can cause fever of long duration, unexplained weight loss, a bad cough (lasting over two weeks), or coughing up blood. As far as you know:</td>
</tr>
<tr>
<td>has your child been around anyone with any of these symptoms or problems? or</td>
</tr>
<tr>
<td>has your child had any of these symptoms or problems? or</td>
</tr>
<tr>
<td>has your child been around anyone sick with TB?</td>
</tr>
<tr>
<td>Was your child born in Mexico or any other country in Latin America, the Caribbean, Africa, Eastern Europe or Asia?</td>
</tr>
<tr>
<td>Has your child traveled in the past year to Mexico or any other country in Latin America, the</td>
</tr>
<tr>
<td>Caribbean, Africa, Eastern Europe or Asia for longer than 3 weeks?</td>
</tr>
<tr>
<td>If so, specify which country/countries?</td>
</tr>
<tr>
<td>To your knowledge, has your child spent time (longer than 3 weeks) with anyone who is/has been an intravenous (IV) drug user, HIV-infected,</td>
</tr>
<tr>
<td>in jail or prison or recently came to the United States from another country?</td>
</tr>
</tbody>
</table>

http://www.dshs.state.tx.us/idcu/disease/tb/forms/
LTBI RISK ASSESSMENT
QUESTIONNAIRE FOR CHILDREN

All risk assessment questionnaire should ask:
1. Was your child born outside the U.S? Where?
2. Has your child traveled (non-tourist, >1 wk) outside the U.S.? Where?
3. Has your child been in contact with anyone with TB?
4. Does your child have contact with anyone with a positive tuberculin skin test?

Screening and testing relationship

TESTING
Factors that cause (false negatives) Decreased Response to Tuberculin

Host-related
- Infections, vaccines
- Chronic disease, malnutrition
- Immunosuppressive diseases (HIV, malignancy, CVD)
- Drugs (corticosteroids)
- Extremes of age, stress
- Overwhelming tuberculosis

Tuberculin-related
- Improper storage or dilution
- Adsorption

Administration-related

Reading-related

PROBLEMS CREATED BY FALSE POSITIVE TUBERCULIN SKIN TEST RESULTS

1. There is no way to distinguish false from true positive results, so all positives should be evaluated and treated
2. Costs of evaluation: doctor/clinic time, xrays, medications, adverse reactions, evaluation of family members
3. Anxiety – who has TB???
Interferon-γ Release Assays (IGRAs)

Measurement of the cell mediated immune response after stimulation with *M. tuberculosis*-specific antigens

ESAT-6, CFP-10, TB 7.7

### SPECIFICITY

Specificity of ESAT-6 and CFP-10

<table>
<thead>
<tr>
<th>Tuberculosis complex</th>
<th>Antigens</th>
<th>Environmental strains</th>
<th>Antigens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ESAT</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>M. tuberculosis</em></td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>M. africanum</em></td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>M. bovis</em></td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>M. microti</em></td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>M. pneuetti</em></td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCG substrains</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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Environmental strains</th>
<th>Antigens</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. abcessus</em></td>
<td>+</td>
</tr>
<tr>
<td><em>M. avium</em></td>
<td>-</td>
</tr>
<tr>
<td><em>M. branderi</em></td>
<td>-</td>
</tr>
<tr>
<td><em>M. celatum</em></td>
<td>-</td>
</tr>
<tr>
<td><em>M. cheloneae</em></td>
<td>-</td>
</tr>
<tr>
<td><em>M. flavescens</em></td>
<td>+</td>
</tr>
<tr>
<td><em>M. fortuitum</em></td>
<td>-</td>
</tr>
<tr>
<td><em>M. gordonae</em></td>
<td>-</td>
</tr>
<tr>
<td><em>M. intracellular</em></td>
<td>-</td>
</tr>
<tr>
<td><em>M. kansasi</em></td>
<td>+</td>
</tr>
<tr>
<td><em>M. marinum</em></td>
<td>+</td>
</tr>
<tr>
<td><em>M. oenavense</em></td>
<td>-</td>
</tr>
<tr>
<td><em>M. scrofulaceum</em></td>
<td>-</td>
</tr>
<tr>
<td><em>M. smegmatis</em></td>
<td>-</td>
</tr>
<tr>
<td><em>M. szulgai</em></td>
<td>+</td>
</tr>
<tr>
<td><em>M. terrae</em></td>
<td>-</td>
</tr>
<tr>
<td><em>M. vaccae</em></td>
<td>-</td>
</tr>
<tr>
<td><em>M. xenopi</em></td>
<td>-</td>
</tr>
<tr>
<td>Performance characteristic</td>
<td>TST</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----</td>
</tr>
<tr>
<td>Technique</td>
<td>In vivo skin test</td>
</tr>
<tr>
<td>Results given in</td>
<td>mm of induration</td>
</tr>
<tr>
<td>Antigen used</td>
<td>PPD</td>
</tr>
<tr>
<td>Time for result (d)</td>
<td>2-3</td>
</tr>
<tr>
<td>Mitogen control to distinguish indeterminate versus false-negative response</td>
<td>No</td>
</tr>
<tr>
<td>Cost per test</td>
<td>Low</td>
</tr>
<tr>
<td>Influenced by prior BOG</td>
<td>Yes</td>
</tr>
<tr>
<td>Influenced by atypical mycobacteria</td>
<td>Yes</td>
</tr>
<tr>
<td>Booster effect if repeated</td>
<td>Yes</td>
</tr>
<tr>
<td>Sensitivity for LTBI</td>
<td>85-90%(^a)</td>
</tr>
<tr>
<td>Specificity for LTBI</td>
<td>60-95%(^a)</td>
</tr>
</tbody>
</table>

