Advancing Tuberculosis Screening Strategies of Immigrants

A National Sounding Board

Advancing Tuberculosis Screening Strategies of Immigrants
Atlanta, GA
March 9, 2013

Randall Reves, MD
Denver Public Health

* No honoraria were offered to speakers or participants. Agenda approved by co-chairs.

Overview

• Background
• Meeting Description
• Summary
• Discussion
• Next steps

Source: U.S. Department of Homeland Security
Estimated Annual International Arrivals, United States, 2010

Refugees 50,000 – 80,000
Immigrants >1,000,000 (half PP, half CS exams)
HIV immigrant extractions
Short-term residents with student, work visas 4 M
Non-residents 35 M

Source: John Parker, CDC DGMQ: Immigration IGRA Sounding Board, Atlanta, March 9, 2013
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TB facts in 2012: Foreign-born TB in the US

- FB cases – 63% of TB cases in the US in 2012 (6243 out of 9551)
- FB rate 11.5 times rate of U.S.-born persons:
  - US-born rate: 1.4
  - FB-born rate: 15.8
- The proportion of TB among the FB continues to increase


TB Screening of Immigrants

- TB screening of immigrants is based on the 2007 CDC Technical Instructions and utilizes the chest radiograph (CXR), Mantoux tuberculin skin test (TST) or interferon-gamma release assays (IGRA) added in 2009 as tools.
- TST use is almost exclusively used for pre-entry screening
- Pre-entry IGRA comparison studies conducted during immigrant screening done by CDC in key countries
- Experience of US TB control programs retesting TST-positive immigrants (B2 and B3 class) post-entry with IGRA show consistently lower positive results and frequent discordance consistent with false-positive results from BCG or NTM
- Recent cost-modeling study on immigrants in the UK suggests that IGRA as an initial test, followed by CXR, may offer additional efficiencies*


2013 IGRA Sounding Board

Advancing Pre-entry Tuberculosis Screening Strategies of Immigrants
March 9, 2013 following the 2013 IPPA meeting
JW Marriott Hotel, Atlanta, Georgia

Overarching goal: Provide a forum for international discussion on how current screening methods could be streamlined without losing sensitivity to active and latent TB

Meeting objectives:

- Review current studies and experience of immigrant evaluation based on screening tools (CXR, TST and IGRA)
- Develop a consensus on whether or not changes to current procedures are needed and the research needed to answer potential advances
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Key Questions:
- Are the data adequate to draw some conclusions on the utility of TST compared to IGRA in screening of immigrants pre-entry?
- Can two-stage TB screening with IGRAs followed by selective CXR replace universal CXR screening?
- Do the current technical instructions need to be revised in its recommendation to use either TST or IGRA?
- What kind of research is needed to advance pre-entry screening of immigrants?

Co-Chairs:
Randall Reves and Angel Contreras

Participants*
- Immigration leads: CDC, Australia, UK
- Investigators of TBESC TO 20 and TO 31
- IPPA – Expert panel physicians from Mexico, Philippines, China, Brazil and Dominican Republic
- International tuberculosis and migrant health experts, including current US TB big city or state controllers, NTCA and CTCA

*No honoraria were offered to speakers, co-chairs or participants

3 Key Perspectives
- Panel Physician
  Freman Cezero (Philippines), Angel Contreras (Dominican Republic), Li Li (China), Luis Todd (Mexico), Joao Leite (Brazil), Masae Kawamura (Qiagen, recorder only)
- Migrant Health
  Pennan Barry, Paul Douglas (Australia), Randall Reves, Nick Walters, Dominik Zenner (UK)
- Public Health – Policy
  Julie Higashi, Kathy Moser, Masa Narita, Charles Wallace, Jon Warkentin
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Presentations of Research and Experience

- Summary of current pre-entry and US in-country status adjustment screening procedures: John Painter, MD
- Outcomes of post-entry evaluation of Class B2 immigrants in San Diego – A domestic program perspective **: Kathleen Moser, MD
- TOs 20 and 31: CDC evaluation of IGRAs in Vietnam, Philippines and Mexico Panel Sites**: John Painter, MD
- Domestic Follow-up of Immigrants with B2-notifications in California **: Pennan Barry, MD
- Linkage of pre-entry TB screening to post-entry disease outcomes in Filipino applicants **: Nicolas Walter, MD
- Cost and Strategies for Pre-Immigration LBTI Screening: Nicolas Walter, MD
  **: unpublished at the time of the Sounding Board

