Replacing suboptimal with WHO-endorsed tests in India

Madhukar Pai, MD, PhD
Manjot Kaur, MD, MBA
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."

WHO is calling for countries to ban the use of blood tests to diagnose active TB after evidence shows the results are inaccurate. Pictured is a patient at a TB ward in Jordan undergoing a blood test.

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
A year later, on 7th June 2012, the Govt of India banned these tests - historic, first ban on any diagnostic!
This ban has created a big opening: for the Indian private sector to transition from suboptimal tests to WHO-endorsed products
TB Diagnostics in India: the big picture

- Despite the scale-up of DOTS, TB incidence continues to remain high
  - By the time TB cases are initiated on treatment in the RNTCP, they likely have already infected many others in the community
- Dominance of the private sector
  - First-contacts largely happen in the private sector where many providers are unqualified; >80% of India’s healthcare is private
  - Considerable delays in TB diagnosis
  - Patients often move from one provider to another, and between private and public sectors, before they are finally diagnosed and put on TB treatment.
The importance of private healthcare in India
70 – 80% of first contact care
>50% of TB care
Patient pathway to TB care in India

Figure 1. Pathways undertaken by the patients to reach the RNTCP (DOTS) Facilities, Delhi, India.

doi:10.1371/journal.pone.0092458.g001

Kapoor SK et al. PLoS ONE 2012
Diagnostic and treatment practices in the private sector

- **Diagnostic practices in the private sector**
  - While the public sector is all about sputum smears (99% of all TB tests), private sector, until recently, was heavily using inaccurate blood antibody tests for TB (~50% of all TB tests)
  - Patients pay out-of-pocket for suboptimal care
  - Drug regimens are chaotic and drug market is unregulated
- **Delayed or incorrect diagnosis and treatment** is a major driver of the TB epidemic, and reduction in TB transmission will require interventions to shorten delays and improve quality of care.
Tuberculosis Management by Private Practitioners in Mumbai, India: Has Anything Changed in Two Decades?

Zarir F. Usdawala1, Lancelot M. Pinto1,2, Mukund W. Uplekar2

1Department of Respiratory Diseases, P D Hinduja National Hospital and Medical Research Centre, Mumbai, India. 2Dept TB 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 national 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 a trend 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.


Tuberculosis by private general practitioners in India

W. UPLEKAR and D. S. SHEPARD1

Institute for Research in Community Health, Bombay, India and 1Department of International Health, Harvard School of Public Health, Boston MA, USA

Rmary — Early detection and optimal treatment constitute the most important measures in control of tuberculosis. This study of prescriptions for tuberculosis recommended by 102 doctors, practising in the slums of Bombay, shows a lack of awareness among doctors who treat tuberculosis patients in their own clinics about the standard drug regimens for treatment of tuberculosis recommended by national and international agencies. While there are a few standard, potent, recommended regimens, 100 private doctors prescribed 80 different regimens, most of which were both inappropriate and expensive. The study highlights the need for effective communication between those implementing national tuberculosis programmes and the practising doctors, continuing education of these doctors for updating their knowledge and their active participation in at least those national disease programme for which their curative functions could contribute significantly to control of a disease.

1990: 100 practitioners had prescribed 80 different drug regimens
2010: 106 doctors prescribed 63 different drug regimens
Private laboratory landscape in India

**Exact number and distribution is not known**

**Large lab networks**
- 6 lab chains with pan-India presence (SRL, Dr Lal Pathlabs, Thyrocare, Metropolis, Quest India, Vimta)
- Can perform sophisticated tests including culture and NAATs

**Regional lab networks**
- Strong presence in a limited geographic region through collection centers
- Can perform sophisticated tests including culture and NAATs

**Small local labs**
- Usually single-owner run, and tend not to have automated systems
- Most do not have any MD or PhD level lab professionals
- May account for the majority of lab testing in India (these labs are close to care providers/patients)
- Highly fragmented and unregulated
- Cannot offer sophisticated tests
- Can offer rapid diagnostics and simpler tests
Private labs in India

