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# Challenges and Opportunities for Programmatic Management of Drug Resistant TB in India

**Yatin Dholakia[1]* and Nerges Mistry[2]**

[1]*Senior Consultant, The Foundation for Medical Research, India*
[2]*Director, The Foundation for Medical Research, India*

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***Corresponding author**

Yatin Dholakia, The Foundation for Medical Research, Dr. Kantilal J. Sheth Memorial Building, 84-A, R.G. Thadani Marg, Worli, Mumbai 400 018, India, Tel: +91 22 2493 4989 / 8601; Email: fmr@fmrindia.org



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## Abstract

Programmatic Management of Drug Resistant TB in India faces stiff contemporary challenges as evinced from four recent publications highlighting high treatment failure and death rates.

The challenges and suggestions for their remediation have been tackled herein, through the themes of amplified drug resistance findings, the strategy to take drug resistant TB (DR – TB) treatment to peripheral health facilities; caring for the wider needs of DR – TB patients and understanding patient behavior.

The strengthening of laboratory infrastructure and competencies is strongly recommended. Technology, both biomedical and epidemiological, is required to design empirical and locally relevant backbone drug regimens. Skills for ground level management of DR – TB, including adverse drug reactions (ADR), need to be rapidly developed and deployed. Programmatic management needs to focus on "care" as much as on "cure".

## Introduction

In line with WHO's END TB Strategy to end TB by 2035 [1], India's National Strategic Plan 2017 – 2025 [2] envisions the country to become a TB free nation targeted to a fast approaching 2025, ten years ahead of the WHO's target. Among the 2.8 million estimated incident TB cases, 130,000 MDR TB cases are estimated annually for India [3]. This figure 1 may be an underestimate, with gaps in diagnostic services and notification. The Revised National TB Control Program's (RNTCP) proposed Programmatic Management of Drug Resistant TB (PMDT) in 2007, is to be implemented in a phased manner. The program had adopted the strategy in 2014 to test for resistance to Rifampicin (RMP) and Isoniazid (INH) to identify multi drug resistant TB (MDR TB) and introduced a standard treatment regimen for managing the cases [4]. This introduction was a welcome one for individuals with drug resistant TB who, hitherto, had to depend on the private sector or nongovernmental organizations for access to the expensive and prolonged treatment and other support [5].

Programs tend to discuss shortcomings in the confines of their structures and rarely publicly. Four recent publications which included patients from RNTCP [6-9] are therefore a refreshing change from the oft perceived denial, and bring to the foreground various issues that are exigent. Figure shows the sites from where the treatment outcomes are reported. (Hereinafter these studies are referred to as basal studies).

Chhadha and colleagues described operational challenges in the diagnosis and treatment of MDR TB in the state of Andhra Pradesh [6]. A significant number of probable DR TB cases were missed by the program staff; of those identified one fourth of patients refused to undertake investigations, and of those diagnosed with DR TB, 34% did not start treatment.

In an analysis from the three states of Kerala, Delhi and West Bengal, Nair and colleagues studied the predictors of unfavorable outcomes [7]. Death, and lost to follow up, contributed to nearly 40% of the outcomes. The median delay in initiating treatment, after diagnosis results were made available, was a lengthy period of 70 days.

Suryavanshi and colleagues analyzed outcomes for the state of Maharashtra [8]. The results are not dissimilar to those reported by Nair et al.

In a recent report, Malik Parmar and colleagues acknowledge poor treatment outcomes viz. low treatment success, high case fatality and lost to follow-up in a large cohort from 15 DR TB centres across seven states, from across the country, [9]. Various issues that may have led to the poor outcomes of these cases (viz. existing high levels of resistance, non availability of universal DST to TB drugs, standardized treatment regimens, centralized DRTB services leading to inadequate case management, poor understanding of patients' needs and priorities, undernutrition and other issues) are discussed herein.

