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REVIEW

Current challenges and future development of India's healthcare system' towards tuberculosis free India – research evidence and programmatic initiatives

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ABSTRACT

Tuberculosis (TB), the single most infectious killer deserves special attention in a focussed manner, to reduce morbidity and mortality. We describe the challenges in the four pillars of TB control: detect or diagnosis, treat, prevent, build and elaborate the success stories, listing out newer and advanced tools like artificial intelligence, whole genome sequencing, clustered regularly interspaced short palindromic repeats based technologies, one health approach and cost effectiveness strategies for an all- round reduction in TB control. Special problems posed by paediatric and extra-pulmonary TB are dealt with. Post TB lung sequalae, reverse zoonosis and behavioural modification that can influence catastrophic costs are explored. Use of molecular and genomic methods of TB detection has revolutionized TB care with increased sensitivity of diagnosis, and timely detection of drug resistance, saving many a precious lives. Undoubtedly, the need of the hour would be shortening TB treatment duration and comprehensive preventive strategies that simultaneously decrease both the incidence and prevalence of TB. The various schemes and initiatives undertaken by the Government of India including the Pradhan Mantri TB Mukt Bharat Abhiyaan – "TB free India" stand as a unique solution in the wake of eliminating TB. India has been extending its success stories to other countries as well, by creating platforms for multilateral research and multinational implementation. This manuscript gives a concise and comprehensive outlook of process involved in TB elimination, amalgamating the research evidences with the programmatic initiatives, enlisting the existing challenges, envisaging the current achievements, providing a road map for TB elimination.

Key Words: TB programme; NTEP; TB; mycobacteriology; ATT

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Introduction

Tuberculosis (TB) has regained its status as the single most infectious killer after the COVID-19 pandemic[1] globally with, 7.5 million new cases of tuberculosis were diagnosed in 2022, with a little over half of these cases affecting the male gender and 12% contributed by the paediatric population as per the World Health Organization (WHO) report 2023. Tuberculosis accounted for 1.3 million deaths and 4.1 Multidrug Resistant Tuberculosis (MDR-TB) patients[1]. India accounted for 23,58,664 cases newly diag-

[1]World Health Organization. Global Tuberculosis Report 2023. World Health Organization website. Accessed August 6, 2024. https://iris.who.int/bitstream/ handle/10665/ 373828/9789240083851-eng.pdf?sequence=1&isAllowed=y

nosed with 90638 (4.2%) deaths during 2022. MDR-TB accounted for 63801 (5.18%) of the population, with a notification to treatment rate of 95.3% (22,48,816 cases)[2]. Pursuing the Sustainable development goals globally, we could achieve only 8.7%, 19% and 49% decline in the incidence, mortality and reduction in catastrophic costs respectively[3].

The chronic and indolent nature of the disease, with the ability to resist drug pressure while modifying its metabolism, makes *Mycobacterium Tuberculosis (M.tb)* formidable [1]. The very challenge in TB management stems from the fact that Pulmonary TB though the most common form, detected with certainty still requires multi-drug therapy even for pan-sensitive organism, with the therapy spanning for months, which is long and cumbersome due to immune evasion [2].

Dealing with such a panoramic predator, challenges are inevitable for the National TB Elimination Programme that has strategically categorized TB control into four domains: Detect Treat, Prevent and Build, through innovative solutions and comprehensive interventions to gear up to expectations of TB elimination by 2025[4]. In the following sections, we discuss these challenges in the same four domains and the solutions offered through research evidences and programmatic implementation for successfully eliminating TB disease.

Diagnostic challenges

For a bacterium that has spent centuries with the human race, dating back to the Vedas where it is termed “Raja Yaksha” or the king of diseases, confirmatory diagnosis becomes the foremost challenge. Luckily, pulmonary TB remains the commonest form of TB in an immunocompetent patient detected by Sputum smear and currently by molecular methods. Complexities increase when it comes to diagnosing TB among immunocompromised individuals, extra pulmonary forms and paediatric population where tissue invasion predominates extracellular forms and hence not captured by the conventional and simple sputum examination. Delay in diagnosis needs to be addressed by upfront molecular diagnosis. Once this is achieved, resistance testing and species identification becomes the next hurdle. To anticipate credible results, transport of specimens has to be given attention apart from point of care tests developed to overcome the rough terrains and inaccessible area.

