Chapter 1: Diagnosis of Pulmonary Tuberculosis: What Every GP Should Know

Madhukar Pai, MD, PhD—Author and Series Editor
1 in 4 TB patients live in India

THE WALL STREET JOURNAL

India in Race to Contain Untreatable Tuberculosis

By Geeta Anand

MUMBAI—India’s slow response to years of medical warnings now threatens to turn the country into an incubator for a mutant strain of tuberculosis that is proving resistant to all known treatments, raising alarms of a new global health hazard.

“We finally have ended up with a virtually untreatable strain” of tuberculosis in India, said Dr. Zahir Udawadi, one of the country’s leading TB authorities.

In December, Dr. Udawadi reported in a medical journal that he had four tuberculosis patients resistant to all treatment. By January, he had a dozen cases, then 15.

A government backlash began immediately. Anonymous health-ministry officials denied the reports through media outlets. They accused Dr. Udawadi and his colleagues of stirring a panic.

A Mumbai city health official seized patient samples for verification in government labs.

In April, the government quietly confirmed the strain, according to internal Indian health ministry documents reviewed by The Wall Street Journal.

Spread of the strain could return tuberculosis to the fatal plague that killed two-thirds of the people afflicted, before modern treatments were developed in the 1940s, said Mario Ravagnolo, director of the Stop TB Department of the World Health Organization. The WHO is now assisting India to combat the strain.

The number of known cases in India is small but geographically dispersed. Dr. Udawadi’s patients are in Mumbai, at the P.D. Hinduja National Hospital & Medical Research Center. In the high-tech hub of Bangalore, St. John’s National Academy of Health Sciences has seen six cases. And in New Delhi, the All India Institute of Medical Sciences has confirmed another two, said officials at the institutions.

“While this handful of cases is worrying, it’s just the tip of the iceberg,” said Dr. Soumya Swaminathan, of India’s National Institute for Research in Tuberculosis. For treatments, Dr. Udawadi said, “We’ve got nothing.”

Aashok Kumar, head of India’s tuberculosis control

How Fight to Tame TB Made It Stronger

The World Health Organization’s longstanding strategy for fighting tuberculosis is showing deadly unintended consequences. By focusing for years on the easiest-to-treat patients, it helped allow TB strains to spread that are now all but untreatable by modern medicine.

By Geeta Anand in Mumbai and Betsy McKay in Atlanta

The World Health Organization’s long-standing strategy for fighting tuberculosis is showing deadly unintended consequences. By focusing for years on the easiest-to-treat patients, it helped allow TB strains to spread that are now all but untreatable by modern medicine.

“The TB community has been too conservative,” said Dinesh Pujari, until recently a senior officer in the WHO’s India tuberculosis program. “We should have pushed sooner for a more aggressive, comprehensive approach toward drug resistance, he said this month in an interview.

“There was a cost to failing to do that. We’re paying that cost today.”

The WHO played a particularly sizable role in designing the tuberculosis program in India, which has seen a steep decline in regular TB. But India and other poor countries are now in the midst of an epidemic of drug-resistant strains—deadlier and harder-to-treat varieties of one of the world’s top infectious disease killers.

Dr. Harsh Vardhan, who heads India’s TB program more than a decade ago, called the epidemic of resistant TB in Mumbai “a recipe for disaster.” The WHO should have known it was so bad and bear responsibility, he said. “What has the WHO been doing?”

In pilot testing across India this year of a new diagnostic method, some 6.6% of untreated TB patients were drug-resistant—suggesting far higher rates than the 2% to 3% levels India and the WHO have cited for years. The test was a collaboration of international aid groups and India’s government.

At one clinic in Mumbai, research showed more than one quarter of 566 TB patients tested in recent months were resistant to the most powerful treatment, according to data obtained by The Wall Street Journal through India’s Right to Information Act. The results are preliminary. In the absence of any nationwide survey they offer a sense of what India’s drug-resistance rates might be.

Please turn to page A12
Why early and accurate diagnosis matters

An average TB patient in India is diagnosed with TB after a delay of 2 months, and is seen by 3 healthcare providers before diagnosis.

