Disclosure

- I serve as co-chair of the Evidence Synthesis subgroup of Stop TB Partnership’s New Diagnostics Working Group

- I am a member of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group
Overview

- Background
- Updated systematic review and meta-analysis
- Cost effectiveness model
- WHO/TDR Laboratory-based…report, 2008
Serological tests for TB

- Antibody-based immune assays
- Have been around for a long time
- Attractive, especially if made into point of care (POC)
- Existing serological tests have failed (3 systematic reviews)
Current situation

- No serological TB test for clinical use is recommended by international guidelines nor approved by the US Food and Drug Administration

- Dozens of commercial serological tests based on detection of antibodies are marketed in many parts of the world, especially in developing countries with weak regulatory systems
Based on a survey of 80+ Indian labs, some preliminary estimates:

• About 50 large and medium private labs alone are doing over 60,000 tests per month

• If all 20,000+ labs/hospitals in India are included, could easily exceed 120,000 per month [~1.5 million per year]

• @ $10 per test**, market is worth at least $15 million [this is highly conservative]

** Cost is actually ~$10 per antibody (e.g. IgG). Combination of all 3 antibodies (IgG, IgA, IgM) is often done at cost of >$30 per patient; for simplicity, we have used $10 per patient, a conservative estimate (RNTCP annual budget ~ $65 million)

Pai et al. Unpublished
Case study from India on how inaccurate serological tests for TB can do harm

- 25 year old male from Chhattisgarh presented with cough, fever, and weight loss for several months

- Seen at community health center where physician advised a TB serology test (USD $4.50)

- Result was negative for TB
Case study continued

• Patient was sent home with a Rx for vitamins and cough syrup

• Within a few weeks, his condition rapidly deteriorated

• Sputum smear microscopy was positive for acid-fast bacilli and the patient eventually died of his disease
LETTER FROM INDIA

A DEADLY MISDIAGNOSIS

Is it possible to save the millions of people who die from TB?

by Michael Specter

November 16, 2010

Michael Specter answers readers' questions about tuberculosis, Thursday at 3 p.m. E.T.
LETTER FROM INDIA

A DEADLY MISDIAGNOSIS

Is it possible to save the millions of people who die from TB?

BY MICHAEL SPECTER

Every afternoon at about four, a slight woman named Runi slips out of the cramped, airless room that she shares with her husband and their sixteen children. She skirts the drainage ditch in front of the building, then walks toward the pile of hardened dung cakes that people in this slum on the edge of the northeastern Indian city of Patna use for fuel. Dressed in a bright-yellow sari shot with gold threads, Runi is followed by several of her children. Although she can’t remember their ages, or her own, Runi must be about forty, because she of the National TB Control Program, told me when we met in New Delhi. “But there are thousands of labs. Shut one down and the next day ten more appear.”

Runi’s test was indeed worthless. It determined the presence of antibodies, which show that a body’s immune system has begun to respond to an infection. But most TB infections are latent: no more than ten per cent will ever cause illness. This means that ninety per cent of people with antibodies for TB in their blood don’t have the disease. Ru-

“Now she really is sick,” he continued, explaining that Runi’s TB was no longer dormant, and that taking drugs when they are not necessary often makes them ineffective when they are. “This is what happens when tests mislead us. She will need the drugs again. If they don’t work properly, she will be in real trouble. She has almost certainly infected some of her children. That makes everything harder, more expensive, more painful.”

