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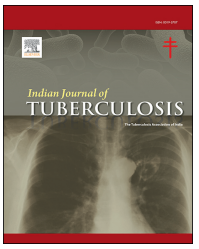

Editorial

End TB – Strategy – A dream to achieve

The Prime Minister of India, while speaking on 2018 World TB Day, has announced to end TB from India by 2025 in presence of Health Ministers of nine countries and TB experts from all over India and overseas. Although the WHO target is to End TB by 2035 globally, it is a welcome initiative and good commitment from the government. The goal set for End TB Strategy is to bring down incidence of TB cases at 44 per lakh per year.

According to Global TB Report 2018, the incidence of TB has reduced from 289 per lakh per year in year 2000 to 217 per lakh per year in 2017.[1] This translates to annual decline rate of 1.5 per year. If we want to end TB by 2025 as the political commitment from highest authority in India, rate of decline of incidence of TB needed be more than 10%–15% per year till 2025.

Based on studies conducted by Indian Council of Medical Research (ICMR) and Harvard Medical School the estimates of TB cases in India have been revised to 27 lakhs TB cases.[2] Out of these, only 14 lakhs TB cases were registered for treatment in the year 2014 and another 3.8 lakhs were notified from private sector including hospitals, clinics and laboratories. This concludes to one million patients missing which may be undiagnosed living in community or with treatment from quacks and continues spreading disease. Diagnosing these missing cases is the biggest challenge for TB control programme to achieve its TB elimination target.

Recently, India has initiated several activities in form of bold and ambitious plans to make India TB Free by 2025, well ahead of global targets. The National Strategic Plan for TB Elimination 2017–2025 describes the stepwise agenda and targets to achieve the goal. Within the country, cities such as Mumbai in Maharashtra have taken leadership to combat the multidrug-resistant TB (MDR-TB) crisis, following reports in 2012 of cases of presumed total drug resistance beyond extensively drug-resistant TB (XDR-TB).[3] The Mumbai Mission for TB Control, set up by the Municipal Corporation of Greater Mumbai in collaboration with partners, has been making excellent strides towards enhancing access to early TB and MDR-TB diagnosis and quality TB treatment in the public and private sectors.[4] Pilot models of private sector engagement in Mumbai, Patna, Bihar and Mehsana, Gujarat, have demonstrated the impact on increased case notifications and improved quality of care by working with intermediary agencies, engaging large numbers of private care providers and utilizing ICT technologies for patients adherence and programme monitoring.[5]

Despite these outstanding achievements, path to reach TB elimination goal is long and full of challenges at administrative and community level. India still carries the by-far highest burden of TB and MDR-TB in the world. According to WHO's 2018 Global TB Report, nearly 2.8 million people fell ill with TB in India in 2017, which alone accounted for nearly a quarter of the world's TB burden. Around 420,000 people lost their lives to TB that same year1. MDR-TB remains a public health security threat in the country, with an estimated 1,33,000 MDR/rifampicin-resistant TB cases. Coupled with the burden are the challenges of a largely unregulated private sector and the underlying social determinants of disease, including poverty, under nutrition, poor living conditions and risk factors such as tobacco use and other co-morbidities, which drive the TB epidemic in the country.

To withstand commitments made for the country to achieve targets, it needs to be backed with adequate resources. According to reports, the government-allocated budget for the implementation of the National TB Strategic Plan needs to be boosted, in addition to the recently announced infusion of funds for nutritional support.[6]

Access to new tools needs to be expanded both in the public and private sectors. Nearly a million people with TB in India miss out on care each year - they either access private sector or public sector TB services but are not diagnosed or are diagnosed but not notified, and/or lost to follow up before starting treatment.[7] In addition, nearly a third of the estimated MDR-TB patients in the country are not diagnosed or put on treatment. India has outlined key steps and actions to close these gaps in its ambitious National Strategic Plan. Effective implementation of this Plan needs to be supported by the government and all stakeholders in the public and private sectors to expand access to rapid molecular tests such as Xpert MTB-RIF and line-probe assays and to scale up access to new drugs and regimens. The Government has already taken few steps towards these. There has been impressive uptake of Bedaqualine throughout the country. But steps are needed to make the drug available outside the conditional access after proper sensitization of private providers about the drug.[8] The switch over to daily from intermittent therapy is also a welcome step in this direction. But what now needed is to sustain it for long.

Engagement with the private sector needs to be scaled up. Over half of the TB patients in India first seek care in the

private sector.[9] The care provided in the private sector, while being more easily accessible, is often unregulated and can be of substandard quality.[10] Efforts to engage private sector are there since beginning of RNTCP. There are specific schemes to involve NGOs and private providers with well defined guidelines. These are being updated from time to time as per need of the programme. Now a push is required to enhance its uptake by private sector. The lessons learnt from these successful projects need to be scaled across the country to reach those missed by publicly provided, affordable care.

The underlying determinants of TB need to be addressed through a multisectoral response. TB is a disease of poverty. Studies show that the poorest quintile in India has over a five-fold risk of TB compared to the general population.[11] This situation is exacerbated with growing urbanization across the country, especially in overcrowded slums where TB prevalence is known to be higher.[12] Other risk factors such as smoking and comorbidities such as HIV and diabetes are associated with a high prevalence of TB in the country.[13]

Going by the current scenario, it is an uphill task to achieve goal of TB elimination by 2025. In order to achieve it, all stakeholders are required to work together. Even the budget allocation for RNTCP need to be increased to implement recently launched initiatives for TB notification by health care providers and chemists. Recently launched fixed drug combinations and rapid molecular diagnostics expansion and findings of recently concluded National Drug Resistance Survey will help a lot in achieving the target. As more than 50% of patients are with private sector, this engagement and support is also very crucial. All notified patients by the private sector require prompt public health action to ensure treatment adherence. Unless all stakeholders come together for cohesive efforts, End TB strategy in India may only remain a distant goal.

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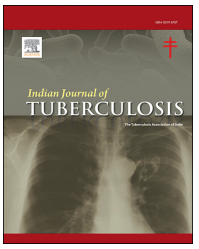

Editorial

Occupational tuberculosis in sewage workers: A neglected domain

Tuberculosis (TB) is a public health priority in most Low and Middle Income countries (LMICs). India accounts for nearly a quarter of the global incident cases and more than one fifths of the global mortality due to TB.[1] India has high rates of MDR TB and XDR-TB as an estimated 850,000 cases of TB per year stay undetected and untreated or are poorly treated.[2]

The new "End TB Strategy" of WHO aims to eliminate TB globally by 2035- an ambitious target which can only be achieved by a paradigm shift in public health approach towards TB. The four pillared "Detect- Treat-Prevent-Build" approach of Indian National Strategic Plan for Elimination of TB 2017–2025 incorporates active screening for case finding along with targeted delivery of diagnostic and treatment services delivery to help in elimination of TB.[3] Nevertheless, the implementation of National Strategy Plan for Elimination of Tuberculosis is not without its unique challenges.

One such challenge is on account of the high-risk groups identified and planned for in the National Strategic Plan for Elimination of Tuberculosis. These high risk group include only limited clinical categories like people living with HIV/AIDS, those having extensive radiological disease, severely underweight individuals, or those with comorbidity, Child Pulmonary Tuberculosis contacts, patients with silicosis, all high risk patients where clinically indicated for example patients on long term corticosteroids or immunosuppressants, high risk adult contacts and "socially vulnerable" population.[3] Further only a few social determinants of TB like urbanization and housing are included in the National Strategic Plan for Elimination of Tuberculosis.[3]

Occupation per se has not been considered as a determinant of contracting TB and its consequent morbidity. The only occupational group planned for surveillance in the national strategic plan are the health care workers.[3] There is no active case finding plan for other occupational groups known to be at risk for TB due to exposure to the Mycobacterium tuberculosis through person to person contact and persistence of Mycobacteria on infected surfaces in the National Strategic Plan for Elimination of Tuberculosis. These include sewage workers, prison staff, commercial sex workers, transgenders, miners, factory workers, farmers, abattoir workers and dairy workers.[4,5]

There has been little research in India on occupational groups at risk for Tuberculosis. But the lack of evidence cannot be interpreted as the evidence of lack.

A recent study on sewage workers in Delhi, the capital of the country has demonstrated a very high rate of TB in sewage workers (more than 20%) who were incidentally diagnosed in a research on respiratory morbidity (in press).

Sewage workers form the backbone of urbanization as formal sewage channels and treatment plants ensure clean urban spaces. With rapid urbanization in India, not just the metros but the Tier I cities (with population more than 100,000) and Tier II cities (with population of 50,000 to 100,000) as well as many small towns now, have extensive sewage networks which protect urban spaces and the citizens from a range of communicable diseases.[6] The expansion of sewage system in India has occurred without any corresponding investigation into the risks faced by the sewage workers as sewage management has its own health hazards.[7]

Sewage workers enter manholes and closed channels as part of their duties and also man the sewage treatment facilities They work in confined spaces, closed channels and sewage treatment plants which employ technologies like Upflow Anaerobic Sludge Blanket, Activated Sludge Process, Fluidized Aerobic Bioreactor, Sedimentation, Trickling Filters, Series of Waste Stabilization Ponds which produce noxious fumes and bioaerosols.[6]

Sewage workers are repeatedly and chronically exposed to a wide variety of chemical gases, bioaerosols and microorganisms which act as respiratory irritants. Such repeated and chronic exposure to noxious agents adversely impacts the respiratory system leading to a wide variety of respiratory symptoms, abnormalities in lung function and respiratory diseases like Toxic Pneumonitis, Asthma and COPD.[8,9]

The denuded lung mucosa secondary to the aforesaid respiratory diseases further compromises the lung defenses thereby increasing the vulnerability to air- borne infections including TB. It is important to note that only 50% of the mycobacterial infection load is removed by primary sewage treatment processes.[10] Further, in India, there is decreased availability of Personal Protective Equipment (PPE) on site and lack of awareness about its usage as well as its importance. In

addition, there is inconsistent enforcement of usage of PPE at different times and across different workplaces of sewage workers; such that a recent study from Kerala found that only 18% of sewage workers used PPEs.[7] Given the current state of sewage management in India, we will soon be faced with an epidemic of occupationally related respiratory disorders in sewage workers.

Amongst all the occupational groups at risk for TB, it is the sewage workers who are the most "socially vulnerable" and yet form the basis of clean urban spaces (a determinant of TB control for others). Most sewage workers have only basic school education and do not completely understand the biological risk of their work. At the same time, lack of education and lack of job opportunities prevent them from leaving their hazardous as well as socially stigmatizing occupation.

They are also economically backward and culturally marginalized as sewage work is considered a stigmatizing occupation and the stigma is extended to their families as well.

Further, sewage workers face social exclusion, cultural marginalization, economic constraint and neglect from medical facilities due to complex interplay of cultural and systemic factors. All these factors also contribute to their compromised health status by influencing medical help seeking and pathways to care for this occupational group. Further, TB in sewage workers may be AFB Negative as fibrotic disease secondary to repeated noxious inhalational exposure may develops early in course of their occupational duties. This can result in delayed diagnosis and misdiagnosis unless there is high index of clinical suspicion.

This makes a strong case for inclusion of such occupational groups like sewage workers with high rates of TB in the "at risk group" category of National Strategy Plan for Elimination of Tuberculosis. As the sewage workers populate urban spaces which include their place of work and often as their place of residence, the Urban Plan of TB Elimination must include sewage workers as a priority group. Sewage workers should be subjected to mandatory screening, case detection and notification for not just TB but also notification of sewage work as an occupational hazard. They must be provided facilities for screening, prophylaxis, appropriate and accessible treatment at workplace sites. Specialized Chest Clinics and DOTS centers must be opened in close proximity of sewage treatment facilities to promote appropriate help seeking by sewage workers and treatment adherence to prescribed regimen.

A thorough systematic multi centric epidemiological investigation is required to evaluate the health profile of sewage workers in India as well as determine the etiopathological aspects and socio-cultural and economic determinants of tuberculosis in sewage workers and their impact on median lifespan and Disability Adjusted Life Years of sewage workers (DALYs). Such a study can lead to development of a targeted strategy for case detection, notification and appropriate management. The results of systematic research on Tuberculosis in sewage workers have the potential to inform revisions in policy guidelines, prevention and intervention strategies.

A person with TB does not just suffer from the disease but also acts as a source of TB to others including family, friends, colleagues and the community at large. In addition, TB is a stigmatizing illness in Indian cultural context. Hence, early and timely diagnosis helps not just the patient but also helps in primary prevention for the at- risk population in the community. At the same time, undiagnosed and untreated tuberculosis is also an occupational hazard of co-workers and increases the risk of transmission of Tuberculosis as well as MDR TB to their own family members thereby worsening the morbidity of the family unit.

The sewage workers who keep our civic spaces clean, prevent spread of diseases and form the bulwark of urbanization must receive the benefits of systematic research and policy measures to prevent and manage their health- related issues and morbidity.

An ambitious target of complete elimination of TB in the new "End TB Strategy" cannot be achieved unless there is a paradigm shift in case detection strategies from conventional groups of clinically at-risk population to unconventional groups like occupational groups at risk for tuberculosis. Only by targeting such occupational groups which have pockets of undiagnosed TB like the sewage workers and others and making concerted efforts to address health inequity, can we achieve complete elimination of TB by 2035.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijtb.2018.09.001.

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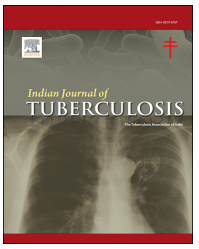

Viewpoint

The end TB strategy for India

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ABSTRACT

India has made great progress towards TB prevention and control with the adoption of the National Strategic Plan 2017-2025 with significantly greater allocated resources and high level political commitment. Aligning with the global End TB Strategy, India has announced the target of ending TB by 2025, five years ahead of the rest of the world. The End TB strategy is comprised of a multi-pronged approach incorporating patient-centered care and prevention, bold policies and supportive systems, and intensified research and innovation. In the past decade, India has made great strides towards ending TB, but the challenges, especially in a high burden setting, are great, and achieving our ambitious targets and goals will require partnering with all stakeholders including civil society and the community.

Tuberculosis (TB) is the leading infectious disease killer in the world and one of the top 10 causes of death worldwide.[1] There were an estimated 10 million cases of TB and 1.3 million deaths due to TB per The World Health Organization (WHO) Global Tuberculosis Report 2018.[2] The WHO has recently adopted the End TB Strategy[3] which has set the ambitious goal of ending the global TB epidemic by 2030, with targets to reduce TB deaths by 95% and new cases by 80%, and to ensure that no family is burdened with catastrophic expenses due to TB. India has set an even more ambitious target of ending TB by 2025. The challenges to reach these targets are great, especially in a high burden TB setting, but the high-level commitment to allocate resources and technical expertise to reach these targets has been achieved.

There are three pillars that comprise the End TB Strategy[3]: 1) Integrated Patient-Centered Care and Prevention; 2) Bold Policies and Supportive Systems; and 3) Intensified Research and Innovation. A multi-pronged approach towards ending TB is delineated within these three pillars. Pillar 1 includes early and accurate diagnosis, universal drug susceptibility testing (DST), systematic screening of high-risk individuals including close contacts to infectious TB, appropriate treatment, especially of drug-resistant (DR)-TB, patient support systems, collaborative TB/HIV activities and addressing other co-morbidities, and, lastly, preventative treatment for latent TB infection (LTBI) and development of an effective vaccine. Pillar 2 includes achieving political will and adequate resources, engagement of all partners including civil society, the community and the private sector, universal health coverage, a framework for case notification, infection control, and social protection. Pillar 3 includes innovation, the development and use of new tools, interventions and strategies, and research to optimize implementation and impact.

India has made great progress with the adoption of the National Strategic Plan 2017–2025 (NSP) with significantly greater allocated resources and high level political

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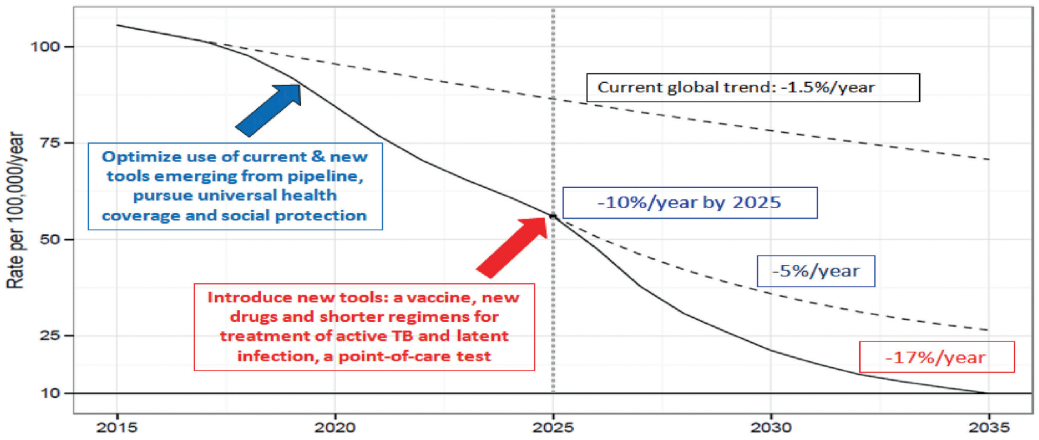

Fig. 1 – Required path of end TB curve – Projected acceleration of Tb incidence decline to target levels (World Health Assembly 2014).

commitment. New diagnostic tools such as GeneXpert MTB/RIF (Cepheid, Sunnyvale, CA) for universal DST and other rapid molecular tests such as first- and second-line Line Probe Assays have been implemented and scaled, culture/DST laboratories have been implemented, and specimen transport systems are being strengthened. New approaches to treatment of drug-sensitive TB with the daily fixed dose combination regimen and DR-TB using new drugs, regimens and algorithms have been implemented and are being scaled. Patient support systems with financial support through direct beneficiary transfer (DBT), ICT-based adherence support, enhanced monitoring and pharmacovigilance, enhanced surveillance through an updated Nikshay platform, and a patient-centered approach to care have been incorporated into the Revised National TB Control Program (RNTCP). Private sector engagement strategies and projects such as the Global Fund supported Joint Effort for Elimination of TB (JEET) have been initiated to find the "missing million" patients and partner with the private sector for improved TB patient care and management to achieve relapse-free cure. Community and civil society engagement have been incorporated in the NSP and are integral components to ensure community-based TB care and to aid in shaping policy. Preventative initiatives for infection control, contact tracing and an LTBI management strategy are being developed to ensure that, as TB incidence drops with implementation of the aggressive interventions noted above, India will be poised to end TB.

Despite the rapid advances that have been achieved in the last decade, the challenges are great. The vast burden of disease and high numbers of multidrug (MDR) and extensively drug (XDR)-TB patients, especially those undetected, is a daunting prospect. Private-public partnerships to find the missing cases early and start appropriate treatment to interrupt transmission of TB and achieve cure for the patient will be crucial to ending TB in India. Expert clinical consultation combined with good patient monitoring for treatment response and adverse drug effects/severe adverse events using systematic pharmacovigilance are needed to minimize patient loss to follow-up, treatment failure and relapse. Patient support systems to ensure zero catastrophic costs for patients and their families are necessary along with the implementation of patient centered care and a humane approach towards people living with TB. Active case finding in high risk populations like household contacts is resource intensive but required for early diagnosis of both TB disease and LTBI. Lastly, without preventative measures such as infection control and a comprehensive strategy for the management of LTBI, we will not end TB. Modeling has shown that, to reach our End TB targets, effective targeted LTBI management of those at high risk for progression to TB disease and a good vaccine to prevent TB are critical[3] (Fig. 1).

We can reach the End TB targets, but it will take commitment at every level of the health care cascade, innovation and dedication. The next decade will be crucial in determining the global and India-specific trajectory of the response to TB. Every one of us can contribute to ending and eliminating this preventable, treatable, and curable disease. It is critical to partner with all stakeholders in our fight against TB.

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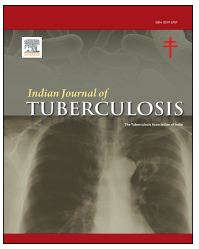

Viewpoint

Reflections on the end TB strategy

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The only infectious disease agent humanity has so far gotten rid of is the variola virus. It 1) could not hide, 2) caused a disease with a clearly defined incubation period, and 3) could be successfully contained by means of a highly efficacious vaccine. In contrast, the tubercle bacillus is 1) a master in hiding, 2) causes a disease with no defined incubation period, and 3) the vaccine provides usually little protection against the transmissible form. These are just the technical components, not even considering the overriding prerequisite of global political will and collaborative climate for having even the slightest chance. A current ascertainment rather suggests that there isn't much of the latter around despite postulating it.[1]

Little surprise then that Donald Henderson (who led the WHO's smallpox eradication program for 10 years[2]) cautioned the overly enthusiastic in the tuberculosis community already 20 years ago "…, I am confident that bright victories lie ahead - but not eradication."[3] Even watering the meaning of "eradication" down to the somewhat ill-defined "end" (that isn't meant to be an end) or "elimination" (that isn't an elimination in the English grammatical sense), it is just not within the realm of a clear epidemiologic strategy. A vision, yes, an objective, no. Realistically, the "End TB Strategy" cannot thus possibly call for the actual "ending" of tuberculosis by a given point in time, it would be akin to elicit the epidemiologist to speak out "The emperor has no clothes". There is, however, an enormous amount of useful practical guidance and a giant amount of work in store with the End TB strategy.[4–6]

Getahun and Varma extract succinctly core contents of the strategy as "… achieving universal access to quality TB care and prevention, eliminating catastrophic costs to affected families, addressing weaknesses in health care delivery systems, and developing innovative approaches".[7] Rather than following here the more common approach to discuss the details of the three pillars of the End TB strategy[4] that others have done proficiently[8,9] i.e. 1) Integrated, patient-centered care and prevention, 2) Bold policies and supportive systems, and 3) Intensified research and innovation, we will look in a bit more detail at the extract glanced from Getahun and Varma.[7] The emphasis will be on the strategy's historical roots and the difficulties, contradictions, and adversities that have been lining the path towards achieving it – and continue to do so.

1. Achieving universal access to quality TB care and prevention

The year 2018 marked the 40th anniversary of the Alma-Ata conference on primary health care.[10,11] The Astana Declaration has followed last year in its footsteps.[12,13] Functional primary health care is a prerequisite for effective tuberculosis control. This has long been recognized, also by the Tuberculosis Association of India,[14] equally recognizing the difficulties and often encountered failures in implementation.[15] The hope to attain it in India by the end of the last century[16] has seemingly been somewhat overly optimistic as

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was the more generic "Health for All by 2000" initiative by the WHO under the leadership of Halfdan Mahler.[17] Nevertheless, health care services that are universally accessible are a *conditio sine qua non* for effective tuberculosis control and a reduction of the problem. We should learn from history though that this cannot just be postulated. A substantive political commitment will require substantial investment of resources that are in competition with other tasks of government responsibility. Conversely, not making such a commitment is a virtual assurance that the End TB strategy cannot be implemented as purported. To what extent it is an ominous sign in this respect that only 20 heads of state turned up for the widely publicized UN high-level meeting on tuberculosis last September in New York, and even leaders from high-burden tuberculosis countries, including Russia and India, were missing, remains to be seen.[18]

2. Eliminating catastrophic costs to affected families

The financial burden as a direct result of illness can be substantial and indeed catastrophic for tuberculosis patients and their families.[19] While it is of course much more complex than can be summarized here briefly, we note that temporally in parallel with the call for universal access to health by WHO, a deep economic crisis was choking poor countries about in the aftermath of the 1970s oil crisis, leading to an unsustainable imbalance between borrowers and lenders. The International Monetary Fund assisted countries with the aim of enabling them to pay their import bills and alleviate temporary instabilities, but it came at the cost of so-called structural adjustment programs. The underlying assumption of these was that appropriate policy changes would lead to sustainable economic growth with "present pain" for "future gain", i.e. short-term austerities would lead to long-term growth and development.[20] However, as Peabody points out, such intertemporal trade-offs are not always acceptable in health.[20] A disastrous example of structural adjustment played out in Nicaragua resulting in deteriorating child health in the 1990s.[21] There would be other examples to cite, but it may just be noted that in India too, concerns were raised in the 1990s about the impact of the World Bank's structural adjustment program on the health of the most vulnerable.[22] As Richard Horton, the Lancet's editor, has pointed out, the rising influence of the World Bank, World Trade Organization, and private foundations has undermined WHO, and we have a deepening democratic deficit in global health.[23] If health is relegated to market mechanisms which seems to be increasingly the case, then we have learned little from the lessons identified by Peabody 20 years ago[20] and we allow the principles of the Alma-Ata and Astana declarations to be sabotaged. The call of the End TB strategy to eliminate catastrophic costs will become harder to achieve by the day.

3. Addressing weaknesses in health care delivery systems

WHO began to promote integration of national tuberculosis programs into primary health care in the 1970s.[24] The quality of tuberculosis care delivery is thus again directly dependent on the quality of the primary health care system, i.e. a weak primary health care system is unlikely to deliver strong tuberculosis services. The health care system needs continuous adaptation and is under constant development. During different periods different viewpoints tend to dominate how this should be done.[25] Blas distinguished three major categories, utilitarian, libertarian, and communitarian. Beginning the mid-1980s, the paradigm shifted to libertarian and utilitarian.[25] Put simply, this point of view reduced the role of the state and increased the role of the market. This demanded "Health Sector Reform", which was essentially developed in the market economies of the western world. It led to the absurdity that countries diverse as Sweden, Viet Nam or Zambia (to name just a few) used the same remedies to address entirely different problems in entirely different settings.[25] The result was unsurprisingly that tuberculosis control and quality of care delivery made unequal progress to put it mildly, depending on the setting. At worst, services virtually collapsed.[26] Meanwhile, challenges and risks for tuberculosis control associated with health sector reform have been clearly identified,[27] but to rectify misled approaches has not been, nor continues to be, an easy task and constructive work to strengthen tuberculosis control within the services is demanding.[24]

4. Developing innovative approaches

From all components, this fourth is the only one that lies – at least in an important part – outside the realm of the health care system *sensu strictu*, to the extent that "innovation" addresses here technical progress in, e.g. development of new diagnostics, often actually even outside medicine. The most conspicuous innovations have been molecular techniques based on multiplication to detectable levels with subsequent identification of specific genome components. While these are generic principles with wide applications, the impact on tuberculosis diagnostic techniques is particularly large because of the intrinsically slow metabolism of *Mycobacterium tuberculosis* – speeding up identification of *Staphylococcus aureus* by switching from a phenotypic to a genotypic system is quantitatively of minor importance compared to the corresponding switch in *M. tuberculosis* diagnosis. There can be little doubt that already the present and certainly the future lies with these technologies. It is natural that many such techniques in development are still beyond the reach of sustainable financial means of national tuberculosis programs in low-income countries for routine use but experience shows that affordability of any new technique comes closer into reach with the passage of time. That this is so, is also in the interest of companies developing such test systems as volume of sale is by definition expected where tuberculosis is most common and corresponding products must thus be affordable in such settings. There is realistic ground to optimism that technical progress will just happen irrespective of what the tuberculosis community demands. After all, Cepheid for instance came into fame as a company in the bioweapons defense program of the United States with the successful development of the GeneXpert® system for detecting *Bacillus*

anthracis.[28] Tuberculosis diagnosis was thus in that sense perhaps just a wonderful afterthought rather than a piece of work following a tuberculosis control script.