Development and validation of open real-time polymerase chain reaction assay for tuberculosis diagnosis and treatment follow up

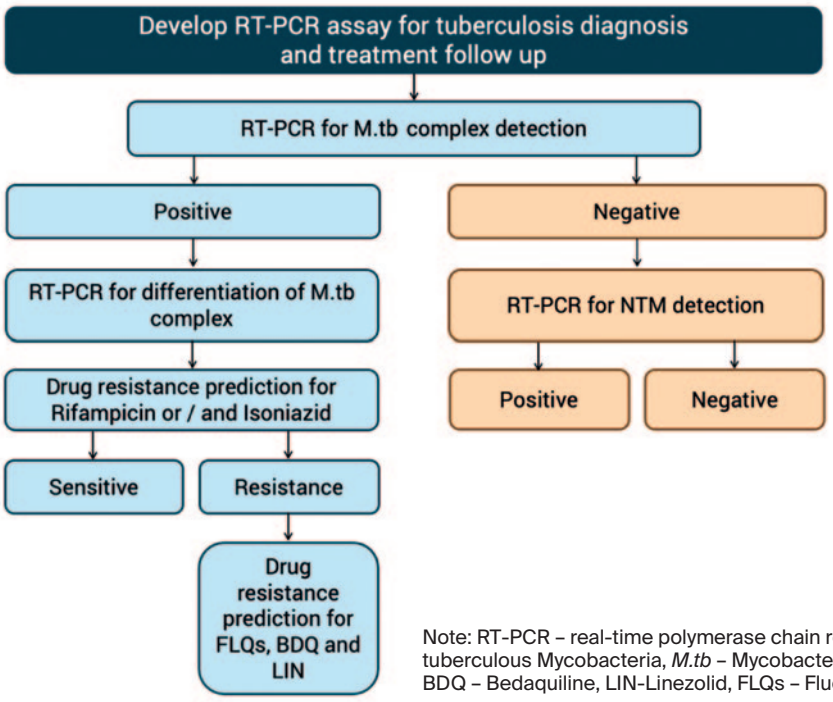
While the gold standard for TB diagnosis is still mycobacterial culture, which is a long drawn process, quick and precise techniques are being developed. With Real Time Polymerase Chain Reaction (RT-PCR) machines available in the farthest regions as part of SARS CoV-2 testing strategy in the country, a study has been designed to make use of these Kits for rapid diagnosis and prognosis of TB. A comprehensive RT-PCR assay is also used for *Mycobacterium Tuberculosis (M.tb)* viability and detection apart from differentiation from its counterparts, the Non-Tuberculous Mycobacteria and the other M. Tb Complex members, along with viability (Fig. 1).

[2] Central TB Division M of H and FW. India TB Report 2023 [Internet]. New Delhi, India; 2023. Accessed August 6, 2024. https://tbcindia.gov.in/showfile.php?lid=3680

[3] World Health Organization. Sustainable Development Goals 2017: Target 3.3. Communicable diseases. World Health Organization website. Accessed August 6, 2024. https://www.who.int/data/gho/data/themes/topics/sdg-target-3_3-communicable-diseases

