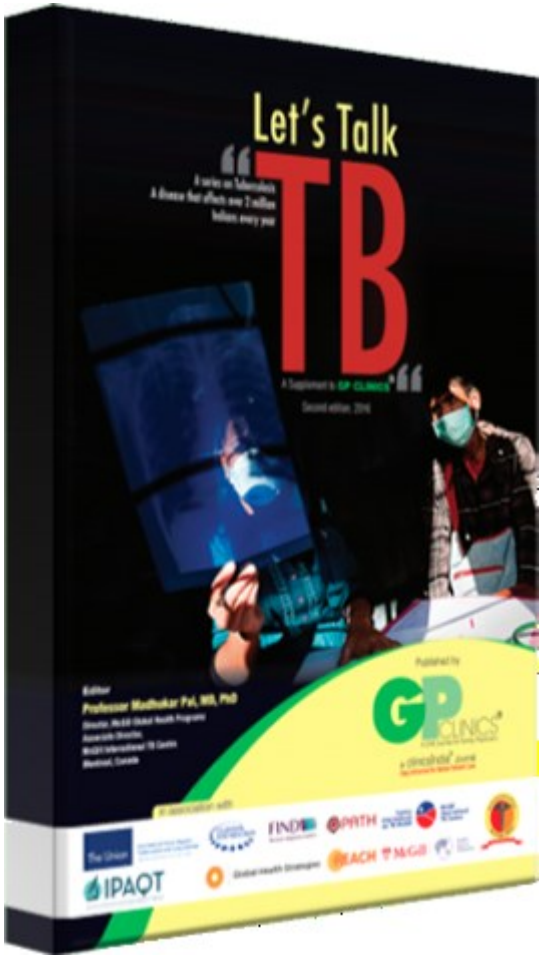


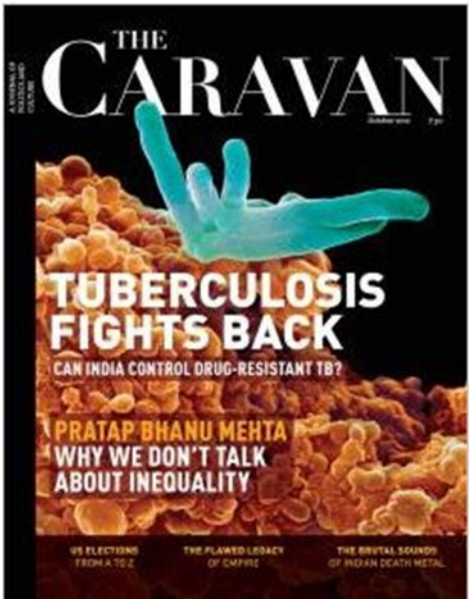
Let's Talk TB:

A Supplement to GP CLINICS

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. Zarir Udwadia, one of the country's leading TB authorities.

In December, Dr. Udwadia 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. Udwadia 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 assisting India to combat the strain.

The number of known cases in India is small but geographically dispersed. Dr. Udwadia'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. Udwadia said, "We've got nothing."

Ashok Kumar, head of India's tuberculosis-con-

Please turn to page A12

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 TB strains to spread that are now all but untreatable by modern medicine.

By Geeta Anand in Mumbai and Betsy 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 Puneet Dewan, 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 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 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, 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

INT J TUBERC LUNG DIS 18(3):255–266

http://dx.doi.org/10.5588/ijtld.13.0585
E-published ahead of print 9 January 2014

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†

*Department of Population Medicine, Faculty of Medicine and Health Science, University Tunku Abdul Rahman, Selangor, Malaysia; †Department of Epidemiology and Biostatistics, McGill International TB Centre, McGill University, Montreal, Quebec, Canada; ‡Division of Infectious Diseases, Brigham and Women's Hospital, Boston, Massachusetts, USA

- 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%

INT J TUBERC LUNG DIS 19(7):000–000

http://dx.doi.org/10.5588/ijtld.15.0186

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*

*Department of Epidemiology, Biostatistics and Occupational Health, and McGill International TB Centre, McGill University, Montreal, Canada; †Center for Operations Research, International Union Against Tuberculosis and Lung Disease, Paris, France; ‡Division of Infectious Diseases, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA; §Partners for Urban Knowledge, Action and Research, Mumbai, India; ¶Curry International Tuberculosis Center, University of California San Francisco, San Francisco, California, USA; #Life Sciences Library, McGill University, Montreal, Canada; **Development Economics Research Group, World Bank, Washington DC, ††The Fenway Institute and Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA; ‡‡Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, McGill University, Montreal, Canada; §§London School of Hygiene & Tropical Medicine, London, United Kingdom

