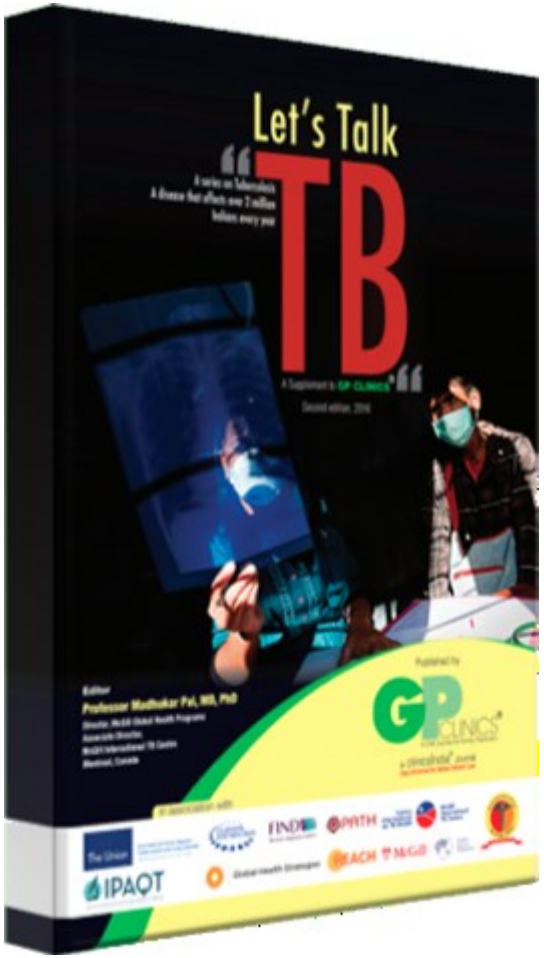


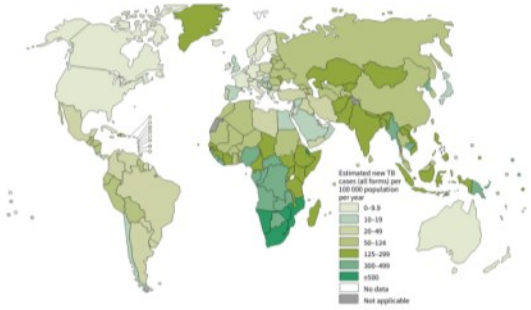
Let's Talk TB:

A Supplement to GP CLINICS

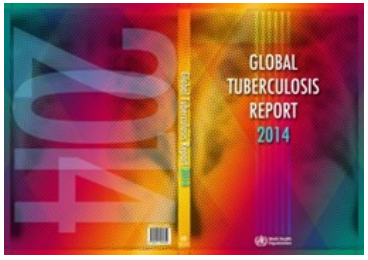
Chapter 11: Management of tuberculosis: common pitfalls to avoid

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

The Global Burden of TB - 2013



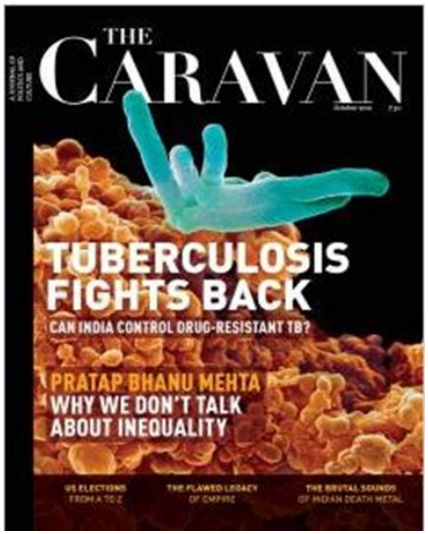
	Estimated number of cases	Estimated number of deaths
All forms of TB	**9** million 126 per 100,000 • 550,000 in children • 3.3 m in women	**1.5** million* • 80.000 in children • 510.000 in women
HIV-associated TB	**1.1** million (13%)	**360,000**
Multidrug-resistant TB	**480,000**	**210,000**



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 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.

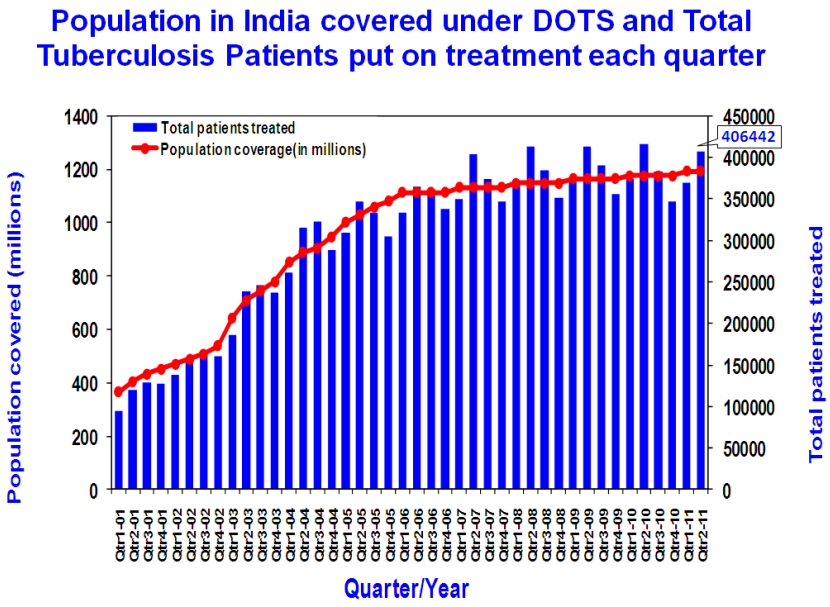
G.R. Khatri, who headed India's TB program more than a decade ago, called the epidemic of resistant TB in Mumbai "a recipe for disaster." The WHO should have known it was so bad and bears responsibility, he said. "What has the WHO been doing?"

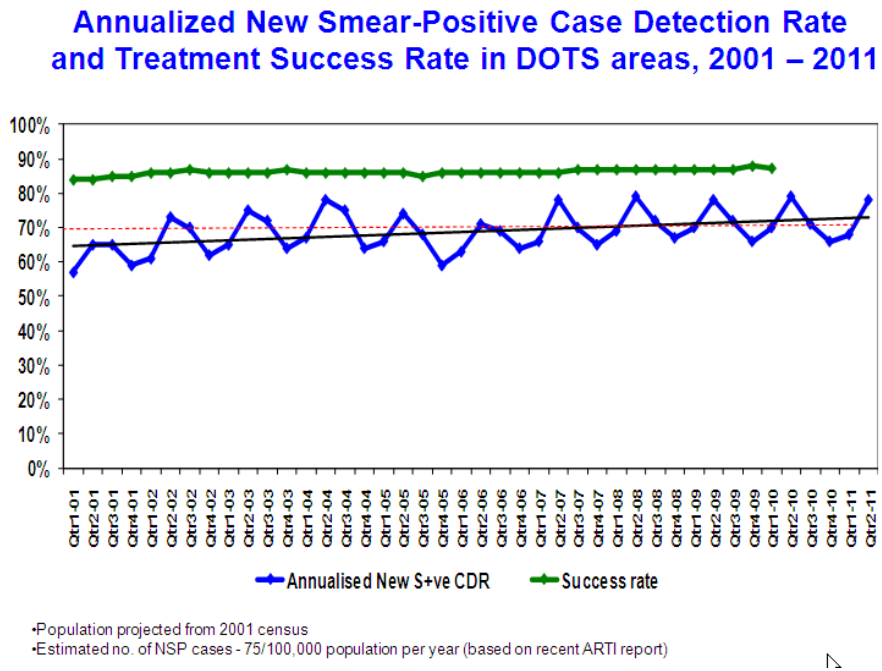
In pilot testing across India this year of a new diagnostic method, some 6.6% of untreated TB patients were drug-resistant—suggesting far higher rates than the 2% to 3% levels India and the WHO have cited for years. The test was a collaboration of international aid groups and India's government.

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

Indian TB Programme: success in scaling up DOTS and in meeting 70/85 targets

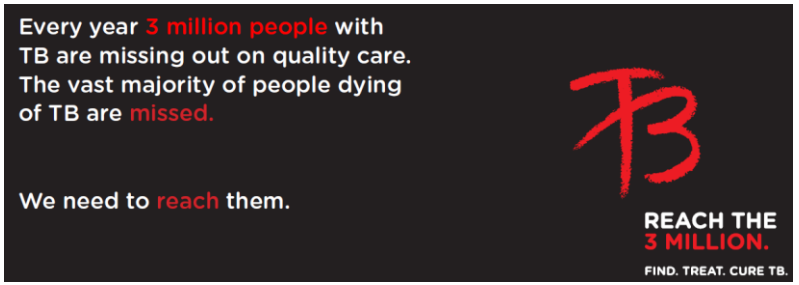




Source: RNTCP

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



MDR, XDR, TDR tuberculosis: ominous progression

Zarir F Udwadia

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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

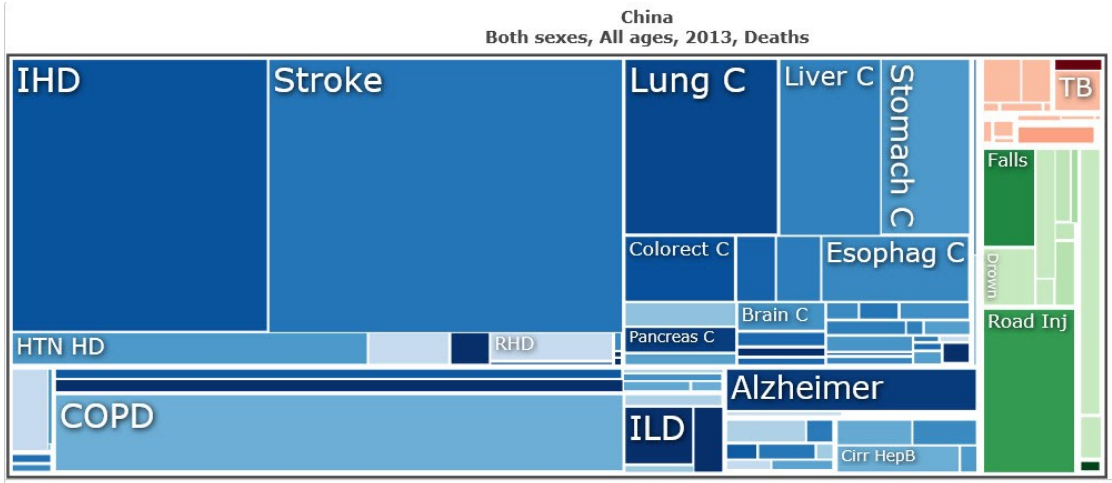
RESEARCH ARTICLE

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

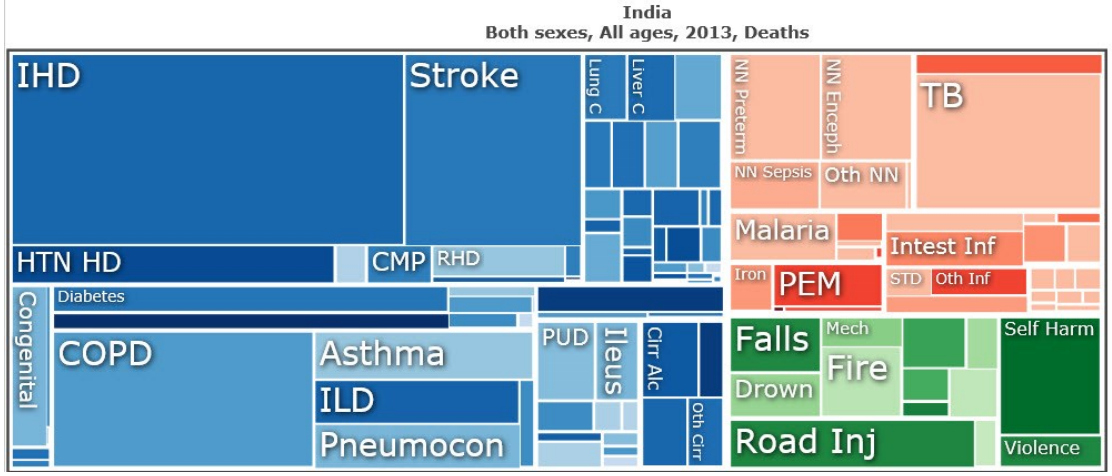
Alpa Dalal[1], Akshay Pawaskar[2], Mrinalini Das[3], Ranjan Desai[4], Pralhad Prabhudesai[5], Prashant Chhajed[6], Sujeet Rajan[7], Deepesh Reddy[8], Sajit Babu[9], Jayalakshmi T. K.[10], Peter Saranchuk[3], Camilla Rodrigues[11], Petros Isaakidis[3]*

