Value chain in action: the story of TB serology in India

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The story of Mohan... (some years ago)

- 'Mohan', 25 year old male from Chhattisgarh state in India
- Cough, fever for a number of months, and weight loss.
- Went to a private clinic in his area for help and the doctor there advised him to undergo a TB serology (antibody) test which cost him Rs. 200 at a local private laboratory
- The rapid serological test was NEGATIVE for TB
- Since this rapid antibody test showed negative, he was sent home with a prescription for some vitamins, iron, and a cough syrup.
PATIENT NAME: Parmat
AGE: 52
SEX: M
DATE: 01-03-08

ION: OBMH
OBSERVED VALUE: 9.2 GM %
NORMAL VALUE: F12-14 M.14-16 GM %
C. COUNT: / CUMM. 4000-12000/ CUMM.

C. COUNT
LEUCOCYTES: % 40-75%
MONOCYTES: % 20-40%
EOSINOPHILS: % 01-05
NEUTROPHILS: % 02-06%

GROUP: O+ MABAT THE END OF 1 ST HOUR
D.R.L.: 1-3 MTS
G.TIME: 2-6 MTS
TEST: T.B: Negative

2/5/08

1. Car Heemo Gold
2. Syrup Trisoli
3. Im Eldolvit 
4. Disposal Vain 5ml

Dr. Tarer

1274 1 Battal

Dr. Tarer
- Within a few days, his condition rapidly worsened, and a sputum smear test showed AFB +++
- Extensive bilateral disease
- Died shortly after….
- Totally preventable death
- In all likelihood, he infected several other people in his community, continuing the cycle of TB transmission in India...
Two weeks ago, I walked into a small lab in a town in India, and got tested for TB.

I paid $5 for the test.

Results in 15 minutes.
Thankfully, I was declared TB negative!
But the Government of India had banned TB serology as of 7th June 2012
Despite the success of India TB control programme, the reality is

- 2 million cases/year
- Nearly 1000 deaths/day
- Very slow decline in TB incidence
- Emergence of MDR/XDR/”TDR”
- Unregulated private sector that is hardly engaged in TB control
- No mandatory notification (no real handle on numbers)- until recently
- Under-funded TB control programme
The problem: the average TB patient in India is caught between two suboptimal options

In both sectors, delayed and undiagnosed cases result in ongoing transmission

Public sector

1. Weak capacity for molecular tests
2. Weak capacity for rapid innovation/experimentation with new tools
3. Heavily dependent on insensitive smears
4. TB suspects access the health system late
5. Poor penetration of RNTCP into general healthcare system
6. Weak sputum transport mechanisms
7. Unclear policy/algorithm for new diagnostics
8. Investments with unclear benefits (Culture/DST labs)
9. Weak engagement with private sector
10. Excessive focus on follow-up testing and MDR-TB
11. Long delays in lab accreditation
12. Paper-based reporting systems that are slow and inefficient

Private sector

1. Lack of attention to bottom of the pyramid
2. Lack of quality assurance
3. Widespread use of serology
4. Overtreatment based on CXR without confirmation
5. Underuse of molecular and culture tests
6. Lack of notification to RNTCP
7. Insufficient uptake of RNTCP schemes by private sector
8. Use of unvalidated technologies (e.g. in-house PCR)
9. Irrational TB treatment practices
10. Poor follow-up and monitoring of patients on treatment
TB treatment in the private sector

Treatment of tuberculosis by private general practitioners in India

W. UPLEKAR and D. S. SHEPARD

Tuberculosis Management by Private Practitioners in Mumbai, India: Has Anything Changed in Two Decades?

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1 Department of Respiratory Diseases, P.D. Hinduja National Hospital and Medical Research Centre, Mumbai, India. 2 Tuberculosis Department, World Health Organization, Geneva, Switzerland

Abstract

Setting: Mumbai, India. A study conducted in Mumbai two decades ago revealed the extent of inappropriate tuberculosis (TB) management practices of private practitioners. Over the years, India’s national TB programme has made significant progress in TB control. Efforts to engage private practitioners have also been made with several successful documented public-private mix initiatives in place.

Objective: To study prescribing practices of private practitioners in the treatment of tuberculosis, two decades after a similar study conducted in the same geographical area revealed dismal results.

Methods: Survey questionnaire administered to practicing general practitioners attending a continuing medical education programme.

Results: The participating practitioners had never been approached or oriented by the local TB programme. Only 6 of the 106 respondents wrote a prescription with a correct drug regimen. 106 doctors prescribed 63 different drug regimens. There was tendency to over treat with more drugs for longer durations. Only 3 of the 106 respondents could write an appropriate prescription for treatment of multidrug-resistant TB.

Conclusions: With a vast majority of private practitioners unable to provide a correct prescription for treating TB and not approached by the national TB programme, little seems to have changed over the years. Strategies to control TB through public sector health services will have little impact if inappropriate management of TB patients in private clinics continues unabated. Large scale implementation of public-private mix approaches should be a top priority for the programme. Ignoring the private sector could worsen the epidemic of multidrug-resistant and extensively drug-resistant forms of TB.