5. Conclusions

Of the four that are listed by Getahun and Varma as core contents of the End TB strategy,[7] three are closely dependent on and intimately linked to the quality of the primary health care system or, as we call it today, universal health coverage.[29] If that is not brought to higher than current levels, any time frame that may be envisaged must by necessity fall apart. The 2017 monitoring report states that at least half of the world's population still lacks access to essential health services and some 800 million people spend more than 10 per cent of their household budget on health care.[30] One wonders what the co-authorship of the report by WHO and the World Bank implies given that a few years ago the International Monetary Fund and the World Bank propagated structural adjustment to include the health sector, impeding the WHO's pushing for improved primary health care. We shall optimistically assume that this is the sign of a truly new era of constructive collaboration. There will be a high-level meeting on universal health coverage in September this year and we join the editor of the Lancet in the hope that it will be more specific than last year's high-level meeting on tuberculosis.[31]

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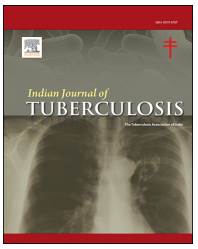

Original article

Journey of tuberculosis control in India

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ABSTRACT

NTP was pilot tested in Anantapur district of Andhra Pradesh during 1961 and thereafter the programme was launched throughout the country.

In 1992, the Government of India together with the World Health Organization (WHO) and Swedish International Development Agency (SIDA) reviewed the National TB Programme and concluded that it suffered from managerial weakness, inadequate funding, over-reliance on x-ray, non-standard treatment regimens, low rates of treatment completion and lack of systematic information on treatment outcomes. Programme review showed that only 30% of patients were diagnosed and only 30% of those treated successfully. Based on the findings and recommendations of the review in 1992, the GOI evolved a revised strategy and launched the **Revised National TB Control Programme (RNTCP)**.

NTP was pilot tested in Anantapur district of Andhra Pradesh during 1961 and thereafter the programme was launched throughout the country. Dr. Raj Narain, Epidemiologist of NTI, conducted the study on BCG efficacy which ranged from 0 to 80 but BCG vaccination was continued among children for protection against childhood TB. The programme was expanded in a phased manner to cover 364 districts of the country. NTI monitored the entire country and concluded that the compliance with anti-TB treatment for 12–18 months was a problem under field conditions. Dr. Wallace Fox introduced the Short course chemotherapy (SCC). With the introduction of Rifampicin and Pyrazinamide in the developed countries in early 1960s, a new era started in the battle against TB.[1] This finding enabled to cut down the duration of treatment to 6–8 months. In 1983, Tuberculosis Research Centre, Madras, pilot tested SCC in 18 districts of the country to assess the feasibility of its implementation on a larger scale. Government of India (GOI) agreed to the policy of implementation of SCC in 1986 and scaled up the coverage to cover 252 districts13 with the regimens. In spite of the introduction of SCC, monitoring report as well as findings of some studies continued to show a high rate of defaulters and the disturbing trend of low compliance in SCC districts. Following the global review of the programme, *WHO in 1993 declared TB as a global emergency*[2].

1. The present RNTCP

In 1992, the Government of India together with the World Health Organization (WHO) and Swedish International Development Agency (SIDA) reviewed the National TB Programme and concluded that it suffered from managerial

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weakness, inadequate funding, over-reliance on X-ray, non-standard treatment regimens, low rates of treatment completion and lack of systematic information on treatment outcomes. Programme review showed that only 30% of patients were diagnosed and only 30% of those treated successfully. Based on the findings and recommendations of the review in 1992, the GOI evolved a revised strategy and launched the **Revised National TB Control Programme (RNTCP)** in the country. Starting as pilots in October 1993, the RNTCP was implemented in a population of 2.35 million in 5 sites in different states (Delhi, Kerala, West Bengal, Maharashtra and Gujarat). The programme was expanded to a population of 13.85 million in 1995 and 16 million in 1996. Having proved both its technical and operational feasibility, a soft loan of US $ 142 million was negotiated with the World Bank in December 1996 and the credit agreement was signed with IDA in May 1997. In 1997 RNTCP was launched as a national programme. It was envisaged to implement RNTCP in 102 districts of the country covering a population of 271 million in a phased manner. Another 203 SCC districts with a population of 447 million were envisaged to be strengthened as a transitional step for introduction of revised strategy at a later stage. Having started in 1997, rapid scale-up began in late 1998, when another 100 million population was covered under RNTCP. By December 2005, around 97% (about 1080 million) of the population had been covered and the entire country was covered under **DOTS by 24th March 2006.**

2. Second phase of RNTCP

In the second phase the programme aimed to firstly consolidate the gains made to date, to widen services both in terms of activities and access and to sustain the achievements for decades to come in order to achieve ultimate objective of TB control in the country. The DOTS strategy is cost-effective and is today the international standard for TB control programmes. To date, more than 180 countries are implementing the DOTS strategy. The Programmatic Management of Drug Resistant TB (PMDT) was rolled out in 2005 and the services were rapidly scaled across the country. Cumulative outcomes of 12,125 MDRTB patients have been reported out of which 5796 (48%) have been successfully treated under PMDT. 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. 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. 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 country wide 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 Government of India and WHO Country Office India in 2014.* 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 Millennium Development Goals (MDGs), TB prevalence has been reduced from 465/lakh/year in 1990 to 211/lakh/year in 2013, incidence of TB has come down from 216/lakh/year in 1990 to 171/lakh/year in 2013 and mortality from 38/lakh/year in 1990 to 19/lakh/year in 2013. In 2012. GoI banned the use of commercial serology for diagnosis of TB and made TB notification mandatory across the country[3,4]. **"Nikshay"** is a case based web online application under RNTCP for monitoring of TB program and TB surveillance.

2.1. *Revised TB estimates*[5]

Updated estimate of incidence are 2.8 million cases in 2015 (217 per 100 000 population), and 2.9 million (223 per 100 000 population) in 2014. These figures can be compared with notifications of 1.7 million new and relapse cases in 2015 (127 per 100 000 population) and 1.6 million new and relapse cases in 2014. India's TB Control "Vision 2020" has laid down strategies for involvement of all care providers *to strengthen TB notification, promote ban on serology*.

Major initiatives undertaken:

- Launch of first nationwide anti-Tuberculosis Drug Resistance Survey of India,
- Daily drug regimen being pilot tested (14) 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
- Release of Standards for TB Care in India
- Bedaquiline
- New drugs in the pipeline
- Second line DST on LPA
- Active case finding project-2017
- NABL accreditation of labs
- TB/HIV collaborative activities

3. First nationwide anti-tuberculosis drug resistance survey of India

The first national anti-tuberculosis drug resistance survey, India 2014–2015 was launched on 6 September 2014 in New Delhi. This first of its kind survey in India is supported by the World Health Organization (WHO). Results of this survey are being analyzed and will be utilized in framing guidelines on

drug resistance in the future. **Draft guidelines were formulated on DST guided treatment for drug resistant TB patients during a meet of national/international experts.**

4. Screening all TB patients for diabetes[6,7] under the program settings

Evidence suggests that the DM population has a significantly increased risk of developing active TB (two or three times higher than in those without DM). Hence a decision was taken whereby all TB patients who have been diagnosed and registered under RNTCP will be referred for screening for diabetes. This guideline is being followed in all centres.

5. Release of standards for TB care in India

The first edition of the Standards for TB Care in India was conceived by a community of clinicians, public health specialists, community workers and patient advocates both within and outside of the Government of India as a necessary step in requiring and monitoring a widely accepted standard of TB care for the people of India. International guidelines and standards for TB care which existed such as International Standards for TB Care 2006 and 2009 editions, American Thoracic Society Standards, European Standards 2011 and WHO Guideline for Treatment of TB 2010 and WHO Guidelines for PMDT 2011 were used as a foundation for developing India's standards. These are reference guidelines for the programme[8] and are based in Indian studies and evidences.

6. Bedaquiline[9,10]

The US Food and Drug Administration (FDA) on 28 December 2012 granted accelerated approval to drug bedaquiline to treat resistant tuberculosis. In India the drug has been introduced under conditional access programme at 6 sites. The drug is a new anti-TB drug for treatment of MDR-TB. This new class of drug is a diarylquinoline that specifically targets Mycobacterial ATP synthase, an enzyme essential for supply of energy to MTB/other mycobacteria. Drug is active against many bacteria; it has been registered specifically for the treatment of MDR-TB. The drug is unique among the anti-tuberculosis drugs currently used in that it interferes with the function of an enzyme required by the tuberculosis bacterium to produce energy and to replicate. Bedaquiline is recommended for use in adults affected with pulmonary (lung) MDR-TB. Special caution is needed when the drug is used for elderly, during pregnancy, and in persons living with HIV who are taking antiretroviral medication. Bedaquiline should not be used to treat latent TB infection. As far as side effects are concerned it disturbs the function of the heart and liver in particular. Interactions with other drugs, especially lopinavir and efavirenz (used in the treatment of HIV), ketoconazole, as well as other drugs used in the treatment of MDR-TB (eg moxifloxacin, clofazimine) may be expected. It is important that patients are closely monitored and that adverse events are systematically reported. The dose and duration is as follows: Bedaquiline should be given for a maximum of six months on top of the WHO recommended combination treatment regimen. 400 mg daily (4 tablets) for 2 weeks followed by 200 mg 3 times per week for the remaining 22 weeks. For more information on dosage and conditions for use please see the references at the end.

7. Delamanid[10]

Delamanid is the active substance in a new TB drug treatment. Delamanid (formerly called OPC-67683) is also known by its trade name of Deltyba. It is the first in a new class of TB drugs called nitroimidazoles. It is currently being developed by the Otsuka pharmaceutical company as a treatment for MDR TB and is under trial. WHO recommends that delamanid may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB (conditional recommendation; very low confidence in estimates of effect). WHO recommends that the use of delamanid in the treatment regimen of MDR-TB be made subject to the following five conditions:

a. Recommendation for the use of delamanid: It is meant for adults (≥18yrs) with pulmonary MDR-TB disease, including people living with HIV. Special caution along with proper clinical judgement should be applied when the drug is to be given to geriatric patients (65 or more). Other vulnerable groups include diabetics, hepatic or severe renal impairment, or those who use alcohol or substances.
b. As per WHO-recommended MDR-TB regimen, Delamanid is to be introduced alongside other anti-TB drugs in composing an effective second-line regimen based on WHO guidelines.
c. Treatment is closely monitored.
d. Active pharmacovigilance along with proper management of adverse drug reactions and prevention of drug–drug interactions.
e. Patient informed consent should be obtained.

Dose of delamanid in adults is 100 mg twice a day, irrespective of body-weight, for a period of six months.

8. Shorter MDR regimen[11]

Recently, a standardized treatment regimen lasting less than 12 months has been used in a number of countries. It has shown promising results in selected MDR-TB patients. Based on data from these studies, WHO updated its treatment guidelines for drug-resistant TB in May 2016 and included a recommendation on the use of the shorter MDR-TB regimen under specific conditions.

9. Features of the shorter MDR-TB regimen

a. Standardized shorter MDR-TB regimen has seven drugs, Treatment duration 9–12 months
b. Indicated in MDR-TB or rifampicin resistant-TB, irrespective of patient's age/HIV status

c. Time to time Monitoring for effectiveness/side effects/ relapse would needed, with patient-centred care and social support to enable adherence
d. Programmatic use is feasible in most settings worldwide
e. Lowered costs
f. Exclusion criteria: 2nd line drug resistance, extra pulmonary disease and pregnancy

REGIMEN COMPOSITION 4–6 Km-Mfx-Pto-Cfz-Z-Hhigh-dose-E/5 Mfx-Cfz-Z-E Km = Kanamycin; Mfx = Moxifloxacin; Pto = Prothionamide; Cfz = Clofazimine; Z = Pyrazinamide; Hhigh-dose = high-dose Isoniazid; E = Ethambutol.

This new recommendation is expected to benefit the majority of MDR-TB patients worldwide; however, there are serious risks for worsening resistance if the regimen is used inappropriately (e.g. in XDR-TB patients). WHO encourages ongoing and future randomized controlled clinical trials to strengthen the evidence base for shorter and more effective regimens.

9.1. *New drugs in pipeline*

New drugs like Pretomanid, Rifapentin, Nitazoxanide, Moropenem/Clavulanate, Levofloxacin, Sutezolid, and High dose Rifa, OPC 167832 etc are under trial.

9.2. *Second line DST by line probe assay*

The World Health Organization (WHO) published the report of the Expert Group meeting held in March 2012 to review evidence on use of molecular line probe assay (LPA) for detection of resistance to second-line anti-tuberculosis drugs. The Expert Group recommended that the Genotype MTBDR assay cannot be used as a replacement test for conventional phenotypic DST (strong recommendation – very low quality of evidence). However, the Expert Group noted that this technology may be used as a rule-in test for extensively drug-resistant tuberculosis (XDR-TB) where line probe assay capacity is available.[11]

9.3. *NABL accreditation of labs*[12]

Laboratory accreditation activities are administered under the direction of the National Accreditation Board for Testing and Calibration Laboratories (NABL), involving Assessment Team and Accreditation Committee as recommending bodies. NABL is a signatory to Asia Pacific Laboratory Accreditation Cooperation (APLAC) and International Laboratory Accreditation Cooperation (ILAC) Mutual Recognition Arrangements (MRA). These are based on mutual evaluation and acceptance of other MRA partner laboratory accreditation systems. It has been decided to get NABL accreditation of 15 selected laboratories in India co-working as NRL/IRL in the first phase.

9.4. *TB/HIV collaborative activities*[13]

These are guidelines for strengthening cross referral mechanism between the 2 programmes. These follow the same framework as the 2004 interim policy document, structuring the activities under three distinct objectives: establishing and strengthening mechanisms for integrated delivery of TB and HIV services; reducing the burden of TB among people living with HIV and initiating early antiretroviral therapy; and reducing the burden of HIV among people with presumptive TB (that is, people with signs and symptoms of TB or with suspected TB) and diagnosed TB. The new component of introducing ATT as FDC on daily basis and drug delivery would be through ART centres.

Rational use of anti TB drugs and early identification of referral of TB suspects for diagnosis and increase community awareness. Guidelines and framework for EP TB have been formulated. Conditional access program has been approved for introduction of new anti-TB drug **Bedaquilline** and 'Universal access to free anti TB drugs' piloted to provide anti-TB drugs to patients in the private sector.

9.5. *Future*

Goal of eliminating TB by 2050 depends on the development of new diagnostics, drugs and vaccine. *Eliminating TB by 2050 means less than 1 case* per *million population. In this regard, a* ***Post 2015 Global Tuberculosis strategy*** *has been drafted. As* per *the draft to achieve this target, it sets a goal of less than 10 cases* per *1 lakh population by 2035.*

The future vision and targets (Source: Post 2015 Global Tuberculosis strategy)

- *The Vision of draft:A world free of TB*
- *Goal is to end the TB epidemic*
- *Targets to be achieved by 2035*
  - 95% reduction in TB deaths (compared with 2015)
  - 90% reduction in TB incidence (<10/100000).
- Milestones to be achieved by 2025: 75% reduction in TB deaths (compared with 2015)
  - 50% reduction in TB incidence rate (less than 55/ 100000)
  - No affected families face catastrophic costs due to TB

10. National strategic plan 2017–2025

Tuberculosis patients and healthcare providers availing cash benefits[14] under the programme have to register with the Aadhaar database. Cash benefits to patients, incentives to health care providers all are going to be through Aadhaar accounts. For these patients bank account details would be entered for DBT.

- The programme has introduced daily regimen in 2017
  a. Drug sensitive
  b. PLHIV
  c. Paediatric patients

The principle is to administer daily fixed dose combinations of drugs which would be supervised by a DOT provider.

FDC WHO recommends the 4-drug FDC to treat tuberculosis, provided that the constituent drugs are of proven quality and are used at WHO recommended strengths. The rationale for recommending the 4-drug FDC is that it simplifies both treatment and management of drug supply and may prevent the emergence of drug resistance. FDC/Daily DOTS initiated pan- India in the year 2017: strategies to rapidly decline TB in the country by 2030 in line with the global End TB targets and SDG's to attain the vision of a TB-free India. The goal of this programme is to achieve a rapid decline in burden of TB, morbidity and mortality while working towards elimination of TB in India by 2025.

10.1. *Index TB guidelines*[15]

These guidelines provide guidance on, uniform, evidence-informed practices for suspecting, diagnosing and managing various forms of extra-pulmonary tuberculosis (EPTB). They can further contribute to the National Programme to improve detection, care and outcomes in extra pulmonary tuberculosis. Other objectives of these guidelines are to help initiate patients treatment, adherence minimize drug toxicity, assess adherence and reduce drug resistance. Another objective is to identify knowledge gaps.

Vaccines: Following vaccines are being looked into:

- BCG (rBCG) vaccines are being looked into, that offer longer-lasting protection. For example, introduction of the RD1 region (encoding ESAT-6 and CFP 10, as described above) results in increased persistence of the rBCG strain. This vaccine induces better protection against disseminated forms of tuberculosis in mouse and guinea-pig models.
- An rBCG that over expresses antigen 85B, shows increased protective immunity against TB in the guinea-pig model and has been tested in a phase I clinical trial in uninfected human volunteers.
- An rBCG strain that expresses listeriolysin O from *Listeria monocytogenes* is awaiting phase I clinical trials.
- Attenuated *M. tuberculosis* strains that are deleted for the gene encoding the transcriptional regulator PhoP or for the RD1 region and *panCD* genes have been tested in animal models.
- Booster vaccines, MVA85A, a replication-deficient recombinant vaccinia virus that expresses antigen 85A (Rv3804c), has entered phase II clinical trials
- Adenovirus-based vaccine expressing Ag85 recently has entered phase I clinical trials.
- In addition, several subunit vaccines have been tested, and some of them, such as Mtb72 in adjuvant AS02A or the Ag85B-ESAT-6 fusion protein in adjuvant IC31, have been tested in phase I clinical trials and are awaiting or entering phase II trials

10.2. *End TB strategy*

Government of India has decided to adopt End TB Strategy whereby target is to eliminate TB by 2025, well before Sustainable Development Goals which stipulate to eliminate TB by 2030.

Targets set for END TB Strategy are as compared to 2015 levels.

- To decrease TB incidence rate from 217 to 44 per lakh per year.
- To decrease mortality rate from 32 to 3 per lakh per year.

10.3. *Key changes in MDR TB treatment*[16,17]

Table 1 indicates the overall approach to designing longer MDR-TB regimens for adults and children based on the revised grouping. The regimen is designed by adding medicines sequentially going down the three groups.

Apart from the ranking by balance of effectiveness and harms, choice is also determined by: a preference for oral over injectable agents; the results of drug-susceptibility testing (DST); the reliability of existing DST methods; population drug resistance levels; history of previous use of the medicine in a patient; drug tolerability; and potential drug–drug interactions.

Consultation on how best to optimise these aspects of MDR-TB treatment is ongoing. This includes the minimum number of medicines required in designing MDR-TB regimens based on the revised grouping, while maximising regimen efficacy in the presence of resistance to or tolerability of individual agents.

Options for the choice of agents for the intensive and continuation phases, more detailed guidance on patient selection criteria, number of medicines and duration of treatment, adult and paediatric dosing, treatment of extensively drug resistant disease (XDR-TB), and the use of DST results will be provided at the time of release of the final WHO guidelines.

Table 1 – Grouping of medicines recommended for use in longer MDR-TB regimens.

Group	Medicine	Abbreviation
Group A:	Levofloxacin OR	Lfx
Include all three medicines	Moxifloxacin	Mfx
(unless they cannot be used)	Bedaquiline[1,4]	Bdq
	Linezolid[2]	Lzd
Group B:	Clofazimine	Cfz
Add both medicines	Cycloserine OR	Cs
(unless they cannot be used)	Terizidone	Trd
Group C:	Ethambutol	E
Add to complete the regimen and when medicines from Groups A and B cannot be used	Delamanid[3,4]	Dlm
	Pyrazinamide[5]	Z
	Imipenem-cilastatin OR	Ipm-Cln
	Meropenem[6]	Mpm
	Amikacin	Am
	(OR Streptomycin)[7]	(S)
	Ethionamide OR	Eto
	Prothionamide	Pto
	p-aminosalicylic acid	PAS

Conflicts of interest

The authors have none to declare.

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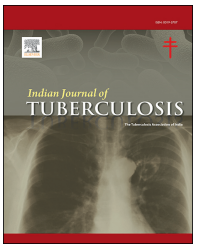

Original article

Early efficacy and safety of Bedaquiline and Delamanid given together in a "Salvage Regimen" for treatment of drug-resistant tuberculosis

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ABSTRACT

Background: Drug-Resistant Tuberculosis (DR-TB) patients for whom a WHO recommended regimen along with Bedaquiline (BDQ) cannot be prescribed, Delamanid (DLM) was added along with other drugs to provide a "Salvage Regimen". The experience of the Institute in respect of early efficacy and safety of both drugs given together is presented.

Objective: To ascertain the early efficacy, safety and tolerability of Bedaquline and Delamanid given together as a part of salvage regimen.

Methods: BDQ and DLM were used together to make regimens along with other drugs where four effective anti TB drugs could not be prescribed as per WHO recommendations. Patients were followed up for sputum smear and culture conversion and adverse events during the treatment.

Results: In this cohort study, 53 DR-TB patients (Median age-24) were initiated on regimens containing both BDQ and DLM. Sputum smear conversion was seen in 35% and 94% patients at the end of 1st week and 3rd month respectively. 84% patients had culture conversion at the end of 4th month. 29 adverse events (AE) were reported among 17 patients and there were 11 deaths. QTc prolongation more than 500 MS was seen in only 1 patient.

Conclusion: BDQ and DLM given together in a salvage regimen is efficacious with low rate of adverse events. The combination provides hope to DR-TB patients with limited treatment options and should be provided as a life saving option.

1. Introduction

The treatment of drug resistant tuberculosis (DR-TB) is a challenge due to poor outcomes as a consequence of drug toxicity, long duration and failure to the existing regimens. In spite of best treatment efforts with the current recommended regimens, treatment success is possible in about 50% of Multi drug resistant tuberculosis (MDR-TB) patients and 11–33% of the extensively Drug resistant tuberculosis (XDR-TB) patients[1]

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The discovery of newer drugs Bedaquline (Bdq) and Delamanid (Dlm) have given some hope and limited reports of effective results are available.[2,3] However, both the drugs exhibit cardio toxicity i.e. prolongation of the QT interval and WHO has not recommended their combined use in the absence of sufficient evidence.[4] Nevertheless both the drugs have been used in patients where a WHO recommended regimen of four effective drugs could not be given without using them and have been found to be both efficacious in terms of sputum smear and culture conversion, safe in terms of QTc prolongation and tolerability[5,6] Clinical trials[7] may subsequently provide the evidence in coming years.

Both Bdq and Dlm are available in India under the Revised National Tuberculosis Control Programme (RNTCP) and are recommended individually for treatment of Pre-XDR and XDR patients with an optimum background regimens (OBR) following the WHO principles of using at least four effective drugs in addition. There are still no recommendations for the use of both the drugs together.

NITRD is a Nodal DR-TB centre under the RNTCP and one of the six sites responsible for rolling out Bdq under the Conditional Access Program. As a Nodal DRTB centre, it was responsible for the treatment and monitoring of Pre –XDR and XDR cases. It was observed that some of the patients had been treated with multiple courses of ATT (first and second line), had varied drug sensitivity pattern (DST) and could not be put on Bdq with an effective OBR due to lack of effective drugs. In such cases there was no option left other than putting them on a individualized treatment option of a "Salvage Regimen" (SR), containing both Bdq and Dlm along with other drugs. The selection of other drugs was based on the combination of resistance pattern of drugs consumed and the previous history of drug exposure.

Early experience of 53 such patients who were put on treatment with regimens containing both Bdq and Dlm is shared.

2. Methods

This patient cohort consisted of those who received both Bdq and Dlm in the regimen and included intake period 22 months. Patients older than 18 years (one patient age 17 years), who consented for Bdq and Dlm combination were put on treatment. After initial hospitalization of minimum two weeks the patients were treated under routine programmatic conditions at DOT centres. The combination of Bdq and Dlm was used as a part of an individualized, treatment regimen (ITR) along with 4–5 other drugs selected as per preference based on resistant pattern and previous exposure (Table-1). All the patients who had failed on Cat V regimen or had clinical failure or where a Bdq regimen as per RNTCP was not possible, were reviewed by the institute DR-TB Review Committee to design an ITR. Written consent was taken from the patients, after informing the potential clinical benefits and adverse effect before starting the treatment.

After admitting, pre-treatment evaluation consisting of base line. ECG, Serum Albumin, Thyroid functions, Heamoglobin, Electrolytes, Renal and Liver function test,

Table 1 – Showing selection of drugs for OBR in decreasing order of preference.

History of exposure to drug	Resistance pattern
Nil	Sensitive
Nil	No documented resistance
present	Sensitive
present	No documented resistance

Ophthalmological examination was done before starting the treatment and repeated as per clinical status of the patients. QTc values (as per Bazetts formula) were obtained directly from the calibrated 12 lead ECG machines. Four tablets (100 mg each) of Bdq was given daily for 2 weeks, followed by two tablets three times a week for 24 weeks whereas Delamanid was given as two tablets (50 mg each) twice a day throughout the 24 weeks. All drugs were administered after a meal and under observation.

ECG was done twice daily during the period of hospitalization and other investigations were done in accordance with the RNTCP guidelines. Adverse drugs reactions (ADR) were reported to DR-TB Review Committee for management and any change in the ITR. The ADRs were also reported to the National Pharmacovigilance Program through the causality panel of the institute which was responsible for assessment of drug causality. Management of ADRs were done as per RNTCP guidelines.

Bacteriological monitoring, consisting of weekly smear and culture (on liquid media) for first month and then subsequently on a monthly basis for six months was done, additional drug susceptibility testing (DST) for first-line and second-line drugs when positive cultures were obtained, was done at the institute microbiology laboratory which is also, the National Reference Laboratory Service (NRL), under the RNTCP.

3. Outcomes

Efficacy is assessed in the cohort using sputum culture conversion i.e. two consecutive negative results taken at least 2 weeks apart in a patient with a positive specimen at baseline[8], where the baseline was defined as the initiation of ITR. Culture status at 6 months was also assessed, as an efficacy outcome and included all people in the study who had a documented negative culture at 6 months regardless of baseline culture status.

Safety was measured by occurrence of serious adverse events and QTc prolongation of more than 500 Ms or increase of more than 60 Ms from baseline during the period of treatment. Serious adverse events were defined as deaths irrespective of cause, hospital admissions, events leading to disability or congenital malformation, and events considered life threatening or otherwise medically significant.