TB is a major cause of mortality in India

CHINA



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

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

INT J TUBERC LUNG DIS 19(7):751–763

http://dx.doi.org/10.5588/ijtld.15.0186
E-published ahead of print 23 April 2015

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*

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

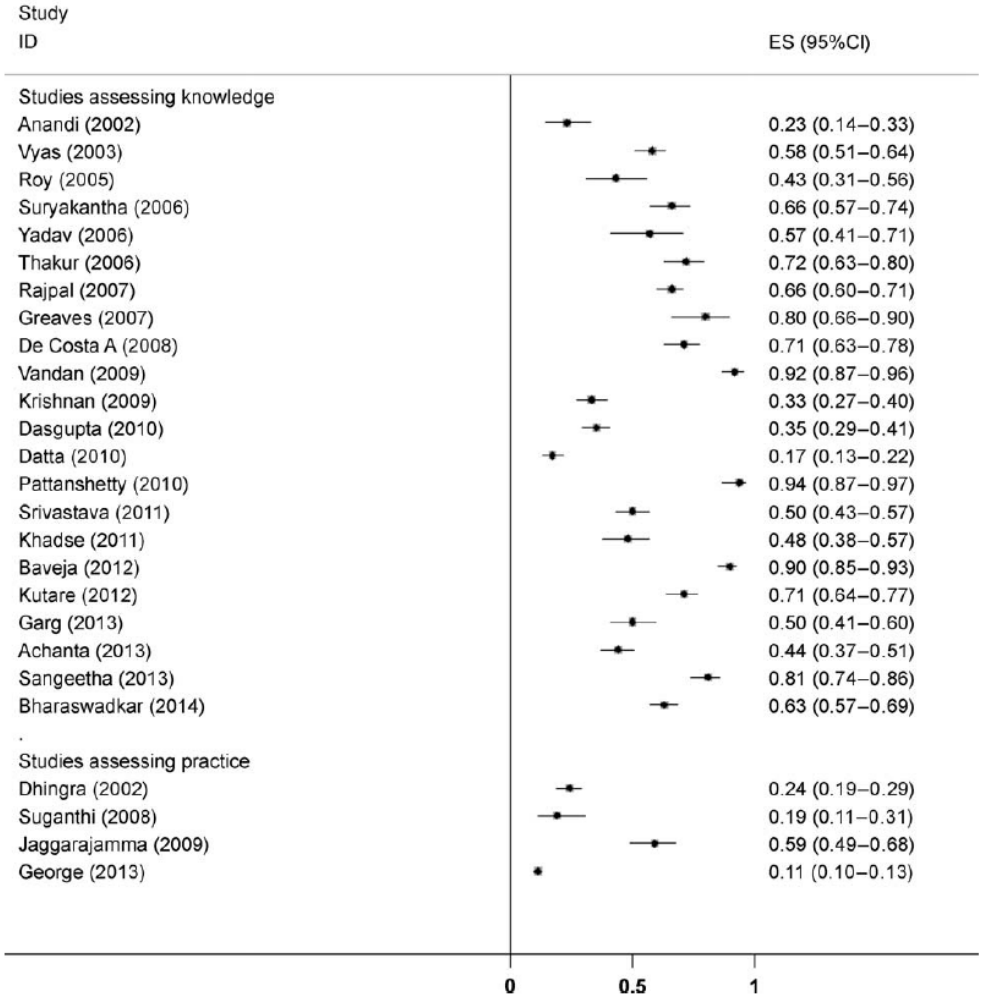


Figure 2 Forest plot of studies on ISTC Standard 2 (awareness/use of sputum smear for persons with presumptive pulmonary TB). ES = effect size (proportion meeting standard); CI = confidence interval; ISTC = International Standards of Tuberculosis Care; TB = tuberculosis.

Treatment

Only a third of the providers were aware of the correct regimen for TB

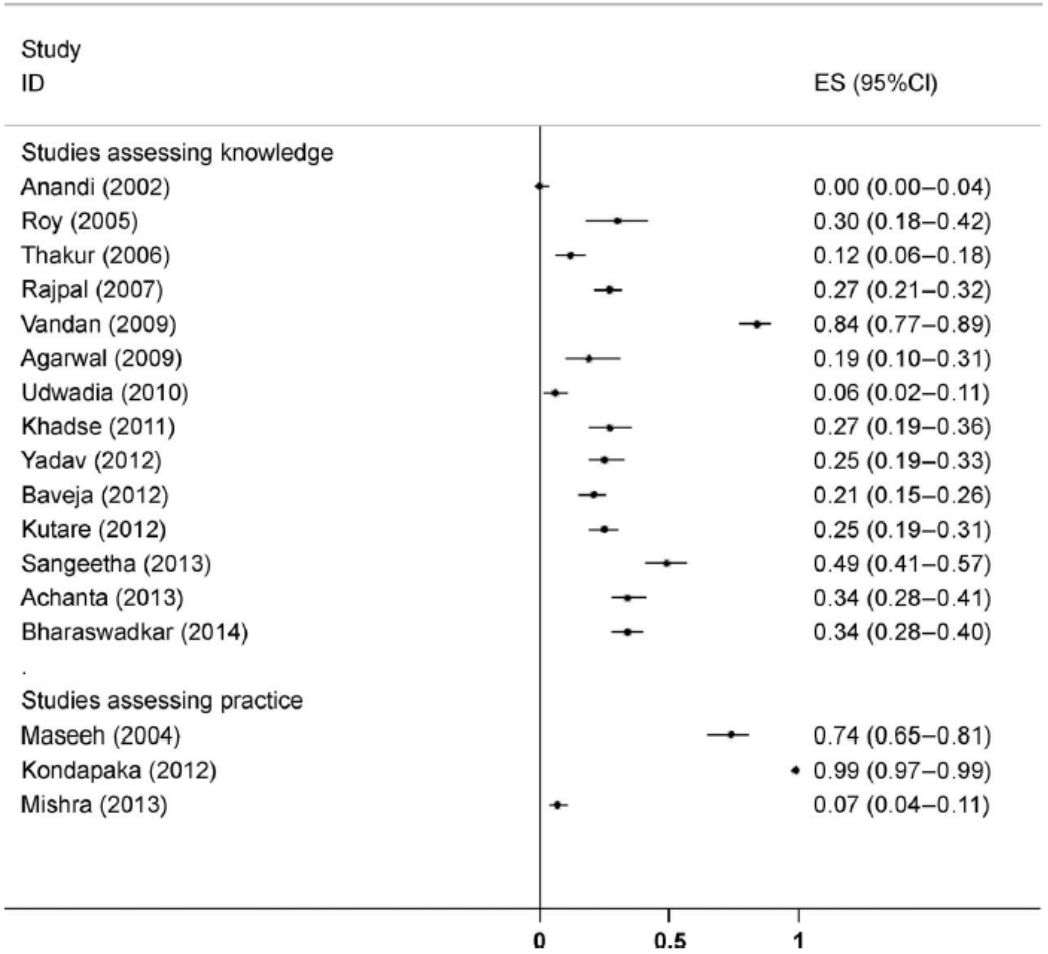


Figure 3 Forest plot of studies in India on ISTC Standard 8 (awareness/use of the correct treatment regimen for a new case of TB). ES = effect size (proportion meeting standard); CI = confidence interval; ISTC = International Standards of Tuberculosis Care; TB = tuberculosis.

TB treatment in the private sector in Mumbai

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PLoS one

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

Zarir F. Udwadia[1], Lancelot M. Pinto[1]*, Mukund W. Uplekar[2]

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. 106 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.

Citation: Udwadia ZF, Pinto LM, Uplekar MW (2010) Tuberculosis Management by Private Practitioners in Mumbai, India: Has Anything Changed in Two Decades? PLoS ONE 5(8): e12023. doi:10.1371/journal.pone.0012023

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 had 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. These 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 bear 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, e18964, 2011). This puts the private market at about the same volume as the public market, the study found. And the discovery that the total in drug sales exceeds the number of cases points to overuse and improper use of

Tuberculosis prognosis: The private drug market can treat two thirds of those who develop TB.

last as long as eight months—or even up to two years for multidrug-resistant tuberculosis (MDR-TB). But in this large and messy private market, no one is ensuring that patients take adequate drug regimens or complete their

operating private market as it is right now, you could spend all of this money developing new drugs, and you could lose them very quickly to resistance."

Wells maintains that the problem can be

1990: 100 practitioners had prescribed 80 different drug regimens

2010: 106 practitioners prescribed 63 different drug regimens

Uplekar M et al. Tubercle 1991

Importance of private sector in TB care

ORIGINAL ARTICLE

Role of Private Sector in Providing Tuberculosis Care: Evidence from a Population-based Survey in India

Indrajit Hazarika

Indian Institute of Public Health, and Public Health Foundation of India, New Delhi, India

ABSTRACT

Background: In India, a large segment of the population seeks health care services from individual or institutional private health-care providers for health care. We analyzed a nationally representative data to identify the role of private providers in delivering health care for patients with tuberculosis. **Materials and Methods:** The primary data source for the present analysis was the 60th round of the National Sample Survey. Distribution frequencies were used to analyze the distribution of key sociodemographic variables and multiple logistic regression was used to analyze the association between these variables and healthcare seeking behavior. **Results:** A sample of 2203 respondents who had received ambulatory care for tuberculosis, and 4568 respondents who had received inpatient treatment were analyzed. About half of the respondents had attended private facilities for TB care. Sociodemographic variables such as paediatric age group, females, higher level of education, and economic groups were associated with attendance at private sector. Dissatisfaction with services in government facilities was cited as the main reason for preferring private facilities. **Conclusions:** Private providers play an important role in providing health care services to a large proportion of patients with tuberculosis. There is a need for innovative measures to increase participation of the private sector in the national TB control program and to improve the quality of services in government facilities.

