Chapter 11: Management of tuberculosis: common pitfalls to avoid

Authors: Madhukar Pai, MD, PhD—Author and Series Editor; Srinath Satyanarayana, MD

http://www.letstalktb.org/
### The Global Burden of TB - 2013

<table>
<thead>
<tr>
<th>Estimated number of cases</th>
<th>Estimated number of deaths</th>
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<tr>
<td><strong>All forms of TB</strong></td>
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<tr>
<td>9 million</td>
<td>1.5 million*</td>
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<td>126 per 100,000</td>
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<tr>
<td>• 550,000 in children</td>
<td>• 80,000 in children</td>
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<td>• 3.3 m in women</td>
<td>• 510,000 in women</td>
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<td><strong>HIV-associated TB</strong></td>
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<td>1.1 million (13%)</td>
<td>360,000</td>
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<td><strong>Multidrug-resistant TB</strong></td>
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<td>480,000</td>
<td>210,000</td>
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*Source: WHO Global TB Report 2014

* Including deaths attributed to HIV/TB
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 Usmani, one of the country's leading TB authorities.

In December, Dr. Usmani 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. Usmani and his colleagues of starting 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 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 asking India to combat the strain.

The number of known cases in India is small but geographically dispersed. Dr. Usmani'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. Usmani said, "We're just getting started."

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-cure patients, it helped allow drug-resistant strains to spread that are now all but untreatable by modern medicine.

By Geeta Anand in Mumbai and Bethany McKee 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 Funeez Dewan, until recently a senior officer in the WHO's India tuberculosis program. "We should have pushed for a more aggressive, comprehensive approach toward drug resistance," he said in a recent 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 bears responsibility, he said. "What has the WHO been doing?"

In pilot testing across India this year of a new diagnostic method, some 50% of untreated TB patients were drug-resistant—suggesting far higher rates than the 2% to 3% 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, but in the absence of any nationwide survey they offer a sense of what India's drug-resistance rates might be.
Indian TB Programme: success in scaling up DOTS and in meeting 70/85 targets

Population in India covered under DOTS and Total Tuberculosis Patients put on treatment each quarter

Annualized New Smear-Positive Case Detection Rate and Treatment Success Rate in DOTS areas, 2001 – 2011

Source: RNTCP

http://www.letstalktb.org/
Despite the success, the reality is

- Hardly any decline in TB incidence
  - 2.2 million cases/year even now
  - Nearly 800 deaths/day

- India accounts for 1 of the 3 million missing cases

http://www.letstalktb.org/
MDR, XDR, TDR tuberculosis: ominous progression

Zarir F Udwadia

Alarming Levels of Drug-Resistant Tuberculosis in HIV-Infected Patients in Metropolitan Mumbai, India

Petros Isaakidis¹,², Mrinalini Das¹,², Ajay M V Kumar², Christopher Peskett¹, Minni Khetarpal³, Arun Bamne⁴, Balkrishna Adsul⁵, Mamtida Manglani⁶, Kuldeep Singh Sachdeva⁷, Malik Parmar⁸, Avinash Kanchar⁹, B.B. Rewari⁹, Alaka Deshpande¹⁰, Camilla Rodrigues¹¹, Anjali Shetty¹¹, Lorraine Rebello¹, Peter Saranchuk¹²

Rescue ARTICLE

Resistance Patterns among Multidrug-Resistant Tuberculosis Patients in Greater Metropolitan Mumbai: Trends over Time

Alpa Dalal¹, Akshay Pawaskar², Mrinalini Das³, Ranjan Desai⁴, Pralhad Prabhudesai⁵, Prashant Chhajed⁶, Sujeet Rajan⁷, Deepeesh Reddy⁸, Sajit Babu⁹, Jayalakshmi T. K.¹⁰, Peter Saranchuk⁹, Camilla Rodrigues¹¹, Petros Isaakidis²⁴

http://www.letstalktb.org/
TB is a major cause of mortality in India

http://www.healthdata.org/gbd

http://www.letstalktb.org/
What can explain the high incidence, TB deaths, missing cases and MDR problem?

- Underlying social determinants are hardly addressed
- There is considerable diagnostic delay and thus ongoing transmission
- Even if diagnosis is made, treatment and monitoring are suboptimal

Working hypotheses:
1) private sector is a major player, and currently not engaged
2) overall quality of TB care is poor

http://www.letstalktb.org/
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.
47 studies, measuring knowledge or self-reported practices
Diagnosis

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.

http://www.letstalktb.org/
Only a third of the providers were aware of the correct regimen for TB.

