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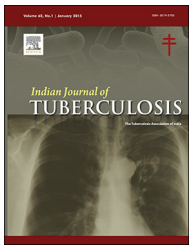

Editorial

Tuberculosis control in India: Journey so far and ahead...

Globally, the basic principles of caring for tuberculosis (TB) disease remain prompt and accurate diagnosis, standardized treatment regimens, and appropriate treatment monitoring supported with essential public health responsibilities.[1] India is the second-most populous country in the world and one-fourth of the global incident TB cases occur in India annually. In 2013, out of the estimated global annual incidence of 9 million TB cases, 2.1 million were estimated to have occurred in India.[2] In the coming decades, the war against TB will worsen further with growing menace of drug resistance, comorbidities, and socioeconomic disparities which accompanies expanding globalization. It is, therefore, pertinent that as TB care providers, the patient management prescribed is made more holistic, encompassing both health and nonhealth sectors. This is especially so for countries like India wherein treating TB goes beyond medical expertise for a futuristic vision of TB elimination.

After being declared as a global health emergency in 1993, the National Tuberculosis Program was revised and renamed as the Revised National Tuberculosis Control Program (RNTCP). The program was started as a small pilot project, and later it was scaled to cover the whole country from 1998 to 2006 with an overall vision of 'TB-free India'. In 2006–2011, the second phase of RNTCP sought to improve the quality and reach of services, and reach global case detection and cure targets. The 12th Five year plan of Government of India (GoI) and the National Strategic Plan to Control TB (2012–2017) envisage universal access to quality TB care for all TB patients in the community.[3] Universal access means to diagnose and treat all forms of TB early to cut the chain of transmission and prevent death. This necessitates enhanced engagement with the private sector which manages nearly half of TB patients in the country.

In the year 2006, the World Health Organization (WHO) and the Stop TB Partnership articulated the impact targets for TB cases and deaths in context with the United Nations Millennium Development Goals (MDGs).[4] In line with these global targets, GoI released the 12th Five year National Strategic Plan to control TB (2012–2017). The National Strategic Plan of RNTCP envisages universal access to quality TB diagnosis and treatment for all. An aide to accomplish this is the countrywide adoption of standard diagnostic and treatment strategies for TB management. Defining the need to strengthen quality diagnosis, treatment, and social factors affecting India's campaign for a "TB-free India", the first edition of Standards for TB Care in India was released as a joint collaborative effort of GoI and WHO Country Office India in 2014.[5]

Over the last two decades, the RNTCP has become the world's largest and successful TB control programs. This flagship program of GoI has diagnosed and successfully treated more than 17.4 million TB cases and 3.1 million additional lives have been saved, since its inception in 1998. In line with the MDGs, TB prevalence has been reduced from 465 lakh^{-1}/year in 1990 to 211 lakh^{-1}/year in 2013, and incidence of TB has come down from 216 lakh^{-1}/year in 1990 to 171 lakh^{-1}/year in 2013 and mortality from 38 lakh^{-1}/year in 1990 to 19 lakh^{-1}/year in 2013.[6]

The Programmatic Management of Drug Resistant TB (PMDT) was rolled out in 2005 and the services were rapidly scaled across the country.[7] Cumulative outcomes of 12,125 MDRTB patients have been reported out of which 5796 (48%) have been successfully treated under PMDT.[6]

In the year 2005, collaboration with National AIDS Control Organization resulted in development of TB-HIV collaborative framework with intensified case finding efforts from both the programs across the country. In 2014, 72% of all registered TB cases knew their HIV status. 94% HIV-infected TB patients were initiated on Cotrimoxazole Prophylactic Therapy and 91% were initiated on anti-retroviral treatment.[6]

In 2012, GoI banned the use of commercial serology for diagnosis of TB and made TB notification mandatory across the country.[8] "Nikshay" is a case-based web online application under RNTCP for monitoring of TB program and TB surveillance.[6]

In addition to several deliberations with national and international experts toward standardized diagnostic framework incorporating new rapid technologies like CBNAAT and Line probe assays along with individualized treatment regimens for several types of drug resistance patterns, yet another important venture of RNTCP has been the implementation of pediatric diagnostic and treatment framework. In 2014, ~75,000 (6%) of all new registered TB patients were in pediatric age group and were offered standardized treatment protocols under the program.[6]

Key to realizing the goal of "Universal access to TB care and treatment for all" lies in synergistic efforts of all stakeholders

involved in TB care and control in the country. The program boasts of innovative ways of private and public sector involvement. Partnership with NGO for provision of TB treatment to marginalized groups residing in night shelters, orphans and elderly in welfare homes, pavement dwellers, transgenders, and social support to MDR-TB patients through NGO interface to name a few. From strengthening notification from private sector, scaling up diagnosis for drug resistance TB, engagement of communities, and Community Systems Strengthening, partners have complemented RNTCP's efforts toward universal access to TB care.[6]

Service decentralization in RNTCP has been possible with health system stewardship under the umbrella of National Health Mission. Collaboration with stakeholders in health and nonhealth sectors, engaging private partners on a large scale has been an ongoing effort under the program. Over 330 out of the 380 Medical Colleges in the country contribute to about 20% of the total registered cases under the RNTCP in addition to supporting the program in PMDT services, TB-HIV collaboration, capacity building, and evidence-based research.[6] During these years of implementation, RNTCP has undertaken several publicity campaigns with renowned personalities and cured TB patients as TB Ambassador.

At the helm of program achievement lay the daunting task of supervision and monitoring with quality reporting, a task spearheaded by not only the dedicated staff at Center, State, and District level program functionaries but also from the strong committed team of Medical Consultants from the WHO Technical support network spread across the country. The technical network has been at the forefront of program implementation, monitoring, and management.[9] They have been a beacon to several program managers, field staff, and several technical partners and have jointly led the program to achieve the vision of TB control across the country.

The year 2014 saw many new initiatives and policy changes in RNTCP. From the launch of first nationwide anti-Tuberculosis Drug Resistance Survey of India, daily drug regimen being pilot tested across 100 districts in the country, draft guidelines being formulated on DST-guided treatment for drug-resistant TB patients, molecular techniques like CBNAAT being deployed at ART sites in 5 high burden settings to detect MTB in presumptive TB cases among People living with HIV, screening all TB patients for diabetes under the program settings, and the release of Standards for TB Care in India, a comprehensive handbook facilitating patient centric standards for TB care for all stakeholders, the RNTCP has come a long way.

India's TB Control ''Vision 2020'' has laid down strategies for involvement of all care providers to strengthen TB notification, promote ban on serology, rational use of anti-TB drugs, early identification of referral of TB suspects for diagnosis and to increase community awareness. In a more recent initiative, guidelines and framework for EP TB have been formulated; conditional access program has been approved for introduction of new anti-TB drug Bedaquiline and 'Universal access to free anti-TB drugs' piloted to provide anti-TB drugs to patients in the private sector.

Lot has been done, lot is being done, and a lot more needs to be done. In the coming decade, India has to join the roadmap for success in TB standards *at par* with other low burden good performing nations across the globe and implement the End TB Strategy. It is imperative that all sectors, public ↔ private; health ↔ nonhealth, contribute effectively toward RNTCPs efforts in achieving a ''TB-Free India''.

Released on World TB Day 2014, the Standards for TB Care in India provide a unique and holistic dimension for Universal access to quality TB care. On one side, these standards propagate best practices in TB control in the private sector, at the same time these also challenge the national TB program to raise the bar and provide highest quality TB care under the program. These standards envisage daily treatment regimen in high-risk groups, DST-guided treatment regimen to tackle the menace of DR-TB, more patient friendly treatment adherence systems including family DOT and ICT-enabled support systems, and psychosocial support systems. The standards for TB care seek to provide an acceptable level of management by the health care providers, both public and private to each and every TB patient and their family members.

This issue provides an overview to the Standards for TB Care in India, WHO End TB Strategy,[10] and related evidence-based research which advocates different facets of standards for TB care in the country. In addition, the journal's interactive forum encourages readers to share their view on the theme: ''Standards for TB Care in India''.

Conflicts of interest

The authors have none to declare.

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Viewpoint

WHO's End TB Strategy: From stopping to ending the global TB epidemic

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ABSTRACT

The 67th World Health Assembly of 2014 adopted the ''End TB Strategy'' with a vision of making the world free of tuberculosis (TB) and with the goal of ending the global TB epidemic by the year 2035. World Health Organization's ''End TB Strategy'' captures this holistic response in its four principles and three pillars. The three high-level indicators of the ''End TB Strategy'' – reductions in TB deaths, reductions in the TB incidence rate and the percentage of TB patients and their households experiencing catastrophic costs – are relevant to all countries.

1. Introduction

1.1. *Progress is evident and so are the constraints to future progress*

As the world reaches the end of the period to meet the Millennium Development Goals (MDGs) this year, the global tuberculosis (TB) community has a reason to celebrate.[1] Twenty years of intensive efforts at global, national and local levels to first implement the DOTS strategy and then expanding it to the Stop TB Strategy have helped make substantial progress. The MDG target to ''halt and begin to reverse'' the TB epidemic (in other words, bring down the TB incidence rate) by 2015 has long been met globally. Furthermore, 37 million lives have been saved between 2000 and 2013. The TB mortality rate fell by 45% and the prevalence rate by 41% between 1990 and 2013.[2] Research and innovation have led to development of new rapid molecular tests, to simultaneously diagnose TB and drug resistance, and of two novel drugs, for the first time in half a century.[2]

The major constraints to making further progress are also well-known.[3] The current average annual decline in global TB incidence by 1.5% is too slow to make any major dent in the TB epidemic in the foreseeable future. TB remains a top infectious killer of men and women; one-third of estimated incident TB cases go un-notified or undiagnosed; close to half a million multidrug resistant TB cases emerge each year; HIV-associated TB affects more than a million people a year; and an estimated two billion people with latent TB infection form a reservoir that sustains the global TB epidemic.[3]

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1.2. *A holistic response to end the epidemic*

Besides progress in health-related goals, the MDG era witnessed the fastest reduction ever in global poverty with half a billion fewer people now living below poverty line.[1] This was possible thanks to political commitment, economic growth, improved policies and enhanced investments. The new Sustainable Development Goals (SDGs) set for 2030 aim for a similarly holistic but greatly expanded action to make the world a better place by eliminating extreme poverty.[4] The TB strategy for the next two decades has also been shaped by the global dialogue around formulating the SDGs that bring equity and social justice to the centre of the development agenda. Taking cognizance of SDGs under formulation and endorsing a comprehensive multisectoral response to fight TB, the 67th World Health Assembly of 2014 adopted the End TB Strategy with a vision of making the world free of TB and the goal of ending the TB epidemic by 2035.[5] Table 1 presents the strategy at a glance.

Ending the TB epidemic implies bringing the levels of TB in the whole world down to those already attained by many rich countries: less than 10 new TB cases occurring per 100,000 population per year amounting to 90% reduction in TB incidence rate, and reduction in TB deaths by 95%. The rich countries could achieve further significant declines in the TB burden not just by offering adequate TB services but also by providing universal access to health care and social protection for the poorest and marginalised segments of population. Ending the TB epidemic in high-incidence countries demands a similar approach: guaranteed access to quality TB care and prevention to all while addressing in parallel the risk factors and social determinants of TB. However, achieving universal access to currently available tools of TB care and prevention may ensure an acceleration of the decline in incidence and mortality; it will not suffice to end the TB epidemic within two decades. Global investments and efforts are essential also to develop better tools to diagnose, treat and prevent TB. The End TB Strategy captures this holistic response in its four principles and three pillars. Equal emphasis on achieving universal access to TB care and prevention, addressing weaknesses in health systems and mitigating the social and economic determinants

Table 1 – The End TB Strategy 2016–2035.

Vision	**A world free of TB** –zero deaths, disease and suffering due to tuberculosis			
Goal	**End the global TB epidemic**			
Indicators	**Milestones**		**Targets**	
	2020	**2025**	**2030**[a]	**2035**
Reduction in number of TB deaths compared with 2015 (%)	35%	75%	90%	95%
Reduction in TB incidence rate compared with 2015 (%)	20% (<85/100 000)	50% (<55/100 000)	80% (<20/100 000)	90% (<10/100 000)
TB-affected families facing catastrophic costs due to TB (%)	0	0	0	0

Principles

1. Government stewardship and accountability, with monitoring and evaluation
2. Strong coalition with civil society organizations and communities
3. Protection and promotion of human rights, ethics and equity
4. Adaptation of the strategy and targets at country level, with global collaboration

Pillars and components

1. Integrated, patient-centred care and prevention
- A. Early diagnosis of TB including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups
- B. Treatment of all people with TB including drug-resistant TB, and patient support
- C. Collaborative TB/HIV activities, and management of co-morbidities
- D. Preventive treatment of persons at high risk, and vaccination against TB

2. Bold policies and supportive systems
- A. Political commitment with adequate resources for TB care and prevention
- B. Engagement of communities, civil society organizations, and public and private care providers
- C. Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control
- D. Social protection, poverty alleviation and actions on other determinants of TB

3. Intensified research and innovation
- A. Discovery, development and rapid uptake of new tools, interventions and strategies
- B. Research to optimise implementation and impact, and promote innovations

[a] Targets for the United Nations "Sustainable Development Goals".

of TB, and pursuing research and innovation for better tools and strategies constitute the core of the End TB Strategy.[6]

The underlying principles that cut across its three pillars are critical for the strategy's success. Government stewardship and accountability are essential in adopting and implementing the strategy as are monitoring and evaluation to track the progress of its implementation. A strong coalition with civil society and communities is necessary for an effective and sustained movement against TB. Promotion of human rights, ethics and equity must be integral to strategy implementation. The fourth important principle is that the strategy has to be adapted to each country setting and the adaptation should be based on a thorough assessment of the country-context.[6]

2. The care and prevention pillar

The first pillar constitutes the core functions of a national TB programme or equivalent. Early detection and treatment of people with all forms of TB is the main objective. In providing care, a patient-centred approach – TB care and support sensitive and responsive to patients' educational, emotional and material needs – is crucial. TB services must address diverse barriers that men, women and children face while seeking care and adhering to treatment. This care and prevention pillar is expected to modernise all aspects of TB care provision through the use of rapid molecular diagnostics, universal drug susceptibility testing, and systematic screening of high-risk individuals along with preventive treatment to those who may benefit from it. Among many new interventions, adding prevention to care is an important advance introduced by the End TB Strategy. The Strategy promotes service integration essential for better managing TB/HIV and other comorbidities, for improving access for women and children, and for gaining efficiencies in general. It also underscores innovations to improve care provision, programme management and surveillance and modernization through swift and wide application of digital technology.[3,6]

3. The policies and systems pillar

This second pillar comprises bold and supportive health and social sector policies to strengthen the systems essential to implement all the components of the care and prevention pillar. The success in achieving the milestones and the targets set for the first decade of the End TB Strategy – 75% reductions in the deaths and 50% reduction in the incidence rate by 2025 – will depend largely on how effectively the broad multisectoral policies that address universal health coverage (UHC) and social protection, and the interventions that tackle risk factors and social determinants of TB are put in place.[7] Priority attention will need to be given to vulnerable people such as those living with HIV, migrants, refugees, prisoners and slum-dwellers necessitating close collaboration across sectors, ministries and programmes.[6] Explicit policies and proven mechanisms are essential to scale up involvement of communities and engagement of all care providers and ensure that high-quality TB care of international standards is accessible and affordable to all who need it. This pillar draws attention to policies and systems to implement hitherto discounted regulatory frameworks for TB care and prevention. The regulatory framework should include mandatory case notification and rational use of TB medicines by all care providers, pharmacovigilance, infection control, and vital registration.[3,6]

3.1. *The research and innovation pillar*

Given the limitations of the current tools to end the TB epidemic, achieving the milestones and the targets set for beyond 2025 will require development and widespread deployment of new and better tools of diagnosis, treatment and prevention. It will also require innovations in implementation strategies and programme operations. This essentially is the purpose of the research and innovation pillar. Research and innovation encompass the whole spectrum from fundamental research for development of new tools to epidemiological, health systems, social and operational research for enhancing performance, introducing innovations and addressing stigma and discrimination.[8] In order to the have the new tools and make them widely accessible over the next two decades, urgent intellectual and financial boost is required now. Operational research is the key for designing, implementing, refining and scaling up many new elements of the End TB Strategy. Engaging all major research institutions, a comprehensive and prioritised research plan should be drawn for each country.[6,8]

3.2. *Measuring progress and impact*

The three high-level indicators of the End TB Strategy – reductions in TB deaths, reductions in the TB incidence rate and the percentage of TB patients and their households experiencing catastrophic costs – are relevant to all countries. However, targets and milestones for these indicators can be adapted at country level, to reflect factors such as different starting points, the main drivers of local epidemics, the overall national strategy related to UHC and social protection and planned interventions. Implementation of the main components of the post-2015 global TB strategy needs to be monitored alongside progress towards the overarching targets. WHO has proposed a set of illustrative indicators.[6] All of these are measurable indicators for which baselines and targets can be set. It is important to monitor some of the indicators at subnational and subpopulation levels as well as national level, for example to monitor the impact of efforts to reduce health inequities.

4. India – a potential pathfinder for operationalizing the End TB Strategy

India bears 17% of the world population and a quarter of the global burden of TB. Each year, 1.2 million Indians are notified with newly diagnosed TB and more than a quarter million Indians die of TB. Global success towards ending the TB epidemic will therefore depend heavily on India's progress in tackling TB. Over the last two decades, India has made significant advances in its fight against TB through nationwide

implementation of the DOTS strategy and its expansion to the Stop TB strategy. More than 17 million TB patients have been detected and treated, and millions of lives saved through the efforts coordinated by the Revised National Tuberculosis Control Programme (RNTCP).[9] A country's economic progress will not automatically result in a win over the TB epidemic. Further progress in that direction will require significant expansion of the scope of actions that go much beyond those currently undertaken by the RNTCP.[10] These actions have to be matched by a sustained flow of adequate resources – financial and human, a collaborative effort that effectively engages all stakeholders making TB everybody's concern, and a greater attention to the affected and vulnerable people. Strengthening its reputed research institutions and their legacy of TB research, India could become a model country in developing and implementing a widely endorsed strategic TB research agenda. To be a pathfinder in moving towards ending the TB epidemic, therefore, India will have to meticulously implement every element of the End TB Strategy. A welcome initial step in that direction has been an in-depth national review of India's efforts to Stop TB undertaken recently by a joint monitoring mission (JMM) comprising all key stakeholders. The findings of the JMM should guide the government's future actions to End TB.

Disclaimer

The authors are staff members of the World Health Organization. The views expressed in this article do not necessarily represent the policies of the organization.

Contribution details

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Review Article

Standards for TB care in India: A tool for universal access to TB care

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ABSTRACT

In 2014, Government of India in collaboration with World Health Organization Country Office for India released the policy document on Standards for tuberculosis (TB) care in India after in-depth deliberation with national and international experts. The standards for TB care represent what is expected for quality TB care from the Indian healthcare system including both public and private systems. The details of each standard have been compiled in this review article. It is envisioned that the standards detailed in the manuscript are adapted by all TB care providers across the country.

1. Introduction

The vision of India's national TB control programme is that the people suffering from TB receive the highest standards of care and support from healthcare providers of their choice.[1] India, with nearly a quarter of the world's annual incidence of TB has one of the largest TB control programmes in the world. Over 15 million patients have been treated, and 3 million additional lives have been saved by the Revised National TB Control Programme (RNTCP) over the entire last decade. Despite having a comprehensive national TB control programme guiding states for implementation of TB diagnosis and treatment, there is still a long way to go. The decline in TB incidence has been slow, mortality remains unacceptably high and the emergence of drug-resistant TB has become a major public health concern.[2]

The private sector has predominance of health care service delivery in India. Nearly half of TB patients are getting treatment from private sector.[3] National TB control Programme has very little information about TB patient managed in the private sector, and the quality of treatment, including treatment outcomes are largely unclear.[4] Engaging the private sector effectively is the single most important intervention required for India to achieve the overall goal of universal access to quality TB care. From the patients' perspectives, the

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public sector and private sector are not two separate universe, and they frequently change the health care providers. Non-uniformity between public and private sector standards make it difficult to ensure continuum of care. A uniform standard for management of TB is critical for prevention of development of drug resistant TB (DR-TB). Thus, it was felt essential to develop and disseminate the standards for TB care, that is particularly relevant in Indian context, applicable to the medical fraternity in both the public and private sectors in India. The new diagnostic tools and strategies for early TB diagnosis, emerging evidences on existing regimens and newer regimens, and the need for better patient support strategies including addressing social inclusiveness have further necessitated the development of Standards for TB Care in India (STCI).[5]

In 2014, Government of India in collaboration with WHO Country Office for India released the policy document on STCI after in-depth deliberation with national and international experts.

The standards detailed in the STCI differ from existing guidelines; in that, the standards present what should be done, whereas guidelines describe how the action is to be accomplished. There are comprehensive national guidelines from the Central TB Division, GoI [www.tbcindia.gov.in] that are regularly reviewed and updated. These standards represent what is expected for quality TB care from the Indian healthcare system including both public and private systems.