\(^a\)Heubner and coworkers, 2003
\(^b\)Menzies and coworkers, 2003
\(^c\)Farrat and coworkers, 2003

Lighter. *Curr Probl Pediatr Adolesc Health Care, March 2009*

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**IGRAS**

What do we know about use in kids?
Comparing *Elispot* and TST to EXPOSURE

Strong Agreement
Concordance 89%
Kappa = 0.72 (p<0.001)

*Elispot* HIGHER correlation with exposure to Index Case
Proximity of exposure (p=0.03)
Duration of exposure (p=0.007)
Objectives

1. What is the value of IGRAs for the diagnosis of LTBI in children?
2. What is the accuracy of IGRAs for the diagnosis of active TB in children?
3. What is the impact of young age, HIV-infection, BCG-vaccination and TB burden of different settings on the performance of IGRAs?
4. Operational aspects of IGRAs
Methodology

Search strategy
- Electronic databases (PubMed, Web of Science)
- Existing database (M.Pai, Academic TB database)
- Reference lists of SRs, selected articles

Eligibility criteria
- Children 0-18 years
- Sample size ≥ 20
- TB low, middle and high income countries
- Commercial IGRA:s: T-SPOT.TB, QuantiFERON-TB Gold (QFT-G), QuantiFERON-TB Gold In-Tube (QFT-IT)

Study selection

31 additional articles for abstract review identified:
- Existing database (M.Pai): 19
- Reference lists of review articles and systematic reviews: 12

Abstract review: 161

6 additional full texts identified during review process

Full text review 68 articles

31 articles included/32 studies
Study characteristics – index tests

- TST (29)
- Tspot (15)
- QFT-Gold (10)
- QFT-GIT (20)
- 33% Industry

N = 5512 all studies; analysis completed on data from 4122

World Bank Income Status of study settings

- HIC (19)
- MIC (10)
- LIC (3)

11-100% of samples include immigrant children

TB incidence: >25/100K in 14 studies representing 10 countries
Study characteristics – reference standard

**Objective #1: IGRAs for the diagnosis of LTBI**
1. Incident active TB - 2 studies
2. TB exposure – 18 studies

**Objective #2: IGRAs for the diagnosis of active TB**
1. Active TB – 20 studies; no TB group - 9 studies

Reference standards

**Objective #1: IGRAs for the diagnosis of LTBI**
1. Incident active TB
2. TB exposure
   a) Dichotomous exposure: exposed/unexposed
   b) Exposure gradients: microbiologic indicators, proximity, time of exposure
### Incident TB

<table>
<thead>
<tr>
<th>IGRA result</th>
<th>Active TB (N)</th>
<th>Predictive value (% , 95% CI)</th>
<th>Issues with Study Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diel 2008 (Germany, QFT-IT)...</strong> contact investigation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (n=7)</td>
<td>3</td>
<td>43%, 16-75%</td>
<td>• Work-up only in symptomatic children?</td>
</tr>
<tr>
<td>Negative (n=161)</td>
<td>0</td>
<td>100%, 0-1%</td>
<td>• Preventive therapy offered to QFT-positive</td>
</tr>
<tr>
<td><strong>Higuchi 2009 (Japan, QFT-G)... school outbreak</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (n=9)</td>
<td>0</td>
<td>0%, 0-35%</td>
<td>• F/u with CXR after 1 year</td>
</tr>
<tr>
<td>Negative (n=301)</td>
<td>0</td>
<td>100%, 0-1.5 %</td>
<td>• QFT-G positive and QFT-G indet./TST pos children received preventive therapy</td>
</tr>
<tr>
<td>Indeterminate (n=3)</td>
<td>0</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

⇒ Predictive value for disease progression is low.
⇒ Low risk of disease progression in case of negative QFT?