Tuberculosis strikes vulnerable people with special ferocity. Victims are seized by severe night sweats, wasted by fatigue, and punished by the bloodtinged cough that is the disease’s defining symbol. In most cases, tuberculosis affects the lungs, but it can invade almost any organ of the body. When an infectious person coughs, sneezes, spits, or even shouts, he sends minute particles of sputum, or phlegm, into the air—ex-
Commercial serological tests for the diagnosis of tuberculosis: an updated systematic review and meta-analysis

Population - active TB, all ages, all countries
Intervention - commercial serological test
Comparison - microscopy smear
Outcomes – sensitivity and specificity

Reference standard – culture
Excluded studies published before 1990 and studies with < 10 TB cases
Results - Pulmonary TB
Flow of studies

Potentially relevant citations identified from electronic databases 4256

Excluded screen1: 4,101
*Reasons:
Duplicate publication: 1509
Relevance: 2592

Papers added from reference review and contact with experts 5

Full papers retrieved for more detailed evaluation 160

Excluded screen2: 149
*Reasons:
Active TB unspecified 1
Antigen detection 16
Could not obtain 1
Duplicate 3
Editorial, commentary 2
Extrapulmonary TB 2
Fewer than 10 TB cases 2
Insufficient data 9
Latent TB infection 2
Noncommercial 98
Other specimen 2
Reference standard lacking 9
Relevance 1
Review 1

Papers added from 2007 systematic review 20

Papers (studies) included in the systematic review of commercial serological tests for pulmonary tuberculosis 31 (67)
Study characteristics

- 67 studies used 18 different serological tests (anda-TB IgG most common, 19% of studies)
- 32 (48%) studies in low/middle-income countries
- Zero studies involved children; 1 study involved HIV-infected individuals
- Median TB patients 41 (IQR 33, 54)
- No studies reported on patient-important outcomes
Plot of sensitivity versus specificity for all 67 studies in the review

Sensitivity range: 0 to 100%
Specificity range: 31 to 100%
**Anda-TB IgG** (Anda Biologicals, Strasbourg, France) studies involving smear-positive patients

<table>
<thead>
<tr>
<th>Feature</th>
<th>Yes (high quality)</th>
<th>Unclear</th>
<th>No (low quality)</th>
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<tr>
<td>Representative spectrum?</td>
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<td>Acceptable reference standard?</td>
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<td>Acceptable delay between tests?</td>
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<td>Partial verification avoided?</td>
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<td>Differential verification avoided?</td>
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<td>Incorporation avoided?</td>
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<tr>
<td>Reference standard results blinded?</td>
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<tr>
<td>Index test results blinded?</td>
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<tr>
<td>Relevant clinical information?</td>
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<td>Uninterpretable results reported?</td>
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<td>Withdrawals explained?</td>
<td></td>
<td></td>
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<tr>
<td>Without conflict of interest?</td>
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</tbody>
</table>

Legend:
- **Green**: Yes (high quality)
- **Yellow**: Unclear
- **Red**: No (low quality)
## anda-TB IgG

### A. Smear +

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tr>
<td>Alifano 1994</td>
<td>35</td>
<td>2</td>
<td>7</td>
<td>92</td>
<td>0.83 [0.69, 0.93]</td>
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<tr>
<td>Alifano 1996 (a)</td>
<td>28</td>
<td>3</td>
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<td>41</td>
<td>0.85 [0.68, 0.95]</td>
<td>0.93 [0.81, 0.99]</td>
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<td>Kalartri 2005 (a)</td>
<td>84</td>
<td>0</td>
<td>21</td>
<td>40</td>
<td>0.80 [0.71, 0.87]</td>
<td>1.00 [0.91, 1.00]</td>
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<tr>
<td>Okuda 2004 (a)</td>
<td>28</td>
<td>10</td>
<td>6</td>
<td>101</td>
<td>0.82 [0.65, 0.93]</td>
<td>0.91 [0.84, 0.96]</td>
</tr>
<tr>
<td>Traunmuller 2005</td>
<td>32</td>
<td>21</td>
<td>6</td>
<td>58</td>
<td>0.84 [0.69, 0.94]</td>
<td>0.73 [0.62, 0.83]</td>
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<tr>
<td>Wu 2004 (a)</td>
<td>58</td>
<td>4</td>
<td>34</td>
<td>30</td>
<td>0.63 [0.52, 0.73]</td>
<td>0.88 [0.73, 0.97]</td>
</tr>
<tr>
<td>Wu 2005</td>
<td>35</td>
<td>19</td>
<td>30</td>
<td>40</td>
<td>0.54 [0.41, 0.66]</td>
<td>0.68 [0.54, 0.79]</td>
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</table>