Pre-entry and US in-country status adjustment screening procedures

- Screening based on 2007 CDC DGMQ Technical Instructions for Panel Physicians (overseas) and Civil Surgeons (domestic)
- **Pre-entry** Panel Physician screening
  - Age 15 and over: CXR screening and no TB testing
  - Under age 15 or contact: TST (>10 mm) or IGRA (added 2009)
  - CXR of TB test+
- **Post-entry** Civil Surgeon domestic immigrant status adjustment exam:
  - Same instruction for all applicants ≥2 years of age
  - Step 1: TST or IGRA as
  - Step 2: If positive skin test (>5 mm) or IGRA → CXR
  - Mycobacterial cultures when TB symptoms or any CXR findings suggest TB

Source: John Painter, CDC DGMQ: Immigration IGRA Sounding Board, Atlanta, March 9, 2013

Task Orders 20 and 31: CDC evaluation of IGRAs in Vietnam, Philippines and Mexico Panel Sites

John Painter, CDC

- **TO 20**
  “Assessing QFT as an initial screening tool for U.S. bound applicants for immigration and feasibility of follow-up in U.S. immigrants”

- **TO 31**
  “Evaluation of Interferon Gamma Release Assays in Overseas Immigration Examination of Children in Moderate- and High-burden Countries”
TO20 Study Objectives

Phase 1

TB screening in Vietnam

1. Is IGRA testing feasible during immigrant examination?

2. Compared with universal radiography, what is effectiveness of using the TST or IGRA to determine the need for chest radiography (LTBI test -> CXR)?

3. Is TST or IGRA more effective at detecting LTBI in highly prevalent, BCG immunized population?

TO20: Culture Positive (N=132)

Estimated Percent Test Positive for All Vietnamese Visa Applicants

* Much higher prevalence of TST 10 compared to QFT in the young age group, followed by a lower annual rate of increase is most consistent with cross reacting antigens due to BCG vaccination with TST.

Source: Dr. John Painter, CDC March 9, 2013 IGRA Sounding Board
TO20 Phase 1 Conclusions

IGRA was feasible and acceptable
- Very low percentage of indeterminate results (~0.5%)

10-20% of culture positive cases have negative QFT or TST
- Implications for cases missed with two-stage screening (LTBI test -> CXR)
- QFT more sensitive, especially among older cases
- Compared with previous studies*, sensitivity higher (Pooled sensitivity = 0.70 [0.63–0.78])

Indirect evidence that specificity of QFT better than TST
- Linear increasing rate with age of positive QFT results was consistent with cumulative exposure, whereas TST positivity started higher, rose more slowly

TST likely overestimates LTBI among those with normal CXR


Source: Dr. John Painter, CDC March 9, 2013 IGRA Sound Board

TBESC TO31: Evaluation of Interferon-Gamma Release Assays in Overseas Immigration Examination of Children in Moderate and High-burden Countries (Mexico, Philippines, Vietnam)

QFT and TST Results in Visa Applicant Children 2-14 years (unpublished)

<table>
<thead>
<tr>
<th>Population</th>
<th>Number of participants</th>
<th>QFT Positive n (%)</th>
<th>RR (95% CI)</th>
<th>TST 10mm Positive n (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family with active TB</td>
<td>75 (3%)</td>
<td>9 (12)</td>
<td>2.3 (1.2, 4.4)</td>
<td>36 (48)</td>
<td>1.8 (1.5, 2.4)</td>
</tr>
<tr>
<td>Family member with CXR-TB</td>
<td>288 (11%)</td>
<td>16 (6)</td>
<td>1.1 (0.6-1.8)</td>
<td>115 (40)</td>
<td>1.7 (1.4, 2.0)</td>
</tr>
<tr>
<td>Family member with Normal CXR</td>
<td>2145 (85%)</td>
<td>117 (6)</td>
<td>1.0</td>
<td>513 (24)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Source: Dr. John Painter, CDC March 9, 2013 IGRA Sound Board

TO31 Conclusions (unpublished)

IGRA was feasible and acceptable among children
- Very low percentage of indeterminate results (~0.5%)
- Results consistent with those among adults

In TB prevalent countries, fewer QFT +
- TST 10mm ->3x QFT & higher prevalence of TST at age 2 yrs
- Suggests that QFT more specific
  - TST likely cross reacting with NTM and BCG

In Mexico, QFT and TST rates surprisingly similar
- Decreased BCG coverage among Mexican visa applicants?
- Increased prevalence of other QFT-antigen strains?
  - e.g. M. bovis, M. Kanasii, M. szulgai, M. mariinum

No direct assessment of sensitivity
- Having a family member with culture-confirmed TB disease associated with 2-fold risk of both positive QFT and TST