### Recent Studies of Incident TB

- Household contact cohort... *up to 4 years of follow-up*
- 10/207 TST+ → TB (4.8%)
- 19/147 QFT+ → TB (12.9%)
  - 6/21 children (28.6%) vs 13/126 adults (10.3%) (p=0.03)
  - *Diel et al. AJRCCM. 2011 Jan 1;183(1):88-95... Germany*

- QFT conversion → 8 fold increase risk of TB progression within 2 years among adolescents
  - *Machingaidze et al. AJRCCM. 2012 Nov 15;186(10):1051-6... S Africa*
Reference standards

**Objective #1: IGRAs for the diagnosis of LTBI**

1. Incident active TB
2. TB exposure
   a) Dichotomous exposure: exposed/unexposed
   b) Exposure gradients: microbiologic indicators, proximity, time of exposure

---

### Exposure gradients

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Description of assignment to exposure gradients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 0</td>
</tr>
<tr>
<td>Adetifa 2010</td>
<td>Different House</td>
</tr>
<tr>
<td>Bergamini 2009</td>
<td>Exposed to probable TB</td>
</tr>
<tr>
<td>Diel 2008</td>
<td>40-59 hrs exposure</td>
</tr>
<tr>
<td>Girardi 2007</td>
<td>Low risk, other students</td>
</tr>
<tr>
<td>Nakaoka 2006</td>
<td>Community controls</td>
</tr>
<tr>
<td>Okada 2008</td>
<td>Exposure to smear - TB</td>
</tr>
<tr>
<td>Petrucci 2008, Brazil</td>
<td>Exposure to scanty TB</td>
</tr>
<tr>
<td>Petrucci 2008, Nepal</td>
<td>Exposure to scanty TB</td>
</tr>
</tbody>
</table>
Correlation of tests with exposure gradients in all income settings

Correlation of tests with exposure gradients in all LMIC settings

Homogeneous comparison groups:
4/5 studies smear status
1/5 proximity

I-squared values
QFT = 0.62
Tspot = 0.0
TST = 0.0-0.48
Recent Studies Quantifying Exposure

- TST & TSpot concordance: exposure & BCG dependent

<table>
<thead>
<tr>
<th>Risk group</th>
<th>N</th>
<th>BCG</th>
<th>No BCG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact</td>
<td>74</td>
<td>88</td>
<td>94</td>
</tr>
<tr>
<td>Risk factors &amp; no contact</td>
<td>78</td>
<td>33</td>
<td>74</td>
</tr>
<tr>
<td>No risk factors</td>
<td>27</td>
<td>20</td>
<td>74</td>
</tr>
</tbody>
</table>


- Tspot and QFT-GIT associated with exposure
  - contacts (N=98) and routinely screened (N=68) children

Recent Studies Quantifying Exposure

- QFT-IT associated with hi burden country origin
  - (AOR = 4.54; 95% CI, 3.22-6.25)

- QFT-IT & TST agreement: exposure & BCG dependent
  - K=0.91 in BCG-negative, child contacts
  - K=0.34 in unexposed “at risk screened children”
  - Tsolia MN et al. PIDJ. 2010. 29:1137–1140....Greece
Factors associated with IGRA results
from the Pediatric Tuberculosis Network European Trials


Factors associated with IGRAs

Factors associated with Indeterminates

### TABLE 7. MULTIVARIATE LOGISTIC REGRESSION ANALYSIS FOR CHILDREN WITH AN INDETERMINATE IFN-γ RELEASE ASSAY RESULT: ASSOCIATION BETWEEN INDETERMINATE IFN-γ RELEASE ASSAY RESULT, AS OUTCOME VARIABLE AND PREDICTOR VARIABLES OF AGE, SEX, AND BACILLUS CALMETTE-GUERIN VACCINATION STATUS ADJUSTED FOR STUDY SITE