1990: 100 practitioners had prescribed 80 different drug regimens

2010: 106 doctors prescribed 63 different drug regimens
Market overlap points to irresponsible use of tuberculosis drugs

People with active tuberculosis infections turn to the private market for treatment far more often than anyone had realized. And when they do, they encounter a chaotic array of treatment choices, many of which do not meet guidelines drawn up by the World Health Organization. These are the conclusions of a paper published on 4 May that counters the prevailing wisdom that the vast majority of people with tuberculosis are treated through publicly funded programs.

The study, conducted by the New York–based Global Alliance for TB Drug Development (TB Alliance), a nonprofit that supports the development of new tuberculosis drugs, examined data on private sources of medicines, such as pharmacies and the companies that stock them. The information was collected by IMS Health, a private consultancy that analyzes pharmaceutical sales data, in ten countries that together bear 60% of the world’s tuberculosis burden.

The analysis, funded in part by the Seattle–based Bill & Melinda Gates Foundation, revealed that vast quantities of tuberculosis treatments are sold through the private market—enough to treat two thirds of the people who develop an active tuberculosis infection each year (PloS ONE 6, e18964, 2011). This puts the private market at about the same volume as the public market, the study found. And the discovery that the total in drug sales exceeds the number of cases points to overuse and improper use of last as long as eight months—or even up to two years for multidrug-resistant tuberculosis (MDR-TB). But in this large and messy private market, no one is ensuring that patients take adequate drug regimens or complete their operating private market as it is right now, you could spend all of this money developing new drugs, and you could lose them very quickly to resistance.”

Wells maintains that the problem can be
Undiagnosed TB and mismanaged TB continues to fuel the TB epidemic in India and elsewhere.

The Population Dynamics and Control of Tuberculosis

Christopher Dye and Brian G. Williams

More than 36 million patients have been successfully treated via the World Health Organization’s strategy for tuberculosis (TB) control since 1995. Despite predictions of a decline in global incidence, the number of new cases continues to grow, approaching 10 million in 2010. Here we review the changing relationship between the causative agent, Mycobacterium tuberculosis, and its human host and examine a range of factors that could explain the persistence of TB. Although there are ways to reduce susceptibility to infection and disease, and a high-efficacy vaccine would boost TB prevention, early diagnosis and drug treatment to interrupt transmission remain the top priorities for control. Whatever the technology used, success depends critically on the social, institutional, and epidemiological context in which it is applied.

“We conclude that control programs have been less effective than expected in cutting transmission mainly because patients are not diagnosed and cured quickly enough.” Dye & Williams, Science 2010
Early detection of Tuberculosis

AN OVERVIEW OF APPROACHES, GUIDELINES AND TOOLS
All barriers exist in India, but which is critical? Which barrier, if fixed, will be most impactful? Will a good test make a big difference if other issues are not fixed??

Figure 1. Pathways to TB diagnosis and treatment, and barriers or entry points for interventions to improve case detection and reduce delays in TB detection (numbers in parentheses represent the corresponding sections for each intervention area)
Both public and private sectors need to improve...

Here are some efforts...
On 20 July 2011, WHO published a historic first-ever negative policy in TB

WHO warns against the use of inaccurate blood tests for active tuberculosis (TB)

20 July 2011 | Geneva | WHO has called for countries to ban the use of serological (blood) tests to diagnose active TB disease in a policy issued today, which described the results from these blood tests as inaccurate and a major risk to the health of patients.

Despite the wide use of these blood tests, evidence reviewed by a WHO expert group and published today concluded that "commercial serological tests provide inconsistent and imprecise estimates" and that "it is strongly recommended that these tests not be used for the diagnosis of pulmonary and extra-pulmonary TB."

More than a million TB blood tests (also known as serodiagnostic or serological tests) are carried out every year, usually at a substantial cost to patients.

Today’s recommendation does not apply to serological tests for latent TB infection, currently under review by WHO and findings expected to be released next month.

For full information read the WHO news release on blood tests
How did we get here, and where are we going from here...
Serological (antibody-detection) tests for TB...

...have been around for a long time

...are attractive, especially if made into point of care tests

- But existing serological tests have variable accuracies and a limited clinical role (based on systematic reviews)
WHO/TDR study of 19 rapid serological tests...2008
While everyone acknowledged these problems

- Nobody quite acted on the evidence…

- While positive results often generate publicity and excitement, negative findings rarely evoke action

- How do you recommend against a test that nobody has ever recommended?!?

- WHO, for quite sometime, declined to consider a “negative” policy recommendation
Do we worry enough about “bad diagnostics”?

- While most regulatory and guideline bodies have mechanisms in place to withdraw or ban irrational/dangerous drugs and vaccines, there is little awareness about the consequences of bad diagnostics.
- In fact, there is little published data on the human and economic impact of bad diagnostics.
- One reason why agencies such as WHO did not act was the perception that TB serological tests were not widely used.
LETTER

Widespread use of serological tests for tuberculosis: data from 22 high-burden countries
Survey of 22 high burden countries re serological tests for TB: 17 of 22 use these tests!

