TB Clinical Pearls and Pitfalls

[especially in the elderly]

24th Annual Four Corners TB & HIV Conference
Santa Fe, New Mexico

6 November 2018

Carlos M. Perez-Velez, M.D.
Pima County Health Department
University of Arizona College of Medicine
CMPerezVelez@Pima.gov
Disclosures

- Financial conflicts: None
- Industry links or funding: None
Objectives

- Keep you awake and attentive
- Review some pitfalls & pearls regarding the diagnosis and management of TB – especially in the elderly, with emphasis on:
  - Clinical manifestations
  - Radiological manifestations
  - Immune-based testing
  - Pathogen-based testing
In patients suspected of having pulmonary TB, does your TB Clinic’s mycobacteriology lab perform diagnostic nucleic acid amplification test (NAAT) on smear-negative sputum samples?

A. Yes

B. No
In patients suspected of having pulmonary TB, does your TB Clinic's mycobacteriology lab perform diagnostic nucleic acid amplification test (NAAT) on smear-negative sputum samples?

Yes

No
Clinical Case #1
Clinical Case #1

Mr. P.E., a 87 year-old Caucasian man, born & raised in Mexico, retired farmer

- **HPI**: 3-week history of a dry cough, dyspnea, loss of appetite and inactivity.
- **ROS**: No sputum production, pleuritic chest pain, fevers, night sweats, weight loss.
- **PMH**: Htn; Atrial fib.; GERD
- **SH**: No smoking, alcohol or illicit drug use
- **TB Exposure Hx**: No known TB contact; BCG vaccine; no hospitalizations
Urgent Care Center

- **Exam:** Afebrile; HR 120; BP 140/90; RR 22; O2 Sat 95%; BMI 22; no apparent distress; attentive; dysphoric; lungs CTA; no HSM; no LAd; no edema.
- **CXR:** RUL consolidation, report no image
- **Labs:** WBC: 8,900 (PMN 60%); Hgb 12.1; CMP WNL
- **Treatment:** Refused hospitalization. Discharged home with amoxicillin-clavulanate 875 mg BID x 14 days
Clinical Case #1

Course
• Partial improvement by end of treatment, but then deterioration with worsening dry cough.

Hospital ER → Medical Ward
• **Interim History**: Persistent dry cough; no sputum production, pleuritic chest pain, dyspnea, fevers, night sweats, weight loss.
• **Exam**
  – Afebrile; HR 120; BP 135/85; RR 22; O2 Sat 95%
  – BMI 22
  – No apparent distress; attentive; dysphoric
  – Lungs clear to auscultation
  – No hepatosplenomegaly
  – No lymphadenopathies
  – No peripheral edema
Clinical Case #1

CXR
• RUL consolidation (previous CXR comparison not available)

Labs
• WBC: 10,000 (PMN 70%); Hgb 11.5
• CMP WNL

TB immune-based testing
• TST: 7 mm of induration (BCG-vaccinated and reported as “Negative”)
• QFT: 0.29 (reported as “Negative”)

Assessment: “TB ruled out”

Microb. Testing
• Coccidioides serology neg.
Clinical Case #1

Question #1
Elderly patients with active pulmonary TB disease are more likely to present with which of the following findings:

A. Cough
B. Dyspnea
C. Fever & night sweats
D. Positive immune-based test result (TST or IGRA)
E. Smear-positive disease
Elderly patients with active pulmonary TB disease are more likely to present with which of the following findings:

- Cough
- Dyspnea
- Fever & night sweats
- Positive immune-based test result (TST or IGRA)
- Smear-positive disease
Clinical Case #1

Answer #1

A. Cough

B. Dyspnea [correct]

C. Fever & night sweats

D. Positive immune-based test result (TST or IGRA)

E. Smear-positive disease
## Evidence

### TB symptoms, diagnosis and treatment in the elderly and younger group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Elderly n = 865</th>
<th>Younger n = 4343</th>
<th>OR (95% CI) (^{\text{b}})</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>834</td>
<td>3943</td>
<td>2.73 (1.88–3.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Case detection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survey (Active)</td>
<td>168</td>
<td>481</td>
<td>1.83 (1.49–2.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Anti-TB treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category I</td>
<td>397</td>
<td>2205</td>
<td>0.82 (0.71–0.95)</td>
<td>0.01</td>
</tr>
<tr>
<td>Category III</td>
<td>356</td>
<td>1447</td>
<td>1.39 (1.20–1.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previously treated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category II</td>
<td>112</td>
<td>691</td>
<td>0.79 (0.63–0.98)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Pulmonary TB</strong></td>
<td><strong>n = 834</strong></td>
<td><strong>n = 3943</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Symptoms (Irrespective of duration)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough*</td>
<td>700</td>
<td>3290</td>
<td>1.04 (0.8–1.3)</td>
<td>0.758</td>
</tr>
<tr>
<td>Breathlessness*</td>
<td>336</td>
<td>1421</td>
<td>1.4 (1.2–1.6)</td>
<td>0.021</td>
</tr>
<tr>
<td>Chest pain*</td>
<td>520</td>
<td>2569</td>
<td>0.9 (0.8–1.04)</td>
<td>0.130</td>
</tr>
<tr>
<td>Hemoptysis*</td>
<td>198</td>
<td>1115</td>
<td>0.8 (0.7–0.9)</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>First action for relief from respiratory complaints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Govt</td>
<td>419</td>
<td>1829</td>
<td>1.2 (1.0–1.4)</td>
<td>0.043</td>
</tr>
<tr>
<td>Private</td>
<td>289</td>
<td>1600</td>
<td>0.8 (0.7–0.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Home/Pharmacy</td>
<td>120</td>
<td>503</td>
<td>1.1 (0.9–1.4)</td>
<td>0.204</td>
</tr>
<tr>
<td>Alternate Medicine</td>
<td>6</td>
<td>11</td>
<td>2.6 (0.8–7.7)</td>
<td>0.052</td>
</tr>
<tr>
<td><strong>Anti-TB treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category I</td>
<td>389</td>
<td>2117</td>
<td>0.7 (0.6–0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Category III</td>
<td>333</td>
<td>1143</td>
<td>1.6 (1.4–1.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previously treated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category II</td>
<td>112</td>
<td>683</td>
<td>0.7 (0.6–0.9)</td>
<td>0.006</td>
</tr>
<tr>
<td>Sputum smear</td>
<td>385</td>
<td>1408</td>
<td>1.54 (1.3–1.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\(^{a}\)Details not available for 2 patients in the younger group.