2. Methods

STCI was developed through series of consultations and review of literature with special attention on data from India. Methodology for developing these standards consisted of extensive consultations based on in-depth analysis of India's programme data and review of literature including findings from various operational researches conducted with in the programme, and other recent national and international evidences available. International standards and guidelines such as International Standards for TB care 2nd edition (2009),[6] WHO treatment of tuberculosis guidelines 4th edition (2010),[7] Guidelines for Programmatic Management of Drug Resistant TB (2011),[15] etc. were used as reference. A workshop was organised to develop these standards, and the expert groups were asked to find out the answers to the following questions:

1. What should be the standard tools and strategies for early and complete detection?
2. What should be the standards of treatment in terms of drugs and regimens for best patient outcome?
3. What should be the public health standards including regulations, strategies and systems for public health impact?
4. What should be standards for patient support systems, both in public and private sectors and for community engagement for social inclusion?

Answers to these questions formed the basis for these standards. Detailed methodology in developing these standards is described elsewhere.[5]

2.1. Standards for TB care in India

These comprise of four basic sets of standards:

- Standards for diagnosis of TB (Standard 1–Standard 6)
- Standards for treatment of TB (Standard 7–Standard 11)
- Standards for public health for TB (Standard 12–Standard 21)
- Standards for social inclusion for TB (Standard 22–Standard 26)

2.2. Standards for diagnosis of TB (Standard 1–Standard 6)

2.2.1. Standard 1: testing and screening for pulmonary TB

Any person with symptoms and signs suggestive of TB including cough >2 weeks, fever >2 weeks, significant weight loss, haemoptysis etc. and any abnormality in chest radiograph must be evaluated for TB. Children with persistent fever and/or cough >2 weeks, loss of weight/no weight gain, and/or contact with pulmonary TB cases must be evaluated for TB.[8,9,11]

People living with HIV (PLHIV), malnourished, diabetics, cancer patients, patients on immunosuppressant or maintenance steroid therapy, should be regularly screened for signs and symptoms suggestive of TB. Enhanced case finding should be undertaken in high risk populations such as health care workers, prisoners, slum dwellers and certain occupational groups such as miners.[8,10]

2.2.2. Standard 2: diagnosis

All patients (adults, adolescents and children, who are capable of producing sputum) with presumptive pulmonary TB should undergo quality-assured sputum test for rapid diagnosis of TB for microbiological confirmation. Wherever available, chest X-ray should be used as a screening tool to increase the sensitivity of the diagnostic algorithm.[8,12] Serological tests are banned and not recommended for diagnosing TB.[14] Tuberculosis skin test (TST) and immunoglobin G release assay (IGRA) are not recommended for the diagnosis of active TB. Standardised TST may be used as a complimentary test in children. CB-NAAT (cartridge-based nucleic-acid amplification test) (GeneXpert) is the preferred first diagnostic test in children and PLHIV.[13]

2.2.3. Standard 3: testing for extra-pulmonary TB

For all patients (adults, adolescents and children) with presumptive extra-pulmonary TB, appropriate specimens from the presumed sites of involvement must be obtained for microscopy/culture and drug sensitivity testing (DST)/CB-NAAT/molecular test/histo-pathological examination.[15,16]

2.2.4. Standard 4: diagnosis of HIV co-infection in TB patients and drug resistant TB

All diagnosed TB patients should be offered HIV counselling and testing.

Prompt and appropriate evaluation should be undertaken for patients with presumptive MDR-TB who have failed treatment with first line drugs, paediatric nonresponders, TB patients who are contacts of MDR-TB, TB patients who are found positive on any follow-up sputum smear examination

during treatment with first line drugs, diagnosed TB patients with prior history of anti-TB treatment, TB patients with HIV co-infection and all presumptive TB cases among PLHIV. All such patients must be tested for drug resistance with available technology, a rapid molecular DST (as the first choice) or liquid/solid culture-DST (at least for R and if possible for isoniazid (H); ofloxacin (O) and kanamycin (K), if R-resistant/MDR). DST should be considered a good offer to all diagnosed TB patients prior to start of treatment. On detection of rifampicin resistance alone or along with isoniazid resistance, patient must be offered sputum test for second line DST.[17–20]

2.2.5. *Standard 5: probable TB*

Presumptive TB patients without microbiological confirmation (smear microscopy, culture and molecular diagnosis), but with strong clinical and other evidence (e.g. X-ray, fine needle aspiration cytology (FNAC, histopathology) may be diagnosed as ''Probable TB'' and should be treated.[21,22] For patients with presumptive TB found to be negative on rapid molecular test, an attempt should be made to obtain culture on an appropriate specimen.

2.2.6. *Standard 6: paediatric TB*

In all children with presumptive intra-thoracic TB, microbiological confirmation should be sought through examination of respiratory specimens (e.g. sputum by expectoration, gastric aspirate, gastric lavage, induced sputum, broncho-alveolar lavage or other appropriate specimens) with a quality assured diagnostic test, preferably CB-NAAT, smear microscopy or culture.[11] In the event of negative or unavailable microbiological results, a diagnosis of probable TB in children should be based on the presence of abnormalities consistent with TB on radiography, a history of exposure to pulmonary TB case, evidence of TB infection (positive TST) and clinical findings suggestive of TB. For children with presumptive extra-pulmonary TB, appropriate specimens from the presumed sites of involvement should be obtained for rapid molecular test, microscopy, culture and DST and histo-pathological examination.

2.3. *Standards for treatment of TB (Standard 7–Standard 11)*[12–34]

2.3.1. *Standard 7: treatment with first-line regimen*

All new patients should receive an internationally accepted first-line treatment regimen for new patients. The initial phase should consist of two months of isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E).[6,7,23] The continuation phase consists of three drugs (isoniazid, rifampicin and ethambutol) given for at least four months.[6,7,24] The duration of continuation phase may be extended to three to six months in special situations such as bone and joint TB, spinal TB with neurological involvement and neuro tuberculosis. The patients should be given dosages of the drugs depending upon body weight in appropriate weight bands. The bioavailability of the drug should be ensured for every batch, especially if fixed dose combinations (FDCs) are used, by procuring and prescribing from a quality-assured source. All patients should be given daily regimen under direct observation.[23,30–33] FDCs of four drugs (isoniazid, rifampicin, pyrazinamide and ethambutol), three drugs (isoniazid, rifampicin and ethambutol) and two drugs (isoniazid and rifampicin) are recommended.[25] After MDR-TB (or R resistance) is ruled out by a quality assured test, TB patients returning after lost to follow-up or relapse from their first treatment course or new TB patients failing with first treatment course may receive the retreatment regimen containing first-line drugs: 2HREZS/1HREZ/5HRE with close follow-up.

2.3.2. *Standard 8: monitoring treatment response*

Response to therapy in patients with pulmonary TB, new as well as retreatment cases, should be monitored by follow-up sputum microscopy (one specimen) at the time of completion of the intensive phase of treatment and at the end of treatment.[6,7,26–28] The extension of the intensive phase is not recommended.[7] If the sputum smear is positive in follow-up at any time during treatment, a rapid molecular DST (as the first choice) or culture-DST (at least for R and if possible for isoniazid (H); ofloxacin (O) and kanamycin (K), if R-resistant/MDR) should be performed as laboratory facilities become available.[29] In patients with extra-pulmonary TB, the treatment response is best assessed clinically. In children, who are unable to produce sputum, the response to treatment may be assessed clinically radiological and other relevant investigations. After completion of treatment, the patients should be followed up with clinical and/or sputum examination at the end of six months and 12 months.

2.3.3. *Standard 9: drug resistant TB management*

Patients with TB caused by drug-resistant organisms (especially M/XDR or only R resistance or with O or K resistance), microbiologically confirmed by quality assured test, should be treated with specialised regimens containing quality assured second-line anti-TB drugs. Patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalisation. If required, a short period of initial hospitalisation is recommended.[34,36] The regimen chosen for MDR-TB may be standardised and/or based on microbiologically confirmed drug susceptibility patterns. At least four drugs (second line) to which the organisms are susceptible, or presumed susceptible, should be used. Most importantly the regimen should include at least a later-generation fluoroquinolone (such as high dose levofloxacin) and a parenteral agent (such as kanamycin or amikacin), and may include pyrazinamide, ethambutol, ethionamide (or prothionamide), and either cycloserine or PAS (p-aminosalicylic acid). Treatment regimen may be suitably modified in case of ofloxacin and/or kanamycin resistance at the initiation of MDR-TB treatment or during early intensive phase, preferably not later than four to six weeks.[29,38] All patients of MDR/XDR-TB should be evaluated for surgery at the initiation of treatment and/or during follow-up. Till newer effective drugs are available with proven efficacy with shorter duration of MDR-TB treatment; total treatment should be given for at least 24 months in patients newly diagnosed with MDRTB (i.e. not previously treated for MDR-TB) with recommended intensive phase of treatment being six to nine months. The total duration may be modified according to the patient's response to therapy. Consultation with a specialist experienced in treatment of patients with MDR/XDR TB should be obtained, whenever

possible. Patient support systems, including direct observation of treatment, are required to ensure adherence. It should be ensured that the patient consumes all the dosages of the drugs.

The patients with MDR-TB found to be resistant to at least ofloxacin and/or kanamycin must be treated with a suitable regimen for XDR TB using second line drugs including Group 5 drugs such as amoxicillin clavulanate, clarithromycin, clofazimine, linezolid, thiacetazone and imipenem to which the organisms are known or presumed to be susceptible. New drugs need to be considered for inclusion in regimens, whenever scientific evidence for their efficacy and safety becomes available as per the national policy for newer antimicrobials. Appropriate regulatory mechanisms for distribution control need to be ensured.

2.3.4. *Standard 10: addressing TB with HIV infection and other co-morbid conditions*

TB patients living with HIV should receive the same duration of TB treatment with daily regimen as HIV negative TB patients. Antiretroviral therapy must be offered to all patients with HIV and TB irrespective of CD4 cell-count, as early as possible.[6,7,35] Patients with TB and HIV infection should also receive co-trimoxazole as prophylaxis for other infections. PLHIV should be screened for TB using four symptom complexes (current cough or, fever or weight loss or night sweats) at HIV care settings and those with any of these symptoms should be evaluated for ruling out active TB. All asymptomatic patients, in whom active TB is ruled out, isoniazid preventive therapy (IPT) should be offered to them for six months or longer.[39]

2.3.5. *Standard 11: treatment adherence*

Both to assess and foster adherence, a patient-centred approach to administration of drug treatment, based on the patient's needs and mutual respect between the patient and the provider, should be developed. Supervision and support should be individualised and should draw on the full range of recommended interventions and available support services, including patient counselling and education. A central element of the patient-centred strategy is the use of measures to assess and promote adherence to the treatment regimen and to address poor adherence, when it occurs. These measures should be tailored to the individual patient's circumstances based on details of the patient's clinical and social history and be mutually acceptable to the patient and the provider.[37] Such measures may include identification and training of a treatment supporter (for TB and, if appropriate, for HIV, Diabetes Mellitus etc.) who is acceptable, accessible and accountable to the patient and to the health system. Optimal use of ICT should be done to promote treatment literacy and adherence.

2.4. *Standards for public health (Standard 12–Standard 21)*[35–39]

2.4.1. *Standard 12: notification of TB cases*

All health establishments must report all TB cases diagnosed and their treatment outcomes to public health authorities (District Nodal Officer for Notification). Proper feedback need to be ensured to all healthcare providers, who refer cases to public health system on the outcome of the patients, which they had referred.[40–42]

2.4.2. *Standard 13: public health responsibility*

Any practitioner treating a patient for TB is assuming an important public health responsibility to prevent on-going transmission of the infection and the development of drug resistance.[6] To fulfil this responsibility the practitioner must not only prescribe an appropriate regimen, but when necessary, also utilise local public health services/community health services, and other agencies including NGOs to assess the adherence of the patient and to address poor adherence, when it occurs.

2.4.3. *Standard 14: maintain records for all TB patients*

A written record of all medications given, bacteriologic response, adverse reactions and clinical/bacteriological outcome should be maintained for all patients.

2.4.4. *Standard 15: contact investigation*

All providers of care for patients with TB should ensure all household contacts and other persons, who are in close contact with TB patients are screened for TB. In case of paediatric TB patients, reverse contact tracing for search of any active TB case in the household of the child must be undertaken.[42]

2.4.5. *Standard 16: isoniazid prophylactic therapy*

Children <6 years of age, who are close contacts of a TB patient, after excluding active TB, should be treated with isoniazid for a minimum period of 6 months and should be closely monitored for TB symptoms.[6,7]

2.4.6. *Standard 17: airborne infection control*

Airborne infection control should be an integral part of all health care facility infection control strategy.

2.4.7. *Standard 18: quality assurance (QA) systems*

All health care providers should ensure that all diagnostic tests used for diagnosis of TB are quality assured. QA system should ensure that all anti-TB drugs used in the country are subjected to stringent QA mechanisms at all levels.

2.4.8. *Standard 19: Panchayati Raj institutions*

Panchayati Raj institutions and elected representatives have an important role to share the public health responsibility for TB control with the healthcare providers, patients and the community.

2.4.9. *Standard 20: health education*

Every TB symptomatic should be properly counselled by the healthcare provider. TB patients and their family members should get proper counselling and health education at every contact with healthcare system.

2.4.10. *Standard 21: deaths audit among TB patients*

All death among TB patients should be audited by a competent authority.

2.5. *Standards for social inclusion of TB (Standard 22–Standard 26)*[40–44]

2.5.1. *Standard 22: information on TB prevention and care seeking*

All individuals especially women, children, elderly, differently abled, other vulnerable groups and those at increased risk should receive information related to TB prevention and care seeking.[43]

2.5.2. *Standard 23: free and quality services*

All patients, especially those in vulnerable population groups, accessing a provider, where TB services are available should be offered free or affordable quality assured diagnostic and treatment services, which should be provided at locations and times so as to minimise workday or school disruptions and maximise access.[44]

2.5.3. *Standard 24: respect, confidentiality and sensitivity*

All people seeking or receiving care for TB should be received with dignity and managed with promptness, confidentiality and gender sensitivity. Ensure that infection control procedures do not stigmatise TB patients.[43]

2.5.4. *Standard 25: care and support through social welfare programme*

Patient support system should endeavour to derive synergies between various social welfare support systems to mitigate out of pocket expenses such as transport and wage loss incurred by people affected by TB for the purpose of diagnosis and treatment.[45]

2.5.5. *Standard 26: addressing counselling and other needs*

Persons affected by TB should be counselled at every opportunity, to address information gaps and to enable informed decision making. Counselling should address issues such as treatment adherence, adverse drug reactions, prognosis and physical, financial, psycho-social and nutritional needs.

3. Discussion

The standards for diagnosis of TB will be an important tool to enhance early diagnosis of all TB cases. Active and systematic screening for high risk population and wider symptomatology for TB, use of chest X-ray up front as a screening tool, preferential use of molecular diagnostics, upfront drug sensitivity tests, focus on paediatric diagnosis, are the means to ensure early and enhanced diagnosis of TB.

Standards for treatment have special significance, the regimens with both first and second line drugs have strong evidence base guided by drug sensitivity pattern. Daily regimen with fist line drugs especially with FDCs will reduce pill count and hence improve treatment adherence. It should also bring down recurrence and amplification of resistance. Patient centred adherence mechanism and utilising treatment supporters and other innovative systems should enhance compliance.

Standards on public health responsibilities including notification of cases, contact investigations, chemoprophylaxis, quality assurance and airborne infection control should enhance the currently absent public health response to TB. Social inclusion standards should help patients to get right information, free diagnosis and treatment with dignity.

These standards should lead to a patient-centred approach both within and outside TB control programme.[46] It is possible to have a same day, single visit diagnosis of TB including rifampicin resistance if proper algorithms are developed based on the standards for diagnosis. The best treatment options include universal drug susceptibility testing (DST) and DST guided treatment for all patients to ensure proper cure. Public health standards including notification, contact tracing, chemoprophylaxis, airborne infection control etc. are crucial for the care of TB patients and families as well as for prevention. Finally the social inclusion standards are crucial to address many of the social determinants for TB.[47]

Amidst the plethora of activities encircling for ending TB epidemic globally, World Health Organization (WHO) formulated the End TB Strategy[48] in the year 2014, which has three pillars for achieving zero TB death. The strategies are synchronous with Government of India's vision for ending the TB epidemic via universal health coverage. In the roadmap to the End TB Strategy, it is essential that access to quality TB care is made universal through dissemination and multisectoral adoption of STCI across the country.

STCI is pivotal in achieving the highest standards for quality TB care. It is reflective of country's needs for ending the TB epidemic. It is envisioned that the standards detailed above are adapted by all TB care providers for ending the TB epidemic across the country.

Conflicts of interest

The authors have none to declare.

Author contributions

All authors contributed to the conceptualisation of the viewpoint and writing of the manuscript. All authors revised the paper for important intellectual content, reviewed the final draft, and agreed on the decision to publish.

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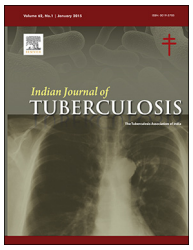

Original Article

Multidrug-resistant TB among previously treated TB cases: A retrospective study in Nagpur, India

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ABSTRACT

Background: Multidrug-resistant TB (MDR-TB) is a major public health concern and threat for tuberculosis control efforts worldwide. Globally, 3.6% of new TB cases and 20.2% of previously treated cases, are estimated to have MDR-TB. The prevalence of MDR-TB in India has been estimated to be 1–3% in new TB cases and around 12–14% in previously treated TB cases. There is limited information of the trends of MDRTB among various types of previously treated cases, i.e. relapse, treatment after failure, treatment after default and other cases. This study was conducted to know the trends of MDR-TB among various types of previously treated cases treated as per Revised National TB Control Program (RNTCP) guidelines.

Methods: This was a retrospective record review of MDRTB cases diagnosed during 2007–2011 who were previously treated for anti-TB treatment under RNTCP.

Results: A total of 249 retreatment tuberculosis patients diagnosed as having MDRTB were included. Majority 84 (34%) of cases were from 25 to 34 years age group, which is productive age group. Among the MDRTB cases, 177 (71%) were male and 72 (29%) were female. The proportion of MDR-TB among different subcategories of retreatment TB cases were relapse 117 (47%), treatment failure 96 (39%), treatment after default 22 (9%) and others 14 (6%).

Conclusion: Study findings highlight high proportion of MDRTB among the relapse and treatment failure cases. Further research is needed to understand high occurrence rates of MDRTB among relapse and failure cases treated under RNTCP and need for early detection of MDR-TB among these high-risk groups.

1. Background

Multidrug-resistant tuberculosis (MDR-TB) threatens global TB control and is a major public health concern in several countries. Levels of MDR-TB remain ominously high in some parts of the world, notably countries in Eastern Europe and Central Asia. In several of these countries, 9–32% of new cases and more than 50% of previously treated cases have MDR-TB.[1] In India, data from studies conducted by National Institute of

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Research in Tuberculosis (erstwhile Tuberculosis Research Centre) and National TB Institute have found MDR-TB levels of 1% to 3% in new TB cases and around 12% in previously treated TB cases.[2–4] MDR-TB is a man-made phenomenon, poor treatment, poor drugs and poor adherence lead to the development of MDR-TB.[4] Previously treated TB cases in Revised National Tuberculosis Control Program (RNTCP) have already received anti-TB treatment in past as per RNTCP guidelines, i.e. 2S3H3R3Z3 E3/1H3R3Z3 E3/5H3R3 E3.[5] Previously treated cases include relapse, treatment failure, treatment after default and others who are treated for more than one month with anti-TB treatment in the past. Although the estimates of drug resistance TB in previously treated cases is known, there is limited knowledge regarding the trends of drug resistance among the various types of previously treated cases in RNTCP. So this study was undertaken to assess the trends of MDRTB in various types of previously treated cases of RNTCP.

2. Material and methods

This study was conducted using record review of those patients who were previously treated under RNTCP and diagnosed as MDRTB cases during 2007–2011. Standard definitions as per RNTCP for previously treated cases, treatment failure, relapse, treatment after default, MDRTB case were used.[4,5] All previously treated cases were screened and diagnosed as MDRTB by mycobacterial culture and drug-susceptibility testing (DST) at the intermediate reference laboratory (IRL) in Nagpur. The process diagnosis of MDRTB is shown in Fig. 1. The retrospective record review included patients from seven RNTCP districts of Nagpur zone in Maharashtra linked to the IRL Nagpur.

Data were collected from: RNTCP TB register, IRL C & DST Register, DRTB Register, Drug-o-gram and Treatment cards.

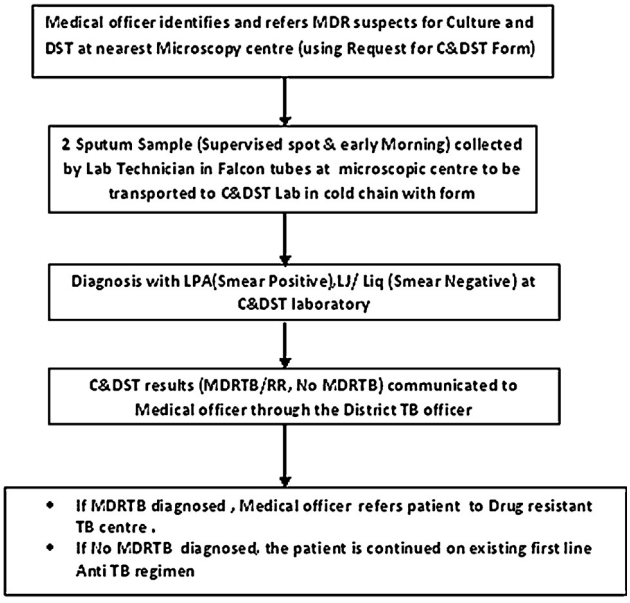

Fig. 1 – Flow of diagnosis of MDRTB patients among the MDRTB suspects, Nagpur.