<table>
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<tr>
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<tr>
<td>Anandi (2002)</td>
<td>0.00 (0.00–0.04)</td>
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<td>Roy (2005)</td>
<td>0.30 (0.18–0.42)</td>
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<td>Thakur (2006)</td>
<td>0.12 (0.06–0.18)</td>
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<td>Rajpal (2007)</td>
<td>0.27 (0.21–0.32)</td>
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<td>Vandan (2009)</td>
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<td>Agarwal (2009)</td>
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<td>Bharaswadkar (2014)</td>
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<td>Maseeh (2004)</td>
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<td>Kondapaka (2012)</td>
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<td>Mishra (2013)</td>
<td>0.07 (0.04–0.11)</td>
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**Figure 3** Forest plot of studies in India on ISTC Standard 8 (awareness/use of the correct treatment regimen for a new case of TB). ES = effect size (proportion meeting standard); CI = confidence interval; ISTC = International Standards of Tuberculosis Care; TB = tuberculosis.

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Let’s Talk TB

A Supplement to GP CLINICS

TB treatment in the private sector in Mumbai

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

Zarir F. Udwadia, Lancelot M. Pinto, Mukund W. Uplekar

1 Department of Respiratory Diseases, P. D. Hinduja National Hospital and Medical Research Centre, Mumbai, India, 2 Stop 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 local TB programme. Only 6 of the 106 respondents wrote a prescription with a correct drug regimen. 196 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.


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 has 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. Those 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 use 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, e18064, 2011). This puts the private market at about the same volume as the public sector, a finding already established. "And the discrepancy that the total in drug sales exceeds the number of cases points to overuse and irreverence of use that could extend drug resistance for years—or even up to two years for multidrug-resistant tuberculosis (MDR-TB)." But in this huge and money private market, no one is ensuring that patients take adequate drug regimens or complete their therapy. "Wells maintains that the problem can be solved if patients are counseled to be aware of their drug regimen and the importance of completing it.

1990: 100 practitioners had prescribed 80 different drug regimens

2010: 106 practitioners prescribed 63 different drug regimens

Uplekar M et al. Tubercle 1991

http://www.letstalktb.org/
Importance of private sector in TB care

50% of TB treatment in India occurs in the private sector

http://www.letstalktb.org/
Even within the private sector, TB patients often seek care from informal providers and pharmacists.

Kapoor et al. PLoS ONE 2012

Figure 1. Pathways undertaken by the patients to reach the RNTCP (DOTS) Facilities, Delhi, India. doi:10.1371/journal.pone.0042458.g001
Use of standardised patients to assess quality of tuberculosis care: a pilot, cross-sectional study

Jishnu Das, Adi Kwan, Benjamin Daniels, Srinath Satyanarayana, Ramnath Szibbarsan, Sofi Bergkivist, Ranendra K Das, Veena Das, Medhukar Pai

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 mostly 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.

Methods We did a pilot, cross-sectional validation study of a convenience sample of consenting private healthcare providers in low-income and middle-income areas of Delhi, India. We recruited standardised patients in apparently good health from the local community to present four cases (two of presumed tuberculosis and one each of confirmed tuberculosis and suspected multidrug-resistant tuberculosis) to a randomly allocated healthcare provider. The key objective was to validate the standardised-patient method using three criteria: negligible risk and ability to avoid adverse events for providers and standardised patients, low detection rates of standardised patients by providers, and high accuracy across standardised patients and audio verification of standardised-patient recall. We also used medical vignettes to assess providers’ knowledge of presumed tuberculosis. Correct case management was benchmarked using Standards for Tuberculosis Care in India (STCI).