In India alone, we estimate > 1.5 million tests @ over 15 million USD per year!

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Grenier J et al. ERJ 2012
The Indian market is full of antibody tests that claim to be nearly perfect!

Table 1. Serological assays for tuberculosis on the Indian market.

<table>
<thead>
<tr>
<th>Company</th>
<th>Kit</th>
<th>Assay Technique</th>
<th>Sensitivity and Specificity from Package Insert</th>
<th>URL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anda Biologicals, Strasbourg, France</td>
<td>anda TB-ELISA</td>
<td>ELISA</td>
<td>Not listed, refers to publications</td>
<td><a href="http://www.andabiologicals.com">http://www.andabiologicals.com</a></td>
</tr>
<tr>
<td>Omega Diagnostics, Alva, Scotland</td>
<td>Pathozyme TB Complex Plus</td>
<td>ELISA</td>
<td>37% and 100%</td>
<td><a href="http://www.omegadiagnostics.com">http://www.omegadiagnostics.com</a></td>
</tr>
<tr>
<td>Tulip Group, Goa</td>
<td>Qualisa TB</td>
<td>ELISA</td>
<td>100% and 99%</td>
<td><a href="http://www.tulipgroup.com">http://www.tulipgroup.com</a></td>
</tr>
<tr>
<td>Tulip Group, Goa</td>
<td>Serocheck-MTB</td>
<td>Rapid⁹</td>
<td>100% and 100%</td>
<td><a href="http://www.tulipgroup.com">http://www.tulipgroup.com</a></td>
</tr>
<tr>
<td>Span Diagnostics, Surat</td>
<td>TB Spot Ver 2.0</td>
<td>Rapid⁹</td>
<td>80% and 99%</td>
<td><a href="http://www.span.co.in">http://www.span.co.in</a></td>
</tr>
<tr>
<td>Bhat Biotech, Bangalore</td>
<td>Bhat Bioscan TB card</td>
<td>Rapid⁹</td>
<td>83% and 99%</td>
<td><a href="http://www.bhatbiotech.com/">http://www.bhatbiotech.com/</a></td>
</tr>
<tr>
<td>Span Diagnostics, Surat</td>
<td>Mycowell</td>
<td>ELISA</td>
<td>“Superior sensitivity and specificity”</td>
<td><a href="http://www.span.co.in">http://www.span.co.in</a></td>
</tr>
<tr>
<td>J Mitra, New Delhi</td>
<td>TB IgG, IgM, IgA Elisa</td>
<td>ELISA</td>
<td>80% and 97%</td>
<td><a href="http://www.jmitra.co.in">http://www.jmitra.co.in</a></td>
</tr>
<tr>
<td>JB Trop Dis Res Centre, Sevagram</td>
<td>SEVA TB ELISA</td>
<td>ELISA</td>
<td>97% and 99%</td>
<td><a href="http://www.jbtdrc.org/SEVA_TB.pdf">http://www.jbtdrc.org/SEVA_TB.pdf</a></td>
</tr>
<tr>
<td>S.D. Bio Standard Diagnostic India</td>
<td>SD BIOLINE Rapid TB</td>
<td>Rapid⁹</td>
<td>98% and 99%</td>
<td><a href="http://sdbiostandard.tradeindia.com/">http://sdbiostandard.tradeindia.com/</a></td>
</tr>
<tr>
<td>Bisen Biotech, Gwalior</td>
<td>TB SCREEN TEST</td>
<td>Rapid⁹</td>
<td>94% and 98%</td>
<td><a href="http://www.bisenbiotechindia.com">http://www.bisenbiotechindia.com</a></td>
</tr>
<tr>
<td>Lab-care Diagnostics Pvt Ltd, Sarigam</td>
<td>Accucare Rapid TB test</td>
<td>Rapid⁹</td>
<td>&gt;80% sensitivity and specificity</td>
<td><a href="http://www.labcarediagnostics.com/RapidTest_sub.html">http://www.labcarediagnostics.com/RapidTest_sub.html</a></td>
</tr>
<tr>
<td>Tashima Inc, Bangalore</td>
<td>TB IgG/IgM 3 Line Rapid test</td>
<td>Rapid⁹</td>
<td>93% and 100%</td>
<td><a href="http://www.tashima.net">http://www.tashima.net</a></td>
</tr>
</tbody>
</table>
Globally, there are more than 70 commercial TB serological kits!