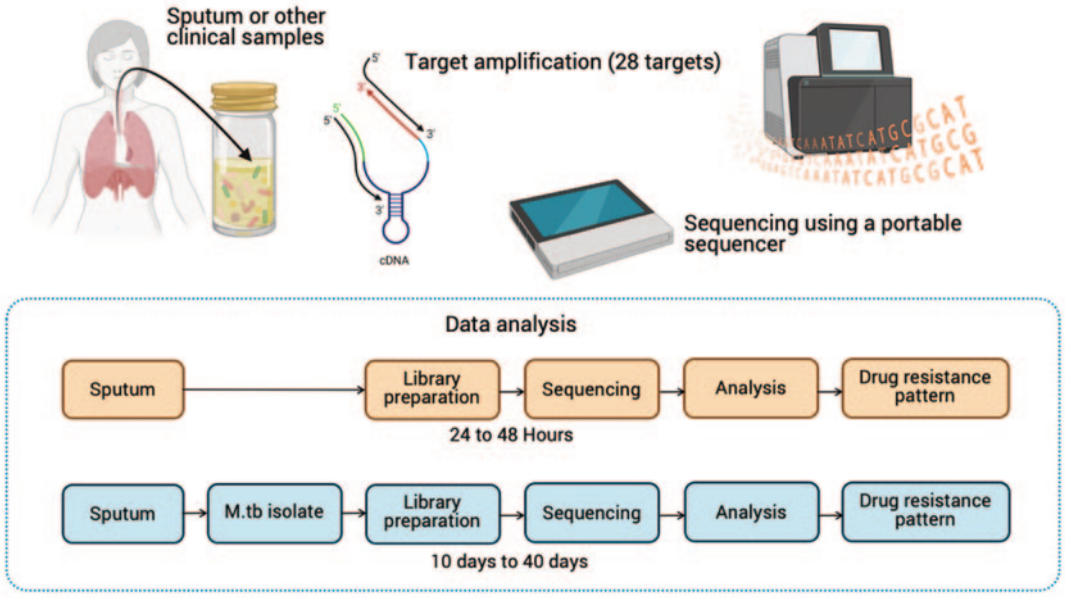
[4] Central TB Division, Ministry of Health with Family Welfare. National Strategic Plan for tuberculosis: 2017-25 elimination BY 2025. Central TB Division website. Published March, 2017. Accessed August 6, 2024. https://tbcindia-wp.azurewebsites.net/wp-content/uploads/2023/05/National-Strategic-Plan-2017-25.pdf

FIG. 1. Algorithm showing testing for tuberculosis using the open Real Time Polymerase Chain Reaction system.



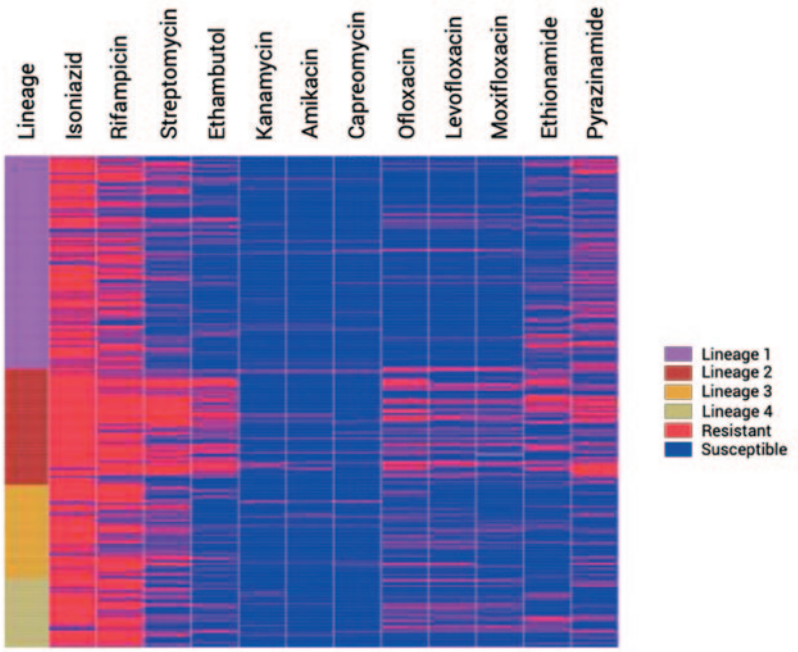
Note: RT-PCR – real-time polymerase chain reaction, NTM – Non-tuberculous Mycobacteria, *M.tb* – Mycobacterium Tuberculosis, BDQ – Bedaquiline, LIN-Linezolid, FLQs – Fluoroquinolones

FIG. 2. Targeted next generation sequencing for culture free detection of drug resistance.



