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Narrative Reviews

National TB elimination programme - What has changed

Ashwani Khanna a, Rumpa Saha b,*, Nadeem Ahmad b

a Government of Delhi, India
b Department of Microbiology, University College of Medical Sciences & GTB Hospital, Dilshad Garden, Delhi, 95, India

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A B S T R A C T

Background: Before the start of Coronavirus (COVID-19) pandemic, TB was the leading cause of death due to a single infectious agent, ranking well above HIV/AIDS. Almost one-fourth of the world's population is infected with M. tuberculosis. TB is curable and preventable. About 85% of people who develop TB can be successfully treated with drug regimens of 6 months. Universal health coverage (UHC) is necessary to ensure that all those with the disease can access these treatments. Research breakthroughs (e.g., newer rapid diagnostic techniques, drugs, newer vaccine) are needed to rapidly reduce the number of new cases each year (TB incidence) worldwide.

Objective: Changes in the National TB Elimination Programme since its inception.

Content: The Government of India launched the “National TB Programme” in 1962 as District TB Centre model involved with BCG vaccination and TB treatment to fight tuberculosis, a major public health problem. The tuberculosis control programme has come a long way since then and has undergone major changes over the past few years The Ministry of Health and Family Welfare has developed the “National Strategic Plan” for Tuberculosis Elimination (2017–25) which encapsulates the bold and innovative steps required to eliminate TB in India by 2025, five years ahead of the global targets. By 2020 it was clear that the NSP 2017–25 will not be able to meet these objectives, so another new NSP India 2025 had been launched in 2020. India has been actively involved in TB control activities for more than 50 years now. TB still continues to be a severe health problem in India. The country is now better prepared to tackle TB than before. It now has advanced and effective interventions and technologies for diagnosis, treatment and care of TB cases.

The Government of India (GoI) launched the “National TB Programme (NTP)” in 1962 as District TB Centre model involved imparting BCG vaccination and TB treatment to fight tuberculosis, a major public health problem. The “Revised National Tuberculosis Control Programme” (RNTCP), based on the internationally recommended Directly Observed Treatment Short-course (DOTS) strategy, was launched in 1997 and expanded across the country by 2006. In the year 2007, GoI introduced the “Programmatic Management of Drug Resistant TB” (PMDT) to combat the threat of drug resistance and subsequently achieved full geographical coverage by the year 2013. RNTCP is in line with other health sector strategies and global efforts, such as the ‘National Health Policy 2017’, World Health Organization’s (WHO) ‘End TB Strategy’, and the Sustainable Development Goals (SDGs) of the United Nations (UN).

The tuberculosis control programme has come a long way since then and has undergone major changes over the past few years. Much effort is being made to make the program more patient-centric and provide comprehensive treatment care and support. The Ministry of Health and Family Welfare (MoHFW) has developed the “National Strategic Plan” for Tuberculosis Elimination (2017–25) which builds on the success and lessons learnt from the last NSP and encapsulates the bold and innovative steps required to eliminate TB in India by 2025, five years ahead of the global targets.

1. National Strategic Plan 2017–2025

This plan was launched in 2017 by the MoHFW, Government of India which sets out how the government proposed to eliminate TB in India describing the activities and interventions that would bring about major and effective changes in the incidence, prevalence and mortality from tuberculosis. This is in addition to what was already practiced.

The goals under NSP 2017–2025 are:

- Improving and expanding early detection in TB & testing drug resistance in TB.
- To correctly treat TB to prevent any emergence of drug resistance and thus cut the chain of transmission.

* Corresponding author.
E-mail addresses: drashwani.khanna@gmail.com (A. Khanna), rumpachatterjee@yahoo.co.in (R. Saha), nadeemahmad411@gmail.com (N. Ahmad).

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WHO-India has also identified the need for continuous surveillance, communication across states and UTs. In addition to all these things, resistant TB, laboratories, TB infection management, and advocacy and surveillance, knowledge management, implementation research, drug-resistant TB, and undiagnosed TB in high-risk populations.

WHO-India is also preparing to implement Project GATIMAN to enhance TB care from private practitioners reaching for patients who are seeking TB care from private practitioners. By 2020 it was clear that the NSP-2017–25 will not be able to meet these objectives, so a new NSP India 2025 was launched in 2020.

2. National Strategic Plan India 2020–2025

NSP India 2020–2025 identifies a number of goals which still need to be carried out for the elimination of TB from India. This plan intends to accelerate the national response to TB.