Findings Between 2 Feb, and March 28, 2014, we recruited and trained 17 standardised patients who had 250 interactions with 100 healthcare providers, 29 of whom were qualified in allopathic medicine (ie, they had a Bachelor of Medicine & Surgery [MBBS] degree), 40 of whom practised alternative medicine, and 31 of whom were informal health-care providers with few or no qualifications. The interactions took place between April 1, and April 23, 2014. The proportion of detected standardised patients was low (11 [5%]) detected out of 232 interactions among providers who completed the follow-up survey, and standardised patients’ recall correlated highly with audio recordings (p=0.63 [95% CI 0.53–0.79]), with no safety concerns reported. The mean consultation length was 6 min (95% CI 5.5–6.6) with a mean of 6–18 (5.72–6.64) questions or examinations completed, representing 35% (33–38) of essential checklist items. Across all cases, only 52 (21% [16–26]) of 250 were correctly managed. Correct management was higher among MBBS-qualified doctors than other types of health-care provider (adjusted odds ratio 2.41 [95% CI 1.17–4.93]; p=0.016). Of the 69 providers who completed the vignette, knowledge in the vignette was more consistent with STCI than their actual clinical practice—eg, 50 (73%) ordered a chest radiograph or sputum test during the vignette compared with seven (10%) during the standardised-patient interaction; OR 0.04 (95% CI 0.02–0.41); p=0.0001.

Interpretation Standardised patients can be successfully implemented to assess tuberculosis care. Our data suggest a big gap between private provider knowledge and practice. Additional work is needed to substantiate our pilot data, understand the know-do gap in provider behaviour, and to identify the best approach to measure and improve the quality of tuberculosis care in India.


Know-do gap

In the vignette, 73% ordered a CXR or sputum test.

In practice, 10% ordered CXR or sputum test.
Let’s Talk TB
A Series on Tuberculosis, A Disease That Affects Over 2 Million Indians Every Year

Management of Tuberculosis:
10 Common Pitfalls To Avoid

Srinath Satyanarayana, MD—Co-author
Madhukar Pai, MD, PhD—Author and Series Editor

http://www.letstalktb.org/
Pitfall 1: Not recognizing and suspecting TB

Doctors in India often miss TB, because they do not suspect TB in patients presenting with cough for 2 weeks or longer.

Multiple rounds of broad-spectrum antibiotics are tried, but tests for TB are rarely ordered.

Even when TB is suspected, history taking is often incomplete – family history of TB is rarely elicited, and previous treatment for TB is also missed.

http://www.letstalktb.org/
Ethnographic research

**TREATMENT PRACTICES**
- Need for symptomatic relief
- Risk of losing patient
- Patients’ limited financial capability
- Antibiotics available and inexpensive
- Frequent antibiotic prescription changes
- Lack of record keeping and systematic diagnostic protocol

**UNCERTAINTY**
- Many TB manifestations
- Slow disease onset and progression
- Lack of a unique and clearly defining symptom
- Symptoms important to practitioners may not align with international standards
- Use of second line drugs as broad spectrum antibiotics

**DIAGNOSTIC LIMITATIONS**
- Perception that many TB patients do not cough or produce sputum
- Paucity of bacteria present on sputum smear examination
- GeneXpert detects rifampicin resistance in a context of severe forms of drug-resistant TB

**EMPIRIC ANTIMICROBIAL TREATMENT AS DIAGNOSTIC**


http://www.letstalktb.org/
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.

- International Standards for TB Care, 3rd Edition
Recognize possible signs and symptoms of Tuberculosis. Early diagnosis and treatment reduces spread. Contact your Health Department or physician for more information.

http://www.letstalktb.org/
On notice of TB symptoms, immediately rush to your doctor

- Cough for more than 2 weeks
- Blood in sputum
- Weakness and fatigue
- Loss of weight
- Reduced appetite
- Evening Temperature

TB HAREGA, DESH JEETEGA.

For more information, consult your doctor.

http://www.letstalktb.org/
Pitfall 2: Inadequate diagnostic work-up

When doctors in India think of TB, they often order non-specific tests such as TC, DC, ESR and CXR.

They seriously underuse sputum-based microbiological tests (smears, cultures, PCR).
Recommended diagnostic options for pulmonary TB

- See the bugs [microscopy]
- Multiply the bugs [NAATs]
- Grow the bugs [cultures]

http://www.letstalktb.org/
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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Pitfall 3: Use of inappropriate diagnostic tests

- Serological, antibody-based tests (e.g. TB ELISA) are inaccurate and banned by the Indian government.
- Mantoux (tuberculin skin test) and IGRAs (e.g. TB Gold, TB Platinum) are being misused for active TB diagnosis.
- These tests were designed to detect latent infection, and cannot separate latency from active disease.

http://www.letstalktb.org/
RESEARCH ARTICLE

Costs and Consequences of Using Interferon-γ Release Assays for the Diagnosis of Active Tuberculosis in India

Kristen M. Little¹*, Madhukar Pai², David W. Dowdy¹

1 Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America. 2 Department of Epidemiology, Biostatistics, and Occupational Health, McGill University and McGill International TB Centre, Montreal, Canada

Conclusion

Using IGRAs for diagnosis of active TB in a setting like India results in tremendous overtreatment of people without TB, and substantial incremental cost with little gain in health.
STCI recommendations

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/
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®
Pitfall 4: Not considering the possibility of drug-resistant TB

Indian physicians under-use DST and this can result in mismanagement.