OPEN ACCESS Freely available online PLoS one

Size and Usage Patterns of Private TB Drug Markets in the High Burden Countries

William A. Wells[1]*, Colin Fan Ge[2], Nitin Patel[2], Teresa Oh[2], Elizabeth Gardiner[1], Michael E. Kimerling[3]

1 Global Alliance for TB Drug Development, New York, New York, United States of America, 2 IMS Health, New York, New York, United States of America, 3 Bill and Melinda Gates Foundation, Seattle, Washington, United States of America

Abstract

Background: Tuberculosis (TB) control is considered primarily a public health concern, and private sector TB treatment has attracted less attention. Thus, the size and characteristics of private sector TB drug sales remain largely unknown.

Methodology/Principal Findings: We used IMS Health data to analyze private TB drug consumption in 10 high burden countries (HBCs), after first mapping how well IMS data coverage overlapped with private markets. We defined private markets as any channels not used or influenced by national TB programs. Private markets in four countries – Pakistan, the Philippines, Indonesia and India – had the largest relative sales volumes; annually, they sold enough first line TB drugs to provide 65–117% of the respective countries' estimated annual incident cases with a standard 6–8 month regimen. First line drug volumes in five countries were predominantly fixed dose combinations (FDCs), but predominantly loose drugs in the other five. Across 10 countries, these drugs were available in 37 (loose drug) plus 74 (FDCs) distinct strengths. There were 54 distinct, significant first line manufacturers (range 2–11 per country), and most companies sold TB drugs in only a single study country. FDC markets were, however, more concentrated, with 4 companies capturing 69% of FDC volume across the ten countries. Among second line drugs, fluoroquinolones were widely available, with significant volumes used for TB in India, Pakistan and Indonesia. However, certain WHO-recommended drugs were not available and in general there were insufficient drug volumes to cover the majority of the expected burden of multidrug-resistant TB (MDR-TB).

Conclusions/Significance: Private TB drug markets in several HBCs are substantial, stable, and complicated. This calls for appropriate policy and market responses, including expansion of Public-Private Mix (PPM) programs, greater reach, flexibility and appeal of public programs, regulatory and quality enforcement, and expansion of public MDR-TB treatment programs.

Citation: Wells WA, Ge CF, Patel N, Oh T, Gardiner E, et al. (2011) Size and Usage Patterns of Private TB Drug Markets in the High Burden Countries. PLoS ONE 6(5): e18964. doi:10.1371/journal.pone.0018964

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From Where Are Tuberculosis Patients Accessing Treatment in India? Results from a Cross-Sectional Community Based Survey of 30 Districts

Srinath Satyanarayana[1,2]*, Sreenivas Achutan Nair[1], Sarabjit Singh Chadha[1], Roopa Shivashankar[3], Geetanjali Sharma[1], Subhash Yadav[1], Subrat Mohanty[1], Vishnuvardhan Kamineni[1], Nevin Charles Wilson[1], Anthony David Harries[2,4], Puneet Kumar Dewan[5]

1 International Union against Tuberculosis and Lung Disease (The Union), South-East Asia Regional Office, New Delhi, India, 2 Center for Operations Research, The Union, Paris, France, 3 Center for Chronic Disease Control (CCDC), New Delhi, India, 4 London School of Hygiene and Tropical Medicine, London, United Kingdom, 5 World Health Organization, India Country Office, New Delhi, India

Abstract

Background: Tuberculosis (TB) notification in India by the Revised National TB Control Programme (RNTCP) provides information on TB patients registered for treatment from the programme. There is limited information about the proportion of patients treated for TB outside RNTCP and where these patients access their treatment.

Objectives: To estimate the proportion of patients accessing TB treatment outside the RNTCP and to identify their basic demographic characteristics.

Methods: A cross sectional community-based survey in 30 districts. Patients were identified through a door-to-door survey and interviewed using a semi-structured questionnaire.

Results: Of the estimated 75,000 households enumerated, 73,249 households (97.6%) were visited. Of the 371,174 household members, 761 TB patients were identified (~205 cases per 100,000 populations). Data were collected from 609 (80%) TB patients of which 331 [54% (95% CI: 42–66%)] were determined to be taking treatment 'under DOTS/RNTCP'. The remaining 278 [46% (95% CI: 34–57%)] were on treatment from 'outside DOTS/RNTCP' sources and hence were unlikely to be part of the TB notification system. Patients who were accessing treatment from 'outside DOTS/RNTCP' were more likely to be patients from rural areas [adjusted Odds Ratio (aOR) 2.5, 95% CI (1.2–5.3)] and whose TB was diagnosed in a non-government health facility (aOR 14.0, 95% CI 7.9–24.9).

Conclusions: This community-based survey found that nearly half of self-reported TB patients were missed by TB notification system in these districts. The study highlights the need for 1) Reviewing and revising the scope of the TB notification system, 2) Strengthening and monitoring health care delivery systems with periodic assessment of the reach and utilisation of the RNTCP services especially among rural communities, 3) Advocacy, communication and social mobilisation activities focused at rural communities with low household incomes and 4) Inclusive involvement of all health-care providers, especially providers of poor rural communities.

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

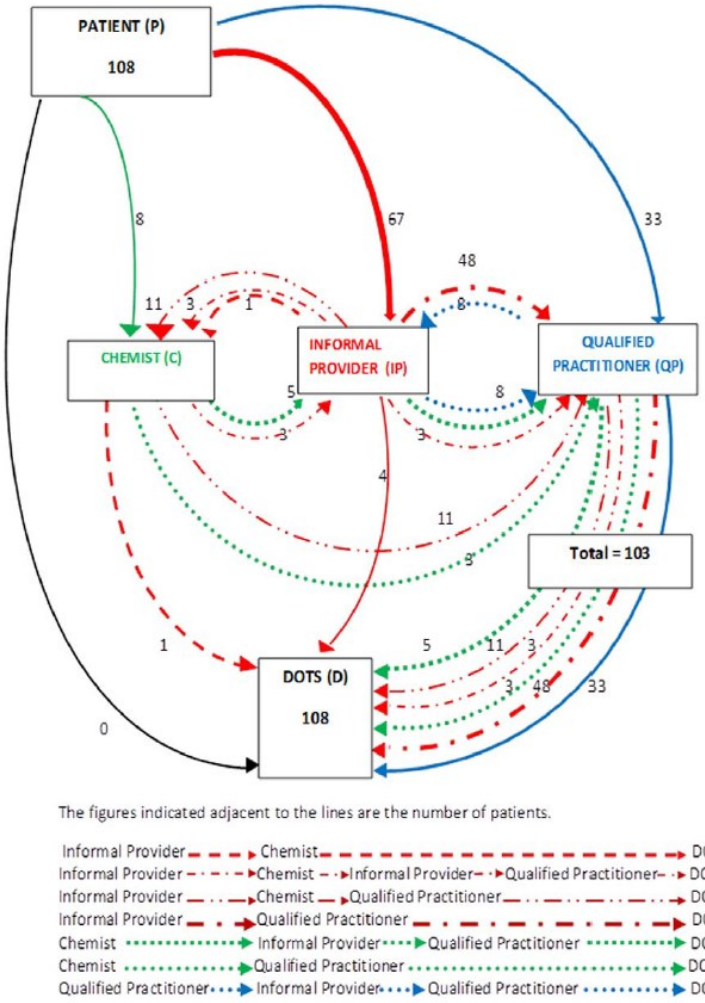

Figure 1. Pathways undertaken by the patients to reach the RNTCP (DOTS) Facilities, Delhi, India.
doi:10.1371/journal.pone.0042458.g001

OPEN ACCESS Freely available online
PLoS one

How Did the TB Patients Reach DOTS Services in Delhi? A Study of Patient Treatment Seeking Behavior

Sunil K. Kapoor[1]*, A. Venkat Raman[2], Kuldeep Singh Sachdeva[3], Srinath Satyanarayana[4]*

1 Harrow Medical Centre, Noida, India, **2** Faculty of Management Studies, University of Delhi, New Delhi, India, **3** Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare, Govt. of India, New Delhi, India, **4** International Union Against Tuberculosis and Lung Disease, South-East Asia Regional Office, New Delhi, India

Even within the private sector, TB patients often seek care from informal providers and pharmacists

Kapoor et al. PLoS ONE 2012

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.

Methods We did a pilot, cross-sectional validation study of a convenience sample of consenting private health-care 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 health-care 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 data 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 Feb 2, and March 28, 2014, we recruited and trained 17 standardised patients who had 250 interactions with 100 health-care 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 (r=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=0·0166). Of the 69 providers who completed the vignette, knowledge in the vignettes 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 0·02–0·11); 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.

Lancet Infect Dis 2015

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See Online/Comment
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http://www.thelancet.com/pdfs/journals/laninf/PIIS1473-3099(15)00077-8.pdf

Das J et al. Lancet Infect Dis 2015

Know-do gap

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

In practice, 10% ordered CXR or sputum test

Das J et al. Lancet Infect Dis 2015

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/

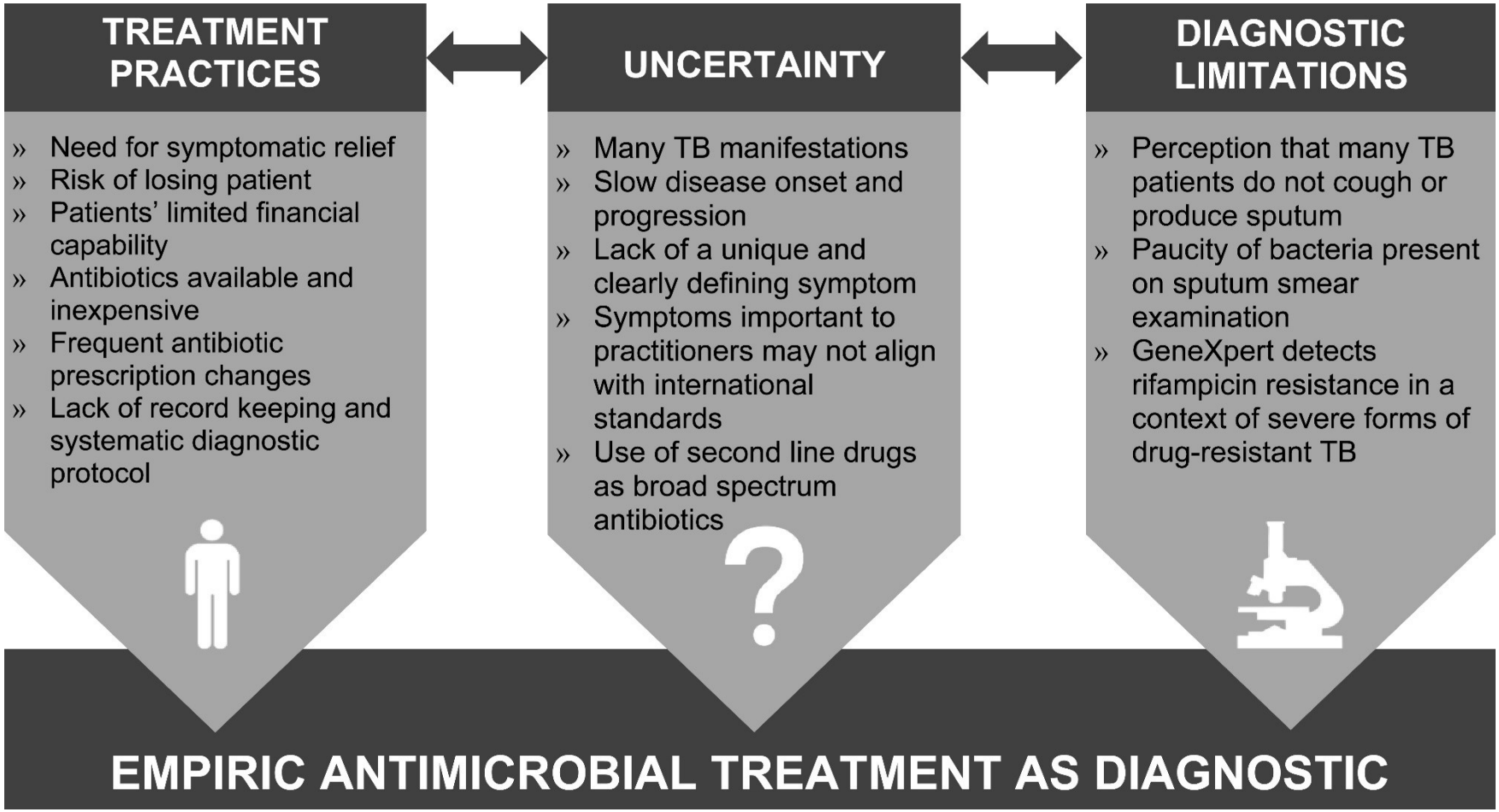
Pitfall 1: Not recognizing and suspecting TB