The recommended actions included:

- To mount a TB elimination campaign inspired by lessons gained from the eradication of Polio;
- Provide top priority reinforcements to the existing workforce;
- Scale up private provider engagement;
- Changes in approach from passive community involvement to full community participation and ownership;
- Investment in TB surveillance staff and systems for accurate, complete and timely information;
- Deployment of new precision diagnostic tools;
- Support patients comprehensively throughout treatment;
- Redesign and pursue targeted active case finding;
- Deploy and evaluate ambitious plans to implement TB preventive treatment in household and other close contacts, children, People living with HIV (PLHIV) and other locally defined 'high risk' groups, using new and short regimens.

3. Tuberculosis (TB) Mukt Bharat Abhiyaan

The MoHFW along with various development partners of the Health Ministry launched the Tuberculosis (TB) Mukt Bharat Abhiyaan in 2021 under the NSP India 2020–25 for TB Elimination in a major mission activity for ending the epidemic of TB by 2025. It is a multi-dimensional approach which aims to detect all TB patients and emphasizes on reaching for patients who are seeking TB care from private practitioners and undiagnosed TB in high-risk populations.

To achieve the ultimate goal of a TB Mukt Bharat (TB-free India), WHO-India is also preparing to implement Project GATIMAN to enhance technical assistance in the areas of public-private partnership, TB surveillance, knowledge management, implementation research, drug-resistant TB, laboratories, TB infection management, and advocacy and communications across states and UTs. In addition to all these things, WHO-India has also identified and adopted 100 difficult-to-reach, and neglected districts for ending TB in India.

Before the start of coronavirus (COVID-19) pandemic, TB was the leading cause of death due to a single infectious agent, ranking well above HIV/AIDS. Almost one-fourth of the world’s population is infected with *M. tuberculosis*. TB is curable and preventable. About 85% of people who develop TB can be successfully treated with drug regimens of 6 months. Universal health coverage (UHC) is necessary to ensure that all those with disease or infection can access these treatments. The number of people acquiring infection and subsequently developing the disease (and thus the number of deaths caused by TB) can also be reduced through multisectoral action to address TB determinants such as poverty, under and malnutrition, HIV infection and smoking. Some countries have already reduced their burden of TB disease to fewer than 10 cases and less than 1 death per 100,000 population per year [1].

The estimated number of MDR and XDR-TB cases to have been put on treatment as per the global TB report was 4 per 100,000 and 1 per 100,000 population, respectively [1]. During the pandemic, a significant reduction was observed in the total number of drug resistant TB (DR-TB) patients who were started on treatment as compared to 2019. In 2020 and 2021, there was a reduction of 14% and 9% in the number MDR patients put on treatment. Higher reductions were also seen in the number of XDR-TB patients being started on treatment in 2020 and 2021 [4].

4. Epidemiology of India

Data from India shows that despite the consistent use of masks by the general public, only a brief decline was seen due to delay in seeking diagnosis for TB around the months corresponding to India’s two major COVID-19 waves, the numbers had actually reclaimed. Accordingly, 2021 witnessed a 19% increase from the previous year in TB patients’ notification—the total number of new and relapse TB patients notified during 2021 were 19,03,415 compared to 2019 [4].

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5. Deterrents to elimination of TB

TB control faces the following daunting challenges in India:

- Decades of unrestrained transmission left hundreds of millions of Indians with latent TB infection, which may re-activate at any time. A significant proportion of the population is undernourished (35% of adults and almost half of children in India) [5], which weakens immunity and drives TB reactivation. A considerable number suffer from risk factors for tuberculosis, including diabetes, indoor air pollution from cook stoves, or smoking [6].
- Tens of millions with previous, inadequately treated TB may recur at any time particularly among patients seeking care from private providers, who alone are ill-equipped to sustain their patients on prolonged and adequate treatment. Patients seeking TB care in the public sector have a better chance of treatment but 1/3rd are lost to follow up between care-seeking and successful cure.
- The over populated congested urban conditions plays an important role in facilitating the transmission of the disease. The infectious TB cases spread the disease to their family and community, thereby maintaining the transmission cycle.
- Despite all these difficulties, there are various countries which have consistently shown that TB can be controlled, as long as it is diagnosed early and treated properly. Thereby interrupting the transmission cycle. The overwhelming challenge facing TB control in India remains delayed diagnosis either due to lack of quality rapid diagnostic services or due to lack of necessary expertise.
- India also has a large burden of multi-drug resistant TB (MDR-TB) and extensively drug resistant TB (XDR-TB) most of whom are undetected and continue to transmit the disease; even those who are detected endure long toxic and costly treatments only to have poor odds of treatment success, along with a high number of lost to follow up cases.