Source: Dr. John Painter, CDC March 9, 2013 IGRA Sound Board
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**San Diego County QFT-GIT results in TST positive - B2 immigrant children, 2010-2012 (unpublished)**

<table>
<thead>
<tr>
<th>Age at entry</th>
<th>&lt;0.35IU</th>
<th>0.35-1.0</th>
<th>&gt;1.0</th>
<th>Total “positive”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mexico</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-4 (21)</td>
<td>85.7%</td>
<td>4.8%</td>
<td>9.5%</td>
<td>14.3%</td>
</tr>
<tr>
<td>5-9 (91)</td>
<td>29.7%</td>
<td>4.4%</td>
<td>65.9%</td>
<td>70.3%</td>
</tr>
<tr>
<td>10-15 (199)</td>
<td>16.6%</td>
<td>6.0%</td>
<td>77.4%</td>
<td>83.4%</td>
</tr>
<tr>
<td>Philippines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-4 (51)</td>
<td>82.4%</td>
<td>3.9%</td>
<td>13.7%</td>
<td>17.6%</td>
</tr>
<tr>
<td>5-9 (123)</td>
<td>89.4%</td>
<td>6.5%</td>
<td>4.1%</td>
<td>10.6%</td>
</tr>
<tr>
<td>10-15 (191)</td>
<td>84.1%</td>
<td>7.9%</td>
<td>11.0%</td>
<td>17.9%</td>
</tr>
<tr>
<td>Vietnam</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-4 (2)</td>
<td>100.0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>5-9 (14)</td>
<td>85.7%</td>
<td>14.3%</td>
<td>14.3%</td>
<td></td>
</tr>
<tr>
<td>10-15 (20)</td>
<td>90%</td>
<td>10%</td>
<td>10%</td>
<td></td>
</tr>
</tbody>
</table>

Source: Dr. Kathy Moser, March 9, 2013 IGRA Sounding Board
San Diego TB Program Experience

**Conclusions**

- **Workload** from follow up of B2 LTBI arrivers substantially increased program workload in San Diego.

- Challenge: Post-entry FB screening is not mandatory (much time and effort contacting B2-LTBI pts).

- Despite higher cost of IGRA, immigrants were willing to pay because of awareness of false positive results from BCG.

- IGRA (QFT) testing from 2009-2012 revealed significant reduction in positive rates in all age groups.

- IGRA-TST discordance varied by country of origin and age of immigrant.

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Domestic Follow-Up of Immigrants with B2 notifications California

Arriver characteristics and outcome of domestic evaluation

Pennan Barry, MD, MPH

March 9, 2012

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What was done during B2 evaluations?

California, 2008–2012

**Total B2 arrivers** 11,208

- Evaluated to final ATS class
  - 6614 (59%) CXR: 3057 (46%)
- No CA test 2222 (34%)

- CA TST/IGRA: 4392 (66%)

- TST only 1109 (17%)
- IGRA only 2766 (42%)
- TST & IGRA 517 (8%)

Source: Dr. Pennan Barry, March 9, 2013 IGRA Sounding Board
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Outcome of domestic evaluation, ATS Class California, 2008–2012 (n=6614)

<table>
<thead>
<tr>
<th>Year</th>
<th>Class 0/1</th>
<th>Class 2</th>
<th>Class 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>25%</td>
<td>31%</td>
<td>53%</td>
</tr>
<tr>
<td>2009</td>
<td>33%</td>
<td>52%</td>
<td>54%</td>
</tr>
<tr>
<td>2010</td>
<td>53%</td>
<td>34%</td>
<td>68%</td>
</tr>
<tr>
<td>2011</td>
<td>54%</td>
<td>29%</td>
<td>68%</td>
</tr>
<tr>
<td>2012</td>
<td>68%</td>
<td>54%</td>
<td>68%</td>
</tr>
</tbody>
</table>

* Cochran-Armitage trend test p<.001

Source: Dr. Pennan Barry, March 9, 2013 IGRA Sounding Board

Potential impact of overseas IGRA on B2 evaluations in California

<table>
<thead>
<tr>
<th></th>
<th>2012 Actual</th>
<th>2012 Estimate* with Overseas IGRA</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total B2 Arrivers</td>
<td>2723</td>
<td>626</td>
<td>-2097</td>
</tr>
<tr>
<td>Evaluated</td>
<td>1154 (43%)</td>
<td>626 (100%)</td>
<td>-528</td>
</tr>
<tr>
<td>CXR</td>
<td>408</td>
<td>225</td>
<td>-183</td>
</tr>
<tr>
<td>Repeat IGRA</td>
<td>788</td>
<td>423</td>
<td>-365</td>
</tr>
<tr>
<td>Repeat TST</td>
<td>300</td>
<td>163</td>
<td>-137</td>
</tr>
</tbody>
</table>

*Estimated by applying proportion of arrivers who received test during 2012 evaluations in California to estimated number B2 arrivers assuming same IGRA positivity rate overseas as recorded during California evaluation.