Private/informal sector was first point of care in >50%

http://www.letstalktb.org/
Only half of the health care providers were aware of the importance of suspecting TB in persons with cough of more than 2-3 weeks duration.
Substantial under-testing for TB, and empirical Rx

Point-of-care testing in India: missed opportunities to realize the true potential of point-of-care testing programs

Nora Engel1, Gayatri Ganesh2, Mamata Pati3, Vijayashree Yellappa2, Caroline Vodnaisi1, Nitika Pant Pai1 and Madhukar Pai2

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Use of standardised patients to assess quality of tuberculosis care: a pilot, cross-sectional study

Johnu Das, Aditi Varma, Benjamin Dandi, Shreethi Satyamangalam, Ramamurthi Subrahmanyan, Sapna Bagchi, Prashant K Das, Virende Das, Madhukar Pai2

Summary
Background Existing studies of the quality of tuberculosis care have relied on recall-based patient surveys, questionnaire surveys of knowledge, and prescription or medical record analysis, and the results mainly show the healthcare provider’s knowledge rather than actual practice. No study has used standardised patients to assess clinical practice. Therefore we aimed to assess quality of care for tuberculosis using such patients.

Use of standardised patients to assess quality of tuberculosis care

In their report, Johnu Das and colleagues showcase a unique method to assess quality of care and the know-do gap through use of standardised patients with tuberculosis. Their results

Gaps in quality of private care are the ubiquitous conclusion of most studies of management practices of providers. We suggest an alternative perspective. When the focus is on the diagnosis of one disease, as in the national tuberculosis programme, a narrow algorithmic approach results in early and appropriate testing. For the generalist private provider...
Objective of the presentation: to describe internationally accepted, best practices for the diagnosis of

- Active TB
- Drug resistant TB
- Latent TB infection

Based on WHO policies and International Standards of TB Care, 3rd edition & STCI, 1st edition

All policies and meta-analyses cited are available at: www.tbevidence.org
Diagnosis of active PTB

All patients, including children, with unexplained cough lasting two or more weeks or with unexplained findings suggestive of TB on chest radiographs should be evaluated for tuberculosis.

- ISTC, 3rd Edition
Recommended diagnostic options for pulmonary TB

• See the bugs [microscopy]

• Multiply the bugs [NAATs]

• Grow the bugs [cultures]
Key ISTC 3rd Ed. recommendation

“All patients, including children, who are suspected of having pulmonary tuberculosis and are capable of producing sputum should have at least two sputum specimens submitted for smear microscopy or a single sputum specimen for Xpert® MTB/RIF testing in a quality-assured laboratory.

Patients at risk for drug resistance, who have HIV risks, or who are seriously ill, should have Xpert MTB/RIF performed as the initial diagnostic test.

Blood-based serologic tests and interferon-gamma release assays should not be used for diagnosis of active TB.”
WHO-endorsed strategy for optimized microscopy: fluorescence staining, LED microscope, two samples, read by a trained technician with EQA

LED-FM pick up 20% more cases than conventional microscopy
Major advance: Xpert MTB/RIF

- Automated nested RT-PCR
- Simple 1-step specimen preparation
- Can be used at the point-of-treatment
- Results in 2 hours
- Detects TB and RIF resistance
WHO Recommendations (2013) for PTB and DST

Xpert MTB/RIF for the diagnosis of pulmonary TB and rifampicin resistance in adults and children

- Xpert MTB/RIF should be used rather than conventional microscopy, culture and DST as the initial diagnostic test in adults presumed to have MDR-TB or HIV-associated TB (strong recommendation, high-quality evidence).
- Xpert MTB/RIF should be used rather than conventional microscopy, culture and DST as the initial diagnostic test in children presumed to have MDR-TB or HIV-associated TB (strong recommendation, very low-quality evidence).
- Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial diagnostic test in all adults presumed to have TB (conditional recommendation acknowledging resource implications, high-quality evidence).
- Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial diagnostic test in all children presumed to have TB (conditional recommendation acknowledging resource implications, very low-quality evidence).
- Xpert MTB/RIF may be used as a follow-on test to microscopy in adults presumed to have TB but not at risk of MDR-TB or HIV associated TB, especially in further testing of smear-negative specimens (conditional recommendation acknowledging resource implications, high-quality evidence).