Culture free detection of extended drug resistance, non-tuberculous mycobacteria (NTM) speciation by in-house primers using portable nanopore sequencer becomes a boon for detection of rapid drug resistance as shown in (fig. 2) [3, 4].

FIG. 3. Indian catalogue of mycobacterium tuberculosis drug resistance mutation along with lineage of Mycobacterium Tuberculosis from India



Whole genome sequencing

Whole genome sequencing of *M.tb* offers the most comprehensive solution to genomic-based drug susceptibility testing, allowing identification of all mutations that may be associated with resistance (and sensitivity) to first-line, second-line, and new or repurposed antituberculosis drugs within a single platform. This also provides valuable data to establish genetic relatedness between strains of *M.tb*, which is necessary for understanding of potential transmission linkages. To address the concerns pertaining the region-specific resistance, and following WHO's recommendation, Indian Council of Medical Research – National Institute for Research in Tuberculosis (ICMR-NIRT) has developed the first 'Indian catalogue of Mycobacterium tuberculosis Mutations and their Association with Drug Resistance' from drug- resistant TB strains collected from across the country. This has been periodically updated for better surveillance (Fig. 3).

Though whole genome sequencing is quite comprehensive, direct sequencing of sputum samples is sometimes challenging due to low amounts of *M.tb* Deoxy Ribonucleic Acid (DNA) [5, 6]. Confirmation of this can be seen in Fig 4.

Challenges in transport of specimens

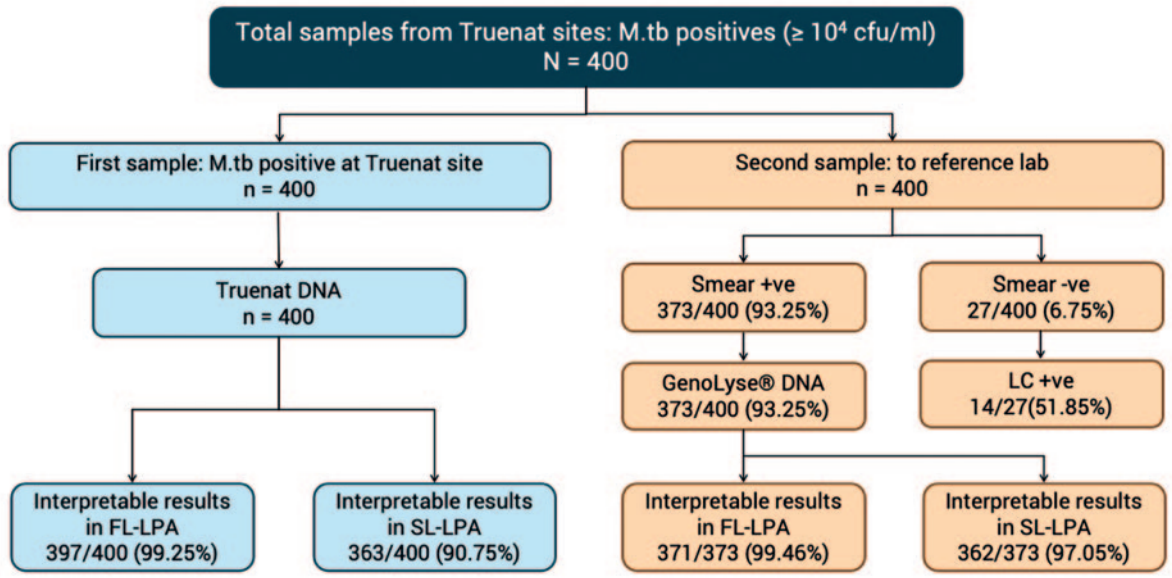
Transport of sputum samples for molecular testing from the periphery to Nucleic Acid amplification test (NAAT) / line probe Assay (LPA) centres may sometimes take more than 10 days in difficult terrains. This problem is obviated by using the principle of LPA testing using Trueprep DNA (Fig. 4).