\(^{b}\)Details not available for 232 patients in the elderly and 1114 patients in the younger group.

\(^{\text{b}}\)Odds ratio (95% CI) calculated with younger group as reference using chi-square test.

[10.1371/journal.pone.0088045.t002]
Clinical presentation of TB disease in elderly patients compared to those < 60-65 years of age

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Cough</th>
<th>Sputum production</th>
<th>Fever</th>
<th>Weight loss</th>
<th>Dyspnea</th>
<th>Fatigue</th>
<th>Pleuritic chest pain</th>
<th>Night sweats</th>
<th>Hemoptysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pérez-Guzmán C et al 1999 (Meta-analysis)</td>
<td>859</td>
<td>=</td>
<td>=</td>
<td>↓</td>
<td>=</td>
<td>↑↑</td>
<td>↑</td>
<td>NR</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Lee J et al 2005 (Meta-analysis)</td>
<td>119</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑↑↑</td>
<td>↑</td>
<td>=</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Velayutham B et al 2014 (Original)</td>
<td>865</td>
<td>=</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>↑↑</td>
<td>NR</td>
<td>=</td>
<td>NR</td>
<td>↓</td>
</tr>
</tbody>
</table>

Compared to younger patients with TB, elderly are more likely…
- to have clinical presentations that are atypical, and that mimic diseases related to aging, and
- to die.
<table>
<thead>
<tr>
<th>System</th>
<th>Symptoms &amp; Signs</th>
<th>Clinical Syndromes</th>
<th>Temporal Patterns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>- Cough, dry or wet</td>
<td>- Low respiratory tract infection</td>
<td>- Subacute-to-chronic</td>
</tr>
<tr>
<td></td>
<td>- Dyspnea</td>
<td>(“phthisis”)</td>
<td>- Acute-on-chronic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Pneumonia</td>
<td>- Fulminant-to-acute</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- [Endo]bronchitis</td>
<td>- Recurrent</td>
</tr>
<tr>
<td></td>
<td>- Pleuritic chest pain</td>
<td>- Pleuritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Subacute-to-Chronic</td>
</tr>
<tr>
<td>Lymphoid</td>
<td>- Wheezing (CXR with mediastinal/hilar</td>
<td>- Wheezing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>lymph nodes compressing bronchi)</td>
<td></td>
<td>- Subacute-to-chronic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Enlarged lymph nodes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(cervical, supraclavicular, axillary)</td>
<td>- Enlarged peripheral lymph node</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Cervical (“scrofula”)</td>
<td></td>
</tr>
<tr>
<td>Immunological</td>
<td>- Fever</td>
<td>- Fever without localizing signs</td>
<td>- Subacute-to-chronic</td>
</tr>
<tr>
<td></td>
<td>- Night sweats</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constitutional</td>
<td>- Decreased appetite</td>
<td>- Wasting syndrome (“phthisis”,</td>
<td>- Chronic</td>
</tr>
<tr>
<td></td>
<td>- Weight loss</td>
<td>“consumption”)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Fatigue</td>
<td>- Chronic fatigue</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Case #1

Question #2

Which of the following radiological findings is found least often in adults with pulmonary TB who are more than 65 years of age, compared to those who are younger?

A. Upper lobe lesions
B. Middle and lower lobe lesions
C. Cavitary lesions
D. Pleural involvement
E. Consolidation
Which of the following radiological findings is found least often in adults with pulmonary TB who are more than 65 years of age, compared to those who are younger?

<table>
<thead>
<tr>
<th>Upper lobe lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle and lower lobe lesions</td>
</tr>
<tr>
<td>Cavitary lesions</td>
</tr>
<tr>
<td>Pleural involvement</td>
</tr>
<tr>
<td>Consolidation</td>
</tr>
</tbody>
</table>
Clinical Case #1

Answer #2

Which of the following radiological findings is found least often in adults with pulmonary TB who are more than 65 years of age, compared to those who are younger?

A. Upper lobe lesions
B. Middle and lower lobe lesions
C. Cavitary lesions [correct]
D. Pleural involvement
E. Consolidation
Radiological presentation of TB disease in elderly patients compared to those < 60-65 years of age

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Lesions in upper lobes</th>
<th>Lesions in middle and lower lobes</th>
<th>Cavitary lesions</th>
<th>Pleural involvement</th>
<th>Consolidation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pérez-Guzmán C et al 1999 (Meta-analysis)</td>
<td>859</td>
<td>↓</td>
<td>↑</td>
<td>↓↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Lee J et al 2005 (Meta-analysis)</td>
<td>119</td>
<td>↓</td>
<td>↑</td>
<td>↓↓</td>
<td>NR</td>
<td>↑</td>
</tr>
</tbody>
</table>

Low prevalence of cavitary pulmonary disease.
Immune-based testing
Question #3

How does the sensitivity of IGRAs *in elderly patients* compare to that in young and middle-aged adults with culture-confirmed TB?