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

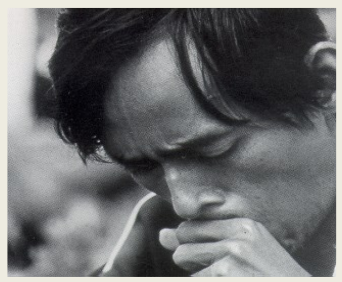
Multiple rounds of broad-spectrum antibiotics are tried, but tests for TB are rarely ordered.

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.

Ethnographic research

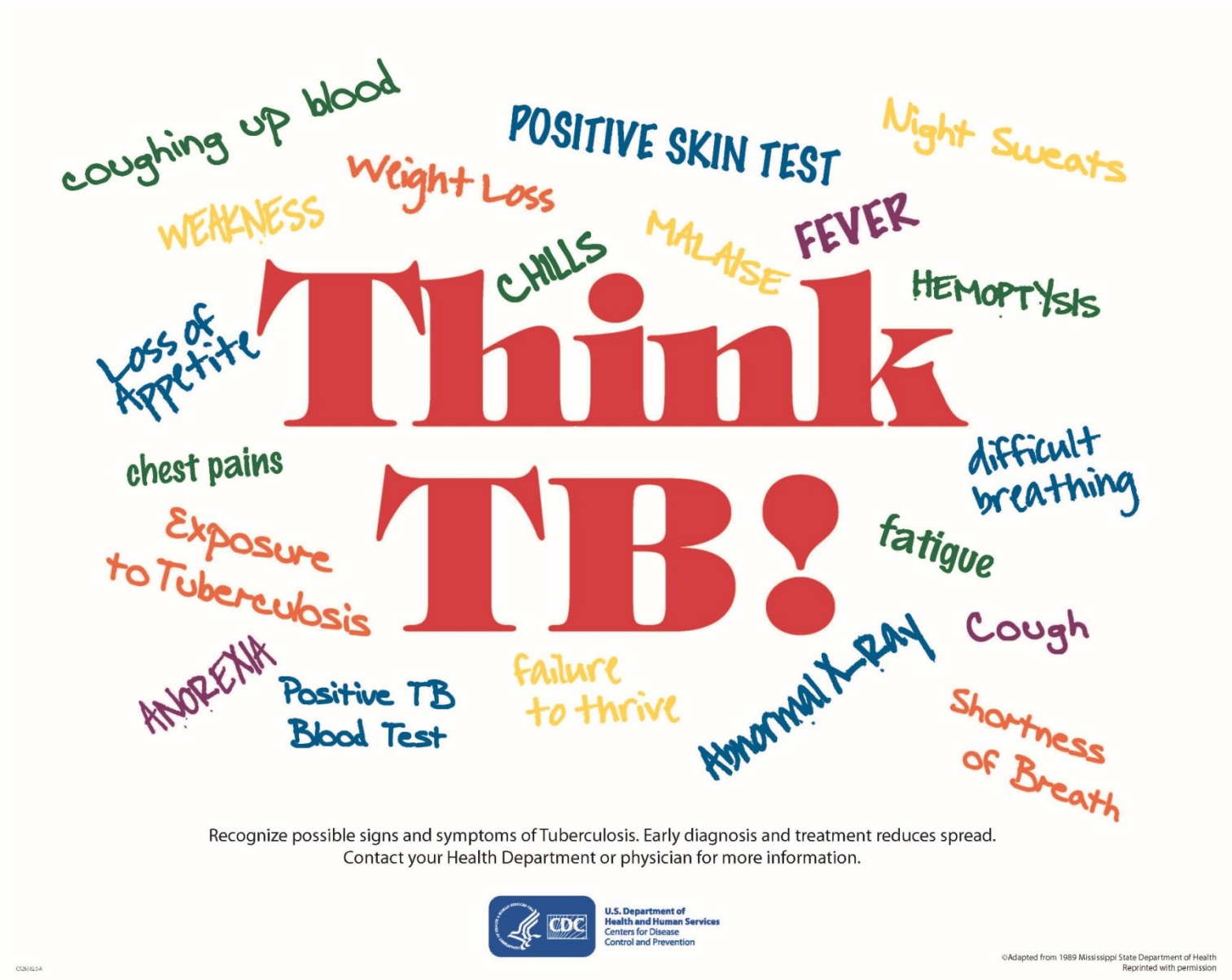


McDowell & Pai. *Int J Tuberc Lung Dis* (In Press)



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


coughing up blood
POSITIVE SKIN TEST
Night Sweats
Weight Loss
WEAKNESS
MALAISE
FEVER
CHILLS
HEMOPTYSIS
Loss of Appetite
Think
TB!
chest pains
difficult breathing
Exposure to Tuberculosis
fatigue
Cough
ANOREXIA
Positive TB Blood Test
failure to thrive
Abnormal X-RAY
Shortness of Breath
Recognize possible signs and symptoms of Tuberculosis. Early diagnosis and treatment reduces spread.
Contact your Health Department or physician for more information.
CDC
U.S. Department of Health and Human Services
Centers for Disease Control and Prevention
©Adapted from 1989 Mississippi State Department of Health
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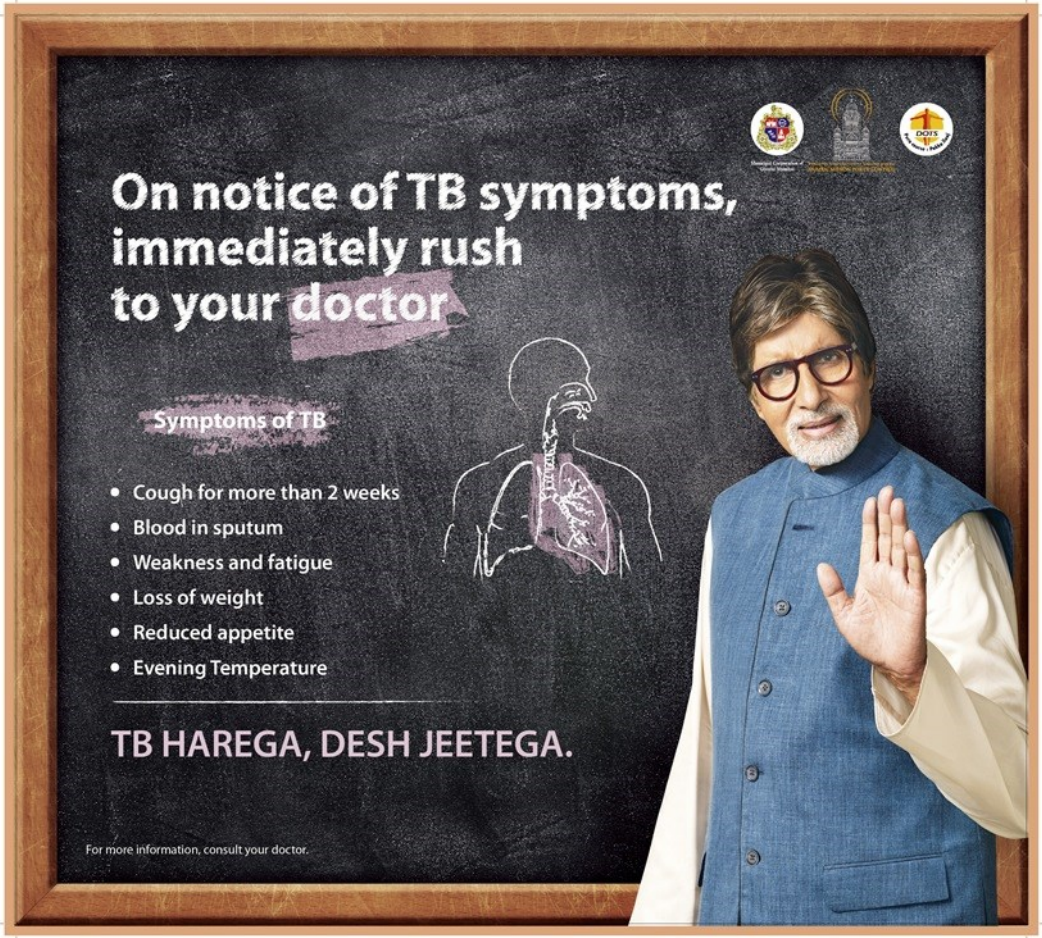

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Pitfall 2: Inadequate diagnostic work-up

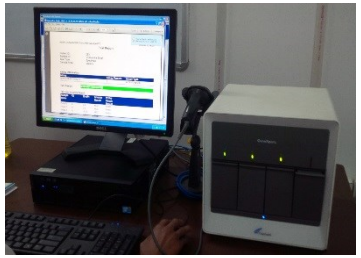
When doctors in India think of TB, they often order non-specific tests such as TC, DC, ESR and CXR.

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]

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

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.

PLOS | ONE

RESEARCH ARTICLE

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

Kristen M. Little[1]*, Madhukar Pai[2], David W. Dowdy[1]

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 over-treatment 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.