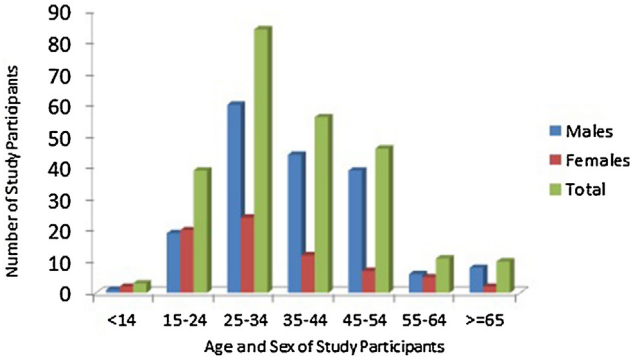

Fig. 2 – Age and sex distribution of MDRTB patients diagnosed among previously treated TB cases, Nagpur.

2.1. *Inclusion criteria*

All previously treated cases considered as MDRTB suspect as per the Programmatic Management of Drug resistant TB (PMDT) national guidelines and with a positive TB culture and DST results available for analysis were included.

2.2. *Exclusion criteria*

All cases with new or extra-pulmonary TB or non-tuberculosis mycobacteria (NTM) were excluded. If cultures were negative, failed to grow, were contaminated or data were missing, the patients were excluded, as MDTB could not be confirmed.

2.3. *Ethics*

The study protocol was approved by the ethics committee of the institutional review board of IGGMC Nagpur. Since this study involved the review of records routinely collected by the national programme and did not involve any patient interactions, informed consent was not needed. While reviewing the TB register and collecting data, every effort was made to maintain the confidentiality of the data set. Names of individual patients were not collected.

2.4. *Statistical analysis*

In the description of subjects, categorical data were expressed by percentages and continuous variables as mean and standard deviation.

3. Results

A total of 249 previously treated tuberculosis cases diagnosed as having MDRTB were included. The demographic characteristics of these patients are given in Fig. 2. Majority 84 (34%) of cases were from 25 to 34 years age group. Almost 140 (56%) of the previously treated MDRTB cases were in 25–44 years age group, which is productive age group. Among the MDRTB cases, 177 (71%) were male and 72 (29%) were female.

The proportion of MDR-TB among different subcategories of retreatment TB cases were relapse 117 (47%), treatment

Table 1 – MDR-TB cases in subcategories of previously treated TB cases, Nagpur.

Sub-category of previously treated TB cases	Sex (*n*)		Total number of patients (*n*)	% (95% CI)
	Male	Female		
Relapse	80	37	117	47 (40.8–53.2)
Treatment after default	15	7	22	9 (5.7–12.8)
Treatment failure	75	21	96	39 (32.6–44.7)
Others	7	7	14	6 (3.2–9.0)
Total	177	72	249	100

failure 96 (39%), treatment after default 22 (9%), and others 14 (6%) as shown in Table 1. Among the previously treated MDRTB cases, relapse and treatment failures constituted majority of cases.

4. Discussion

Several studies in India and globally have shown higher levels of drug resistance among previously treated cases.[6,7] Drug resistance surveys in India also demonstrated 12% of drug resistance among the previously treated cases.

In our study, we observed that almost 56% of the MDRTB cases among previously treated TB cases were in 25–44 years age group. Similar age distribution has been observed in studies conducted previously in many countries.[8–11] These results suggest that the productive age groups and predominantly males have higher risk of MDRTB and this points out towards various other factors like employment, migration, transmission of infection, economy, etc., which will have direct and indirect impact on socio-economic fabric of the families and country.

The results from our analysis suggest that high proportion of Relapse cases and treatment Failure cases among the previously treated cases developed MDRTB. Results from this study are consistent with Peru study where treatment failure, treated with short course chemotherapy regimens was highly predictive of active MDRTB.[12] High levels of MDRTB were identified in treatment failure cases from RNTCP in India as well.[13,14]

Study findings suggest that the proportion of MDRTB among Relapse cases of previously treated cases in RNTCP was very high. Study conducted by Panda et al. found high proportion of drug resistance among relapse cases as compared to new cases treated with supervised chemotherapy.[15]

Results of these studies draw attention towards the debated issue of adequacy of previously treatment regimen under the current programmatic settings as highlighted in many other studies.[16,17] There is growing evidence regarding higher risk of acquired drug resistance in those treated with thrice weekly regimen as compared to daily regimen.[18]

5. Limitations

This study had certain limitations. The sample size in our study may not have been large enough to have sufficient power to detect significant differences among different demographic and types. Second, as this was retrospective record review we could not evaluate the validity of the diagnosis.

6. Conclusion

Study findings suggest that high proportion of MDRTB among the relapse and treatment failure cases are threat to TB control and need prompt attention for introspection. Further research should be directed towards understanding why there are high rates of MDRTB among relapse and failure cases treated with short course chemotherapy and new strategies like redesigning appropriate regimen and use of rapid diagnostics for early detection of MDR among these high risk groups should be strongly considered.

Conflicts of interest

The authors have none to declare.

Author contributions

RM, DR, TKB contributed to the conceptualisation of this viewpoint and writing manuscript. All authors revised the paper for important intellectual content, reviewed the final draft, and agreed on the decision to publish.

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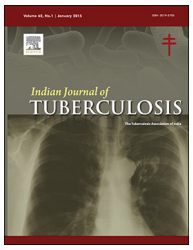

Original Article

Airborne infection control in India: Baseline assessment of health facilities

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ABSTRACT

Background: Tuberculosis transmission in health care settings represents a major public health problem. In 2010, national airborne infection control (AIC) guidelines were adopted in India. These guidelines included specific policies for TB prevention and control in health care settings. However, the feasibility and effectiveness of these guidelines have not been assessed in routine practice. This study aimed to conduct baseline assessments of AIC policies and practices within a convenience sample of 35 health care settings across 3 states in India and to assess the level of implementation at each facility after one year.

Method: A multi-agency, multidisciplinary panel of experts performed site visits using a standardized risk assessment tool to document current practices and review resource capacity. At the conclusion of each assessment, facility-specific recommendations were provided to improve AIC performance to align with national guidelines.

Result: Upon initial assessment, AIC systems were found to be poorly developed and implemented. Administrative controls were not commonly practiced and many departments needed renovation to achieve minimum environmental standards. One year after the baseline assessments, there were substantial improvements in both policy and practice.

Conclusion: A package of capacity building and systems development that followed national guidelines substantially improved implementation of AIC policies and practice.

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1. Background

The risk of nosocomial transmission of airborne infections like *Mycobacterium tuberculosis* from individuals with disease to health care workers (HCWs) and other patients has been recognized for many years.[1–13] A systematic review of 51 studies conducted in low- to middle-income countries found that TB incidence among HCWs was high, ranging from 69 to 5780 per 100,000.[1] Evidence shows that TB is a significant occupational problem among HCWs,[1–13] especially in hospitals with no TB control measures in place.[2] Nosocomial outbreaks of airborne infections like influenza H1N1, H5N1, drug-susceptible, multidrug-resistant TB (MDR TB), and extensively drug-resistant TB (XDR TB), especially among HCWs with HIV infection, and reported high rates of morbidity and mortality have been linked to the absence or limited application of airborne infection-control strategies.[6,7,14] Since then, there has been renewed interest in understanding the impact of infection control measures in medical facilities.

India is the highest TB burden country accounting for one-fourth of the global incidence with 2.2 million incident TB cases emerging annually.[15] In 2012, India's Revised National TB Control Program (RNTCP) managed 1.46 million TB cases,[16] and unknown thousands more were managed in the private sector.[17–20] Prevailing infection control practices in India revolve around biomedical waste management and disposal of sharps; while airborne infection control (AIC) measures are largely absent from the health care facilities' policies and practices.[21] Nosocomial TB has in large part not been addressed by researchers in India, but those few studies that have been published have uniformly reported much higher TB disease rates among HCW than estimated to occur in the general population.[9,12,13]

To address the need for a simple, effective, and affordable AIC program in health care facilities in India, National Guidelines on Airborne Infection Control in Health Care and other settings in India – 2010 (NAIC) were published as the first, formal national guidelines on reducing the risk of airborne infections in health care facilities and special high-risk settings in India (e.g. respiratory disease wards, MDR-TB wards, Antiretroviral treatment centers, and TB culture and drug susceptibility testing laboratories).[21]

Till date, there has not been any large-scale, representative assessment of AIC practices over a broad spectrum and at multiple levels of health care in India. Therefore, as part of the national effort to assess the baseline implementation of the NAIC guidelines, we conducted systematic facility assessments to assess the risk of airborne transmission in 35 selected health care facilities, ranging from tertiary level medical colleges to primary health centers from the 3 states of West Bengal, Gujarat, and Andhra Pradesh. Each site received a tailored set of recommendations of administrative, environmental, and personal protective measures, in line with national guidelines.

We also sought to reassess the implementation of NAIC recommended administrative and managerial control measures by the administrators at state, district, and health care facilities, one year after baseline recommendations.

2. Objectives

- To conduct systematic baseline assessments of AIC administrative, environmental, and personal protective policies and practices within HCF in India and
- To assess the level of NAIC guidelines implementation after one year.

3. Methods

During October 2009–September 2011, 35 HCFs across 13 districts in 3 states of India – West Bengal, Gujarat, and Andhra Pradesh – were selected for facility-based assessments for the risk of airborne disease transmission. The states, districts, and facilities were a nonrepresentative convenience sample, but were purposefully selected to provide experiences with AIC practices at all levels of the health system. Of the 35 facilities, 11 were from West Bengal (across 3 districts), 11 were from Gujarat (across 7 districts), and 13 were from Andhra Pradesh (across 3 districts). At the conclusion of each assessment, a series of written recommendations were provided to HCF administrators to improve policies and practice, based on the NAIC guidelines. After one year, each facility was reassessed to compare NAIC implementation as compared to baseline assessment results.

A multi-agency, multidisciplinary panel of experts conducted standardized risk assessments, including field-based observational visits to document infection control practices, human resource capacity, and administrative and environmental controls. The expert panel included members from the respective state AIC committees with support from the Central TB Division – India (CTD), World Health Organization (WHO), and the Program for Appropriate Technology in Health (PATH). The principal investigator and most of the coauthors were members of these baseline assessments. A standardized risk assessment methodology utilized a structured reporting format covering a range of AIC interventions [i.e., equipment/material to conduct baseline assessment like incense sticks to assess direction of air flow, measuring tape to measure volume of rooms, Vaneometer™ (i.e., swing-vane aneometer) (Dwyer Instruments, Michigan City, IN, USA) and DCFM700 Digital Anemometer (General Tools, New York, NY USA) to measure air velocity from openings, AirMeter 460 (Dwyer Instruments, Michigan City, IN, USA) to measure air velocity from ducts, and digital and mobile phone cameras to take pictures for documentation]; quarterly reports on AIC to monitor implementation of AIC guidelines; structured checklist to monitor coordination mechanisms for tracking administrative activities of the state and district level coordination mechanism; and a predetermined set of monitoring indicators covering administrative and managerial control measures at state, district, and facility levels for data compilation and analysis.

4. Variables and data collection

A predetermined set of indicators of AIC policies and practices were used for describing key administrative, environmental, and personal protective measures (Table 1).

Table 1 – Component-wise themes to assess administrative, environmental, and personal protective AIC measures.

Component	Themes
1. Administrative AIC measures	(i) HCF administrative IC systems with AIC components (e.g., established IC Committees, IC Focal points, written AIC plan) (ii) Administrative AIC practices (e.g., screening, fast-tracking, segregation of infectious cases, TB surveillance in health care workers.)
2. Environmental AIC measures	(i) Environmental IC aspects of various general health departments like Registration, outpatient and inpatient areas, Radiology, Pharmacy. (ii) Environmental IC aspects of special high-risk settings like ART Centers, Integrated HIV Counseling and Testing Centers, Microscopy Centers, MDR TB Wards, MTB Culture-DST laboratories, and Bronchoscopy Centers (e.g., minimum air change per hour, building designs facilitating minimum air change per hour)
3. Personal protective AIC measures	(i) Availability and use of N95 particulate respirators in high-risk settings (e.g., ART Centers, MDR TB wards, Bronchoscopy suits.)

Data were extracted from the detailed reports of the baseline facility risk assessment of all the 35 HCFs. We used a structured checklist to monitor coordination mechanisms and the quarterly AIC reports from the state, district, and facility level submitted to CTD.

5. Data entry, quality assurance, and analysis

All data were entered twice by independent data entry operators in Epi-Info (Centers for Disease Control and Prevention, Atlanta, GA, USA) and checked for internal validation for quality and consistency. The two databases were then compared for discrepancies and a final database was created after correcting discrepancies by referring to the original records and consulting with the concerned HCF administrators. We compared baseline AIC practices and policies, and assessed any change one year later.

6. Ethical approval

As this study represents evaluation of programmatic implementation of national guidelines for AIC in health care facilities, there were no patient-based data and hence no human subjects involved as study population. No formal ethical review was required; however, approval for the activity was sought from the Central TB Division, Ministry of Health and Welfare, Government of India (MoHFW, GoI), as per the recommendation of the National Airborne Infection Control Committee.

The activities undertaken by the state, district, and HCF administrators and AIC committees for this evaluation were within normal scope of their work and there were no additional duties associated with this study. Additional review by CDC institutional review board was not required because CDC investigators were determined not to be engaged in human subjects research as defined by relevant US government regulations (i.e., CDC investigators did not interact with study subjects or have access to identifiable data for study subjects).

7. Results

The characteristics of the 35 HCFs assessed in the study are described in Table 2. Amongst the 35 HCFs, 21 had specific high-risk departments of interest: 10 (29%) had antiretroviral treatment (ART) centers, 7 (20%) had a bronchoscopy suite, and 4 (11%) had departments specializing in MDR-TB treatment. While of the highest proportion of HCFs were secondary-level institutes (46%), 8 (23%) were primary health centers, 7 (20%) were tertiary-level medical colleges, 2 (6%) were for profit, private multi-specialty hospitals, and 2 (6%) TB laboratories.

7.1. *HCF administrative IC systems*

Few facilities had infection control committees (31%), infection control plans (14%), or infection control related activities (e.g., annual IC training) in place at baseline, and among those infection control systems in place, 'airborne' related activities were not included (Table 3).

7.2. *Administrative AIC practices*

Administrative measures specific to AIC were negligible. None of the facilities offered masks to patients with respiratory symptoms, applied fast-track screening algorithms, or isolated potentially infectious patients in separate waiting areas. Six (18%) facilities informed patients on cough hygiene, including 2 (6%) where patients were observed practicing proper cough hygiene/etiquette. TB surveillance among HCW (passive or active) was practiced only in 1 facility.

Table 2 – Characteristics of the Health Care Facilities assessed (*N* = 35).

Characteristic	*n* (%)
State	
Andhra Pradesh	13 (37%)
Gujarat	11 (31%)
West Bengal	11 (31%)
Type of facility	
Medical college	7 (20%)
Private tertiary	2 (6%)
District or subdistrict hospital	11 (32%)
Primary health care center	8 (23%)
TB hospital or clinic	4 (12%)
TB laboratories	2 (6%)
ART only	1 (3%)
Facilities with specific high-risk departments	
ART Centers	10 (29%)
Bronchoscopy suites	7 (20%)
MDR TB Wards	4 (11%)

Table 3 – Results of baseline HCF AIC risk assessment: Administrative IC systems and practices; environmental and personal protective AIC measures (N = 35).

Indicator	N = 35 (%)
HCF administrative IC systems with AIC components	
IC Committee in place	11 (31%)
IC Committee met regularly (>2 times per year)	8/11 (73%)
Written IC plan available	5 (14%)
Written plan includes AIC	0/5 (0%)
IC focal point in place	7 (20%)
Funds routinely available for IC	7 (20%)
IC training for health care workers conducted annually	5 (14%)
IC training includes AIC	1/5 (20%)
Administrative AIC practices	
Cough hygiene information in registration/waiting areas	6/33 (18%)[a]
Patients observed to practice cough hygiene	9/33
Chest symptomatics given masks/tissues/counseling	0/33 (0%)
Dustbins for disposal of any masks/tissues	9 (26%)
Screening and fast-tracking of chest symptomatics	0/33 (0%)
Separation of chest symptomatics in waiting areas	0/33 (0%)
Inpatient segregation practiced by nursing staff	3/23 (13%)
Designated staff responsible for opening windows/vents	0
TB surveillance among HCW (passive or active)	1 (3%)
Environmental AIC measures	
Number of departments assessed	187 (100%)
Minimum ACH possible with natural ventilation alone (including those where minor renovation required)	137 (73%)
Waiting areas that need decompression or relocation	85/165 (52%)
Requiring renovation to achieve minimum ACH, decompression, or segregation	86 (46%)
Personal protective AIC measures	
HCFs where N95 respirators were observed to be used by HCWs in high-risk settings	2/21 (10%)

[a] Labs excluded.

Table 4 – Uptake of the administrative and managerial control measures: one-year follow-up results from AIC reporting system.

Indicator of administrative AIC measures	Baseline (n/N)	One year (n/N[a])	Percent change
HCF with IC Committee in place	11/35	27/34	48%
IC committee meeting regularly	8/11	21/27	5%
Written IC plan available	5/35	19/34	42%
Written IC plan includes AIC	0/5	19/19	100%
IC focal point in place	7/35	30/34	68%
Health care worker surveillance (passive/active)	1/35	17/34	47%
Cough hygiene information	6/33	21/34	44%
Screening and fast-tracking[b]	0/33	20/32	63%
Separation of suspects[b]	0/33	18/32	56%

[a] 1/35 HCF did not report.
[b] 2 labs excluded.

Table 5 – Lessons learnt: one-year follow-up of pilot implementation of national AIC guidelines.

Challenges	Mitigation measures
Gap in engineering capacity to implement environmental recommendations	4 architects from India trained in AIC at Boston (PIH-CDC) followed by in-country training of architects/engineers of 6 states with support of PATH in 2010–11
Routine quarterly AIC reporting	Intensive efforts to generate reasonable levels of reporting
Slow actions by HCF on recommendations from baseline assessments	Periodic reviews of progress made by HCF on recommendations from baseline assessments and site visits if required
Frequent change IC focal point in many facilities of Andhra Pradesh state	Resensitization of new IC focal points in the state

Table 6 – Minimum air-changes per hour (ACH) required for various health care settings.[21]

Type of health care setting	Minimum ACH	Minimum ventilation rate (l/s/patient)
Registration/Waiting	>6	>40
Outpatient departments	>6	>40
Inpatient departments	>6	>40
High-risk settings	>12	80–160
ART Centers		
TB/Chest departments		
Bronchoscopy procedure rooms		
MDR-TB wards and clinics		
Airborne isolation rooms		

7.3. *Environmental AIC measures*

In total, 187 various departments across the 35 HCFs, ranging from registration and outpatient departments to high-risk settings, were assessed for minimum recommended (Table 6) air changes per hour (ACH). Almost half of the departments assessed ($n = 103$) did not have the minimum recommended ACH at the time of testing. Notably, minimum ACH was determined to be achievable in 73% of the departments with natural ventilation alone (i.e., by virtue of the design of the health care facility structures), or through minor renovation. However, 51 (27%) of the departments tested required major renovations, decompression, or relocation of waiting areas to achieve the minimum ACH and prevent airborne transmission from infectious patients.

7.4. *Personal protective AIC measures*

Among the high-risk departments where infectious TB was most likely to be encountered (e.g. TB culture and drug susceptibility testing laboratories, MDR-TB treatment wards, and ART Centers), routine N95 respirators use was observed in only 2 of the 21 facilities with specific high-risk departments listed in Table 2. Unfortunately, in both departments, proper technique for use and fit needed improvement; there was no record of proper fit testing or training for the respirators issued.

7.5. *Reported improvements in AIC activities one year after baseline assessments*

The implementation of administrative and managerial control measures reported by the administrators at state, district, and health care facilities, one year after issuance of baseline recommendations, are described in Table 4. It was encouraging to observe that the efforts of advocacy, capacity building, coordination mechanisms, baseline assessments, and follow-up with state and districts officials and HCF administrators lead to substantial improvement in AIC policy and practice. Moreover, the lessons learnt to mitigate the challenges faced after the baseline assessment and recommendations are summarized in Table 5. As a health system strengthening activity, this experience has developed into a broader initiative to ensure greater accountability, systematic scale-up, and sustainability of AIC systems in the country.

8. Limitations

Our assessment and intervention involved purposively selected states and a limited number of purposively selected health care facilities. These may not be representative or applicable across all settings in India. The effect of the intervention on infection control policies and practices was assessed from regular reports provided by the facilities, and those results were not independently validated. Follow-up assessment on adherence to environmental recommendations has not yet been conducted at the time of preparation of this paper. A sequel to this study is planned in which all the 35 health care facilities will be subjected to post-assessments using the same methodology as the baseline. This will give a comparison with greater validity and also open the opportunity to assess the effectiveness of environmental and personal protective measures recommended in the baseline risk assessments in line with the national guidelines. Although, air velocity was measured in various settings to assess ACH, measurement of ventilation, e.g., using tracer gas (e.g., CO_2) dilution methods, could not be undertaken as the objectives focused around assessing feasibility of implementation of AIC measures in health care settings in India. The study also does not assess the impact of these interventions on reduction of nosocomial transmission, neither by surveillance among HCWs nor use of tuberculin skin tests at entry level and annually, as there were no human subjects involved and this is beyond the scope of the study objectives.