Treatment challenges

Challenges to therapy include the following:

- The long duration of TB therapy, adverse drug reactions, and Drug-drug interaction has increased the attrition rates, leading a considerable number of patients, not completing therapy in the prescribed

FIG. 4. Deoxyribonucleic acid collected from samples are transported, to perform line probe assay in intermediate reference laboratories – an innovation to curb infectivity and sample transport challenges.



Note: FL-first line, SL-second line, LPA-line probe assay, LC-liquid culture, cfu – Colony-forming unit, +ve - positive, -ve - negative.

period, not only progressing to failure but also adding on to the pool of emerging drug-resistant cases. Shorter and oral regimens are the need of the hour, which would directly translate to better cure rates.

- Lack of social support and catastrophic cost take a toll on patients continuing misery, with an ardent urge to resume their work that drives the attrition rates. Shortening TB treatment has been a global priority, but careful attention should be given to recurrences.
- TB mortality and post TB lung disease or Tb sequalae cripples not only the patient family but the overall economy and productivity of the community as such.

The evolution and legacy of tuberculosis treatment shortening

For a long time until the 1950's, there was no medication for TB except for admitting the patient in a sanatorium that translated to requirement of 23,000 beds. Of those admitted, there were 50% deaths, 30% – naturally cured, leaving 20% chronically smear positive [7]. To overcome the requirement of sanatorium and explore the efficacy of domiciliary treatment, the first ever randomized trial was started by Tuberculosis Chemotherapy Centre (currently ICMR-NIRT) in September 1956, headed by Professor Wallace Fox, comparing anti-tuberculosis therapy (ATT) given at home versus same therapy with admission in the TB Sanatorium , coordinated by WHO [8]. This was the first ever global non-inferiority trial conducted in India, that showed that treatment at home was not only Non-inferior (86% vs 92%), with comparable rates of recurrence being 7% in home and 10% at sanatorium respectively, but also with no additional risk of transmission at home, revolutionising TB treatment with the psychosocial support of the family [8]. Mycobacterium Tuberculosis has a peculiar characteristic called the Lag Phase, where the bacilli do not grow after exposure to ATT, even after 2–3 days also called the post antibiotic

Table. The evolution of tuberculosis chemotherapy through dedicated research for the last five decades.

Study number	Years	Conclusive findings
Home San study [8]	1956-1959	Rx at home was as effective as sanatorium Rx. Diet was of minor importance not only concerning immediate response to treatment but also to in the occurrence of relapse. There was no evidence that the close family contacts of patients treated at home incurred an increased risk of contracting tuberculosis.
VA [11]	1961-1963	Twice weekly regimen of streptomycin and INH was as effective as daily treatment with PAS+INH. Cost was also less.
IX [12]	1970-1972	Twice weekly oral regimens of PAS+INH were comparable to that of a standard daily regimen of PAS and INH.
XII [9]	1974-1977	The findings with the non-rifampicin regimen Z7 (Pyrazinamide given daily) are highly encouraging. Rifampicin makes an important contribution to the efficacy of regimens in patients who have initial resistance to INH and streptomycin as well. Steroids have no role in short course chemotherapy.
XVIII [10]	1995-1998	Regimens containing ofloxacin of duration of 4&5 months were found to be highly effective with relapse rates of 4% and 2% when the regimens were 4 and 5 months respectively.
XXA [13]	2001-2005	In HIV–TB, a 6 months regimen was equivalent to 9 months. Intermittent anti-tuberculosis therapy at the end of treatment except that Acquired rifampicin resistance was prevalent in both the arms and bacteriological relapses were more in the 6 months regimen in HIV.
XXII [14]	2004-2006	4-month thrice-weekly regimens of gatifloxacin or moxifloxacin with isoniazid, rifampicin and pyrazinamide, were inferior to standard 6-month treatment, in patients with newly diagnosed sputum positive pulmonary TB.
XXIII [15]	2006 - 2008	In HIV –TB, once daily regimen of Nevirapine failed to be non-inferior to an Efavirenz based regimen co-administered with rifampicin containing anti-tuberculosis therapy.
XXIV [16]	2008- 2018	A moxifloxacin based 4 months regimen given with the standard 4 drugs daily and followed up for 24 months was non-inferior to a six months intermittent regimen of anti-tuberculosis therapy.
XXV [17]	2008-2016	A daily regimen in HIV with pulmonary TB was more efficacious than an intermittent regimen, especially reducing emergence of Acquired rifampicin resistance, but at the expense of increased incidence of hepatotoxicity which was manageable.