All persons who have previously received TB therapy must be considered to have suspected DR-TB.

If patients have any risk factors for drug-resistance, or live in a high MDR-TB prevalence area (e.g. Mumbai city), or do not respond to standard drug therapy, they must be investigated for MDR-TB using GeneXpert or line probe assays, and cultures.

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

http://www.letstalktb.org/
In cities like Mumbai, ALL TB patients should get a DST!

MDR, XDR, TDR tuberculosis: ominous progression
Zarir F Udwadia

Alarming Levels of Drug-Resistant Tuberculosis in HIV-Infected Patients in Metropolitan Mumbai, India
Petros Isaakidis¹, Mrinalini Das¹, Ajay M V Kumar², Christopher Peskett¹, Minni Khetarpal², Arun Banne³, Balkrishna Adsul⁴, Mamta Manglani⁵, Kuldeep Singh Sachdeva⁶, Malik Parmar⁸, Avinash Kanchar⁹, B.B. Rewari⁹, Alaka Deshpande¹⁰, Camilla Rodrigues¹¹, Anjali Shetty¹¹, Lorraine Rebello¹, Peter Saranchuk¹²

Resistance Patterns among Multidrug-Resistant Tuberculosis Patients in Greater Metropolitan Mumbai: Trends over Time
Alpa Dalal¹, Akshay Pawaskar², Mrinalini Das³, Ranjan Desai⁴, Pralhad Prabhudesai⁶, Prashant Chhajed⁶, Sujeet Rajan⁷, Deepesh Reddy⁷, Sajit Babu⁷, Jayalakshmi T. K.¹⁰, Peter Saranchuk², Camilla Rodrigues¹¹, Petros Isaakidis²

http://www.letstalktb.org/
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

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

Answer: Rapid molecular TB testing, followed by culture confirmation

http://www.letstalktb.org/
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
Xpert MTB/RIF: evidence from India

Feasibility of Decentralised Deployment of Xpert MTB/RIF Test at Lower Level of Health System in India

Neeraj Raizada¹, K. S. Sachdeva², Achuthan Sreenivas³, Bhavin Vadera¹, R. S. Gupta⁴, Malik Parmar⁵, Shubhangi Kulsange⁶, Ameet Babre⁷, Rahul Thakur⁸, Christen Gray⁹, Ranjani Ramachandran¹⁰, Umesh Alavadi¹¹, Mayank Ghedia¹², Balasangameshvara Voilepore¹³, Puneet Dewan¹⁴, Catharina Boehme¹⁵, C. N. Paramasivan¹⁶

¹ Foundation for Innovative New Diagnostics, New Delhi, India, ² Central TB Division, Government of India, New Delhi, India, ³ World Health Organization, Country Office, New Delhi, India, ⁴ Foundation for Innovative New Diagnostics, Geneva, Switzerland

Enhancing TB Case Detection: Experience in Offering Upfront Xpert MTB/RIF Testing to Pediatric Presumptive TB and DR TB Cases for Early Rapid Diagnosis of Drug Sensitive and Drug Resistant TB

Neeraj Raizada¹, Kuldeep Singh Sachdeva₂, Sreenivas Achuthan Naïr³, Shubhangi Kulsange⁴, Radhey Shyam Gupta⁵, Rahul Thakur⁶, Malik Parmar⁷, Christen Gray⁸, Ranjani Ramachandran⁹, Bhavin Vadera¹⁰, Shobha Ekka¹¹, Shikha Dhawan¹², Ameet Babre¹³, Mayank Ghedia¹⁴, Umesh Alavadi¹⁵, Puneet Dewan¹⁶, Mini Khetrapal¹⁷, Ashwini Khamna¹⁸, Catharina Boehme¹⁹, Chinmambodu Nainarappan Paramasivan²⁰