9. Discussion

Across a broad range of health facilities in 3 states, AIC practices were poorly implemented prior to the adoption of the NAIC guidelines. Specifically, AIC systems in India were underdeveloped, the airborne component was generally not included in existing infection control systems, and administrative controls were not commonly practiced. There were IC systems in place in many settings, and those could be leveraged for AIC through training and education of key staff members. About half of the departments surveyed within the participating facilities needed minor renovation to achieve minimum environmental standards. Most environments could be effectively ventilated with natural ventilation, but nonusage of available ventilation (i.e., shut windows) or layered modifications, such as deliberate blocking of windows, had reduced the potential ventilation. This is substantiated by the study on natural ventilation by Escombe et al.,[22] which concluded that opening windows and doors maximizes natural ventilation so that the risk of airborne contagion is much lower than with costly, maintenance-requiring mechanical ventilation systems. Natural ventilation is particularly suited to limited-resource settings and tropical climates, where the burden of TB and institutional TB transmission is highest. The tendency toward better climate control with air-conditioners created AIC risk and engineers will need to be sensitized on optimizing the balance of cooling expense and risk and comfort.

Use of personal protective measures by HCWs was found to be negligible even in high-risk settings. This challenge might

be overcome through proper training, education, and monitoring mechanisms. It was observed that HCWs were well trained and demonstrated competency with other infection control practice, such as biomedical waste management. Integrating AIC principles into existing general infection control training and education modules was recommended.

Despite poor implementation of AIC practices at baseline, we found substantially improved AIC practices after raising awareness of the NAIC guidelines and offering facility-specific recommendations to enhance policy and improve practice. This suggests that concerted effort to implement NAIC guidelines can effectively improve facility infection control standards and limit the risk of nosocomial airborne infection transmission, even in settings where AIC measures were lacking.

Our experience demonstrates that AIC implementation is fundamentally feasible, even in low-resource settings. India needs to move toward scale-up of the intervention package, with emphasis on integration of AIC into existing health system IC activities that include development and implementation of an integrated comprehensive infection control training material for frontline HCWs. The systematic scale-up across all health care facilities in the country can serve as preparedness plan for airborne pathogens of pandemic potentials. This can also help curb transmission of endemic diseases like TB and M/XDR TB, as a primary prevention intervention to complement the larger TB control efforts in India.

Conflicts of interest

The authors have none to declare.

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Original Article

Evaluation of use of line probe assay on smear-positive direct specimen from extra-pulmonary tuberculosis site

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ABSTRACT

Background: Line probe assay (LPA) is used for first-line drug susceptibility testing (DST) of smear-positive pulmonary tuberculosis (TB) patients. For extra-pulmonary (EP) and smear-negative TB patients, the samples are inoculated in culture and isolates of *Mycobacterium tuberculosis* (MTB) are tested on LPA. This results in considerable delay and loses the benefit of rapid diagnostics. In the present study, smear-positive EP specimens were tested directly on LPA and their results were compared with LPA conducted on culture isolates of same specimens.

Method: All EP specimens received from different parts of Gujarat State in 2014 were subjected to ZN smear microscopy and inoculated on liquid culture. Smear-positive samples were directly tested with LPA. Simultaneously, culture isolates of MTB were also subjected to LPA. Results of LPA conducted on both direct specimen and culture isolates were compared.

Result: Of 391 extra-pulmonary specimens, 177 were smear positive and tested directly on LPA. Simultaneously, 88 were culture positive and their isolates were tested on LPA. With LPA on direct specimen, 127 (32%) had valid results with median time to diagnose rifampicin resistance of 5 days (IQR 2-7). In comparison, 88 (23%) specimens had valid results with culture isolates tested on LPA and with longer turnaround time (18–40 days). Among 51 samples, with valid LPA results both on direct samples and isolates, 50 (98%) had concordance for drug resistance pattern.

Conclusion: There is advantage in testing extra-pulmonary smear-positive samples directly on LPA and the results would also be available rapidly.

1. Background

Drug-resistant (DR) tuberculosis (TB) has been a growing challenge for TB control. Globally, 450,000 cases of DR-TB were estimated to occur in 2013.[1] Diagnosis of DR-TB early has always been a constraint. Rapid and more sensitive diagnostic tools based on molecular detection of TB bacilli like line probe assay (LPA) and Cartridge Based Nucleic Acid Amplification Test (CB-NAAT) have emerged and are used, while many more such diagnostic tools are in the pipeline. These molecular techniques have certainly been able to diagnose DR-TB patient more

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efficiently and rapidly. Early and definitive diagnosis of TB and DR-TB in extra-pulmonary (EP) samples has always remained a challenge. Drug susceptibility testing (DST) in EP-TB patients is still relied upon phenotypic method (solid/liquid culture). These methods are always having limitation of time consumption.

LPA is one of the rapid diagnostics tools that was introduced early for diagnosis of DR-TB. And, it has been endorsed for the use of first-line drug susceptibility testing (DST) of smear-positive sputum specimens of pulmonary TB patients.[2] However, for the extra-pulmonary and smear-negative TB patients, the samples are inoculated in culture and isolates of MTB are tested on LPA. Culture inoculation and growth of TB bacilli before LPA results in considerable delay, and such patients are deprived of the benefit of rapid diagnostics. Testing of EP-TB-positive samples direct on may yield results in a short time and give all those advantages of molecular testing to the EP-TB patients as well.

In the present study, a concurrent comparison was made on the LPA results obtained on smear-positive extra-pulmonary specimens and their corresponding LPA results obtained from culture growth.

2. Methods

It was a cross-sectional study.

The study was conducted at Intermediate Reference Laboratory in the state of Gujarat in western part of India. This laboratory was one of the sites that participated in the LPA validation study, based on which LPA was introduced under Revised National TB Control Programme in the country. The laboratory has also LJ and Liquid culture and DST facilities for both first- and second-line drugs. LPA facilities are available since 2009. External Quality Assurance systems are in place in laboratory as per programmatic guidelines and certified by RNTCP.

Ethical committee approval was received from the IEC of the BJ Medical College, Ahmedabad, while administrative approval was received from the State TB Cell, Gujarat.

All extra-pulmonary specimens received in 2014 at the laboratory from different parts of Gujarat state were included in the study. The laboratory receives samples of TB patients with history of anti-TB treatment for more than one month, HIV-reactive TB patients and contact of DR-TB patients who are eligible for drug susceptibility testing under programmatic conditions.

Two specimens of eligible patients were collected and transported in cold chain to the laboratory without addition of any transport media. Specimens were opened in bio-safety cabinets. Each EP specimen was processed as prescribed in SOP of the RNTCP for processing EP specimens.[8] Smear microscopy examination was carried out with Zehil Neelsen (ZN) staining procedures on concentrated specimen.[3] Specimens with smear-positive result were directly subjected to LPA using Genotype MDRplus version II following standard operating procedures, as recommended by manufacturer.[4] Simultaneously, all processed samples with smear-positive or -negative results were inoculated into MGIT 960 Liquid Culture.[5] Isolates from MTB-positive culture were also subjected to LPA. Results of LPA conducted on both direct specimen and culture isolates were compared.

We have used single terminology 'Invalid' for MTB not detected by LPA and not amplified properly or not amplified completely, and processing of specimen may be compromised at lesser extent.

To overcome contamination in MGIT, we have re-decontaminated all MGIT tubes and re-inoculated on MGIT and L-J media. We have given final negative results by Liquid culture and also if declared by Solid L-J media.

3. Results

In year 2014, extra-pulmonary specimens of 419 patients were received for drug susceptibility. At the time of study, 391 patients had both smear microscopy and culture results available and were included in the study. Of those patients included in the study, 12% were children (below 15 years), 64% were between 15 and 55 years and 15% were above 55 years age. Male–female ratio of patients included in the study was 1.6.

Out of all extra-pulmonary specimens, 98 (25%) were pleural fluid, 48 (12%) CSF, 54 (14%) other fluid (ascitic, joint, and spinal), 109 (28%) samples were of pus, 40 (10%) were lymph node tissue and 11 (3%) were other tissue biopsy, 4 (1%) urine samples and 27 (7%) others.

Out of 391 specimens, 177 were found to be smear-positive, and direct specimens could be tested on LPA. Among those specimen tested directly on LPA, 127 samples had valid LPA results with presence of TUB band, 43 samples had invalid results and another 7 samples could not be tested due to scanty 1 or 2 results on smear/blood in the samples. Hence, among all EP samples, 32% (127) valid drug susceptibility results could be attained by testing direct sample on LPA. All 391 extra-pulmonary samples were also inoculated on culture irrespective of their smear results. On culture, 88 (22.5%) specimens had MTB growth and their isolates were tested on LPA with valid results (Fig. 1).

Overall, 42% (164) valid results were reported by conducting LPA on both direct specimen and culture isolates of all the extra-pulmonary specimens processed. 51 (13%) had valid results of LPA on both direct specimen and on culture isolates, 76 (19%) specimens had valid LPA results only on LPA and 37 (9%) specimens had valid LPA results only on culture isolates (Table 1).

There was no contamination in LPA and all negative controls were clear with each run. With regard to MGIT, the contamination was handled as described in Section 2.

On comparing resistance pattern of these specimens tested with two different methods, concordance for rifampicin was 98% and same proportion of concordance was observed for isoniazid resistance (Table 2).

The median time to diagnose rifampicin resistance was 5 days (IQR 2-7) when LPA is carried out on direct EP specimens. In comparison, the turnaround time was longer (18–40 days) in specimens, which were inoculated in culture, and then, their isolates were tested on LPA.

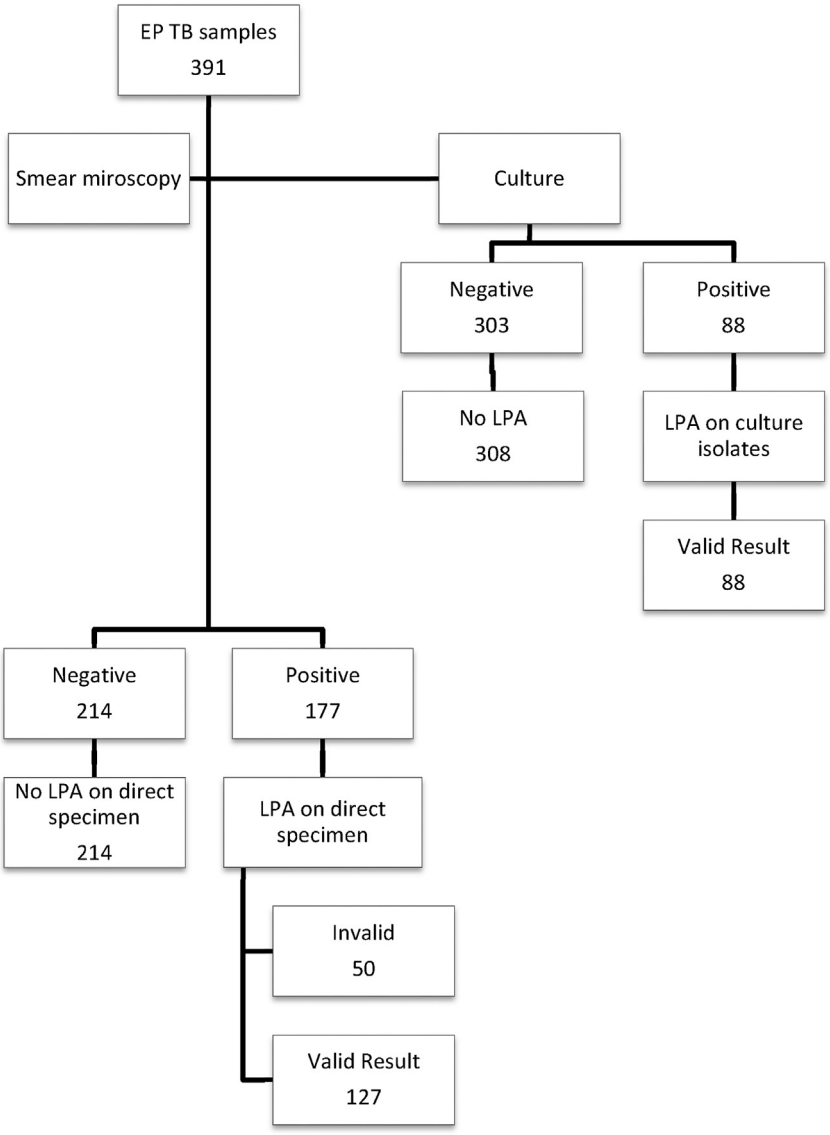

Fig. 1 – Results of LPA on direct samples and on culture isolates.

Table 1 – Comparison of results of LPA conducted on direct specimen and culture isolates.

LPA on direct specimen	LPA on culture isolates		Total
	MTB growth on culture and valid LPA result	No MTB growth on culture and LPA not done	
Smear-positive and valid LPA result	51	76	127
Smear-positive and invalid or no result	7	43	50
Smear-negative and LPA not done	30	184	214
Total	88	303	391

4. Discussion

LPA has been endorsed for use in the diagnosis of MDR-TB; and Genotype MTBDRplus assay in particular has been labelled for use on isolates from solid and liquid cultures as well as directly on, smear-positive pulmonary specimens.[2] The present study explored the use of Genotype MTBDRplus assay directly in smear-positive extra-pulmonary clinical specimen for the first time in India under programme conditions. The study found that Genotype MTBDRplus gives a good proportion of valid results (32%) when used directly on smear-positive extra-pulmonary specimen presumptive of DR-TB. In fact, this method gave better yield than inoculating specimen in culture, and subsequently, testing culture isolates with Genotype MTBDRplus.[9] Because of the paucibacillary level in extra-pulmonary TB type, chances of recovery of viable bacilli on

Table 2 – Comparison of resistance pattern of valid results of LPA conducted on direct specimen and culture isolates.

LPA on direct specimen	LPA on culture isolates				Total
	Resistant to both R and H	Resistant to only R	Resistant to only H	Sensitive to both R and H	
Resistant to both R and H	12			1	13
Resistant to only R		2			2
Resistant to only H			3		3
Sensitive to both R and H			1	32	33
Total	12	2	4	33	51

processed samples will be less and hence, the yield. This may be the basis of getting higher yield in testing direct specimen with Genotype MTBDRplus assay as compared to testing culture isolates in the present study. Low yield of recovery of MTB in extrapulmonary specimens has been documented in earlier evidence.[10]

In addition, turnaround time for diagnosis of rifampicin resistance patients was reported to be 5–6 times lower as compared to conventional method of growing bacilli on culture and then subject isolates for LPA in this study. This is similar to observations reported on use of LPA for pulmonary TB.[2,6,7] The present observation suggests the advantage of testing extra-pulmonary smear-positive samples directly on LPA and should be considered for fast tracking the management of DR-TB patients with EP site involvement.

For smear-negative extra-pulmonary specimen, use of culture isolates for testing on LPA had given 14% additional valid results. Hence, testing of isolates on specimens that did not have results on direct specimen due to smear-negative or invalid results should be considered.

With regard to results of DR pattern, a high concordance was observed when comparing the two methods. We have received very less quantity of specimens and those were processed for smear, culture and DNA extraction for LPA. We have stored processed deposits in some specimens where quantity of EP specimens was sufficient, but for these discordant specimens, deposits were not available. Hence, we were unable to recheck with another method.

In the study, a notable 50 samples had no valid or invalid results. This is due to scanty smear positivity and extraction of DNA may be low and not enough to amplify at detectable level. Also, there are blood-tinged specimens, which was put on LPA and may result into invalid due to PCR inhibitors. One more reason is NTM. One more limitation was that 58% of the specimens could not have valid results because either smear was negative or there was no detectable growth on culture.

In conclusion, LPAs on smear-positive direct specimen reduces time to diagnosis as well as it gives better number of valid results as compared to conventional method of testing culture isolates on LPA among EP-TB patients. Limitation of low recovery of MTB in EP specimen will still prevail, though as in the case of culture.

Conflicts of interest

The authors have none to declare.

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Original Article

Emerging applications: Screening OSA by Modified Pictorial Epworth Sleepiness Scale in Indian subjects

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pESS (Pictorial Epworth Sleepiness Scale)
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OSA (obstructive sleep apnoea)
AHI (apnoea and hypopnoea index)
Receiver operating curve
Area under curve

ABSTRACT

Background: The Epworth Sleepiness Scale (ESS) is a widely used scoring to measure excessive daytime sleepiness. This scale was designed to be self-completed by the subjects, but unfortunately in a developing country with low literacy this had affected its outcome interpretation. The Traditional ESS has been translated into a Modified Pictorial version for easy comprehension by the patients.

Method: Subjects were evaluated for their competence to self-complete the ESS (Conventional and Pictorial) in Sleep Clinic at Respiratory Department of Santosh Medical College and Hospital, Ghaziabad. Modified Pictorial representations were designed along with 5 newer questions incorporated as sub-questions in 8 original domains prepared and labelled as Pictorial Scale. The Traditional (ESS) and Pictorial (Modified) representations were compared for agreement by receiver operating curve and the area under curve.

Results: It was found that time taken to complete the Traditional ESS was significantly higher in comparison to Modified Pictorial Epworth Sleepiness Scale with reduced errors (Pictorial ESS 4.67 min than Traditional ESS 14.43 min).

Conclusions: Modified pictures scale showed statistically significant improvements over ESS and hence can be used as an alternative for subjects with low literacy level.

1. Introduction

Obstructive sleep apnoea-hypopnoea (OSAH) is characterised by recurrent episodes of upper airway collapse and obstruction during sleep. These episodes of obstruction are associated with recurrent oxyhaemoglobin desaturations and arousals from sleep. OSAH associated with excessive daytime sleepiness (EDS) is commonly called obstructive sleep apnoea-hypopnoea syndrome (OSAHS). Despite being a common disease, OSAHS is under-recognized by most primary care physicians in India. Comorbidities like hypertension and diabetes further exacerbate the symptoms of obstructive sleep apnoea (OSA) and make control of blood pressure and sugar more difficult.

Pictures or pictorial aids are a useful adjunct to medical information and aid the transfer and comprehension of written and spoken information. It has been observed and proven that instruction of medication or any utility, manual understanding of instructions has been shown to be better when pictures are used in conjunction with, or instead of, the written words. Even in those with normal literacy skills, such interventions are important as they can improve both understanding and compliance with medical treatment.

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Keeping in view of the socio-economic factors and high illiteracy in our country, it was decided to translate the Traditional Epworth Sleepiness Scale (ESS) into Pictorial scales and customizing it as per the needs of the Indian rural as well as urban class of population.

2. Methods

The study was carried out in tertiary care hospital, Santosh Medical College & Hospital, Ghaziabad, U.P. Data were

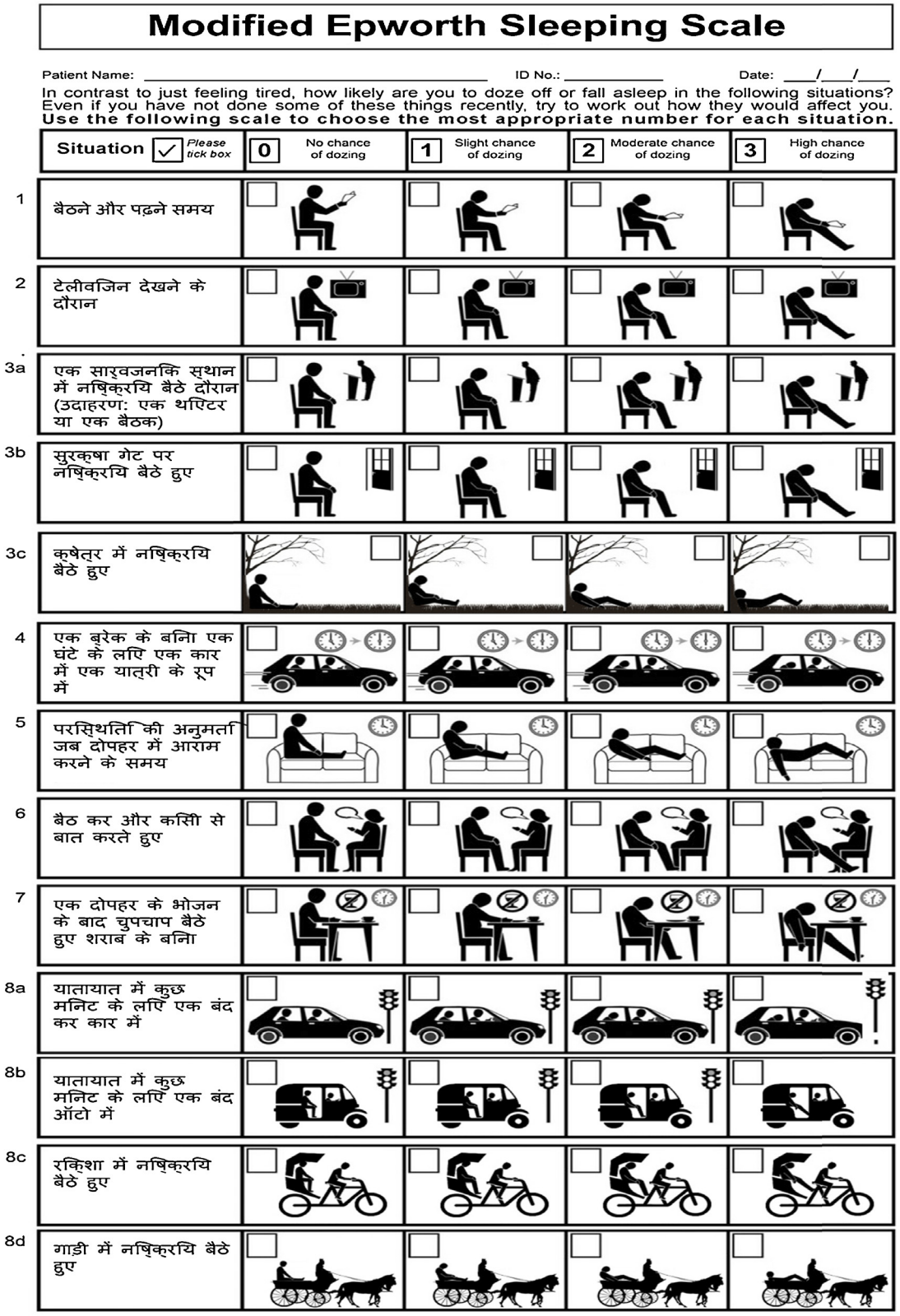

Fig. 1 – Modified Pictorial Scale of Azmat Karim and Vijay Kumar Arora.