### B. Smear –

<table>
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<tr>
<th>Study</th>
<th>TP</th>
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<th>FN</th>
<th>TN</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tr>
<td>Alifano 1996 (c)</td>
<td>23</td>
<td>3</td>
<td>13</td>
<td>41</td>
<td>0.64 [0.46, 0.79]</td>
<td>0.93 [0.81, 0.99]</td>
</tr>
<tr>
<td>Luh 1996 (b)</td>
<td>50</td>
<td>33</td>
<td>20</td>
<td>260</td>
<td>0.71 [0.59, 0.82]</td>
<td>0.89 [0.85, 0.92]</td>
</tr>
<tr>
<td>Okuda 2004 (b)</td>
<td>19</td>
<td>10</td>
<td>7</td>
<td>101</td>
<td>0.73 [0.52, 0.88]</td>
<td>0.91 [0.84, 0.96]</td>
</tr>
<tr>
<td>Wu 2004 (b)</td>
<td>30</td>
<td>4</td>
<td>56</td>
<td>30</td>
<td>0.35 [0.25, 0.46]</td>
<td>0.88 [0.73, 0.97]</td>
</tr>
</tbody>
</table>

### Bivariate meta-analysis pooled estimates

- **Smear+**  Sensitivity = 76% (63,87);  Specificity = 92% (74, 98)
- **Smear–**  Sensitivity = 59% (10,96);  Specificity = 91% (79, 96)

Steingart et al. Unpublished
Summary ROC plots for Anda-TB IgG showing better performance in studies of smear-positive patients (A) than in studies of smear-negative patients (B). The red squares are summary sensitivity and specificity.
Limitations

- Majority studies not representative or blinded
- Meta-analysis limited by small number of studies for a particular serological test
- Tests used different cut-points
- Children & HIV-infected individuals, data insufficient
- No data on patient-important outcomes
SeroLogic testing for tuberculosis in India: cost-effectiveness model
Hypothetical “Study Population”

- 1.5 million TB suspects
  - Conservative estimate of annual volume of serologic tests in India (sensitivity analysis on 3 mil)
- 1 in 7 actually have TB
  - Estimate from FIND, comparable to other studies
- Among TB patients, 53% are “highly infectious”
  - Would be diagnosed with 2 sputum smears in an ideal lab
- 5% HIV prevalence
  - 10% with access to ART (UNAIDS 2009)
  - Does not affect model results

David Dowdy, 2010 unpublished
What is the cost for 1.5 million TB suspects who undergo serologic testing in India?

- Diagnosis (Cost of Diagnostic Test)
- False-Positives (Wasted Money)
- TB Treatment (Desirable Costs)

David Dowdy, 2010 unpublished
Table 3. Cost-Effectiveness of Diagnostic Strategies for 1.5 Million TB Suspects in India, Relative

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Cost (US$)</th>
<th>Additional TB Cases Treated</th>
<th>Additional False-Positive Cases Treated</th>
<th>Secondary Cases Averted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum smear microscopy</td>
<td>$11.9 million</td>
<td>44,000</td>
<td>36,000</td>
<td>443,000</td>
</tr>
<tr>
<td>Sputum smear + TB culture</td>
<td>$45.0 million</td>
<td>71,000</td>
<td>48,000</td>
<td>555,000</td>
</tr>
<tr>
<td>Serological testing</td>
<td>$47.5 million</td>
<td>58,000</td>
<td>157,000</td>
<td>411,000</td>
</tr>
<tr>
<td>Rapid molecular testing</td>
<td>$52.8 million</td>
<td>86,000</td>
<td>12,000</td>
<td>629,000</td>
</tr>
</tbody>
</table>