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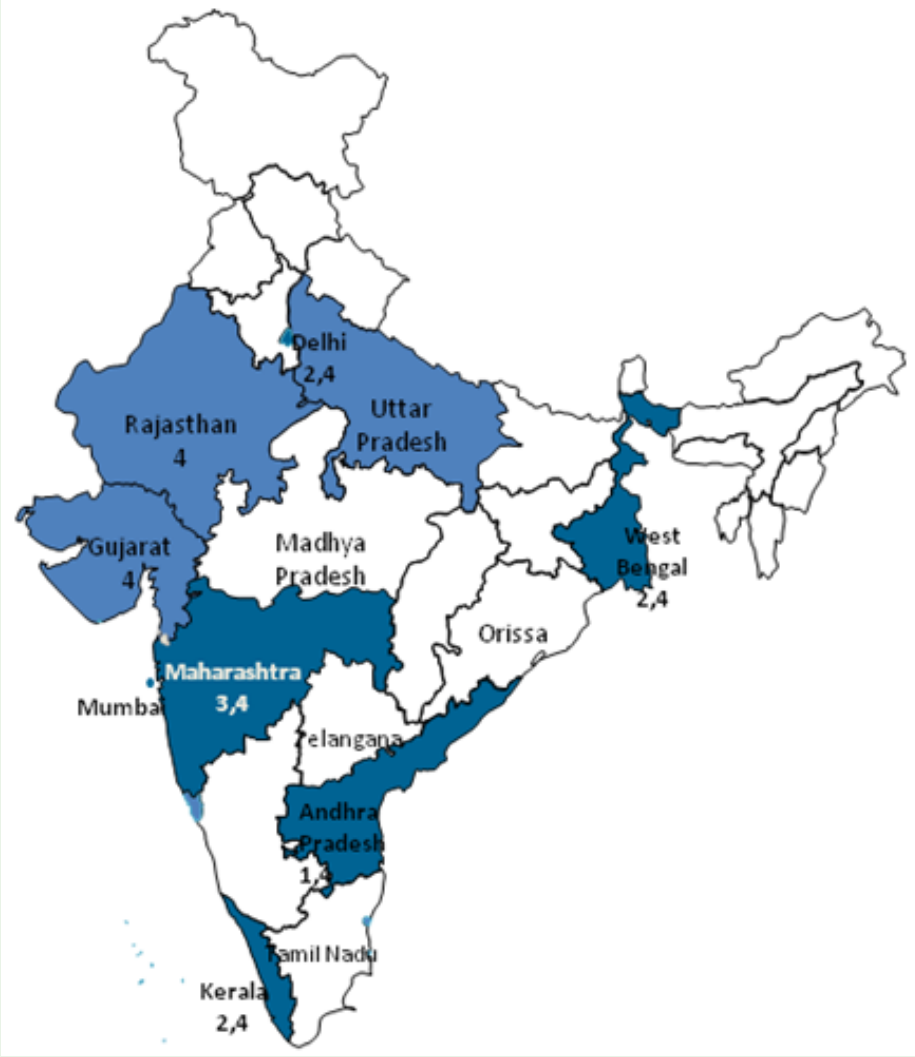


**Figure 1:** Map showing sites reporting DR TB treatment outcomes. (1) Chadha et al. 2011 [6]. (2) D Nair et al. 2017 [7]. (3) Suryavanshi SL et al. 2017 [8]. (4) Parmar M et al. 2018 [9].

## High Levels of Amplified Resistance

The last decade and a half has witnessed a large volume of data being published on drug resistance levels in Mumbai, primarily due to the fact that the metropolis has the laboratory and technological capacity to undertake such studies.

Even as early as 2005 – 2008 D'Souza et al, while reporting 24% primary MDR, noted that only 4% were pure MDR (resistant to RMP and INH alone), with another 20% of strains showing additional resistance to the other two first line drugs viz Ethambutol (EMB) and Pyrazinamide (PZA) [10]. By 2013, a perceptible shift of the DR TB profile from MDR to pre XDR and XDR was noted in the studies of Alpa Dalal and Ganatra and colleagues [11,12]. Additionally, Dholakia and colleague reported that 45% of DR TB cases under treatment had resistance to at least one second line drug [13]. The recent results of national drug resistance survey also reported high levels of resistance to both first and second line TB drugs in both new and retreatment cases [14].

The amplification evolution of the drug resistance profile in Mumbai, and the rest of the country, is a good rationale for the implementation of the downstream algorithms recently developed for PMDT [15]. These rely on cartridge based nucleic acid amplification test (CB NAAT) – XpertMTB- Rif test, line probe assay (LPA) and liquid cultures to provide diagnosis of DR TB and its patterns. A continuing feed of data from National Reference Laboratories (NRLs) and Intermediate Reference Laboratories (IRLs) would be able to discern dynamics of drug pressures in different locations to inform prescribing patterns, provided that the analysis of the drug resistance patterns is undertaken in real-time and made use of rapidly for designing of appropriate drug regimens.