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

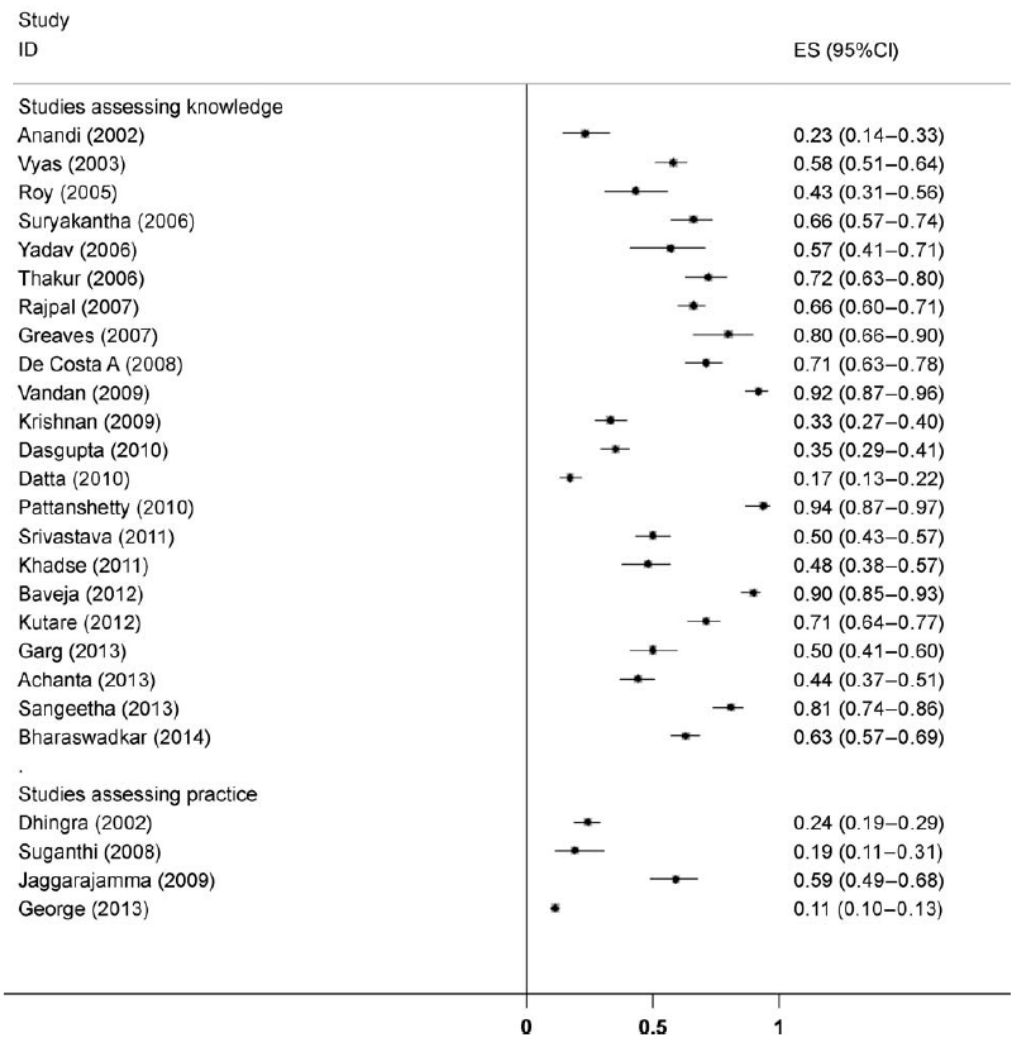


Figure 2 Forest plot of studies on ISTC Standard 2 (awareness/use of sputum smear for persons with presumptive pulmonary TB). ES = effect size (proportion meeting standard); CI = confidence interval; ISTC = International Standards of Tuberculosis Care; TB = tuberculosis.

Substantial under-testing for TB, and empirical Rx

Engel et al. BMC Health Services Research (2015) 15:550
DOI 10.1186/s12913-015-1223-3

BMC Health Services Research

RESEARCH ARTICLE Open Access

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

Nora Engel[1*], Gayatri Ganesh[2], Mamata Patil[2], Vijayashree Yellappa[2], Caroline Vadnais[3], Nitika Pant Pai[4] and Madhukar Pai[3]

INT J TUBERC LUNG DIS 20(4):000–000
© 2016 The Union
http://dx.doi.org/10.5588/ijtld.15.0562

Treatment as diagnosis and diagnosis as treatment: empirical management of presumptive tuberculosis in India

A. McDowell, M. Pai

McGill International TB Centre & Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada

PLOS | ONE

RESEARCH ARTICLE

How Do Urban Indian Private Practitioners Diagnose and Treat Tuberculosis? A Cross-Sectional Study in Chennai

Liza Bronner Murrison[1,2], Ramya Ananthakrishnan[3], Sumanya Sukumar[3], Sheela Augustine[3], Nalini Krishnan[3], Madhukar Pai[4], David W. Dowdy[1,2]*

Use of standardised patients to assess quality of tuberculosis care

In their report, Jishnu Das and colleagues[1] showcase a unique method to assess quality of care and the know-do gap through use of standardised patients with tuberculosis.[2] 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 providers

This study was funded by the Bill & Melinda Gates Foundation. We declare no competing interests.

*Yatin Dholakia, *Nerges Mistry, Eunice Lobo, Sheela Rangan,
fmr@fmrindia.org

The Foundation for Medical Research, Mumbai, Maharashtra 400018, India (YD, NM, EL, SR); and Maharashtra Association of Anthropological Sciences-Centre for Health Research and Development, Savitribai Phule University, Aundh, Pune, India (SR)

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

Jishnu Das, Ada Kwan, Benjamin Daniels, Srinath Satyanarayana, Ramnath Subbaraman, Sofi Bergkvist, Ranendra K Das, Veena Das, Madhukar 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 health-care 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.

Lancet Infect Dis 2015
Published Online August 10, 2015
http://dx.doi.org/10.1016/S1473-3099(15)00077-8

PLOS | ONE

RESEARCH ARTICLE

Barriers to Point-of-Care Testing in India: Results from Qualitative Research across Different Settings, Users and Major Diseases

Nora Engel[1]*, Gayatri Ganesh[2], Mamata Patil[2], Vijayashree Yellappa[2], Nitika Pant Pai[3], Caroline Vadnais[4], Madhukar Pai[4]

Trans R Soc Trop Med Hyg 2016; **110**: 192–198
doi:10.1093/trstmh/trw009

Alternative medicine: an ethnographic study of how practitioners of Indian medical systems manage TB in Mumbai

Andrew McDowell and Madhukar Pai*

McGill International TB Centre & Department of Epidemiology, Biostatistics and Occupational Health, McGill University, 1020 Pine Avenue West, Montreal, QC, Canada H3A 1A2

Purohit et al. BMC Infectious Diseases (2015) 15:322
DOI 10.1186/s12879-015-1037-2

BMC Infectious Diseases

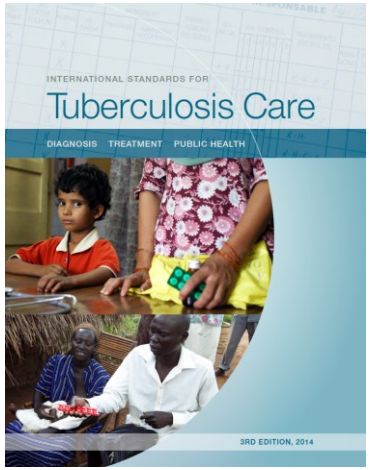
RESEARCH ARTICLE Open Access

'Multiple-test' approach to the laboratory diagnosis of tuberculosis -perception of medical doctors from Ujjain, India

Manju Raj Purohit[1,2,3*], Megha Sharma[3,4], Senia Rosales-Klintz[3] and Cecilia Stålsby Lundborg[3]