Note: HIV – human immunodeficiency virus, INH – Isoniazid, PAS – Para Amino salicylic acid. TB – tuberculosis.

effect[5]. This property was capitalised for initiating intermittent therapy that would reduce cost as well as toxicity. In the journey towards shortening TB treatment, the trial of 5-months and 7-months regimen containing rifampicin showed cure rates of 100% with recurrence rates of 9–12% [9]. Table provides the sequence of trials in pulmonary TB towards enhancing cure rates and the salient findings deduced in each of them. India was one of the first to introduce quinolones into TB therapy, aimed at shortening TB treatment to less than 6 months in the early 90s [10]. This study showed that a daily regimen with addition of ofloxacin given for 4 and 5 months had a relapse rate of 4% and 2% respectively [10].

However, with the advent of human immunodeficiency virus (HIV), regimens required a strategic alignment taking into account the ease of bacillary dissemination in a vulnerable immune compromised environment leading to extra pulmonary forms, disseminated TB and atypical presentations [18]. The most dreaded complication of intermittent ATT therapy was Acquired rifampicin resistance in the phase of immune-compromisation, first reported in thrice weekly rifampicin, that was not offset by the initiation of antiretroviral therapy alone [13, 19]. This compelled researchers to perform the trial comparing daily vs intermittent therapy of

[5] Toman K, Frieden TR. Toman's tuberculosis: case detection, treatment, and monitoring : questions and answers / edited by T. Frieden, 2nd ed. World Health Organization website. Published 2004. Accessed August 6, 2024. https://iris.who.int/handle/10665/42701

ATT of 6 months along with prompt introduction of ART. This trial stands even today as the only global evidence of a direct comparison of daily vs intermittent therapy where it was found that a daily regimen for 6 months was necessary for enduring success rates and preventing MDR-TB in HIV despite antiretroviral therapy initiation [17]. Shortening TB treatment to four months in HIV seronegative pulmonary TB patients with addition of Moxifloxacin was introduced. This trial, with a cure rate of 91% at the end of treatment and relapse rate of 4% at 24 months, became one of the early pieces of evidences to prove that shortening of TB treatment to under six months was a possibility [16]. This regimen is currently being tried in a pragmatic mode before programmatic implementation.

In the domain of MDR-TB trials, ICMR-NIRT participated in two landmark trials; one was the first triple regulatory trial in Multidrug resistant TB was the Standardized Treatment Regimen of Anti-tuberculosis Drugs for Patients with MDR-TB (STREAM) stage 2, multinational multicentric trial sponsored by vital strategies and Medical Research Council London. From a cumbersome period of 18–24 months, which had a severe attrition rate, this trial brought down the time period to 6–9 months, a great advancement in MDR-TB regimens. This was the Food and Drug Administration licensing trial for Bedaquiline and established its safety beyond 6 months in the Indian population. With Bedaquiline, playing the "captains knock" in all regimens used in Drug resistant TB, this trial assumes greater importance. Apart from Treatment shortening, the trial offered a fully oral regimen which is currently the shorter regimen (slightly modified) in the national programme [20]. The other (unpublished data) trial offers a simplified treatment for pre-extensively Drug resistant TB and in-tolerant MDR TB treatment further by giving just 3 drugs (Bedaquiline, Pretomanid and modifying doses of Linezolid) for 6 months and the results are gratifying, achieving cure rates of above 90% at the end of treatment. With linezolid toxicity especially after 2 months causing drug interruption, this dosage modification gives a dual advantage of ensuring safety with ease of drug intake.