Attempts have been made recently to design regional empiric regimens for the treatment of MDR cases in India. The Technical Advisory Group of WHO [16] devised a targeted regimen profile for managing MDR TB in areas where point of care diagnosis of drug resistance is yet to be introduced. Such a "pan TB" regimen could

be used empirically without delay and it is recommended that such a regimen would include four new TB antibiotics to which the patient has not been exposed excluding RMP, INH and PZA. In a selected cohort from a private tertiary care hospital, Mullerpatan and colleagues [17] attempted, for the first time, to develop a model to design an empiric regimen for MDR TB cases in Mumbai. They found high levels of resistance to both EMB and PZA: 77% and 83% respectively, in addition to resistance to the remaining ten anti TB drugs in the presence of RMP resistance. They concluded that drugs such as EMB and PZA could not be recommended in the management of MDR TB. The standardized treatment for MDR TB currently being followed by the national TB control program, i.e. continuing EMB and PZA in addition to only four second line drugs, is therefore likely to fail.

The RNTCP has yet to implement the Universal DST and tailored treatment of DR TB guidelines, which were developed at a national level workshop in 2014 [18]. This is due to a shortage of DST laboratories, and subsequently a lack of data and unknown local patterns of drug resistance, with a consequent ill constructed drug regimen. As a result, patients being treated under PMDT and not responding to the standard treatment have to wait up to a full six months to get second line DST and be declared failures of Cat 4 [19]. A rapid implementation of the recommendations is highly desirable in the patients' interest of timely and ethical care [20]. The implementation of tailored treatment also implies that concurrent and elaborate planning is needed for the supply chain management of drugs, to avoid the undesirable scenario of drug stock outs.

## Taking Treatment to the Periphery

Management of DR TB is perceived to be a specialized intervention by policy makers and program managers. This has resulted in concentration of knowledge and authority to manage DR TB at the central level. Decentralized care for MDR TB on the other hand has been shown to improve treatment adherence, treatment outcomes and lowering of catastrophic costs to patients, but has less significant impact on deaths and adherence to treatment compared to centralized care [21]. In public health terms, decentralized treatment and care would also minimize DR TB transmission due to reduction in frequent travel to distant centers [22] and encourage surrounding communities to actively seek care sooner rather than later. Thus there is an urgent need to decentralize quality service delivery for DR TB to the peripheral health facilities to improve access. This will require strengthening of infrastructure, capacity building of various staff cadres involved in prescribing and supporting treatment, establishing efficient communication systems between the central and peripheral functionaries and also ongoing regular supportive supervision. Perceptions of the community in seeking care for DR TB in their vicinity, and the quality of service delivery at such local centers, are therefore areas worthy of study.

A model e- platform, developed along the lines of The European Respiratory Society-World Health Organization Tuberculosis Consilium, would facilitate case management at the peripheral facility, ensure continuum of care in case of migration and assist DR TB cases in requesting specific care [23]. A similar program - the ECHO platform [24] has been initiated in the national capital. This is a web based program that supports the various district public health doctors on case management through prescheduled weekly interactions between providers and groups of expert clinicians. Additionally the identification of DR TB "hotspots" through a visual surveillance system could help to plan for the scaling up such services in areas where such virtual treatment and management skills need to be located.

## Catering to and Understanding the Needs of Patients

Although there is a shift in TB treatment from inpatient management to ambulatory care, there are times when individuals may need to be hospitalized, especially for managing adverse drug reactions or complications. While there is no data to support this, the paucity of dedicated beds at the district and peripheral level is sorely perceived. There is an urgent need for the district and rural/ block level hospitals to be equipped to manage such situations- both in terms of medical and paramedical manpower, as well as the availability of investigation facilities, biosafety measures and other infrastructure. The Mumbai initiative of identifying private facilities for these services needs to be lauded and accelerated with the provision of adequate and timely funding (personal knowledge of authors).

One would expect treatment to be initiated soon after diagnosis. However, it took 40 to 70 days for patients to start treatment in the four states, as reported in the basal studies [7,8]. Even if one considers the pretreatment evaluation time, this period is excessively extended and poses an increased risk for transmission to naïve exposed individuals. This duration is in contrast with another study from Mumbai, where treatment was reportedly started on the same day of receiving the DR TB diagnosis [25]. A plausible reason for this divergent finding could be that the private sector initiated treatment on receiving the DST reports and simultaneously performed the relevant evaluations, whereas the program waited for the pretreatment evaluation to be completed before initiating treatment. Further analysis is needed to validate these findings.