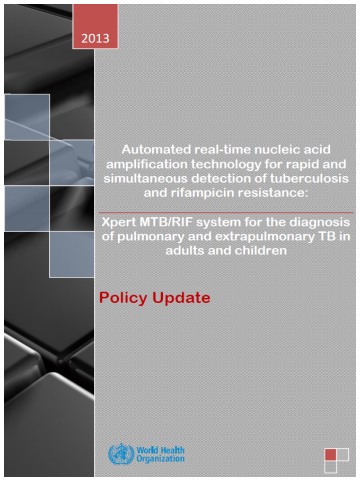
Objective of the presentation: to describe internationally accepted, best practices for the diagnosis of

- Active TB
- Drug resistant TB
- Latent TB infection

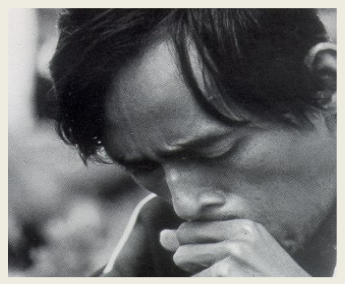


Based on WHO policies and International Standards of TB Care, 3rd edition & STCI, 1st edition

All policies and meta-analyses cited are available at: www.tbevidence.org



Diagnosis of active PTB



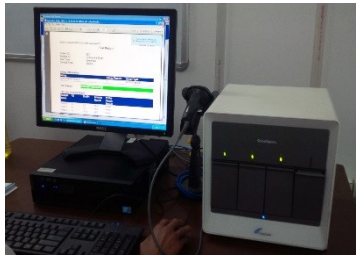
All patients, including children, with unexplained cough lasting two or more weeks or with unexplained findings suggestive of TB on chest radiographs should be evaluated for tuberculosis.

- 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

Public Health Action
International Union Against Tuberculosis and Lung Disease
Health solutions for the poor
VOL 3 NO 3 PUBLISHED 21 SEPTEMBER 2013

SHORT COMMUNICATION

LED fluorescence microscopy increases the detection of smear-positive pulmonary tuberculosis in medical colleges of India

L. W. Reza,[1] S. Satyanarayana,[1] A. Pandey,[1] S. Kumar,[1] N. M. Devendrappa,[1] L. Anand,[1] G. Singh,[1] A. M. V. Kumar,[1] S. S. Chadha,[1] N. Wilson,[1] K. S. Sachdeva,[2] S. A. Nair[3]

OPEN ACCESS Freely available online
PLOS ONE

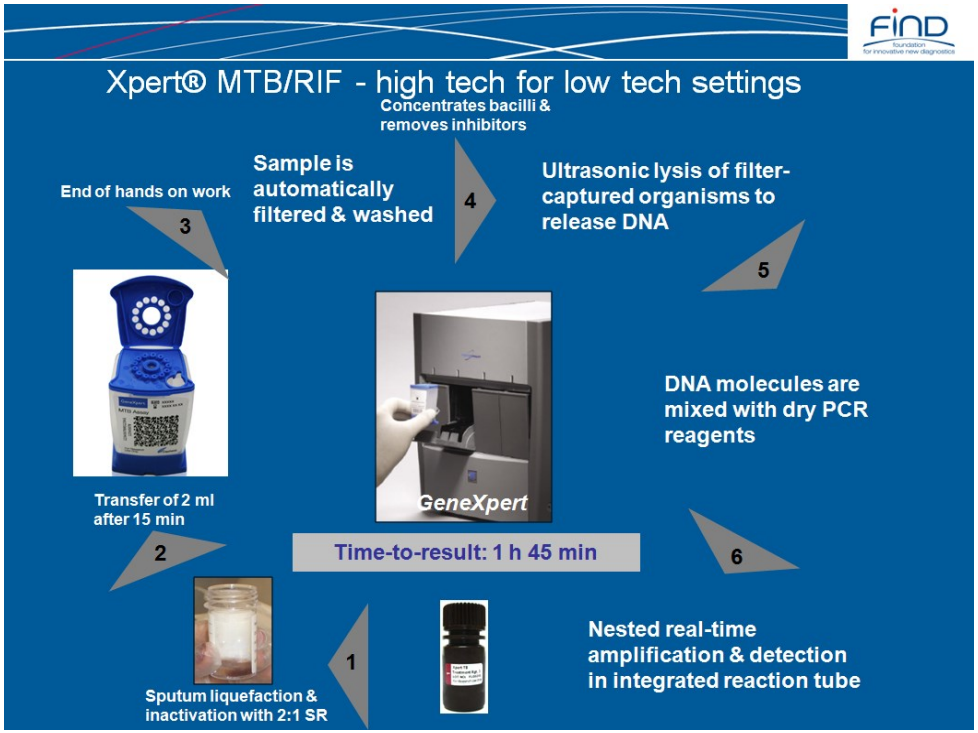
LED-Fluorescence Microscopy for Diagnosis of Pulmonary Tuberculosis under Programmatic Conditions in India

Lord Wasim Reza[1]*, Srinath Satyanarayana[1], Donald A. Enarson[2], Ajay M. V. Kumar[1], Karuna Sagili[1], Sujeet Kumar[1], Levi Anand Prabhakar[1], N. M. Devendrappa[1], Ashish Pandey[1], Nevin Wilson[1], Sarabjit Chadha[1], Badri Thapa[1], Kuldeep Singh Sachdeva[3], Mohan P. Kohli[1,3]
1 International Union against Tuberculosis and Lung Disease(The Union), South-East Asia Regional Office, New Delhi, India, 2 International Union against Tuberculosis and Lung Disease, Paris, France, 3 Central TB Division, Directorate general of health services, Ministry of Health and Family Welfare, New Delhi, India