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Name of the test</th>
<th>Manufactured by</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>One step TB test</td>
<td>Hangzhou Chongmei Biotech Co. Ltd.</td>
<td>China</td>
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<tr>
<td>2</td>
<td>TB Rapid diagnostic test</td>
<td>New-Scen Coast Bio-Pharmaceutical Co. Ltd.</td>
<td>China</td>
</tr>
<tr>
<td>3</td>
<td>TB sputum test and TB whole blood test</td>
<td>AcellaBiotec Ltd.</td>
<td>China</td>
</tr>
<tr>
<td>4</td>
<td>One Step Easy Use Accurate TB Rapid Test</td>
<td>Jiaxi Chemicals Ltd.</td>
<td>China</td>
</tr>
<tr>
<td>5</td>
<td>TB Test Cassette</td>
<td>World of Health Biotech Co. Ltd.</td>
<td>China</td>
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<tr>
<td>6</td>
<td>Diagnostic TB strip test</td>
<td>Beijing Easyway Biomedicine Science And Technology Co. Ltd.</td>
<td>China</td>
</tr>
<tr>
<td>7</td>
<td>TB Test kits</td>
<td>Shaanxi Huguan Biochip Co. Ltd.</td>
<td>China</td>
</tr>
<tr>
<td>8</td>
<td>One Step TB (recombinant) Rapid Tests</td>
<td>Orient Innovation E.I. (Beijing) Co. Ltd.</td>
<td>China</td>
</tr>
<tr>
<td>9</td>
<td>Anti-tuberculosis test</td>
<td>Beijing Kangshabao Imp &amp; Exp Co. Ltd.</td>
<td>China</td>
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<tr>
<td>10</td>
<td>TB test</td>
<td>Core Technology Co. Ltd.</td>
<td>China</td>
</tr>
<tr>
<td>11</td>
<td>TB test</td>
<td>Nanping Kao-Lashen Medical Instrument Company Ltd.</td>
<td>China</td>
</tr>
<tr>
<td>12</td>
<td>TB rapid Test</td>
<td>Hangzhou Chongmei Biotech Co. Ltd.</td>
<td>China</td>
</tr>
<tr>
<td>13</td>
<td>One Step accurate TB Rapid Cassette Test</td>
<td>Jilin Medical Co. Ltd.</td>
<td>China</td>
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<tr>
<td>14</td>
<td>TB tuberculosis rapid test kits (cassette)</td>
<td>Bioneer Co. Ltd.</td>
<td>Korea</td>
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<tr>
<td>15</td>
<td>iCARE TB Rapid Screen Diagnostic Test Kit</td>
<td>JAL Innovation (Pte Ltd.</td>
<td>Singapore</td>
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<tr>
<td>16</td>
<td>TB test Cassette</td>
<td>Nantong Fengs Biotechnology Co. Ltd.</td>
<td>China</td>
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<td>17</td>
<td>TB rapid Test</td>
<td>Zhejiang Cheqian Biotech Co. Ltd.</td>
<td>China</td>
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<td>18</td>
<td>Rapid TB test</td>
<td>Nongbo Qiaoao International Trade Co. Ltd.</td>
<td>China</td>
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<td>19</td>
<td>MTB Ab Rapid Test Kit</td>
<td>Shanghaidi Diagnostics Co. Ltd.</td>
<td>China</td>
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<td>20</td>
<td>One Step Anti-TB (M Tuberculosis)</td>
<td>K &amp; K-Chemoprotect Co. Ltd.</td>
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<td>TB rapid test</td>
<td>Debiao Biotechnological Co. Ltd.</td>
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<td>22</td>
<td>One Step Tuberculosis (TB) Antibody rapid Test Kit</td>
<td>Wuxi Med Tech Co. Ltd.</td>
<td>China</td>
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<td>23</td>
<td>One Step Mycobacterium tuberculosis (TB) Rapid Test Kit (Strip Cassette)</td>
<td>Jai Daniel Biotech Corp.</td>
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<td>EZ-TRUST Anti-Tuberculosis (TB) Rapid Screen Test Kit</td>
<td>CS Innovation Pte Ltd.</td>
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<td>25</td>
<td>Rapid TB test</td>
<td>Neocare Life Science Co. Ltd.</td>
<td>South Korea</td>
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<td>26</td>
<td>HR-TB-SCAN TB Card Test</td>
<td>Sabina Biotech India Pvt. Ltd.</td>
<td>India</td>
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<td>27</td>
<td>Accurate Rapid TB test</td>
<td>Labcare Diagnostics Pvt Ltd.</td>
<td>India</td>
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<td>SD BIOLINE Rapid TB Rapid Test</td>
<td>S.D. Bio Standard Diagnostic</td>
<td>India</td>
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<td>Serotech-MTB Rapid Test</td>
<td>Tulip Group (Zephyr Biomedical)</td>
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<td>TB SCREEN TEST Rapid</td>
<td>Bionetech</td>
<td>India</td>
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<td>TB Spot Var 2.0 Rapid test</td>
<td>Span Diagnostics</td>
<td>India</td>
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<td>AM rapid TB test</td>
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<td>dTest One step Tuberculosis test</td>
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<td>Rapid TB test</td>
<td>Bio-Medical Products Corporation</td>
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<td>TB Smp-Pak II</td>
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<td>CTK Biotech Inc.</td>
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<td>Rapid 1-2-3 HEMA Tuberculosis test</td>
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<td>TB Instant</td>
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<td>Immun+Sure TB Plus</td>
<td>Millennium Biotechnology Inc.</td>
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<td>V Scan</td>
<td>Minerva Biotech Corporation</td>
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<td>43</td>
<td>MyoDetect's 9 Easy Steps</td>
<td>Mission Associates Inc.</td>
<td>USA</td>
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<td>Bioline Tuberculosis test</td>
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<td>First Response Rapid TB Test</td>
<td>Premier Medical Corporation</td>
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<td>BiQuick Tuberculosis IgGaM Cassette</td>
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<td>TB antibody Rapid Test</td>
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<td>TB Spot Version 2.0</td>
<td>ViTech Meditech Inc.</td>
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<td>58</td>
<td>Human Immunoglobulins</td>
<td>Human Gesellschaft fur Biochemische und Diagnostik</td>
<td>Germany</td>
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<td>SDHO MTB</td>
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<td>TB IgM ELISA Immunoadsorbent Test Kit</td>
<td>Wuhan Kangshen Biotech Co. Ltd.</td>
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<td>AntiTB ELISA</td>
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<td>France</td>
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<td>Pathacteria TB Complex Plus and Pathacteria MYCO IgM, IgA, IgG</td>
<td>Omega Diag Ltd.</td>
<td>Scotland</td>
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<td>64</td>
<td>Detect TB</td>
<td>Aids—Advanced Laboratory Diagnostics Systems</td>
<td>Italy</td>
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<td>Tuberculosis Specific Antigen</td>
<td>Chengdu Pharmacia</td>
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<td>Mycobacterium tuberculosiis IgG</td>
<td>IBL, Hamburg</td>
<td>Germany</td>
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<td>Acid TB Detect</td>
<td>InBiotech International</td>
<td>USA</td>
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<td>68</td>
<td>TB Enzyme Immunomany</td>
<td>Krestech, Amsterdam</td>
<td>Netherlands</td>
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<tr>
<td>69</td>
<td>Determiner TB Glycolipid Assay</td>
<td>Kyowa Medex, Tokyo</td>
<td>Japan</td>
</tr>
<tr>
<td>70</td>
<td>Myocel ELISA test</td>
<td>Span Diagnostics</td>
<td>India</td>
</tr>
<tr>
<td>71</td>
<td>QuicksTB</td>
<td>Tulip Group</td>
<td>India</td>
</tr>
<tr>
<td>72</td>
<td>TB IgG, IgM, IgA ELISA</td>
<td>J Mitra</td>
<td>India</td>
</tr>
<tr>
<td>73</td>
<td>SEVA TB ELISA</td>
<td>JS TDR Centre, Seva gram</td>
<td>India</td>
</tr>
</tbody>
</table>
Market segmentation of TB serology in India