Tolerability was defined as a person still on treatment for drug-resistant tuberculosis 6 months after initiation of the combination of Bdq and Dlm regimen.

4. Results

4.1. Patients profile

Fifty three patients were initiated on regimens containing both Bdq and Dlm from March 2017 to November 2018 (Table 2). The median age at initiation was 24 years (IQR 21–33). 24 (45%) patients were men and had a median BMI of 20 (IQR 17.5–25). Of the 53 patients, 17 (32%) had XDR treatment failures, 02 (4%) had failed on a DST based drug regimen and 34 (64%) had DST pattern in which an Bdq based regimen could not be designed as per RNTCP guidelines. None of the patients was HIV positive.

4.2. Regimen

The regimen used contained a median of 7 drugs IQR (6–8) including Bdq and Dlm. Twenty four (45%) of the patients had at least one more QTc prolonging drug i.e. either Clofazimine or high dose Moxifloxacin while, in 27 (51%) patients both of these drugs were used. A core regimen of Bedaquiline, Delamanid, Imipenimen and Moxifloxacin was used along with other drugs in 42 (79%) patients. Both Bdq and Dlm were planned for a minimum period of 6 months (taken as intensive phase of the regimen) and was extended beyond 6 months in 5 patients.

Table 2 – Profile of patients put on salvage regimen (n = 53).

Median age (years)	24 (21–33)
Sex	
Men	24 (45%)
Women	29 (55%)
Body-mass index, kg/m^2	20 (17.5–25)
Drug resistant tuberculosis classification	
Multidrug-resistant	35 (67%)
Pre-extensively drug-resistant	01 (2%)
Extensively drug-resistant	17 (32%)
Type of patient	
Failed on Cat-V regimen	17 (32%)
Bdq based regimen not possible due to DST pattern	34 (64%)
Clinical failure while on DST based drug regimen	2 (4%)
No. of drugs along with BDQ and DLM	
5	1 (2%)
6	17 (32%)
7	19 (36%)
8	14 (26%)
9	1 (2%)
10	1 (2%)
Core-regimen used with OBR	21
Bdq+Dlm	53 (100%)
Bdq+Dlm+Imp	21 (40%)
Bdq+Dlm+Imp+Mfx(H)	42 (79%)
Bdq+Dlm+Mfx(H)	31(58%)
Bdq+Dlm+Imp+Mfx(H)+Lzd+Cfz	22 (42%)
Other QTc prolonging drugs along with BDQ & DLM	
1 QTc prolonging drugs	24 (45%)
2 QTc prolonging drugs	27 (51%)
Adverse events reported	
Adverse events	29
Serious adverse events including death	21

4.3. Conversion status

All the 53 patients initiated on treatment had positive smear and culture at baseline. Of them 42 patients have completed 6 months of intensive phase while 11 are still on intensive phase. Among the 42, 31 are on the OBR, 10 died and 1 was lost to follow up (LTFU) (Table-3). Among the 31 patients on OBR, sputum conversion was seen in 11 (35%) by the end of 1st week of treatment initiation, 29 (94%) had converted by the 3rd month and remained negative at the end of 6th month. Sputum culture conversion was seen in 7 (23%) of these 31 patients by end of 1st week and 26 (84%) had converted by end of 4th month. Among these 26, culture re-conversion was seen in 1 patient only. Culture results were not available among 10 (32%) patients at the end of 6th month due to non production of sputum, contamination and results still pending (Table-4).

Two out of the 10 patients died during the 1st month of treatment and had positive smear and culture at the time of death. The remaining 8 patients died at various points till completion of 13th months of treatment and had the last sputum smears and cultures negative at the time of death. The LTFU patient also had a negative smear and culture at the time of outcome.

4.4. AE/SAE

Adverse Events (AE) and Serious Adverse Events (SAEs) were reported during the initial hospitalization and during the follow up period by the DOT providers. Seventeen patients (32%) had reported at least 1 serious adverse event excluding death among the total of 29 adverse events reported. Among these 29 adverse events 21 were serious. Bdq and Dlm were suspected in 12 (41%) instances but could not be confirmed to be the casual agent. More than 1 AE (maximum 5) were reported in 5 patients who accounted for 14 AEs of which 08 were serious. Among the 53 patients both baseline and follow-up ECGs were available for 50 (94%). Among them 07 (0.14%) patients had increase of QTc >60Ms at any time. QTc prolongation >480 Ms (requiring intervention as per RNTCP guidelines) was seen in 11(20%) patients but was resolved with correction of electrolytes and interruption of the drugs within permissible limits. Seven (64%) out of these 11 patients were on 4 QTc prolonging drugs however did not require any discontinuation of drugs. Only 01 of the patients had both QTc >500Ms and increase of >60Ms. 01 patient with associated cor-pulmonale presented with cardiac arrhythmia (Bigeminy) and the drug regimen had to be discontinued. Of the 11 deaths QTc prolongation had been reported in 05 patients (03 with >60Ms increase) at any one time but was resolved and could not be

Table 3 – Current status of patients started on salvage regimen.

Outcome	No.
Death	10
LTFU	1
On treatment with OBR after completion of 6 months of Bdq & Dlm	31
On IP with Bdq & Dlm regimen	11

Table 4 – Smear and culture status of patients currently on treatment (n = 31).

Period	Smear			Culture		
	Positive	Negative	N/A	Positive	Negative	N/A
Week 1	17	11	3	19	7	5
Month 3	1	29	1	14	11	6
Month 4	1	29	1	1	26	4
Month 6	0	29	2	2	19	10

confirmed as cause of death in any patient. This was followed by reporting of symptoms of peripheral neuropathy in 5 (1%) and Gastrointestinal symptoms in 3(0.6%) patients. The ADRs were more due to the accompanying drugs in the regimen rather than the combination of Bdq and Dlm.

5. *Discussion*

This is first reported cohort of patients, who have been treated with both Bdq and Dlm due to lack of at least 4 effective anti tubercular drugs as per WHO recommendations under programmatic conditions. Although not recommended by RNTCP due to similar potential for QTc prolongation of both the drugs, they were used along with other drugs on compassionate grounds as these patients did not have any other effective regimen. The preliminary results show the combination is safe, has high culture conversation rates and tolerated in these patients who otherwise have a low chance of cure and survival. The findings are interim as the patients have yet to complete their full treatment; however the data supports the safety and tolerability of the combination in spite of the theoretical risk of synergistic risk of QTc prolongation.[9]

There was no cardiac arrhythmias (except in one patient) and only 01 patient had an absolute QTc interval greater than 500 Ms. Eleven patients in the cohort had QTc prolongation over 480 Ms requiring intervention. However, these events were managed without permanent discontinuation of either Bdq or Dlm when used in combination contrary to QTc prolongation requiring permanent discontinuation of Bdq reported by Guglielmetti et al in 6% of their patients.[10] Our findings are similar to those of Gabriella and colleagues[5] who could give the Bdq and Dlm combination in spite of transient QTc prolongation. Of the11 deaths which occurred, none could be attributed to QTc prolongation. One patient who presented with Bigeminy had associated cor-pulmonale and expired within 24 hours due to poor general condition resulting from her Tuberculosis condition. Of note is the higher ADRs which were reported attributing them to the concomitant drugs, which were used along with Bdq and Dlm. The reporting of ADRs were done under the programmatic conditions and some may have been missed, but this also shows that it is feasible to provide the treatment under the programme conditions.

Our data though interim in nature, supports the efficacy of Bdq and Dlm combination to treat complex resistant patterns of Tuberculosis. We report 94% sputum conversion and 23% culture conversion at the end of 1st month among patients (n-31) who completed 6 months of Bdq and Dlm combination and continue to take treatment, for these patients smear and culture conversion at the end of 4th month is 94% and 61% respectively. Sputum conversion rate of all the patients (n-53) is 52% and culture conversion is 27% at the end of 1st month. This culture conversion is higher and faster than reported by Pietersen and colleagues who found conversion in 21% patients, with a median time to culture conversion of 8.7 months (IQR 5·6–26·4)[11] leading to a lower transmission in the community. Further, the fact that majority of patients who died, were sputum smear and culture negative at the time of death indicates that transmission risks are reduced to a considerable extent even from seriously ill patients. Culture conversion is closer to that achieved in patients reported by Gabriella and colleagues i.e. 74% against 61% at 6 months (with 32% still pending, and contaminated). Only 1 patient showed re-conversion with impending failure at 6th month culture.

Tolerability of the regimens prescribed including Bdq and Dlm is evident as 42 (79%) of patients continue to take treatment while 31 (58%) have completed the Bdq and Dlm duration in spite of ADRs.

5.1. *Limitation*

This interim analysis reflects the treatment of an observational non-controlled cohort under programmatic conditions, of Tuberculosis patients with few treatment options and has several limitations.

Adverse events, specifically QTc prolongation after initial admission could have been missed as it was hardly reported by the DOT providers or the absence, of such data could be that the QTc prolongation is transient and occurs in the initial treatment period only. This needs to be confirmed with a larger cohort with more intensive ECG monitoring.

The small size of the cohort and absence of final outcomes also needs to be kept in mind while interpreting the results. Since the patients had a varying resistance patterns, exposure and response to anti tubercular drugs, it was not possible to conduct a controlled trial with a larger number. However the LTFU is not as expected and may be due to the patients, continuing treatment in spite of ADRs due to the limited treatment options. Bdq and Dlm being new drugs for Tuberculosis, baseline sensitivity was not available/done so they were added considering that they would not yet be resistant however this needs to be evaluated in further cohorts.

6. Conclusion

To conclude 53 patients, started on regimens containing both Bdq and Dlm show a promising safety profile and culture conversion results, at the end of 6 months. This is important

considering the patients who have a very limited treatment, option as a result of exposure, resistance to anti tubercular drugs and clinical status of these patients. This combination should be extended to these patients more frequently and may be the only hope for cure in them, till the time results of clinical trials are made available.

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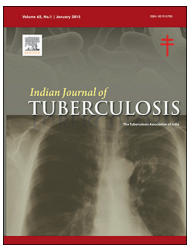

Continuing Medical Education

Drug resistance among TB cases and its clinical implications

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ABSTRACT

The emergence of *M. tuberculosis* strains resistant to at least, Isoniazid (INH) and Rifampicin (RIF), the two most potent drugs of first-line anti-TB therapy is termed multidrug drug-resistant TB (MDR-TB). This is a cause of concern to TB Control Programmes worldwide. When MDR-TB strains become resistant to the major second-line drugs, one of the fluoroquinolones and one of the three injectable drugs (Amikacin, Kanamycin and Capreomycin), it is defined as extensively drug resistant TB.[1,2]

MDR-TB is a manmade, costly and deadly problem. Rapid diagnosis of MDR-TB is essential for the prompt initiation of effective second-line therapy to improve treatment outcome and limit transmission of the disease.

1. Global burden

Cases of multidrug drug-resistant TB (MDR-TB) have been reported in every country.[1,2] As of 2014, 3.5% of new TB cases have MDR-TB.[3] Levels are much higher in those previously treated for TB (about 20%). Approximately 0.5 million new MDR-TB cases were estimated in the world in 2011.[4] About 60% of these cases occurred in Brazil, China, India, the Russian Federation and South Africa. Estimated number of MDR-TB cases in 2011 were reported to be 630,000 out of an approximate of 12 million prevalent TB cases. In 2014, MDR-TB estimated cases were reported to be 424,203, which included both new and previously treated cases, whereas in 2000, the estimate was 272,906.[1,5]

2. Indian scenario

India has the highest estimated MDR-TB cases amongst notified TB patients in the world with estimated MDR-TB emerging annually to 99,000.[3] Data from studies conducted by NIRT and NTI have found MDR-TB levels of 1–3% in new cases and around 12% in re-treatment cases. RNTCP has recently undertaken three community-based state level drug resistance surveillance (DRS) studies in Gujarat, Maharashtra and Andhra Pradesh. These surveys have estimated the prevalence of MDR-TB to be about 3% in new cases and 12–17% in re-treatment cases. XDR among MDR-TB isolates in Gujarat and Andhra Pradesh survey were 3–7%, while ofloxacin resistance in these two states surveys was 21–24%.

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3. Causes of increase in drug-resistant tuberculosis

Suboptimal TB control practices (e.g., poor DOT, inadequate infection control measures, and treatment without drug susceptibilities or culture) are the major cause in MDR-TB. From a microbiological perspective, the resistance is caused by genetic mutation that makes a drug ineffective against the mutant bacilli. An inadequate or poorly administered treatment regimen allows drug-resistant mutants to become the dominant strain in a patient infected with TB.

4. Programmatic management of drug resistant TB (PMDT) Services in India

After successfully establishing the DOTS services across the country in 2006, RNTCP rolled out the PMDT services in 2007.[6] There was an exponential scale up during 2011–12 to achieve complete population coverage in March 2013. PMDT prioritises diagnosis and management of M/extensively drug resistant TB (XDR-TB) cases and mono- and Poly-FLD resistant cases without M/XDR-TB treated with FLD regimes. Early implementing states used phenotypic DST for the diagnosis of DR-TB. Since 2012, all patients undergo rapid molecular DST (mostly LPA) for diagnosis. Criteria for MDR-TB are as follows:

- Criteria A
  - All new TB patients failing first-line regimen
  - All previously treated patients who remain smear-positive at the end of extended IP or later (CAT II)
  - Smear-positive contacts of known MDR cases
- Criteria B
  - All Sm +ve re-treatment PTB cases at diagnosis
  - Any Sm +ve follow-up of new or RT cases
- Criteria C
  - Sm −ve re-treatment PTB cases at diagnosis
  - HIV TB co-infected cases

5. TB diagnostics

The care of patients with tuberculosis (TB) starts with a quality assured diagnosis. Arguably, the most important component of health systems is the laboratory services. An unprecedented effort to improve and expand TB laboratory capacity is under way, spearheaded by WHO and the Stop TB Partnership, Global Laboratory Initiative and its network of international collaborators. For an increased output, a given lab can conduct DST on many more patients by molecular and liquid than solid culture method. The rapid diagnosis reduces patient loss, mortality and operational complexity of current system. The infrastructure requires flexible capacity, with molecular, solid and liquid capacity for testing. Thus, for DST at certified laboratory, wherever available Molecular DST (e.g. Line Probe Assay (LPA)) is preferred diagnostic method because of the rapid and highly accurate rifampicin results, followed in preference by Liquid C-DST and then Solid C-DST. Similarly for follow-up cultures, wherever available, liquid culture will be preferred over solid culture. However, this will be liquid cultures for at least the crucial months of follow-up (IP-3, 4, 5, 6 and CP-18, 21, 24) and over and beyond this, it will be determined by the workload of individual laboratories.

6. Non-MDR-TB cases in India

Currently, there is no policy for the management of non-MDR cases in India. New smear positive cases remaining positive after 2 or 3 months of therapy are continued on the same regimen. Also smear positive retreatment cases at baseline are initiated on retreatment regimen, i.e., Cat II. If they remain positive after 3 or 4 months of treatment, same schedule is continued, and DST is repeated for patients failing to first-line category treatment.

To know the prevalence of non-MDR-TB cases, data of about 7000 cases treated under programmatic conditions were reviewed to find out prevalence of resistance to individual drug and treatment outcome of such patients taking either Cat I or Cat II treatment. Data revealed H mono resistance to the tune of 34% (17% among Cat I and 83% among Cat II patients). Among these cases, failure rate was around 49%. Worse than this on repeat DST, there was implication of resistance up to 40% against rifampicin among these patients.

Clinical implications include treating mono- and poly-resistant cases, in which first-line regimen is associated with high risk of unfavourable outcomes including failure to treatment. This risk increases with the number of drugs, against which the bacilli are resistant. Significant risk of amplification of resistance to rifampicin was observed in mono- and poly-resistant patients treated with FLD.

On the other hand, in a study conducted in NDTB Centre (unpublished data) among 1200 MDR suspects, 12% were found to be pan sensitive on DST. Patients got Cat I or Cat II treatment, based on previous history of anti-TB treatment. Their treatment outcome was correlated. Only 60% cases responded to treatment. More than 14% cases failed to treatment may be due to in vitro, in vivo variation in susceptibility of organisms. Some of them may have taken irregular treatment.

Baseline second-line DST among confirmed MDR cases also found 22% strains resistant to ofloxacin and 2% to both ofloxacin and kanamycin. Impact on treatment outcome and implication of resistance to other drugs is yet to be seen.

7. Effect of drug resistance on treatment outcome with first-line drugs (FLDs)

The effect of drug resistance on the outcome of TB treatment using standard regimens depends on type and number of drugs to which the strain is resistant versus the potency of treatment regimen.

Modern first-line short-course treatment regimens for TB use R for the full 6-month duration. R resistance leads to

increased rates of failure or relapse, depending on sensitivity to other drugs in the regimen (H, Z, E, sometimes S). Using only FLDs, MDR-TB has less than 50% chance of relapse-free cure, barely better than natural course of untreated TB. H monoresistance has little impact on the treatment outcome. Influence of E monoresistance is not known because it is very rare and less reliable DST. Influence of Z monoresistance is also unclear, however initial Z resistance would be expected to lead to increased relapse. Resistance to H with E or S increases risk of failure and relapse to approximately 10% patients using R-throughout regimen, 40% without R regimen in CP. Resistance to H + E + S leads to failure to any FL regimen in approximately 1/3 to 1/2 of patients, due to acquisition of R resistance with the strain developing into true MDR-TB. Because of poor growth of some MDR-TB strains, concomitant R resistance may be missed by conventional DST. It is the probable cause of more failures among retreatment patients with initial H-resistant, R-susceptible disease.[7]

8. Amplification of drug resistance

Except for MDR-TB and combined resistance to H, S and E, majority of patients with initial drug resistance will be cured using standard FLD regimen. Risk of amplification of resistance with development of MDR-TB in failure cases is a real problem. Because of poor growth of some MDR-TB strains, concomitant R resistance may be missed by conventional DST. This can be a possible explanation for studies reporting significantly more failures among retreatment cases with initially H-resistant, R-susceptible disease compared with the same initial resistance, but treated with less powerful 6 month R throughout regimens. It is therefore reasonable to assume that some patients who carry H or R resistant strains, but not both, will fail or relapse with an unmodified FLD regimen. The revised FLD regimen should be used with repeat rapid R DST in case of delayed conversion or even a switch to the MDR regimen at any time in first-line retreatment, with correlating clinical conditions. The alternative recommendation in some guidelines is replacing H by FQ, but this would create pre-XDR strains out of MDR strains that are difficult to grow and may be misclassified as H + E, H + S, or H + E + S-resistant.[7]

9. Effect of drug resistance on treatment outcome with SLDs

Very little data are available regarding impact of initial second-line resistance on standard MDR-TB treatment regimens. FQ resistance seems to be most important and only about 10% of those with initial FQ resistance have failed or relapsed from the regimen for 'new' MDR-TB patients. Thiomide resistance has a minimal impact on the outcome of the regimen. Resistance to thiomides in strains from patients never exposed to these drugs will often be caused by cross resistance with H, due to *inhA* mutation. The remaining SLDs (PAS and CS) have little activity and are vulnerable as these are companion drugs only. Resistance to these drugs will only matter when there is already some resistance to FQ or other companion drugs, and possibly with weaker regimens.[7]

10. Effect of drug resistance on treatment monitoring parameters

There is confusion regarding the meaning of positive smears at the end of intensive phase. Sputum smear conversion depends mainly on the extent of the disease and bacillary load at the start of the treatment, and much less on regularity of drug intake and drug resistance. Only MDR-TB clearly delays smear conversion during standard first-line treatment, even with the most powerful IP Cat II treatment – prolonged excretion of dead bacilli. In principle, culture is a better parameter for treatment monitoring. However, with referred sputum samples, results of these often paucibacillary specimens become less reliable and delays, and would reduce their usefulness. With solid media and drug-susceptible extensive disease, culture conversion often precedes smear conversion. With serious drug resistance, culture may never convert, contrary to the smear, or may revert to positive sooner than a smear.[7]

11. Are drug-resistant strains as transmissible as drug-susceptible strains?

A case–control study by Snider et al. demonstrated that contacts of patients with drug-resistant and drug-susceptible cases of TB had an equal prevalence of positive tuberculin skin test. In contrast, animal studies have shown that isoniazid-resistant strains caused significantly less disease in guinea pigs than drug-susceptible strains.[8]

12. Are drug-resistant strains likely to progress to active disease once infection is established?

In San Francisco, Burgos et al. found that strains that were resistant to isoniazid either alone or in combination with other drugs were less likely to result in secondary cases than were drug-susceptible strains. In this setting, isoniazid-resistant and MDR-TB cases were not likely to produce new, incident drug-resistant TB cases. This presumed effect on pathogenicity may be related to mutations in the *katG* gene.[9] In addition to this data, other molecular epidemiological studies observed that cases of TB caused by drug-resistant strains were less likely to be in clusters. The implication is that drug-resistant strains were less likely to be transmitted and/or to cause active TB.[10]

Factors affecting drug-resistant strains to progress to active disease are

(a) Pathogen related
- Undefined virulence factors
- Variability in virulence between genotypes
- Size of the infecting inoculum

(b) Host related
- Presence of immunosuppression
- Ethnic susceptibility to various strains

In clinical practice, often ST pattern and clinical response do not correlate. The reasons for discordant DST results are:

- Bacterial population (isolate vs. subculture)
- Differential growth kinetics
- Different inoculation methods (size, clumps)
- Different methods or media
- Cross-contamination
- Transcription and labelling errors
- MIC-critical concentration.

13. Management of MDR cases

Management decisions of a resistant case depend on finding the probable cause if prior poor adherence is recognized, may be addressed and DOT ordered. If risk of drug resistance is due to non-adherence and treatment failure is identified, drug susceptibility tests should be ordered and regimen should be changed as per history of drug intake.[11] The clinical response should be correlated with report of MDR and treatment should be changed after report of drug resistance despite a good initial response. Common errors in Management of MDR-TB cases:

(a) When initiating or revising therapy, always attempt to employ at least 3 previously unused drugs to which there is in vitro susceptibility. Common errors committed are:
  – Used 3 drugs that were part of previous failed treatment are prescribed and
  – Ethambutol and PZA are used alone for continuation phase
(b) The use of drugs to which there is demonstrated in vitro resistance is not encouraged, because there is a little or no efficacy of these drugs, e.g., ciprofloxacin resistance should have alerted providers to ofloxacin resistance because of cross resistance.
(c) Bactericidal drugs with proven efficacy should be used. Many a times Clofazamine (a weak drug with unknown efficacy) is added in regimen.
(d) 12 months of injectable therapy following culture conversion is generally recommended and exact duration determined by extent of disease and drug resistance. Many a times, streptomycin stopped after month 6.
(e) Two years of total treatment after conversion of cultures to negative is usually recommended. Occasionally patients with limited disease are declared cured after 18 months or sometimes treatment stopped at 13 months.

14. Should we treat or follow contacts to MDR/XDR?

The answer is…yes. Guidelines for MDR and drug resistance recommend following the contact for at least two years. But Data to support strategies for managing contacts are very sparse.[12]

15. Clinical Implications of resistance among TB cases

DST results must be available as soon as possible to guide treatment choices. Testing algorithms including molecular tests for rif-R may expedite decisions. Lab tests do not replace clinical judgement. Clinicians need data to interpret results based on performance parameters of the test and potential impact of prevalence of resistance on predictive value, etc. Relying on Clinical and X-ray manifestations has many limitations for the diagnosis of DR-TB as no symptoms or radiological findings differentiating susceptible from resistant TB. Prognosis and response cannot be decisively assessed through radiological examination, because lesion regression may require 3–9 month. For follow-up patients, no specific symptoms or radiological findings suggesting failure due to drug resistance, only lack of improvement compared with clinical and X-ray manifestations. Lack of improvement must be seen merely as arousing suspicion of DR-TB and supporting a request for DST. Diagnosis of DR-TB based only on clinical and radiological criteria should never be accepted, even if there is no improvement after several months of treatment.

16. Challenges for TB control programmes

Insufficient public sector MDR and XDR-TB diagnosis and treatment services is one of the main challenge as the country scaled up basic TB services via RNTCP DOTS through 2006, MDR-TB services began pilot testing only in 2007. There is poor quality of TB and MDR-TB laboratory diagnosis in the private sector. TB is often diagnosed with serology, which frequently misdiagnoses TB. The use of TB serological testing has been recommended against by RNTCP, WHO, and some expert groups from India, but such tests are widely available and widely used in the private sector. There is also lack of information about patients diagnosed with TB and MDR-TB in the private sector. Patients properly diagnosed with TB and MDR-TB in private laboratories are not notified to public health authorities.

There is irrational use and sale of anti-TB drugs and diagnostics outside the Programme. First-line TB drugs were sold to the extent of 65–117% of the estimated annual incident cases in India in private markets. Among second-line drugs, fluroquinolones are widely available with significant volume used for TB in India.

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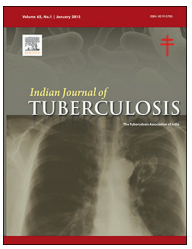

Original article

Catastrophic costs of treating drug resistant TB patients in a tertiary care hospital in India

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SUMMARY

Background: Private healthcare is choice of point of care for 70% of Indians. Multidrug resistant tuberculosis (MDR-TB) treatment is costly and involves duration as long as 2 years.
Aim: To estimate costs to patients undergoing treatment for MDR-TB.
Methods: A health-economics questionnaire was administered to 50 consecutive patients who successfully completed ambulatory private treatment for MDR-TB. Direct costs included drug costs, investigations, consultation fees, travel costs, hospitalisation and invasive procedures and cost prior to presentation to us. Indirect costs included loss of income.
Results: Of our cohort of 50 patients, 36 had pulmonary TB while 14 had extra-pulmonary TB (EPTB). 40 had MDR-TB and 10 had XDR-TB. There were 15 males and 35 females. Mean age was 30 years (range 16–61 years). Treatment cost for pulmonary MDR-TB averaged $5723 while it averaged $8401 for pulmonary XDR-TB and $5609 for EPTB. The major expense was due to drug costs (37%) while consultation fees were only 5%. Annual individual income for the cohort ranged from $0 to $63,000 (mean $11,430). On average, the cost of treatment ranged from 2.56% to 180.34% of the annual family income. 34/50 (68%) had total costs greater than 20% of annual family income and 39/50 (78%) had total costs greater than 10% of annual family income. The number of patients with total costs >40% of total family income was 22.
Conclusion: MDR-TB in the private sector results in ''catastrophic health costs''. Financial and social support is essential for patients undergoing treatment for MDR-TB.

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1. Introduction

India has the highest number of multidrug resistant tuberculosis (MDR-TB) patients in the world.[1] Treatment of MDR-TB involves expensive, toxic and less effective drugs requiring prolonged treatment of up to 2 years. Figures from across the world have shown the cost of treating MDR-TB patients ranges from $3230/patient in South Africa[2] to $225,000/patient in New Zealand.[3]

In India, more than 70% (72% in the rural areas and 79% in the urban areas) spells of ailment were treated in the private sector.[4] Employers pay for 9% of spending on private care, health insurance 5–10%, and 82% is from personal funds.[5] In such a situation, MDR-TB imposes a huge financial burden for the patient as well as the family.