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

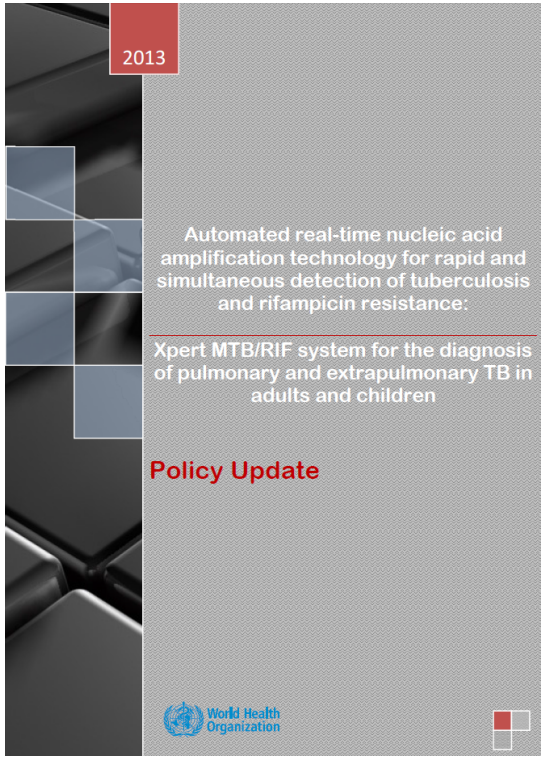


WHO Recommendations (2013) for PTB and DST

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

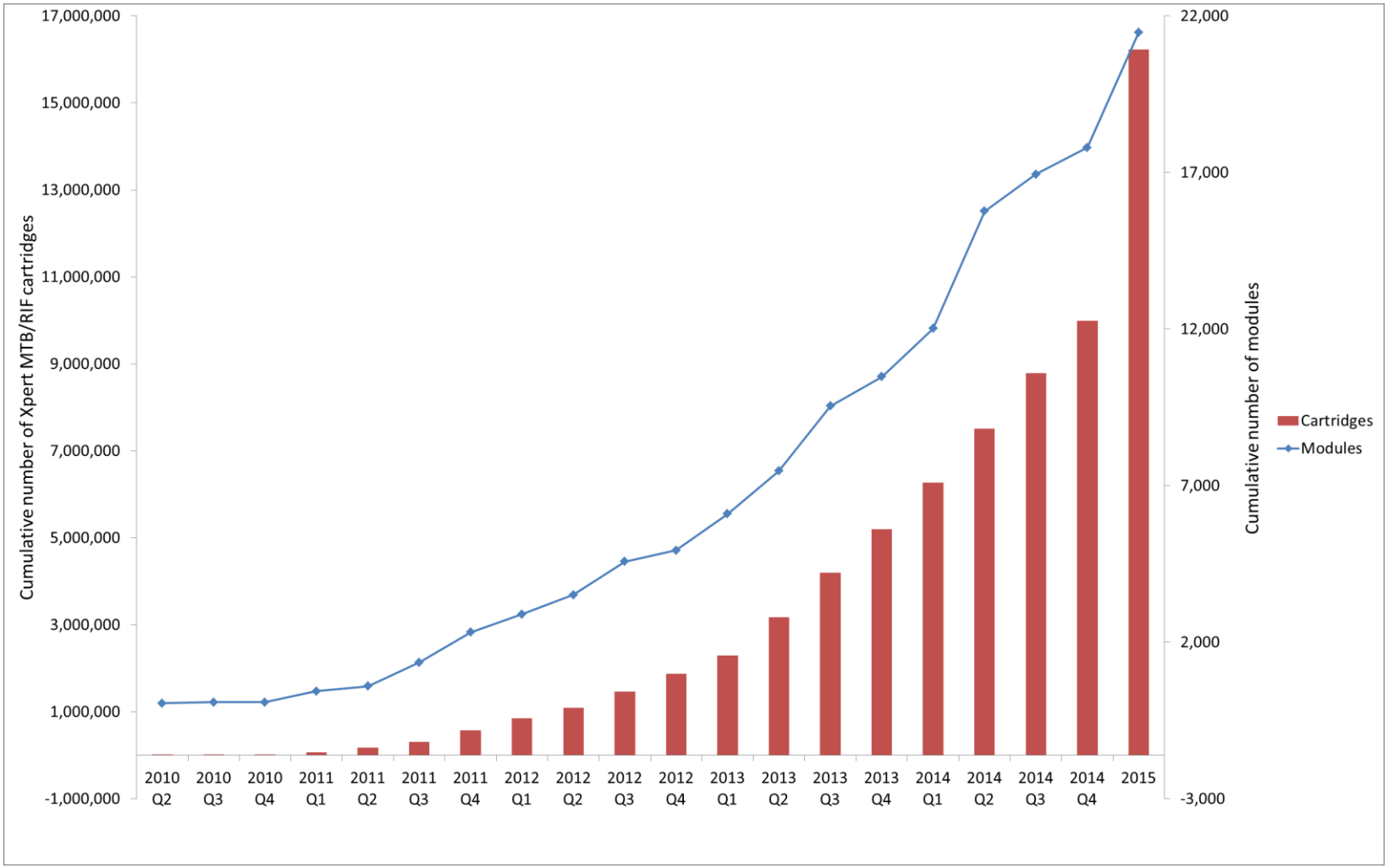
- Xpert MTB/RIF should be used rather than conventional microscopy, culture and DST as the initial diagnostic test in **adults** presumed to have MDR-TB or HIV-associated TB (strong recommendation, high-quality evidence).
- Xpert MTB/RIF should be used rather than conventional microscopy, culture and 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



http://www.stoptb.org/wg/gli/assets/documents/WHO%20Policy%20Statement%20on%20Xpert%20MTB-RIF%202013%20pre%20publication%2022102013.pdf

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



http://www.who.int/tb/laboratory/mtbrifrollout/en/index.html

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

THE COCHRANE COLLABORATION®

Citation: Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, Dendukuri N. Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. *Cochrane Database of Systematic Reviews* 2014, Issue 1. Art. No.: CD009593. DOI: 10.1002/14651858.CD009593.pub3.

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
http://tbevidence.org/wp-content/uploads/2014/01/Steingart-Cochrane-Library-2014-Updated-Xpert-SR.pdf

India has shown that Xpert can greatly increase MDR detection in adults & children

PLOS | ONE

RESEARCH ARTICLE

Use of Xpert MTB/RIF in Decentralized Public Health Settings and Its Effect on Pulmonary TB and DR-TB Case Finding in India

Kuldeep Singh Sachdeva[1], Neeraj Raizada[2]*, Achuthan Sreenivas[3], Anna H. van't Hoog[4], Susan van den Hof[4,5], Puneet K. Dewan[3¤], Rahul Thakur[2], R. S. Gupta[1], Shubhangi Kulsange[2], Bhavin Vadera[2], Ameet Babre[2], Christen Gray[2], Malik Parmar[3], Mayank Ghedia[1], Ranjani Ramachandran[3], Umesh Alavadi[2], Nimalan Arinaminpathy[6], Claudia Denkinger[2], Catharina Boehme[2], C. N. Paramasivan[2]