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Descriptor</th>
<th>Outcome Variable (Indeterminate Result)</th>
<th>OR</th>
<th>P Value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Continuous</td>
<td>QFT-GIT</td>
<td>0.83</td>
<td>0.004 (0.73-0.94)</td>
</tr>
<tr>
<td></td>
<td>≥2 yr</td>
<td>T-SPOT.TB</td>
<td>0.70</td>
<td>0.26 (0.74-1.09)</td>
</tr>
<tr>
<td></td>
<td>≥5 yr</td>
<td>QFT-GIT</td>
<td>0.53</td>
<td>0.34 (0.15-1.94)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T-SPOT.TB</td>
<td>0.50</td>
<td>0.44 (0.06-4.52)</td>
</tr>
<tr>
<td>BCG</td>
<td>Vaccinated</td>
<td>QFT-GIT</td>
<td>0.25</td>
<td>0.006 (0.09-0.67)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>T-SPOT.TB</td>
<td>0.34</td>
<td>0.19 (0.07-1.71)</td>
</tr>
</tbody>
</table>

### NB: very low indeterminate rates: QFT-GIT ~ 1.8% and T.Spot-TB ~ 1.6%


### TABLE 6. IFN-γ RELEASE ASSAY RESULTS FOR CHILDREN WITH NEGATIVE TUBERCULIN SKIN TEST RESULTS, AS DEFINED BY THREE DIFFERENT CUTOFFS

<table>
<thead>
<tr>
<th>TST Results</th>
<th>IGRA Results</th>
<th>All Ages</th>
<th>Age, &lt;2 yr</th>
<th>Age, 2-5 yr</th>
<th>Age, &lt;5 yr</th>
<th>Age, &gt;5 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 mm</td>
<td>QFT-GIT, n (%)</td>
<td>11/199 (5.5)</td>
<td>2/38 (5.3)</td>
<td>3/75 (4.0)</td>
<td>5/103 (4.9)</td>
<td>6/96 (6.3)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>180/199 (90.5)</td>
<td>33/38 (86.8)</td>
<td>69/75 (92.0)</td>
<td>92/103 (89.3)</td>
<td>88/96 (91.7)</td>
</tr>
<tr>
<td></td>
<td>Indeterminate</td>
<td>8/199 (4.0)</td>
<td>3/38 (7.9)</td>
<td>3/75 (4.0)</td>
<td>6/103 (5.8)</td>
<td>2/96 (2.1)</td>
</tr>
<tr>
<td>T-SPOT.TB, n (%)</td>
<td>Positive</td>
<td>2/57 (3.5)</td>
<td>0/8 (0.0)</td>
<td>2/22 (9.1)</td>
<td>2/29 (6.9)</td>
<td>0/28 (0.0)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>54/57 (94.7)</td>
<td>8/8 (100.0)</td>
<td>19/22 (86.4)</td>
<td>26/29 (89.7)</td>
<td>28/28 (100.0)</td>
</tr>
<tr>
<td></td>
<td>Indeterminate</td>
<td>1/57 (1.8)</td>
<td>0/8 (0.0)</td>
<td>1/22 (4.6)</td>
<td>1/29 (3.5)</td>
<td>0/28 (0.0)</td>
</tr>
<tr>
<td>&lt;10 mm</td>
<td>QFT-GIT, n (%)</td>
<td>6/439 (1.4)</td>
<td>8/54 (14.8)</td>
<td>36/339 (27.7)</td>
<td>43/54 (79.6)</td>
<td>11/439 (2.5)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>363/439 (82.7)</td>
<td>43/54 (79.6)</td>
<td>12/339 (3.6)</td>
<td>3/54 (5.6)</td>
<td>1/439 (0.2)</td>
</tr>
<tr>
<td></td>
<td>Indeterminate</td>
<td>11/439 (2.5)</td>
<td>3/54 (5.6)</td>
<td>12/339 (3.6)</td>
<td>3/54 (5.6)</td>
<td>1/439 (0.2)</td>
</tr>
<tr>
<td>T-SPOT.TB, n (%)</td>
<td>Positive</td>
<td>18/141 (12.8)</td>
<td>1/14 (7.1)</td>
<td>18/141 (12.8)</td>
<td>1/14 (7.1)</td>
<td>1/14 (7.1)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>120/141 (85.1)</td>
<td>12/14 (85.7)</td>
<td>18/141 (12.8)</td>
<td>1/14 (7.1)</td>
<td>1/14 (7.1)</td>
</tr>
<tr>
<td></td>
<td>Indeterminate</td>
<td>3/141 (2.1)</td>
<td>1/14 (7.1)</td>
<td>18/141 (12.8)</td>
<td>1/14 (7.1)</td>
<td>1/14 (7.1)</td>
</tr>
<tr>
<td>&lt;15 mm</td>
<td>QFT-GIT, n (%)</td>
<td>140/692 (20.2)</td>
<td>13/76 (17.1)</td>
<td>27/156 (17.3)</td>
<td>34/203 (16.8)</td>
<td>106/489 (21.7)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>539/692 (77.9)</td>
<td>60/76 (78.9)</td>
<td>124/156 (79.5)</td>
<td>161/203 (79.3)</td>
<td>378/489 (77.3)</td>
</tr>
<tr>
<td></td>
<td>Indeterminate</td>
<td>13/692 (1.9)</td>
<td>3/76 (4.0)</td>
<td>5/156 (3.2)</td>
<td>8/203 (3.9)</td>
<td>5/489 (1.0)</td>
</tr>
<tr>
<td>T-SPOT.TB, n (%)</td>
<td>Positive</td>
<td>50/209 (23.8)</td>
<td>3/23 (13.0)</td>
<td>9/51 (17.7)</td>
<td>10/66 (15.2)</td>
<td>40/143 (28.0)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>154/209 (73.7)</td>
<td>19/23 (82.6)</td>
<td>40/51 (78.4)</td>
<td>54/66 (81.8)</td>
<td>100/143 (69.9)</td>
</tr>
<tr>
<td></td>
<td>Indeterminate</td>
<td>5/209 (2.4)</td>
<td>1/23 (4.4)</td>
<td>2/51 (3.9)</td>
<td>2/66 (3.0)</td>
<td>3/143 (2.1)</td>
</tr>
</tbody>
</table>