6. Advancements in diagnosis

Free of cost laboratory services to patients attending public health facilities and those referred from the private sector has been the...
programmatic ethos since the inception of the tuberculosis program in India. Staying true to its history of ever-increasing spread in both public and private sector and up-gradation to newer diagnostic technologies, by the end of 2021, 80 laboratories are equipped to support liquid culture system, of which 60 are certified for First-Line Liquid Culture Drug Susceptibility Testing (FL LCDST), and 49 are certified for Second-Line Liquid Culture Drug Susceptibility Testing (SL LCDST) [7]. Moreover, Liquid culture-based DST has been expanded to include Linezolid, Clofazimine and Pyrazinamide. Concerning Line Probe Assay (LPA), 74 Laboratories are certified for First-Line LPA, and out of these, 61 are additionally certified for Second-Line LPA [7]. The momentum to improve TB diagnostic services does not end here. The programme division has developed an Annotation tool for interpretation of the LPA results through Machine Learning (ML). Moreover, besides the 19 NABL accredited laboratories till 2021 under the NTEP, in 2022, 15 additional laboratories have been accredited with the NABL [7]. The Microbiology laboratory plays an active role in all diagnostic modalities, drug sensitivity testing as well as in accreditation of laboratories and notification to health authorities.

Identifying people with a high probability of having active TB in the early course of the disease is very important for breaking the transmission cycle. To achieve this, it is essential to reach the unreached and targeted groups through Active case finding (ACF) for early detection of TB cases and initiating treatment on time. In India, ACF has been comprehensively regulated across all the States/UTs since 2017. In January 2021, an important campaign was started for active case finding (ACF) for early detection of TB cases and initiating treatment on time. The programme division has developed an Annotation tool for interpretation of the LPA results through Machine Learning (ML). Moreover, besides the 19 NABL accredited laboratories till 2021 under the NTEP, in 2022, 15 additional laboratories have been accredited with the NABL [7]. The Microbiology laboratory plays an active role in all diagnostic modalities, drug sensitivity testing as well as in accreditation of laboratories and notification to health authorities.

Table 1

| Test             | Sensitivity (all patients) | Sensitivity (SS patients) | Sensitivity (SS+ patients) | Specificity (all patients) |
|------------------|---------------------------|--------------------------|---------------------------|---------------------------|
| Truenat          | 0.73                      | 0.91                     | 0.37                      | 0.98                      |
| MTB              | 0.80                      | 0.96                     | 0.46                      | 0.97                      |
| MTB Plus         | 0.84                      | 0.88                     | 0.67                      | 0.95                      |
| MTB-RIF Dx       | 0.73                      | 0.91                     | 0.37                      | 0.98                      |

Now there is a shift in approach to diagnosis of TB from conventional microscopy to molecular techniques, thus increasing sensitivity from 65% to 85%.

**TrueNat MTB and Rif Plus** - The TrueNat™ (Molbio Diagnostics, Goa, India) testing system is a rapid test which uses portable, battery-operated devices to rapidly detect *Mycobacterium tuberculosis* complex bacteria (MTBC) and rifampicin resistance even in peripheral laboratories with minimal infrastructure.

Based on a review of the data shown in Table 1, WHO recommends use of TrueNat MTB or MTB Plus on sputum specimens as the initial diagnostic test for TB rather than smear microscopy or culture in adults and children [8].

**CBNAAT** - Cartridge based nucleic acid amplification test (CB-NAAT/ GeneXpert) is an automated cartridge-based molecular technique. It can detect *Mycobacterium tuberculosis* as well as rifampicin resistance within 2 h and has been endorsed by WHO as an initial diagnostic test in children suspected of having tuberculosis both in pulmonary and specific forms of extra-pulmonary tuberculosis as well as in adults and children with HIV and suspected of having TB or MDR-TB. The utility of CB-NAAT testing for TB is now expanded to all other types of extra-pulmonary samples in pediatric patients.

The disadvantages of CB-NAAT test include a stable electrical power supply requirement, temperature control and calibration of instrument annually. Sufficient measures must be taken so that power supply remains uninterrupted (with additional batteries, a generator or solar panels), cartridges must be stored at the recommended temperature range (2–28 °C), and the equipment itself between 15 °C and 30 °C. Irrespective of all these disadvantages, Xpert MTB/RIF remains a very important tool because of its definitive, rapid results, and high sensitivity and specificity.