In our study, we attempted to find the total cost of treating Indian patients with DR-TB in the private sector. The majority of these patients were treated on an outpatient basis.

2. Materials and methods

The study was conducted at the Department of Respiratory Medicine at Hinduja Hospital, Mumbai, which is a tertiary care private hospital with a busy TB OPD which sees about 250 new cases of MDR-TB every year. We report here a single physician, single centre experience of 50 consecutive patients with DR-TB who had been registered between August 2013 and February 2014 and successfully completed 2 years of TB treatment between August 2015 and February 2016. The study was approved by the institutional review board of P.D. Hinduja National Hospital and MRC, Mumbai, India. All participants gave informed, written consent to be part of the cohort.

Out of pocket expenses as well as indirect costs incurred by the patients were calculated. The total cost of the treatment was divided into direct and indirect costs. Direct costs involved costs of drugs, investigations, hospitalisations and invasive procedures including surgery, doctor consultation fees and travelling costs. Indirect costs included loss of income due to loss of days of work for the patient but not of the companion. This was taken as the earning per day of work multiplied by the number of days lost. Costs for diagnosis and treatment prior to presentation at Hinduja Hospital were also considered. The total period of for which costs were estimated were from diagnosis of DR-TB till completion of treatment. The cost of treatment as a percentage of the family and individual income was also calculated. The exchange rate of 1US dollar = Rs. 66.67 was taken for the study.

The WHO has defined catastrophic health costs as comprising more than 40% of the discretionary income.[6] Certain studies have looked at 20% of the total annual income as the cut off.[7,8] We looked at the proportion of patients that fitted the definition of Catastrophic costs by both criteria. The National Health Policy of 2017 defines Catastrophic household health care expenditures as health expenditure exceeding 10% of its total monthly consumption expenditure or 40% of its monthly non-food consumption expenditure.[9]

3. Results

The patients were mostly young (mean age 30 years), bread earners of their family with females more commonly represented than males (M:F ratio 1:2.3). Pulmonary TB was more commonly encountered than extra-pulmonary TB. Extra-pulmonary TB ($n = 14$) included TB of the lymph nodes (5), spine (5), knee (2), pleura (1), and chest wall (1). Most patients had MDR-TB but significant numbers (52%) had more extensive grades of resistance (Table 1).

The total costs for pulmonary TB (MDR and Pre XDR) ranged from Rs. 115,280 to Rs. 2,159,344 with a mean of Rs. 3,815,633. The total drug costs ranged from Rs. 66,648 to Rs. 302,268 with a mean of Rs. 148,217. The costs for investigations averaged Rs. 26,789 while that for hospitalisation and invasive procedures averaged Rs. 57,000. The indirect cost due to loss of income averaged Rs. 64,592. The costs incurred by XDR-TB were higher with total costs for pulmonary TB (XDR) ranging from Rs. 179,060 to Rs. 1,586,200 with a mean of Rs. 560,086. The total drug costs ranged from Rs. 112,560 to Rs. 269,830 with a mean of Rs. 198,366. The costs for investigations averaged Rs. 29,008 while that for hospitalisation and invasive procedures averaged Rs. 66,000. The indirect cost due to loss of income averaged Rs. 160,000. The detailed break-up of costs for MDR and XDR TB are tabulated here (Table 2).

The total costs for extra-pulmonary TB (Table 2) ranged from Rs. 125,101 to Rs. 761,380 with a mean of Rs. 373,964. The total drug costs ranged from Rs. 51,901 to Rs. 189,792 with a mean of Rs. 129,416. The costs for investigations averaged Rs. 42,307 while that for hospitalisation and invasive procedures averaged Rs. 70,929. The indirect cost due to loss of income averaged Rs. 58,286.

The annual family income of our cohort ranged from Rs. 0 to 4,200,000 ($0-$63,000) with a mean of Rs. 762,000 ($11,430). The total cost of treatment (mean of Rs. 398,820 – $5847) ranged from 2.56% to 180.34% (2 families reported zero income hence proportion could not be calculated) of the total family income with a mean of 26.1% of the total family income for the treatment period. The number of patients with total costs >40% of total family income was 22. 34/50 (68%) had total costs greater than 20% of annual family income and 39/50 (78%) had total costs greater than 10% of annual family income.

Drugs costs (37%) accounted for the largest proportion of total expenditure while travel costs (2%) comprised the least. Indirect costs due to loss of income comprised a significant 20% of the total costs in our cohort (Fig. 1).

4. Discussion

Treatment of drug susceptible tuberculosis usually lasts for only 6 months and is extremely cost effective at $20 per patient.[10] Treatment of DR-TB is much more prolonged – up to 2 years – with more expensive and toxic drugs. There are other costs involved such as daily injectables in the intensive phase, management of side effects, investigations and prolonged days of work lost. Cost analysis of MDR-TB treatment is limited, and the variation in delivery mechanisms, as well as

Table 1 – Costs for pulmonary TB.

Cost in Rs./$ for:	MDR + pre-XDR pulmonary TB: Mean (range) (*n* = 26)	XDR pulmonary TB: Mean (range) (*n* = 10)	MDR + pre-XDR extrapulmonary TB
Anti-TB drugs	Rs. 138,216 (65,699–275,218) $2073 ($985–$4128)	Rs. 182,672 (107,360–246,870) $2740 ($1610–$3703)	Rs. 115,140 (49,711–172,112) $1727 ($745–$2581)
Additional drugs	Rs. 10,001 (949–27,050) $150 ($14–$405)	Rs. 15,694 (5200–29,346) $235 ($78–$440)	Rs. 14,276 (949–54,042) $214 ($14–$810)
Total drug cost	Rs. 148,217 (66,648–302,268) $2223 ($999–$4534)	Rs. 198,366 (112,560–269,830) $2975 ($1688–$4047)	Rs. 129,416 (51,901–189,792) $1941 ($778–$2846)
Investigations	Rs. 26,879 (14,050–71,850) $403 ($210–$1077)	Rs. 29,008 (12,600–39,625) $435 ($189–$594)	Rs. 42,307 (12,275–89,550) $634 ($184–$1343)
Hospitalisation and Invasive procedures	Rs. 57,000 (0–910,000) $855 ($0–$13,650)	Rs. 66,000 (0–250,000) $990 ($0–$3750)	Rs. 70,929 (0–400,000) $1063 ($0–$6000)
Doctor's consultation	Rs. 21,237 (11,250–40,400) $318 ($168–$606)	Rs. 23,183 (18,150–29,900) $347 ($272–$448)	Rs. 20,720 (10,725–43,250) $310 ($160–$648)
Travel cost	Rs. 15,869 (390–160,000) $238 ($5–$2400)	Rs. 8030 (500–30,000) $120 ($7–$450)	Rs. 7200 (800–30,000) $108 ($12–$450)
Indirect cost	Rs. 64,592 (0–840,000) $968 ($0–$12,600)	Rs. 160,000 (0–1,200,000) $2400 ($0–$18,000)	Rs. 58,286 (0–336,000) $874 ($0–$5040)
HH cost (cost after registering at Hinduja Hospital)	Rs. 269,201 (106,098–1,269,344) $4038 ($1591–$19,040)	Rs. 324,586 (164,060–481,562) $4868 ($2460–$7223)	Rs. 270,571 (95,101–573,866) $4058 ($1426–$8607)
Pre-HH cost (prior to registering at Hinduja hospital)	Rs. 47,769 (0–200,000) $716 ($0–$3000)	Rs. 75,500 (0–200,000) $1132 ($0–$3000)	Rs. 45,107 (0–250,000) $676 ($0–$3750)
Total direct cost	Rs. 316,970 (115,280–1,319,244) $4754 ($1729–$19,788)	Rs. 400,086 (179,060–531,562) $6001 ($2685–$7973)	Rs. 315,678 (125,101–603,866) $4735 ($1876–$9057)
Total cost (direct + indirect)	Rs. 381,563 (115,280–2,159,344) $5723 ($1729–$32,390)	Rs. 560,086 (179,060–1,586,200) $8401 ($2685–$23,793)	Rs. 373,964 (125,101–761,380) $5609 ($1876–$11,420)

Table 2 – Summary of various studies of cost of MDR TB.

Study	Cost per MDR TB patient
Cox et al. South Africa 2015[16]	$8359 ($2585–$32,506)
Diel et al. Germany 2014[12]	€82,150–€108,733 ($85,436–$113,082)
Ramma et al. South Africa 2015[2]	$269.2 (in-patient); $122.1 (out-patient) (per month)
John and Chatterjee India 2016[18]	$404 (home based); $2310 (facility based)
Kundu et al. India 2015[19]	$2000 (private); $61 (public)
McNaughton et al. New Zealand 2016[3]	$225,000 (single patient)
White and Moore-Gillon UK 2000[11]	£60,000 ($73,200)
Marks et al. USA 2005–2007[13]	$134,000 (MDR); $430,000 (XDR)
Lawrence et al., 2015 (Systematic review)[14]	$83,365 (High Income Countries), $5284 (High-Middle Income Countries), $6313 (Low-Middle Income Countries) and $1218 (Low Income Countries).
Diel et al., 2014 Systematic review – Europe[20]	€57,213 ($59,501) (MDR); €170,744 ($177,573) (XDR) – Cyprus, Malta, Slovenia €24,166 ($25,132) (MDR-TB/XDR-TB) – other EU states
Zimbabwe[15]	$2571 (MDR); $ 31,000 (XDR)
Our study	$5683 (MDR); $8401 (XDR)

the rapidly evolving diagnosis and treatment regimens, means that it is essential to increase the number of studies assessing the cost from both the provider and patient perspectives.

In our country, with the highest number of MDR-TB cases worldwide,[1] and with over 70% patients accessing private health care without insurance,[4] there is scarce data on the cost borne by these patients and their families for treatment of this disease, despite tuberculosis undoubtedly being India's biggest public health problem. This study aimed to provide the data by studying the costs in a private setting, in patients with no insurance cover (as outpatient expenses are usually not covered by insurance in India).

Studies from all over the world have shown great variation in costs for treating DR-TB. Higher costs are reported from the Western world where White et al. reported costs of £60,000 ($73,200) from London[11] while managing their MDR-TB patients. Diel et al. simulated the cost to be between €82,150 ($85,436) and €108,733 ($113,082).[12] Marks et al. estimated US costs to be $134,000 per patient with MDR-TB and $430,000 per patient XDR-TB.[13] Most of these studies involved inpatient and outpatient costs as well as estimation of productivity losses. Costs for treating DR-TB have been reported to be much lower from low income countries such as Cambodia showing provider costs of $1218, direct costs of

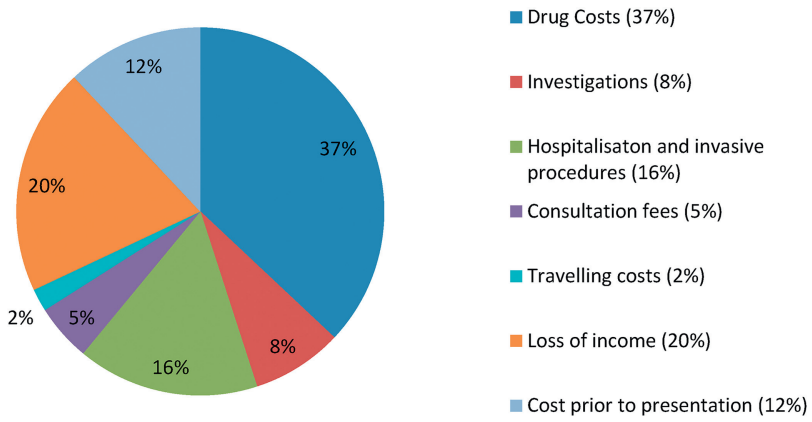

Fig. 1 – Break up of costs.

Table 3 – Comparative costs of second line anti-TB drugs in USA and India.

Second line drug	Cost in USA ($/month)	Cost in India ($/month)
Amikacin	810	51
Capreomycin	161	142
Kanamycin	552	22
Cycloserine	345	45
Clofazimine	15	1
Ethionamide	253	15
Levofloxacin	378	7
Moxifloxacin	130	12
Para amino salicylic acid	47	9
Linezolid	2744	16

$4016 and productivity losses of $1256.[14] Costs in Zimbabwe were about $2571 for MDR TB and $31,000[15] for XDR TB while reports from South Africa have reported monthly costs of $134 in intensive phase and $122 in continuation phase.[16]

Our results show that treating MDR-TB in the private sector in India had a slightly higher cost per patient compared to low income countries though our rates were much lower than high and high mid income countries. The average cost of treating a patient with MDR-TB was $5683 while it was $8401 per patient with XDR-TB. Although XDR-TB did cost more per patient than MDR-TB, the difference in our cohort was not as striking as in other studies. In fact, certain patients with MDR-TB in our cohort had a higher cost than XDR-TB patients due to higher costs of certain investigations as well as surgeries undergone in those patients leading to higher upper limit expenditure in the MDR-TB cohort than XDR-TB cohort.

Drug costs took up the largest portion of total costs at 37%. The cost of pharmaceuticals, as a percentage of total health care spending has been rising worldwide. India is a global hub of generic drug manufacturing being the largest provider of generic drugs globally. Branded and unbranded generic versions of anti-TB drugs are available in this country (Table 3). Despite this, MDR TB treatment incurs high drug costs leading to catastrophic health costs. Travel costs and doctor consultation fees were the smallest components at 2% and 5% respectively. Indirect costs due to loss of income also were a significant component at 20% of the total costs in our cohort suggesting social support is essential for this group of patients. This is similar to other studies from low income countries as opposed to studies from high income countries where hospitalisations formed the largest component of total costs.[14]

The WHO has defined catastrophic health costs as comprising more than 40% of the discretionary income.[6] Certain studies have looked at 20% of the total annual income as the cut off.[7,8] The National Health Policy of 2017 defines Catastrophic household health care expenditures as health expenditure exceeding 10% of its total monthly consumption expenditure or 40% of its monthly non-food consumption expenditure.[9] Annual individual income for the cohort ranged from $0 to $63,000 (mean $11,430). On average, the cost of treatment ranged from 2.56% to 180.34% of the annual family income.

The average cost of treatment was 26.1% of the total family income in our cohort. In our cohort, 34/50 (68%) patients had total costs >20% total family income and 39/50 (78%) and 22/50 had total costs >40% of total family income. Thus, a large proportion of patients from our cohort bore catastrophic health costs. The per capita income for India is $1670.[17] Which is lower than that of our cohort. The number of patients in the general population bearing catastrophic costs would be much higher.

Various studies have looked at measures for mitigation of catastrophic health costs in patients with TB. Opting for ambulatory treatment instead of inpatient treatment would result in 80% saving as per John and Chatterjee.[18] Our patients were almost all (78%) treated on an out-patient basis with only 11 of 50 patients being hospitalised for surgeries. A study from Peru showed that transfer of $173 per family of patient with TB mitigated 20% of TB related costs and caused less families to incur catastrophic health costs.[7] A state insurance scheme in the state of Chhattisgarh sponsored by the government provided coverage of INR 30,000 per annum for a registration fee of only $0.42 per enrolment. A total catastrophic expenditure of $20,000 was estimated to be saved through processing of 207 claims of MDR-TB.[19]

Limitations of our study include the fact that we chose to include only patients who had successfully completed treatment in this cohort. Treatment failures and defaulters

were not included which might have changed the costing figures. Secondly, there were no XDR-TB in the extra-pulmonary cohort. This was a single physician cohort with no comparison group.

5. Conclusion

This study is the first from India to enumerate the costs of treating MDR-TB in the private sector. Despite most patients being treated on an ambulatory basis, these costs are prohibitive and result in catastrophic expenses for these patients and their families. Since 70% of Indian TB patients choose to go private, these costs are usually borne out of pocket. Urgent financial and social support is needed for these patients. A public private partnership between the government programme and private practitioners is essential.

Conflicts of interest

The authors have none to declare.

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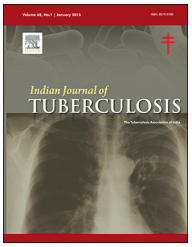

Review article

Active tuberculosis case finding in India – The way forward

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ABSTRACT

Community based active case finding (ACF) for tuberculosis (TB) has seen resurrection in the current armamentarium of many TB managers in their fight toward eliminating TB. This article explores the accuracy and approximate cost of various ACF algorithms currently in vogue in India or those which could be useful, while inputting the sensitivity and specificity of screening and diagnostic tools as estimated from recently conducted community based surveys. This analysis informs that ACF may be prioritized to higher prevalence settings and the diagnostic algorithm for specific setting may be chosen taking into account the expected prevalence, estimated accuracy of the algorithm and resource availability. Further, chest X-ray cannot be used alone as a diagnostic tool and can be relied upon for this purpose when at least one of the three sputum specimen is smear positive. Accuracy of Xpert MTB/RIF as a diagnostic tool in community situations needs to be investigated further.

The review brings out significant proportions of initial default and default during treatment among cases detected through ACF thus emphasizing the need for heightened efforts toward preventing the same. The article rounds off emphasizing priority to addressing barriers to speedy scale up of more sensitive diagnostic tools for health center based case finding including in private sector and ACF in high risk clinical groups for early and efficient case detection. It concludes by putting forth certain research areas that would strengthen future efforts.

1. Background

Active case finding (ACF) implies that the health care provider takes proactive action in systematically screening any patient or population group to rule out TB, to distinguish it from the so called passive case finding wherein the patient on his/her own takes action when suffering from symptoms or signs suggestive of TB. Therefore, ACF may be broadly sub-divided into two categories:

i. ACF in clinical groups when the patients seek health care for ailments or conditions other than TB, for example, patients with diabetes and pregnant mothers.

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ii. ACF in population groups when the providers reach out to groups of people in settings other than health care and systematically rule out TB e.g. prisoners, miners, etc.

For major part of this article, we will dwell on various issues related to the second category.

Some of the principles of Active Case Finding are[1]:

a. A baseline analysis should be completed to demonstrate that the potential benefits outweigh the risk of doing harm.
b. The case finding algorithm should be chosen based on assessment of accuracy.
c. Before embarking on ACF, an evaluation should be done to demonstrate that the required investments are reasonable in relation to expected benefits.

Harm accrues when:

i. When we generate a large number of false positive cases.
ii. When resources including manpower are diverted from other activities which may be more cost effective.

To bring home the points with respect to the above principles, let us examine the algorithms that have been used for ACF for pulmonary TB in India or could be used. For this evaluation, we applied the sensitivity and specificity of various primary and secondary screening criteria and of smear examination as given in Table 1. These values have been estimated by us on meta-analysis of recently carried out community based sub-national prevalence surveys in India and are under publication,[2–6] except for CXR shadow suggestive of TB which was based on meta-analysis by Hoog et al.[7] Using these values, we estimated the expected yield, positive predictive value (PPV), number needed to screen (NNS) to detect one case, number of tests required to be performed and the likely cost per case detection, by different algorithms.

Cost analysis was based on following considerations:

i. 250 individuals to be screened each day by a team of six field staff (2 enumerators, 2 interviewers, 1 Lab Attendant, 1 team leader).
ii. Average salary of the above staff was taken at INR 18,000 per month which is at par with the minimum wage currently recommended by government. To this we added daily food allowance @ INR 100 per person.
iii. Charges for vehicle hiring were taken at INR 2500 per day in line with current market rates.
iv. Cost per smear examination was taken at INR 25 per smear,[8,9] which includes the cost of only consumables and not the capital costs and salary of laboratory staff since all the tests are to be performed in routine program laboratories.
v. Cost per chest X-ray (CXR) was taken at INR 300 after market research.

It may be noted that these costs are only indicative and could be different in different states but suffice here for the purpose of arriving at recommendations for policy makers.

Algorithm 1 (Fig. 1)

An international NGO has been undertaking ACF in general community and more recently in prisons by screening for cough ≥2 weeks and either referring those found screen positive to DMC or collecting sputum and transporting to DMC for smear examination (2 specimen, one positive being considered as confirmation of TB).[10,11] This algorithm has the potential to detect 26% of prevalent culture positive PTB cases.

The table embedded in the figure shows that at the level of prevalence in the general community worked out after meta-analysis of recently conducted prevalence surveys in 10 sites,[2–6,12–15] there will be about one false positive case out of every three cases detected by the algorithm. Adjudicating the criteria of no harm, we set ourselves a target that we will not tolerate more than one false positive case per 10 cases diagnosed. We see that PPV exceeds 90% only when the prevalence in the population is ≥1500 per 100,000 populations. Therefore, this algorithm would have acceptable accuracy in settings having prevalence ≥1500 such as the prisons but not in populations having lower prevalence such as the general population. At this prevalence, the cost per case diagnosed works out to be about INR 7000; it drops to <INR 5000 when the prevalence is ≥2500 per 100,000 populations.

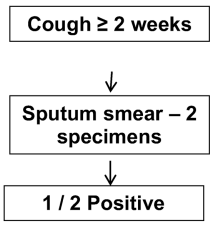
The coverage of sputum examination in the general population when referred to DMCs was reported at 52%.[10]

In view of the above and keeping the cost per case below an arbitrarily decided cut-off of INR 5000, this algorithm should be

Table 1 – Pooled sensitivity and specificity of screening and diagnostic tools.

Screening criteria	Sensitivity (%)	Specificity (%)	Source
Cough ≥ 2 weeks as a primary screening tool	56.2 (46.7, 65.4)	95.3 (94.4, 96.1)	Indian sub-national TB surveys
Any symptom[a] as a primary screening tool	66.0 (56.3, 74.5)	93.8 (92.7, 94.8)	
Any pulmonary abnormality on CXR as a secondary screening tool after any symptom positive	65.6 (59.7,71.0)	89.3 (85.4,92.2)	
CXR with pulmonary shadows suggestive of TB as a diagnostic tool	86.8 (79.2,94.5)	89.4 (86.7,92.0)	Hoog et al.[15]
Smear (one out of 2 smear positive) as a diagnostic test	46.2% (36.9, 55.6)	99.3% (98.9, 99.5)	Indian sub-national TB surveys
Second smear positive after one positive result	84.9 (77.6,90.2)	73.0 (42.7,90.7)	

Figures in parenthesis are confidence intervals.
[a] Persistent cough for ≥2 weeks/Fever for ≥1 month/Chest pain for ≥1 month/History of hemoptysis in last 6 months.
CXR: chest X-ray.



Potential yield = 26%

Prevalence */ lakh	PPV (%)	NNS/ Case	No. smears/ case	Cost/case (INR)
263^	67.5	1464	142	39272
500	79.9	770	76	20688
1000	88.9	385	42	10444
1500	92.3	257	28	6971
2000	94.2	193	22	5259
2500	95.3	154	18	4208

*Prevalence of culture positive PTB
^Pooled prevalence, sub-national surveys
PPV: Positive predictive value, NNS : Number needed to screen

Fig. 1 – Diagnostic Algorithm 1.

applied to population groups with prevalence ≥2500 per 100,000 populations such as the household contacts, prisoners, silica and organic textile dust exposed workers and the homeless.[16–26] The accuracy is compromised when applied in general population and even in urban slums and hard to reach tribal areas where the prevalence though higher than the general population has been invariably found to be <1000 per 100,000.[2,27,28]

Algorithm 2 (Fig. 2)

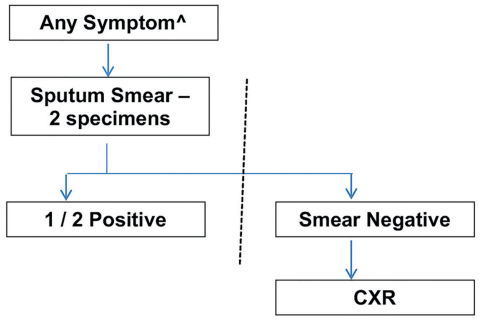
This algorithm currently followed by many Indian states for ACF aims to screen for presence of any of the four symptoms suggestive of PTB – cough or fever ≥ 2 weeks, history of hemoptysis anytime in last 6 months or significant weight loss (personal communication, State TB Officers, selected states). In the prevalence surveys, screening was done for cough or fever ≥2 weeks, hemoptysis anytime in last 6 months and chest pain ≥1 month. We applied the sensitivity and specificity of this criterion presuming that these won't differ much from the criteria as used by states. The algorithm envisages sputum examination (2 specimen, one positive being considered as confirmation of TB) among screen positives. This part of the algorithm has the potential to detect 30.5% of prevalent culture positive PTB cases. As per the algorithm, CXR is advised among those who are smear negative.

For a smear positive result, PPV crosses 90% at prevalence of 1500 per 100,000 populations and the cost per case drops to <INR 5000 when the prevalence is ≥2500 per 100,000 populations, as in algorithm 1. However, PPV of X-ray based diagnosis is abysmally low such that X-ray should not be used as a diagnostic tool thus making the part of the algorithm to the right of the dashed line redundant. Besides, the coverage of the so-called eligibles for CXR has been too poor during ACF in the states as they were referred to fixed X-ray facility.

Also, the activity is performed using the existing manpower in the public sector thus diverting them from their routine activities.

Algorithm 3 (Fig. 3)

This algorithm is being used for a TB free mission in a north Indian state.[29] First part of the algorithm is the same as in algorithm 2. However, after a smear negative result, secondary screening is undertaken by CXR and those with suggestive

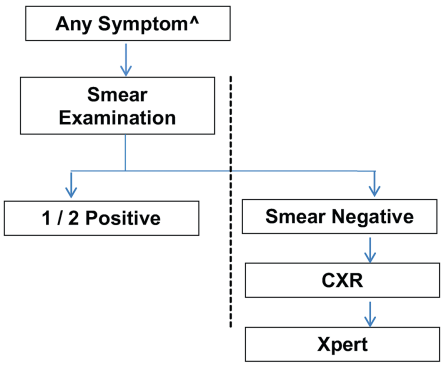


Potential yield (sm+ve) = 30.5%

Preval./ lakh	PPV (%)	NNS / Case	No. smears / case	Cost / case (INR)	PPV (%) CXR
263	64.9	1247	159	34401	11.1
500	77.9	656	85	18131	19.2
1000	87.6	328	45	9128	32.3
1500	91.5	219	31	6119	41.8
2000	93.5	164	24	5201	49.1
2500	94.7	131	20	4601	54.8

^Cough or fever ≥ 2 weeks / Hemoptysis anytime in last 6 months / significant weight loss
CXR: Chest X-ray;
PPV: Positive predictive value, NNS: Number needed to screen

Fig. 2 – Diagnostic Algorithm 2.