Large and private network labs

= ELISA - IgA, IgG, IgM

(mostly imported – e.g. Anda TB & Pathozyme)

Rs 300 – 750 per antibody
Market segmentation of TB serology

Small stand-alone labs

= 

RDTs - lateral flow/strip tests

(mostly domestic – e.g. TB IgG/IgM by SD Bioline ; TB Spot by Span, etc.)

Rs 250 - 500 per test

No capital investment or highly skilled personnel required
Growing awareness of the problem of bad diagnostics... and the magnitude of the problem in countries like India

>1.5 m serological tests in India per year
In 2010

- WHO finally agreed to consider a policy recommendation!
  - Updated meta-analysis was commissioned (Steingart et al. PLoS Med 2011)
  - Cost-effectiveness model was also conducted (Dowdy et al. PLoS Med 2011)
  - WHO EG meeting was held in summer of 2010
- WHO EG recommendations were endorsed by STAG in 2010
- Final WHO policy was published on 20 July 2011
Commercial Serological Tests for the Diagnosis of Active Pulmonary and Extrapulmonary Tuberculosis: An Updated Systematic Review and Meta-Analysis

Karen R. Steingart¹, Laura L. Flores²,³, Nandini Dendukuri⁴, Ian Schiller⁴, Suman Laal⁵,⁶,⁷, Andrew Ramsay⁸, Philip C. Hopewell²,³, Madhukar Pai⁴*

“Despite expansion of the literature since 2006, commercial serological tests continue to produce inconsistent and imprecise estimates of sensitivity and specificity. Quality of evidence remains very low.”

As an initial test for active TB among adults in India, serology results in more human suffering, secondary infections, and false-positive diagnoses than sputum smear microscopy, while increasing per-patient costs to the Indian TB control sector. In areas where high-quality sputum microscopy is available, adding MGIT culture (a WHO-recommended diagnostic test that generates far fewer false-positive results) is both more effective and less costly than adding serology.
Negative policy from WHO

- Commercial serological tests provide inconsistent and imprecise estimates of sensitivity and specificity. There is no evidence that existing commercial serological assays improve patient-important outcomes, and high proportions of false-positive and false-negative results adversely impact patient safety.

- Overall data quality was graded as very low, with harms/risks far outweighing any potential benefits (strong recommendation).

- It is therefore recommended that these tests should not be used in individuals suspected of active pulmonary or extra-pulmonary TB, irrespective of their HIV status.

- Note: WHO policy does not discourage research on TB serology… or ban the use of platforms such as ELISA or ICT
Immediately after the WHO policy, RNTCP released an advisory against serological tests.
India alert against TB blood tests

G. S. Mudur

New Delhi, July 20: India's health ministry has issued an unprecedented warning against the use of blood tests to detect antibodies to tuberculosis widely used in the private health care sector despite abundant evidence that they are unreliable and may endanger patients' lives.