PLOS | ONE

RESEARCH ARTICLE

Piloting Upfront Xpert MTB/RIF Testing on Various Specimens under Programmatic Conditions for Diagnosis of TB & DR-TB in Paediatric Population

Neeraj Raizada[1]*, Kuldeep Singh Sachdeva[2], Soumya Swaminathan[4], Shubhangi Kulsange[1], Sunil D. Khaparde[2], Sreenivas Achuthan Nair[7], Ashwani Khanna[3], Kamal Kishore Chopra[3], Mahmud Hanif[3], Gulshan Rai Sethi[3], K. R. Umadevi[4], G. Keshav Chander[5], Brojakishore Saha[6], Amar Shah[2], Malik Parmar[7], Mayank Ghediya[2], Jyoti Jaju[2], Catharina Boehme[1], Chinnambedu Nainarappan Paramasivan[1]

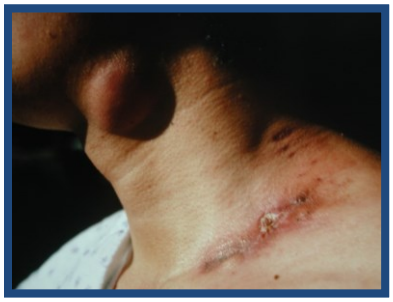
1 Foundation for Innovative New Diagnostics, New Delhi, India, 2 Central TB Division, Government of India, New Delhi, India, 3 New Delhi TB Centre, New Delhi, India, 4 National Institute of research in Tuberculosis, Chennai, India, 5 Intermediate Reference Laboratory, Hyderabad, India, 6 Intermediate Reference Laboratory, Kolkata, India, 7 World Health Organization, Country Office for India, New Delhi, India

"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

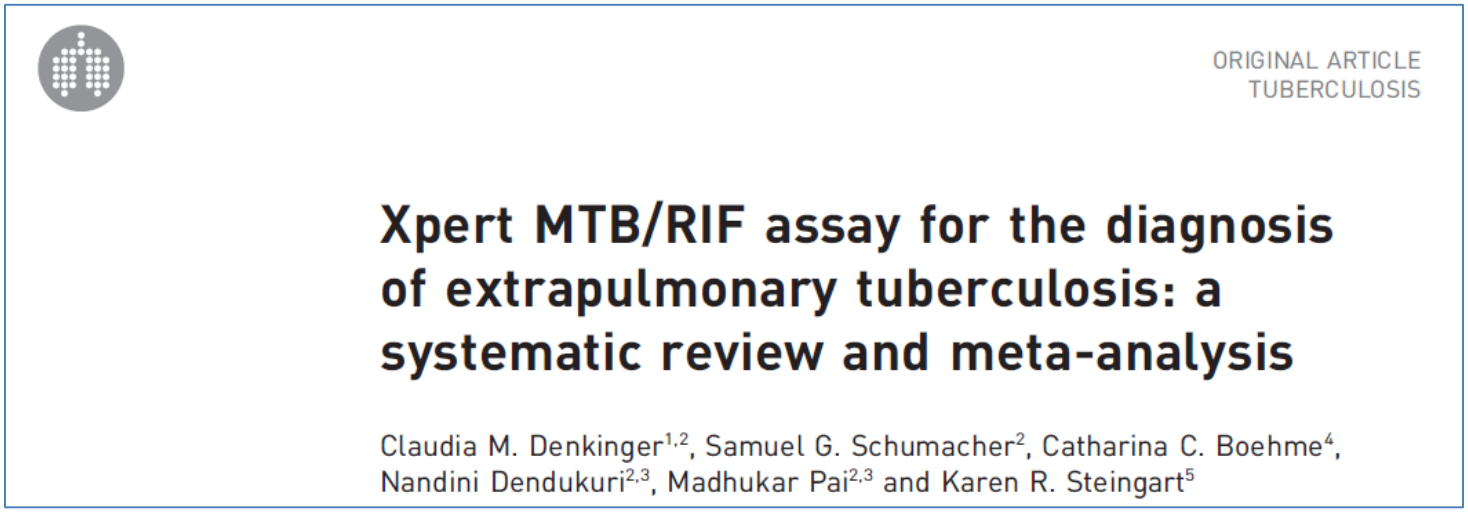
- Xpert MTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test in testing **cerebrospinal fluid specimens** from patients presumed to have TB meningitis (strong recommendation given the urgency of rapid diagnosis, very low quality of evidence).

- 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***

http://www.stoptb.org/wg/gli/assets/documents/WHO%20Policy%20Statement%20on%20Xpert%20MTB-RIF%202013%20pre%20publication%2022102013.pdf

Evidence in EPTB

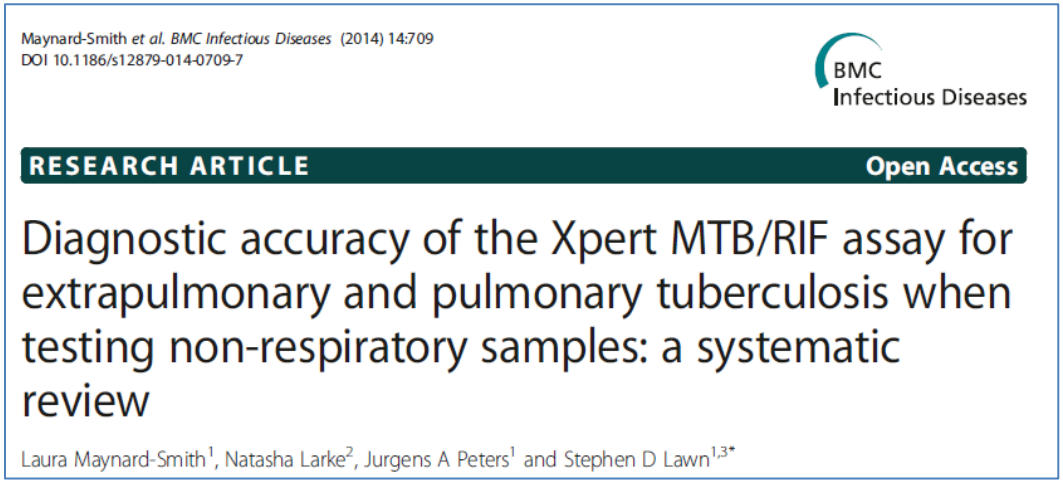


ORIGINAL ARTICLE
TUBERCULOSIS

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

Claudia M. Denkinger[1,2], Samuel G. Schumacher[2], Catharina C. Boehme[4], Nandini Dendukuri[2,3], Madhukar Pai[2,3] and Karen R. Steingart[5]