*Policy recommendations to be read in conjunction with the remarks in section 5.1*


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Global roll-out of Xpert MTB/RIF: over 15 million tests...


http://www.letstalktb.org/
Roll-out of Xpert is based on strong evidence

**Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults (Review)**

Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, Dendukuri N

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http://www.letstalktb.org/
Summary of updated Cochrane review of Xpert for PTB (based on 27 studies)

- Overall, compared to culture, Xpert detected 88% of TB cases with high specificity (99%)
  - Xpert sensitivity for smear-positive, culture+ TB = 98%
  - Xpert sensitivity for smear-negative, culture+ TB = 68%
- Used as an initial test replacing phenotypic DST, Xpert detected 95% of rifampicin-resistant TB cases with specificity of 98%

Steingart KR et al. Cochrane Database of Systematic Reviews, 2014
India has shown that Xpert can greatly increase MDR detection in adults & children.

“Compared with the baseline strategy of selective drug-susceptibility testing only for PTB cases at high risk of drug-resistant TB, Xpert MTB/RIF implementation increased rifampicin resistant TB case detection by over five-fold.”
Diagnosis of extrapulmonary TB (EPTB)

“For all patients, including children, suspected of having extrapulmonary TB, appropriate specimens from the suspected sites of involvement should be obtained for microbiological, and histological examination.

An Xpert MTB/RIF test is recommended as the preferred initial microbiological test for suspected TB meningitis because of the need for a rapid diagnosis.”

ISTC, 3rd Ed
Detecting EPTB

• Clinical suspicion
• Right sample – from site of the disease
• Options: need to use a combination of tests
  – Smears [likely to be negative]
  – NAAT [Xpert is now endorsed]
  – Culture [helpful but 2 – 3 weeks turn around time]
  – Biopsy [very helpful]
• If nothing works, empiric TB treatment
• No role for blood tests (antibodies or IGRAs)
  – Blood is NOT a sample for EPTB

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WHO Recommendations for EPTB

**Xpert MTB/RIF for the diagnosis of extrapulmonary TB and rifampicin resistance in adults and children**

- Xpert MTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test in testing cerebrospinal fluid specimens from patients presumed to have TB meningitis (strong recommendation given the urgency of rapid diagnosis, very low quality of evidence).

- Xpert MTB/RIF may be used as a replacement test for usual practice (including conventional microscopy, culture, and/or histopathology) for testing of specific non-respiratory specimens (lymph nodes and other tissues) from patients presumed to have extrapulmonary TB (conditional recommendation, very low quality of evidence).

*Policy recommendations to be read in conjunction with the remarks in section 5.2*
Evidence in EPTB

Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis


http://www.letstalktb.org/

Systematic review of Xpert for EPTB (included in the 2013 WHO policy)

<table>
<thead>
<tr>
<th>Sample</th>
<th>Sensitivity*</th>
<th>Specificity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph nodes</td>
<td>83%</td>
<td>94%</td>
</tr>
<tr>
<td>CSF</td>
<td>81%</td>
<td>98%</td>
</tr>
<tr>
<td>Pleural fluid</td>
<td>46%</td>
<td>99%</td>
</tr>
</tbody>
</table>

*Compared to culture as the reference standard


http://www.letstalktb.org/
Evaluation of Xpert MTB/RIF assay performance in diagnosing extrapulmonary tuberculosis among adults in a tertiary care centre in India

Xpert MTB/RIF assay can help in improving the diagnostic picture for extrapulmonary TB in lymph node and CSF http://ow.ly/yMjuk

Surendra K. Sharma¹, Mikashmi Kohli¹, Jigyasa Chaubey¹, Raj Naraya Vishnubhatla Sreenivas², Abhishek Sharma¹, Rohit Bhatia³, Deepali Ja¹Dept of Internal Medicine, All India Institute of Medical Sciences, N Institute of Medical Sciences, New Delhi, India. ³Dept of Neurology, AI India. ²Dept of Pathology, All India Institute of Medical Sciences, New Delhi, India.

Genotypic, Phenotypic and Clinical Validation of GeneXpert in Extra-Pulmonary and Pulmonary Tuberculosis in India

Urvashi B. Singh¹*, Pooja Pandey¹, Girija Mehta¹, Anuj K. Bhatnagar², Anant Mohan³, Vinay Goyal⁴, Vineet Ahuja⁵, Ranjani Ramachandran⁶, Kuldeep S. Sachdeva⁷, Jyotish C. Samantaray⁸

Xpert MTB/Rif for the diagnosis of extrapulmonary tuberculosis- an experience from a tertiary care centre in South India

Shirly Suzana³, Marilyn M Ninan¹, Mahasampath Gowri², K. Venkatesh³, Priscilla Rupali⁴, Joy S Michael⁵