**Line Probe Assay** (LPA) is a rapid technique based on polymerase chain reaction (PCR) that is used to detect *Mycobacterium tuberculosis* (MTB) complex as well as drug sensitivity to rifampicin (RPM) and isoniazid (INH) through the Revised National Tuberculosis Control Programme (RNTCP) of India. It is used to diagnose drug-resistant TB under programmatic conditions [9]. Only sputum samples that are smear positive for acid-fast bacilli (AFB) are tested by LPA.

7. Newer diagnostic modalities

**Whole genome sequencing (WGS):** WGS provides a comprehensive review of the entire Mtbo genotype with a 96% concordance for culture-based sensitivity testing [9a]. It provides genotypic sensitivity to most drugs required for treatment of MDR-TB [9b].

**Computer aided detection for chest radiographs:** Given the limitations, in terms of time, cost and infrastructure, it has become clear that there need to be affordable, accessible methods of screening available in high-burden areas to assist with risk stratification for allocating further testing. One such proposed method is the use of computer software to digitally interpret chest radiographs, and assign a score indicating the likelihood of TB. The most commonly studied software is CAD4TB, currently on version 6. When compared with NAAT, CAD4TB has been shown to have 90–100% sensitivity, and 23–45% specificity at detecting TB disease [9c].

8. Diagnostic dilemmas

Rapid, sensitive, accurate and portable diagnostic techniques are the mainstay of modern-day medicine. There have been important developments in the diagnostic devices for tuberculosis like CB-NAAT, LPA, however, these are expensive, often prone to error, lack the necessary sensitivity or accuracy and not sufficiently portable and thus not applicable in the remote, rural areas, where they are most needed.

Diagnosis is done by a combined use of molecular detection methods, culture and microscopy. These methods however, have known limitations such as, being less effective in individuals with latent infection, and in children unable to produce significant sputum containing *Mycobacterium tuberculosis*. Furthermore, these methods often require a steady supply of electricity, well-trained personnel which are seldom available in the often-under-resourced laboratories in low- and middle-income countries (LMIC) [10].

In terms of diagnosing extrapulmonary TB, diagnosis often remains the same as with pulmonary or latent TB, though it is often combined with the use of invasive biopsies taken from the suspected site of infection [1]. Diagnosis of EPTB is difficult due to the pauci-bacillary nature of the disease, variable clinical presentation, need for invasive procedures to secure appropriate sample, and lack of appropriate laboratory facilities in the resource constraint settings.

Timely and effective diagnosis for combatting and eradicating TB is at the heart of world health organization (WHO) guidelines [11] where management of latent infections is being considered a key component in the eradication process [12]. There is, therefore, an urgent need to apply
cheap, accurate and rapid diagnostic means to diagnose TB particularly, in rural settings.

**Biomarkers for TB - upcoming prospects** - When an individual is infected with *Mycobacterium tuberculosis*, the pathogen will inevitably activate the immune response of the host leading to changes in host biomarkers. Specific antibodies against the pathogens are the most commonly used host biomarkers diagnostics as they are easy to perform, inexpensive and are available for point-of-care testing (POCT).

More recently, several highly antigenic *Mycobacterium tuberculosis* antigens have been developed for diagnostics with improved sensitivity and specificity than the classical ESAT-6- and CFP-10-based assays such as RV0310c-E and RV1255c-E. Receiver operating characteristic (ROC) analyses have shown that serum IgG against both RV0310c-E and RV1255c-E antigens has better sensitivity and specificity (AUC = 0.8 and 0.808, respectively) in diagnosing MTB compared to ESAT-6 and CFP-10 (AUC = 0.665 and 0.623, respectively) [13].

Apart from these, several other biomarkers like nucleic acids in sputum, proteins such lipoarabinomannan in blood and urine, metabolites in sputum, blood and urine, detection of mycolic acid/lipids in the urine sample are still an ongoing work and it is expected that these will be in place very soon.

As far as drug susceptibility testing for TB is concerned, NAAT and LPA remains the first choice for the detection of DR-TB; liquid culture isolation and doing a LPA DST is the second choice, and the third choice remains liquid culture, isolation, and liquid DST.

**Treatment guidelines:** The present treatment regimen for drug sensitive TB (DS-TB) is of 6 months with 4 drugs for the first 2 months and 3 drugs for the next 4 months (Fig. 1).

However, if a patient is found to be rifampicin sensitive and INH resistant, there is another regimen which is called INH mono and poly resistant regimen, which is of 6–9 months and here INH is replaced by levofloxacin.