Denkinger CM et al. Eur Respir J 2014



Maynard-Smith *et al. BMC Infectious Diseases* (2014) 14:709
DOI 10.1186/s12879-014-0709-7

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

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

Laura Maynard-Smith[1], Natasha Larke[2], Jurgens A Peters[1] and Stephen D Lawn[1,3*]

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

Sample	Sensitivity*	Specificity*
Lymph nodes	83%	94%
CSF	81%	98%
Pleural fluid	46%	99%

*Compared to culture as the reference standard

Denkinger CM et al. Eur Respir J 2014

EPTB: evidence from India

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

@ERSpublications
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. Sharma[1], Mikashmi Kohli[1], Jigyasa Chaubey[1], Raj Naraya Vishnubhatla Sreenivas[2], Abhishek Sharma[1], Rohit Bhatia[3], Deepali Ja
[1]Dept of Internal Medicine, All India Institute of Medical Sciences, N Institute of Medical Sciences, New Delhi, India. [3]Dept of Neurology, Al India. [4]Dept of Pathology, All India Institute of Medical Sciences, Nev India Institute of Medical Sciences, New Delhi, India.

RESEARCH ARTICLE

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

Urvashi B. Singh[1]*, Pooja Pandey[1], Girija Mehta[1], Anuj K. Bhatnagar[2], Anant Mohan[3], Vinay Goyal[4], Vineet Ahuja[5], Ranjani Ramachandran[6], Kuldeep S. Sachdeva[7], Jyotish C. Samantaray[1]

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

Shirly Suzana[1], Marilyn M Ninan[1], Mahasampath Gowri[2], K. Venkatesh[3], Priscilla Rupali[4], Joy S Michael[1]

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

MGIT

BacT/ALERT 3D

Evidence in childhood TB

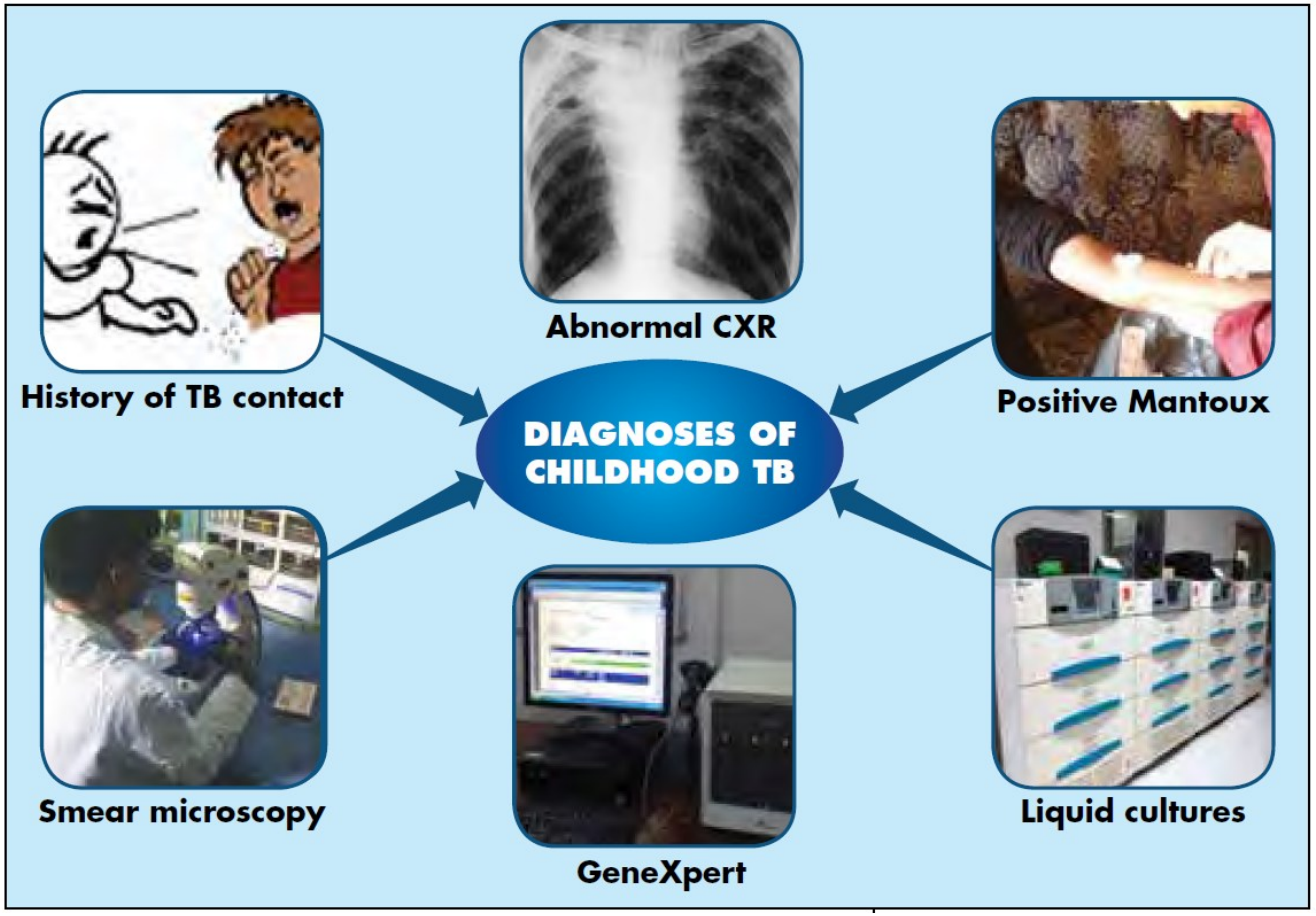
Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis in children: a systematic review and meta-analysis

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

How to diagnose childhood TB?



What about immune-based tests for active TB?