Source: Dr. Pennan Barry, March 9, 2013 IGRA Sounding Board

Conclusions

Majority of B2 arrivers who underwent repeat testing found to be negative for LTBI; increasing trend

Proportion of B2 arrivers with negative domestic IGRA:
- decreased with increasing age
- highest among arrivers from China, Philippines

Overseas IGRA might reduce workload (and cost) of B2 evaluations in California
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Risk of incident tuberculosis among Filipino immigrants to the US
(Walter et al – unpublished)

Study Question: Can pre-immigration records be linked to a US TB case registry to estimate incident TB among immigrants with no B-classification?

Pre-immigration evaluation “No TB” → US Entry (further TB exposure unlikely) → TB diagnosis in US

US assumptions – FB Cases
Rate of TB diagnosis highest during first 5 years

Ratio of TB in non-Bs vs. those with B-classification after US entry:

After year 1, most TB occurs in non-Bs

Source: Dr. Nicolas Walter, March 6, 2013 IGRA Sounding Board
Key findings – Linkage Study

1. Rate of incident TB is stable over 9 years
   - No evidence that risk of LTBI reactivation declines
   - Inconsistent with current US LTBI guidelines

2. After year 1, most TB diagnosed in non-Bs
   - 76% of TB in years 2-9 diagnosed in non-Bs

3. Pre-immigration evaluation and post-arrival follow-up detects imported TB
   - 81% decline in imported TB after 2007 TIs
   - TB in B notes detected at earlier possibly less infectious stage

Source: Dr. Nicolas Walter, March 9, 2013 IGRA Sounding Board

Sounding Board Discussion

1. Are the data adequate to draw some conclusions on the utility of TST screening of immigrants pre-entry? Yes

2. Do the current technical instructions need to be revised in its recommendation to use either TST or IGRA?
   General consensus:
   1. If cost were not the limiting factor, the IGRA is a better test than the TST for pre-entry screening per current TIs
      Rationale:
      - Pre-entry: IGRAs would facilitate the immigration process (single visit and fewer needing medical evaluation)
      - Post-entry: significantly reduce B2 and B3 classifications needing follow-up and thereby reducing cost
   2. Policy and Panel physician group strongly in favor of TI revision to have IGRA replace TST
      - Panel physicians expressed need for guidelines that do not include the TST (Choice would prevent adoption of IGRAs by State Department)
      - Migration experts proposed IGRA alone strategy or IGRA as confirmatory test

Discussion

Other important points raised

General consensus:
1. Pre-entry LTBI treatment should not be mandated
   - Costly and would delay migration

2. B2 LTBI follow-up should be mandated

Important considerations:

- Expansion of pre-entry LTBI testing to those up to age 18 or all immigrants
- Linkage study suggests that more cases will be prevented if adequate follow up and preventive treatment is provided domestically
- Expansion of TB screening of long term workers and students for visas >3 months
- Quality assessment and on-site of US Civil Surgeons are lacking
Discussion

What kind of research is needed to advance pre-entry screening of immigrants?

1. Need for socio-economic studies on true cost of TST to the applicant for pre-entry screening (beyond applicant fees)
   - Cost of IGRA may be a barrier to the applicant but TST may add significant time and expense for applicants far distances to the panel site
2. Cost studies on program costs using TST compared to IGRA
3. Active case finding with CXRs by age
4. Screening all temporary workers and students entering the US (> 3 months)
   - UK and Australia experts noted the significant amount of TB found on migrants entering for short stays
5. NAAT testing of sputum from smear negative TB suspects

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Conclusions

- Meeting was highly informative
- The different perspectives created a meaningful exchange of experience and knowledge toward improving overall international TB screening of immigrants

Action Steps taken or planned since....

1. Meeting proceedings completed and approved by participants
2. Dr Contreras has completed a social impact study of using TST in Dominican Republic showing hidden costs of TST to immigrant applicants.
3. NTCA president John Warkentin plans to put the Sounding Board on the agenda of ACET
4. Julie Higashi (CTCA president) has briefly discussed the Sounding Board at CTCA business meeting. Plan for CTCA to weigh in on national discussion

Thank you!