Editorial

Pai & Rodrigues. *Lung India* 2015

Management of latent tuberculosis infection: An evidence-based approach

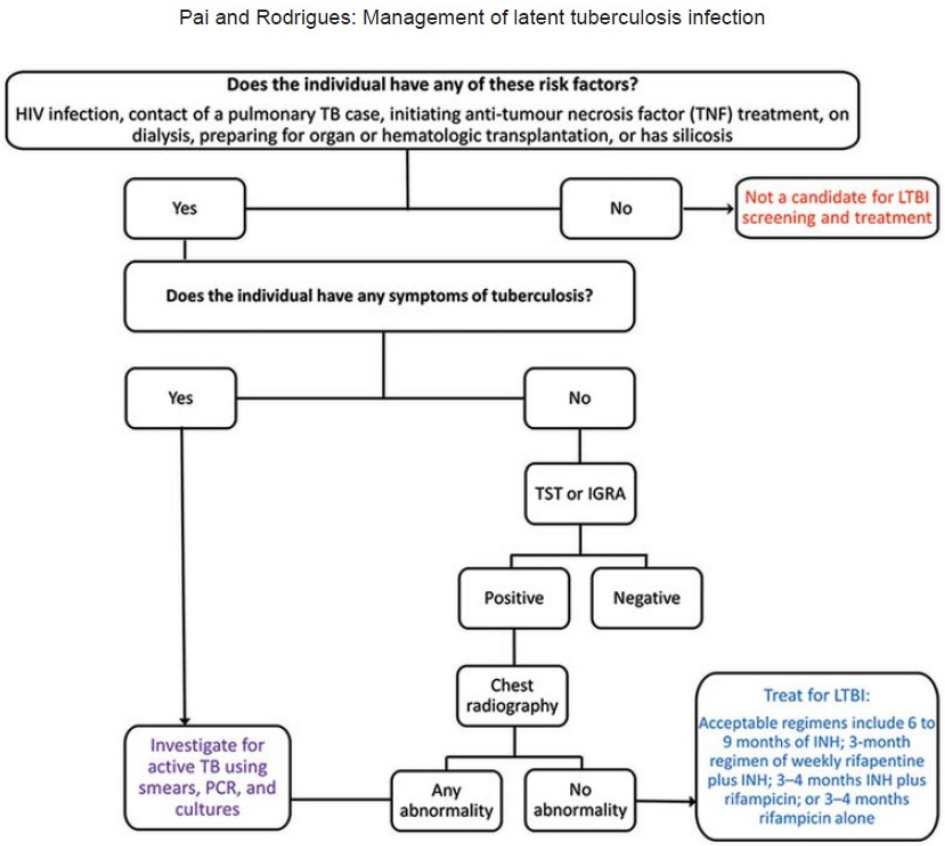


Figure 1: World Health Organization algorithm for latent tuberculosis infection management. Source: Adapted from WHO, Geneva[8]

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.

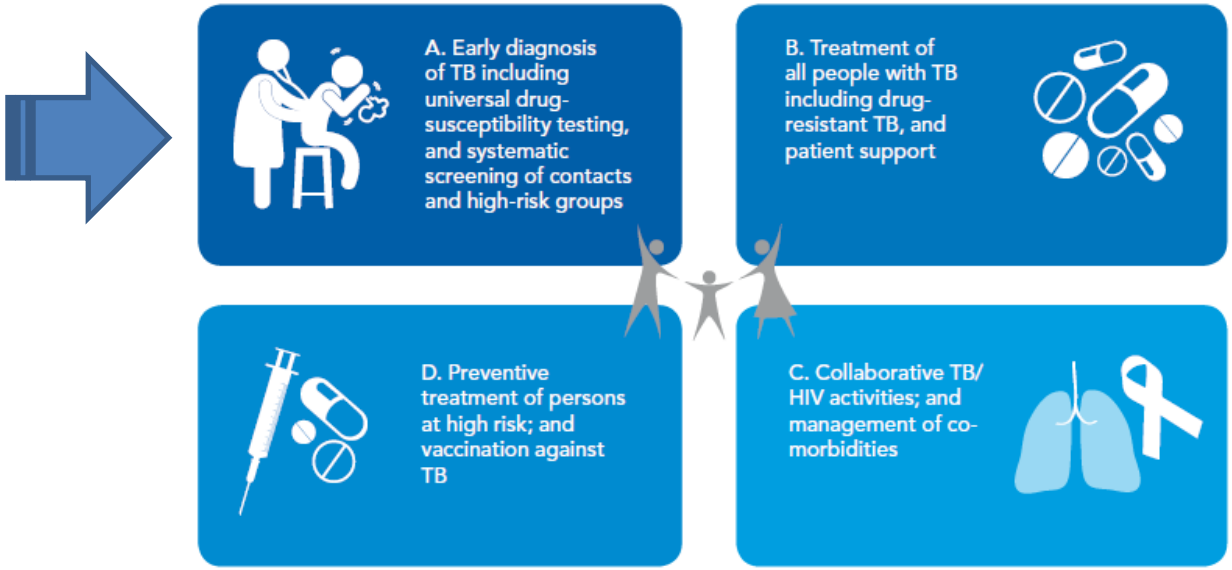
If patients have any risk factors for drug-resistance, or live in a high MDR-TB prevalence area (e.g. Mumbai city), or do not respond to standard drug therapy, they must be investigated for MDR-TB using GeneXpert or line probe assays, and cultures.

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 quickest route to universal DST?

Answer: Rapid molecular TB testing, followed by culture confirmation

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

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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

CrossMark
click for updates

"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

OPEN ACCESS Freely available online PLOS ONE

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

Neeraj Raizada[1]*, K. S. Sachdeva[2], Achuthan Sreenivas[3], Bhavin Vadera[1], R. S. Gupta[2], Malik Parmar[3], Shubhangi Kulsange[1], Ameet Babre[1], Rahul Thakur[1], Christen Gray[4], Ranjani Ramachandran[3], Umesh Alavadi[1], Mayank Ghedia[3], Balasangameshwara Vollepore[1], Puneet Dewan[3], Catharina Boehme[4], C. N. Paramsivan[1]

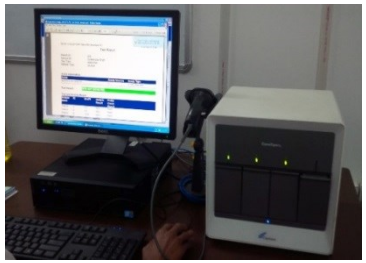
1 Foundation for Innovative New Diagnostics, New Delhi, India, 2 Central TB Division, Government of India, New Delhi, India, 3 World Health Organization, India Country Office, New Delhi, India, 4 Foundation for Innovative New Diagnostics, Geneva, Switzerland

OPEN ACCESS Freely available online PLOS ONE

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 Raizada[1]*, Kuldeep Singh Sachdeva[2], Sreenivas Achuthan Nair[3], Shubhangi Kulsange[1], Radhey Shayam Gupta[2], Rahul Thakur[1], Malik Parmar[3], Christen Gray[4], Ranjani Ramachandran[3], Bhavin Vadera[1], Shobha Ekka[1], Shikha Dhawan[2], Ameet Babre[1], Mayank Ghedia[3], Umesh Alavadi[1], Puneet Dewan[3], Mini Khetrapal[5], Ashwini Khanna[6], Catharina Boehme[4], Chinnambedu Nainarappan Paramsivan[1]

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



PLOS ONE

RESEARCH ARTICLE

Has introduction of rapid drug susceptibility testing at diagnosis impacted treatment outcomes among previously treated tuberculosis patients in Gujarat, India?

Paresh Dave[1], Bhavin Vadera[2,7]*, Ajay M V Kumar[3], Palanivel Chinnakali[6], Bhavesh Modi[4], Rajesh Solanki[5], Pranav Patel[1], Prakash Patel[1], Kirit Pujara[1], Pankaj Nimavat[1], Amar Shah[2], Sandeep Bharaswadkar[2], Kiran Rade[2], Malik Parmar[2], Sreenivas Achuthan Nair[2]

INT J TUBERC LUNG DIS 18(8):958–960

http://dx.doi.org/10.5588/ijtld.13.0328

SHORT COMMUNICATION

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

V. P. Myneedu, D. Behera, A. K. Verma, M. Bhalla, N. Singh, J. Arora, R. Singhal, M. Mathur, P. Lal, R. Sarin

Department of Microbiology, Lala Ram Sarup Institute of Tuberculosis and Respiratory Diseases, New Delhi, India

SUMMARY

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

PLOS ONE

RESEARCH ARTICLE

Catching the Missing Million: Experiences in Enhancing TB & DR-TB Detection by Providing Upfront Xpert MTB/RIF Testing for People Living with HIV in India

Neeraj Raizada[1]*, Kuldeep Singh Sachdeva[2], Achuthan Sreenivas[3], Shubhangi Kulsange[1], Radhey Shyam Gupta[2], Rahul Thakur[1], Puneet Dewan[3], Catharina Boehme[4], Chinnambedu Nainarappan Paramsivan[1]

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


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

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.

Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data

Thomas P Van Boeckel, Sumanth Gandra, Ashvin Ashok, Quentin Caudron, Bryan T Grenfell, Simon A Levin, Ramanan Laxminarayan

Lancet Infect Dis 2014; 14: 742–50
Published Online July 10, 2014 http://dx.doi.org/10.1016/S1473-3099(14)70780-7
See Comment page 667

Department of Ecology and Evolutionary Biology, Princeton University, Princeton, NJ, USA (T P Van Boeckel PhD, Q Caudron PhD, Prof B T Grenfell PhD, Prof S A Levin PhD); **Center for Disease Dynamics, Economics, and Policy, Washington, DC, USA** (Prof R Laxminarayan, S Gandra MD, A Ashok MPP); **Princeton Environmental Institute, Princeton, NJ, USA** (Prof R Laxminarayan, Prof S A Levin, Prof B T Grenfell); **Public Health Foundation of India, New Delhi, India**

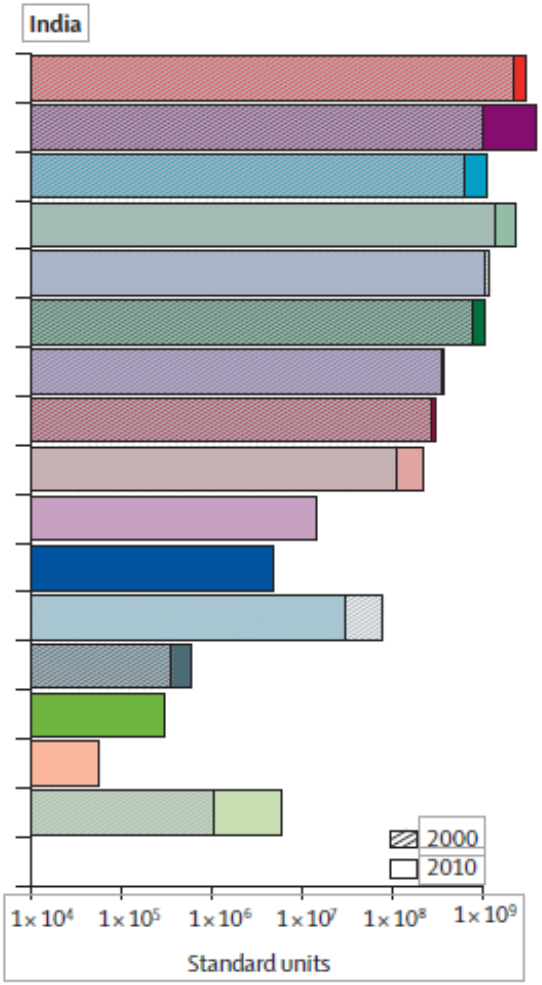
Summary

Background Antibiotic drug consumption is a major driver of antibiotic resistance. Variations in antibiotic resistance across countries are attributable, in part, to different volumes and patterns for antibiotic consumption. We aimed to assess variations in consumption to assist monitoring of the rise of resistance and development of rational-use policies and to provide a baseline for future assessment.

Methods With use of sales data for retail and hospital pharmacies from the IMS Health MIDAS database, we reviewed trends for consumption of standard units of antibiotics between 2000 and 2010 for 71 countries. We used compound annual growth rates to assess temporal differences in consumption for each country and Fourier series and regression methods to assess seasonal differences in consumption in 63 of the countries.

