Diagnosis of PTB, EPTB and MDR-TB

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Conflicts of interest

No financial/industry conflicts
  No industry funding, stocks, consultancies, advisory boards

I serve as a consultant to the Bill and Melinda Gates Foundation

I serve on the Governing Council of IPAQT
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 growing 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. Zarin Udoudia, one of the country's leading TB authorities.

In December, Dr. Udoudia, 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. Udoudia and his colleagues of starting a panic. A Mumbai city health official said patient samples for confirmation 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 people afflicted, before modern treatments were developed in the 1940s, said Mario Raviglione, 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. Udouida's patients are in Mumbai, at the RD. Bajaj Hospital & Research Center. In the high-tech hub of Bangalore, St. John's National Academy of Medical Sciences has seen six cases. And in New Delhi, the All India Institute of Medical Sciences has confirmed another two, said officials at the institution.

"While this handful of cases is worrying, it's just the tip of the iceberg," said Dr. Kumar, director, of India's National Institute for Research in Tuberculosis. For treatments, Dr. Udoudia said, "We've got nothing."

Ashok Kumar, head of India's tuberculosis-con

How Fight to Tame TB Made It Stronger

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.

By Geeta Anand in Mumbai and Betty McKay in Atlanta

The WHO and a growing chorus of global health experts are now calling for a significant overhaul in the way nations with widespread drug-resistant TB combat the disease. It amounts to a de facto acknowledgment that the WHO's TB strategy, and the countries that use it, failed to adapt quickly enough as the disease formed more powerful, resistant strains.

"The TB community has been too conservative" on a global scale, said Pameet Dhowan, until recently a senior officer in the WHO's India tuberculosis program. "We should have pushed sooner for a more aggressive, comprehensive approach to treatment." To resist.

he said this month in an interview. "There was a cost in 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.

G.R. Khatri, who headed 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 60% 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 the 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, but 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

Delays in diagnosis and treatment of pulmonary tuberculosis in India: a systematic review

C. T. Sreeramareddy,* Z. Z. Qin,† S. Satyanarayana,† R. Subbaraman,‡ M. Pai†

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• 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%
Quality of tuberculosis care in India: a systematic review

S. Satyanarayana,* † R. Subbaraman,‡§ P. Shete,¶ G. Gore,# J. Das,** A. Cattamanchi,‖ K. Mayer,†† D. Menzies,‡‡ A. D. Harries,†‡§ P. Hopewell,¶ M. Pai*

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47 studies from India
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.
Several initiatives to improve diagnostic and treatment practices
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 picked up 20% more cases than conventional microscopy

“We recommend replacing conventional microscopy with LED-FM in high workload microscopy centres in India.”
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
Updated WHO policy on Xpert MTB/RIF
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*
Global roll-out of Xpert MTB/RIF: over 10 million tests…

As of 31 December 2014, a total of 3,763 GeneXpert instruments (comprising 17,883 modules) and 10,013,600 Xpert MTB/RIF cartridges had been procured in the public sector in 116 of the 145 countries eligible for concessional pricing.

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

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.”

Sachdeva KS et al. PLoS ONE 2015

Raizada N et al. PLoS ONE 2015
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
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

Claudia M. Denkinger¹,², Samuel G. Schumacher², Catharina C. Boehme⁴, Nandini Dendukuri²,³, Madhukar Pai²,³ and Karen R. Steingart⁵


Diagnostic accuracy of the Xpert MTB/RIF assay for extrapulmonary and pulmonary tuberculosis when testing non-respiratory samples: a systematic review

Maynard-Smith et al. BMC Infectious Diseases (2014) 14:709
DOI 10.1186/1471-2334-14-709-7

Laura Maynard-Smith¹, Natasha Larke⁶, Jurgens A Peters¹ and Stephen D Lawn¹,⁷
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>
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</table>

*Compared to culture as the reference standard
EPTB: evidence from India

Evaluation of Xpert MTB/RIF assay performance in diagnosing extrapulmonary tuberculosis among adults in a tertiary care centre in India