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Pleural TB

• Pleural fluid
  – Adenosine deaminase or free interferon-gamma
  – Xpert MTB/RIF
  – Fluid cultures

• Pleural biopsy, if possible
  – Xpert MTB/RIF on tissue
  – Tissue bits sent for liquid cultures
  – Histopathology of tissue
Genitourinary TB

• Urine
  – Xpert MTB/RIF
  – Liquid cultures

• Endometrial curettage
  – Xpert MTB/RIF on tissue
  – Tissue bits sent for liquid cultures
  – Histopathology

• Menstrual blood is not a good sample

http://www.letstalktb.org/
Liquid cultures for PTB and EPTB

- “Gold Standard” and WHO-endorsed
- High Sensitivity, Isolate Available for DST and molecular typing
- Ideal test for smear-negative and EPTB
- 2 week turn-around time
- Very helpful for treatment monitoring
- Now more affordable via IPAQT

http://www.letstalktb.org/
Evidence in childhood TB

Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis in children: a systematic review and meta-analysis
Anne K Detjen, Andrew R DiNardo, Jacinta Leyden, Karen R Steingart, Dick Menzies, Ian Schiller, Nandini Dendukuri, Anna M Mandalakas

- Compared with culture, the pooled sensitivities and specificities of Xpert for TB detection:
  - 62% and 98% with expect or induced sputum
  - 66% and 98% with gastric juice
- Xpert sensitivity was 36–44% higher than smears
- For rifampicin resistance, sensitivity was 86% and specificity was 98%

Lancet Resp Med 2015
http://www.letstalktb.org/
How to diagnose childhood TB?

- History of TB contact
- Abnormal CXR
- Positive Mantoux
- Smear microscopy
- GeneXpert
- Liquid cultures
What about immune-based tests for active TB?

2.3 Serological tests:
   • Serological tests are banned and not recommended for diagnosing tuberculosis.

2.4 Tuberculin Skin Test (TST) & Interferon Gamma Release Assay (IGRA)
   • TST and IGRA are not recommended for the diagnosis of active tuberculosis. Standardised TST may be used as a complimentary test in children.

http://www.letstalktb.org/
What about chest X-rays?

- Excellent screening test
- High sensitivity for TB
- Inexpensive
- Easy access in urban areas
- High yield of GeneXpert positives among those with x-ray abnormalities

But since specificity is modest, CXR should be followed-up by a microbiological test (smears or GeneXpert)
Detecting Drug Resistance: towards universal DST

“DST should be performed at the start of therapy for all patients at a risk of drug resistance...” ISTC, 3rd Ed

http://www.letstalktb.org/
INTRODUCING
THE
END TB
STRATEGY

How pillar 1 works: Key components

A. Early diagnosis of TB including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups

B. Treatment of all people with TB including drug-resistant TB, and patient support

C. Collaborative TB/HIV activities; and management of co-morbidities

D. Preventive treatment of persons at high risk; and vaccination against TB

http://www.who.int/tb/End_TB_brochure.pdf
In cities like Mumbai, ALL TB patients should get a DST!
We should move towards universal DST for ALL TB patients in India

http://www.letstalktb.org/
Q: What is the quickly route to universal DST?

Answer: Rapid molecular TB testing, followed by culture confirmation

http://www.letstalktb.org/
Xpert MTB/RIF is a rapid DST option

- RIF resistance is a strong correlate of MDR-TB
  - One study from AIIMS showed reduced sensitivity in cases with RIF mono-resistance (Singh S, JCM 2014)
  - Not clear if RIF mono-resistance is a major problem in India

- Xpert detects 95% of rifampicin-resistant TB cases with specificity of 98%

- RIF resistance can be used to make rapid treatment decisions, but will need to be confirmed by culture and DST (or LPA)


http://www.letstalktb.org/
Line Probe Assays

WHO policy statement: molecular line probe assays for rapid screening of patients at risk of multidrug-resistant tuberculosis

2008

GenoType MTBDRplus assay
Hain Lifescience GmbH, Germany

GenoType MTBDR assays for the diagnosis of multidrug-resistant tuberculosis: a meta-analysis

D.I. Ling*, A.A. Zwerling* and M. Pai*,

98% sens and 99% spec for RIF
84% sens and 99% spec for INH

http://www.letstalktb.org/
Sensitivity and specificity for RIF: 96% and 99%

Sensitivity and specificity for INH: 72% and 97%

Average time to MDR-TB Rx reduced from 157 days to 38 days
Conventional Drug Susceptibility Testing