- While the exact number of laboratories in India is unknown (estimated to range from 20,000 to 100,000), only 400 laboratories have any sort of accreditation.
- Market structure – organized (only ~11%) and unorganized segments.
- Rapid growth of organized segment through the hub-and-spoke model:
  - 6 large network chains
  - But 1000s of small, stand-alone labs (number and quality unknown).
- Current value chain for diagnostic delivery – resulting in high patient price:
  - Private labs excluded from FIND negotiated pricing agreements – distributor prices are much higher than negotiated prices.
  - Import duties, lab and distributor margins, and provider incentives further inflate the price to patients (which can be as high as 3X or 4X the reagent costs).
  - This premium pricing approach has resulted in underuse of WHO-endorsed tests such as liquid culture, line probe assays and GeneXpert.
Market segmentation of TB serology in India (until the ban)

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 (until the ban)

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
The Indian market was full of antibody tests that claimed 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>Pathozone 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>Rapida</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>Rapida</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>Rapida</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_TBPdf.pdf">http://www.jbtdrc.org/SEVA_TBPdf.pdf</a></td>
</tr>
<tr>
<td>S.D. Bio Standard Diagnostic India</td>
<td>SD BIOLINE Rapid TB</td>
<td>Rapida</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>Rapida</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>Rapida</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>Rapida</td>
<td>93% and 100%</td>
<td><a href="http://www.tashima.net">http://www.tashima.net</a></td>
</tr>
</tbody>
</table>
Why did TB serologies 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?

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Reasons why sputum smear microscopy is not popular in the private sector in India.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Doctors</td>
</tr>
<tr>
<td>Clinical</td>
<td>Doctors think smears are not sensitive and are antiquated</td>
</tr>
<tr>
<td></td>
<td>Sputum-based tests are not suitable for diagnosis of Extrapulmonary TB, smear-negative and childhood TB</td>
</tr>
<tr>
<td></td>
<td>Unlike tests such as chest X-ray, doctors cannot directly see the smear result (have to rely on lab interpretation)</td>
</tr>
<tr>
<td></td>
<td>Doctors have been told that 3 sputum specimens need to be examined and this is not convenient for patients and drop-outs are likely</td>
</tr>
<tr>
<td></td>
<td>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</td>
</tr>
<tr>
<td>Economic</td>
<td>Smears are cheap and referral fees are too low (referral fees to doctors are higher for x-rays, serology, PCR, etc.)</td>
</tr>
<tr>
<td></td>
<td>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</td>
</tr>
<tr>
<td>Cultural</td>
<td>Doctors want to be perceived as &quot;modern&quot; by the community and refrain from antiquated techniques</td>
</tr>
</tbody>
</table>
If a new test has to succeed in India, how should it look like?

<table>
<thead>
<tr>
<th>Test characteristic</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<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 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 drop out. 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 (genito-urinary 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>
</tbody>
</table>
Recent changes in the landscape

- Recent government initiatives
  - Compulsory notification of TB cases
    - Until now, private sector was not required to notify
    - Development of a new web portal for tracking notifications - Nikshay
  - Ban on serological antibody tests, following 2011 WHO negative policy
    - India is the only country to have banned these tests
  - Ban got a fair bit of media attention and ads
- By summer of 2013, serological tests are hard to find in India!
**Let Us Stop Malpractices in TB Diagnosis**

MINISTRY OF HEALTH AND FAMILY WELFARE
(Deartment of Health and Family Welfare)

**NOTIFICATION**
New Delhi, the 7th June, 2012

O.S.R. 432(E)- Whereas the Central Government is satisfied that the use of the serodiagnostic test kits for diagnosis of tuberculosis are grossly inconsistent and imprecise results leading to wrong diagnosis, and the users are also at risk to human beings and therefore safer alternatives are available;
And whereas the Central Government is satisfied that it is necessary and expedient to prohibit the manufacture, sale, distribution and use of the said test kit in public interest;
Now, therefore, in exercise of the powers conferred by Section 26A of the Drugs and Cosmetics Act, 1940 (23 of 1940), the Central Government hereby prohibit the manufacture for sale, distribution and use of the following test kit with immediate effect:
"Serodiagnostic test kits for diagnosis of tuberculosis"

**Frequently asked questions on the notification**

Q. What is the consequence of inconsistent and imprecise results?
ANS: The dependence on such serodiagnostic test kits, can be harmful as many patients will end up undergoing TB treatment without any need for it as they are wrongly diagnosed as TB. At the same time, the test also misses many TB patients thus delaying treatment at the right time. Such patients will continue to suffer and even spread the infection to other healthy individuals.