Findings Between 2000 and 2010, consumption of antibiotic drugs increased by 36% (from 54 083 964 813 standard units to 73 620 748 816 standard units). Brazil, Russia, India, China, and South Africa accounted for 76% of this increase. In most countries, antibiotic consumption varied significantly with season. There was increased consumption of carbapenems (45%) and polymixins (13%), two last-resort classes of antibiotic drugs.

Interpretation The rise of antibiotic consumption and the increase in use of last-resort antibiotic drugs raises serious concerns for public health. Appropriate use of antibiotics in developing countries should be encouraged. However, to prevent a striking rise in resistance in low-income and middle-income countries with large populations and to preserve antibiotic efficacy worldwide, programmes that promote rational use through coordinated efforts by the international community should be a priority.



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)

International Journal of Infectious Diseases 15 (2011) e211–e216

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

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,*]

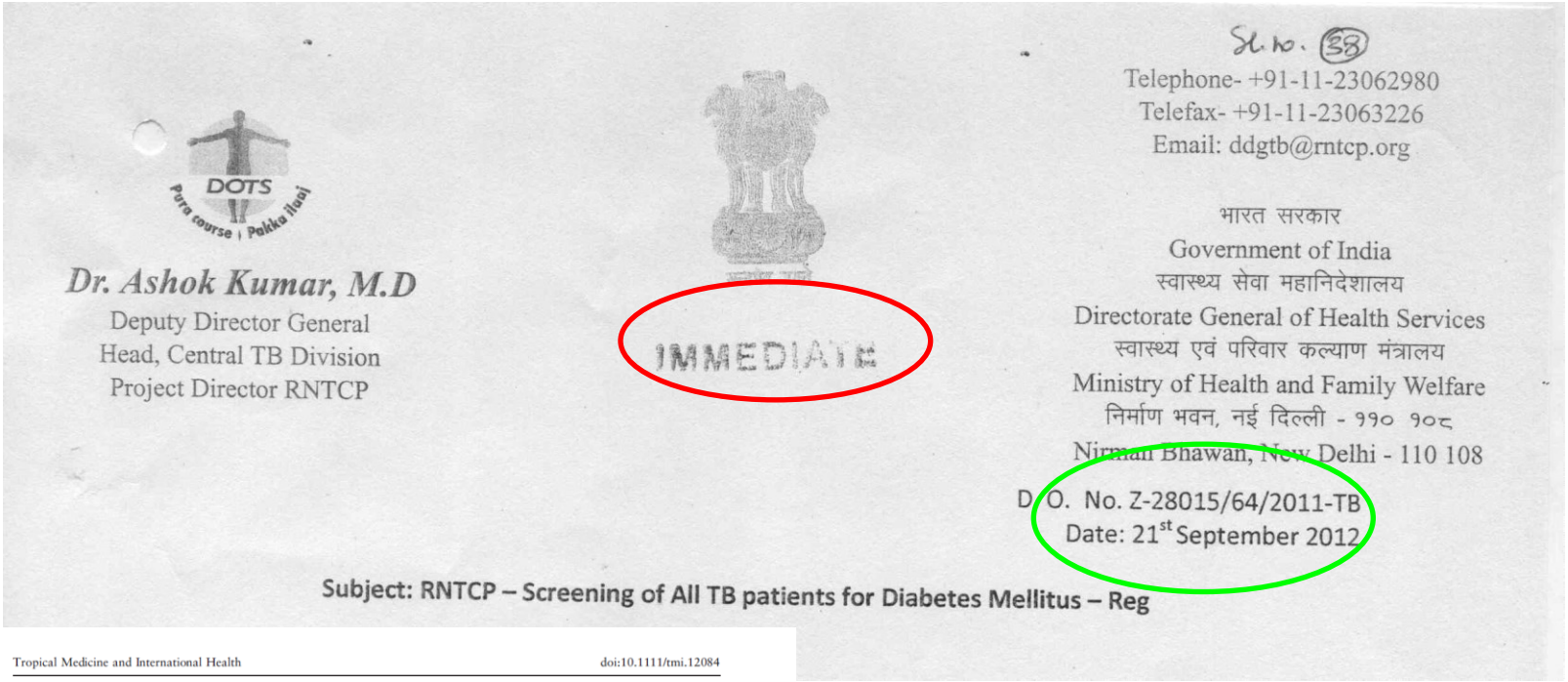
[a] *Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung City, Taiwan*
[b] *Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung City, Taiwan*
[c] *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.



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Ministry of Health and Family Welfare
निर्माण भवन, नई दिल्ली - ११० १०८
Nirman Bhawan, New Delhi - 110 108

DOTS
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Dr. Ashok Kumar, M.D
Deputy Director General
Head, Central TB Division
Project Director RNTCP

IMMEDIATE

D.O. No. Z-28015/64/2011-TB
Date: 21st September 2012

Subject: RNTCP – Screening of All TB patients for Diabetes Mellitus – Reg

Tropical Medicine and International Health doi:10.1111/tmi.12084
VOLUME 18 NO 5 PP 636–645 MAY 2013

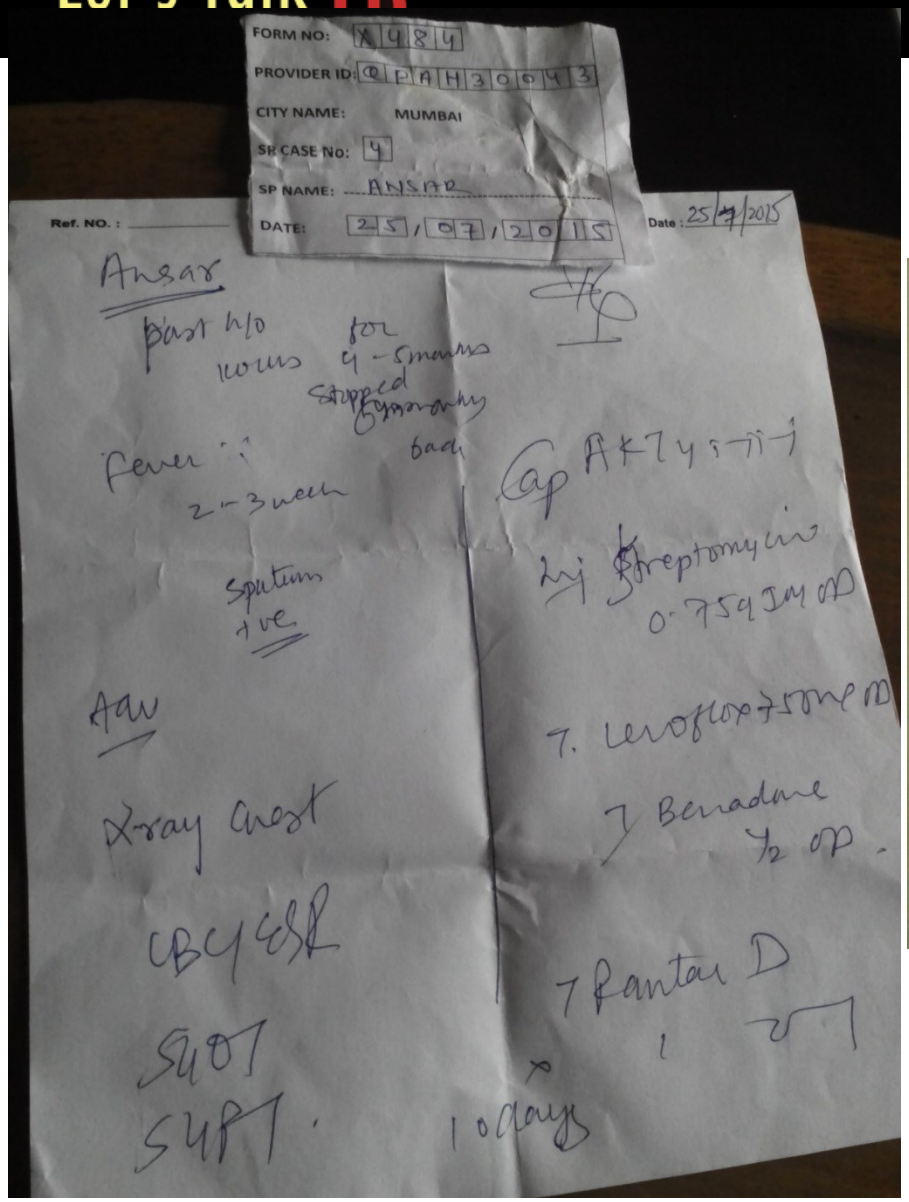
Screening of patients with tuberculosis for diabetes mellitus in India

India Tuberculosis-Diabetes Study Group*

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

Let's Talk TR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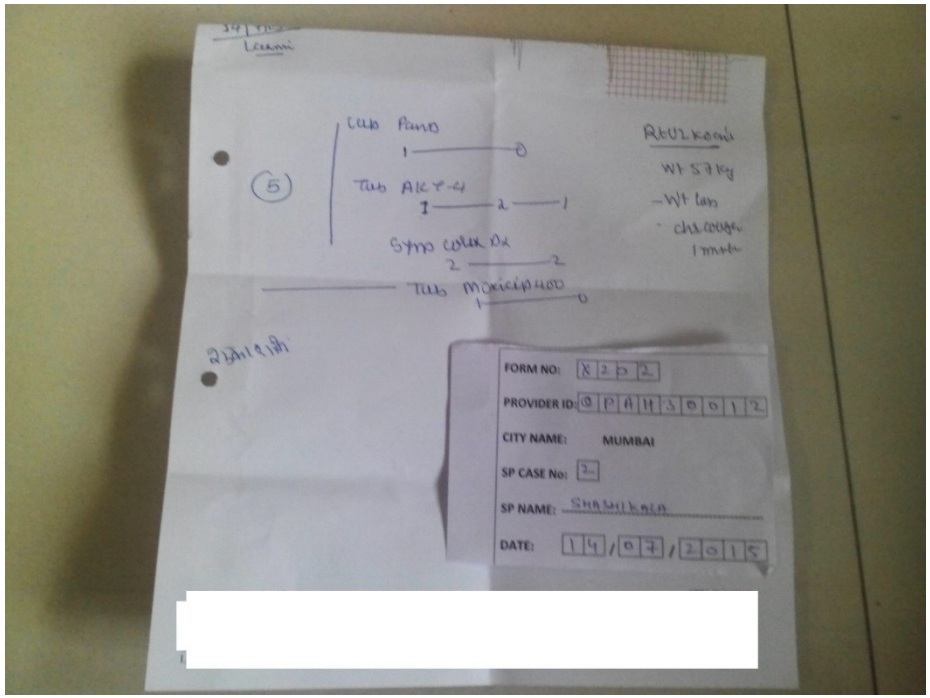
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Pitfall 8: Not ensuring treatment adherence

- 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.