Table 1 – Characteristics of the study subjects of different studies.

Characteristics	Portuguese[5]				German[4]	Study (new) (mpESS)
	Control N = 21	Insomnia N = 21	Primary snoring N = 34	OSAHS N = 59	Normal subject N = 159	Normal subject N = 40
Age						
Mean ± SD	36.1 ± 8.0	40.8 ± 12.6	43.1 ± 12.0	49.7–8.6	35 ± 13	55.9 ± 10.2
95% CI	23–46	18–61	19–60	26–60	33–37	53.0–59.0
Gender						
F/M	12/9	14/7	26/8	25/34	75/84	10/30
BMI						
Mean ± SD	23.0 ± 2.7	24.2 ± 2.9	27.8 ± 6.9	31.3 ± 6.8	30.2 ± 7.4	30.1 ± 6.4
95% CI	18.4–29.2	17.4–30.1	19.5–48.1	18.3–58.4	29.1–31.3	28.0–32.1
AHI						
Mean ± SD	0.8 ± 0.9	0.7 ± 0.9	2.2 ± 1.4	29.9 ± 24.2		27.4 ± 30.9
95% CI	0.0–3.7	0.0–3.7	0.0–4.5	5.4–104.8		17.5–37.2
ESS						
Mean ± SD	5.2 ± 3.0	5.3 ± 2.6	8.8 ± 3.5	13.5 ± 5.1	5.7 ± 3.0	13.0 ± 3.0
95% CI					5.2–6.2	12.0–14.0

collected from the patients attending, pulmonary functions testing lab, Sleep Lab and patient going for their pre-assessment for respiratory disease during pre-anaesthesia clearance. The translated Traditional ESS was named Indian version of ESS (IESS) and pictorial version was called Modified Pictorial Epworth Scale (mPESS).

The main objective of translating the Traditional ESS Questionnaire to pictorial changes was to have clarity and better understanding by the illiterate population in the study group.

Five new Pictorial Layouts of the Questionnaire was created against the Traditional ESS, and the choices of scores for the individual items were displayed as an array of scales from 0 to 3 with their corresponding value. In Original Pictorial ESS,[1,2] a sub-group of new category pictures was incorporated to make it easier for the subjects to respond (as shown in Fig. 1).

3. Results and discussion

Forty subjects participated in this study and were evaluated and have their ability to self-complete the ESS Questionnaire. This study was undertaken in sleep and non-sleep respiratory clinics. Errors or problems encountered were recorded on a standard questionnaire.

The study results were compared with the other study[3] reported in the literature. They have evaluated 82 subjects who completed the Traditional written ESS and pESS. Total scores range from 0 to 24 and mean pESS and Traditional ESS questionnaire score of 9.24 (±4.48) and 9.56.46 (±4.99) were mostly similar. Results reported in different studies[4,5] are similar and comparable. pESS was preferred (54.9%) over the Traditional word only ESS (45.1%). However, in the present study, 96% reported the pESS as very easy to complete in contrast with the word ESS questionnaire and 100% preferred mPESS, indicating it as being a better tool not only in self-completing the questionnaire quickly but also for better understanding (Table 1).

Such a significant data difference in the above study[6] and a follow-up study[7] suggests that the pictorial format would explain the sleepiness scale better. The patients with OSAS may find the need for better understanding of Pictorial form of information.

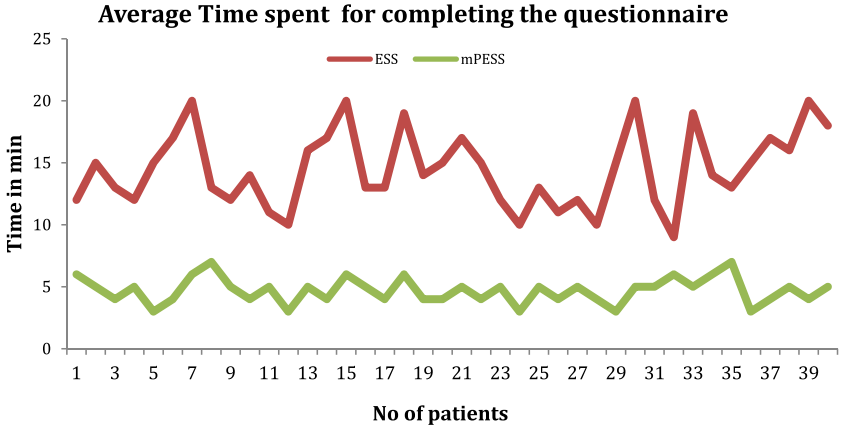

Fig. 2 – Time graph showing time spent in Traditional ESS and mPESS.

In the present study, time spent for completing the questionnaire by both the group was calculated. Time taken to complete each scale was noted (using stop clock) from the time of distribution of questionnaire by the counsellor to all the subjects till they completed and returned it back. Separate logbooks were maintained to record the time spent on both the ESS and mPESS. It was found that time spent on Traditional ESS and modified Pictorial had significant difference of 14.43 min on Traditional ESS versus 4.67 min on Pictorial ESS, which is statistically significant as has been shown in Fig. 2.

Our study validates the Indian version of the Modified Pictorial Epworth Sleepiness Scale (mPESS) and has provided a better alternative for screening subjects in busy OPD settings; communication time with patients is less and hence, Modified Pictorial scale may be used as an important tool for Screening OSA.

4. Limitation of study

This study was completed in a hospital setting. There is more need for operational/clinical research using mPESS, to evaluate further its impact in diagnosing OSA in resource-constraint settings.

5. Recommendation

The mPESS can be used in Indian subjects (i.e. busy OPDs) as a better screening tool, which will be easier to administer for patients with OSA.

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Conflicts of interest

The authors have none to declare.

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Short Communication

Does effect of BCG vaccine decrease with time since vaccination and increase tuberculin skin test reaction?

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ABSTRACT

The protective efficacy of BCG was studied for over 15 years, from 1968, in South India. A secondary analysis of data was performed to investigate the relationship between Bacille Calmette-Guérin (BCG) and tuberculosis (TB) disease and between BCG and positive tuberculin skin test for different time periods among children aged less than 10 years. A randomized controlled trial was conducted, where 281,161 persons were allocated to receive BCG 0.1 mg, BCG 0.01 mg or placebo. Tuberculin skin test was performed at baseline and at 4 years after BCG vaccination. Surveys were conducted every 2.5 years to detect all new cases of culture-positive/smear-positive TB occurring in the community over a 15-year period. Relative risk (RR) was obtained from the ratio of incidence among the vaccinated and the placebo groups. Among those children vaccinated with 0.1 mg of BCG, the RR for TB was 0.56 (95% CI: 0.32–0.87, $P = 0.01$) at 12.5 years but increased to 0.73 later. Similar pattern was seen with 0.01 mg. The increase in the number of skin test positives with 0.1 mg of BCG was 57.8%, 49.4% and 34% for cut-off points at ≥10 mm, ≥12 mm and ≥15 mm, respectively. The study suggests that the effect of BCG may decrease since vaccination and the tuberculin positive was higher at post-vaccination test period due to BCG.

1. Introduction

The 2014 WHO Global Tuberculosis (TB) Report showed that there were 9 million people who developed TB in 2013. India alone accounted for 24% of the total cases in the world in that year.[1] It is a well known fact that the efficacy of presently available Bacille Calmette-Guérin (BCG) vaccine varies widely with geographical latitude.[2,3] It was proved that the use of BCG vaccination did not offer any protection against pulmonary TB disease especially among the adult population, and only a low level of overall protection of 27% in children aged <10 years based on the Chingleput BCG trial.[4] TB still remains a major problem worldwide and especially for India. Prevention will be

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greatly facilitated by the development of a new vaccine that would show consistent protection. The cut-off point of 12 mm was defined for tuberculin positive for the BCG trial data as the antimode of the distribution of reaction sizes was at 12 mm.[5] BCG given in childhood or at an older age results in a positive tuberculin reaction.[6] Studies have shown that the protective efficacy of BCG against TB may decrease with time since vaccination.[7] We presented a secondary analysis of data from the BCG trial to investigate the relationship between BCG and TB disease, and between BCG and positive tuberculin skin test.

2. Methods and materials

A double-blind, randomized controlled trial was initiated in 1968 in a large rural community in Chingleput district in south India, to assess the protective efficacy of BCG vaccination, employing a 0.01 mg of BCG and a 0.1 mg of BCG. A total of 281,161 individuals were allocated randomly to receive vaccine or placebo. They were tested with 3 international units (IU) of PPD-S and 10 units of PPD-B at baseline. Also, a post-vaccination allergy was tested with 3 IU of PPD-S at a different site than used for the first two tests at baseline at 4 years on a selected sample of population. Case finding for TB was continuous in this area with resurveys, selective case finding and an activated passive case finding.[5] Relative risk (RR) was obtained from the ratio of incidence among the vaccination and the placebo groups.

The full study details have been published earlier.[4,5] The Institutional Ethics Committee of the National Institute for Research in Tuberculosis, Indian Council of Medical Research, approved the trial.

3. Statistical methods

Logistic regression model was employed to assess the RR for TB for two BCG vaccinated groups. The relationship between BCG vaccinated groups and tuberculin skin test was evaluated using chi-square test. A *P*-value of less than 0.05 was considered as statistically significant.

4. Results

This analysis considers children aged <10 years with the tuberculin skin test reaction of 0–7 mm to PPD-S and normal radiograph in three groups, i.e., 0.01 mg of BCG, 0.1 mg of BCG and placebo. At baseline, the study subjects were 20,265, 20,372 and 20,344, respectively. The same cohort of children was investigated over six follow-up periods (0–2.5, 0–5.0, 0–7.5, 0–10.0, 0–12.5 and 0–15.0 years) to estimate the RR due to BCG vaccination. For 0.01 mg of BCG vaccination group, in 0–2.5 years, the RR was estimated to be 2.01, and increased to 2.51 in 0–5.0 years and decreased steadily to 1.00, 0.93 and 0.69 at subsequent follow-up periods, and later increased to 0.79 in 0–15 years. Similar pattern (RRs: 1.66, 2.00, 0.83, 0.81, 0.53 and 0.73) was also seen for 0.1 mg of BCG group (Table 1). BCG was not significantly effective at any point except for 0.1 mg of BCG at 12.5 years. In terms of BCG efficacy, higher level of protection was estimated to be 31% (95% CI: −9 to 56%) and 47% (95% CI: 13–68%) due to 0.01 mg of BCG and 0.1 mg of BCG vaccination, respectively, in 0–12.5 years.

The cohort of children aged <10 years at baseline, who were also given post-vaccination tuberculin test at 4 years, was 11,741, 11,610 and 11,641 in placebo, 0.01 mg of BCG and 0.1 mg of BCG groups, and their data were analyzed to confirm whether the BCG vaccination increases the tuberculin skin test reaction size at post-vaccination test period. The cut-off point of 12 mm was defined for tuberculin positive for the BCG trial data as the antimode of the distribution of reaction sizes was at 12 mm. However, the tuberculin positive subjects were classified according to different cut-offs, ≥10 mm, ≥12 mm and ≥15 mm at baseline and post-vaccination test periods. BCG vaccination time point was significant. The positive skin test in all the cut-off points was more than twice at post-vaccination testing period when compared by baseline survey and thus BCG vaccination was significantly associated with tuberculin skin test results.

The proportions of tuberculin positive in cut-offs ≥10 mm, ≥12 mm and ≥15 mm increased to 41.5%, 33.9% and 23.4%, respectively, in 0.01 mg of BCG group at post-vaccination testing period. Similarly, in 0.1 mg of BCG group, the tuberculin

Table 1 – Effect of BCG vaccine over study duration among children aged <10 years with 0–7 mm PPD-S and normal radiograph at baseline.

Follow-up duration (years)	Placebo		0.01 mg of BCG				0.1 mg of BCG			
	TB cases, *n*	Person-years, *n*	TB cases, *n*	Person-years, *n*	Relative risk (95% CI)	*P*-Value	TB cases, *n*	Person-years, *n*	Relative risk (95% CI)	*P*-Value
0–2.5	3	50,853	6	50,648	2.01 (0.50–8.03)	0.32	5	50,918	1.66 (0.40–6.96)	0.49
0–5.0	6	101,698	15	101,273	2.51 (0.97–6.47)	0.06	12	101,818	2.00 (0.75–5.32)	0.17
0–7.5	18	152,513	18	151,890	1.00 (0.52–1.93)	0.98	15	152,710	0.83 (0.42–1.65)	0.60
0–10.0	26	203,308	24	202,493	0.93 (0.53–1.61)	0.79	21	203,588	0.81 (0.45–1.43)	0.47
0–12.5	45	254,055	31	253,078	0.69 (0.44–1.09)	0.11	24	254,458	0.53 (0.32–0.87)	0.01[a]
0–15.0	60	304,765	47	303,623	0.79 (0.54–1.15)	0.21	44	305,278	0.73 (0.50–1.08)	0.12

CI, confidence interval.
[a] Statistically significant.

positive increased to 57.8%, 49.4% and 34.0%, respectively. To investigate the relationship between tuberculin positive and BCG vaccinated groups related to placebo, the RRs were estimated for the above cut-off points. The RR of positive test of 1.04 (95% CI: 0.97–1.11) in 0.01 mg of BCG group at baseline increased to 1.39 (95% CI: 1.35–1.44) at post-vaccination testing period, and also in 0.1 mg of BCG group the RR increased to 1.94 (95% CI: 1.88–2.00) from 1.0 (95% CI: 0.94–1.09) for cut-off ≥10 mm. Similar increase in RR of tuberculin positive was seen for other cut-off points and BCG vaccinated groups (not tabulated).

5. Discussion

In the larger study conducted, it was shown that the BCG did not protect the adults from TB and only a low level of overall protection of 27% in children aged <10 years over a 15-year period. Also, the protective efficacies seen among non-reactors to PPD-B did not differ significantly from those seen among reactors to PPD-B.[4] On the other hand, we had an opportunity to re-analyze the data to investigate the level of BCG protection since with vaccinated time point at different follow-up durations, and the increase in tuberculin positive due to BCG vaccination in children below 10 years at baseline. It is seen that the effect of BCG over different study periods varied. The RRs in 0.01 mg of BCG measured varied from 2.01 at 0–2.5 years to 0.69 at 0–12.5 years follow-up and later increased to 0.79 at 0–15.0 years. In the first 5 years, the children appear to be at a higher risk of developing TB. Similarly, the RR in 0.1 mg of BCG measured was 0.53 ($P = 0.01$) at 0–12.5 years follow-up and later increased to 0.73 at 0–15.0 years. This shows that the protective efficacy decreases with time since vaccination. A significant protective effect of BCG was seen only at 12.5 years after vaccination in 0.1 mg of BCG in our study. In a meta-analysis that addressed whether the efficacy of BCG changes with time, using 10 randomized controlled trials of BCG against TB in which data for separate time periods after vaccination were available and reported, there was no good evidence that BCG provided protection for more than 10 years after vaccination.[7] A retrospective follow-up study among American Indians and Alaska Natives who participated in a placebo-controlled BCG vaccine trial during 1935–1938 reported an effective BCG vaccine can have a long duration of protection for 50–60 years.[8] Many controlled trials have followed efficacy for 10–15 years and have shown some decline with time and could only be expressed as an efficacy lasting up to 15 years.[9]

Some children who were not infected might had a reaction due to infection with other mycobacterial species or to BCG vaccine, and it was evident from our study due to BCG that the children with positive results increased to 41.5% (RR = 1.39, $P < 0.0001$) at post-vaccination testing from 11.6% (RR = 1.05) at baseline in 0.01 mg of BCG group with cut-off ≥10 mm, and similarly, the proportion increased to 57.8% (RR = 1.94, $P < 0.0001$) from 11.3% (RR = 1.01) in 0.1 mg of BCG. Similar pattern was observed in other cut-off points also for BCG groups. Thus, our study confirms with a study conducted elsewhere, which shows that those with a prior history of BCG vaccination were more likely to boost their reaction.[10] Therefore, the children who were recently vaccinated are more likely to be tuberculin skin test positive due to BCG vaccination.

6. Limitations

We have assumed that the fairly large number of children included in the post-vaccination tuberculin test only comprised about half of the initial baseline of children and would not have affected the results. We do not have few more survey results beyond 15 years follow-up to confirm whether the BCG vaccine efficacy wanes steadily with time.

7. Conclusion

Our study finding suggests that BCG efficacy may decrease with time since vaccination and increase the positive tuberculin skin test reactions. A new vaccine would take these into account to protect against TB infection and disease.

Conflicts of interest

The authors have none to declare.

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Short Communication

Social inclusion: An effort to end loss-to-treatment follow-up in tuberculosis

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ABSTRACT

Situation analysis: Pathanamthitta district is implementing Revised National Tuberculosis Control Program as a pilot district since 1993. The district programme was reporting approximately 5% of their diagnosed smear positive patients as never put on treatment (Initial lost to follow up – ILFU) and 5% of the new smear positive [NSP] Pulmonary TB patients as lost to follow up [LFU] during treatment. Attempts based on reengineering of DOTS were not largely successful in bringing down these proportions.

Intervention: A treatment support group [TSG] is a non-statutory body of socially responsible citizens and volunteers to provide social support to each needy TB patient safeguarding his dignity and confidentiality by ensuring access to information, free and quality services and social welfare programs, empowering the patient for making decision to complete treatment successfully. It is a complete fulfilment of social inclusion standards enumerated by Standards for TB Care in India. Pathanamthitta district started implementing this strategy since 2013.

Outcomes: After intervention, proportion of LFU among NSPTB cases dropped markedly and no LFU were reported among the latest treatment cohorts. Proportion of ILFU keeps similar trend and none were reported among the latest diagnostic cohorts.

Lessons: Social support for TB care is feasible under routine program conditions. Addition of standards for social inclusion in STCI is meaningful. Its meaning is translated well by a society empowered with literacy and political sense.

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1. Introduction

TB care is complex. Morbidity, catastrophic expenditures, difficult access, social stigma, confidentiality issues and adverse reactions to drugs often weave a tricky web around the sick patient. Quite often these rank high among the determinants of patient's adherence to TB treatment. Supervised treatment by a health worker has proven to be effective in experimental models and under program conditions in significantly improving adherence to treatment and outcomes of treatment.[1] However, Direct Observation of Treatment (DOT) alone has not resulted in 100% adherence to treatment and a significant proportion of patients are lost to follow up [LFU] even in settings, where DOT is practiced well. Adherence to TB treatment is important in preventing relapse and emergence of resistance. There may be effective interventions beyond DOT to promote adherence to treatment.

2. Situation analysis

India is implementing Revised National Tuberculosis Control Program (RNTCP) since 1997. The erstwhile National TB Control Program (NTP) was accused of detecting only 30% of the estimated TB cases and successfully treating only 30% of the notified TB cases. RNTCP based on DOTS strategy has dramatically improved the situation by enhancing case detection to 70% and favourable treatment outcomes to 85%, among the newly smear positive pulmonary TB patients. However, 5% or more of such patients were being LFU during treatment at country level.[2] Studies have described social stigma, access issues, alcohol addiction, adverse reactions to drugs, co-morbidities, etc. as to the cause of this loss.[3] It varies from state to state. LFU during treatment was beyond the entity termed as ''initial lost to follow up'' [ILFU] which literally translates into ''diagnosed but not put on treatment'' that amounts to approximately another 5% of the cohort of diagnosed patients.

Kerala, the southernmost state of India, is implementing RNTCP since 1998. It is estimated to have a relatively low TB burden compared to other parts of the country.[4] Since then, the state was reporting approximately 5% LFU among new smear positive (NSP) cases and approximately 6% ILFU among all diagnosed smear positive cases.

Pathanamthitta district started implementing RNTCP since 1993 as a pilot district [Fig. 1]. This rural district has 1.2 million population with a density of 452/km^2, moderately hilly terrain with reasonable access to health care services including TB care. Urban segment is 11% and adult literacy rate is 97%. Being the national pilot district, RNTCP infrastructure is ideal, with adequate human resources provided by the state health services. During each quarter year, the district program approximately tests 4000 presumptive TB cases, diagnoses

Fig. 1 – Political map of Kerala showing Pathanamthitta district.

175 smear positive cases, registers 300 TB cases in total including all types, of which 150 are NSP. Since launching, the district program was reporting approximately 5% of NSP being LFU during treatment and 5% of all smear positives as ILFU. DOT was difficult to implement during the early days of program implementation, which led to high rates of failure and relapse among those who did not receive treatment under strict supervision.[5] However, later on DOT has gained wide acceptance among the patients and in the community, and supervision of treatment has become the norm.