For drug-resistant TB, when patients are resistant both to rifampicin and INH, the duration is 9–11 months and this is only given if the patient is found sensitive to levofloxacin, all oral regimens. These two important drugs form the basis of this treatment. So the duration has cut down from a longer 24–36 months’ therapy to 9–11 months.

**Newer drugs:** The development of new TB drugs is finally making progress. Although there are two new drugs namely, Bedaquiline (Bdq) and Delamanid, further new TB drugs are still needed to combat the disease.

The new TB drugs need to provide short, simple, less toxic but still affordable, multidrug regimens for DS-TB, DR-TB, LTBI, HIV-TB and with few drug interactions.

Pretomanid is a nitroimidazo-oxazole developed by the TB Alliance. It can be used for the treatment of both DS-TB and DR-TB. It has shown activity against both latent TB and active TB disease. Pretomanid received US approval for the use in combination regimens with Bdq and linezolid for people with XDR TB or treatment intolerant or non-responsive MDR TB in 2019. Studies for its place in national programme in India are ongoing.

9. **Programmatic management of drug-resistant tuberculosis (DR-TB) in India (PMDT)**

The increasing burden of DR-TB has led to the rapid expansion of Programmatic Management of Drug Resistant Tuberculosis (PMDT) services in recent times. Endorsed by the World Health Organization (WHO) in 2002, India adopted the PMDT services in 2007 and complete geographic coverage was achieved in 2013. Since then, PMDT, a comprehensive document on diagnosis and treatment of DR-TB is updated regularly anticipating the current needs in providing for the DR-TB services.

The WHO recently revised the definition of extensively drug resistant tuberculosis (XDR-TB), who have also defined pre- XDR-TB for the first time, highlighting the seriousness of these forms of TB. XDR and Pre-XDR TB are defined on the basis of resistance to certain key drugs. The WHO had issued an updated interim guidance in 2019 which re-classified anti DR-TB drugs into three categories (A, B, and C). The update was based on evidence of the high effectiveness of levofloxacin/moxifloxacin, Bdq, and linezolid in DR-TB. The PMDT-2021 India update has now officially adopted this new classification. The drugs which form Group-A, are the key pillars on which the new PMDT regimens stand. Since these key pillars have evolved, and the second-line injectable drugs (SLIDs) are given less importance now, these definitions have also been changed appropriately. New definitions for pre-XDR and XDR-TB aim to define more precisely the groups of TB patients who require complex treatment regimens. The (SLID) resistance-based criteria for the diagnosis of Pre-XDR/XDR TB have been removed.

Pre-XDR TB is now defined as Multi drug resistant/rifampicin-resistant (MDR/RR) TB with FQ resistance.

XDR-TB is now defined as Pre-XDR TB with additional resistance to Bdq and/or linezolid. These new definitions are not only expected to lead to better reporting, surveillance and monitoring of DR-TB, but also, stimulate the development of better treatment regimens for these dangerous forms of TB. PMDT-2021 also focuses on the challenges with the available diagnostic modalities for DR-TB in India. All samples that

![Fig. 1. TB treatment regimen.](106)
to the district-specific requirements in coordination with the district administration.

Apart from the current support provided to the TB patient under National TB Elimination Programme (NTEP) like free diagnostics, free drugs and Nikshay Poshan Yojana, there is also a need for augmenting community involvement in meeting India’s commitment to end TB by 2025 and leveraging Corporate Social Responsibility (CSR) activities.

12. Conclusion

India has been actively involved in TB control activities for more than 50 years now. Still TB continues to be India’s most severe health problem. The country is now better prepared to tackle TB better than before. It now holds advanced and effective interventions and technologies for diagnosis, treatment and care of TB cases. The NSP for 2020–25 for TB elimination in India embraces these opportunities to leverage its full potential and proposes transformational changes to TB care service delivery. Over the last National Strategic period, significant gains were made in strengthening the support structures, programme architecture and implementation environment for TB control. This included mandatory notification of all TB cases, integration of the TB programme with the general health services (National Health Mission), expansion of diagnostics services, expansion of programmatic management of the drug resistant TB service, single window service for TB-HIV cases, national drug resistance surveillance and revision of partnership guidelines. However, there is a need to recognize that more needs to be done to drastically reduce the TB incidence in India. The NSP 2017–2025 builds on the success and learnings of the last NSP and enacts the bold and novel steps required to eliminate TB in India by 2025.

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