A. ~10% higher
B. Same
C. ~10% lower
D. ~20% lower
E. ~30% lower
How does the sensitivity of IGRAs in elderly patients compare to that in young and middle-aged adults with culture-confirmed TB?

- ~10% higher
- Same
- ~10% lower
- ~20% lower
- ~30% lower
Clinical Case #1

Answer #3

A. ~10% higher
B. Same
C. ~10% lower [correct]
D. ~20% lower
E. ~30% lower
TB immune-based tests (TST/IGRA) in the elderly are just as sensitive as in young and middle-aged adults.
Sensitivity of TB immune-based tests in elderly patients

Latent TB infection
• In > 60 y.o., the sensitivity of IGRA (78%) is higher than 10 mm-TST (43%).

Active TB disease
• In ≥ 65 y.o., sensitivity of one-step 10-mm-TST was only 62%.
• Sensitivity of IGRA (77%) is greater than one-step 5mm-TST (27%).
  Kobashi et al. *Chest.* 2008;133:1196
• Sensitivity of IGRAs in elderly patients with culture-confirmed TB disease

<table>
<thead>
<tr>
<th>Study</th>
<th>&lt; 65 years of age</th>
<th>≥ 65 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kwon et al. PLoS ONE 10: e0129792</td>
<td>89% (764/859)</td>
<td>79% (318/405)</td>
</tr>
<tr>
<td>Kobashi et al. Chest. 2008;133:1196</td>
<td>87% (87/100)</td>
<td>77% (23/30)</td>
</tr>
<tr>
<td>Tan et al. <em>J Am Geriatr Soc</em> 2009;57:2361</td>
<td>84% (47/56)</td>
<td>78% (18/23)</td>
</tr>
</tbody>
</table>
Pearl

TB immune-based tests (TST & IGRA) can have false-negative results due to immunosenescence-related anergy (waning of delayed-type hypersensitivity) to cutaneous antigens.
Pearl

TB immune-based tests (TST & IGRAs) can have false-negative results due to immunologic immaturity.
Recommendations for decreasing false-negative TST results in elderly patients

• Using a cut-off of 5 mm in those with suspected TB disease, recent exposure, or immunocompromised.

• Measuring at 48-72 hours and then again at 5-7 days

• Repeating TST in 2 weeks (aka, “two-step TST”) to improve immunologic recall (“booster effect”)
  Finucane TE. J Am Geriatr Soc. 1988; 36:77
IGRAs are reliable for the diagnosis of active TB disease
Pearl

For the diagnosis of *active* TB disease, IGRAAs should *not* be relied upon.
Immune-based test results in elderly patients compared to those < 60-65 years of age

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>TST-Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pérez-Guzmán et al 1999 (Meta-analysis)</td>
<td>859</td>
<td>↓</td>
</tr>
<tr>
<td>Lee et al 2005 (Meta-analysis)</td>
<td>119</td>
<td>NR</td>
</tr>
<tr>
<td>Velayutham et al 2014 (Original)</td>
<td>865</td>
<td>NR</td>
</tr>
<tr>
<td>Chitnis et al 2015 (Original)</td>
<td>211</td>
<td>↓</td>
</tr>
</tbody>
</table>

Elderly are less likely to have positive results of tuberculin skin tests.


TST-positive elderly are less likely to die while undergoing TB Tx (OR=0.39;95% CI=0.16-0.96).
Pitfall

A negative TB immune-based test (TST/IGRA) rules out active TB disease.
A negative TB immune-based test (IBT) does not rule out active TB disease -- especially not in an immune-compromised host
In a retrospective study carried out by the Tuberculosis Network European Trials Group (TBNET), approximately 33% (221/664) of patients with bacteriologically-confirmed TB disease had a negative IGRA (QFT and/or T-SPOT) result.

devissers et al. *Eur Respir J.* 2015; 45:279
### Accuracy of TB immune-based tests in patients with active TB disease (ATS/IDSA/CDC 2017)

<table>
<thead>
<tr>
<th>IBT</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>~80% (71%–82%) (95-98% in clinically well persons with previously treated TB)</td>
<td>Unvaccinated: 97%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vaccinated: ~60% *</td>
</tr>
<tr>
<td>QFT</td>
<td>~80% (81%–86%)</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>T-SPOT.TB</td>
<td>~90% (90%–95%)</td>
<td>&gt;95%</td>
</tr>
</tbody>
</table>

* If BCG in infancy, > 10 years prior to the TST, then cross reactivity is < 1%, so sensitivity will be ↑↑
* If BCG in post-infancy and/or revaccination, then cross reactivity is ~9%, so sensitivity will be ↓

A positive TST in the setting of a negative IGRA (QFT or T-SPOT.TB) is *always* false-positive TST.
Pearl

Discordant results of TB immune-based tests (TST/IGRA) are well recognized; in the setting of a patient with findings consistent with TB disease, and epidemiological risk factors for TB infection, any positive immune-based test result should be interpreted as positive.

- TST and IGRAs are complementary (not redundant) immune-based tests...
  - measuring different cell-mediated immune responses (delayed type hypersensitivity vs. IFN-γ release)...
  - to different mycobacterial antigens (PPD-Tuberculin versus ESAT-6 & CFP-10)...
  - detecting cases that another immune-based test may not.
Pitfall

BCG vaccination causes false-positive TSTs for the rest of the person’s life.
False-positive tuberculin skin tests: what is the absolute effect of BCG and non-tuberculous mycobacteria?