¹ Foundation for Innovative New Diagnostics, New Delhi, India, ² Central TB Division, Government of India, New Delhi, India, ³ World Health Organization, Country Office for India, New Delhi, India, ⁴ Foundation for Innovative New Diagnostics, Geneva, Switzerland, ⁵ District Tuberculosis Center, Mumbai, India, ⁶ District Tuberculosis Center, New Delhi, India

Xpert® MTB/RIF assay for tuberculosis diagnosis: evaluation in an Indian setting

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INT J TUBERC LUNG DIS 18(8):958-960 © 2014 The Union
http://dx.doi.org/10.5588/ijtld.13.0328

The present study was conducted to evaluate the performance of the Xpert® MTB/RIF assay and compare Xpert results with solid and MGIT 960 liquid culture system. A total of 134 patients who had failed the Category I or II regimen were recruited for evaluation. Xpert correctly identified all Mycobacterium tuberculosis isolates. The sensitivity and specificity of the Xpert assay for the detection of rifampicin resistance was respectively 98.2% and 97.0% when compared with MGIT 960 results.

Key Words: Mycobacterium tuberculosis; Xpert® MTB/RIF assay; Löwenstein-Jensen media

http://www.letstalktb.org/
Algorithm for DST: very important to complete this!

Suspected drug-resistance → Rapid molecular test (Xpert MTB/RIF) or LPA → 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/
Pitfall 5: Empirical management of suspected TB with quinolones and steroids

- When doctors suspect TB or other lower respiratory tract infections, they frequently use broad-spectrum fluoroquinolones (e.g. levofloxacin, moxifloxacin) for short periods.

- Empiric fluoroquinolone monotherapy for respiratory tract infections has been associated with delays in initiation of appropriate anti-tuberculosis therapy and acquired resistance to the fluoroquinolones.

- Doctors also tend to use steroids in individuals with history of chronic cough. Steroids, again, can result in temporary clinical improvement, but delay the diagnosis and treatment of underlying tuberculosis.

http://www.letstalktb.org/
India was the largest consumer of antibiotics in 2010 with $12.9 \times 10^9$ units (10.7 units per person).

Study showed large increase in cephalosporin and fluoroquinolone consumption, mainly in middle-income countries (India and China).
Fluoroquinolones are associated with delayed treatment and resistance in tuberculosis: a systematic review and meta-analysis

Tun-Chieh Chen a,b,c, Po-Liang Lu b,c, Chun-Yu Lin b,c, Wei-Ru Lin b, Yen-Hsu Chen b,c,d,*

a Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung City, Taiwan
b Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung City, Taiwan
c Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung City, Taiwan
d Tropical Medicine Research Center, College of Medicine, Kaohsiung Medical University, Kaohsiung City, Taiwan
Pitfall 6: Once TB is diagnosed, not addressing co-morbidities and contacts

- Once TB is diagnosed, it is important to make sure the patient is not suffering from co-morbid conditions such as HIV and diabetes.

- It is also important to check if the patient is a smoker/alcoholic and provide them advice on smoking/alcohol cessation.

- It is also necessary to ask about TB symptoms among family members. In particular, small children living in the same family as the adult case must be tested for TB.

http://www.letstalktb.org/
India TB

India Tuberculosis-Diabetes Study Group

Screening of patients with tuberculosis for diabetes mellitus in India

http://www.letstalktb.org/
Pitfall 7: Use of irrational TB drug regimens

- When private practitioners initiate anti-TB treatment (ATT), they tend to use drug regimens that are not recommended by WHO or the Standards of TB Care in India (STCI).
- There is no need to add additional drugs such as quinolones to the standard drug regimen.
- No need to extend the duration of treatment beyond 6 months, unless there is evidence of treatment failure, or there are complications (e.g. bone & joint TB, spinal TB with neurological involvement and neuro-tuberculosis).
- No need for second-line drugs (unless MDR/XDR is confirmed).
- Drug dosages should be based on body weight, and daily dosing is preferable.

http://www.letstalktb.org/
Ref. NO.: 
Date: 25/07/2015

Ansar
Past H/O for 10 months of cough stopped dyspnoea 60 days no symptoms since

Fever 2-3 week

Sputum +ve

A/S

X-ray chest

CBC 488

S+T

Levofox 500mg OD

7. Benadine ½ OD

7. Antacid D

Sup 1 daily

http://www.letstalktb.org/
Pitfall 8: Not ensuring treatment adherence

- Private practitioners struggle to ensure adherence.
- Most do not maintain any medical records, and this makes it very difficult to follow-up patients.
- Patients often do not receive sufficient counseling about the importance of completing the full course of ATT.
- Drug-related side effects (if not adequately counselled on at the outset) is another common reason for non-adherence, and possible treatment default.

http://www.letstalktb.org/
Complete your full DOTS course to cure TB successfully

- TB becomes more complex and difficult to treat
- Cost of treatment increases
- Can increase chances of side effects
- Treatment gets prolonged

TB HAREGA, DESH JEETEGA.