• Agar Proportion Method
  – Long turn-around times (2 months)
  – Inexpensive
  – Limited impact on clinical decisions

• Liquid cultures
  – High accuracy
  – 2 weeks turn-around time
  – Can inform treatment decisions
  – Only technology that can assess resistance to first and second line drugs
  – Should be used more widely

http://www.letstalktb.org/
Suspected drug-resistance → Rapid molecular test (Xpert MTB/RIF) → If RIF positive, begin MDR-TB Rx

Modify MDR therapy based on DST profile → Liquid Culture and DST

“For patients in whom drug resistance is considered to be likely an Xpert MTB/RIF test should be the initial diagnostic test. If rifampicin resistance is detected, culture and testing for susceptibility to isoniazid, fluoroquinolones and second-line injectable drugs should be performed promptly if RIF resistance is detected.” – ISTC, 3rd Ed

http://www.letstalktb.org/
Diagnosis of latent tuberculosis infection (LTBI): goal is to prevent active TB by giving preventive therapy

Systematic testing and treatment of LTBI should be performed in people living with HIV, adult and child contacts of pulmonary TB cases, patients initiating anti-tumour necrosis factor (TNF) treatment, patients receiving dialysis, patients preparing for organ or haematologic transplantation, and patients with silicosis. Either interferon-gamma release assays (IGRA) or Mantoux tuberculin skin test (TST) should be used to test for LTBI. (*Strong recommendation, low to very low quality of evidence*).

Treatment options recommended for LTBI include: 6-month isoniazid, or 9-month isoniazid, or 3-month regimen of weekly rifapentine plus isoniazid, or 3–4 months isoniazid plus rifampicin, or 3–4 months rifampicin alone. (*Strong recommendation, moderate to high quality of evidence*).


http://www.letstalktb.org/
How do we test for LTBI?

• **Tuberculin skin test**
  – Mantoux method, using purified protein derivative (PPD)
• **Interferon-gamma release assays (IGRAs)**
  – QuantiFERON-TB Gold In Tube (TB Gold)
  – T-SPOT.TB
  – TB Platinum

• *Neither test can separate latent infection from active disease*
• Both Mantoux and IGRAs are valid for latent infection but imperfect


http://www.letstalktb.org/
Do Indian physicians treat LTBI?
Data from previous IPAQT CMEs

Hyderabad

<table>
<thead>
<tr>
<th>How often do you treat latent TB infection in your clinical practice? This means giving isoniazid (INH) for 6 - 9 months, to prevent latent infection from progressing to active TB disease. (N=51)</th>
</tr>
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<tbody>
<tr>
<td>Never</td>
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<tr>
<td>30</td>
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<td>59%</td>
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Mumbai

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<th>How often do you treat latent TB infection in your clinical practice? This means giving isoniazid (INH) for 6 - 9 months, to prevent latent infection from progressing to active TB disease. (n=26)</th>
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<tr>
<td>Never</td>
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<tr>
<td>14</td>
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<td>54%</td>
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Chennai

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<th>How often do you treat latent TB infection in your clinical practice? This means giving isoniazid (INH) for 6 - 9 months, to prevent latent infection from progressing to active TB disease. (N=56)</th>
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<tr>
<td>Never</td>
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<tr>
<td>15</td>
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<tr>
<td>27%</td>
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Kolkata

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<th>How often do you treat latent TB infection in your clinical practice? This means giving isoniazid (INH) for 6 - 9 months, to prevent latent infection from progressing to active TB disease. (n=21)</th>
</tr>
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<tbody>
<tr>
<td>Never</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>38%</td>
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Key message: Mantoux and IGRAs should be restricted for latent infection screening of high risk groups

- If used for persons with suspected active TB, these tests will be positive in a large proportion (since ~40% of Indians have latent infection)

- Serious over-treatment with ATT with economic and health consequences for patients [Little K et al. PLoS One 2015]

- If used to diagnose and treat latent infection, then active disease must be RULED OUT, before starting INH therapy
Management of latent tuberculosis infection: An evidence-based approach

Figure 1: World Health Organization algorithm for latent tuberculosis infection management. Source: Adapted from WHO, Geneva®
What will the future look like?

http://www.letstalktb.org/
Let's Talk TB

In 2015, 2.2 million people developed TB in India...

« Explore and learn the best practices in the diagnosis and treatment of TB »

www.letstalktb.org