Q. What is meant by “serodiagnostic test kits” for tuberculosis?
ANS: Serodiagnostic test are tests that detect the antibody response to tuberculosis causing bacteria in blood samples of suspected tuberculosis patients.

Q. Is the test kit applicable to Indian as well as imported TB serodiagnostic kit?
ANS: Yes, the test kit is applicable to all kits manufactured in India as well as all types of imported kits.

Q. How can TB be detected if all blood tests have been banned? Are there any alternative tests available?
ANS: Government of India has approved the following tests for diagnosis of TB:
- Sputum examination under microscope (SxM) test
- Culture test
- Newer molecular tests.

Q. What are interferon gamma release assay(IGRAs)?
ANS: IGRAs are laboratory blood test that measure the cell-mediated immune response to TB in infected individuals.

Q. In which situation should IGRA not be used?
ANS: IGRA blood tests have limited use as they cannot differentiate between active pulmonary TB disease and latent TB infection. Hence IGRA should not be used as stand alone tests to detect active TB disease.

**REVISED NATIONAL TUBERCULOSIS CONTROL PROGRAM**
Ministry of Health and Family Welfare, Government of India

---

**Revised National TB Control Programme**

SERODIAGNOSTIC TEST FOR THE DIAGNOSIS OF T.B. ARE BANNED

For Example: ELISA TEST FOR IgG, IgM & IgA FOR THE DIAGNOSIS of T.B. Are Banned In India.

VIOLATION CAN BE COMMUNICATED AT 011-23646049, EMAIL: stodi@mtcp.org

IGRAs (QUANTIFERON GOLD & T-Spot) are not recommended for the Diagnosis of T.B.

Issued in public interest by:
STATE TB CONTROL DEPARTMENT, DIRECTORATE OF HEALTH SERVICES, GOV'T. OF DELHI  Ph.: 011-23646049

For more information visit our website: www.tbcindia.nic.in, www.dotsdelhi.org

REGULAR AND FULL COURSE OF TREATMENT UNDER DOTS PREVENTS MDR/XDR TB
THE FACILITY OF DIAGNOSIS AND TREATMENT OF TUBERCULOSIS IS FREE AT 159 MICROSCOPY CENTERS AND 702 DOT CENTERS IN DELHI UNDER DOTS
But, some unexpected consequences...

- Since the ban on serology, private market has become chaotic:
  - Providers still want a rapid blood test

- Labs want a test that will give them sufficient channel margin
  - “TB serology, as all of us know, in my country, it had nothing to do with diagnosis of TB, it was asked only for sake of margin money, it created in market. It was creating INR Rs.1500 to 2000 as margin money in the market” [private lab owner]

- Banned antibody tests replaced by IGRAs (e.g. TB Gold, TB Platinum) and blood PCRs;

- WHO-endorsed tests are substantially more expensive than the banned serological tests
  - FIND-negotiated reduced price not available to private sector in India
  - Buy-down price of $9.98 for Xpert does not apply to private sector
Some of the large private labs have switched to QuantiFERON-TB Gold (marketed as “TB Gold”) for active TB diagnosis.

---

Dr Lal's PathLabs

Dear All

The following codes will be blocked and discontinued for registration in Axapta and reporting from 16 August onwards.

<table>
<thead>
<tr>
<th>Code</th>
<th>Test Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z105</td>
<td>MYCOBACTERIUM COMBO TEST PANNEL IgG, IgM, IgA, SERUM</td>
</tr>
<tr>
<td>S031</td>
<td>MYCOBACTERIUM COMBO TEST IgA SERUM</td>
</tr>
<tr>
<td>S032</td>
<td>MYCOBACTERIUM COMBO TEST IgG SERUM</td>
</tr>
<tr>
<td>S030</td>
<td>MYCOBACTERIUM COMBO TEST IgM SERUM</td>
</tr>
</tbody>
</table>

All locations to promote and register alternate test available

<table>
<thead>
<tr>
<th>Code</th>
<th>Test Description</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>B160</td>
<td>QUANTIFERON-TB GOLD; GAMMA INTERFERON</td>
<td>Rs 2250/-</td>
</tr>
</tbody>
</table>

Report - Sample by Monday through Saturday 4pm
Report Next day
New blood-based assays have emerged to take up the serology market

“Immucheck TB Platinum – The IGRA test method will be a boon for detection of active TB and LTBI and thus for containment of its transmission!!!!”