		Culture		
		+ve	-ve	Total
Xpert MTB/RIF	+ve	159	236	395
	-ve	69	15778	15847
Total		228	16014	16242

Source: National Prevalence Survey, 2017, Philippines[30]
PPV of Xpert MTB/RIF = 40.2%
^Cough or fever ≥ 2 weeks / Hemoptysis anytime in last 6 months / significant weight loss
CXR: Chest X-ray; PPV: Positive predictive value

Fig. 3 – Diagnostic Algorithm 3.

shadows are subjected to repeat sputum examination using Xpert MTB/RIF (Xpert).

In the recently conducted national prevalence survey in Philippines, while there were 159 culture positive and Xpert positive results, 236 were Xpert positive and culture negative.[30] The PPV of Xpert is thus estimated at 40%. This raises serious questions about using Xpert in ACF situations and thus makes the algorithm to the right of the dashed line redundant as of now. It need be mentioned that the intention here is not to question the accuracy of Xpert in clinical setting which is a different situation altogether.

Algorithm 4 (Fig. 4)

In the earlier years of RNTCP, the algorithm for passive case finding involved collection of 3 sputum specimen from presumptive PTB patients and labeling the patient a bacteriologically confirmed case if at least 2 specimen were smear positive. In case of smear positivity on only one of three specimens, CXR was advised and the patient labeled a confirmed case if it was suggestive of TB. This algorithm has the potential to detect about 30% of prevalent culture positive PTB cases. PPV crosses 90% at a prevalence of 500 per 100,000 populations but the cost is prohibitive at this prevalence and drops below INR 5000 per case at prevalence of ≥2500 per 100,000 like in algorithms 1 and 2.

As the maximum requirement of X-rays with this algorithm is <150 per 100,000 population for a prevalence of 2500 and lower with decreasing prevalence, the mobile X-ray unit may not be cost effective for this purpose. Thus, the eligible subjects may be transported to fixed X-ray facility where the cost of X-ray is lower but the total cost including transportation has been kept constant for our calculation at the same level as for mobile unit.

Algorithm 5 (Fig. 5)

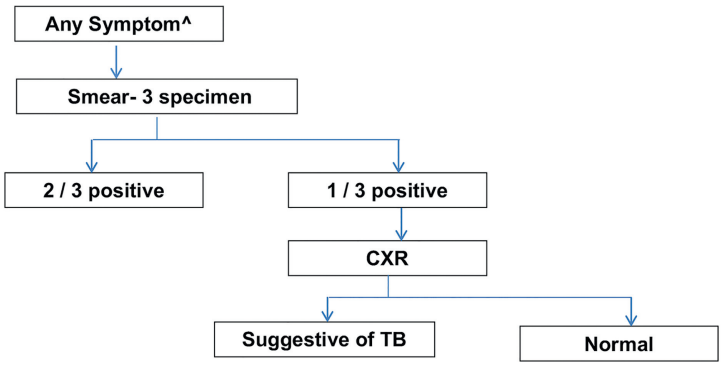
The algorithm proposed herewith includes primary screening for pulmonary symptoms followed by secondary screening using CXR among the symptomatics and examination of 2 sputum specimen by smear among those with any pulmonary abnormality and labeling it a bacteriologically confirmed case in the event of positivity on any one specimen. This algorithm has the potential to detect 20% of the prevalent culture positive PTB cases. PPV of over 90% is attained even at the level of prevalence in general population but this algorithm has a much higher cost as compared to other algorithms except of course algorithm 3 for which we have not provided calculations. This algorithm will require a mobile X-ray unit.

The above algorithms are for participants with HIV status as negative or unknown. Known HIV positive persons should be referred to HIV care settings for ruling out TB and not included in community based ACF.[1]

We have not modeled for an algorithm using CXR as a primary screening tool since that would be too cost prohibitive. We have also not modeled for culture which is time consuming and the quality assured culture laboratories available under the Revised National TB control program (RNTCP) for diagnosis and follow up of drug resistant cases will not be able to share the additional workload.

What does this analysis inform us?

a. The accuracy in terms of PPV of ≥90% is achievable using the criteria of one out of 2 sputum specimens being positive among those with any of the pulmonary symptoms among groups having prevalence of ≥1500 per 100,000 population. When the criteria of 2 out of 3 smears positive or one smear positive with CXR suggestive of TB is used as the diagnostic

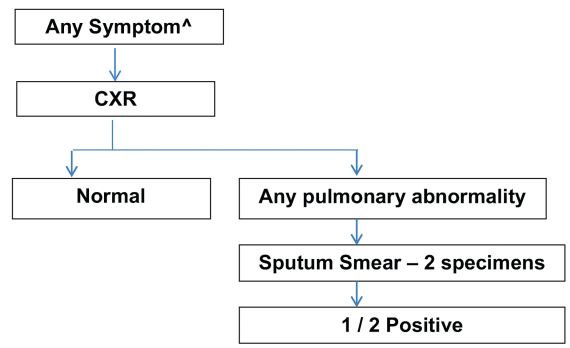


Yield (2 smear positive / 1 smear positive & CXR suggestive of TB) = 29.9%

Prevalence/ 100,000	PPV (%)	NNS / Case	No. smears /case	No. CXR/case	Cost / case (INR)
263	83.9	1272	243	0.5	43337
500	90.9	669	130	0.4	22935
1000	95.2	335	68	0.3	11652
1500	96.8	223	47	0.2	7857
2000	97.6	167	37	0.2	5988
2500	98.1	134	31	0.2	4880

^*Cough or fever ≥ 2 weeks / Hemoptysis anytime in last 6 months / significant weight loss*
CXR: Chest X-ray; PPV: Positive predictive value, NNS: Number needed to screen

Fig. 4 – Diagnostic Algorithm 4.



Yield (smear +ve) = 20%

Preval./ lakh	PPV (%)	NNS / Case	No. CXR /case	No. smears / case	Cost / case (INR)
263	91.9	1901	121	29	83409
1000	97.8	500	34	11	22675
2000	98.9	250	18	8	11700
3000	99.3	167	13	6	8129
4000	99.4	125	11	6	6500
5000	99.6	100	9	6	5290
6000	99.6	83.0	8	5	4550

^*Cough or fever ≥ 2 weeks / Hemoptysis anytime in last 6 months / significant weight loss*
CXR: Chest X-ray; PPV: Positive predictive value, NNS: Number needed to screen

Fig. 5 – Diagnostic Algorithm 5.

accuracy is achievable at a prevalence of ≥500 per 100,000. High accuracy is achievable in the general population when CXR is used a secondary screening tool followed by the criterion of one smear positivity as confirmation of TB.

b. CXR can be relied upon as a diagnostic tool only when at least one of the three sputum specimen is smear positive and cannot be used alone as a diagnostic tool.
c. The accuracy of Xpert MTB/RIF as a diagnostic tool in community situations is questionable and needs to be investigated further.
d. The program managers should evaluate the cost to be incurred per case detection that they are willing to accept. Taking a cut off of INR 5000 as an example, symptom screening followed by 2 sputum specimen examination and algorithm 4 are suitable only at prevalence of ≥2500 per 100,000. Algorithm 5 achieves this cut off at a high prevalence of ≥6000 per 100,000 only.
e. The potential yield of different algorithms discussed above varies between 20-30% of the expected prevalence which should be acceptable since ACF is complementary to passive case finding.

WHO guide states that systematic screening may be considered for populations having prevalence >1000/lakh and that it may not be possible to implement this recommendation in resource constraint settings owing to high cost and considerable requirement for human resources.[1]

At this juncture, it is appropriate to point out that the actual PPV in ACF situation is likely to be lower than our estimations and cost/case higher in view of the following:

i. Quality of symptom screening in survey situations is generally better as the surveys are carried out in research mode after intensive training and evaluation.
ii. In prevalence survey data, sensitivity is overestimated due to not collecting sputum from every individual. Specificity is less affected since large number of screened negative are not suffering from TB.
iii. Actual NNS in ACF activities undertaken so far have generally been found to be much higher in the states where ACF has been conducted recently (personal communication: RNTCP staff) and as also made out from a few publications.[31,32]
iv. In prevalence surveys, X-rays were read by experts. In ACF when X-rays are read by field based doctors, sensitivity is generally higher but specificity is lower,[7] which would further decrease PPV.

Another principle of ACF

All options for health center based case finding approaches are being implemented efficiently[1] and that there is no further scope for increasing case finding through approaches such as:

i. Increasing detection of smear negative cases by employing more sensitive diagnostic test such as Xpert MTB/RIF. The new RNTCP diagnostic algorithm for passive case finding under the Revised National TB Control Program (RNTCP) does encompass such an approach[33]; however, much concerted efforts are required to make the resources available in terms of CXR and Xpert availability and achieve the desired implementation efficiency.
ii. Systematic case finding in clinical risk groups – those with compromised immune system, people with diabetes mellitus, antenatal and postnatal mothers, hospitalized patients, elderly attending for other ailments, undernourished, smokers and alcohol users. These groups require much lesser NNS for every detected case as demonstrated by a meta-analysis.[16]

    Some of these populations though small in proportions might be responsible for significant contribution to the overall TB transmission. For example, a recent meta-analysis revealed that the prisons in developing countries account for 6.3% of the overall transmission of tuberculous infection.[25]
iii. Free diagnostic services for private patients – this strategy has been included as one of the key components of National Strategic Plan for TB control in India 2017–23 but much needs to be done to achieve the desired efficency.[34]

If the desired efficiency has not been achieved, then the emphasis should be on addressing the barriers to passive case-finding before embarking on ACF. Guidelines for some of these clinical groups – PLHIV, people having diabetes mellitus, those with any pulmonary abnormality on CXR are in place but the implementation efficiency has much to improve.[31]

Other issues

a. One may argue in favor of ACF that there is a large pool of undetected cases in the community at any given point of time as revealed by prevalence surveys and that ACF detects cases early. However, it was observed in Thiruvallur that 80% of smear positive cases having symptoms found in the survey had already visited a health provider without being diagnosed.[35] Therefore, a more effective passive case finding would have higher efficacy and lead to even earlier case detection.
b. Generally, studies have demonstrated about 30% initial default among cases found on ACF and a similar proportion defaulting during treatment.[35,36] In Thiruvallur, all of 57 initial defaulters had zero mortality putting a question mark on the diagnostic accuracy during ACF.[36]
c. Treatment success rates among cases found by ACF have generally been poorer in India compared to those found on passive case finding.[35,37] Even if equal treatment success rate was to be achieved among cases detected by ACF as among those by passive case finding, success rates would be poorer if standardized for severity of illness as cases found on ACF are generally less severe.[38,39]
d. Since there will be many false negative cases during ACF, all those screened positive but not confirmed to have TB should be advised for follow-up at the nearest health facility in the event of continuation of symptoms.
e. The evidence on impact of ACF on epidemiological burden remains weak.[1]

Key research questions

Research undertaken in the following areas will guide in evidence based practice:-

1. Assess accuracy and performance of different algorithms, operational challenges and acceptability in different risk groups and settings. India TB Research Consortium has taken upon itself to do this part of implementation research in various clinical groups and congregate settings.
2. What should be ideal periodicity of ACF in different settings?
3. Controlled trials comparing impact on transmission and cost effectiveness of ACF with other interventions to increase case finding e.g. whether ACF in hard to reach tribal areas would be more cost effective compared to changing health seeking behavior of masses and TB case finding practices of local providers.

2. Conclusion and recommendations

1. Efficient implementation of strategies aimed at increasing case finding efficiency in health center settings and systematic screening in clinical risk groups should be the first priority.
2. Priority for ACF should be given to groups with highest prevalence such as household contacts and congregate settings like prisons, silica and organic textile dust exposed workers and the homeless.
3. Choose the best algorithm for specific setting taking into account the expected prevalence, estimated accuracy and resource availability.
4. Integration with other community based activities like the on-going community based National level Non-communicable disease prevalence survey in India would be more cost effective especially if all those found to be having say diabetes were subjected to ACF for TB.
5. All efforts should be made to undertake CXR and sputum collection at an appropriate place within the community setting since the acceptability is seen to reduce on referral for testing.[1]
6. Ensure Low rate of initial default and default during treatment among TB cases detected by ACF.

Conflicts of interest

The authors have none to declare.

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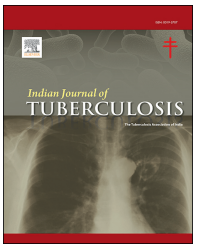

Review Article

Tuberculosis control in India: Refocus on nutrition

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ABSTRACT

Many western societies have eliminated tuberculosis years before the advent of potent anti-tuberculous drugs, as a result of the improved standards of living and good nutrition. But even with the availability of powerful anti-tuberculous drugs, India still has a long road ahead to reach the "End TB by 2025" goal. One of the major reason is that tuberculosis control program in India till now have focused primarily on case detection and medical treatment of active tuberculosis. Drug treatment alone does not completely prevent the occurrence of new infections in the community and also contributes to development of drug resistant strains if used improperly or incompletely. Although the treatment of active cases can reduce the period of transmission of disease, a significant amount of transmission to contacts occurs even before they have been diagnosed and treated. Additionally, this approach cannot prevent re-activation to active TB in the vast pool of persons with latent TB infection. Tuberculosis occurs in those with suppressed cell mediated immunity mainly due to poor nutritional status. Improving the nutritional status of the society by several social interventions hand-in-hand with utilizing the available anti-tuberculous drugs is possibly the only effective strategy. Promising programmatic guidance for nutritional support in TB patients have been formulated by the Central TB division of India but it needs a refocusing of TB control strategies towards nutrition at all levels and strong public health actions for effective implementation.

1. Introduction

Tuberculosis (TB) has been present in humans since antiquity, and it is still thriving despite the many social, political and economic shifts and advances in medical science and pharmaceutics[1]. India bears a major brunt of this disease, with one fourth the share of the global burden[2]. Many western societies have eliminated this disease, years before the advent of potent anti-tuberculous drugs (ATD)[3]. But even with the availability of powerful ATD and the Revised National Tuberculosis Control program (RNTCP) on the run, India still has a long road ahead to achieve its target "End TB by 2025" which aims to reduce the TB incidence to 44 per 100,000 population[4]. Over the past two decades, India could only bring down the incidence of new cases of TB from 289 in the year 2000 to 211 in 2016 (per 100,000 people)[5].

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2. How was TB control achieved in western societies?

To understand the crux of the matter, we need to evaluate how the western societies have done it long before. Incidence and mortality rates of TB first began to decline in the early and mid-19th century, largely abetted by a growing prosperous middle class who were less vulnerable to TB, created by the industrial revolution. Though there was an initial peaking of TB cases due to overcrowding and poor working conditions, incidence started declining during the later stages of the industrial revolution as a result of improved standards of living and good nutrition[6]. This decline in the incidence of TB in western societies has continued to the present time, largely unrelated to effective chemotherapy, and today tuberculosis incidences in these societies are at historic lows[7].

Decline in TB incidence due to improvement in socioeconomic conditions has been proved in "The Papworth experiment" conducted in the pre-antibiotic era (1918–1943), in Papworth village settlement of England[8,9]. Social interventions in the form of initiatives to improve employment, housing and nutrition resulted in almost complete prevention of disease development in children born in that settlement. This protection against clinical disease in children was attributed to adequate nutrition as a result of adequate income and dietetic advice and decreased intensity of exposure due to proper housing, better ventilation, segregation of patients, and scrupulous attention to respiratory hygiene[9]. It was noteworthy that even in the absence of BCG vaccination and chemoprophylaxis, social interventions were associated with reduced incidence of TB.

3. The pitfalls of medical measures alone

The major drawbacks of medical measures alone are that they do not completely prevent the occurrence of new TB infections in the community and also contributes to development of drug resistant strains if used improperly or incompletely, as it depends primarily on the number of people exposed to antituberculous drugs. Treatment of active cases can reduce the period of transmission of M. Tuberculosis, but a significant amount of transmission to contacts occurs even before they have been diagnosed and treated. This period can be substantial, considering the patient-related and health care system-related delays that are common in low and lower-middle income countries like India. The median delay in diagnosis due to patient and health care system delays in a study from south India was 60 days[10]. Another pitfall is that medical treatment alone cannot prevent re-activation to active TB in the vast pool of persons with latent TB infection (LTBI). Treating all LTBI with Isoniazid, even if it is effective, is clearly impractical in India, where an estimated 400 million persons have LTBI[11]. In addition, this form of treatment for LTBI could lead to the emergence of more drug resistant organisms in the community. A large trial in south India found that BCG vaccination had zero efficacy in prevention of the adult infectious forms of TB[12]. Hence, BCG vaccination plays no role in controlling TB at the population level in India.

4. The role of nutrition

Tuberculosis and under-nutrition interact in a two-way process. Tuberculosis can lead to weight loss and micronutrient deficiencies by increasing nutritional requirements, changing metabolic processes and decreasing appetite resulting in reduction in food intake[13]. More importantly, a poor nutritional status can depress the cell-mediated immunity, the key host defense against TB bacilli[14–16]. In those with a robust immune system, the bacilli cannot multiply during the initial infection to cause primary progressive TB, nor can it reactivate to cause secondary TB. Under nutrition increases the susceptibility to active tuberculosis and delays recovery[14–18]. In this regard, it is the children who need a major focus, as childhood nutrition is the major determinant of health status as an adult. Equally important is the nutritional status of women, especially those of child bearing age, as mother's nutritional status plays an important role in the immune status of the newborn. Nutrition in the fetal period may exert a crucial influence on thymic development, early programming of cell mediated immunity and thereby on susceptibility to tuberculosis[19].

In India, the immunodeficiency associated with undernutrition or 'nutritionally acquired immune deficiency syndrome' is a major driving force of the TB epidemic[20]. The Jan Swasthya Sahyog study on the nutritional status of adult patients with pulmonary TB and its impact on TB outcomes was conducted in 1695 active TB cases in rural Chhattisgarh (in central India). In this study, moderate to severe undernutrition (BMI<17.0) was present in more than two-thirds of men and more than three-quarters of women at diagnosis. In comparison to reference values for BMI (18.5 kg/m^2 both sexes), women with TB with the median BMI of 15.0 had a 2.5 fold higher risk of death, and men with median BMI of 16.0 had a 1.9 times increased risk of death. If the relationship between under-nutrition and TB death is considered causal, then nearly 50% of deaths during treatment in both sexes in the entire cohort could have been prevented, if their pre-treatment weights (nutritional status) had been in the ideal range. Apart from the risk of mortality, being underweight at baseline has been shown to be an independent risk factor for relapse of TB (Hazard ratio 3.0, 95% CI 1.8–4.9)[21]. Nevertheless, it should be noted that BMI is not an absolute marker of nutritional status as it does not reflect the adequacy of protein, vitamin and other micronutrient intake. It is purely by chance that the overweight individuals are better off nutritionally because they could be getting essential nutrients too during the process of eating more as compared to the underweights. Even those with a normal or increased BMI can be equally susceptible to TB if they are protein and micronutrient deficient.

5. Contact with a TB case

Household contact with an individual with active tuberculosis is an important risk factor for developing tuberculosis[22]. For this reason, if there is a history of tuberculosis in the family of a patient, he/she is perceived to have acquired the infection through contact with the affected family member. This

perception may hold true only in countries where TB is under control, but not in India, where majority of the population are already infected with TB especially at an early age and having dormant bacilli in different organs waiting for an opportunity to multiply[11]. So, much more vital than close contact, might be the same dietary pattern and nutritional status among the family members which makes them more susceptible to manifest the infection they have contracted at a younger age. It is interesting to note that in a study from South Delhi, among 1608 household contacts of pulmonary tuberculosis, 6.9% were found to have culture positive TB, of which 4.3% was co-prevalent TB, indicating that high incidence of TB among family members of cases was more due to similar susceptibility to disease, rather than spread through contact. Moreover, on studying the contact relationship status of these patients with index patients, 64% were first degree relatives and 19% were spouses[23]. The nutritional status and dietary habits of a patient would naturally be more similar to their parents and other first degree relatives rather than their spouses who have different upbringing, which could be the reason for less risk of TB in spouses in spite of close contact.

6. Vitamin D deficiency and risk of developing tuberculosis

Vitamin D plays an important role in macrophage activation and restriction of mycobacterial growth. Low serum vitamin D levels appear to increase the risk for TB infection[16,24–29]. Serum concentrations of 25- hydroxyl cholecalciferol in patients presenting with TB are on average, lower than in healthy matched controls, and the prevalence of TB is higher among those with low serum 25- hydroxyl cholecalciferol concentrations[16,28]. Vitamin D deficiency is also associated with an increased risk of developing active TB in those subjects with latent TB infection[28]. The very high prevalence of vitamin D deficiency in the Indian population (70%–100% in the general population) can therefore multiply the TB menace manifold[30,31]. Studies from India on vitamin D deficiency in tuberculosis noted that the deficiency was due to inadequate dietary intake and not due to decreased sunlight exposure. In other words vitamin D deficiency itself is a marker of clinical or subclinical malnutrition[16,32].

7. The combined approach to control TB

TB eradication in India and other low and lower-middle income countries is surely challenging but definitely possible. TB control programs in India till now, have focused primarily on case detection and medical treatment of active TB cases by providing drugs free of cost to the patients as directly observed therapy. A combined approach, with considerable emphasis on nutritional interventions (empowering the people to consume a balanced diet by social, educational and agricultural reforms), hand-in-hand with the available anti-tuberculous drugs would be a more effective strategy to tackle TB. Nutritional interventions for TB control can be considered in two differing contexts-first is nutritional supplementation (macronutrients and micronutrients) for patients with active TB with the aim of improving TB related outcomes and quality of life. Second is implementing strong public health strategies to improve the nutritional status of the entire population to reduce new infection and reactivation of TB[33]. Particular emphasis should be given for family members of active TB cases considering their increased risk, mainly attributed to poor nutritional status. Such a refocus on nutritional interventions should take place among healthcare providers in the public and private sectors at all levels, program managers in TB control program, health administrators as well as among patients and the community at large. In 2013, World Health Organization (WHO) released operational guidelines for nutritional care and support of patients with TB[34]. These guidelines recommended nutritional assessment, counseling and support as integral parts of management of patients with TB, and suggested country-specific adaptation of the guidelines. Efforts to this effect have indeed been pursued in the latest (2017) guidance document specifically for nutritional care and support for TB patients issued by the Central TB Division of India[35]. This promising initiative needs to be given due emphasis during policy implementation at all levels. These nutritional strategies may also be integrated with the broader programs like the national nutrition mission to become effective at the wider community level, so as to encompass not just TB patients, but also their contacts as well. There is also a need for further research to clarify the nutritional management of TB patients, especially by using culturally acceptable, locally available foodstuffs, and to study the role of nutritional supplementation in preventing TB, and the cost-benefit analysis of such interventions[36]. Limited research in this field should not refrain us from implementing nutritional interventions, as the characteristic epidemiology of TB is self-explanatory regarding the role of nutrition. It is also important to focus on improving the living conditions of TB patients and their contacts on the whole so as to reduce further transmission and improve treatment outcomes as well.

8. Conclusion

High-income countries had experienced significant decline in TB incidence as a result of improved nutrition and living conditions. In low and lower-middle income countries like India with no concomitant improvement in nutrition and living conditions, the impact of control programs focusing only on case detection and treatment will be minimal. A combined approach with emphasis on nutritional interventions is promising, but needs a refocusing at all levels of care and strong-willed action to ensure effective implementation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijtb.2018.10.001.

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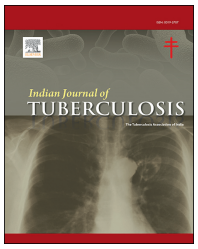

Editorial

Can sputum microscopy be replaced?

TB is diagnosed by finding *Mycobacterium tuberculosis* bacteria in a clinical specimen taken from the patient. In case of paucibacillary and extra-pulmonary forms, early confirmation of the diagnosis of tuberculosis is a challenging problem. Conventional methods available for diagnosis namely, tuberculin test, radiological examination and other imaging methods and sputum smear microscopy have their own advantages and their own limitations.

Since its inception, microscopy remains a cornerstone of tuberculosis control because it identifies sputum-smear-positive (most infectious) cases and is rapid and cheap, although has a limited specificity. The standard smear microscopy test has limitations. It usually finds it difficult to diagnose TB when the bacterial load is less than 10,000 per millilitre of the sputum sample, giving erroneous negative results for some patients.[1] Smear microscopy sensitivity is increased by using various fluorochrome dyes such as auramine and rhodamine, and Fluorescent-staining methods.

Some of the important methods which are adopted by RNTCP and are endorsed by WHO are: (i) **MGIT (Mycobacteria growth indicator tube)**: In this method growth is detected by a non-radioactive detection system using fluorochromes for detection and drug screening. (ii) Line Probe assays (LPA). LPA is a multiplex PCR based genotypic assay used for the screening of Rifampicin & Isoniazid drug resistance and *M. tuberculosis* complex simultaneously. (iii)The Xpert MTB/RIF – a rapid, fully-automated nucleic acid amplification test (NAAT). In addition, some test which was introduced recently shows some promises are described below:

i. Xpert MTB/RIF is costlier than microscopy but use of this test will increase the number of cases with microbiologically confirmed TB because of its higher sensitivity. WHO policy statement strongly advises that Xpert MTB/RIF be used as the initial diagnostic test in adults and in children who are at risk of MDR TB or HIV associated TB and these two groups should be prioritized for testing with Xpert MTB/RIF when resources are limited.[2] Following this RNTCP has also endorsed this test and issued guidelines to use this test as initial diagnostic test for the patient group mentioned above and has scaled up the procurement of Xpert MTB/RIF modules since 2016[3] and has placed them in almost all the districts across the country so that all can have access to universal DST. Although Xpert MTB/RIF is suitable for use at all levels of the health system, implementation in a diagnostic facility requires stable and uninterrupted electrical supply and also the challenges associated with instrument maintenance, training, quality assurance. To overcome the challenge, Cepheid, manufacturer of the instrument, continues to develop a new platform called the GeneXpert Omni. The Omni device is smaller, lighter and less expensive and suitable for use for point-of-care nucleic acid detection as it comes with a built-in 4-hour battery.[4]
ii. The World Health Organization (WHO) issued a recommendation in 2017 that Xpert MTB/RIF Ultra can be used as an alternative to the existing Xpert MTB/RIF test for the diagnosis of TB and detection of rifampicin resistance in all settings.[5] The Xpert MTB/RIF Ultra assay was redesigned to boost analytical sensitivity more than tenfold and to improve reliability of detecting mutations associated with rifampin resistance. In a multi centre study conducted by FIND it was found that the newly introduced Xpert MTB/RIF ultra assay was found to be non inferior to the original Xpert MTB/RIF for the diagnosis of TB as well as detection of rifampicin resistance, especially in smear negative culture positive cases this assay was found to be superior.[6]
iii. Loop mediated thermal amplification test (LAMP) is another molecular test endorsed by WHO which issued guidance in 2016 for the use of TB LAMP as a potential replacement for smear microscopy.[7] This test was found to be cheaper than Xpert MTB.RIF and the results are available in 40 min.[8]
iv. The TrueNat TB test is a new molecular test that can diagnosis TB in 1 h as well as testing for resistance to the drug rifampicin. The TrueNat machine is more of a point of care machine, which is not fully automated and which is designed for situations where there may not be electricity and where the need is for one test to be done at a time. With this test, samples can be tested as soon as a patient with symptoms of TB is seen. As the entire set-up is both battery operated and portable, it can be used at the most basic parts of the health care system.[9] It takes about 25 min to do the DNA extraction. It takes

another 35 min to diagnose TB. It takes an additional one hour for testing for rifampicin resistance.[10]

v. Gene amplification methods have been found to be highly sensitive and specific for diagnosis of tuberculosis directly from clinical specimens. Depending upon the bacteriological status and copy number of target sequence, sensitivity has ranged from 70 to 100 per cent whereas specificity between 80 and 100 per cent has been reported by different investigators. Whole-genome sequencing (WGS) of bacterial genomes allows simultaneous identification of all known resistance mutations as well as markers with which transmission can be monitored.[11] Whole genome sequencing is being used extensively in developed countries. New generation sequencing is cheap, easy to use and is manufactured by many companies worldwide. Gene Sequencing and analysis could allow individualized approach to treatment to ensure maximum safety efficacy without side effects.