The health ministry plans to circulate its advisory against the tests to medical associations across India amid concerns that about 1.5 million patients suspected to be infected by TB are taking the unnecessary tests each year on recommendations of private practitioners.

India's decision to warn the public about the blood tests for active TB disease follows a scientific review by the World Health Organisation (WHO) and a similar first-ever negative policy advisory from the WHO urging countries to ban the blood tests.

"It's sad that such tests with no predictive value at all are so widely used in our private sector," said Ashok Kumar, the head of the TB division in the health ministry. The tests are considered unreliable as they lead to unacceptably high levels of false positive and false negative results.

"False positive results would mean patients may be treated and become exposed to medications and their risks without reason, while false negative results may lead to patients with TB being denied the treatment they urgently need," Kumar said.

Blood test to detect TB is unreliable: WHO

Kashmir Raj, New Delhi, July 22, DHNS

The Union Health Ministry on Tuesday dispatched a letter to hundreds of officials and doctors associated with the National Tuberculosis Programme asking them not to use these antigen antibody tests due to their "inconsistent and inaccurate results.

A wrong diagnosis-common with these tests-means these with tuberculosis will not get the much needed therapy and continue to spread the disease, while people without the illness are subjected to unnecessary treatments leading to wasted resources and socio-economic impact on livelihood.

WHO says TB blood tests unreliable

OSmania University, August 2011

The World Health Organisation (WHO) has warned against using blood tests to detect tuberculosis (TB) due to unreliable results. The blood tests are conducted on about two million people every year to detect tuberculosis, of which the WHO says about half of the results are wrong.

"They are a waste of time, and they are a waste of money, and very importantly, they put at risk those people who suffer from TB," Mario Raviglione, director of WHO's Stop TB department said, while releasing a negative policy recommendation for the tests.

This comes after WHO started investigating the blood tests in 2005 after governments reported increase in prevalence of TB despite massive investments to private medical aid to the patients.

"The tests may have failed to detect TB and by the time it got detected it was too late," said a senior health ministry official.

The same goes for our guests.
Translating of the policy into practice in India...
We need to first understand why TB serologics became so popular in India

Why are inaccurate tuberculosis serological tests widely used in the Indian private healthcare sector? A root-cause analysis

Szymon Jarosławski a, Madhukar Pai b,*

a Institute of Bioinformatics and Applied Biotechnology, Bangalore, India
b McGill University, Montreal, Canada
Root causes for popularity of serology

- **Technical/medical:**
  - RNTCP’s low budget does not allow scale-up of newer, WHO-endorsed technologies. Thus, under the RNTCP, most patients have access to only smear microscopy, a test that is insensitive and underused in the private sector.
  - Because there is no accurate, validated, point-of-care test for TB, serological tests meet a felt need among doctors and patients.

- **Economic:**
  - While imported molecular or liquid culture tests are too expensive, there are no affordable Indian versions on the market, leaving serological tests as the main alternative.
  - Although serological tests are inaccurate, various players along the value chain profit from their use, and this sustains a market for these tests.

- **Regulatory:**
  - TB tests are poorly regulated and a large number of serological kits are on the market.
  - Private healthcare in general is poorly regulated, and doctors in the private sector are outside the scope of RNTCP and do not necessarily follow standard guidelines.
Why are sputum smears unpopular in the private sector?

| Reasons why sputum smear microscopy is not popular in the private sector in India. |
|---------------------------------|-------------------|-------------------|-------------------|
|                                | Doctors           | Patients           | Labs              |
| **Clinical**                   | Doctors think smears are not sensitive and are antiquated | Some patients are not able to produce sputum | Labs think that smears are antiquated and are keen on replacing them with a more modern technology |
|                                 | Sputum-based tests are not suitable for diagnosis of Extralmonary TB, smear-negative and childhood TB | | |
| **Practical**                  | Unlike tests such as chest X-ray, doctors cannot directly see the smear result (have to rely on lab interpretation) | Patients ask for a test that requires a single visit | ELISA is a "bench" technique and is perceived as "cleaner" than smear |
|                                 | Doctors have been told that 3 sputum specimens need to be examined and this is not convenient for patients and drop-outs are likely | | Technician training is necessary for microscopic examination of smear. |
|                                 | In case of respiratory infections or chronic fevers, patients are giving blood sample for blood counts / ESR and ELISA can be performed on the same sample | | RNTCP does not reach the private labs to give guidance on the quality assurance for sputum smears |
| **Economic**                   | Smears are cheap and referral fees are too low (referral fees to doctors are higher for x-rays, serology, PCR, etc.) | Some patients are ready to pay more than approximately 100 Rs for the smear if they believe that they are offered a better test | Smears are cheap and give low profit margins so labs do not promote them to doctors |
|                                 | Doctors want to start TB treatment to keep patients with them for 6 months, and because smear is perceived as having low sensitivity, they do not like to use it | | |
| **Cultural**                   | Doctors want to be perceived as "modern" by the community and refrain from antiquated techniques | Patients associate sputum with TB and that increases their fear of stigmatization; so, patients may prefer a blood-based test over sputum testing | Labs want to be perceived by doctors and by patients as "modern" and refrain from antiquated techniques |
If a new test has to succeed in India, how should it look like?