Open letters from TB CAB about these tests...

Treatment Action Group

14 May 2013

Peer M. Schatz
Chief Executive Officer and Managing Director
QIAGEN Benelux B.V.
Spoorstraat 30
3911 KJ Venlo
The Netherlands
Email: peer.schatz@qiagen.com

RE: Marketing and Use of QuantiFERON-TB Gold for active TB in India and high TB burden countries

Dear Mr. Schatz,

As you know, the Government of India banned the use of serodiagnostic antibody-based tests for TB in 2012. Treatment Action Group (TAG) and members of the Global TB Community Advisory Board (TB CAB) as well as civil society in India have been made aware that QIAGEN’s QuantiFERON-TB Gold, is now being used to detect active TB disease in the private sector (where serology use was rampant). Because of the void created by the serology ban, it appears that private laboratories have essentially replaced the banned serological tests with “TB-Gold” (please see the attached memo, sent to franchisees labs by a leading private network lab in India) and doctors now think this is a better serological test than the antibody enzyme-linked immunosorbent assays that existed until the ban.

The Indian Revised National TB Control Programme (RNTCP) has discouraged the use of interferon-gamma release assays (IGRAs) for TB diagnosis (please see the attached gazette notice by RNTCP), and a World Health Organization policy also states that IGRAs should not be used to diagnose active TB in high burden settings where the prevalence of latent TB infection (LTBI) is very high (nearly 40% of the Indian population is estimated to be latently infected and therefore positive by latent TB tests).

We are concerned that your test, which is indicated for LTBI detection only, is being used in an off-label manner, and are worried about the implications for individuals with suspected TB in India. We understand that you are marketing QuantiFERON-TB Gold as “TB Gold” (and not “Latent TB Gold”), which may lead users to believe it is the gold standard for active TB disease diagnosis. There is great potential for this test to become a replacement for antibody blood tests that the Government of India (and WHO) has worked so hard to ban. We are now aware of other IGRAs being sold in India as “TB

http://www.tbonline.info/
Challenge: how do we replace suboptimal tests with WHO-endorsed tools and make them more affordable?
Initiative for Promoting Affordable Quality TB Diagnostics in the Indian Private Sector

08 July 2013
TB in India: India has 3.8 Million patients and over 60% rely on treatment in the private sector

India suffers from the highest TB burden in the world

Breakdown of TB cases

- India 30%
- Rest of the World 80%

Total TB patients in the world (2011) = 11 million

Timely and accurate diagnosis is key to disease control

Impact of various interventions on TB cases reduction in India

- Most effective intervention: Reducing diagnostic encounters

Private sector plays a key role since it is the first point of contact for majority of patients

Break-up of TB suspects by sectors

- Public sector 40%
- Private sector 50%

Total TB suspects in India (2011) = 19 million

SOURCE: 1. RNTCP TB India Report 2011: Annual TB Incidence (India) is 2 million, prevalence is 3.8 million; 2. Goodchild et al. (2010). The health and economic burden of tuberculosis in India; 3. Analysis by Shekhar Menon and Minal Madhavankandi (IIMB) and CHAI
For diagnostic providers in private sector, serodiagnostic tests and in-house PCRs were preferred over WHO-approved tests.

**Higher commercial incentives on poor tests**

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Lab margins</th>
<th>Network margins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum smear</td>
<td>$0.8</td>
<td>$0.6</td>
</tr>
<tr>
<td>Serology</td>
<td>$5.5</td>
<td>$4.6</td>
</tr>
<tr>
<td>In-house PCR</td>
<td>$7.0</td>
<td></td>
</tr>
</tbody>
</table>

**Too many intermediaries in the value chain**

Ex-factory price (x)
Taxes & transport charges (1.3x)
Distributor margins (1.9x)
Reference lab margins (2.5x)
Franchisee lab margins (2.9x)
Provider margins (3.3x)
Patient price

**WHO-approved diagnostics are expensive**

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Price of WHO-approved tests in private sector¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear</td>
<td>$2</td>
</tr>
<tr>
<td>Hain</td>
<td>$58</td>
</tr>
<tr>
<td>GeneXpert</td>
<td>$64</td>
</tr>
<tr>
<td>MGIT + DST</td>
<td>$73</td>
</tr>
</tbody>
</table>