2.3 Serological tests:

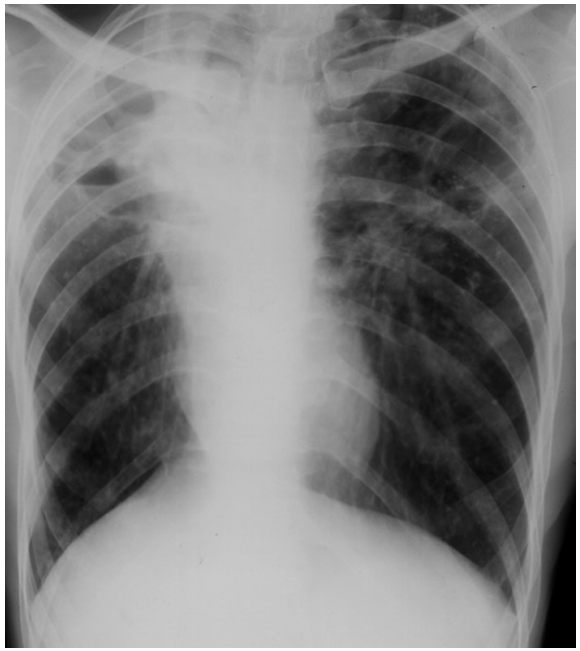
- Serological tests are banned and not recommended for diagnosing tuberculosis.

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.

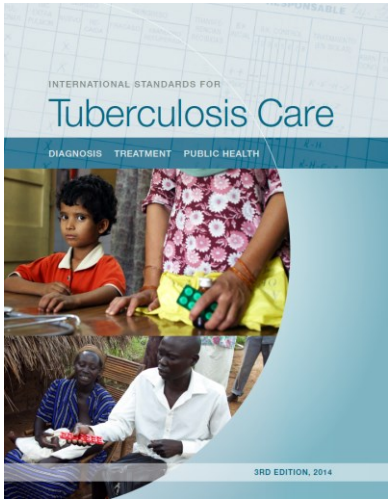
What about chest X-rays?

- 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)

Detecting Drug Resistance: towards universal DST



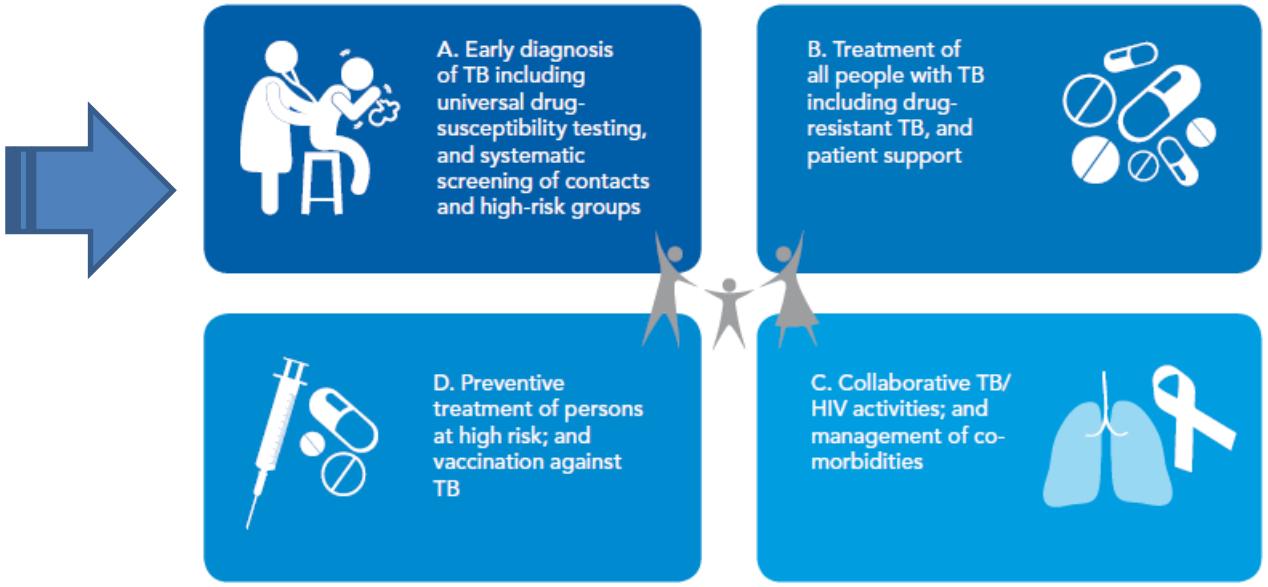
"DST should be performed at the start of therapy for all patients at a risk of drug resistance..." ISTC, 3rd Ed

INTRODUCING

THE END TB STRATEGY

World Health Organization

How pillar 1 works : Key components



http://www.who.int/tb/End_TB_brochure.pdf

In cities like Mumbai, ALL TB patients should get a DST!

MDR, XDR, TDR tuberculosis: ominous progression

Zarir F Udwadia

OPEN ACCESS Freely available online

PLOS | ONE

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

Petros Isaakidis[1]*, Mrinalini Das[1], Ajay M V Kumar[2], Christopher Peskett[1], Minni Khetarpal[3], Arun Bamne[4], Balkrishna Adsul[5], Mamta Manglani[6], Kuldeep Singh Sachdeva[7], Malik Parmar[8], Avinash Kanchar[9], B.B. Rewari[9], Alaka Deshpande[10], Camilla Rodrigues[11], Anjali Shetty[11], Lorraine Rebello[1], Peter Saranchuk[12]

PLOS | ONE

RESEARCH ARTICLE

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

Alpa Dalal[1], Akshay Pawaskar[2], Mrinalini Das[3], Ranjan Desai[4], Pralhad Prabhudesai[5], Prashant Chhajed[6], Sujeet Rajan[7], Deepesh Reddy[8], Sajit Babu[9], Jayalakshmi T. K.[10], Peter Saranchuk[3], Camilla Rodrigues[11], Petros Isaakidis[3]*

We should move towards universal DST for ALL TB patients in India

BMJ 2015;350:h1235 doi: 10.1136/bmj.h1235 (Published 23 March 2015)

VIEWS & REVIEWS

PERSONAL VIEW

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 monoresistance 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)

Steingart KR et al. Cochrane Review on Xpert MTB/RIF. 2014

Line Probe Assays

World Health Organization

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

Eur Respir J 2008; 32: 1–10
DOI: 10.1183/09031936.00061808

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

India: evidence on LPA

OPEN ACCESS Freely available online PLOS ONE

A Multi-Site Validation in India of the Line Probe Assay for the Rapid Diagnosis of Multi-Drug Resistant Tuberculosis Directly from Sputum Specimens