<table>
<thead>
<tr>
<th>Test characteristic</th>
<th>Rationale</th>
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<tr>
<td>Should be perceived by doctors as a more sensitive and sophisticated test than sputum smears</td>
<td>Doctors often fear under-diagnosis of TB. They do not want to miss a TB case for ethical as well as monetary reasons (the patient will be under their treatment for months). They fear that their reputation will suffer if they offer to patients sputum smears or refer them to an RNTCP centre.</td>
</tr>
<tr>
<td>Should be a rapid test — either a point-of-care test which can be done in the clinic or a laboratory test that can produce results within the same day</td>
<td>Given the doctor-centric nature of the private healthcare, doctors need to draw monetary benefit from the procedure. A rapid test result ensures that patients will stay with the doctors and will not dropout. Tests such as cultures are very unpopular among doctors because of the lengthy time delays and because they rarely influence doctor’s clinical decisions.</td>
</tr>
<tr>
<td>Should be done on blood or urine sample and a single test should be sufficient for diagnosis</td>
<td>Stigma related to TB makes sputum a less desired sample. Also, patients with suspected TB or chronic fevers often give blood samples for other lab tests (ESR, CBC) and this will make a test based on sputum disadvantaged as compared to a test which can be done on the same blood sample. Also, doctors might be afraid that patients will not show up for a second visit if more than one test is needed to make diagnosis.</td>
</tr>
<tr>
<td>Should be suitable for the detection of extrapulmonary TB</td>
<td>Neither sputum smear nor X-ray is suitable for detection of extrapulmonary TB. There is a highly unmet need for a test for this type of TB (gastro-intestinal TB in particular because it is considered a major cause of infertility in India).</td>
</tr>
<tr>
<td>Labs should not need to make big investments in infrastructure/equipment</td>
<td>Labs might be reluctant to invest in equipment/facility if they are not certain of a good volume of samples. This applies also to reagent rental schemes which oblige labs to buy a certain amount of reagents in a given time.</td>
</tr>
<tr>
<td>It should not be too cheap or too expensive, but be in the middle range of about rupees 500 (price to the patient) in the private sector</td>
<td>The current private health care system is to a large extent driven by referral fees which are about 20–50% of the price which patients pay for the test. Any diagnostic test to be successful in the current scenario must assure a referral fee to doctors in a range of 150–300 Rupees per patient. Patients’ affordability dictates that the test should not significantly exceed rupees 500 (approx. 10 US$) or so.</td>
</tr>
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Jaroslawski & Pai. JEGH 2012
Progress in the past few months...
TB budget is increasing, and new TB diagnostics is a key part of the next phase (2012 – 17)

Budget 2012: Rs 710 crore to combat tuberculosis in next fiscal

Kounteya Sinha, TNN  Mar 4, 2012, 03:01AM IST

Tags: Tuberculosis | Revised National TB Control Programme | health budget | Budget Allocation for TB | budget 2012

NEW DELHI: The annual budget to combat tuberculosis (TB), the deadly air-borne disease, for 2012-13 will see about 80% increase over last fiscal. While, the country's annual health budget is set to increase by a meagre 13% this year, the Planning Commission has decided to raise allocation for the TB control programme to about Rs 710 crore for 2012-13.

(The health ministry aims to roll out complete geographical coverage of multiple drug-resistant tuberculosis (MDR-TB) treatment services up to district level by 2013.)
Thanks to multiple overlapping efforts, the price of GeneXpert is now reduced to under $10

- But price is still high for private sector in high burden countries
- Import duties are high and TB does not fall under life-saving products for duty exemption
- How do we make molecular tests more affordable in the Indian private sector, so that serology can be replaced?
On 7th May 2012, GOI order on notification of TB cases

Z-28015/2/2012-TB
Government of India
Ministry of Health and Family Welfare

Nirman Bhavan, New Delhi
Dated: 7th May 2012

Notification of TB cases

TB continues to be a major public health problem accounting for substantial morbidity and mortality in the country. Early diagnosis and complete treatment of TB is the cornerstone of TB prevention and control strategy. Inappropriate diagnosis and irregular/incomplete treatment with anti-TB drugs may contribute to complications, disease spread and emergence of Drug Resistant TB.

In order to ensure proper TB diagnosis and case management, reduce TB transmission and address the problems of emergence and spread of Drug Resistant-TB, it is essential to have complete information of all TB cases. Therefore, the healthcare providers shall notify every TB case to local authorities i.e. District Health Officer / Chief Medical Officer of a district and Municipal health Officer of a Municipal Corporation / Municipality every month in a given format (attached).

For the purpose of case notification, a TB case is defined as follows:

- A patient diagnosed with at least one sputum specimen positive for acid fast bacilli, or Culture-positive for Mycobacterium tuberculosis, or RNTCP endorsed Rapid Diagnostic molecular test positive for tuberculosis OR

- A patient diagnosed clinically as a case of tuberculosis, without microbiologic confirmation, and initiated on anti-TB drugs.