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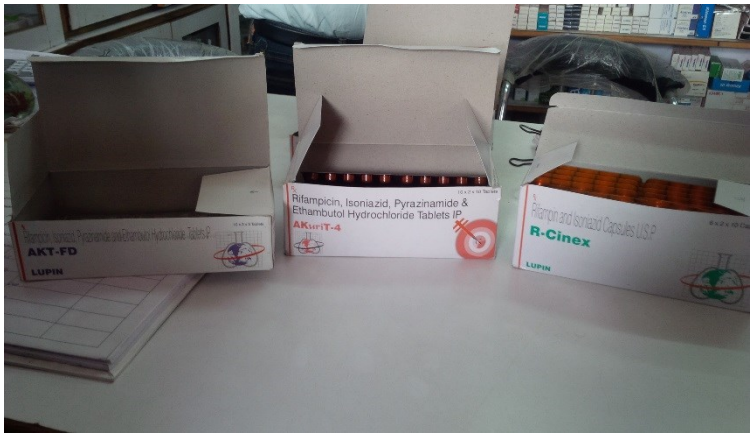
Simple tools we can use today



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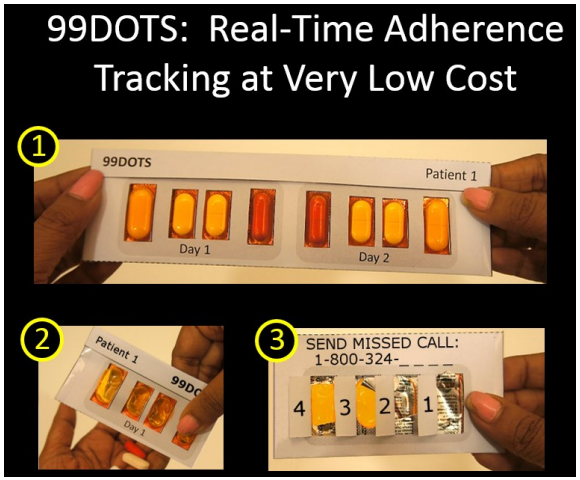

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HRZE for 2 months
HR for 4 months
Fixed dose combination
Daily therapy
With adherence support

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.

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.

PLOS ONE

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

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PLOS ONE

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

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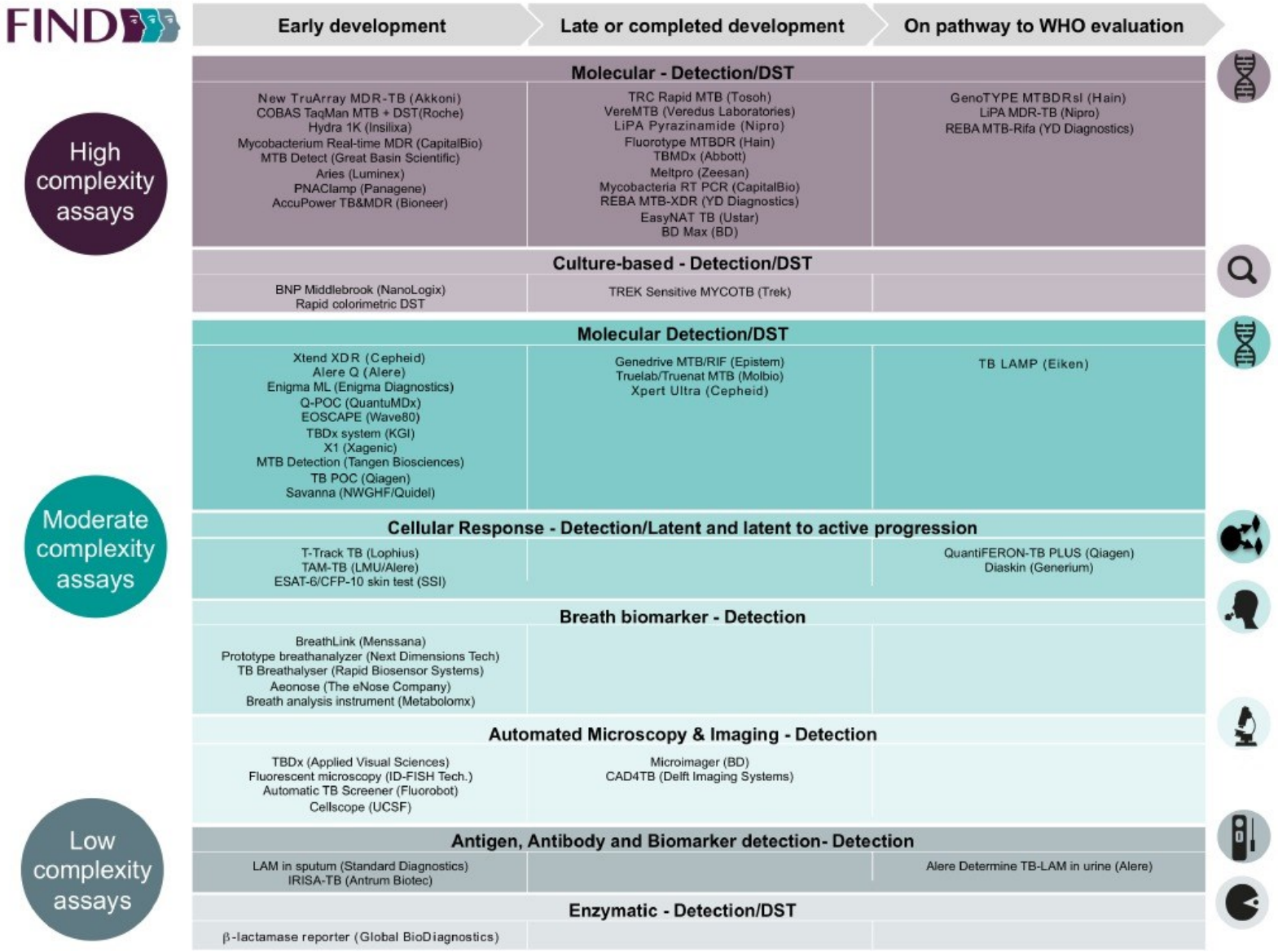
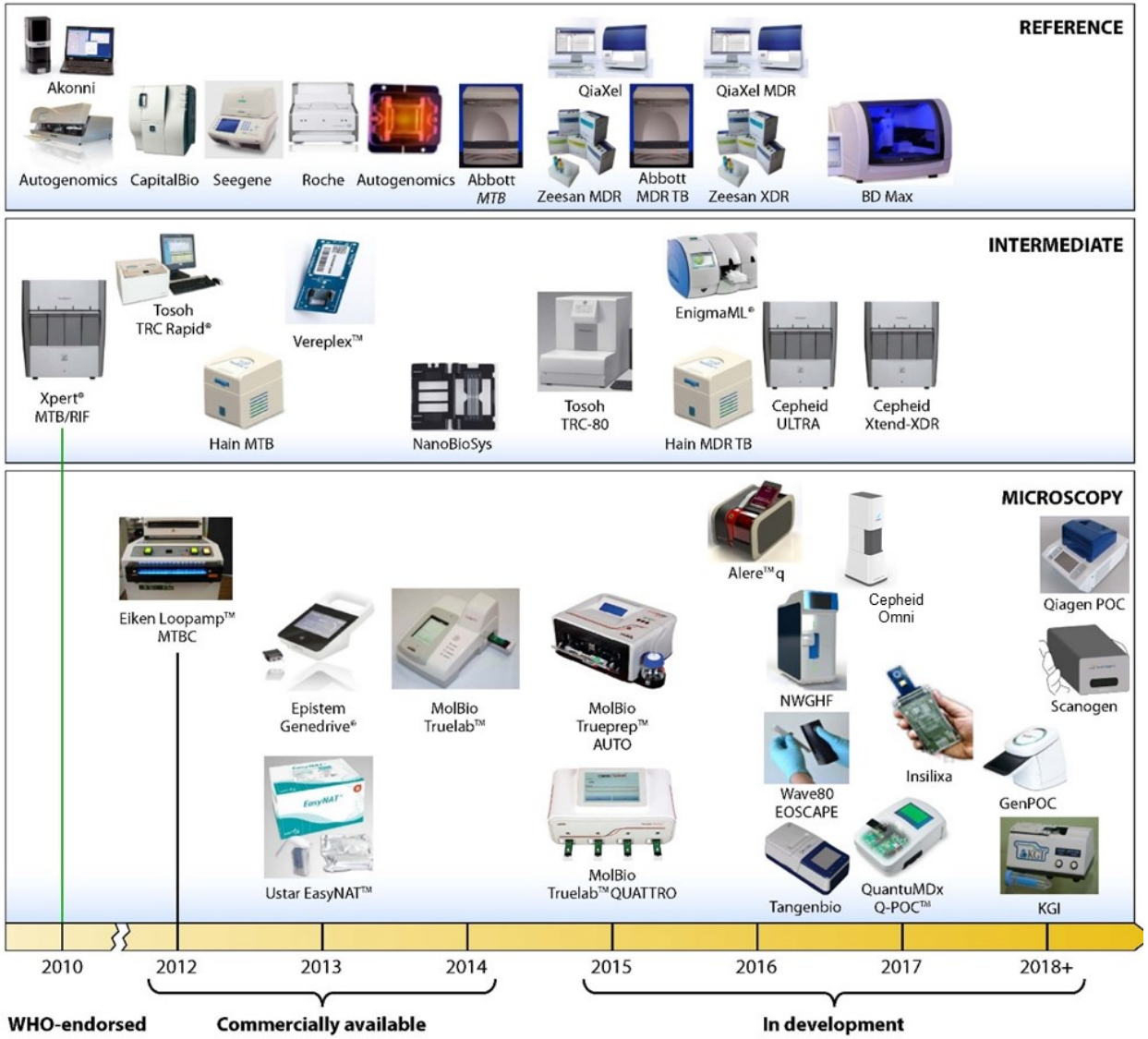
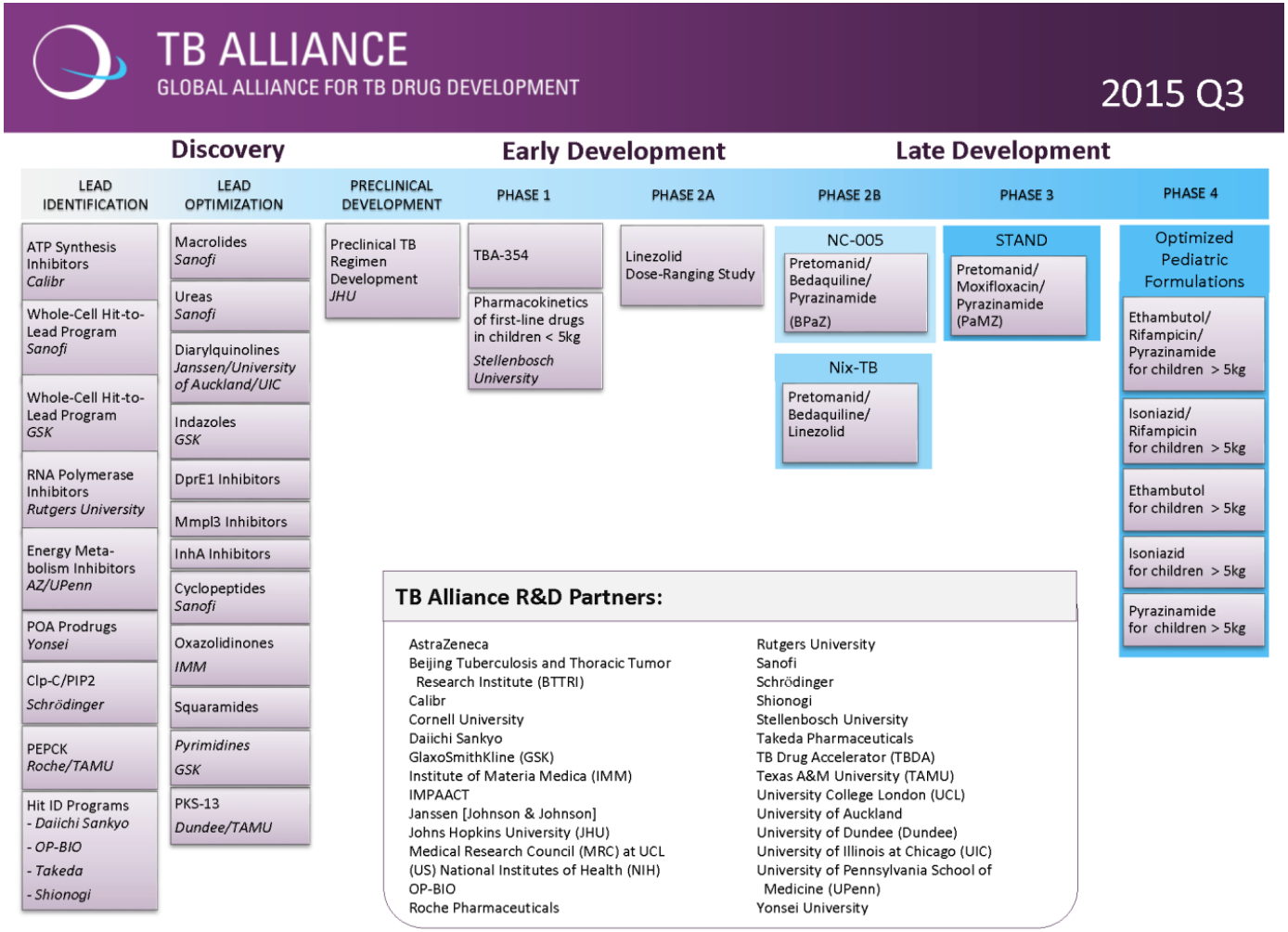
WHAT WILL THE FUTURE LOOK LIKE?