For more effective implementation of DOT to prevent LFU, the district programme introduced the concept of a ''DOT triad'' in 2012. A DOT triad is a three-way transaction among the patient, DOT provider and the representative of health system, who is often a multipurpose health worker [MPHW] designated by the primary health centre for every 5000 population. Thrice weekly regime followed by RNTCP necessitates thrice weekly transaction between the patient and DOT provider at the base of the triad. The MPHW acting as a monitoring agent for DOT and a link to health care delivery from the primary health centre forms the common apex of all such triads in the population. The relatively stronger health system in the state provided a contusive environment for this reengineering of DOTS strategy. However, even this attempt to reinforce DOT did not have the desired impact on LFU or ILFU.

3. Treatment support groups [TSGs] – the novel intervention strategy

Standards for TB Care in India released on 24th March 2014 is bold and loud in enumerating the standards for social inclusion.[6] In parallel to the drafting stages of STCI, the program management team of Pathanamthitta district was developing plans to implement the social inclusion standards to improve case holding. Patient-centred approaches were developed to provide social support to each patient from the diagnosis to successful completion of treatment. A call to develop the novel concept of a ''treatment support group'' to support every patient in each Panchayat of the district was responded well; thanks to the strong political commitment of the three-tier Panchayat Raj system implemented with its high democratic principles in the state.

4. Methodology/model

A TSG is a non-statutory body of socially responsible citizens and volunteers to provide social support to each needy TB patient safeguarding his dignity and confidentiality by ensuring access to information, free and quality services and social welfare programs, empowering the patient for making decision to complete the treatment successfully. The group is usually chaired by the president of Gram Panchayat (the lowest tier local self-government), its health standing committee chairperson or a local opinion leader. Members of the group are the Medical Officer [MO], MPHW, community DOT provider, experienced informal counsellors, community-based or faith-based organization [FBO] members, Janamythri police (citizen-friendly police), local philanthropists and other community volunteers. This group supports the DOT triads. Routine house visits, contact screening, provision of DOT and follow-up services delivery are done by the community DOT provider and MPHW and clinical monitoring and screening for adverse reaction to drugs are done by the MO. Not all, but only the needy patients are provided additional support by TSG, the need being assessed by the MO, MPHW or DOT provider. TSG links the patient to social welfare schemes, District Panchayat's nutritional support project, Alcohol de-addiction or local benevolence. For example, a patient needs transportation support to go to DOT centre, a community volunteer or taxi driver may pick and drop him free of cost, or a local philanthropist may pay for the service. A patient tends to interrupt treatment would be counselled by the counsellor member. Emotional and spiritual support would be provided by the FBO member. This support on occasions has provided shelters to homeless TB patients, attendant service at hospital indoors and provision of resources to manage comorbidities such as diabetes and cardiovascular diseases.

5. Resources

The model does not burden the health system for additional resources. Camaraderie, which is the most valuable resource, is the cheapest and most universal. Additional nutritional support is provided through the district Panchayat's project. A TB pension is provided at Rs. 1000 per month till the completion of treatment through a revenue department scheme. Hospital expenditures when incurred by the patient are supported by Rashtriya Suraksha Bima Yojana [RSBY], the public health insurance scheme.

6. Outcomes

The district was implementing the concept of DOT triad, the reengineered DOTS strategy from mid-2011 to end 2012. TSG strategy was launched by end 2012 through recruitment, sensitization and linkage. Trend of LFU among NSP cases explains correlation of intervention strategies with outcomes (Fig. 2). LFU rates of NSP patients of quarterly cohorts till 3rd quarter [July to September] 2011 was unacceptably high around 6% and reaching around 10% on odd occasions. During the DOT triad period, these quarterly cohorts reported a slight drop in LFU rates to below 5%. Since the roll out of TSG strategy, LFU rate was falling markedly to strike zero for the cohort initiated on treatment during 3rd quarter [July to September] 2013. After 2013, there were absolutely no LFU among NSP pulmonary TB patients in Pathanamthitta district.

Initial defaulting also followed similar trend (Fig. 3. Trend of proportion of ILFU among NSPTB cases, Kerala state and Pathanamthitta district, India). Year 2013 marked drastic decrease of ID that touched zero for many quarterly cohorts afterwards. Odd upswings were reported to be due to unannounced switching of worksites by one or two migrant labourers from neighbouring states during the process of their TB diagnosis.

During the period of social inclusion interventions in Pathanamthitta district, there was minimal decline in the

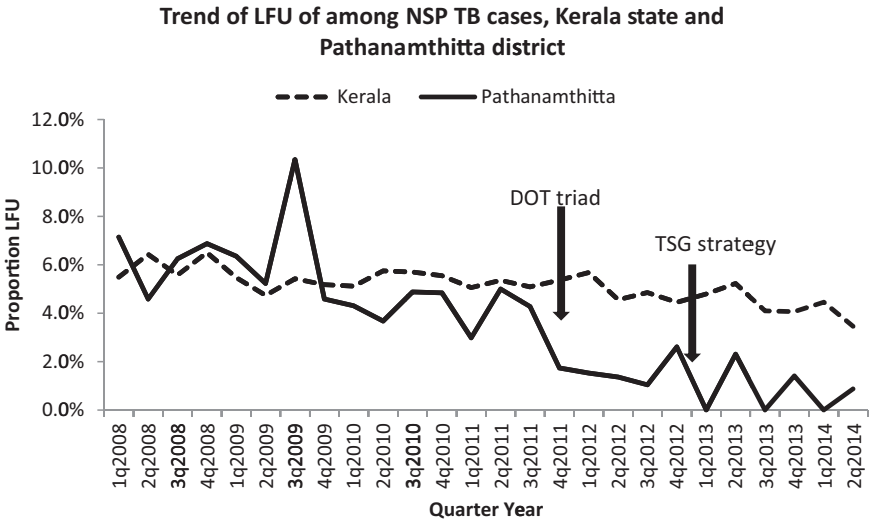

Fig. 2 – Trend of LFU of among NSP TB cases, Kerala state and Pathanamthitta district, India. LFU, loss to follow up; NSPTB, new smear positive tuberculosis.

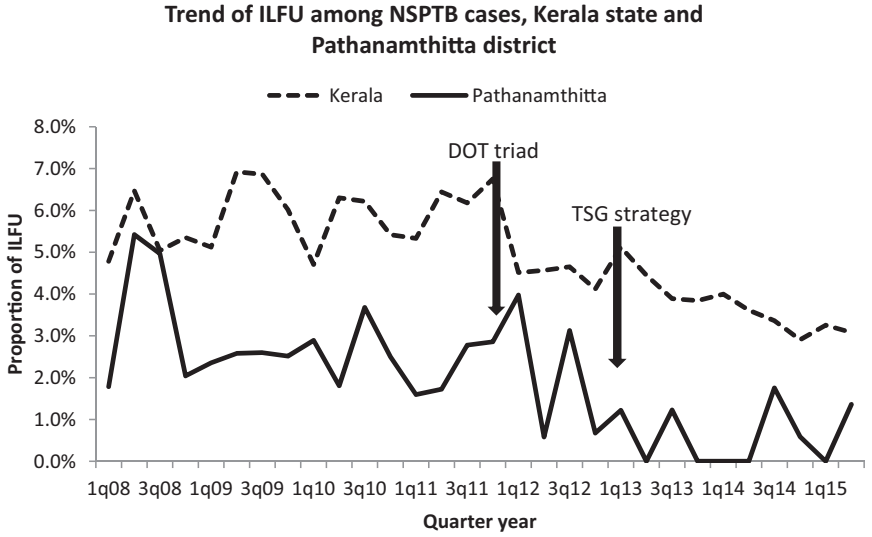

Fig. 3 – Trend of proportion of ILFU among NSPTB cases, Kerala state and Pathanamthitta district, India. ILFU, initial loss to follow up; NSPTB, new smear positive tuberculosis.

proportion of LFU in the entire state. Proportion of ILFU in the district was always lesser than that of the entire state. There was considerable decline in the proportion of ILFU in the entire state during the period of intervention in the Pathanamthitta district.

7. Challenges

Advocacy to community on TSG strategy in each of the Gram Panchayat and demand generation was highly challenging. Holding together individuals with diverse interests to a common goal of TB care is more challenging, especially when a few of the groups may be idling for long periods in the low TB prevalent and relatively affluent setting of the district. Most challenging is the delivery of support without compromising the dignity and confidentiality. It requires continuous monitoring and capacity building. The high literacy rate of the district may have facilitated the capacity building of TSGs.

8. Lessons

TB care is complex, more so in program settings. It remains so only in the absence of high social and political commitment. The bends and curves of TB care pathway entangles into chaos in the absence of hands to untwine them. Social support for TB care is no more a dream. It is a reality feasible under routine program conditions. Addition of standards for social inclusion

in STCI is meaningful. Its meaning is translated well by a society empowered with literacy and political sense.

Implementation of DOT triad concept reduced LFU to a limited extend, but not ILFU. It may be because DOT triad concept applies only after initiation of treatment. However, TSG strategy starts with diagnosis, thus proving effective in preventing both ILFU and LFU.

Conflicts of interest

The authors have none to declare.

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Forum

Public–private mix for TB care in India: Concept, evolution, progress☆

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ABSTRACT

To achieve ''Universal access to TB care and treatment for all'', Revised National Tuberculosis Control Programme (RNTCP) has taken steps to reach the unreached by synergizing the efforts of all partners and stakeholders. RNTCP is engaging with private sector partners in major cities of India with primary focus on notification through innovative partnership mechanisms. The manuscript details the concept behind the public–private mix for TB Care in RNTCP, its evolution and progress over the decades in India.

1. Background

1.1. *The relevance of PPM in India*

The non-government sector is a critical part of health care delivery in India. The private sector in India consists of a vibrant but varied set of sub-groups that provide services that are preferred by the majority of the population. The sector offers services that are generally described as being more accessible and responsive to the needs of patients. On the other hand, this sector remains largely unorganized, unregulated and unempowered, with the technical quality of some sections of the sector remaining a concern. India has millions of private health-care providers (PPs), including qualified and unqualified health practitioners, pharmacies and laboratories. They account for roughly 80% of the first contact of patients (from all socioeconomic groups) with health-care providers, and at least half of those treated for TB in India.[1] Studies conducted since the 1990s have documented the extent to

☆ Sreenivas Achuthan Nair, K. Rade, and A. Moitra A are technical staff of the World Health Organization. The views expressed in this article do not necessarily represent the policies of the organization.

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which TB is diagnosed and treated in the private sector, as well as the prevalence of largely inappropriate diagnostic and treatment practices.[2–4] Private providers rarely request sputum microscopy and rely excessively on chest X-rays and inappropriate tests, such as TB serology, which has recently been banned by the GoI.[5] Despite the ban, serological tests continue to be performed in some laboratories, while other laboratories have replaced these with tests, such as IGRA, which are not indicated for diagnosis of active TB.[10] Most people with active TB visit more than one private provider (mostly local informal providers and chemists) and take antibiotics or other treatments, even if most of them eventually register with the RNTCP.[6] If patients do start on anti-TB drugs, they can rarely afford the full treatment and usually stop taking them as soon as they feel better. TB drugs are freely available over the counter, and prescription audits have shown that irrational prescription of TB drugs is a widespread practice, which might partially explain the emergence of MDR and XDR-TB in India.[3,4,11] Patients from low-income households lose several months of their income in the process of paying for inappropriate diagnostics and treatments before starting therapy under the RNTCP.[7] As a result, there are delays in diagnosis, unnecessary patient expenditure, and irrational or unsupported treatment. When patients finally reach the public sector, they are financially constrained, and in many cases, they have developed drug-resistant TB. Thus, diagnosis and treatment of TB in the private sector is both a problem and an opportunity.

Revised National Tuberculosis Control Programme (RNTCP) has established itself as a strong and effective way to deliver TB care in the public sector providing a firm base upon which PPM efforts can be built. While, the reality of this sector creates constraints as well as potential for improvements in service delivery of public health programmes, its integration into public health systems is the way to enable provision of service elements in a seamless continuum of care, increase coverage of health services, decrease delays in treatment, and ultimately improve patient outcomes and disease control.

2. Challenges

Many small pilot projects have been undertaken in India to engage private providers in quality-assured TB care, as specified by the national guidelines.[8] Most of these have been conducted at a very small scale, and the best business model for engaging with the private sector remains elusive.[9] Private providers are the first point of care for the vast majority of TB cases and yet, it is estimated that they contribute just 2–3% of case finding and less than 1% of case management under the RNTCP. The many challenges hampering meaningful engagement of private providers include poor relationship between the private providers and the state, which is often characterized by a deep mutual mistrust. Market forces are often powerful impediments to the adherence of private providers to government protocols. Private providers very often make considerably more profit from practices that are not in the best public health interest than from practices recommended by the RNTCP. These irrational practices are supported by the concerted marketing efforts of pharmaceutical and diagnostic companies, and often conform to the client's expectations of what constitutes quality care. The state's regulatory enforcement mechanisms are too weak to control the private market, considering its size and fragmentation.

3. Early experiments

PPM had been recognized as a requirement for effective TB control early in the programme. There are some important PPM initiatives early in the programme; one of the better examples is the systematic efforts to involve medical colleges in RNTCP. By creating national, regional, state and medical college task forces, RNTCP was successful in engaging this large sector, with about 20% of TB case notification being from these medical colleges. As early as 2003, a pilot PPM project was implemented in 14 urban sites in India. WHO-PPM medical consultants and peripheral field supervisors were recruited and posted to these districts. An expanded version of the existing routine RNTCP surveillance system collected disaggregated data from the different health-care providers. Providers were involved through a systematic process of situational analysis and listing of health-care facilities, sensitization and training of practitioners on RNTCP, training of RNTCP staff on PPM-DOTS, identification of facilities for RNTCP service delivery, memoranda of understanding and RNTCP service delivery. The data from the intensified PPM sites have shown an overall increase in the number of TB cases notified under RNTCP.

3.1. *Mahavir Project, Hyderabad*

This is one of the early models where a private sector hospital was engaged with RNTCP. The setting was that of a non-profit hospital providing DOTS services to a population of 100,000 for 3 years, and then expanded coverage to 500,000 in October 1998 in which a Tuberculosis Unit model was developed. The detection rate increased from 50 to 200/100,000 over the first 2–3 years of the project.[12]

Another early PPM project was the Kannur project (in India's southern state of Kerala). The project targeted private laboratories and was credited with a 21% increase in detection of NSP TB cases.[13]

On reviewing various early PPM projects in India, we can see some commonality. The public sector tuberculosis programme provided training and supervision of private providers; case notification rates were higher after implementation of a public–private mix project; in many projects, private providers exceeded the programme target of 85% treatment success for new patients positive for acid fast bacilli. A number of cost effectiveness studies were carried out for the PPM. The overall conclusion drawn from such studies is that PPM requires additional investment costs but if implemented on a large scale, the costs to the programme for PPM are comparable to public sector costs and much less than a situation where there is no standard management practices for TB in private sector. The overall societal costs for treatment in PPM settings would be much lower because of savings to patients in terms of reduced shopping before and opportunity costs during treatment.[13–15] Using the experiences gained from the collaborations with

NGOs and the private sector, the Central TB Division (CTD) published guidelines for the participation of the NGOs (2001) and private practitioners (2002).[16] These guidelines were revised in 2008 and again in 2014.

4. Current status

To achieve "Universal access to TB care and treatment for all," RNTCP has taken steps to reach the unreached by synergizing the efforts of all partners and stakeholders. This change is reflected through increased allocation for partnerships, increase in manpower through sanction of dedicated positions to focus on partnership at state and district levels, greater flexibility to allow for innovation, capacity building through focussed training and an enabling environment to pilot new initiatives. RNTCP is now engaging with private sector partners in major cities of India with primary focus on notification through innovative partnership mechanisms.[17]

Major PPM initiatives include:

4.1. *The IMA RNTCP PPM project*

The IMA RNTCP PPM project started in the year 2008 in five states and one union territory of India, covering 167 districts. Subsequently 10 more states were added. The objective of this project was to improve access to the diagnostic and treatment services of RNTCP and thereby, improve the quality of care for patients suffering from tuberculosis through the involvement of Indian Medical Association. The key activities undertaken as part of the project include state/district level workshops, publication of quarterly TB/RNTCP newsletter, publication in JIMA, district level CME's of all the IMA branches in the target states, produce IEC materials, assist DTOs in training of private providers, etc.[18]

4.2. *CBCI-CARD Project*

Catholic Bishops Conference of India-Coalition for AIDS & Related Diseases (CBCI-CARD) is a civil society organization comprising over 3000 healthcare and social work facilities, associated with the Catholic Church in India. The CBCI-CARD Project works to improve access to TB diagnostic and treatment services within the Catholic Church Healthcare Facilities (CHFs). Under this partnership, across 19 states of India, field consultants visit CHFs, conduct situational analysis and liaise with programme managers and other CHF personnel to participate in TB control and care.[18]

4.3. *Involvement of pharmacists*

As community pharmacies are often the first port of call for patients seeking healthcare, systematic and comprehensive engagement of pharmacists and chemists is crucial for early diagnosis and proper treatment of patients. The CTD collaborated with the Indian Pharmaceutical Association (IPA), All India Organization of Chemists & Druggists (AIOCD), Pharmacy Council of India (PCI) and SEAR Pharm Forum representing World Health Organization (WHO) – International Pharmaceutical Federation (FIP) Forum of National Associations in South East Asia for engaging pharmacists in TB control in India.[18]

There have been several other positive developments in the recent years. National consultations were held for better PPM engagements and a National Technical Working Group has been established. Serological testing for TB has been banned and TB has been made a notifiable disease, with a case-based electronic notification (NIKSHAY) system developed for the notification of cases. Standards for TB Care in India (STCI) were developed for bringing together the right standards in diagnosis, treatment, public health and social inclusion for all.[19] STCI has become the yardstick in measuring quality standards in TB care, including in public and private sector. This has levelled the playing field for the private sector also and is helping better PPM engagement in a large way. Strategic opportunities are presented by several key developments, such as the emergence of new diagnostic technologies and advances in mobile phone penetration and applications.

4.4. *The national guideline for partnership*

The National Guideline for Partnership[20] was developed in 2014 on how different stakeholders can supplement the efforts of the government for TB control in India. The National Guideline for partnership consists of four thematic areas: Advocacy Communication and Social Mobilisation (ACSM); Diagnosis and treatment; TB and Co-morbidities; Programme Management.

Diagnosis and treatment partnership, which will have more scope for involvement of private sector, consists of 6 categories for working to provide diagnostic services namely microscopy services in hard to reach areas and also providing treatment services with microscopy services as per the need of the programme. There is an option to provide quality diagnostic culture and DST services through partnership with laboratories in the private sector or laboratories run by NGOs. A new partnership option is to start MDR TB centre in the partnership with private hospitals on outdoor or indoor basis or to provide specialist services in government MDR TB centres. There is a new partnership option for involvement of corporate hospitals for notification, referral and management of TB patients by incentivizing the services offered. There is partnership option for involvement of NGOs/partners for TB control services in urban slums. There are opportunity for providing ART services treating TB-HIV cases, intervention for TB-HIV patients at community level and for involvement of paediatricians for childhood TB.

4.5. *Universal access to free anti-TB drugs*

Encouraging results have come from three pilot projects in which free anti-TB drugs for all TB patients including private sector are provided to achieve universal access following STCI. Once a qualified practitioner diagnose and decide to treat a TB patient outside the scope of RNTCP, s/he will notify the case using Information and communication Technology (ICT) enabled mechanisms and prescription details relevant to anti-TB drugs are shared with contact centre. Based on it, a unique voucher number is generated and shared with practitioner and patient. The voucher number written on prescription is carried by patient to chemist. The voucher is validated by chemist with help of contact centre and free anti-TB drugs are given to patients. Patient is contacted telephonically for confirmation of receipt of free medicine and later at

home, for extending public health services like contact screening, chemoprophylaxis, adherence and infection control counselling, HIV testing and DST services, etc.

5. Future prospects

The National Strategic Plan 2012–2017 of RNTCP prescribes the development and deployment of engagement models that will overcome the barriers of mutual mistrust, conflicting market forces and fragmentation, so that the TB care provided by the private sector can be improved and encompassed within the programme.[17] At the national and state levels, a technical support group (TSG), which will focus on effective contract management and other partnership-strengthening functions, will be established within the RNTCP. Private Provider Interface Agencies (PPIAs) contracted in the states manages the activities required for engaging the private sector. The other measures required for future PPM includes rapid uptake by the national TB programme of internationally approved diagnostic and treatment protocols, more reliance on market forces rather than normative exhortation, increased use of accreditation and contracting for further outreach to private laboratories, stronger regulations on anti-TB drugs and innovative use of information and communication technologies.

The main impediments to the successful execution of the PPM strategy include the lack of capacity within the programme in areas, such as cost analysis and contract design, and protracted procurement processes. The persistent mistrust of the private sector, both in the context of the programme as well as in the broader political and administrative context, may lead to a lack of commitment to the new strategy in some states and districts. The success of the strategy is to some extent dependent on developments outside the TB programme, such as the strengthening of regulatory processes and the development of IT systems. Strong leadership will be of the utmost importance in tackling the possible pitfalls. A new spirit of genuine partnership will be needed, sufficient resources will have to be allocated and accountability will have to be established.

Conflicts of interest

The authors have none to declare.