The End TB Strategy by WHO calls for early diagnosis and prompt treatment of all persons of all ages with any form of drug-susceptible TB or DR-TB. This requires ensuring access to WHO-recommended rapid diagnostics and universal access to DST for all patients with signs and symptoms of TB. WHO defines universal access to DST as rapid DST for at least rifampicin, and further DST for at least fluoroquinolones and second-line injectable agents in all TB patients with rifampicin resistance.[12] WHO endorsed molecular methods are available now for the detection of TB as well as its drug resistance for first and second line drugs. New molecular detection tools including the faster and simpler NAAT and WGS, have resulted in a shorter time for diagnosis and, therefore, faster TB treatments.[13]

Although Xpert is currently being rolled out in multiple countries, this technology is challenging to deploy at the microscopy center level. Many companies are developing tools that can be used in lower-tier laboratories, countries which include the TrueNAT assay (Molbio Inc, Goa, India), Genedrive platform (Epistem, Manchester, UK), and EasyNAT (Ustar Biotechnologies, Hangzhou, China). While these products are already on the market, large scale evaluations are still on the way to collect evidence for policy development. Though currently there is no test which can replace microscopy, there are number of tests available in the market which have potential to replace microscopy and therefore the future of TB diagnosis looks brighter.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ijtb.2018.08.005.

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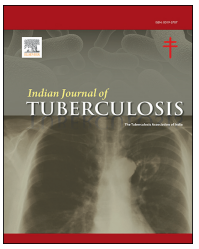

Original article

Burden of pulmonary tuberculosis in modern prison: A cross sectional prevalence survey from south India

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ABSTRACT

Background: The risk of spread of Pulmonary Tuberculosis (PTB) disease depends on several factors. One important factor is the situational and environmental vulnerabilities of the prison setting. Study was conducted in central prison in Chennai, south state, India to estimate the prevalence of PTB disease in 2013.

Methods: All inmates aged 15 years and above were available during survey period screened for symptoms suggestive of PTB and X-ray taken chest PA view. Two sputum specimens were collected for smear and culture examination. All culture positive samples were used for drug sensitivity testing for first line anti-TB drugs. Information on demographic, life style characteristics, past history of PTB treatment were collected through pre-coded interview schedule.

Results: Of 1854 jail inmates were screened, prevalence of symptoms suggestive of PTB was 35% and it was dominated by males. Out of all screened 16 PTB cases are diagnosed and the estimated overall prevalence of PTB among prison inmates was 16/1854 (863/100,000 population).

Conclusions: Prevalence PTB was 2.5 times higher as compared to prevalence of PTB in general population in the same areas, and 3.4 times higher as compared to national average.

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1. Introduction

People in prisons have a higher prevalence of several communicable diseases than the general population. The risk of spread of Pulmonary Tuberculosis (PTB) disease depends on several factors. One important factor is the situational and environmental vulnerabilities of the prison setting (e.g. overcrowding, poor ventilation) increases the risk of contracting PTB among prisoners. PTB prevalence rates are up to 83.6 times higher among inmates as compared to the general population.[1]

To control PTB, government of India conducted prevalence survey among key population to find out the burden of PTB. But there is no systematic survey conducted among prison inmates. Studies on health status of prison inmates conducted in different part of the country in different time points reported 2–7.5% of PTB.[2–4] The National Institute of Research in Tuberculosis, Indian Council of Medical Research, Chennai, conducted a pilot study to estimate the prevalence of PTB disease among the prison inmates in modern jail, Chennai city, in 2013.

2. Materials and methods

2.1. Study area

This study was conducted in three jails (one male convict, one male remand and one both female convict and remand) in a Puzhal Central Prison complex located in Chennai city, Tamil Nadu, south state, India. It is among the largest prison complex in India operational since 2006. This was built in larger area with modern facilities of well ventilation. The facilities include cells and dormitories with windows, lavatories with doors, meditation hall, library, amphitheatre, auditorium, jail court with video-conferencing facility, mechanised kitchens, high-security blocks with exclusive kitchen and hospital, gym, canteen, public music system, rehabilitation block for men and women prisoners. It has an overall capacity to occupy 3000 inmates.

2.2. Study population

All individuals both male and females aged 15 years and above incarcerated in the jail during May to September 2013 formed study population.

2.3. PTB screening strategy

All were questioned about chest symptoms suggestive of PTB disease, such as cough for more than two weeks, chest pain, fever and haemoptysis. Mass Miniature Radiography (MMR) chest posterior anterior (PA) view was done for all individuals and radiograph was read independently by two medical officers. In cases of disagreement, the radiograph was read by a third medical officer. Those with chest symptoms suggestive of PTB disease and abnormal chest radiograph, two sputum samples were collected (on the spot and early morning of the next day). The samples were transported to the laboratory on the same day and examined by aurmine staining for Acid Fast Bacilli (AFB) and culture on Lowenstein–Jensen (LJ) for the detection of *Mycobacterium tuberculosis*. Culture positive samples were used for species identification and drug sensitivity testing (DST) for first line anti tuberculosis drugs to identify multi drug resistance PTB (MDR-PTB). Those symptomatic negative on smear and culture were treated with antibiotics. Demographic characteristics, life style characteristics and self-reported past history of PTB treatment were collected.

2.4. Data management

We formed five members team consisting of two field investigators, one X-ray Technician, one attender and one driver. On the spot the senior person checked all data collected and random checks done by Principal Investigator. All the filled records scrutinized by statistician and send to electronic data processing (EDP) unit for data entry.

2.5. Statistical analysis

To ensure accuracy, two independent data entry operators keyed twice. Data were checked for errors and analysed using SPSS 14.0 software (SPSS Inc., Chicago, IL, USA). Prevalence of PTB was estimated per 100,000 populations.

3. Results

Of the total 1854 inmates screened, 1729 (93%) were males and majority were from the age group of 26–45 years. Among the males 66% had tobacco smoking and 63% had alcohol consumption. Among individuals screened overall 1200 (65%) were asymptomatic. The prevalence of symptoms suggestive of PTB disease was 35% and it dominated by males. The symptoms are 17% cough more than two weeks, 14% chest pain and 5% haemoptysis. In addition 3% of inmates had history of PTB treatment (Table 1). Out of all 1854 inmates screened 16 PTB cases are diagnosed and the estimated overall prevalence among prison inmates was 16/1854 (863/100,000 population). The prevalence of smear positive PTB was 4 (216/100,000 population), smear negative and culture positive 6 (324/100,000) and 6 (324/100,000) were both smear and culture positive PTB. The prevalence was high among elderly people of age 56 and above (3226/100,000). It was high among those who had past history of PTB treatment. The prevalence of PTB among asymptomatic was 417/100,000 (Table 1). Among prisons inmates we found one participant with rifampicin resistance.

4. Discussion

The present study showed that the number of positive PTB in inmates of modern jail, Chennai city was 863 per 100,000 prison population. The rate of prevalence was 2.5 times higher as compared to prevalence of PTB in general population (349/100,000) in the same area,[5] and 3.4 times higher as compared to national average (256/100,000).[6] A recent study form Karnataka prevalence of PTB among prison population reported that 400/100,000 population.[7] Another study on active case finding among prisoners in 157 prisons and 300 districts all

Table 1 – Profile of study subjects (N = 1854).

	Male		Female		Total		TB	
	No	%	No	%	No	%	No	/00 000
Age (in years)								
15–25	338	20	7	6	345	19	2	580
26–35	618	36	26	21	644	35	3	466
36–45	439	25	42	34	481	26	7	1455
46–55	182	11	30	24	212	11	1	472
56+	79	5	14	11	93	5	3	3226
Life style								
Smoking								
Yes	1136	66	0	0	1136	61	10	880
No	446	26	125	100	571	31	6	1051
Alcohol								
Yes	1087	63	0	0	1087	59	5	460
No	494	29	125	100	619	33	11	1777
Clinical features								
Chest symptomatics								
Cough	313	18	1	1	314	17	10	3185
Chest pain	251	15	0	0	251	14	7	2789
Hemoptysis	88	5	1	1	89	5	4	4494
Asymptomatic	1077	62	123	98	1200	65	5	417
H/o TB treatment	61	4	0	0	61	3	7	11,475
No H/o TB treatment	1668	96	125	100	1793	97	9	502
	1729	100	125	100	1854	100	16	863

over the India screened 5093 inmates, 8% were found smear positive PTB.[8] This seems to be extremely high 8000/100,000 may be due to the old prison setting that exacerbates disease transmission. In addition prisons are not mere static venues holding large population; they came from different places where at risk groups congregate. In general, prisoners do not represent a homogenous segment of the society. Many come from the marginal society, poorly educated, and socioeconomically disadvantaged groups. This finding corroborate with the findings from other parts of the world.[9]

Women prisoners represent about 5% of the total prison population.[10] The current study 125 (6.7%) were females inmates and we didn't find PTB case among females inmates. This is consistent with the prevalence of PTB in the community which is low among the female population (140 vs 571 per 100,000).[5] The similar finding was reported from other parts of the country in the same region.[5]

Other finding was one participant (1/16) 6.25% had drug resistant PTB and it was almost similar to the general population.[5] In contrast, high levels (up to 24% of PTB cases) of MDR-TB have been reported from prisons.[10] This high rate of MDR-PTB is complicate management in a setting already overcrowded, inferior budgets and lack of health infrastructure in prison. These factors that encourage the spread of PTB in prisons also promote the spread of MDR-TB.[9] The development of drug resistance PTB is more important in TB control programme because it is much more difficult and expensive to treat than fully drug-susceptible PTB.

5. Conclusion

The prevalence of pulmonary PTB among prions inmates in modern jail is less as compared to other jails. However it was 2.5 times higher as compared to general population in the same areas, and 3.4 times higher than to national average. All prisons should be screened or to be asked about symptoms suggestive of PTB upon their entry to be implemented properly.

Author contributions

Chandrakumar Dolla, Baskaran Dhanaraj are Epidemiologists were conceived, designed and conducted study; Baskaran Dhanaraj, Padma Priyadarshini Chandrasekar were read X-rays; Muniyandi Malaisamy, Syeed Hissar, Rajendran Krishnan analysed and interpreted the data; Mohan Natarajan, Srikanth Prasad Tripathy, were overall supervised the study; all authors contributed writing and editing the manuscript.

Ethical

Written informed consent was obtained from all inmates willing to participate. The trained field investigators approached the inmates and explained the procedures, risks and benefits of the study in their language. Who are not known the Tamil language (local) to read, were explained by jail officers, with witness of jail officers written informed consent was obtained. All positive participants for PTB were referred to RNTCP for their treatment and counselling was provided to adherence to full course of treatment.

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Conflicts of interest

The authors have none to declare.

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Appendix A. Supplementary data

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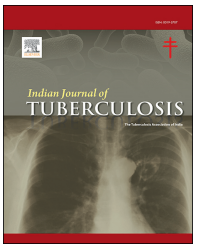

Original article

N-TB: A mobile-based application to simplify nutritional assessment, counseling and care of patients with tuberculosis in India

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ABSTRACT

Undernutrition is the most prevalent comorbidity in patients with tuberculosis (TB) in India. Undernutrition is often severe and results in higher risk of death, drug toxicity during treatment, poor functional status at end of treatment and a higher risk of relapse after successful treatment. A World Health Organization guideline has recommended nutritional assessment, counseling, and care as integral parts of TB care. The Revised National Tuberculosis Control Programme has recognized undernutrition as a significant comorbidity, released a guidance document for improving nutritional care and support, and launched a scheme for direct bank transfer of monthly cash benefit to TB patients. However, there are gaps at the provider level on nutritional assessment, due to challenges in calculation and interpretation of body mass index (BMI). A mobile based application has been developed for use in the programme, which makes estimation of BMI possible, classifies the severity of undernutrition, suggests triage and clinical actions based on the BMI, indicates desirable body weight corresponding to a BMI of 21 kg/m^2, and the daily caloric and protein intake for underweight patients with active TB. The app also provides tips for dietary counseling for TB patients, information on the major food groups, emphasizes an adequate and balanced diet from locally available foods for nutritional recovery of TB patients.

In the pre-chemotherapy era, a nutritious high protein diet was an essential component in the sanatorium-based management of tuberculosis (TB). However, the success of home-based chemotherapy and the closure of sanatoria led to nutrition falling off the radar of TB programmes. In many high-TB burden countries like India, "consumption" is still an apt descriptor for TB which literally means 'wasting away'. In a cohort of patients with pulmonary TB (PTB) in central India,

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undernutrition was nearly universal.[1] Adult men and women had median body mass indices (BMIs) of 16 kg/m^2 and 15 kg/m^2, and a BMI as low as 10 kg/m^2 was also documented.[1] Data on weights of adult patients from India's Revised National Tuberculosis Control Programme (RNTCP) also revealed severe undernutrition with median weights of 42 kg and 38 kg in men and women respectively.[2] In the absence of nutritional support, undernutrition persists even at the end of therapy.[1,3]

Undernutrition in patients with TB has numerous implications such as increasing the risk mortality by 2–4-fold.[1,4] Low BMI is a risk factor for drug-induced hepatotoxicity and drug malabsorption.[5,6] Low baseline weight and inadequate weight gain during treatment are risk factors for relapse.[7] Poor nutritional recovery affects the performance status and return to active life following cure.

The high prevalence and serious implications of undernutrition in patients with TB, led the World Health Organization (WHO) to frame a guideline for nutritional care and support of TB patients.[8] It emphasized the need for nutritional screening, assessment and management as key components to the TB care cascade. Further, it also alluded to an adequate diet being essential for proper health for all, including TB patients.[8]

India, the country with the largest global burden of TB, where undernutrition is a co-epidemic, has seen recent policy initiatives in addressing the TB-undernutrition link. A guidance document, which is a context-specific adaptation of the WHO guideline, has been formulated.[9] Undernutrition has now been regarded as co-morbidity and a key driver of the TB epidemic by the programme, in addition to HIV and diabetes.[10] The Government of India has also announced a direct benefit transfer (DBT) scheme of 500 Indian rupees per month for TB patients to ensure access to a nutritious diet under the Nikshay Poshan Yojana.[11] These initiatives in India are aligned with the priorities of patient-centered care and management of co-morbidities of the END TB strategy.

Nutritional assessment, counseling and care in patients with TB are all linked activities. Nutritional assessment requires measurement of height, weight, calculation of BMI and classification of nutritional status based on BMI. This should be followed by nutritional counseling emphasizing an adequate and balanced diet with focus on locally available foods and patient preferences. Provision of food/supplements occurs in many programmes, and their choice is guided by scientific rationale, cultural acceptability, operational feasibility and cost considerations.

Implementing of nutritional assessment and support in programmatic setting for frontline care providers has numerous challenges. For example, in India, heights were not included in routine patient data till the recent past. Currently heights are being measured as per the new TB card but are not being translated into BMI values and/or categories. In an ongoing operational research study we found that primary care providers were unfamiliar with calculation of BMI and BMI-based nutritional classification of nutritional status.[12] As a result, they assessed nutritional status by variable and arbitrary weight-based cutoffs for underweight patients (35 kg or 40 kg). Ideally, nutritional assessment should lead to clinical decisions relevant to patients and care providers. The recognition of high risk patients with severe undernutrition and their management is one such clinical action. Counseling on adequate intake of calories and proteins assumes knowledge of calorie and protein requirement for patients based on their nutritional status, which may be challenging for care providers.

1. N-TB app: an enabler for nutritional assessment, monitoring and counseling for frontline care providers of patients with tuberculosis

An android and iOS based application called N-TB has been developed to address some of these challenges in the domain of nutritional care of TB patients. It has been endorsed by the RNTCP and WHO (India).[13] The only input values required are height in cm and weight in kg of adult TB patients. Based on these input values it provides the following information (Fig. 1):

1.1. *Nutritional assessment at diagnosis and follow up*

It calculates the BMI and categorizes the patient into different color coded nutritional categories using WHO recommended cut-offs. It also mentions an extremely underweight category for those at or below a BMI of 14 kg/m^2, which are at extremely high risk of adverse outcomes, including death.

The app gives an estimate of the desirable weight as a function of the height of the patient, defined as the weight corresponding to a BMI of 21 kg/m^2, and the minimum acceptable weight corresponding to a BMI of 18.5 kg/m^2. It also uses these weights to estimate the weight gain required in the patient to reach a desirable or minimum acceptable BMI, which can help assess adequacy of weight gain during follow up.

1.2. *Triage for patients with severe acute malnutrition*

The app provides a red-flag alert in case the BMI is less than 16 kg/m^2, and indicates a requirement of hospital admission if there is coexisting poor performance status, pedal edema, and severe anemia. Any patient with a BMI less than 14 kg/m^2 also mandates admission. The app also provides an overview of the management of severe malnutrition in adults.

1.3. *Counseling tips for an adequate and balanced diet*

Furthermore, the app provides a recommended daily intake of calories for underweight patients based on the requirements of 40 kcal/kg of desirable body weight. To note here, the daily caloric intake is measured based on a sedentary lifestyle. It also recommends a daily protein intake of 1.2–1.5 g/kg of desirable body weight.[9] The app has information on major food groups, their caloric and protein values. It provides counseling tips on diet emphasizing locally available foods, clarifying many common misconceptions and myths.

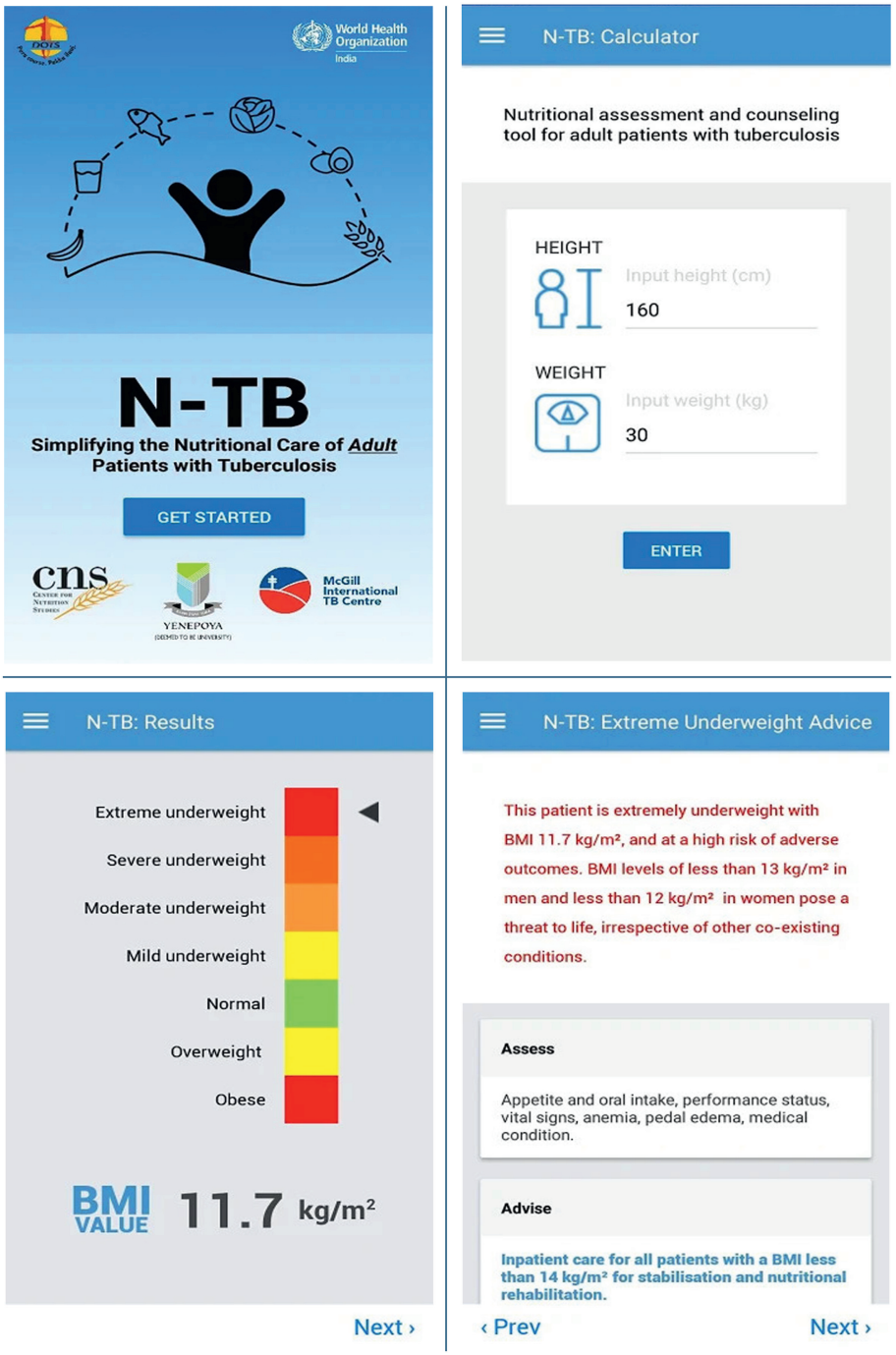

Fig. 1 – Screen shots of N-TB app.

Further development plans for the app include linking the outputs to customized meal plans, availability in other languages and a patient version with more graphic content. Operational research and field validation studies may lead to better understanding of its strengths and limitations as an operational tool at programmatic setting.

Conflicts of interest

The authors have none to declare.

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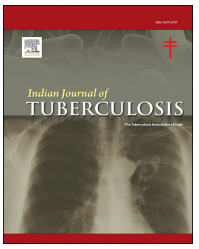

Original Article

Tuberculosis - Depression syndemic: A public health challenge

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ABSTRACT

Introduction: Depression is common in Tuberculosis (TB) and associated with adverse outcomes through pathogenic mechanisms and impaired self-care behaviours including reduced treatment adherence. Undiagnosed depression can threaten the robustness of DOTS model despite large public health investment. The Depression-Tuberculosis Syndemic requires collaborative partnership with mental health professionals.

Aim: To study the evidence base for Depression-Tuberculosis Syndemic.

Methodology: A Pubmed and Google Scholar search was conducted using the key words "Depression", "Tuberculosis" and "Syndemic" and abstracts screened for appropriateness and relevance.

Result: Depression-TB Syndemic is common with a bidirectional relationship. Depression is associated with higher hazard ratio and increased prevalence of TB. Depression is independently associated with higher morbidity, mortality, drug resistance, risk of TB reactivation and community TB transmission. The underlying biopsychosocial mechanism of Depression- Tuberculosis Syndemic includes biological factors like inflammatory cascade, HPA axis dysregulation and psychosocial factors like perceived stigma and treatment non-adherence.

Discussion: Depression is a poor prognostic factor in TB. The National Mental Health Programme (NMHP) and National Strategic Plan (NSP) for Tuberculosis Elimination (2017–2025) work in independent verticals with no integration at policy or at ground level. This results in lack of identification and appropriate management of depression in patients with Tuberculosis despite repeated contact with health care personnel in DOTS centres. A collaborative approach for early diagnosis and management of depression in patients with Tuberculosis (Secondary Prevention) can help decrease the burden of disease and improve outcomes.

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Conclusion: Depression-TB Syndemic requires collaborative approaches at the program level and at the point of service delivery.

1. Introduction

Tuberculosis (TB) is a chronic infectious disease caused by mycobacterium tuberculosis[1] and is among the leading causes of morbidity and mortality in the world.[2–4] As per the World Health Organization (WHO) over two billion people, are harbouring latent TB[5,6] and over nine million people are having active TB results in death in one third of the cases, most of which are reported from developing countries of Asia and Africa.[7–9] India produces the maximum new cases of TB each year than any other country and accounts for one-fifth of global TB burden.[10]

Depression is a treatable mental health disorder which affects upto half of all the patients of tuberculosis. Many patients with depression possess one or more of the risk factors like homelessness, alcohol abuse, congregate housing, exposure to active case,[11,12] and, consequently, TB is more common in this population. Conversely, psychiatric illness may develop subsequent to TB infection, and depression seems to be particularly common in TB patients and is associated with increased mortality, morbidity and drug resistance.[13–17] A study conducted in Vellore, south India has shown that about one-fifth of the tuberculosis patient suffer from some psychiatric co-morbidity, depression being the commonest.[18] In two other studies conducted in Rajasthan, North India, depression was found to be present in about half of the TB patients.[19,20] This bidirectional relationship between the TB and Depression needs to be recognized to control the global TB epidemic.

However, the National Strategic Plan (NPS) for Elimination of Tuberculosis by Government of India[21] does not focus on screening for depression as a diagnostic algorithm at DOTS Centres despite its ambitious target of achieving elimination of TB by 2025 ahead of WHO's End TB Goal by 2030.[22]

2. Methodology

A Pubmed and Google Scholar search was conducted using the key words "Depression", "Tuberculosis" and "Syndemic" in various permutations and combination revealing 3 articles with all 3 key words and 999 other articles. The abstracts were screened for appropriateness and relevance. The evidence base synthesized and presented below.