**Average monthly Household income of TB patients²**

- Sputum smear: $52
- Serology: $58
- In-house PCR: $64
- GeneXpert: $73

**Breakdown of TB tests in the private sector (2011)²**

- Serology, 52%
- Hain LPA, 0%
- Smear microscopy, 26%
- TB-Gold, 2%
- Culture, 10%
- PCR, 10%

**Annual TB tests in the private sector (2011) = 11.5 million*”

*Does not include TST and Chest X-ray

SOURCE: 1.Discussions with manufacturers (Cepheid), distributors (Labindia, Biomerieux) and labs; 2.CHAI and IIMB student analysis

NOTE: *Does not include TST and Chest X-ray
For manufacturers of WHO-approved tests, potential profits from the premium model were high, but volumes were limited.

Charging high prices for WHO-approved tests gave access to a small fraction of the total market…

### Monthly household incomes of the TB patients in the non-RNTCP segment

<table>
<thead>
<tr>
<th>Household income</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;$201</td>
<td>0.7%</td>
</tr>
<tr>
<td>$161-200</td>
<td>3.0%</td>
</tr>
<tr>
<td>$80-160</td>
<td>8.2%</td>
</tr>
<tr>
<td>&lt;$80</td>
<td>88.1%</td>
</tr>
</tbody>
</table>

Assuming a patient is willing to pay up to half a month’s household income for a TB test; at the premium price of $64, only 3.7% of market would be available.

…and although profit margins were high, the volumes were small.

### GeneXpert MTB/ RIF

<table>
<thead>
<tr>
<th>Manufacturer's profit (‘000)</th>
<th>Reagent volumes (‘000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$18,000</td>
<td>Maximum (12% premium market)</td>
</tr>
<tr>
<td>$15,000</td>
<td>439 (Base case (4% premium market))</td>
</tr>
<tr>
<td>$12,000</td>
<td>$5,284 (Minimum (0.7% premium market))</td>
</tr>
<tr>
<td>$9,000</td>
<td>439 (Minimum (0.7% premium market))</td>
</tr>
<tr>
<td>$6,000</td>
<td>439 (Minimum (0.7% premium market))</td>
</tr>
<tr>
<td>$3,000</td>
<td>439 (Minimum (0.7% premium market))</td>
</tr>
<tr>
<td>$0</td>
<td>439 (Minimum (0.7% premium market))</td>
</tr>
</tbody>
</table>

Ex-factory premium pricing ($19)

SOURCE: 1. Community-based survey conducted across 30 districts on ‘From Where Are Tuberculosis Patients Accessing Treatment in India?'; 2. CHAI analysis
that are highly exposed to the actual size of the premium market

Mass market strategy can yield significantly higher volumes and profit than a premium strategy…

Ex-factory premium pricing ($19)
Ex-factory mass market pricing ($10)

$35,367,335
$5,284,114

Reagent volumes
Installed bases
Manufacturer’s profit

GeneXpert MTB/ RIF

Relative profits varying by size of the premium market

Ex-factory premium pricing ($19)
Ex-factory mass market pricing ($10)

If the premium market as % of total market is <25%, then mass-market pricing would generate higher returns

SOURCE: CHAI analysis

NOTE: Assumes uptake rates of 100% of potential customers in the premium market and a premium market of 4% of total TB patient population.
IPAQQT emerged as a result of recent developments that presented an opportunity for various stakeholders.

Government ban on serological tests provided a chance for the public health community, diagnostics manufacturers and private sector labs to facilitate change...

IPAQQT emerged as a result of recent developments that presented an opportunity for various stakeholders.

... a partnership was set up to replace serology with appropriate and optimal tests.

Breakdown of TB tests in private sector²

- **ELISA**: 25%
- **Lateral flow assay**: 75%
- **Smear microscopy**: 26%
- **TB-Gold**: 2%
- **PCR**: 10%
- **Culture**: 10%
- **Serology**: 52%

**Diagnostic manufacturers**
- Huge revenue potential to capture serology market share

**Private labs**
- Need to replace serology volumes of with alternative tests

**Price of alternative tests to be comparable to serological tests (ELISA ~$20)**

**Annual TB tests in the private sector (2011) = 11.5 million*\**

**SOURCE**: 1.Discussions with manufacturers (Cepheid), distributors (Labindia, Biomerieux) and labs; 2.CHAI and IIMB student analysis; **NOTE**: *Excludes X-rays and TST**
CHAI engaged with manufacturers to make the WHO-approved tests available to the private sector at the same prices as the public sector.