M. Farhat, C. Greenaway, M. Pai, D. Menzies

<table>
<thead>
<tr>
<th>Comparison</th>
<th>BCG in infirmity</th>
<th>BCG older (after age of 1 year)</th>
<th>n positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n$ subjects</td>
<td>Criteria</td>
<td>$n$ (%)</td>
</tr>
<tr>
<td>Overall effect from all studies</td>
<td>240 203 (24)</td>
<td>10+</td>
<td>20 406 (8.5)</td>
</tr>
<tr>
<td>By interval</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\leq 10$ years</td>
<td>234 464 (16)</td>
<td>10</td>
<td>4 930 (8.7)</td>
</tr>
<tr>
<td>$&gt; 10$ years</td>
<td>5 739 (8)</td>
<td>10</td>
<td>56 (1.0)</td>
</tr>
<tr>
<td>By TST size</td>
<td>71 289 (13)</td>
<td>10–14</td>
<td>3 297 (4.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15+</td>
<td>1 340 (1.9)</td>
</tr>
<tr>
<td>By interval and TST size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\leq 10$ years</td>
<td>170 401* (9)</td>
<td>10–14</td>
<td>13 854 (8.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15+</td>
<td>6 346 (3.7)</td>
</tr>
<tr>
<td>$&gt; 10$ years</td>
<td>5 271 (5)</td>
<td>10–14</td>
<td>73 (1.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15+</td>
<td>0 (0)</td>
</tr>
<tr>
<td>By type of TST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5TU PPDS</td>
<td>170 401 (13)</td>
<td>10+</td>
<td>15 878 (9.3)</td>
</tr>
<tr>
<td>1TU RT23</td>
<td>39 791 (6)</td>
<td>10+</td>
<td>2 701 (6.8)</td>
</tr>
<tr>
<td>2TU RT23</td>
<td>30 011 (5)</td>
<td>10+</td>
<td>2 056 (6.9)</td>
</tr>
</tbody>
</table>

* Of the 10 studies using 5TU PPDS to test subjects vaccinated at an older age, 5 involved average intervals of $\geq 10$ years between vaccination and TST. On the other hand, both studies using 2TU RT23 involved shorter intervals of 5 or 8 years.

BCG = bacille Calmette-Guérin; TST = tuberculin skin test.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All children</td>
<td>5.80 (2.58 to 13.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0 to &lt;2</td>
<td>16.2 (1.69 to 155)</td>
<td>0.001</td>
</tr>
<tr>
<td>2 to &lt;5</td>
<td>9.85 (1.11 to 87.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>5 to &lt;10</td>
<td>3.05 (0.93 to 10.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>10 to &lt;15</td>
<td>4.16 (0.77 to 22.3)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Probability of having a TST of 5 mm induration in children with a negative IGRA who have been vaccinated with BCG at birth versus Children who are not vaccinated with BCG
Pearl

Persons vaccinated with BCG in the first year of life may have low-level TST reactivity (typically <10 mm), but it rarely persists after 10 years of age.

Among individuals with high likelihood of having acquired TB infection, and/or high risk of progression to TB disease if infected, potential causes of false-positive tests should not influence the decision to treat the TB infection.
Pitfall

The values of TB immune-based tests can be reliably interpreted in a binary manner, i.e., positive or negative.
### TB immune-bases tests

#### Cut-off points zones/ranges

<table>
<thead>
<tr>
<th>TB immune-based test</th>
<th>Negative</th>
<th>Borderline*</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculin skin test</td>
<td>0 - 4 mm</td>
<td>5 - 9 mm</td>
<td>≥ 10 mm</td>
</tr>
<tr>
<td>T-SPOT-TB</td>
<td>0 - 4 spots</td>
<td>5 - 7 spots</td>
<td>≥ 8 spots</td>
</tr>
<tr>
<td>QuantiFERON-TB</td>
<td>0.0 - 0.34 UI/mL</td>
<td>≥ 0.35 UI/mL</td>
<td>≥ 0.81 UI/mL</td>
</tr>
<tr>
<td></td>
<td>0.0 - 0.24 UI/mL</td>
<td>0.25 - 0.80 UI/mL</td>
<td></td>
</tr>
</tbody>
</table>

* Some authors use instead the terms Gray, Uncertainty, Equivocal

- Metcalfe et al. 2013; 187:206
The results of immune-based tests for TB are continuous variables – and not binary outcomes (e.g., positive/negative) – that need to be interpreted in the context of degree of risk of TB infection, as well as status of immunological competence/compromise.
### Reproducibility / Variability of IGRAs

Serial testing studies of interferon-gamma release assays in health care workers (HCWs) in low and intermediate incidence countries

<table>
<thead>
<tr>
<th>Author (reference), year, country</th>
<th>Duration between testing</th>
<th>Conversion, n/N (%)</th>
<th>IGRA reversions*, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joshi et al (15), 2012, USA</td>
<td>2 to 30 days</td>
<td>Tuberculin skin test: N/A</td>
<td>IGRA*: 18/45 (40)</td>
</tr>
<tr>
<td>Rafiza et al (16), 2012, Malaysia</td>
<td>1 year</td>
<td>N/A</td>
<td>14/59 (23.7)</td>
</tr>
<tr>
<td>Fong et al (17), 2012, USA</td>
<td>1 year or 1 to 6 months for repeat of positive IGRA</td>
<td>N/A</td>
<td>8/10 (80)*</td>
</tr>
<tr>
<td>Torres Costa et al (18), 2011, Portugal</td>
<td>1 year</td>
<td>61/199 (30.7)</td>
<td>51/462 (11)</td>
</tr>
<tr>
<td>Schablon et al (19), 2010, Germany</td>
<td>High-risk HCWs tested annually, all others evaluated every other year</td>
<td>Reversion rates: 15/245 (6.1)</td>
<td>46/208 (22.1)</td>
</tr>
<tr>
<td>Ringshausen et al (20), 2010, Germany</td>
<td>18 weeks</td>
<td>N/A</td>
<td>3/162 (1.9)</td>
</tr>
<tr>
<td>Park et al (21), 2010, South Korea</td>
<td>1 year</td>
<td>N/A</td>
<td>14/244 (5.7)</td>
</tr>
<tr>
<td>Lee et al (22), 2009, South Korea</td>
<td>1 year</td>
<td>N/A</td>
<td>21/146 (14.4)</td>
</tr>
<tr>
<td>Chee et al (23), 2009, Singapore</td>
<td>1 year</td>
<td>16/75 (21.3)</td>
<td>9/182 (4.9)</td>
</tr>
<tr>
<td>Yoshiyama et al (24), 2009, Japan</td>
<td>2 and 4 years</td>
<td>0/18 (Note: denominator includes only baseline concordant positives)</td>
<td>5/277 (1.8)</td>
</tr>
<tr>
<td>Pollock et al (25), 2008, USA</td>
<td>1 to 7 months</td>
<td>N/A</td>
<td>2/43 (4.6). Selected HCWs at 'increased risk' and negative at baseline</td>
</tr>
</tbody>
</table>