One of the basal studies [6] reported that nearly 45% of cases suspected to have MDR TB did not have the requested investigations performed, and that 34% diagnosed DR TB cases refused to take treatment [6]. The plausible reasons for this could be related stigma, gender disparity in access to care, pressing personal priorities, and other, ill understood issues. Studies towards understanding why patients refuse to undertake investigations and initiate treatment need to be initiated, so as to achieve better uptake of program services, especially with the availability of need based and responsive counseling.

In the study from Maharashtra [8] and the 15 DR TB centres across seven Indian states [9], a large number of cases (49%) initiated on second line medicines were lost to follow up in the first three months. This is the period during which patients on second line medications typically experience drug related adverse events / reactions. Training of doctors in the management of adverse drug reactions (ADR), and the provision of drugs to manage ADRs at the facilities managing DR TB, would prevent drop outs. Counseling, both before starting treatment and ongoing periodically throughout the treatment schedule, helps to improve coping mechanisms both to minor side effects of medicines, psychological disturbances like depression, anxiety and also improves treatment adherence. In the absence of professional counselors, local counseling cadres trained

adequately from within the community could be enlisted to form a trusted support base for patients. Such interventions would go a long way in improving treatment outcomes and making patients compliant in undertaking timely investigations and availing adequate treatment. Besides clinical counseling, services like occupational counseling, re-skilling opportunities would provide motivation and hope to patients in taking ownership for their own care. The Farmer model, successfully implemented in Lima, Peru, achieved good rates of cure in MDR TB patients [26], demonstrating that 'care' of DR TB patients is as important as achieving 'cure'.

It is striking that none of the basal studies reported on extrapulmonary drug resistant TB and children with DR TB. This could reflect program priorities and reach. Diagnostic facilities for both these have been seriously lacking and need to be developed with concurrent availability of drug formulations for children, if the issue of DR TB is to be tackled in totality.

The other unfavorable outcome quoted [7-9] was death, with rates of 15%, 19%, 17% 21% and 28% in the states of Kerala, Delhi, West Bengal and Maharashtra respectively and the 15 DR TB centres across seven Indian states respectively. That most of these deaths in Maharashtra occurred in the continuation phase is surprising. Deaths were more common amongst people with low body weights, pulmonary disease, and with HIV co infection. It is, however, surprising that 32% of deaths occurred in cases initiated on treatment within fourteen days of diagnosis as against 24% whose treatment was initiated after 15 days of diagnosis [8]. More in depth studies into the cause of deaths need to be carried out. Verbal autopsies or death reviews by trained personnel or experts respectively on all deaths in PMDT at multiple sites would yield vital information as to the causation, for better management. Some of the plausible causes could be extensive disease due to late diagnosis with resultant cardio – respiratory compromise, severe unrecognized adverse drug reactions, and infection with highly virulent strains of Mycobacterium tuberculosis [27,28], which would call for studying the strain characteristics and unrecognized co morbid conditions. The NSP [2] has tried to address the issue of late diagnosis through active case finding among at risk populations, and creating a need in the community, through awareness programs and engagement of TB champions.

Recent years have rightly seen a growing focus on the role of nutrition in the treatment of TB, which has been relatively underplayed previously. That deaths and poor outcomes are more common in individuals with low body weights underscores its importance. Bhargava [29] has called poor nutrition both an unrecognized driver of the TB epidemic and an important co-morbidity. Malnourished MDR TB patients are more likely to have advanced disease, experience side effects and increased risk of death [30]. Well designed, effective and region specific nutritional diets need to be incorporated in treatment programs. Only recently, the government has announced a direct benefit transfer of money to support nutrition for DR TB cases [2,31]. Although this will help in meeting some of the food expenses during the treatment, efforts of far greater magnitude are needed to prevent these cases from falling back into the cycle of under / malnutrition.