The lower input prices of equipment and reagents made it possible for labs to make the test available at affordable prices to patients.

<table>
<thead>
<tr>
<th>Test type</th>
<th>Hain</th>
<th>GeneXpert</th>
<th>MGIT</th>
<th>Bact/Alert</th>
</tr>
</thead>
<tbody>
<tr>
<td>Line Probe Assay</td>
<td>Biomerieux (Distributor)</td>
<td>Cepheid (Manufacturer)</td>
<td>BD (Manufacturer)</td>
<td>Biomerieux (Manufacturer)</td>
</tr>
<tr>
<td>CBNAAT</td>
<td><strong>Final price - ₹1,600</strong>  (vs. ₹3,200-5,000)</td>
<td><strong>Final price - ₹1,700</strong> (vs. ₹3,000-5,000)</td>
<td><strong>Final price - ₹900</strong> (vs. ₹1,000)</td>
<td>Pricing model under development</td>
</tr>
<tr>
<td>Liquid culture</td>
<td>Liquid culture</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Although no volume guarantees have been agreed upon, it is strongly believed that these lower patient prices will result in wider uptake and higher profits for both the stakeholders in spite of the lower margins.
All stakeholders in the value chain agreed to drop their margins - translating into lower prices for the TB patient.

**Xpert MTB/ RIF**

- Pricing in the private sector
- Pricing through IPAQT

Although the per unit returns are lower, all the players could make higher aggregate returns on basis of higher volumes.

**Hain Genotype**

NOTE: 1. New price calculation accounts for a 5% error rate and assumes 80% utilization, advance payment and an outright equipment purchase model; *Calculated as a percentage of patient price minus franchisee lab margins and provider incentives; ** Calculated as percentage of patient price
The initiative was set up as a partnership of laboratories – and created a win-win-win partnership for all stakeholders

<table>
<thead>
<tr>
<th>Diagnostic manufacturers</th>
<th>NGOs and Academia</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Higher volumes</td>
<td>✓ Controlled patient price of quality TB tests</td>
</tr>
<tr>
<td>✓ Lower transaction costs</td>
<td>✓ Opportunity to influence diagnosis practices in the private sector through guiding principles</td>
</tr>
<tr>
<td></td>
<td>✓ Opportunity to ensure case notification transparency and quality</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>National TB Programme</th>
<th>Private laboratories</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Ability to track positive cases in the private sector for treatment follow-up</td>
<td>✓ Access to quality assured TB tests at lower prices</td>
</tr>
<tr>
<td></td>
<td>✓ Gain market share by offering better tests than non-IPAQT labs</td>
</tr>
</tbody>
</table>

| Patient in the Private Sector | | Key guiding principles of IPAQT – to be followed by all IPAQT labs |
|------------------------------|-------------------|
| ✓ Access to affordable quality diagnostics | Use of only high-quality TB tests |
| ✓ Faster diagnosis, thereby shortened time to proper treatment | - Only WHO/ RNTCP-approved tests to be included in IPAQT |
|                                           | - All member labs to undergo periodic EQA |

<table>
<thead>
<tr>
<th>Affordable price to patients</th>
<th>Linking diagnosis to treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>- The partner labs to charge the patients below a ceiling price</td>
<td>- The partner labs to notify all the positive cases to RNTCP</td>
</tr>
<tr>
<td>- GeneXpert – Rs. 1700</td>
<td></td>
</tr>
<tr>
<td>- Hain Genotype – Rs. 1600</td>
<td></td>
</tr>
<tr>
<td>- MGIT liquid culture – Rs. 900</td>
<td></td>
</tr>
</tbody>
</table>
IPAQT has made considerable progress since its start in September 2012

- Private sector labs use ~1000 GX tests in FY 2012-13
- GeneXpert at negotiated pricing
- No. of member labs = 5

Sept - 2012

- Two tests added - Hain LPA and MGIT Culture
- Test usage in pvt sector:
  - 5250 GX tests
  - 2500 LPA tests
- No. of member labs = 41 (~3000 franchise labs and +10,000 collection centers)