Pai & Elwood. *Can Respir J.* 2012; 19:81
Reproducibility / Variability of IGRAs

Potential sources of variability

• Patient
  – Variability (conversions and reversions) is highest in persons whose initial result is in borderline zone

• QFT variability under identical conditions
  – Overall: ± 0.47 IU/mL (CV 13%)
  – If initial result is in borderline zone: ± 0.26 IU/mL (CV 30%)

• Knowledge of the relative contribution and extent of the individual sources of variability (immunological, preanalytical, or analytical) could help optimize testing protocols.
Sources of IGRA Variability

- Phlebotomy, Tube Order, and Time of Blood Draw
- Immunomodulation and Boosting
- Analytical Error
- Manufacturing Defects
- Incubation of Processing Delay
- Incubation Duration
Continuation of Clinical Case #1…

**Microbiol. Testing**

“*Unable to collect sputum*” → BAL

- Gram stain: neg.
- Bacterial culture: neg.
- Fungal stain: neg.
- Fungal culture: pending
- AFB smear: neg.
- *M.tb* PCR: *not ordered*
- Mycobacterial culture: pending

**Hospital Course**

ceftriaxone + clarithromycin, with partial clinical improvement
Clinical Case #1

Question #4
In a patient who does not expectorate sputum spontaneously, and who cannot produce an adequate sample after one sputum induction procedure, what specimen collection strategy would you order?

A. Order another sputum induction
B. Order a bronchoalveolar lavage
C. Order a gastric aspirate
D. Order nasopharyngeal aspirate
E. Order stool
In a patient who does not expectorate sputum spontaneously, and who cannot produce an adequate sample after one sputum induction procedure, what specimen collection strategy would you order?

- Order another sputum induction
- Order a bronchoalveolar lavage
- Order a gastric aspirate
- Order nasopharyngeal aspirate
- Order stool
Clinical Case #1

Answer #4

A. Order another sputum induction \[suggested\]
B. Order a bronchoalveolar lavage
C. Order a gastric aspirate
D. Order nasopharyngeal aspirate
E. Order stool
Once a BAL is collected, additional specimens are not indicated
Pearl

The rate of bacteriological confirmation of TB can be significantly improved through implementation of a specimen collection strategy.
Specimen collection strategy

• Variety of specimens
  • Respiratory (sputum; gastric aspirate, BAL, nasopharyngeal aspirate)  
  • Non respiratory (lymph node, stool, serosal tissue biopsy; serosal fluid)

• Quality of sample

• Quantity of sample
  • Sputum  
    • AFB smear & culture: 5-10 mL  
    • Mtb PCR: 2 mL
  • CSF: 10 mL

• Number of samples: at least 3

• Pooling (samples of same or different specimens)
  • By requiring minimum of 5 mL, and pooling daily samples until reached, yield increased 20% (72.5% to 92.0%)  
    [Warren et al, 2000; AJRCCM]
If a sample of sputum – expectorated or aspirated from stomach (i.e., gastric aspirate) – is positive by both AFB smear microscopy and *M.tuberculosis* PCR, there is no need for further invasive procedures such as BAL or gastric aspiration.

Clinical Case #1

Question #5

Compared with younger adults, what is the probability that geriatric patients with pulmonary TB have a positive sputum smear?

A. Greater
B. Similar
C. Lower
Compared with younger adults, what is the probability that geriatric patients with pulmonary TB have a positive sputum smear?

Greater

Similar

Lower
Clinical Case #1

Answer #5
Compared with younger adults, what is the probability that geriatric patients with pulmonary TB have a positive sputum smear?