David Dowdy, 2010 unpublished
WHO/TDR Laboratory-based…2008

- Rapid - test result (< 15 mins)
- Simple - 1 or 2 steps, minimal training and no equipment
- Easy to interpret - card or strip format with visual readout
- Gold standard - culture plus clinical follow-up
- Archived specimens
Table 4. Performance of 19 rapid tests for pulmonary tuberculosis

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Rapid Test</th>
<th>Sensitivity % (95% CI)</th>
<th>Specificity % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABP Diagnostics</td>
<td>Focus Sure Check TB</td>
<td>8 (4-11)</td>
<td>95 (92-99)</td>
</tr>
<tr>
<td>Advanced Diagnostics</td>
<td>Tuberculosis Rapid Test</td>
<td>40 (33-46)</td>
<td>53 (45-61)</td>
</tr>
<tr>
<td>American Bionostica</td>
<td>Rapid Test for TB</td>
<td>20 (15-26)</td>
<td>80 (73-86)</td>
</tr>
<tr>
<td>Ameritek dBest</td>
<td>One Step TB Test</td>
<td>34 (27-40)</td>
<td>68 (61-76)</td>
</tr>
<tr>
<td>BioMedical Products Corp</td>
<td>TB Rapid Screen Test</td>
<td>49 (42-56)</td>
<td>57 (49-65)</td>
</tr>
<tr>
<td>Chembio</td>
<td>TB Stat-Pak II</td>
<td>32 (25-38)</td>
<td>83 (76-89)</td>
</tr>
<tr>
<td>CTK Biotech TB Antibody</td>
<td>Onsite Rapid Screening Test</td>
<td>27 (21-33)</td>
<td>69 (62-77)</td>
</tr>
<tr>
<td>Hema Diagnostic</td>
<td>Rapid 1-2-3 TB Test</td>
<td>36 (29-42)</td>
<td>72 (65-80)</td>
</tr>
<tr>
<td>Laboratorio Silanes</td>
<td>TB-Instantest</td>
<td>38 (31-44)</td>
<td>70 (62-77)</td>
</tr>
<tr>
<td>Millenium Biotechnology</td>
<td>Immuno-Sure TB Plus</td>
<td>2 (0-5)</td>
<td>99 (97-100)</td>
</tr>
<tr>
<td>Minerva Biotech</td>
<td>V Scan</td>
<td>21 (16-27)</td>
<td>89 (84-94)</td>
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<tr>
<td>Mossman Associates</td>
<td>MycoDot</td>
<td>36 (30-42)</td>
<td>87 (81-92)</td>
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<tr>
<td>Pacific Biotech</td>
<td>Bioline TB</td>
<td>19 (14-25)</td>
<td>95 (91-98)</td>
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<tr>
<td>Premier Medical Corporation</td>
<td>First Response Rapid TB</td>
<td>21 (16-27)</td>
<td>95 (92-99)</td>
</tr>
<tr>
<td>Princeton BioMeditech</td>
<td>BioSign M tuberculosis</td>
<td>1 (0-2)</td>
<td>99 (97-100)</td>
</tr>
<tr>
<td>Span Diagnostics</td>
<td>TB Spot ver 2.0</td>
<td>38 (32-45)</td>
<td>78 (71-85)</td>
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<tr>
<td>Standard Diagnostics</td>
<td>SD Rapid TB</td>
<td>21 (15-26)</td>
<td>96 (93-99)</td>
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<tr>
<td>UniMED International Inc</td>
<td>FirstSign MTB Card Test</td>
<td>60 (53-66)</td>
<td>58 (50-66)</td>
</tr>
<tr>
<td>Veda Lab</td>
<td>TB Rapid Test</td>
<td>13 (8-17)</td>
<td>98 (96-100)</td>
</tr>
</tbody>
</table>
ROC curve, commercial rapid tests for the diagnosis of pulmonary TB (n=355)

Sensitivity range: 1 to 60%
Specificity range: 53 to 99%
In conclusion

- Published data on commercial serological tests produce inconsistent and imprecise estimates of sensitivity and specificity

- There is no evidence that existing serological assays improve patient-important outcomes
Acknowledgements

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