3. Biopsychosocial model of tuberculosis-depression syndemic

The convergence of the two conditions like TB and depression that are acting synergistically to magnify the overall disease burden is known as syndemic.[23] There are various biological, social and behavioral factors that promote synergistic association between TB and depression contributing to the biopsychosocial framework of TB- Depression Syndemic (Fig. 1).[24]

3.1. *Biological factors*

Inflammatory response system (IRS) plays an important role in the pathogenesis of both infectious and non-infectious diseases.[25] Depression is often identified as co-morbidity with both infectious (like tuberculosis) and non-infectious diseases (like Diabetes, Cancer).[26–28] Previous studies reveals that patients with chronic inflammatory diseases and major depression have reduced circulating tryptophan (TRP) levels and increased levels of metabolites of enzyme Indolamine-2,3-dioxygenase (IDO) like kynurenine.[29]

IDO is the rate-limiting enzyme in the TRP –kynurenine pathway that converts TRP, the precursor of Serotonin, to kynurenine, resulting in a diminished synthesis of central serotonin27. Pro-inflammatory cytokines like IFN-γ and TNF-α can up regulate IDO expression[30–33] activating kynurenine pathway reducing central serotonin levels. The resultant decreased synthesis of serotonin could possibly explain the development of depressive symptoms as per the prevalent monoamine hypothesis of depression. The metabolites of the kynurenine pathway are also neuroactive and may have a causative role, because the ratio of kynurenine to TRP is positively associated with depressive symptoms.[34,35] Thus, the enzyme IDO lies at the interface between chronic inflammatory disease and depression.[36] The depressive symptoms often seen as adverse effect in patients receiving cytokine immunotherapy provides clue to the causative role of IRS in depression.[37]

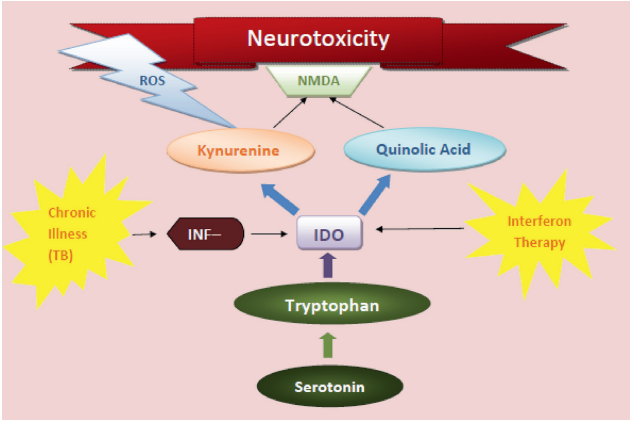

Fig. 1 – Tryptophan metabolism by Indolamine-2,3-dioxygenase (IDO) in TRP–kynurenine pathway.

Tuberculosis is a chronic infection which leads to increase in synthesis of IFN-ɣ, inducing IDO enzyme and diverting TRP towards the kynurenine pathway from the serotonin pathway (Fig. 2).[38] The neurotoxic metabolites of the kynurenine pathway like 3-hydroxy-kynurenine and quinolinic acid are also generated which cause free radicals mediated neuronal damage. Also, quinolinic acid can cause exitotoxicity either by stimulating N-Methyl-D-aspartate (NMDA) receptors or directly causing the release of glutamate.[39]

3.2. *Social factors*

Poverty is recognized as a common risk factor for both TB and depression. People living in poverty have overcrowded and poorly ventilated conditions which promote TB transmission. People living in poverty have greater exposure for stressors like violence, social exclusion and drug abuse, which are also risk factors for depression.Malnutrition is commonly seen in people living in poverty due to lack of food security and it is an independent risk factor for both TB and depression.

Stigma from TB can increase the risk of depression due to fear of the diagnosis and outcome as well as risk of social isolation. Further, both Tuberculosis and Depression are stigmatising conditions in themselves resulting in social and cultural exclusion and economic marginalisation consequent to exclusion from mainstream community. The setting of socio-cultural isolation and economic deprivation is a context in which a patient of Tuberculosis-Depression Syndemic negotiates life and treatment seeking on a daily basis. Poverty is in itself a stigmatised condition and combined with Tuberculosis-Depression Syndemic have negative synergies on patient health outcome. Stigma for diagnosis of both TB and Depression also prevents seeking of medical help early in the course of illness, resulting in chronicity and poor outcomes.[24]

3.3. *Behavioral factors*

Depression can mimic and magnify ancillary symptoms of TB like poor appetite, loss of weight and easy fatigability. People with depression often have negative coping behavior such as drug abuse, which further contributes to poverty, malnutrition and poor immunity. This increases the incidence of TB in such patients due to reactivation of latent tuberculosis and also increases the morbidity and mortality due to delay in health seeking and poor treatment compliance.[40]

In addition, depressed individuals are also likely to exhibit poor self care behaviour, poor dietary intake and inability to adherence to complex treatment regimens. Depression may also lead to cognitive impairment, poor concentration, poor motivation which can result in missed dosages and non-adherence to treatment. Depressed individuals often have poor health care communication with service providers and inability to adequately express their symptoms and concerns or process and recall advice given by doctors and nurses. Depression is also associated with lower health system usage and trust; there is frequent change of doctors resulting in poor treatment outcomes. Many of these factors have been examined in depth for other comorbidities of depression like diabetes but can easily be extrapolated to all chronic diseases comorbid with depression including TB.[41]

4. Impact of Tuberculosis-Depression Syndemic

Depression in TB patients is a particularly concerning as it is associated with non-adherence with therapy, chronicity and worse outcomes . Non-adherence with anti-Tubercular therapy results in prolonged infectiousness, drug resistance and is seen as a major hurdle in eliminating TB. Despite adopting different approaches including DOTS to improve adherence with therapy the problem still persists.[42] Various social, behavioural and cultural factors have been cited as factors for poor treatment adherence in TB patients. Screening and early identification of patients with risk factors for non-adherence will help in dealing with this problem.[42,43] The presence of co-morbid psychiatric disorders like depression has been seen as an important risk factor for non-adherence. TB patients who are depressed are less likely to seek medical advice and adhere to prescribed treatment regime which results in prolong infectiousness, emergence of drug resistance, increased

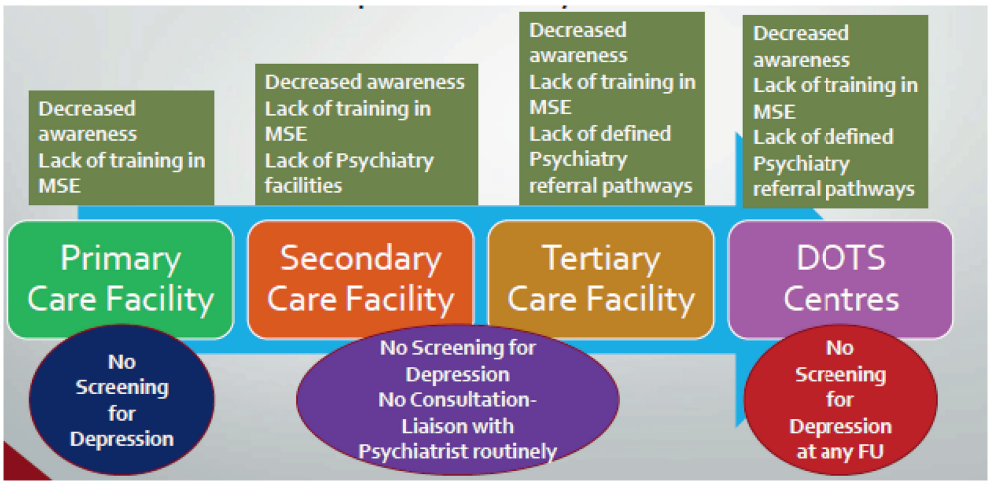

Fig. 2 – Missed diagnostic opportunities for TB-Depression syndemic.

morbidity and mortality.[44] Thus, depression may have been the silent driver of global TB epidemic and emergence of Multi drug resistant (MDR) TB.[45]

Studies have shown that mental disorders are commonly seen as comorbidity among TB patients but are not easily recognised by health workers and treating physicians.[46] Psychological factors and patient perception about illness are important factors for adherence to a long term therapy required in chronic illness like TB. Thus, identifying psychological problems and treating coexisting mental disorders may substantially improve treatment adherence in TB patients.[47] Indeed, DOTS programme when integrated with deaddiction programme were able to improve adherence and achieve better TB control.[48,49] The DOTS-Plus guidelines for MDR-TB patients recommend screening all such patient for psychological issues and work closely with the available psychiatric services.[50] Thus integration of mental health services in TB control programmes is required to screen and manage any comorbid psychopathology and promote adherence with therapy in such patients.[51]

5. Management considerations for Tuberculosis-Depression Syndemic

Depression is a well recognised adverse effect of anti tubercular medicine like Cycloserine.[52] Anti depressants also have drug–drug interactions with Anti Tuberculosis agents especially Isoniazid and Linezolid. Rifampicin, another antitubercular medicine decreases drug levels of antidepressants like Sertraline and Nortryptiline through Cytochrome P 450 mediated pathways.[53] A high index of clinical suspicion and alertness for possible drug interaction can help in early detection of such interactions in clinical practice.

6. Integrated approach for Tuberculosis-Depression Syndemic

The frequent comorbidity of TB and depression implies a high probability that a primary care physicians treating TB will encounter undiagnosed cases of depression. Likewise, psychiatrists are likely to encounter TB among the mentally ill patients. Both primary care physicians and psychiatrists need to be familiar with the clinical features of each disease and an integrated approach is required so that an early diagnosis can be made and appropriate treatment and referrals ensured.[17]

The National Mental Health Programme and National Strategic Plan for Tuberculosis Elimination 2017–2025[21] work in independent verticals with no integration at policy or at ground level. This results in lack of identification and appropriate management of depression in patients with Tuberculosis despite repeated contact with health care system.

There are multiple contacts with medical professionals in primary care, secondary care, tertiary care facilities and DOTS centre as summarised. Decreased mental health awareness in the community as well as health care providers, lack of training in mental status examination by non-psychiatrist health care providers, lack of psychiatry facilities and referral pathways contribute to the missed diagnosis of depression. A collaborative approach with mental health professionals for early diagnosis and management of depression in patients with Tuberculosis (Secondary Prevention) can help decrease the burden of disease and improve outcomes.

From a public health perspective, linkages between National Strategic Plan for Elimination of TB and National Mental Health Programmes are required with scope for periodic review of program delivery and outcome metrics. There should be mandatory screening for depression in DOTS Centres at first contact and quarterly with defined referral mechanisms to psychiatric facilities near the DOTS Centres. Further, multi centric epidemiological research on TB Depression Syndemic is required including prevalence rates, determinants in Indian/South Asian contexts and impact of the Depression-TB syndemic on composite physical and mental health outcomes.

7. Conclusion

WHO's Global End TB Strategy focuses on integrated patient-cantered care and prevention linked to social protection and innovative research. Improving diagnostic rates of depression in patients with TB and its appropriate management can help in decreasing burden of disease and global TB burden. At the same time, understanding that TB is not only a chronic infection but a biopsychosocial disease with comorbid depression and concomitant social conditions like poverty, unemployment and stigma is the key for addressing TB, MDR-TB and XDR-TB epidemics globally.

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Conflict of interest

None

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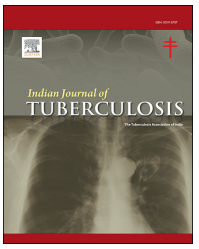

Original article

Identifying and mapping TB hot spots in an urban slum by integratingGeographic positioning system and the local postman – A pilot study

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ABSTRACT

Setting: Mahavir DOT Centre, Hyderabad, Telangana, India
Introduction: Urban slums are characterized by crowding, poverty. In such setting due to lack of infection control the transmission of tuberculosis is known to rise, thereby creating a "Hot" spot. Distribution of residences in such areas does not necessarily follow postal codes, making it difficult for health workers to locate TB patients unless accompanied by the STLS.
Objective: To investigate the utility of integrating the help of local postman and geographic positioning system (GPS) to identify and create map of hot spots in an area under a regional DOT centre.
Materials & methods: Retrospective and prospective demographic data of TB patients enrolled during 12 years (1999–2011) was analysed from the TB register at a ward where number of cases continued to increase despite active implementation of DOTS strategy. Non-Spatial data was generated with the local postman identifying individual house addresses. The corresponding co-ordinates were recorded with GPS and uploaded in Google Earth to identify the locations.

Area map was created by software (AutoCAD, Map R3, MapInfo Pro 7.5 Trial Version and MS office Tools). Residences of Index patients were marked in different colours year wise on the map.
Results: Maps displayed in the DOT centre area helped in identifying HOT SPOT and visualization of the clustering of TB cases in the area. Time interval between subsequent infections (3 months–5 years) could be calculated in the locality, within household, neighbourhood and random contacts. Average distances (<1 m) between houses indicated the probable source of infection. Risk factors included crowding, poor ventilation and sanitation contributed to TB transmission in HOT spot area.
Conclusion: Integrating local postman and information technology to identify HOT SPOT in RNTCP, will help in early intervention by health personnel to arrest TB transmission.

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1. Introduction

The sustained ongoing TB epidemic and our inability to break the transmission cycle is due to limited diagnostic and screening strategies for identifying and selecting of sub populations with increased TB incidence especially in urban slums[1]

Urban slums are characterized by crowding, poverty and ill ventilated houses. Clustering of TB cases in pockets of urban slum is defined as a HOT SPOT. The probable transmission occurs in household contacts of index patients, neighbours or random contacts. Achieving TB control targets in a hotspot containing 6% of a city population can have a similar impact on city wide TB incidence as achieving the same targets throughout the remaining community[2]

Distribution of residences in such areas does not necessarily follow postal codes making it difficult for health workers to locate TB patients unless accompanied by STLS.

One of the latest tools applied to understand transmission dynamics is Geographical information System (GIS) and Geographical positioning system (GPS). GPS is a navigation system which uses signals from the satellites orbiting the earth and provides the precise location of the object or person or place anywhere around the world. A handheld GPS receiver records the longitude, latitude and altitude of a particular location and assigns the location in a unique code or number. This information is recorded and transferred to a computer database. To create maps from GPS, data is transferred to data management software. Some of the studies utilizing GIS and GPS have explored the associations like socio economic variables at population levels with TB transmission. Identification of risks at population and individual levels has helped health authorities to come up with innovative interventions to minimize transmission[3–5]

1.1. *Study background*

PPM -DOTS project was implemented in Bhagawan Mahavir Hospital and Research Centre charitable hospital with free TB clinic having six wards covering five lakhs population. The case detection increased by 25% and achieved treatment success rate of 90% close to or exceeded WHO target.[6] Despite this success story a retrospective analysis of the new cases registered during five years (1999–2004) at TB clinic, revealed that some of the blocks accounted for a disproportionate increase indicating an active ongoing TB transmission despite robust DOTS implementation.With this background the present study proposes to investigate the possible reasons for TB transmission with application of information technology.

2. Objective

To investigate the usefulness of integrating the help of local postman and GPS system to:

a. Identify and create map of HOT SPOTS and NON-HOT SPOTS in an area under a regional DOT centre
b. Map the transmission pattern

3. Materials & methods

The study was approved by Bhagawan Mahavir Medical Research Centre Institutional.

Ethical Committee.

3.1. *Inclusion criteria*

- Pulmonary tuberculosis patients with sputum smear positive for acid fast bacilli (AFB).
- Evident radiological findings.
- Registered at DMC (designated microscopy centre for TB) implementing DOTS under revised national control programme (RNTCP) at Mahavir Hospital.

3.2. *Mapping the study area with application of global positioning system (GPS)*

3.2.1. *Selection of the study area*

Mahavir TB clinic covers 6 wards out of which Ward no 13 block I was selected. The study area was selected based on the retrospective analysis of the patients registered between 1999 and 2004. The number of patients reporting from this area continued to increase despite an active implementation of DOTS strategy indicating an active ongoing transmission.

Based on the retrospective (1999–2007) and prospective (2008–2011), documentation and analysis was performed for the patients enrolled during 11 years (1999–2011). The following information of the patients was obtained from the TB register:

- The residential address of the patients on treatment between 1999 and 2011 were arranged in ascending order, and the house numbers were segregated in groups of 100 (e.g. 13-1-1233/A/1to 99; 100–199 upto 13-1-1233/600).
- Sputum status, treatment category for both pulmonary and extra pulmonary cases,
- Gender and age
- Demographic details included housing conditions, socio economic status, employment details, types of toilets, cooking fuel, average number of family members sharing the family space etc.

According to RNTCP protocol before advocating DOTS the STLS has to accompany the patient for residential address confirmation and note down the nearby landmarks.

3.3. *Limitations encountered during initial survey*

Without the presence of STLS locating the houses based on the residential addresses due to random distribution of houses proved a herculean task especially for a lay person, or health personal.

Hence a novel way was adopted, with the help of local area POSTMAN, houses with numbers arranged in sequential order where identified, simultaneously with the help of GPS the co-ordinates of these locations were recorded. The co-ordinates

recorded were uploaded in Google earth to locate the aerial view of the study area. This formed Non Spatial data.

Demarcation and updating on Locality Map was done using Software AutoCAD Map R3.

MapInfo Pro 7.5 Trial Version MS office Tools.

Auto CAD and Map R3 was used to locate the area, road network and interpolate the individual houses with postal code in the area demarcated.

Based on the postal addresses as documented in treatment register, houses of TB patients in block 1 Jirra (study) area put on DOTS –period 1999–2011 were marked with colour codes year wise.

Mapping area away from the study area (Sarwarnagar): Similarly the area away from study area was mapped and house numbers interpolated on the map. Colour codes given year wise and marked on houses of registered TB patients on DOTS treatment. Period (1999–2011).

4. Results

4.1. *Demographic details of study area ward-13 block 1–1233*

Jirra area lies within latitude 17.3783968 and longitude 78.45292261.It covers an area of 1.5 sq km. It is a slum area with a total population of 64,062 (2010 census).It has 3 DOTS centre,1 CGHS; 1 Private clinic. It has around 800 houses. Most of the houses are segregated into areas called wadas. A wada is an independent portion having on an average 5 to 6 rooms with a small open courtyard in the centre. Each room on an average is 10 × 10 feet dimension with or without windows, common toilet and drinking point within or community taps. The water is collected and stored in pots for utility purpose.

The average family unit consists of 5 members. Majority of the people residing here have been staying in the same premises for >5 years. Most of the people from this area belonged to the same ethnic group. They were daily labourers, fruit vendors, carpenters, electricians or others. Most of them belonged to low socio economic strata.

Between 1999 and 2011 total number of patients identified and put on TB treatment was n- 216.

4.2. *Demographic details of area away from the study area*

Sarwarnagar area lies within latitude 17.37979179 and 17.37784245 and in longitude 78.44764535 and 78.4531477. It covers an area of 500 sq km with about 400 houses.

The land is dry, rocky and arid. The houses in this area comprised of both wadas and small independent blocks. Wadas had similar 10 × 10 room and had average 4 to 5 rooms in one portion. The total population based on 2010 census was 4420. Majority of the people in this area also belonged to the same ethnic group. Average income varied between 4000 and 10,000 per month. Occupations included daily wage earner, carpenters, electricians etc. Cooking fuel consisted of gas and kerosene. Basically the people belonged to middle and lower socio economic strata. Drinking water consisted of both sharing and individual tap connections. Common sanitation was evident in wadas. The total number of patients registered for DOTS treatment was n- 96.

A comparison between the two blocks revealed a disproportionate increase in number of TB patients in the study area during the study period. Hence this area was designated as 'HOT SPOT' (HS) and the adjacent area as NON-HOT SPOT (NHS).

Between (1999–2011) out of 216 confirmed TB cases put on DOTS treatment in HS n-133 were pulmonary TB (PTB) and n-83 were Extra pulmonary TB cases (EPTB)

In the same time period in NHS out of 96 confirmed TB on DOTS n- 68 were PTB and n-28 were EPTB.

The total number of cases was significantly higher in HS compared NHS region.The ratio observed between HS and NHS was 2.3.

The affected age group in both male and female in HS and NHS was analysed.

The frequency of affected age group in males out of total HS n- 130 and NHS (n-52) in both region predominant affected age group was between 15 and 45 (HS-n-110) and NHS (n-43) (85% vs. 83%)

Similarly the affected age group in females out of total HS (n-86) and NHS (n-43) in both regions were predominantly between 15 and 45 in HS(n-80), NHS (n-41) (93% vs. 95%)

It is observed that in both HS and NHS, TB was found predominantly in the age group 15–45 there was no significant difference in the affected gender too.

The male female ratio in both areas was found to be 1.5:2.

Analysing the impact of DOTS intervention during the 13 years it was observed that detection and treatment of TB has increased two folds in females compared to men in both HS and NHS.

Positive response to DOTS treatment was evident in NHS compared to HS despite a rise and fall phenomenon (Graph 1.0) (See Fig. 1 and Fig. 2).

Based on RNTCP guidelines the patients were categorised as New case (CAT1), relapse (Cat 2) and smear negative/.EP cases (CAT 3).

A gradual increase in both new cases and EP cases was observed in HS compared to NHS suggesting an active ongoing transmission (Graph 2.0).

5. Discussion

The United Nations Human Settlements Programme defines a slum household as lacking more than one of the following-a) adequate access to water and sanitation, b) sufficient living space c) durability of housing and d) security of tenure. Rapid urbanization has resulted in proliferation of densely populated slums that lack basic urban planning including address system. This is a very common phenomenon observed in low and middle income countries especially in cities.[7]

TB is known to cluster in hyper endemic 'Hot spots' often characterized by crowding poverty,[8] HIV infection[9] and other social determinants.[10] As a result the degree to which hotspots contribute to community –wide transmission of TB remains uncertain. Apart from identifying TB cases in high transmission areas (e.g. crowded urban slums, poorly ventilated houses) preventing transmission in such areas would

Fig. 1 – Outcome of DOTS in Ward - HS (1999–2011).

require more efforts compared to low transmission areas. Secondly it would be an herculean task to identify such HOT spot in urban slums just based on addresses registered in TB centres under DOTS programme.

Before implementation of successful DOTS strategy[11] one of the contributing factors for high default rate due to interrupted treatment was tracing the patients due to inadequate addresses and topography.[12] A report on quality improvement report on the TBCP in Mzuzu district, Malawi identified incorrect addresses as being a major problem contributing to low case retention.[13] To overcome this problem in Tamilnadu two novel address card responses were tried resulting in 82% of returning with correct addresses in the card given.[14–16] Though the methods adopted by previous community based studies were useful in tracking patients based on address system in a resource limited setting it could be labour intensive. In this context new technologies like GIS and GPS have been used to assess the spatial epidemiology of malaria, tuberculosis and other infectious diseases. These technologies have also been used to evaluate the distribution of TB health facilities and effectively helped in documenting and quantifying the impact of community based tuberculosis treatment or access to treatment.[16]

The present pilot study under PPM DOTS programme in RNTCP is the first to investigate the usefulness of integrating the help of local postman and GPS system for tracking and mapping addresses of TB patients, since the distribution of the houses followed no logical pattern. By creating a map of the area with house numbers and interpolating the patients data with colour codes year wise, when displayed in the DOTS centre helped in actual 3D visualization of the distribution of the cases within the household, neighbourhood, and locality. This helped in tracing the probable source of contact.

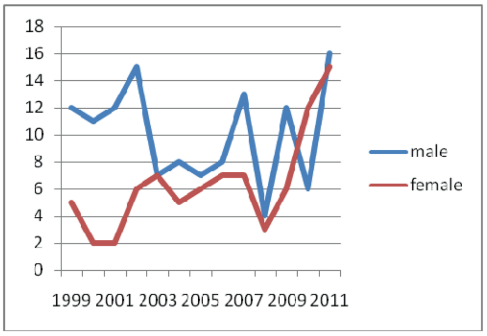
By applying GIS identified HOT Spot within high burden communities. They studied high risk of TB transmission in multiple public gathering places especially shebeens, clinics and churches GIS/GPS technology was applied to document and quantify improved access to tuberculosis treatment through a community based programme in Hlabisa south Africa by plotting supervision points and measure the mean distance from each homestead in the district to hospital.[17]

Integrating map book system and GPS for use in urban slums with no municipal address system in Blantyre, Malawi, where the accurate categorization for ART initiators could be initiated without home visits.[7]

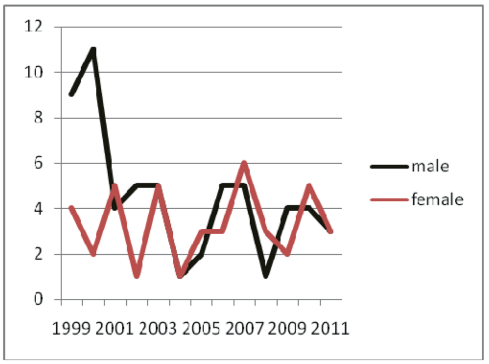
The present study mapped the actual location of houses in a specific area. By identifying the registered TB patients put on DOTS treatment in the map and colour coding them year wise, transmission pattern could be studied for the eleven year period within household, in neighbours and among random contacts in the community. By analysing the data, the time interval for subsequent disease in different areas in the same locality in these three settings could be derived. Time interval varied between three months to 5 years, and could be calculated based on the colour codes used year wise.

In the present study by mapping, both hot spot and non hot spot area. The transmission pattern could be visualized by identifying the clustering of TB patients in certain locality. It

Graph: 1 OUT COME OF DOTS in Ward - NHS (1999-2011)



Graph: 2 OUT COME OF DOTS in Ward - NHS (1999-2011)



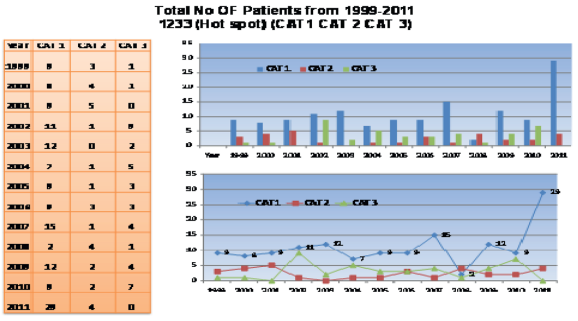


Fig. 2 – PTB (n-135 blue) and Extra pulmonary (n- 83 Red) TB patients in HOT Spot (1999–2011).

was seen that in hot spot clustering of cases in specific areas was higher compared to Non hot spot. The distribution of houses were more spaced out in Non Hot spot area compared to Hot spot, despite having a common denominator of crowding and poor economic conditions.

In a retrospective study conducted at tertiary DOTS centre on implications of pulmonary TB based on gender it was found the male female ratio was 2:1.Smear positive to smear negative ratio was 4.4:1.Large number of patients were in young and reproductive age group and approximately one fifth of patients belonged to geriatric age group.[18]

Our study indicate that the affected age was predominantly in the reproductive age between 15 and 45 both in HOT SPOT and Non Hot spot, but surprisingly the male female ratio was 1:2. This could be due to greater awareness and accessibility to treatment from DOTS provider under the public private mix initiative. The DOTS provider being within the locality, the female patients could adjust their household chores, timings and reach out to treatment.

In the present study population census data and mapping was used to identify the risk factor and associate crowding with TB transmission in HOT Spot. People living in closed environment are at higher risk of infection compared to persons living in non crowded quarters. Using TB surveillance and census data identified, that the census unit (CAU) level, TB incidence in New Zealand was associated with household crowding.[19] However progression to disease might be enhanced by other factors modifying the hosts immune system[20]

In the present study mapping helped in visualizing increased transmission in the HOT spot compared to Non Hot Spot area reiterating that crowding increases the risk of infection leading to disease progression. Studies from India are sparse on role of socio economic variables and its association with TB transmission. In a case controlled study in form of structured questionnaire, determined the socio economic and demographic characteristics of TB patients in the area in and around Chandigarh. Their findings suggest that TB increases with lowering of Socio economic status.[21] The observations in the present study also indicated similar association of low economic status with increased risk of TB.