A. Greater

B. Similar

C. Lower [correct]
TB symptoms, diagnosis and treatment in the elderly vs. younger group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Elderly n = 865</th>
<th>Younger n = 4343</th>
<th>OR (95% CI) (^{b})</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of disease</td>
<td>Pulmonary</td>
<td>834 96</td>
<td>3943 91</td>
<td>2.73 (1.88-3.96)</td>
</tr>
<tr>
<td></td>
<td>Survey (Active)</td>
<td>168 19</td>
<td>481 11</td>
<td>1.83 (1.49-2.23)</td>
</tr>
<tr>
<td>Anti-TB treatment</td>
<td></td>
<td>(n = 834)</td>
<td>(n = 3943)</td>
<td></td>
</tr>
<tr>
<td>New patients</td>
<td>Category I</td>
<td>397 46</td>
<td>2205 51</td>
<td>0.82 (0.71-0.95)</td>
</tr>
<tr>
<td></td>
<td>Category III</td>
<td>356 41</td>
<td>1447 33</td>
<td>1.39 (1.20-1.63)</td>
</tr>
<tr>
<td>Previously treated</td>
<td>Category II</td>
<td>112 13</td>
<td>691 16</td>
<td>0.79 (0.63-0.98)</td>
</tr>
<tr>
<td>Pulmonary TB</td>
<td></td>
<td>(n = 834)</td>
<td>(n = 3943)</td>
<td></td>
</tr>
<tr>
<td>Symptoms (Irrespective of duration)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough*</td>
<td>700 84</td>
<td>3290 83</td>
<td>1.04 (0.8-1.3)</td>
<td>0.758</td>
</tr>
<tr>
<td>Breathlessness*</td>
<td>336 40</td>
<td>1421 36</td>
<td>1.4 (1.2-1.6)</td>
<td>0.021</td>
</tr>
<tr>
<td>Chest pain*</td>
<td>520 62</td>
<td>2569 65</td>
<td>0.9 (0.8-1.04)</td>
<td>0.130</td>
</tr>
<tr>
<td>Hemoptysis*</td>
<td>198 24</td>
<td>1115 28</td>
<td>0.8 (0.7-0.9)</td>
<td>0.008</td>
</tr>
<tr>
<td>First action for relief from respiratory complaints*</td>
<td>419 50</td>
<td>1829 46</td>
<td>1.2 (1.0-1.4)</td>
<td>0.043</td>
</tr>
<tr>
<td>Private</td>
<td>289 35</td>
<td>1600 41</td>
<td>0.8 (0.7-0.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Home/Pharmacy</td>
<td>120 14</td>
<td>503 13</td>
<td>1.1 (0.9-1.4)</td>
<td>0.204</td>
</tr>
<tr>
<td>Alternate Medicine</td>
<td>6 1</td>
<td>11 &lt;1</td>
<td>2.6 (0.8-7.7)</td>
<td>0.052</td>
</tr>
<tr>
<td>Anti-TB treatment</td>
<td></td>
<td>(n = 834)</td>
<td>(n = 3943)</td>
<td></td>
</tr>
<tr>
<td>New patients</td>
<td>Category I</td>
<td>389 47</td>
<td>2117 54</td>
<td>0.7 (0.6-0.9)</td>
</tr>
<tr>
<td></td>
<td>Category III</td>
<td>333 40</td>
<td>1143 29</td>
<td>1.6 (1.4-1.9)</td>
</tr>
<tr>
<td>Previously treated</td>
<td>Category II</td>
<td>112 13</td>
<td>683 17</td>
<td>0.7 (0.6-0.9)</td>
</tr>
<tr>
<td>Sputum smear</td>
<td>Negative</td>
<td>385 46</td>
<td>1408 36</td>
<td>1.54 (1.3-1.8)</td>
</tr>
</tbody>
</table>

*Details not available for 2 patients in the younger group.
\(^{a}\)Details not available for 223 patients in the elderly and 1114 patients in the younger group.
\(^{b}\)Odds ratio (95% CI) calculated with younger group as reference using chi-square test.


\[\text{doi:10.1371/journal.pone.0088045.t002}\]
Pathogen-based test results in elderly patients compared to those < 60-65 years of age

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>AFB smear-positive</th>
<th>Culture-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pérez-Guzmán et al 1999 (Meta-analysis)</td>
<td>859</td>
<td>↓</td>
<td>NR</td>
</tr>
<tr>
<td>Lee et al 2005 (Meta-analysis)</td>
<td>119</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Velayutham et al 2014 (Original)</td>
<td>865</td>
<td>↓</td>
<td>=</td>
</tr>
<tr>
<td>Chitnis et al 2015 (Original)</td>
<td>211</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

Elderly are more likely to have sputum that is negative by AFB smear microscopy (15-59 y.o., 46% vs. 36%, ≥60 y.o.)

Outpatient Course:

- Mycobacterial culture reported positive at 6 weeks…
- Started on RIPE the same day as lab notification.
- Died 3 weeks later.
- DST: Pan-susceptible to R-I-P-E
Pitfall

The clinical and radiological features, and the immune-based and pathogen-based test results, of TB disease in the elderly are similar to those of young- and middle-aged adults.
Pearl

Compared with young- and middle-aged adults, the elderly with TB disease may have uncharacteristic clinical presentations, atypical radiological features, negative immune-based test results, and negative sputum-smear-microscopy results, therefore require a high index of suspicion to diagnose.
Clinical Case #2
Clinical Case #2

Mr. R.B., a 65 y.o. Caucasian man, born in USA, no foreign travel, homeless

**HPI:** Found unconscious on street; taken to ER; concern for head trauma vs. seizure; CT of head & neck w/o acute lesions, but captures upper chest and incidentally reveals LUL cavity.

**ROS:** Progressive weight loss ("pants falling down");
No cough, sputum production, pleuritic chest pain, dyspnea, fevers, night sweats, fatigue or malaise

**Allergies & Adv. Rxns:** Penicillins ("rash"); clarithromycin (nausea/vomiting)

**PMH:** seizure d/o; community-acquired pneum. (2 wks prior, Tx’ed w/ Lvfx)

**SH:** (+) Smoking (1 PPD x 40 years); (+) Alcohol use disorder; (-) Illicit drugs

**TB Exposure Hx:** H/O TB at ~40 y.o.; no known recent TB contact; no BCG vaccine; >40 ER visits in past year; 9 hospitalizations in past year
Clinical Case #2

**Exam:** Afebrile; HR 86; BP 145/95; RR 18; O2 Sat 93%; BMI 18; no apparent distress; lungs decreased breath sounds at bases, but no adventitious sounds; no HSM; no LAd

**Chest Imaging:** cavity in LUL; reticular opacities and pleural thickening in both apices

**TB Immune-based Testing:** QFT > 10 (pos.)

**Labs:** WBC: 7,500; Hgb 13.1; CMP WNL

**Infectious Disease Testing**
- *Coccidioides* serology: neg.
- Sputum AFB smear: neg. x 3 samples
- Sputum fungal culture: neg. x 1 sample
- Sputum Gram stain: neg.
- Sputum bacterial culture: oral flora
Clinical Case #2