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Forum

Transitioning to daily treatment for drug-sensitive TB in India

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ABSTRACT

World Health Organization in its treatment guideline for tuberculosis 2010 recommended daily dosing as the preferred regimen in treatment of drug-sensitive TB patients. The Revised National Tuberculosis Control Program took a decision to implement daily regimen in five states of India in 2015. This article describes the policy-making chronology, evidences used, stakeholders involved, and process of decision making.

1. Background

The Revised National Tuberculosis Control Program (RNTCP) was launched in India in 1997, based on World Health Organization recommended Directly Observed Treatment Short Course (DOTS) strategy, with treatment given three times a week (intermittent regimen).[1] In spite of evidence from randomized controlled trial from South India,[2] feasibility of supervising each dose consumption and adherence to treatment, and lower cost of implementation of thrice-weekly regimen with limited resources were factors thought to favor adoption of intermittent treatment regimen.

With emergence of new evidences bally, World Health Organization in its treatment guideline for tuberculosis 2010 recommended daily dosing as the preferred regimen in treatment of drug-sensitive TB patients.[3] By 2012, worldwide, 127 out of 132 countries that started with intermittent treatment regimens have switched to daily treatment.[4] In year 2015, RNTCP took a decision to implement daily regimen as a policy and initially roll out in selected states of the country. This article describes the policy-making

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chronology, evidences used, stakeholders involved, and process of decision making.

2010–2012	The type of regimen to be used for drug-sensitive TB patients was discussed at various forums such as national program review meetings, technical committees, national task force of medical colleges, and expert groups. The discussions led to recognition of the need for in-depth analysis of program data and review available scientific literature in country context.
Joint Monitoring Mission (JMM) September 2012	Tuberculosis JMM India (2012), a team of international and national experts reviewed the program performance and recommended that: '*In line with the international recommendations and WHO TB treatment guidelines, India needs to consider changing the RNTCP regimen to a daily regimen including the feasibility to using fixed-dose combination (FDC) for harmonizing the national TB treatment policy.*'[5]
Standards for TB Care in India (STCI) December 2012	In 2012, the program convened a high level national consultation to develop the standards of care for TB patients in India. Around 140 national and international experts perused the in-country data. The experts noted a high proportion of previously treated cases, relapses, baseline resistance to Isoniazid (INH), and MDR TB among relapses. STCI recommended that '*All patients should be given daily regimen under direct observation. However, the country program may consider daily or intermittent regimen for treatment of TB depending on the available resources and operational considerations as both are effective provided all doses are directly observed. All pediatric and HIV infected TB patients should be given daily regimen under direct observation.*'[6]
National Expert Committee on TB diagnosis and Treatment January 2013	RNTCP National Expert Committee on TB diagnosis and Treatment endorsed the recommendations of the national consultation on standards for TB care. This included the adoption of daily regimen harmonizing TB treatment practices across public and private sector. The merits of these recommendations were perused by the policy makers and additional evidences were sought from the program.
First meeting of High level expert committee to examine the type of regimen to be used under RNTCP September 2013	A high level expert committee was constituted to examine the additional evidences to guide the policy makers for transitioning to daily anti-TB regimen considering both technical and operational aspects. The following were considered by the committee. Intermittent therapy in tuberculosis is pharmacologically acceptable, and is based on the premise that all patients receiving such a regimen would be receiving at least more than 80% of the doses without interruption. However, even if one dose is missed in the thrice-weekly regimen, it essentially could result in a twice-weekly dosing, which is suboptimal for TB treatment. RNTCP has consistently achieved the objective of treatment success of 85%.[7] However, the program does not routinely monitor long-term treatment outcomes (relapse) and the emergence of acquired drug resistance. Relapse rate of 10–12% was noted in several studies from India among patients who received intermittent treatment.[8,9] A systematic review of 20 studies concluded that the risk of relapse is related to the total dose administered and that the relapse rate remains within the acceptable limit of 5% only with either daily administered six month regimens or regimens that incorporate a daily intensive phase followed by a thrice-weekly continuation phase.[10,11] Another key factor influencing successful outcomes for first line anti-TB therapy is the presence or absence of isoniazid resistance. Systematic reviews have shown that in the presence of isoniazid resistance, intermittent regimen is associated with higher rates of acquired rifampicin resistance than daily regimen.[12] It is also well documented that in the presence of isoniazid resistance, intermittent treatment performed far worse, with relapse rates of up to 20% within 18 months.[13] National data on drug resistance have shown consistently high resistance to isoniazid, with rates of up to 10–15% in new patients, and 30–40% among previously treated patients.[14] Thus, intermittent therapy can no longer be considered an effective regime in these groups. The committee acknowledged the fact that relapse rates of TB under the RNTCP are more than 10% consistently for more than a decade (as against the internationally acceptable limit of relapse rate below 5%). However, the committee desired further analyses on relapse and in country evidence on INH resistance.
National Technical Working Groups (NTWG) on pediatric TB and HIV associated TB July–October 2013	National Technical Working Groups (NTWG) on pediatric TB and on HIV associated TB also recommended use of daily dosing using FDC in first line TB treatment for children and HIV associated TB respectively. The policy makers also referred these recommendations to the high level expert committee to examine the type of regimen to be used under RNTCP.
Second Meeting of the high level Expert committee to examine the type of regimen to be used under RNTCP March 2014	The second meeting of the expert committee to examine the type of regimen to be used under RNTCP for drug-sensitive TB subsumed experts from the NTWGs. The committee examined the program data and evidences from India on relapse, development of acquired drug resistance, and treatment outcome among patients treated with intermittent regimen. [15–18] The committee noted that there were convincing evidences on a consistent trend of high mortality and acquired drug resistance among HIV-associated TB patients. The committee observed that the interim data available from on-going researches at National AIDS Research Institute (NARI) and National Institute for Research in Tuberculosis (NIRT) suggest a daily regimen has the potential to decrease mortality and prevent development of drug resistance. The committee endorsed the recommendations of NTWGs to roll out daily regimen for treatment of TB patients including TB in PLHIV in selected areas of the country. The committee also advised the program to develop a protocol for implementation pilot in action research mode representative areas of all regions in the country.
Policy for roll out of daily regimen for TB-HIV patients September 2014	The policy was made to roll out daily regimen for TB/HIV patients in identified ART centers in high HIV burden states in September 2014.

Third high level Expert committee to examine the type of regimen to be used under RNTCP	The program developed the protocol for implementing daily regimen for drug-sensitive TB patients in identified 100 districts, and the expert committee approved the same.
November 2014	
Formulation of technical specifications for first line FDCs for daily regimen	As a next step, a technical committee deliberated on specifications of first line Anti-TB drugs in daily dosages for adults and children. The technical committee recommends the use of FDCs as per the drug requirement in different weight bands and combinations in line with the STCI.
February 2015	
Sixth JMM	The sixth JMM, in its debriefing meeting, reiterated the strong scientific evidence for daily regimen and recommended immediate transition to daily regimen.
April 2015	
Development of operational plan to roll out daily regimen under RNTCP	A panel of experts, while developing the operational plan recommended statewide implementation in few states instead of 100 districts due to operational considerations. The experts also delved on the issue of incremental cost to the program, the utilization of existing drug stocks, the supply chain management, and quality assurance mechanisms. The committee also noted that in view of the recent decentralization of TB Units (basic program management units) to block level, additional human resources may not be required for adherence support. The panel of experts also advised the program to draw a plan for engagement of all stakeholders, development of technical and operational guidelines, capacity building of the existing staff, and assessing preparedness of the selected states to roll out daily regimen concurrent with the process of procurement of drugs. This should be complemented by intensive communication and social mobilization strategies, a plan for identification and management of adverse drug reactions as well as a plan for monitoring and evaluation of the rollout.
April–May 2015	
Policy Decision	The rollout of daily regimen was approved in identified five states covering 104 districts. These include Maharashtra (west zone), Sikkim (North East zone), Bihar (East zone), Kerala (South zone), and Himachal Pradesh (North zone). A detailed operational plan for transitioning to daily dosing first line TB treatment and for procurement of drugs has since been developed and the process of procurement of daily FDCs has been initiated. It is expected that the initial rollout would commence in first quarter of 2016.
June 2015	

2. Likely impact

With implementation of daily regimen, it is expected that over a period of 5 years, RNTCP would be able to avert 5,80,726 active pulmonary TB cases (due to aversion of relapse and new infections), 40,390 deaths, and 23,450 MDR-TB cases. The indirect benefits of implementing daily regimen would far outweigh the direct incremental costs in terms of reduction in mortality, improvement in quality of life, fall in new infections, and would thus lead to accelerated decline in incidence and reduction in acquired drug resistance. It is also expected that harmonization of treatment practices across public and private sector would lead to better engagement of the program with the private sector in order to move toward universal access to quality TB care.

3. Conclusion

Transitioning to daily anti-TB treatment regimen is a good example of how the program data be analyzed and presented to the policy makers to enable them to arrive at an evidence-based decision in the context of delivering high quality services for the larger public good. This process also showed of how involvement of all stakeholders can influence the processes of decision making to shape evidence based policy. It also underscores the need to keep the policy makers informed of the emerging evidences in the scientific arena for timely absorption and adoption of newer tools and strategies. Scientific knowledge will continue to evolve with time and as new evidences become available, every program will need to make necessary changes in its policies and program management practices.

Conflicts of interest

The authors have none to declare.

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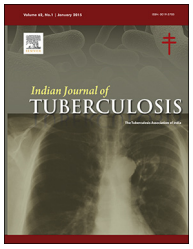
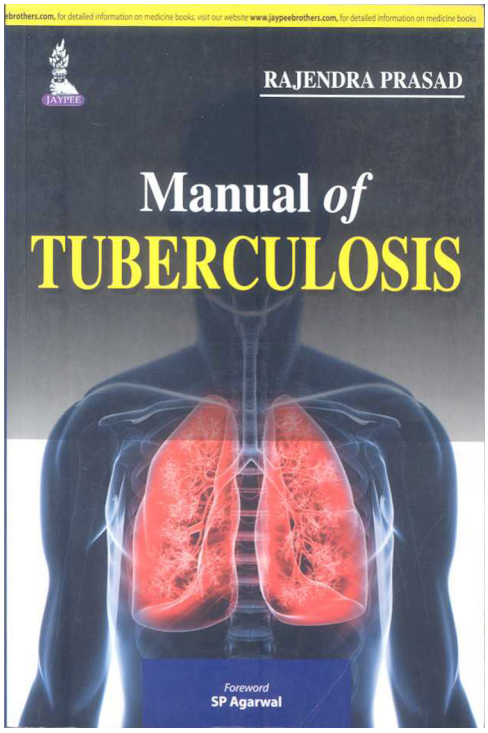


Book review

R. Prasad, N. Gupta, Manual of Tuberculosis, Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, India (2015).
ISBN: 978-93-5152-222-5



The paper-bound book consists of 36 chapters dealing with primary and post-primary tuberculoses, DOTS strategy, epidemiological and diagnostic aspects and chapters on some basic concepts in treatment of tuberculosis. Extra-pulmonary tuberculosis chapter gives an insight into the current concepts and strategies for re-treatment. The preventive aspect consists of discussion on BCG and newer vaccines. TB with co-morbidities such as diabetes and HIV has been discussed. Adverse reactions owing to anti-tubercular therapy and anti-retroviral therapy have also been discussed in the manual. There are five colour plates showing fluorescence staining method and Ziehl Neelsen staining method.

The book could have been enriched with separate chapters on geriatric and paediatric tuberculoses.

Having written in a simple language, it will be useful for undergraduate and postgraduate students. The book is recommended as a useful addition in the library of medical institutes.

Conflicts of interest

The author has none to declare.

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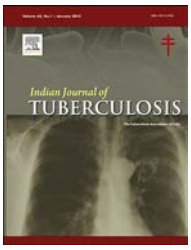

Abstracts

Ventilator-associated tracheobronchitis and pneumonia

Palmer LB. *The Lancet Respiratory Medicine* 2015;**3(11)**:823–900. http://dx.doi.org/10.1016/S2213-2600(15)00361-6

The diagnosis and treatment of respiratory tract infections in mechanically ventilated patients have become increasingly controversial. In addition to the clinical importance of prevention and treatment of ventilator-associated infections, there are now political and economical pressures to reduce the incidence of ventilator-associated pneumonia. However, as long as endotracheal intubation remains the gold standard method of providing ventilator support to critically ill patients, pathogenic bacteria will migrate to and, in some cases, flourish in the airway in the milieu of damaged mucosa and impaired host defences.

http://dx.doi.org/10.1016/j.ijtb.2016.01.009

Comparison of interferon gamma release assay & tuberculin skin tests for diagnosis of latent tuberculosis in patients on maintenance haemodialysis

Agarwal SK, Singh UB, Zaidi SH, Gupta S, Pandey RM. *Indian Journal of Medical Research* 2015;**141(4)**:463–468. http://dx.doi.org/10.4103/0971-5916.159297

Background & objectives: Tuberculosis (TB) is a common infection in patients on haemodialysis. There is a definite role of treatment of latent TB (LTB) in these patients. However, diagnosis of LTB in these patients by tuberculin skin test (TST) is unreliable. There is suggestion that interferon gamma release assay (IGRA) will be more reliable test for diagnosis of LTB in this setting. Thus, we evaluated value of IGRA and TST for the diagnosis of LTB in patients on dialysis in an Indian setting.
Methods: Patients with end stage kidney disease on dialysis were included. Patients with active TB were excluded. Each patient was subjected to TST (induration of ≥10 mm was taken as positive) and QuantiFERON TB Gold In-Tube test (QFT-GIT) for diagnosis of LTB. Results: A total of 185 patients were included; 129 (69.7%) were males and mean age was 36.7 ± 12.3 yr. Past history of TB was present in 18 (9.7%) patients. One hundred and thirty four (72.4%) patients had scar of BCG vaccination. QFT-GIT test was positive in 66 (36%), TST in 32 (17%) and both in 13 (7%) patients. Of the 66 patients positive with QFT-GIT, only 13 (19.6%) were positive for TST. Of the 32 patients positive with TST, only 13 (40.6%) were positive with QFT-GIT; 100 (54%) patients were negative for both the tests. Overall, 85 (45.9%) patients were positive for either of the two tests. Poor agreement was shown between the two methods. On logistic regression analysis, odds of QFT-GIT to be positive in patients with BCG vaccination was 1.23 and with history of TB 0.99, both being insignificant. Odds of tuberculin skin test to be positive in patients with BCG vaccination was 1.04 and with history of TB 0.99, both again being insignificant. Interpretation & conclusions: Our findings showed that more number of patients (36%) on haemodialysis were positive for QuantiFERON Gold In-Tube test as compared to TST (17%). There was poor agreement between the two tests. No significant effect of BCG vaccination and history of TB in past was observed on both tests.

http://dx.doi.org/10.1016/j.ijtb.2016.01.010

Double trouble: Tuberculosis and substance abuse in Nagaland, India

Shenoy R, Das M, Mansoor H, Anicete R, Wangshu L, Meren S, Ao I, Saranchuk P, Reid AJ, Isaakidis P. *Public Health Action* 2015;**5(3)**:180–182. http://dx.doi.org/10.5588/pha.15.0019

The diagnosis and treatment of tuberculosis (TB) in people who use and/or inject illicit drugs (PWUIDs) remains a barrier to achieving universal coverage for TB in India and globally. This report describes treatment outcomes in PWUIDs who received treatment for drug-susceptible TB at the Mon District Hospital in Nagaland, India, during 2012–2013. The median age of the patients was 39 years, and most (92%) were males. Two thirds (33/49) of the patients had a successful TB treatment outcome. A previous TB episode and residence in a semi-urban area were associated with unsuccessful treatment outcomes. Separate diagnostic and treatment algorithms, including regular adherence counselling and opioid substitution therapies, should be considered for PWUIDs.

http://dx.doi.org/10.1016/j.ijtb.2016.01.011

Genetic and chemical validation identifies *Mycobacterium tuberculosis* topoisomerase I as an attractive anti-tubercular target

Ravishankar S, Ambady A, Awasthy D, Mudugal NV, Menasinakai S, Jatheendranath S, Guptha S, Sharma S, Balakrishnan G, Nandishaiah R, Ramachandran V, Eyermann CJ, Reck F, Rudrapatna S, Sambandamurthy VK, Sharma UK. *Tuberculosis* 2015;**95(5)**:589–598. http://dx.doi.or//10.1016/j.tube.2015.05.004

DNA topoisomerases perform the essential function of maintaining DNA topology in prokaryotes. DNA gyrase, an essential enzyme that introduces negative supercoils, is a clinically validated target. However, topoisomerase I (Topo I), an enzyme responsible for DNA relaxation has received less attention as an antibacterial target, probably due to the ambiguity over its essentiality in many organisms. The *Mycobacterium tuberculosis* genome harbors a single *topA* gene with no obvious redundancy in its function suggesting an essential role. The *topA* gene could be inactivated only in the presence of a complementing copy of the gene in *M. tuberculosis*. Furthermore, down-regulation of *topA* in a genetically engineered strain of *M. tuberculosis* resulted in loss of bacterial viability which correlated with a concomitant depletion of intracellular Topo I levels. The *topA* knockdown strain of *M. tuberculosis* failed to establish infection in a murine model of TB and was cleared from lungs in two months post infection. Phenotypic screening of a Topo I overexpression strain led to the identification of an inhibitor, thereby providing chemical validation of this target. Thus, our work confirms the attractiveness of Topo I as an anti-mycobacterial target.

http://dx.doi.org/10.1016/j.ijtb.2016.01.012

Vitamin D deficiency in Malawian adults with pulmonary tuberculosis: Risk factors and treatment outcomes

Sloan DJ, Mwandumba HC, Kamdolozi M, Shani D, Chisale B, Dutton J, Khoo SH, Allain TJ, Davies GR. *International Journal of Tuberculosis and Lung Disease* 2015;**19(8)**:904–911. http://dx.doi.org/10.5588/ijtld.15.0071

Setting: Vitamin D deficiency is common in African adults with tuberculosis (TB), and may be exacerbated by the metabolic effects of anti-tuberculosis drugs and antiretroviral therapy (ART). It is unclear whether vitamin D deficiency influences response to anti-tuberculosis treatment.

Objectives: To describe risk factors for baseline vitamin D deficiency in Malawian adults with pulmonary TB, assess the relationship between serum 25-hydroxy vitamin D (25 [OH]D) concentration and treatment response, and evaluate whether the administration of anti-tuberculosis drugs and ART is deleterious to vitamin D status during treatment.

Design: A prospective longitudinal cohort study.

Results: The median baseline 25(OH)D concentration of the 169 patients (58% human immunodeficiency virus [HIV] infected) recruited was 57 nmol/l; 47 (28%) had vitamin D deficiency (<50 nmol/l). Baseline 25(OH)D concentrations were lower during the cold season ($P < 0.001$), with food insecurity ($P = 0.034$) or in patients who consumed alcohol ($P = 0.019$). No relationship between vitamin D status and anti-tuberculosis treatment response was found. 25(OH)D concentrations increased during anti-tuberculosis treatment, irrespective of HIV status or use of ART.

Conclusions: Vitamin D deficiency is common among TB patients in Malawi, but this does not influence treatment response. Adverse metabolic effects of drug treatment may be compensated by the positive impact of clinical recovery preventing exacerbation of vitamin D deficiency during anti-tuberculosis treatment.

http://dx.doi.org/10.1016/j.ijtb.2016.01.013

Editorial on "Childhood OSA syndrome: Patience for your patients is a virtue"

Nathanson I. *Chest* 2015;**148(5)**:1129–1130. http://dx.doi.org//10.1378/chest.15-1041

In this issue of *Chest*, Chervin et al. provide important information that should influence how we treat young children who have OSA syndrome (OSAS). The reported data came from the Childhood Adenotonsillectomy Trial (CHAT), a multicenter research project that included 464 children 5 to 9 years of age who had OSAS. Each child underwent polysomnography (PSG), neuropsychologic testing, and symptom scoring using widely accepted questionnaires before being randomly assigned to either an early adenotonsillectomy (AT) group or a watchful waiting group. The protocol called for repeat PSG, neuropsychologic testing, and symptom scoring 7 months later. Of the 397 children who completed CHAT, PSGs normalized in 79% of the AT group and 46% of the watchful waiting group. Symptom scores also improved following AT, but neuropsychologic testing showed no significant improvement in attention or executive function. These findings raised important questions for clinicians about the indications of AT in a child with OSAS. Chervin et al present a detailed look at the children who did not have AT.

http://dx.doi.org/10.1016/j.ijtb.2016.01.014

Risk of incident active tuberculosis and use of corticosteroids

Lai C-C, Lee M-TG, Lee S-H, Lee S-H, Chang S-S, Lee C-C. *International Journal of Tuberculosis and Lung Disease* 2015;**19(8)**:936–942. http://dx.doi.org/10.5588/ijtld.15.0031

Objective: To examine the association between corticosteroid use and risk of active tuberculosis (TB) disease.

Methods: We conducted a population-based nested case–control study based on Taiwan's National Health Insurance Research Database between January 1999 and December 2011. Each case of incident active TB was matched to 100 controls using a risk-set sampling scheme.

Results: From a participant cohort of 1 million, 6229 cases of new active TB and 622 900 controls were identified. Current, recent, past, ever and chronic use of corticosteroids were associated with an increased risk of developing incident active TB, with adjusted rate ratios of respectively 2.76 (95% CI 2.44–3.11), 1.99 (95% CI 1.73–2.31), 1.17 (95% CI 1.06–1.29), 1.60 (95% CI 1.49–1.72), and 1.58 (95% CI 1.43–1.75). For subgroup analysis, the increased risk of TB in chronic corticosteroids users was substantially higher in subjects aged ≤70 years and female subjects.