One of the studies from India reported that that persons living in household using biomass like cow dung or wood for cooking had higher prevalence of tuberculosis compared to households using safer cooking fuels.[22] In a case controlled study found no association between the type of fuel used and TB. However, low socio economic status, smoky rooms, location of the kitchen, poor ventilation and associated respiratory symptoms during cooking are likely to be important contributors in Indian women.[23] similar findings in the present study suggested that ventilation in the kitchen plays an important role especially in Indian homes where women spend major time. Proximity to smoke could impair women's respiratory system, affect the immune system ability to fight off bacteria. Higher risk in women due to biomass fuel is evident from the fact that higher number of females was affected with TB in the present study. This could be one of the contributing factor for increased ratio of women observed in the study.

Linking TB with environment, WHO reports poverty and urbanization create the perfect conditions for TB transmission. Urbanization leads to higher population densities, crowded living condition and increased mobility among migrants seeking temporary work.

.In the present study the negative impact i.e. increase in number of new cases despite a high cure rate in HOT spot could be attributed to the crowded living conditions and higher population density, when compared to Non HOT Spot area despite having a similar socio economic background. This could be attributed to better living shelters.

This is the first report from Hyderabad in a homogenous population.

6. Conclusion

Health care workers or STLS from DOTS centre can be trained to use a simple devise like GPS. By integrating the postal

network and information technology in TB control programme, area maps with house numbers displayed in DOTS centre will help in visualizing transmission patterns, calculate time interval between subsequent cases, distance between houses, trace the probable source of infection. Thus early intervention by the health authorities will help in preventing further transmission.

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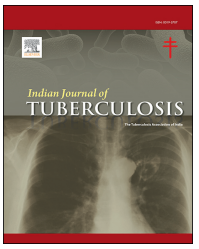

Original article

Initial experience of bedaquiline implementation under the National TB Programme at NITRD, Delhi, India

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ABSTRACT

Background: Bedaquiline (BDQ) was approved for treatment of drug resistant TB (DR-TB) under Conditional Access Programme (CAP) of Revised National Tuberculosis Control Programme (RNTCP) and was also implemented in the National Institute of TB and Respiratory Diseases (NITRD). We present early efficacy and safety of BDQ containing regimens for DR-TB.

Objective: To ascertain the early efficacy and safety of Bedaquline containing regimens in treatment of DR-TB.

Methods: BDQ containing regimens along with other drugs were designed as per WHO recommendations for DR-TB patients. They were followed up for sputum smear and culture conversion, adverse events during the treatment.

Results: A cohort of 290 DR-TB patients (Median age-29.77) were initiated on BDQ containing regimens. Of the available Sputum results, smear conversion was seen in 51% and 91% patients at the end of 1st week and 3rd month respectively. Similarly, 93% and 98% patients had culture conversion at the end of 3rd and 6th month respectively. 201 adverse events (AE) including 47 deaths were reported among 109 patients. QTc prolongation was seen in 29% patients but only 4 required discontinuation of BDQ. Lost to follow up of treatment was about 6%.

Conclusion: Bedaquiline along with an optimized background regimen has shown early sputum conversion in larger number of difficult to treat patients having additional resistance of second line drugs along with INH and Rifampicin. The regimen is feasible in programmatic conditions and is relatively safe.

1. Introduction

India has the dubious distinction of being one of the high burden countries for TB, TB-HIV and MDR-TB as per WHO classification. There are an estimated 79,000 multi drug resistant TB patients among the notified cases of pulmonary TB each year.

Drug Resistant TB can be of various types. Multi Drug Resistant Tuberculosis (MDR TB) is defined as TB resistant to Rifampicin and Isoniazid. Pre-XDR TB is MDR TB with

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resistance to either fluroquinolone or second line injectable drug and Extensively drug resistant TB (XDR-TB), is defined as MDR with additional resistance to a fluroquinolone and second-line injectable agents.

In view of the poor treatment outcomes in MDR-TB patients[1] newer drugs (bedaquiline[2,3] and delamanid[2]) are being tried along with other agents (repurposed drugs[4–6]- linezolid and clofazamine) in order to have better success rates.

WHO recommends the use of bedaquiline for a maximum duration of 24 weeks. Nausea and hepatitis are the most common side-effects associated with this drug. The Revised National TB Control Programme (RNTCP) recommended use of Bedaquiline in 2016 under Conditional Access Programme (CAP). The National Institute of TB and Respiratory Diseases (NITRD) was one of the initial implementing sites under the CAP. The experiences of the Institute in respect of effectiveness and feasibility of Bedaquiline implementation under field conditions and the ADRs and there management are being shared.

2. Methods

As per RNTCP guidelines, the Laboratory confirmed Rifampicin resistant patients from the RNTCP-Bedaquiline implementing area of the Institute (4 million population) were subjected to second line LPA and those resistant to any/all fluroquinolone and/or resistant to any/all second line injectable were considered eligible for Bedaquiline. These patients were referred to the DR-TB review committee for recommending on the regimen based on the Bedaquline guidelines of RNTCP. The Institute is a nodal DRTB Centre for managing such patients under the CAP. Data for 290 patients have been studied.

2.1. *Inclusion and exclusion*

All Eligible patients had a laboratory confirmed diagnosis of pulmonary TB with resistance to Rifampicin and additional resistance to any/all Fluroquinolone and/or any/all second line injectable i.e. preXDR-TB or XDR-TB. Other criteria included: 18 years or older, negative pregnancy test.

Patients with any of the following were excluded: uncontrolled cardiac arrhythmias repeated demonstration of QTc intervals >450ms; heart failure, eye changes such as optic neuritis or uveitis and significant laboratory abnormality relating to kidney function, liver function, bone marrow suppression as pr the DAIDS grading of adverse events. QTc was reported by a calibrated 12 lead ECG machine which gave the reading by Bazett's formula.

2.2. *Treatment initiation and follow-up*

All eligible patients, after pre-treatment evaluation, counseling and consent were discussed in the DR-TB Review Committee comprising of Pulmonologists, Medical Specialists, Microbiologists and Epidemiologists. The Committee designed the optimum background regimen (OBR) to be given along with bedaquline for these patients. These drugs included at least three to four second-line drugs to which the patient's TB had proven susceptibility or likely to be effective from amongst the WHO grouping of drugs, in order of effectiveness. Initiation of treatment was done after hospitalization and the patient was closely monitored with regular ECG and other investigations.

Bedaquiline 400mg was given for first 2 weeks followed by 200mg on alternate days for 22 weeks. Hospitalization was done for minimum of 2 weeks and some time longer as required. Subsequently, patients were referred to their respective DOT sites for continuing the treatment. The sputum cultures, ECG monitoring and blood tests were done as per the Bedaquline guidelines.

Sputum Smear/Culture conversion was defined as two consecutive negative samples taken at least 30 days apart.

2.3. *Monitoring of adverse drug reactions*

The treatment supporter at the DOT centre monitored the adverse events. Some events were easy to recognize and were reported by patients when they experienced them. Few adverse events however, were recognized during routine monitoring and investigations. All treatment supporters at Peripheral DOT centres were trained to screen for adverse events. Treatment supporters were also informed to refer the mild adverse events to Medical Officer at the peripheral facility, and for major events to district or nodal DRTB center.

3. Results

Among the 290 study subjects, 53% were male and 47% were female with mean age of 29.77 years, mean BMI was 22.8 kg/m^2. The male female ratio increased with age (Table 1).

Nearly 80% of the patients were pre-XDR (228/290), and around 20% were XDR (60/290). The individual drug sensitivity pattern showed 73.8% (214/290) were Fluroquinolone resistance, 4.8% (14/290) were Second line injectable resistant and 20.7% (60/290) were both Fluroquinolone and Second line injectable resistance (Table 2). In addition, the DST profile

Table 1 – Demographic characteristics of the study population.

Patient characteristics	N	%
Male	152	53
Female	134	47
Age (years) Median	29.77	
BMI (Mean)	22.8 kg/m^2	
HIV-positive	1	0.3

Table 2 – Drug sensitivity profile of the study population.

classification	No.	%
PRE-XDR	228	78.6
FQ (resistance) only	214	73.8%
SLI only	014	4.8%
XDR (FQ + SLI)	060	20.7
MDR-TB (failure)	002	0.7

from amongst the available reports also indicated a high level of Ethionamide resistance of 84.1% (58/69) and over 83% Pyrazinamide resistance (53/64). Resistance to other second line drugs was less than 2%.

Most of the patients received high dose Moxifloxacin (around 40%), second line injectable (73%), linezolid (90%), Clofazamine (86%), Ethionamide (58%) and Cycloserine (60%). Some patients required in addition other WHO group D3 (currently group C) drugs.

Among the available smear results more than 51% (129/252) were smear negative at the end of first week, 90.9% were negative by 12th week and 98% (175/179) by 24th week. Among the available culture results 93.4% by 3rd month and 97.9%, were culture negative at the end of 6 months.

Of the 47 patients who have expired till date most deaths were in the initial months due to poor general condition (nearly 1/3rd by first month and 50% within two months). Of the deaths nearly 2/3rd were smear negative at their last available result. There were 16 patients who were lost to follow up and 18 patients have been transferred out from the cohort study.

The number of adverse events reported among the study subjects was 201 episodes in 109 patients. 32.8% episodes were mild, 28.3% were moderate and 38.8% were severe adverse events. QTc prolongation was reported in 29.4% (50 patients). QTc prolongation between 480 and 500 Ms were reported in 37 patients and >500 Ms in 13 patients. Bedaquiline was temporarily withheld and reintroduced in 46 patients and permanently discontinued in 4 patients. Most of the QTc prolongation could be addressed by correcting the electrolytes (magnesium, potassium, calcium). The other notable ADRs like neuropathy, eye changes and bone marrow suppression were related to linezolid There were significant coordination issues during treatment in the field conditions in context of follow up investigations (ECG, sputum examination and blood tests) and reporting and management of ADRs.

4. Discussion

Bedaquline is a novel drug which was used for treatment of pre-XDR and XDR TB patients as per RNTCP guidelines under CAP at the National Institute of Tuberculosis & Respiratory Diseases. For the current analysis all patients enrolled from 1st July 2016 to 31st December 2018 were enrolled. A total of 290 eligible patients were enrolled for Bedaquline with optimized background regimen. Majority were in younger age group and male female ratio increased with age. Only one patient was HIV reactive among the study subjects.

Resistance to Pyrazinamide was much higher at 83% as compared to other studies (3–42%).[7] This is important in context of designing the OBR. The OBR of individual patients was designed by the DR-TB Review Committee based on the patient's previous treatment history, exposure to previous anti-TB drugs, drug sensitivity pattern and pre-treatment evaluation reports. The regimen was designed based on National guidelines for programmatic management of drug resistant tuberculosis.

Smear conversion (Table 3) happened early (more than 50% converting within first week and over 90% by 12th week) and similar results were observed with culture. Similar observations have also been reported in other studies.[8] The interim analysis of this cohort of MDR- TB patients receiving bedaquiline shows a culture conversion rates of 96% at 6 months. This was comparable with other patient cohorts.[8,9] The lost to follow up is only around 6% (16/290) which is much less than other studies wherein it has been reported as above 20%.[1,10,11]

The reported adverse events were 201 episodes, (Table 4) with 38.8% serious adverse events. The main safety concern of Bedaquiline is cardio toxicity. Bedaquiline has been shown to prolong the QT interval and the association with other drugs such as clofazamine or moxifloxacin can enhance this effect. Among the serious adverse events, 75.6% had QTc prolongation (Table 5). However, more than 500 Ms was reported in less than 5% (13/290) patients. The QTc prolongation in other studies[12] by Fridericia method is around 10%. The QTc prolongation was detected through routine monitoring with regular electrocardiography. In most cases it was found to be

Table 3 – Smear and Culture conversion of the study population after initiation of treatment.

Period	Smear		Culture	
	Positive	Negative	Positive	Negative
Week 1	123 (44%)	129 (43%)	144 (44%)	90 (29%)
Month 3	18 (6%)	181 (76%)	10 (5%)	142 (67%)
Month 4	12 (4%)	165 (78%)	06 (3%)	139 (62%)
Month 5	07 (4%)	152 (73%)	05 (3%)	117 (57%)
Month 6	04 (2%)	175 (75%)	03 (2%)	143 (62%)

Table 4 – Frequency of adverse drug events grouped by body system.

Reported AE by body system	AE	
	n	(%)
Gastrointestinal	11	5.5
Respiratory	3	1.5
Hepatotoxicity	3	1.5
Peripheral neuropathy	29	14.4
QT prolongation	56	29.4
Neurological disorder/headache	20	10
Cardiac event (includes hypotension)	4	2.0
Ototoxicity	13	6.5
Others	1	0.5
Dermatological	21	10.4
Nephrotoxicity	0	0
Haematological	21	10.4
Musculoskeletal	2	1
Ophthalmologic	14	6.9
Total	201	100

Table 5 – Frequency of QTc values of 480–500 msec, >500 msec and arrhythmia of the study population.

QTc VALUES	No of Patients	No of Episodes
480–500 ms	37	47
>500 ms	13	13

Table 6 – Number of deaths and smear status at the time of death.

Month	No.of Death	Sputum at the time ofDeath	
		Negative	(Positive)
Less than 1 month	06	00	06
1st month	07	04	03
2nd month	07	04	03
3rd month	05	04	01
4th month	03	02	01
5th month	04	03	01
6th month	00	00	00
7th month	03	03	00
8th month	00	00	00
9th month	07	06	01
10th month	00	00	00
11th month	01	01	00
15th month	04	04	00
Total	47	31 (66%)	16 (34%)

related to electrolyte disturbances however it did not result in permanent discontinuation of Bedaquiline. It was temporarily withheld and once the electrolytes were corrected the bedaquiline and other QTc prolonging drugs could be reintroduced. It was permanently discontinued in only in four patients. This is important because most patients received at least one other QT-prolonging drug (clofazamine or high dose moxifloxacin) in addition to Bedaquline. The management of cardio toxicity needed timely ECG, electrolyte testing and correction of electrolytes. Linezolid was also found leading to a large number of adverse events like anemia, thrombocytopenia, peripheral and optic neuritis. The same has also been reported by other researchers.[13,14] Training the treatment supporters in recognizing the commonly occurring adverse reactions and referring the patient to appropriate treatment facility providing timely action can lead to greater adherence to treatment and reduction in loss to follow-up. There are 47 (16.45%) deaths reported in the study (Table 6), most of these were due to poor general condition at the onset of treatment. This was comparable to the 13% deaths reported by Diacon et al.[15] Most deaths (53%) happened in first three months of the treatment. More than 2/3rd (66%) of all deaths were culture converted before dying, reducing the risk of spread of Pre-XDR/XDR TB.

Regular training for all levels of health personnel including treatment supporters is important in management of MDR/XDR TB.

5. Conclusion

This study concluded that regimens containing Bedaquiline are effective as they lead to early smear and culture conversion. Adverse reactions do occur with these regimens but are manageable. Implementation in the field is feasible however it requires strengthening of infrastructure in terms of training the peripheral staff for early identification and management of common adverse drug reaction and making ECG and electrolyte testing available. Also needed is developing coordination and linkages mechanisms for timely referral and management of adverse drug reactions.

6. Limitations

This was an observational study conducted under programmatic conditions hence data was not collected under research mode and some of the information was not available under field conditions. Data relating to adverse drug reactions though available but may be deficient. Similarly cause of death is not known for patients who died at home. It is known only for the patients admitted in the hospital at the time of death.

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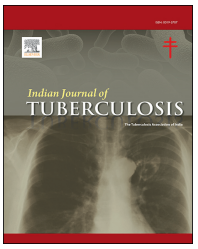

Original article

Emerging treatment trends in pediatric TB

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ABSTRACT

The WHO's End TB Strategy and the United Nations' (UN) Sustainable Development Goals (SDGs) share the common aim to end the global TB epidemic. Specific targets have been set in the End TB Strategy, for the period 2016–2035, which include a 90% reduction in TB deaths and an 80% reduction in TB incidence (new cases per year) by 2030, in comparison with 2015. Globally, though the TB incidence and mortality is falling at the rate of about 2% and 3% per year, by 2020, these figures need to improve to 4–5% per year and 10%, respectively, so that incidence can fall faster to reach the first (2020) milestones of the End TB Strategy[3]. Newer treatment trends have emerged to achieve these targets in children.

Tuberculosis (TB) is the leading cause of morbidity and mortality worldwide from a single infectious agent, Mycobacterium *tuberculosis* (M.*tb*), ranking above HIV/AIDS. According to the Global TB Report 2018, in 2017, out of an estimated 10 million new cases who fell ill with TB, 10% were children. India accounts for about a quarter of this global burden.[1] Furthermore, drug-resistant variants, multi-drug resistant (resistance to at least INH and rifampicin), extensively drug resistant (MDR with resistance to any one of 3 second line injectables SLI (Kanamycin, Amikacin, Capreomycin)and any fluoroquinolone (Ofloxacin, Levofloxacin, Moxifloxacin) TB continues to be a menace even in children in India, posing a challenge and an ever increasing threat to the available TB control srategies, anti-TB drugs and treatment regimens.[2]

The WHO's End TB Strategy and the United Nations' (UN) Sustainable Development Goals (SDGs) share the common aim to end the global TB epidemic. Specific targets have been set in the End TB Strategy, for the period 2016–2035, which include a 90% reduction in TB deaths and an 80% reduction in TB incidence (new cases per year) by 2030, in comparison with 2015. Globally, though the TB incidence and mortality is falling at the rate of about 2% and 3% per year, by 2020, these figures need to improve to 4–5% per year and 10%, respectively, so that incidence can fall faster to reach the first (2020) milestones of the End TB Strategy.[3] Roadmap towards ending TB in children and adolescents has also been laid down as children need to be accorded executional priority and included in the TB control strategies keeping in view their peculiar needs and by appropriate modification of the adult management guidelines maintaining maximum uniformity between the adult and pediatric TB control programme.[4,5] Achieving these targets in India, though a mammoth task for our TB control programme on account of the sheer numbers, requires a well planned consorted multipronged action plan eyeing towards provision of universal health coverage, inclusion of children in TB care and prevention strategies.[6] Rapid diagnosis, prompt effective treatment

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using pre-defined management algorithms and protocols, ensuring compliance under direct observation not only ensures an overall success rate (cure and treatment completion) of >90% in children with pulmonary and extrapulmonary TB patients but also goes a long way into breaking the chain of transmission.[7–9]

Diagnosis of pulmonary TB (PTB) is based on a combination of definite symptoms and signs, contact with an infectious case, a positive mantoux/ TST (tuberculin skin test), a suggestive CxR (hilar/mediastinal Lymph nodes, chronic fibrocavitatory disease or miliary pattern are considered highly suggestive).[10–12] These perlude microbiological confirmation by WHO approved Rapid Diagnostic Tests (WRDT)on sputum or alternative specimens (GA,IS,BAL) depending on age of the patient and availability in the hospital setting.[13,14] Ruling out alternative diagnosis also becomes important in patients with negative WRDTs. Although disease is usually paucibacillary in children and sample collection is difficult but children of all ages do have bacilli in their biological specimens and an attempt should always be made to demonstrate the M.*tb*.[7–9] Advances in TB diagnostics using WHO approved Rapid Diagnostic Tests (WRDT) include Cartridge Based Nucleic Acid Amplification Test (CBNAAT) Xpert MTB/RIF™or Gene Xpert, Line Probe Assay and Liquid culture and Mycobacterial Growth indicator tubes (MGIT).[14,15] These tests have a higher sensitivity, specificity and a faster turn around time than the conventional smear microscopy and solid (LJ) culture. WRDTs are used as priority in diagnosing TB children among presumptive TB cases under the programme. These tools help in labelling a presumptive TB child as either microbiologically confirmed or clinically diagnosed TB. Clinically diagnosed TB includes both probable and possible TB cases, where bacteriological confirmation fails despite using WRDTs and pediatric diagnostic algorithm followed for these presumptives. Therefore, despite these newer WRDTs, which have limited sensitivity in children, clinicians often face diagnostic dilemmas.[16] Treatment in these probable and possible TB cases should only be initiated once the clinician is sure that it is TB. Following up these patients, clinically and/or radiologically, usually resolves most of these diagnostic issues and gives a sort of certainity to the treating pediatrician while initiating treatment, as definitely there is no role of "trial of ATT". This strategy of following up the presumptives limits both over and under diagnosis. Therefore, as a National strategy, Drug Sensitivity Testing (DST) by culture or molecular methods is being used for all retreatment TB cases and in future for all cases at diagnosis, known as universal DST. Also, this has lead to a policy change in the treatment of TB in children. Treatment should be initiated in all these situations. Once the diagnosis is made, treatment is guided by the drug sensitivity pattern of the M.*tb* in microbiologically confirmed cases. In general, in all new cases, whether bacteriologically confirmed, clinically diagnosed, extrapulmonary TB and drug sensitive previously treated cases (failure, recurrent TB, lost to followup for 1 month after taking 1 month of anti-tubercular treatment). Combination chemotherapy is used with each drug targeting a particular bacillary subpopulation, depending upon the metabolic activity, namely the *rapid growers, intracellular slow growers, spurters* in the caseous material and the intracellular *dormant* bacilli.[17] The recent WHO and RNTCP Guidelines recommend at least four drugs in the initial intensive phase (IP) for 2 months Rifampicin (R) 15mg/kg (10–20 mg/kg; max 600mg/day), Isoniazid (H) 10 mg/kg (7–15 mg/kg; max 300mg/day), Ethambutol (E) 15–25 (max 1500mg/day), pyrazinamide (Z) 30–40 (max 2000mg/day) and 4 months of Continuation phase (CP) with HRE.[12,18] This is keeping in line with the WHO Recommendations 2014 of using ethambutol in CP in settings with high baseline Isoniazid resistance or high prevalence of HIV. Contrary to the earlier practice, previously treated cases are offered WRDTs and if found drug sensitive are restarted 2RHZE/4RHE, as category 2 has been withdrawn even in children, in line with the adult guidelines. Moreover, there is no provision of extension of IP and all effort is made at 8 weeks of treatment to confirm drug sensitivity. Also, children with CNS TB (TB Meningitis, Spinal TB) and bone-joint TB should be treated for 12 months (2 months of IP and 10 months of CP) instead of the recommended six month course of therapy for children with other forms of TB disease. Ethambutol, being an oral drug and relatively safe in children except in cases of optic neuritis, is preferred over the injectable streptomycin, should be used for all age groups in cases of TBM under ophthalmological supervision. Daily drug therapy with higher dosages meant a greater pill burden for the child. This led to the introduction of child-friendly dispersible, fruity flavoured, taste masked three drug fixed-dose combination (FDCs) tablets containing rifampin, isoniazid and pyrazinamide in the correct ratios of H:R:Z: 1:1.5:3 of proven bioavailability.[19] Ethambutol being hygroscopic is marketed as a separate dispersible tablet and is given alongside the three drug FDCs. These drugs are given as per 6 weight bands. A child upto 24kg is given all dispersible tablets while adult FDC is added at 25kg and above, assuming that this older child would be able to swallow non-dispersible tablets. Prophylactic and therapeutic dose of Pyridoxine 10mg and 50–100mg respectively is given to all patients. A child moves to a higher or lower weight band if he/she crosses over to another weight band due to any weight gain/loss.[12]

A presumptive DRTB case is any child failing first-line TB treatment despite adherence, relapses, lost to follow up, HIV, contact with a patient on irregular ATT or MDR TB case or death in the family due to TB. The susceptibility results of the index case are helpful in designing the regimen. WRDTs are done on all presumptive DRTB patients. The diagnosis of drug-resistant TB is based on the results of the WRDT. In some DRTB presumptives, bacteriological confirmation is not achieved using WRDTs and the suspicion is high based on their clinical and/or radiological deterioration despite 2 months of adequate ATT, taken under supervision ensuring compliance.[2,20] This problem is more in cases of extra pulmonary MDR, which does exist in children.[21] These are the probable DRTB patients and a call to start DRTB treatment is taken by an authorized DR Committee of that area. But there must be cases who may never be diagnosed or started on therapy.[22] The case definitions, DRTB regimens used in children are essentially the same as in adults. When a child is diagnosed as drug-resistant TB, the pediatrician should always treat such a

child in consultation with a TB expert. The regimens being currently used are as follows:[23]

- Mono-Poly Drug Resistant TB (resistance to INH with or without any non-Rifampicin first line drug resistance): uniphasic regimen of (6) Levoflox R E Z, with a provision to extend to 9–12 mo in extensive pulmonary or severe extrapulmonary disease
- RR/MDR-TB without additional drug resistance to FQ and/or SLI (Conventional Shorter Regimen) for Pulmonary TB, unilateral pleural effusion or isolated lymphnode disease with Intensive phase (4–6) Km Mfx^h Eto Cfz Z H^h E and Continuation phase (5) Mfx^h Cfz Z E
- RR/ MDR-TB without additional drug resistance to FQ and/or SLI (Conventional Standard Treatment regimen) for pulmonary, disseminated or severe extra-pulmonary disease with Intensive phase (6–9) Km Lfx Eto Cs Z E and Continuation phase (18) Lfx Eto Cs E
- Pre XDR – TB/ XDR – TB: (6–9)Cm Lfx/Mfx^h Lzd Cfz CsH^hZ E and Continuation phase 18 Lfx/Mfx^h Lzd (l) Cfz CsE^{24-28}

Children with DR-TB tolerate these regimens better and have better outcomes than their adult counterparts when offered therapy.[2,20] There is increasing evidence regarding the safety of fluoroquinolines in children with DRTB.[29] But Ototoxicity of the second-line injectables kanamycin, capreomycin and amikacin—is a matter of serious concern with almost 25% children developing hearing loss hindering the child's mental and cognitive developmental progress.[30] Recently two new drugs, bedaquiline (BDQ) and delamanid (DLM), which have been used for quite sometime in the treatment of DR-TB in adults with a significant benefit in the treatment success rate and mortality rate,[28] are being recommended for use in children. WHO December 2018 guidelines recommend using bedaquiline (BDQ) and delamanid in children $\geq$6 and $\geq$ 3 years respectively.[28] These drugs are important treatment options in children for injection sparing regimens. Therefore, the regimen being recommended for children in future could be:

- Longer full oral regimen for RR/MDR/PreXDR/XDR: Intensive phase (6–8) (Dlm/Bdq) (6)Mfx^h Lzd Cfz Cs and Continuation phase 12 Lfx/Mfx^h Lzd (l) Cfz Cs to be used in children > 6 years (Bdq to be replaced by Dlm between 6 and 12yrs of age for PTB and isolated lymphnode disease or pleural effusion. In the CP, Mfx^h can be replaced by Lfx if FQ intolerance and dose of linezolid can also be reduced from 10mg/kg to 5–7mg/kg for adverse effects of linezolid.

To conclude, the future appears promising as regards to diagnosis and treatment of both drug sensitive and drug resistant TB in children in an effort to End TB. The use of new drugs in all-oral shorter regimens should make treatment of DR-TB in children safer and more effective.[5] The problem is availability of Child-friendly formulations of most second-line TB drugs, though FDC of first-line drugs are available. Early inclusion of children in drug trials without compromising their safety is the need of the hour.[31]

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