Hospital Course:
• First 3 sputum samples were smear-negative (\textit{M.\textit{tb}} PCR not ordered)
• \textit{Discharge not recommended by TB Controller}
• 4th sputum sample was smear-neg. and PCR-neg.
• 5th sputum sample was smear-neg., \textit{but PCR-positive} (rifampin resistance gene not detected)
Clinical Case #2

**Question #6**
Which of the following NAATs is approved by the FDA for detecting *M.tbc* complex (MTC) in smear-negative respiratory samples?

a) Amplified MTD  
b) COBAS TaqMan MTB  
c) Xpert MTB/RIF  
d) Amplified MTD and COBAS TaqMan MTB  
e) Amplified MTD and Xpert MTB/RIF  
f) COBAS TaqMan MTB and Xpert MTB/RIF
Which of the following NAATs is approved by the FDA for detecting M.tb complex (MTC) in smear-negative respiratory samples?

<table>
<thead>
<tr>
<th>Amplified MTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>COBAS TaqMan MTB</td>
</tr>
<tr>
<td>Xpert MTB/RIF</td>
</tr>
<tr>
<td>Amplified MTD and COBAS TaqMan MTB</td>
</tr>
<tr>
<td>Amplified MTD and Xpert MTB/RIF</td>
</tr>
<tr>
<td>COBAS TaqMan MTB and Xpert MTB/RIF</td>
</tr>
</tbody>
</table>

Start the presentation to see live content. Still no live content? Install the app or get help at PollEv.com/app
Clinical Case #2

**Answer #6**

a) Amplified MTD
b) COBAS TaqMan MTB
c) Xpert MTB/RIF
d) Amplified MTD and COBAS TaqMan MTB
e) **Amplified MTD and Xpert MTB/RIF [correct]**
f) COBAS TaqMan MTB and Xpert MTB/RIF
Pitfall

All FDA-approved *M. tb* NAATs require sample to be smear-positive in order for result to be reliable.
Pearl

Newer generation *M. tb* NAATs have levels of detection sensitive enough to be useful in AFB smear-negative samples.
Continuum of TB states and correlations with bacterial load and with radiological and clinical manifestations


*M. tb* detection by microscopy
[level of detection: 5,000 (fluorescent) to 10,000 (light microscopy) CFU/ml]

*M. tb* detection by PCR
[level of detection: 20 (Xpert Ultra) to 120 (Xpert) CFU/ml]

*M. tb* detection by culture
[level of detection: 10 (liquid) to 100 (solid) CFU/ml]
<table>
<thead>
<tr>
<th>NAAT</th>
<th>Type</th>
<th>Gene Encoding Target</th>
<th>Drug-Resistance: Gene Encoding Target of Mutations</th>
<th>Analytical Sensitivity (Limit of Detection) (CFU/mL)</th>
<th>Recommended Smear Status for Detecting <em>Mtb</em></th>
<th>Turnaround Time</th>
<th>Required Risk Level of Laboratory</th>
<th>Year of Release</th>
<th>Endorsement/Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>GenoType MTBDR&lt;sup&gt;+&lt;/sup&gt; plus version 2 (Hain)</td>
<td>Line probe assay</td>
<td>- <em>M. tb</em> complex: 23SrRNA</td>
<td>- Rmp: <em>rpoB</em>  - INH: <em>katG, inhA</em></td>
<td>1000-10,000</td>
<td>Only positive</td>
<td>4-6 hours (manual)</td>
<td>High</td>
<td>2012 (version 1 in 2004)</td>
<td>WHO</td>
</tr>
<tr>
<td>GenoType MTBDR&lt;sup&gt;sl&lt;/sup&gt; version 2 (Hain)</td>
<td>Line probe assay</td>
<td>- <em>M. tb</em> complex: 23SrRNA</td>
<td>- Fluoroquinolones: <em>gyrA</em>  - Aminoglycosides &amp; Cyclic Peptides: <em>rrs</em> - Emb: <em>embB</em></td>
<td>1000-10,000</td>
<td>Only positive</td>
<td>4-6 hours (manual)</td>
<td>High</td>
<td>2012 (version 1 in 2009)</td>
<td>WHO</td>
</tr>
<tr>
<td>COBAS TagMan MTD Test (Roche)</td>
<td>RT-PCR</td>
<td>- <em>M. tb</em> complex: 16S rRNA</td>
<td>N/A</td>
<td>20</td>
<td>Only positive</td>
<td>6.5 hours (automated)</td>
<td>Moderate</td>
<td>2010</td>
<td>FDA</td>
</tr>
<tr>
<td>Amplified MTD (Gen-Probe Hologic)</td>
<td>TMA</td>
<td>- 16S rRNA</td>
<td>N/A</td>
<td>100</td>
<td>Positive &amp; Negative</td>
<td>2.5-3.5 hours (automated)</td>
<td>Moderate</td>
<td>1995</td>
<td>FDA</td>
</tr>
<tr>
<td>Xpert MTB/RIF (Cepheid)</td>
<td>RT-PCR</td>
<td>- <em>M. tb</em> complex: <em>rpoB</em></td>
<td>- Rmp: <em>rpoB</em></td>
<td>114</td>
<td>Positive &amp; Negative</td>
<td>1-2 hours (automated)</td>
<td>Low</td>
<td>2010</td>
<td>WHO FDA</td>
</tr>
<tr>
<td>Xpert MTB/RIF Ultra (Cepheid)</td>
<td>RT-PCR</td>
<td>- <em>M. tb</em> complex: <em>rpoB</em></td>
<td>- Rmp: <em>rpoB</em></td>
<td>16</td>
<td>Positive &amp; Negative</td>
<td>1-2 hours (automated)</td>
<td>Low</td>
<td>2017</td>
<td>N/A</td>
</tr>
</tbody>
</table>
AFB smear microscopy and mycobacterial cultures of sputum are sensitive enough to rule out PTB -- especially if cavitary
Currently available mycobacterial tests for TB are not sensitive enough to rule out pulmonary TB (even cavitary TB disease)
Evidence