**IGRA positive/TST negative ranging from 3.5 – 23.9%**

Factors associated with IGRAs

- Low indeterminate rates
  - statistically associated with younger age for QFT-GIT

- High incidence of TST negative/IGRA positive

- Protective affect of BCG against *M.tb* infection

**QUESTION:**

What is the role currently for the interferon-gamma release assays in diagnosing LTBI in children and adults?

IGRAs AND THE 2012 AAP “RED BOOK”

- Can use IGRAs in immunocompetent children > 4 years of age in all situations when a TST would be used.
- Particularly useful/preferred for children who have received a BCG vaccination.
- Same recommendations as TST for risk factors and frequency of testing.
- Use with caution in children < 5 years of age and immunocompromised children.
- Neither IGRAs nor the TST are perfect therefore one must always use clinical judgment!

TST preferred, IGRA acceptable

- Children < 5 years of age when testing for TB infection
  [Many experts would not use an IGRA in children < 2 years of age because of lack of data for this age group and high risk of progression to disease]

IGRA preferred, TST acceptable

- Children > 5 years of age who have had BCG vaccine
- Children > 5 years of age who are unlikely to return for TST reading
Both TST and IGRA should be considered for children when:

- The initial and repeat IGRA results are indeterminate
- The initial test (TST or IGRA) is negative and:
  - There exists clinical suspicion for TB disease*
  - Risk of infection with poor outcome is higher*
  *[Either positive test is considered significant]
- The initial TST is positive and:
  - ≥ 5 years of age and history of BCG vaccination
  - Need additional evidence to increase compliance
  - NTM disease is suspected

IGRAs IN CHILDREN:

*Some Clinical Considerations*

- Should +TST in a BCG-vaccinated child always be followed by an IGRA? [Strategy 1]

- Should only IGRAs be used in a previously BCG-vaccinated child? [Strategy 2]

- Low risk child, TST ≥ 15 mm, IGRA neg. Treat or no treat? [??]

- High risk child [contact], TST ≥ 10 mm, IGRA neg. Treat or no treat? [Yes]
BCG vaccinated?

No

Likely to return for TST reading?

Yes

Age <5 yrs?

No

Either TST or IGRA acceptable

TST preferred

IGRA preferred

Negative result - testing complete

Positive result - testing complete

Indeterminate

Repeat IGRA

Negative result - testing complete

Positive result - testing complete

Testing complete unless criteria A met, then IGRA

Testing complete unless criteria B** are met, then IGRA

Age >5 yrs?

Likely to return for TST reading?

Yes

Either TST or IGRA acceptable

TST preferred

IGRA preferred

Negative result - testing complete

Positive result - testing complete

Indeterminate

Repeat IGRA

Negative result - testing complete

Positive result - testing complete

Testing complete unless criteria A met, then IGRA

Testing complete unless criteria B** are met, then IGRA

**Criteria A
1) High clinical suspicion for TB disease and/or
2) High risk for infection, progression or poor outcome

**Criteria B
1) Additional evidence needed to ensure adherence and/or
2) Child healthy and at low risk and/or
3) NTM suspected

THANK YOU