Conclusion: In this relatively high TB prevalence setting, we found that use of corticosteroids was associated with an increased risk of TB. Current use of corticosteroids was associated with the highest risk of TB.

http://dx.doi.org/10.1016/j.ijtb.2016.01.015

Comparing multidrug-resistant tuberculosis patient costs under molecular diagnostic algorithms in South Africa

du Toit E, Squire SB, Dunbar R, Machekano R, Madan J, Beyers N, Naidoo P. *International Journal of Tuberculosis and Lung Disease* 2015;**19(8)**:960–968. http://dx.doi.org/10.5588/ijtld.14.0703

Setting: Ten primary health care facilities in Cape Town, South Africa, 2010–2013.

Objective: A comparison of costs incurred by patients in GenoType® MDRTB*plus* line-probe assay (LPA) and Xpert® MTB/RIF-based diagnostic algorithms from symptom onset until treatment initiation for multidrug-resistant tuberculosis (MDR-TB).

Methods: Eligible patients identified from laboratory and facility records were interviewed 3–6 months after treatment

initiation and a cost questionnaire completed. Direct and indirect costs, individual and household income, loss of individual income and change in household income were recorded in local currency, adjusted to 2013 costs and converted to $US.
Results: Median number of visits to initiation of MDR-TB treatment was reduced from 20 to 7 ($P < 0.001$) and median costs fell from US$68.1 to US$38.3 ($P = 0.004$) in the Xpert group. From symptom onset to being interviewed, the proportion of unemployed increased from 39% to 73% in the LPA group ($P < 0.001$) and from 53% to 89% in the Xpert group ($P < 0.001$). Median household income decreased by 16% in the LPA group and by 13% in the Xpert group.
Conclusion: The introduction of an Xpert-based algorithm brought relief by reducing the costs incurred by patients, but loss of employment and income persist. Patients require support to mitigate this impact.

http://dx.doi.org/10.1016/j.ijtb.2016.01.016

Treatment outcomes for HIV and MDR-TB co-infected adults and children: Systematic review and meta-analysis

Isaakidis P, Casas EC, Das M, Tseretopoulou X, Ntzani EE, Ford N. *International Journal of Tuberculosis and Lung Disease* 2015;**19 (8)**:969–978. http://dx.doi.org/10.5588/ijtld.15.0123
Background: The incidence of multidrug-resistant tuberculosis (MDR-TB) is increasing in high human immunodeficiency virus (HIV) prevalence settings, with high associated mortality. Treatment outcomes in HIV-co-infected adults and children are poorly documented.
Objective: To systematically assess treatment outcomes among HIV-MDR-TB co-infected patients.
Methods: We searched two databases and the proceedings of an annual international conference up to November 2014 for studies reporting on major clinical outcomes among HIV-MDR-TB-co-infected adults and children, and pooled the results using random-effects meta-analysis.
Results: Of 4812 abstracts and articles screened, 30 studies providing data on 2578 adults and 147 children were included. Overall pooled treatment success was 56.9% (95% confidence interval [CI] 46.2–67.6), 49.9% (95% CI 38.5–61.2) among adults and 83.4% (95% CI 74.7–92) among children. Mortality was 38% in adults (95% CI 28–48.1) and 11.4% (95% CI 5.8–17.1) in children. Loss to follow-up was higher among adults (16.1%, 95% CI 9–23.2) than among children (3.9%, 95% CI 0.9–6.9). Adverse events were experienced by the majority of patients; however, this was inconsistently documented. The use of fluoroquinolones, aminoglycosides and Group IV drugs appeared to be associated with treatment success.
Conclusion: The proportion of HIV-MDR-TB-co-infected patients achieving treatment success was similar to success rates reported among MDR-TB patients in general, regardless of HIV status; however, mortality was higher, particularly among adults, highlighting the need for early diagnosis and more effective treatment regimens.

http://dx.doi.org/10.1016/j.ijtb.2016.01.017

Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: An interim cohort analysis

Ndjeka N, Conradie F, Schnippel K, Hughes J, Bantubani N, Ferreira H, Maartens G, Mametja D, Meintjes G, Padanilam X, Variava E, Pym A, Pillay Y. *International Journal of Tuberculosis and Lung Disease* 2015;**19(8)**:979–985. http://dx.doi.org/10.5588/ijtld.14.0944
Background: South Africa has a large burden of extensively drug-resistant tuberculosis (XDR-TB); only 15% of XDR-TB patients have successful outcomes.
Objective: To describe the safety and effectiveness of bedaquiline (BDQ) in the South African BDQ Clinical Access Programme.
Design: An interim cohort analysis.
Results: Of the first 91 patients enrolled between March 2013 and July 2014 (with follow-up until August 2014), 54 (59%) were human immunodeficiency virus (HIV) infected. The median CD4 count was 239 cells/μl, and all patients were on antiretroviral therapy (ART) at initiation of BDQ; 33 had XDR-TB, 41 were pre-XDR-TB with fluoroquinolone resistance and 17 were pre-XDR-TB with resistance to an injectable. Of the 91 patients, 58 (64%) had completed 24 weeks of BDQ, 28 were still on BDQ, 3 were lost to follow-up, 1 had died and 1 had BDQ withdrawn following atrial fibrillation. Of the 63 patients with 6 months follow-up, 48 (76%) had either culture-converted or remained culture-negative after initiation of BDQ. QTcF was monitored monthly and exceeded 500 ms in three participants; this resolved in all three.
Conclusion: Interim safety and culture conversion outcomes for patients accessing BDQ in South Africa, including HIV-infected patients on ART and patients with pre-XDR- and XDR-TB, suggest that BDQ may be both efficacious and safe.

http://dx.doi.org/10.1016/j.ijtb.2016.01.018

Concomitant tuberculosis and lung cancer diagnosed by bronchoscopy

Morales-García C, Parra-Ruiz J, Sánchez-Martínez JA, Delgado-Martín AE, Amzouz-Amzouz A, Hernández-Quero J. *International Journal of Tuberculosis and Lung Disease* 2015;**19(9)**:1027–1032. http://dx.doi.org/10.5588/ijtld.14.0578
Setting: South Granada Health Area (SGHA), Spain.
Objective: To describe the characteristics of concomitant tuberculosis (TB) and lung cancer cases.
Design: A total of 319 TB cases diagnosed between January 2003 and December 2010 were evaluated and identified using a prospective database. During this period, samples of bronchial secretions were obtained from all patients who underwent fibreoptic bronchoscopy (FBS) as part of a TB screening programme. A descriptive study was conducted.
Results: Concomitant TB and lung cancer were diagnosed in 15 cases (4.7% of total TB cases). The most common radiographic finding was atelectasis (53.3%), and the most common histological type was epidermoid carcinoma (60%). Lung cancer stage was advanced (III–IV) in 60% of the cases.
Conclusion: The association between TB and lung cancer found in the SGHA after implementing a TB screening programme was higher than in other studies. This suggests that it would be advisable to perform acid-fast bacilli smear and mycobacterial culture of bronchial aspirates in all patients with presumed lung cancer, particularly in high TB prevalence areas.

http://dx.doi.org/10.1016/j.ijtb.2016.01.019

Evaluation of mobile digital light-emitting diode fluorescence microscopy in Hanoi, Viet Nam

Chaisson LH, Reber C, Phan H, Switz N, Nilsson LM, Myers F, Nhung NV, Luu L, Pham T, Vu C, Nguyen H, Nguyen A, Dinh T, Nahid P, Fletcher DA, Cattamanchi A. *International Journal of Tuberculosis and Lung Disease* 2015;**19(9)**:1068–1072. http://dx.doi.org/10.5588/ijtld.15.0018
Setting: Hanoi Lung Hospital, Hanoi, Viet Nam.

Objective: To compare the accuracy of CellScopeTB, a manually operated mobile digital fluorescence microscope, with conventional microscopy techniques.
Design: Patients referred for sputum smear microscopy to the Hanoi Lung Hospital from May to September 2013 were included. Ziehl-Neelsen (ZN) smear microscopy, conventional light-emitting diode (LED) fluorescence microscopy (FM), CellScopeTB-based LED FM and Xpert® MTB/RIF were performed on sputum samples. The sensitivity and specificity of microscopy techniques were determined in reference to Xpert results, and differences were compared using McNemar's paired test of proportions.
Results: Of 326 patients enrolled, 93 (28.5%) were Xpert-positive for TB. The sensitivity of ZN microscopy, conventional LED FM, and CellScopeTB-based LED FM was respectively 37.6% (95% CI 27.8–48.3), 41.9% (95% CI 31.8–52.6), and 35.5% (95% CI 25.8–46.1). The sensitivity of CellScopeTB was similar to that of conventional LED FM (difference −6.5%, 95% CI −18.2 to 5.3, $P = 0.33$) and ZN microscopy (difference −2.2%, 95% CI −9.2 to 4.9, $P = 0.73$). The specificity was >99% for all three techniques.
Discussion: CellScopeTB performed similarly to conventional microscopy techniques in the hands of experienced TB microscopists. However, the sensitivity of all sputum microscopy techniques was low. Options enabled by digital microscopy, such as automated imaging with real-time computerized analysis, should be explored to increase sensitivity.

http://dx.doi.org/10.1016/j.ijtb.2016.01.020

False-negative BD MGIT™ TBc identification test results in routine tuberculosis diagnosis: A New Zealand perspective

Basu I, Bower JE, Henderson GK, Lowe O, Newton S, Vaughan R, Roberts SA. *International Journal of Tuberculosis and Lung Disease* 2015;**19(9)**:1073–1075. http://dx.doi.org/10.5588/ijtld.15.0032
We previously reported on a comparison of the AccuProbe® Gen-Probe® MTBC assay (AccuProbe) (BioMérieux, Marcy L'Etoile, France) with the Becton Dickinson (BD) MGIT™ TBc Identification (TBc) Test (BD, Franklin Lakes, NJ, USA) in our laboratory. In the period following the shift from the AccuProbe assay to the TBc test, we obtained six false-negative results. On sequencing the *mpt64* gene, we found that these false-negative cases had mutations in the *mpt64* gene due to deletion, insertion or substitution. Despite the occurrence of false-negative results, we found that the reduced cost and minimal technical expertise, combined with a new testing algorithm, still make this test the preferred option for rapidly identifying *Mycobacterium tuberculosis* complex in MGIT cultures in a low TB burden country such as New Zealand.

http://dx.doi.org/10.1016/j.ijtb.2016.01.021

Impact of point-of-care implementation of Xpert® MTB/RIF: Product vs. process innovation

Schumacher SG, Thangakunam B, Denkinger CM, Oliver AA, Shakti KB, Qin ZZ, Michael JS, Luo R, Pai M, Christopher DJ. *International Journal of Tuberculosis and Lung Disease* 2015;**19(9)**:1084–1090. http://dx.doi.org/10.5588/ijtld.15.0120
Background: Both product innovation (e.g., more sensitive tests) and process innovation (e.g., a point-of-care [POC] testing programme) could improve patient outcomes.
Objective: To study the respective contributions of product and process innovation in improving patient outcomes.
Design: We implemented a POC programme using Xpert® MTB/RIF in an out-patient clinic of a tertiary care hospital in India. We measured the impact of process innovation by comparing time to diagnosis with routine testing vs. POC testing. We measured the impact of product innovation by comparing accuracy and time to diagnosis using smear microscopy vs. POC Xpert.
Results: We enrolled 1012 patients over a 15-month period. Xpert had high accuracy, but the incremental value of one Xpert over two smears was only 6% (95% CI 3–12). Implementing Xpert as a routine laboratory test did not reduce the time to diagnosis compared to smear-based diagnosis. In contrast, the POC programme reduced the time to diagnosis by 5.5 days (95% CI 4.3–6.7), but required dedicated staff and substantial adaptation of clinic workflow.
Conclusion: Process innovation by way of a POC Xpert programme had a greater impact on time to diagnosis than the product per se, and can yield important improvements in patient care that are complementary to those achieved by introducing innovative technologies.

http://dx.doi.org/10.1016/j.ijtb.2016.01.022

Management and treatment outcomes of MDR-TB: Results from a setting with high rates of drug resistance

Ahmad N, Javaid A, Basit A, Afridi AK, Khan MA, Ahmad I, Sulaiman SAS, Khan AH. *International Journal of Tuberculosis and Lung Disease* 2015;**19(9)**:1109–1114. http://dx.doi.org/10.5588/ijtld.15.0167
Settings: Although Pakistan has a high burden of multidrug-resistant tuberculosis (MDR-TB), little is known about the management and treatment outcomes of MDR-TB patients in Pakistan.
Objective: To evaluate management and predictors of unsuccessful treatment outcomes among MDR-TB patients.
Methods: In this observational cohort study, 196 MDR-TB patients enrolled at the Programmatic Management Unit for drug-resistant TB of Lady Reading Hospital, Peshawar, Pakistan, between 1 January 2012 and 28 February 2013 were included. Patients were followed until an outcome was recorded or 31 January 2015.
Results: Extensive concurrent resistance to ofloxacin (OFX) and pyrazinamide (54.6%) was observed. Among 181 patients for whom treatment outcome was available, 135 (74.6%) were cured, 1 (0.6%) completed treatment, 35 (19.3%) died, 8 (4.4%) failed treatment and 2 (1.1%) defaulted. In multivariate analysis, predictors of unsuccessful treatment outcome (death, failure and default) were age >40 years (OR 3.412, $P = 0.009$), baseline body weight < 40 kg (OR 2.966, $P = 0.020$), concurrent comorbidity (OR 3.785, $P = 0.023$), resistance to OFX (OR 2.777, $P = 0.023$), lung cavitations at baseline chest X-ray (OR 5.253, $P < 0.001$) and regimen modification due to adverse events (OR 3.492, $P = 0.037$).
Conclusion: The treatment outcome results were encouraging. Patients with identifiable predictors of poor treatment outcome should receive enhanced clinical management. Early detection and management of mild adverse effects can help prevent regimen modification and may improve treatment outcomes.

http://dx.doi.org/10.1016/j.ijtb.2016.01.023

Barriers to the diagnosis of childhood tuberculosis: A qualitative study

Chiang SS, Roche S, Contreras C, Alarcón V, del Castillo H, Becerra MC, Lecca L. *International Journal of Tuberculosis and Lung Disease* 2015;**19(10)**:1144–1152. http://dx.doi.org/10.5588/ijtld.15.0178
Setting: In 2012, Peru's National Tuberculosis Program (NTP) reported that children aged 0–14 years accounted for 7.9% of

the country's tuberculosis (TB) incidence. This figure is likely an underestimate due to suboptimal diagnosis of childhood TB.
Objective: To identify barriers to childhood TB diagnosis in Lima, Peru.
Design: Using semi-structured guides, moderators conducted in-depth interviews with four NTP administrators and five pulmonologists specializing in TB and 10 focus groups with 53 primary care providers, community health workers (CHWs), and parents and/or guardians of pediatric TB patients. Two authors independently performed inductive thematic analysis and identified emerging themes.
Results: Participants identified five barriers to childhood TB diagnosis: ignorance and stigma among the community, insufficient contact investigation, limited access to diagnostic tests, inadequately trained health center staff, and provider shortages.
Conclusion: Recent efforts to increase childhood TB detection have centered on the development of new technologies. However, our findings demonstrate that many diagnostic barriers are rooted in socio-economic and health system problems. Potential solutions include implementing multimedia campaigns and community education to reduce ignorance and stigma, prioritizing contact investigation for high-risk households, and training primary care providers and CHWs to recognize and evaluate childhood TB.

http://dx.doi.org/10.1016/j.ijtb.2016.01.024

Can social network analysis assist in the prioritisation of contacts in a tuberculosis contact investigation?

Kawatsu L, Izumi K, Uchimura K, Urakawa M, Ohkado A, Takahashi I. *International Journal of Tuberculosis and Lung Disease* 2015;**19 (11)**:1293–1299. http://dx.doi.org/10.5588/ijtld.15.0378
Objectives: To evaluate the effectiveness of social network analysis (SNA) in prioritising contacts in a tuberculosis (TB) contact investigation.
Method: We reviewed and analysed patient and contact investigation data from a large outbreak that occurred in Tokyo, Japan, between 2010 and 2012. Relevant data were extracted to create a social matrix, which was then analysed using SNA software to visualise the network and calculate SNA metrics (degree and betweenness) for all patients and contacts. Statistical analyses were conducted to examine whether degree and betweenness centrality scores could prioritise contacts for in-depth investigation by calculating the odds of latent tuberculous infection (LTBI) being diagnosed among contacts with high scores compared to those with low scores.
Results: The data on a total of 8 patients and 376 contacts, of whom 56 were diagnosed with LTBI, were analysed. Centrality scores did not show a statistically significant association with the risk of contacts being diagnosed with LTBI. However, contacts with high betweenness scores were more likely to be diagnosed with LTBI than contacts with lower scores (OR 2.88, 95% CI 1.31–5.83, $P = 0.007$).
Conclusion: Our results showed the potential of a betweenness score in prioritising contacts during TB contact investigation.

http://dx.doi.org/10.1016/j.ijtb.2016.01.025

Diagnostic accuracy of nucleic acid amplification tests in urine for pulmonary tuberculosis: A meta-analysis

Marangu D, Devine B, John-Stewart G. *International Journal of Tuberculosis and Lung Disease* 2015;**19(11)**:1339–1347. http://dx.doi.org/10.5588/ijtld.15.0209
Objective: To determine the diagnostic accuracy of tuberculosis (TB) nucleic acid amplification tests (NAATs) in urine samples for individuals with active pulmonary tuberculosis (PTB).
Design: Systematic review and meta-analysis. Electronic databases and reference lists were searched without age or setting restrictions up to May 2015. Eligible articles examined *Mycobacterium tuberculosis* NAATs in urine samples for PTB diagnosis in patients with sputum culture as the reference standard, and reported sufficient data to separately calculate sensitivity or specificity.
Results: Eight studies, including 1212 participants from seven countries with a mean age ranging from 28 to 48 years, were included. Polymerase chain reaction (PCR) with insertion sequence (IS) *6110*, *rpo*B or cfp32/hf6 as gene targets was used for NAATs. The pooled sensitivity and specificity was respectively 0.55 (95% CI 0.36–0.72) and 0.94 (95% CI 0.78–0.99), with slightly higher sensitivity in human immunodeficiency virus positive individuals, at 0.59 (95% CI 0.20–0.89). Sensitivity was higher in sputum microscopy-positive than -negative individuals. Storage temperatures below −70 °C, centrifuge speed <5000 rpm and IS*6110* increased sensitivity on meta-regression.
Conclusions: Urine *M. tuberculosis* PCR for active PTB diagnosis had high specificity but modest sensitivity (55%). Optimizing specimen handling, gene targets or PCR techniques may improve diagnostic accuracy. Reproducibility data are needed.

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Rifampicin-moxifloxacin interaction in tuberculosis treatment: A real-life study

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Setting: Rifampicin (RMP) has been reported to reduce moxifloxacin (MFX) levels, which may interfere with the effectiveness of MFX in treating tuberculosis (TB).
Objective: To study the MFX-RMP interaction in patients receiving MFX with or without RMP as part of their antituberculosis treatment regimen.
Design: Patients with pulmonary TB followed up by the Tuberculosis Out-patient Clinic of the Pulmonary Department, Aristotle University of Thessaloniki, Greece, who underwent treatment with MFX during the periods 1 May 2012–30 April 2014 and 1 January–31 March 2015, were included in the study. MFX levels were compared between 12 patients who were receiving RMP (Group 1) and 10 who were not (Group 2).
Results: The participants did not significantly differ in body mass index, days of MFX treatment or MFX dose/kg. Neither the peak concentration (C_{max}) nor the 24 h area under the curve (AUC_{24}) differed significantly between the two groups (Group 1, C_{max} median 3.9 [range 1.9–4.5] mg/l; AUC_{24} 29.1 [10–47.4] mg h/l and Group 2, C_{max} 4.1 [2–6.4] mg/l; AUC_{24} 36.5 [14.6–54.2] mg h/l).
Conclusion: Although a decrease in MFX exposure was observed in the RMP-treated group, the effect was lower than previously reported in a real-life setting. The large variability observed in MFX pharmacokinetics in both groups may suggest the need for dose readjustment in some patients, regardless of RMP co-administration.

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Resistance profile and risk factors of drug resistant tuberculosis in the Baltic countries

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The rates of multi- and extensively drug-resistant tuberculosis (X/MDRTB) in the Baltic countries are the highest within the European Union hampering recent achievements of national TB control programmes.

We included all consecutive culture-confirmed X/MDRTB patients registered for treatment in 2009 in Latvia, Lithuania and Estonia into this multicenter case–control study. Cases were compared with randomly selected controls with non-MDRTB registered for treatment in the same year across these sites.

Of 495 MDRTB patients, 243 (49.7%) showed resistance to at least one second-line drug, 206 (42.1%) had pre-XDRTB (i.e. MDRTB with additional resistance to a second-line injectable or fluoroquinolones) and 64 (13.1%) had XDRTB. Younger age, male gender and known contact with an MDRTB case were associated with increased risk of primary infection with X/MDRTB strains. Previous treatment and alcohol abuse were strong predictors for MDRTB acquisition; defaults and failures in the past triggered XDRTB development. All patients received appropriate therapy; less than half of the patients were fully adherent.

An erroneous treatment strategy is unlikely to drive resistance development. Increasing patients' compliance, addressing issues of social support, rapid detection of drug resistance and improving infection control is crucial for prevention of further spread of X/MDRTB and achieving higher cure rates.

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