Jul - 2013

- Expansion of portfolio to include more approved tests - BacTAlert 3D and LED microscopes under discussion
- Increase the uptake of tests through demand generation activities
- Expansion to other geographies
- Further lowering of test costs

2014 (planned)

IPAQT currently has 41 member laboratories, including 5 of the 6 national lab chains; collection centers are present in 390 Indian districts (60% of total)
IPAQT is getting noticed as an innovative model for increasing affordability of quality diagnostics.
However, there are several challenges in managing the varied, often competing, interests of the different stakeholders:

### CHALLENGE

**Limited awareness about the ban on serology**
- Total serology testing market
  - Lateral Flow Assay, 75% (Small, standalone labs will continue serology)
  - ELISA, 25%
    - Large labs may discontinue serology

**Higher margins on in-house PCR tests and IGRAs**
- In-house PCR: ₹1600, GeneXpert: ₹1700
  - Cost to distributor: 83%
  - Distributor margins: 23%

**Poor Quality Control**
- Private laboratories may not always follow correct diagnostic protocols or quality control measures

**Resistance towards use of sputum as a sample**
- Patients, providers and laboratories dislike sputum and trend towards using blood as a sample for TB testing

### MITIGANT

**Collaborate with RNTCP and other partners to spread awareness about the serology ban**

**Targeted time-bound subsidy to create a market for the validated tests (under discussion)**
- Physician-directed awareness campaigns

**Only accredited labs accepted as IPAQT members**
- Only tests supported by clinical evidence to be offered

**Work with partner organizations like the Union who are already working on spreading awareness about the use of sputum as a sample for TB diagnosis**
We envisage three key factors for enabling success of IPAQT

Monitoring and Evaluation

- Activities on periodic basis:
  - Website for information; toll-free number, mystery calls for prices compliance
  - Quarterly External Quality Assurance (EQA) panel
  - Continuous follow up on labs for compliance with charter
  - Data gathering through remote monitoring (GXAlert)

Advocacy and demand generation

- Advocacy, Communication and Social Mobilization (ACSM) activities with partners
  - Physician directed CMEs and publications
  - Campaigns directed at patients’ education
  - Education of providers through sales forces of lab partners and drug manufacturers

National TB Program Support

- Work with the government and health ministry
  - Support in implementation of serology ban
  - Assist in case notification

A Governing Council has been set up to monitor and regulate the activities of IPAQT labs, and as a think tank for future plans

Dr Arvind Lal – Dr Lal Path Labs
Dr Sanjeev Chaudhary – SRL Diagnostics
Ms. Ameera Shah – Metropolis Labs
Dr Navin Dang – Dr Dang’s Laboratories

Dr Nalini Krishnan – TB REACH
Dr Madhukar Pai – McGill University
Dr Sarabjit Chadha – The UNION
Mr Harkesh Dabas - CHAI
Next Steps

**ICT: Key M&E component**
- GXAlert - application to track results remotely from IPAQT labs
- Plans for automated transfer of results to NIKSHAY (government’s case notification platform) – to support linkage of cases to appropriate treatment

**EQA**
- WHO-approved panels to be used for proficiency testing at all IPAQT labs

**Expansion Plans**
- Expansion to include other approved tests
- Expansion to other geographies with similar, large private sector diagnostics markets

*Illustration of dashboard to track results from IPAQT labs*
IPAQT’s vision is to continue to make quality TB tests widely available at affordable prices and to increase the adoption of these tests in the private diagnostics market. We will measure the impact of this initiative through 5 indicators:

- **Affordability** - % reduction in prices of WHO-endorsed tests and how it compares to prices of alternative tests on the market
- **Access** - % districts where IPAQT member labs operate, and number of collection centers where patients can visit for testing
- **Adoption** - Number of patients tested using WHO-endorsed tests, and trends over time (total volume of WHO-endorsed tests)
- **Replacement and Disruption of inappropriate tests** – Reduction in the volume of inappropriate tests among member labs, with a corresponding increase in the volume of WHO-endorsed tests; reduction in the price of WHO endorsed tests in the non-IPAQT labs because of competition from IPAQT member labs
- **Linkages** – % of TB cases diagnosed in the IPAQT network that are successfully notified to the RNTCP
Thank you!

Please visit www.ipaqt.org for more information