Neeraj Raizada[1]*, K. S. Sachdeva[2], D. S. Chauhan[3], Bharti Malhotra[4], Kishore Reddy[1], P. V. Dave[5], Yamuna Mundade[6], Pranav Patel[5], Ranjani Ramachandran[7], Ram Das[3], Rajesh Solanki[5], Douglas Fraser Wares[8], Suvanand Sahu[9], Rick O'Brien[10], C. N. Paramasivan[1], Puneet K. Dewan[7]

1 Foundation for Innovative New Diagnostics, New Delhi, India, 2 Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India, New Delhi, India, 3 National JALMA Institute for Leprosy and Other Mycobacterial Diseases, Agra, India, 4 Sawai Man Singh Medical College, Jaipur, India, 5 State TB Cell, Directorate of Health Services, Gujarat, India, 6 UNITAID, Geneva, Switzerland, 7 World Health Organization, New Delhi, India, 8 Global TB Programme, World Health Organization, Geneva, Switzerland, 9 Stop TB Partnership, Geneva, Switzerland, 10 Foundation for Innovative New Diagnostics (FIND), Geneva, Switzerland

Sensitivity and specificity for RIF : 96% and 99%

Sensitivity and specificity for INH : 72% and 97%

OPEN ACCESS Freely available online PLOS ONE

Impact of Introducing the Line Probe Assay on Time to Treatment Initiation of MDR-TB in Delhi, India

Neeta Singla[1]*, Srinath Satyanarayana[2], Kuldeep Singh Sachdeva[3], Rafael Van den Bergh[4], Tony Reid[4], Katherine Tayler-Smith[4], V. P. Myneedu[1], Engy Ali[4], Donald A. Enarson[5], Digamber Behera[6], Rohit Sarin[1]

1 National Institute of Tuberculosis & Respiratory Diseases, Delhi, India, 2 International Union against Tuberculosis & Lung Disease, South-East Asia Regional Office, New Delhi, India, 3 Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India, New Delhi, India, 4 Médecins Sans Frontières – Operational Centre Brussels, Operational Research Unit (LuxOR), Luxembourg, 5 International Union against Tuberculosis & Lung Disease, Paris, France, 6 Postgraduate Institute of Medical Education & Research, Chandigarh, India

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

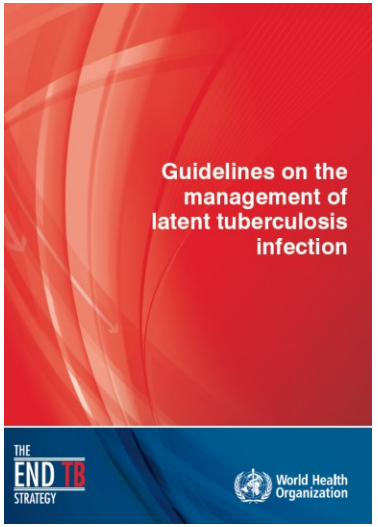
Algorithm for DST: very important to complete this!

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

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).*

http://www.who.int/tb/publications/ltbi_document_page/en/

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

Pai M et al. Clin Micro Rev 2014

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)

Never	Rarely	Frequently	NA
30	15	4	2
59%	**29%**	**8%**	**4%**

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)

Never	Rarely	Frequently	NA
14	10	1	1
54%	**38%**	**4%**	**4%**

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)

Never	Rarely	Frequently	NA
15	17	8	16
27%	**30%**	**14%**	**29%**

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)

Never	Rarely	Frequently	NA
8	8	0	5
38%	**38%**	**0%**	**24%**

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

Editorial

Pai & Rodrigues. *Lung India* 2015

Management of latent tuberculosis infection: An evidence-based approach

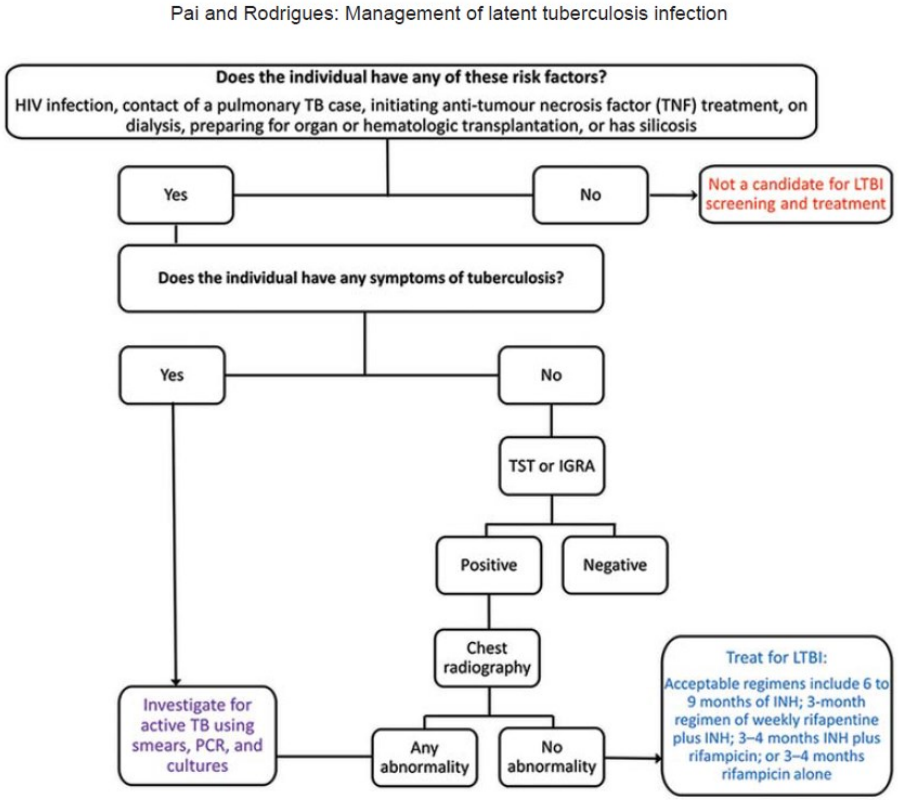


Figure 1: World Health Organization algorithm for latent tuberculosis infection management. Source: Adapted from WHO, Geneva[8]

What will the future look like?

www.letstalktb.org