For more information, consult your doctor.

http://www.letstalktb.org/
Simple tools we can use today

HRZE for 2 months
HR for 4 months
Fixed dose combination
Daily therapy
With adherence support

http://www.letstalktb.org/
Pitfall 9: Not monitoring response to therapy and changing regimens without DST

- Once ATT is started, doctors have the responsibility of monitoring the patients to check whether therapy is working.
- This requires follow-up smear and culture testing. Negative smears at the end of therapy is important to ensure cure.
- If a patient is not responding to ATT, it important to investigate why.
- Addition of a single drug to a failing regimen is a big concern. Many physicians add a quinolone to the 4 first-line drugs (HRZE) when the standard therapy does not result in improvement.
- Sometimes, patients end up moving from one doctor to another, and each time the drug regimen gets modified without adequate drug-susceptibility testing (DST) to guide the choice of drug combinations.

http://www.letstalktb.org/
Pitfall 10: Not notifying all cases and using free public sector services for vulnerable patients

- Irrespective of where the patients are diagnosed and treated, it is mandatory for private practitioners to notify all TB cases to their respective District or Corporation TB Officers.
- TB treatment is available free of cost to all patients in India via the Revised National TB Control Programme (RNTCP); other services are also available. Patients need to be informed about these services.

http://www.letstalktb.org/
RESEARCH ARTICLE

“They Know, They Agree, but They Don’t Do” - The Paradox of Tuberculosis Case Notification by Private Practitioners in Alappuzha District, Kerala, India

Sairu Philip¹ *, Petros Isaakidis²*, Karuna D. Sagili³, Asanaripillai Meharunnisa¹, Sunil Kumar Mrithyunjayan¹, Ajay M. V. Kumar³*

1 Government T.D. Medical College, Alappuzha, Kerala State, India, 2 Operational Research Unit, Médecins Sans Frontières, India, 3 International Union Against Tuberculosis and Lung Disease, South-East Asia Regional Office, New Delhi, India, 4 State TB Training and Demonstration Centre, State TB Cell, Directorate of Health Services, Thiruvananthapuram, Kerala, India

RESEARCH ARTICLE

The Usefulness and Feasibility of Mobile Interface in Tuberculosis Notification (MITUN) Voice Based System for Notification of Tuberculosis by Private Medical Practitioners – A Pilot Project

Banurekha Velayutham¹, Beena Thomas¹, Dina Nair¹, Kannan Thiruvengadam¹, Suma Prashant¹, Sathyapriya Kittusami¹, Harivanjan Vijayakumar¹, Menachi Chidambaram¹, Shri Vijay Bala Yogendra Shivakumar¹, Lavanya Jayabal¹, Ashok Jhunjhunwala¹, Seumya Swaminathan¹*

1 National Institute for Research in Tuberculosis (formerly Tuberculosis Research Centre), Chennai, Tamil Nadu, India, 2 Indian Institute of Technology Madras (IITM)’s Rural Technology and Business Incubator (RTBI), Chennai, Tamil Nadu, India, 3 District Tuberculosis Officer, Chennai, Tamil Nadu, India

http://www.letstalktb.org/
WHAT WILL THE FUTURE LOOK LIKE?

http://www.letstalktb.org/
<table>
<thead>
<tr>
<th>FIND</th>
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<th>On pathway to WHO evaluation</th>
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<td>Molecular Detection/DST</td>
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<td>LAM in sputum (Standard Diagnostics)</td>
<td>LAM in sputum (Standard Diagnostics)</td>
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<td>β-lactamase reporter (Global BioDiagnostics)</td>
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http://www.letstalktb.org/
New TB drugs and regimens

**TB Alliance**

**Global Alliance for TB Drug Development**

**2015 Q3**

### Discovery

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<tr>
<th>Lead Identification</th>
<th>Lead Optimization</th>
<th>Preclinical Development</th>
<th>Phase 1</th>
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<td>Macrolides</td>
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**TB Alliance R&D Partners:**