Conclusion: This assay performs better than the currently available conventional laboratory methods. The rapidity with which results are obtained is an added advantage, and its integration into a routine diagnostic protocol must be considered.
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
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
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%
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.
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)
Diagnostic Algorithm for Pulmonary TB

PLHIV → Presumptive TB Case

- Smear Examination
- CXR

Smear Positive & CXR suggestive of TB → Smear Positive but CXR not suggestive of TB

Smear Negative but CXR suggestive of TB → Smear Negative or not available/CXR not suggestive of TB or not available

Clinical Suspicion High

CBNAAT

- PMDT criteria, high MDR settings
- MTB Positive
- MTB Negative or CBNAAT result unavailable

Consider alternative diagnosis and refer to specialist

Rif Sensitive → Rif Indeterminate → Rif Resistant

Follow PMDT Guidelines

Microbiologically confirmed MTB → Repeat CBNAAT on 2nd sample → Indeterminate on 2nd sample, collect fresh for LC/LPA

# : Settings identified as per Global Guidelines & the programme data
CBNAAT: Cartridge Based Nucleic Acid Amplification Test
CXR: Chest X-ray
MTB: Mycobacterium Tuberculosis

Source: RTNCP
Detecting Drug Resistance: towards universal DST

“DST should be performed at the start of therapy for all patients at a risk of drug resistance. Patients who remain sputum smear-positive at completion of 3 months of treatment, patients in whom treatment has failed, and patients who have been lost to follow-up, or relapsed following one or more courses of treatment should always be assessed for drug resistance...” ISTC, 3rd Ed
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

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

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

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

India should screen all tuberculosis patients for drug resistant disease at diagnosis
India’s national programme needs to embrace comprehensive screening and test for the isoniazid mono-resistance that precedes multidrug resistant disease, says Yogesh Jain

Yogesh Jain public health physician and paediatrician, Jan Swasthya Sahyog (People’s Health Support Group), Village and Post Office Ganiyari, Bilaspur 495112, India
Q: What is the quickly route to universal DST?

Answer: Rapid molecular TB testing, followed by culture confirmation
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)
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

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

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

D.L. Ling*, A.A. Zwerling* and M. Pai*<sup>a</sup>
India: evidence on LPA

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
Algorithm for DST: very important to complete this!

Suspected drug-resistance → Rapid molecular test (Xpert MTB/RIF) → If RIF positive, begin MDR-TB Rx

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

“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
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).
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
Do Indian physicians treat LTBI?
Data from previous IPAQT CMEs

**Hyderabad**

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)

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<td>30</td>
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<td>4</td>
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<td>Percent</td>
<td>59%</td>
<td>29%</td>
<td>8%</td>
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**Mumbai**

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)

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<tr>
<td>Percent</td>
<td>54%</td>
<td>38%</td>
<td>4%</td>
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**Chennai**

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)

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<td>15</td>
<td>17</td>
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<tr>
<td>Percent</td>
<td>27%</td>
<td>30%</td>
<td>14%</td>
<td>29%</td>
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**Kolkata**

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)

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<td></td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Percent</td>
<td>38%</td>
<td>38%</td>
<td>0%</td>
<td>24%</td>
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47
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

Pai and Rodrigues: Management of latent tuberculosis infection

Does the individual have any of these risk factors?
HIV infection, contact of a pulmonary TB case, initiating anti-tumour necrosis factor (TNF) treatment, on dialysis, preparing for organ or hematologic transplantation, or has silicosis

Yes

No

Not a candidate for LTBI screening and treatment

Does the individual have any symptoms of tuberculosis?

Yes

No

TST or IGRA

Positive

Negative

Chest radiography

Any abnormality

No abnormality

Investigate for active TB using smears, PCR, and cultures

Treat for LTBI:
Acceptable regimens include 6 to 9 months of INH; 3-month regimen of weekly rifapentine plus INH; 3–4 months INH plus rifampicin; or 3–4 months rifampicin alone

Figure 1: World Health Organization algorithm for latent tuberculosis infection management. Source: Adapted from WHO, Geneva.
What will the future look like?
www.letstalktb.org/
Thank you!!

@paimadhu