For the purpose of this notification, healthcare providers will include clinical establishments run or managed by the Government (including local authorities), private or NGO sectors and/or individual practitioners.

For more detailed information, the concerned State TB Officers / District TB Officers, whose details are available on www.tbcindia.nic.in may be contacted.

Encl: As mentioned

(Manoj Sinha)
Under Secretary to the Government of India
On 7th June 2012, GOI order was notified on serology ban - historic, first ban on any diagnostic!
The ban, by itself, is unlikely to change anything...

**Sero test for TB continues despite ban**

Binod Dubey
*hitletters@hindustantimes.com*

**PATNA:** Despite a ban imposed by the Centre on the use of sero-diagnostic kits for diagnosis of tuberculosis, pathological laboratories in Bihar are rampantly using it, risking lives of patients.

Invoking the provisions of section 26(A) of the Drugs and Cosmetics Act, 1940, the Union ministry of health and family welfare has banned manufacture, sale and distribution of the kits, as they have resulted in inconsistent and inaccurate findings. A notification to this strongly recommended that these tests not be used for the diagnosis of pulmonary and extra-pulmonary TB (adult and
We need business models to help replace bad with validated tests
High-level, expert meeting on specimen transport and centralized TB testing project

Date: 20 June 2012

Venue: India Habitat Centre, Lodhi Road, New Delhi

Participants: High-level representatives from GOI (RNTCP/CTD) Donors (World Bank), Technical partners to the RNTCP (WHO, BMGF, CHAI, FIND, WHP, UNION), Industry (private laboratory service providers, diagnostics and device manufacturers, logistics/courier/ICT/supply chain experts), and advocacy groups (GHS, GHA).

Goals of the meeting:

1. To convene and engage various stakeholders who could potentially contribute to RNTCP’s vision of achieving universal access to quality TB diagnosis in public and private sectors.
2. To brainstorm and generate ideas which will inform new business models for engaging private laboratories in India to promote and deploy improved, RNTCP-approved tests for TB diagnosis.
3. To share the India TB diagnostics market analyses with private labs and diagnostic companies, to encourage more affordable, mass market pricing strategies for India, and attract more diagnostic companies (and technologies) into the TB space.
3 business models that we need to integrate in India:

- What the RNTCP can pay to the private sector for each TB case diagnosed?
- What diagnostic companies are willing to do re pricing, to make tests more affordable?
- What private labs are willing to do, to pass on the benefits to TB patients, and engage with RNTCP?
Getting BRICS to invest in affordable diagnostics development

Context and rationale

The scale-up of DOTS in India is a great public health accomplishment, and yet undiscovered and poorly managed TB continues to fuel the epidemic. Recognizing these challenges, the Government of India has set an ambitious goal of providing universal access to quality diagnosis and treatment for all TB patients. Innovative tools and delivery systems in both the public and private sectors are critical for reaching this goal. This current in-vitro diagnostics market in India is dominated by imported and generic products, virtually no innovations. But India has the potential to solve its TB problem with “home-grown” solutions, just as Indian pharma and biotech companies revolutionized access to high-quality, affordable AIDS drugs and hepatitis vaccines through generic production. Indian diagnostic companies could also become the world’s hub for high-quality generic diagnostics. India also has the potential to lead the world in developing innovative TB diagnostics. For this to happen, Indian industry must move from the import and imitation approach to genuine innovation in both product development as well as delivery. This will require permission policies, enhanced funding, and collaboration between government, donor, researchers, and the private industry. The goal of this conference is to engage these stakeholders to stimulate interest and investments in TB innovations.

India, Aug 2011

China, Sept 2012
India has the ability to develop accurate and affordable new TB diagnostics that can transform TB control.
Meeting industry needs = Market analyses + TPPs

Patients in India spend about $220 million on TB dx every year
TrueNAT MTB, Molbio (Indian fast-follower)
Advocacy for TB in India

India: As the middle class rises, so does tuberculosis

By Jason Overdorf
Create 2006-03-31 14:29

India must lead the way in developing new diagnostic tools for TB

As India grows, tuberculosis control must not be left behind

Tuberculosis does not normally receive much media or political attention within India. But thanks to the needless panic and fear caused by a report of a few cases of so-called totally drug-resistant tuberculosis in Mumbai, there is some interest at present. Much has been said and written in the media about totally drug-resistant tuberculosis, including discussion of whether it public health contribution by expanding basic directly observed therapy, short-course services to cover 100% of the Indian population—no mean feat in a country of 1.2 billion people. The programme has also successfully met the Stop TB targets for case detection and cure, and yet over 2 million cases of tuberculosis occur every year in India, with nearly 1000 deaths every day. In 2010, only

TB control in India: Time to get ambitious, innovative

Dr Madhukar Pai

The question: Can we intensify detection to turn the tide?

As India grows, tuberculosis control must not be left behind

Madhukar Pai
This story is evolving as we speak…

Thank you!