## Introduction of New Drugs and Regimen

Two new drugs – Bedaquiline (BDQ) and Delaminid have been investigated and proved to be effective in the treatment of tuberculosis. Although India has prepared guidelines [32] for use of BDQ through conditional access, the national program reported only 207 cases having received this drug as of December 2016 [3]. By September 2017, 691 cases had received BDQ, including those who received it on compassionate grounds earlier (personal communication – Mullerpatan JB). With the current thrust of strengthening diagnostic capacities, more patients are likely to avail of this new drug. These facilities could identify an ideal drug backbone to BDQ and provide information on basal levels of BDQ resistance in the region. In certain places, like Mumbai, due to the high levels of resistance encountered, the difficulty to identify a suitable backbone regimen has been of grave concern. The presence of specific resistance associated mutations ascertained in circulating strains, through TB genome sequencing, may provide evidence for continuing use of conventional drugs at higher concentrations in contrast to the lower doses that show phenotypic resistance [33]. Notwithstanding these deficiencies, the recent judicial activism has pushed the program to initiate more cases on this new drug [34]. Pharmacovigilance and management of ADR require expertise which India needs to build rapidly if this drug is to be effectively used and development of resistance prevented. Resistance to BDQ has been documented elsewhere through genotyping and conventional bacteriological tests [35]. India needs to accelerate the use of phenotypic and genotypic technology for BDQ and eventually Delaminid susceptibility testing so as to improve case management. Delaminid, the other new, effective drug, has only just recently been approved for clinical use by the Drug Controller General of India [36].

WHO recommends a treatment regimen of nine months for the management of MDR TB [1]. Results from the STREAM clinical trials have shown favorable outcomes in 78% of cases on nine month treatment, as compared to 80% in MDR TB cases taking the 20 to 24 month treatment. It is postulated that results of the nine month treatment will be better than those of 20 – 24 months treatment under program conditions, given that there will be greater compliance [37]. India is in the process of adopting this regimen in PMDT. Faiz Ahmad and colleagues [38] performed aggregate data meta analysis and studied individual patient data, to identify the effectiveness of such shorter regimens for MDR TB treatment. They have cautioned against the extrapolation of the high treatment success rates to its introduction in programmatic settings in less selected populations, particularly in the absence of DST to key drugs. A recent study from a private clinic in Mumbai reported that from 230 participants screened using XpertMTB- Rif test, LPA and phenotypic tests, only a third were found to be eligible for the short course DR TB regimen [39]. The National Strategic Plan 2017 – 2025 is expected to provide universal DST for all cases of tuberculosis [2]. However, the processes are painfully slow and the program has yet to identify laboratories which will be able to provide these services on a sustainable basis. Shorter regimens should be applied only when there is adequate capacity for a reliable DST proximal to patient location. In the presence of amplified resistance to various drugs [14], unless universal DST is available, initiating patients suspected as MDR TB on a baseless drug regimen with reliance on the XpertMTB- Rif test alone, will only add fuel to the already raging DR TB fire.

Areas with high rates of amplified resistance highlight the dire need of rapid gene-based technologies that not only forecast multi drug resistance but also provide rapid identification of drugs that can be applied for effective treatment. The time gap between a sample being obtained and its results being available to the physician, often leads to drop out of patients from accessing care, and may enhance resistant disease transmission. Currently, whole genome sequencing (WGS) provides the means to accomplish this with a minimal turnaround time of eight to 48 hours, with tested computational software such as Mykrobe Predictor and PhyResSE [40,41]. The commissioning of six WGS sites in India by the RNTCP is a welcome start that needs to be followed up, with respect to strengthening of technical capacity, handling of big data and above all its applicability to patient treatment.

## Conclusion

In conclusion, India's National Strategic Plan 2017 – 2025 [2] envisions a TB-free India, with elimination targeted to a fast approaching 2025. The plan is formulated in line with the WHO's END TB Strategy [1] with an aim to reduce TB deaths by 95% and incidence rates by 90%, compared to those in 2015, and eliminate catastrophic expenses to the affected population – ambitiously ten years ahead of the WHO vision. Notwithstanding whether this goal is reachable (especially with relatively less focus on the challenging multisectoral preventative approaches of infection control, environmental pollution regulation etc [2]), India needs to address the multiplicity of issues involved in DR TB management discussed here strategically and expeditiously. Not that any one issue is less important, but the issues to be prioritized foremost are: (a) strengthening diagnostic laboratory infrastructure and quality; (b) the creation of a reliable visual information and epidemiological base from all parts of the country (this should include drug resistance patterns and TB strain surveillance allowing formatting of appropriate regimens); (c) providing projections for an efficient, non-interrupted drug supply, and the tracking of local epidemics of drug resistant tuberculosis to minimize transmission; and (d) upskilling of distal workers in DR TB management, and increasing ground level support networks to enable patients to complete the last mile of their treatment. While much has been done by the RNTCP in recent years, there are still miles to go before a TB free India can be realized.

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