FIND
Early development
Late or completed development
On pathway to WHO evaluation
High complexity assays
Moderate complexity assays
Low complexity assays
Molecular - Detection/DST
New TruArray MDR-TB (Akkoni)
COBAS TaqMan MTB + DST(Roche)
Hydra 1K (Insilixa)
Mycobacterium Real-time MDR (CapitalBio)
MTB Detect (Great Basin Scientific)
Aries (Luminex)
PNAClamp (Panagene)
AccuPower TB&MDR (Bioneer)
TRC Rapid MTB (Tosoh)
VereMTB (Veredus Laboratories)
LiPA Pyrazinamide (Nipro)
Fluorotype MTBDR (Hain)
TBMDx (Abbott)
Meltpro (Zeesan)
Mycobacteria RT PCR (CapitalBio)
REBA MTB-XDR (YD Diagnostics)
EasyNAT TB (Ustar)
BD Max (BD)
GenoTYPE MTBDRsl (Hain)
LiPA MDR-TB (Nipro)
REBA MTB-Rifa (YD Diagnostics)
Culture-based - Detection/DST
BNP Middlebrook (NanoLogix)
Rapid colorimetric DST
TREK Sensitive MYCOTB (Trek)
Molecular Detection/DST
Xtend XDR (Cepheid)
Alere Q (Alere)
Enigma ML (Enigma Diagnostics)
Q-POC (QuantuMDx)
EOSCAPE (Wave80)
TBDx system (KGI)
X1 (Xagenic)
MTB Detection (Tangen Biosciences)
TB POC (Qiagen)
Savanna (NWGHF/Quidel)
Genedrive MTB/RIF (Epistem)
Truelab/Truenat MTB (Molbio)
Xpert Ultra (Cepheid)
TB LAMP (Eiken)
Cellular Response - Detection/Latent and latent to active progression
T-Track TB (Lophius)
TAM-TB (LMU/Alere)
ESAT-6/CFP-10 skin test (SSI)
QuantiFERON-TB PLUS (Qiagen)
Diaskin (Generium)
Breath biomarker - Detection
BreathLink (Menssana)
Prototype breathanalyzer (Next Dimensions Tech)
TB Breathalyser (Rapid Biosensor Systems)
Aeonose (The eNose Company)
Breath analysis instrument (Metabolomx)
Automated Microscopy & Imaging - Detection
TBDx (Applied Visual Sciences)
Fluorescent microscopy (ID-FISH Tech.)
Automatic TB Screener (Fluorobot)
Cellscope (UCSF)
Microimager (BD)
CAD4TB (Delft Imaging Systems)
Antigen, Antibody and Biomarker detection- Detection
LAM in sputum (Standard Diagnostics)
IRISA-TB (Antrum Biotec)
Alere Determine TB-LAM in urine (Alere)
Enzymatic - Detection/DST
β-lactamase reporter (Global BioDiagnostics)



http://unitaid.org/images/marketdynamics/publications/Tuberculosis_diagnostics_technology_and_market_landscape_4th_edition_Oct_2015.pdf

New TB drugs and regimens

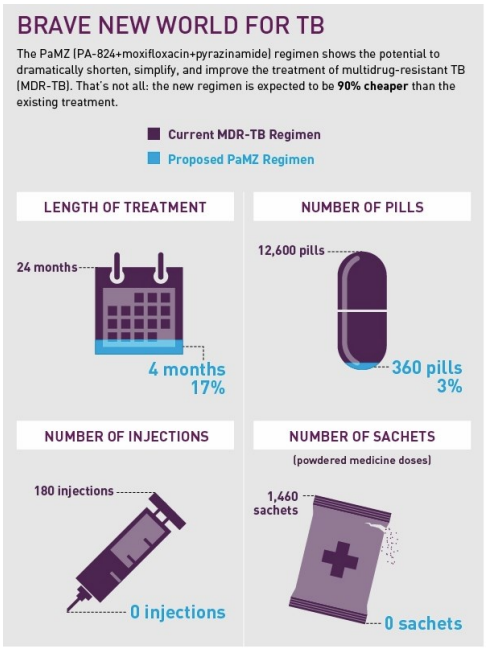


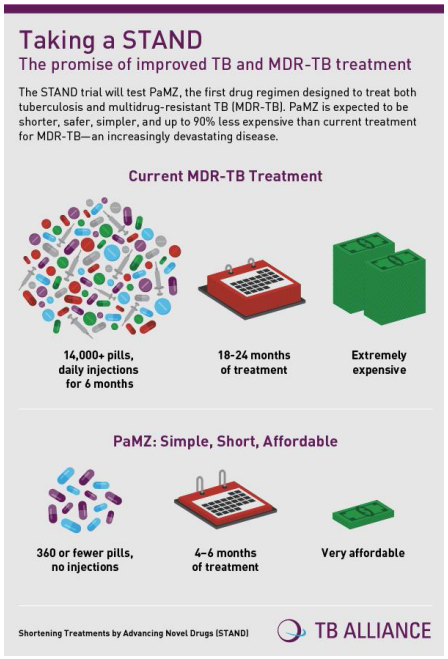
http://www.letstalktb.org/

Source: http://www.tballiance.org/

PaMZ Phase 3 clinical trial has begun

PaMZ = PA-824 + Moxifloxacin + Pyrazinamide





New Tuberculosis Drug Regimen Will Move to Landmark Phase 3 Clinical Trial

STAND trial 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.

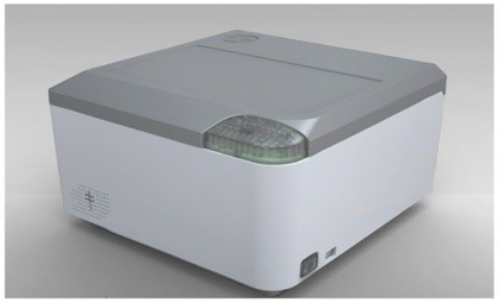
The announcement by Bill Gates, co-chair of the Bill & Melinda Gates Foundation, accompanied a commitment of significant funding by the Gates Foundation to determine the safety and efficacy of the new drug regimen, which is known as PaMZ. Mr. Gates called on other organizations to support the effort 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.

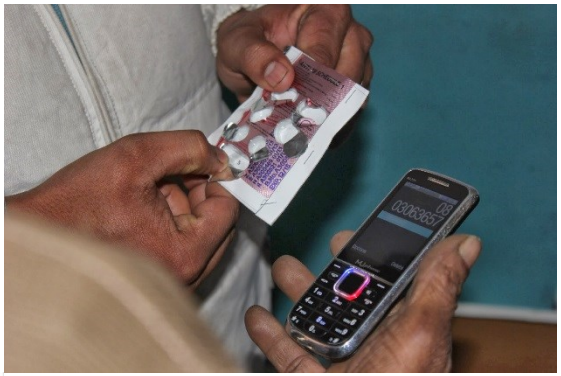
"The results from early phase research suggest that this new drug regimen could provide the breakthrough we need to accelerate progress against this deadly and dangerous disease," said Mr. Gates. "PaMZ could dramatically reduce the time required to cure drug-resistant TB from two years to just six months, 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. Now we need funders to step forward to make next-generation TB drugs like PaMZ a reality."

Source: http://www.tballiance.org/portfolio/regimen/pamz

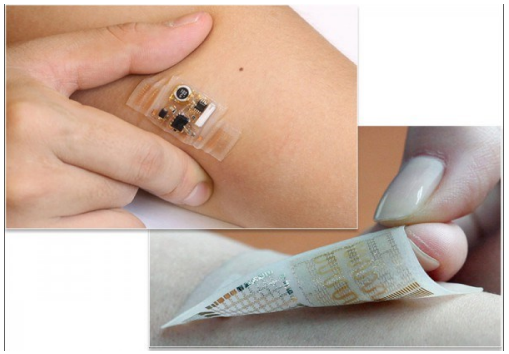
New adherence monitoring tools

Smart Pill Boxes



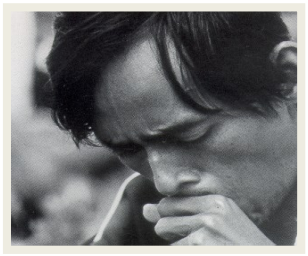


99DOTS

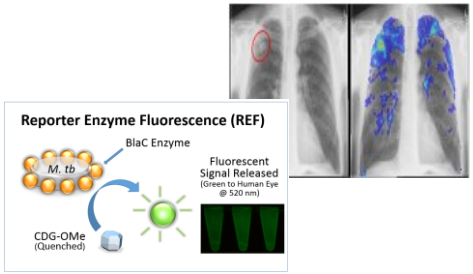


Patches/Ingestibles

How will TB get diagnosed and treated in 2020?

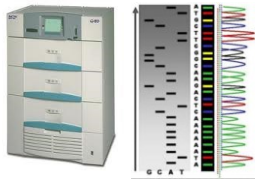


Symptomatic



Rapid Triage Test

Rapid Molecular Dx & Upfront DST



Culture/ sequencing confirmation at referral labs

Shorter drug regimens

Adherence monitoring tools

Electronic notification & tracking

eTB ICT system


Let's Talk
TB
A series on Tuberculosis
A disease that affects over 2 million Indians every year
A Supplement to GP CLINICS®
Second edition, 2016
Editor
Professor Madhukar Pai, MD, PhD
Director, McGill Global Health Programs
Associate Director,
McGill International TB Centre
Montreal, Canada
Published by
GP CLINICS®
A CME Journal for Family Physicians
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REACH
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