• Cavitary pulmonary disease was smear-negative in 5-10% of HIV-uninfected culture-positive patients [Kim et al. Am Rev Respir Dis 1984;129 264]

• PTB was smear-negative & culture-negative in 21% (21/99) of patients diagnosed
  – microbiologically (with molecular tests),
  – histopathologically,
  – ruling out alternative diagnoses, and

• Patients with smear-negative & culture-negative PTB were less likely to have:
  – Cough (70% vs. 91%, \( P = 0.02 \))
  – Sputum production (30% vs. 64%, \( P < 0.01 \))
  – Weight loss (25% vs. 54%, \( P = 0.02 \))
  – Cavitation on chest CT (12% vs. 68%, \( P < 0.01 \))
Lung cavity in a person with history of TB can be assumed to be a “scar”...

Old “Dogma”: the likelihood of recurrent TB is extremely low.
Recurrent TB, in patients who have been successfully treated, is not uncommon -- even in low-incidence countries -- and is not always due to relapse of previous TB disease.
Evidence

**Definition** of recurrent TB: TB that recurs after a patient has met criteria for cure (i.e., clinical resolution, radiological improvement, microbiological conversion, and treatment completion)

**Low-incidence settings** (based on 44 studies, with a median follow-up of 7.8 years (IQR 5–12, range 2–33) [Rosser et al. *Int J Tuberc Lung Dis*. 2018;22(2):139–150]

- TB patients experiencing an episode of recurrent TB after treatment completion: **3.4%** (IQR 1.6 – 6.0, range 0.4 – 16.7)
- Recurrences attributable to *reactivation*: **81%** (IQR 73.1 – 85.5, range 49 – 100)
- Risk factors for recurrence
  - HIV infection
  - Low socioeconomic status
  - Birth in a country of high- or intermediate-incidence of TB
  - Infection with drug-resistant *Mtb*
  - Predisposición inmuno-genética?

- **Annual country-level incidence rate of TB in those with prior TB:** 720 (IQR 473–2024, range 71–3780) per 100,000 person-years of follow-up
  - Median **31.5** (IQR 11.8–57.1, range 7.3–497.8) *times* higher than TB incidence rate in all (i.e., new + recurrent)

**All settings, worldwide** [WHO. *Global TB Database*. 2017]

- Notified ATBD cases in 2016 that were recurrences: 7.7% (of 6.3 million new & relapse TB cases)
Pitfall

Not starting empiric treatment for TB because AFB microscopy and *M. tb* PCR are negative on all specimens, on a patient who meets criteria for presumptive TB.
### Pearl

<table>
<thead>
<tr>
<th></th>
<th>Risks of not starting TB treatment in a timely manner</th>
<th>Benefits of starting TB treatment in earlier stages of severity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient</strong></td>
<td>- Increased morbidity/mortality</td>
<td>- Reduced morbidity/mortality</td>
</tr>
<tr>
<td></td>
<td>- Lower rate of tolerability</td>
<td>- Higher rate of tolerability</td>
</tr>
<tr>
<td><strong>Transmission of TB</strong></td>
<td>Increased</td>
<td>Reduced</td>
</tr>
</tbody>
</table>

RIPE is well-tolerated (i.e., without adverse effects) in \(~90\%\) of cases, mild adverse effects in 6-8\% of cases, and severe adverse effects in 1-2\% of cases

Key Points

- The timely diagnosis of TB disease in all age groups requires an appreciation for the myriad of clinical and radiological (and laboratory and histopathological) features with which TB disease can present.

- A significant proportion (~20%) of patients with TB infection are not possible to detect with currently available immune-based tests.

- A significant proportion (~20%) of adult patients with TB disease are not possible to bacteriologically confirm with currently available pathogen-based tests.

- Both a diagnostic testing strategy, and a specimen collection strategy, are very important to optimize attaining an accurate diagnosis of the TB state of a patient.

- Given the very high morbidity and mortality of TB, and the effectiveness of therapy of each of the multiple states of TB (i.e., exposure-infection-disease), the initiation of therapy should not be delayed until positive immune-based or pathogen-based test results are obtained.
Acknowledgments

• Claudia L. Roya-Pabon, M.D. (Pediatric Pulmonologist)
Tuberculosis Control Program
Pima County Health Department

Clinical Unit
- Carlos M. Perez-Velez, M.D. (Adult & Pediatric Infectious Diseases)
- Nancy Kowalski, M.S.N., F.N.P. (Nurse Practitioner)
- Belinda Davis, R.N., B.S.N. (Nurse Case Manager)
- Susana Marr, R.N., B.S.N., M.S. (Nurse Case Manager)
- Tawnie Augustin, R.T. (Radiologic Technologist & Medical Assistant)
- Sylvia Molina (Treatment Adherence Community Health Worker)

Epidemiology Unit
- Anissa Taylor, M.P.H. (Epidemiologist)
- Fernando Silvas, B.S. (Disease Investigator)

Administrative Unit
- Susanna K. Feingold, M.P.H. (Program Manager)
- Yvette Piña (Administrative Assistant)

Education & Training Unit
- Claudia L. Roya-Pabon, M.D. (Pediatric Pulmonologist, Volunteer)
Tuberculosis Control Program
Pima County Health Department