- AstaZeneca
- Beijing Tuberculosis and Thoracic Tumor Research Institute (BTTRI)
- Calibr
- Cornell University
- Daiichi Sankyo
- GlaxoSmithKline (GSK)
- Institute of Materia Medica (IMM)
- IMPAACT
- Johns Hopkins University (JHU)
- Medical Research Council (MRC) at UCL
- (US) National Institutes of Health (NIH)
- OP-BIO
- Roche Pharmaceuticals
- Rutgers University
- Sanofi
- Schrödinger
- Shionogi
- Stellenbosch University
- Takeda Pharmaceuticals
- TB Drug Accelerator (TBDA)
- Texas A&M University (TAMU)
- University College London (UCL)
- University of Auckland
- University of Dundee (Dundee)
- University of Illinois at Chicago (UIC)
- University of Pennsylvania School of Medicine (UPenn)
- Yonsei University

Source: [http://www.tballiance.org/](http://www.tballiance.org/)

http://www.letstalktb.org/
PaMZ Phase 3 clinical trial has begun

PaMZ = PA-824 + Moxifloxacin + Pyrazinamide

BRAVE NEW WORLD FOR TB
The PaMZ (PA-824+moxifloxacin+pyrazinamide) regimen shows the potential to dramatically shorten, simplify, and improve the treatment of multidrug-resistant TB (MDR-TB). That’s not all; the new regimen is expected to be 90% cheaper than the existing treatment.

<table>
<thead>
<tr>
<th>Current MDR-TB Regimen</th>
<th>Proposed PaMZ Regimen</th>
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</thead>
<tbody>
<tr>
<td><strong>LENGTH OF TREATMENT</strong></td>
<td></td>
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<tr>
<td>24 months</td>
<td>4 months</td>
</tr>
<tr>
<td>12,400 pills</td>
<td>360 pills</td>
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<tr>
<td>17%</td>
<td>3%</td>
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<tr>
<td><strong>NUMBER OF PILLS</strong></td>
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<tr>
<td>180 injections</td>
<td>0 injections</td>
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<tr>
<td><strong>NUMBER OF SACHETS</strong></td>
<td></td>
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<tr>
<td>1,440 saches</td>
<td>0 saches</td>
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</table>

Taking a STAND
The promise of improved TB and MDR-TB treatment

The STAND trial will test PaMZ, the first drug regimen designed to treat both tuberculosis and multidrug-resistant TB (MDR-TB). PaMZ is expected to be shorter, safer, simpler, and up to 90% less expensive than current treatment for MDR-TB—an increasingly devastating disease.

New Tuberculosis Drug Regimen Will Move to Landmark Phase 3 Clinical Trial
STAND that will test the first regimen designed to significantly shorten and simplify the treatment of drug-sensitive and drug-resistant TB

Based on positive results from earlier clinical studies, TB Alliance is advancing the first-ever drug regimen designed to treat both drug-sensitive and some forms of multi-drug-resistant tuberculosis (TB) to a global Phase 3 clinical trial.

The announcement by Bill Gates, co-chair of the Bill & Melinda Gates Foundation, accompanied a commitment of significant funding by the Gates Foundation to determine the safety and efficacy of the new drug regimen, which is known as PaMZ. Mr. Gates called on other organizations to support the effort to develop new treatments for TB, a disease that kills an estimated 1.3 million people annually and remains a leading cause of death globally, especially among people who are co-infected with HIV.

“The results from early phase research suggest that this new drug regimen could provide the breakthrough we need to accelerate progress against this deadly and dangerous disease,” said Mr. Gates. “PaMZ could dramatically reduce the time required to cure drug-resistant TB from two years to just six months, and it could cut the cost of curing drug-resistant TB in low-income countries from thousands of dollars to just a fraction of that cost. How we need funders to step forward to make next-generation TB drugs like PaMZ a reality.”

http://www.letstalktb.org/

Source: http://www.tballiance.org/portfolio/regimen/pamz
New adherence monitoring tools

Smart Pill Boxes

99DOTS

Patches/Ingestibles

http://www.letstalktb.org/
How will TB get diagnosed and treated in 2020?

Symptomatic

Rapid Triage Test

Rapid Molecular Dx & Upfront DST

eTB ICT system

Culture/sequencing confirmation at referral labs

Electronic notification & tracking

Adherence monitoring tools

Shorter drug regimens

http://www.letstalktb.org/