Various modalities are being tried to provide a reliable four months regimen in drug sensitive TB, that includes stratified medicine approach [21, 22], multi-arm, multistage design, adaptive sample size[6] and use of newer drugs [23], all of them aiming to provide a relapse free survival from TB in the long run.

One of the strategies used by Indian physicists to achieve effective shortening maintain the relapse free survival is by using high dose rifampicin as a surrogate for rifapentine. A dose of 25 mg per kilogram (kg) of rifampicin given along with other ATT produces a viable option towards effective TB treatment shortening, as it has the same efficacy of higher doses while possess comparative toxicity as the conventional regimen of 10 mg/kg [24].

Achievements in extra pulmonary tuberculosis

Extra pulmonary Tuberculosis is another physician's enigma with peculiar attributes that include difficulty in establishing microbiological proof in specimens, paradoxical reaction or immune reconstitution inflammatory syndrome that mimics failure and drug resistance [25]. Overall, 440 150 patients with extra pulmonary tuberculosis (EPTB) were notified across different states in the year 2022, of which 28 to 32 % was

[6] Nicholas Paton, National University Hospital, Singapore. Two-month Regimens Using Novel Combinations to Augment Treatment Effectiveness for Drug-sensitive Tuberculosis (TRUNCATE-TB). National Library of Medicine website. Published March 21, 2018. Updated August 14, 2023. Accessed August 6, 2024. https://www.clinicaltrials.gov/ct2/show/NCT03474198?term=NCT03474198&draw=2&rank=1

contributed by the paediatric population[7]. EPTB varies from lesser morbid lymph node TB, debilitating spinal, pleural TB to severe life-threatening forms such as tuberculosis meningitis, and tuberculous pericarditis. The burden of EPTB, especially based on different organs, is largely unknown nor are they clear cut definitions of treatment outcomes. Monitoring the treatment response is another challenging area in EPTB.

Challenges in Diagnosis of extra pulmonary tuberculosis

The rapid molecular diagnostic tests such as NAAT play the crucial supportive role for faster diagnosis in EPTB. Multicentric evaluation of Truenat (MolBio Diagnostics, India) showed that the sensitivity and specificity was 73.7% and 90.4% respectively against GeneXpert (Xpert *M.tb* rifampicin, Cepheid) with highest sensitivity in pus samples (89%) and highest specificity (92%) in cerebrospinal fluid samples by Truenat, similar to GeneXpert was observed [26]. Pauci-bacillary nature of EPTB, varied presentations, expertise for taking samples, quantity of the samples available for testing, infrastructure and expertise required for testing these samples are some for the reasons for diagnostic challenges. A study from central part of India showed that median time of health system for EPTB was 7 (0.6–16.4 weeks), shortest for tuberculosis meningitis and longest for abdominal TB [27]. Strengthening the knowledge of health care staff and awareness of the Index TB guidelines for EPTB[8], training module of EPTB (2023)[9] and the standard treatment workflow for EPTB which describe the algorithms of EPTB management[10] is vital for early diagnosis or appropriate referral for further management.

Though ATT recommended for EPTB is similar to pulmonary TB, A longer duration is required for TB Meningitis and osteoarticular TB due to penetration issues. An important study carried out by the tuberculosis Research Centre formerly the tuberculosis research centre was the TB spine study with patients followed up to 15 years post treatment completion that demonstrated that effective chemotherapy had a success rate of 96% with surgery required only among those with neurological complication and more than three vertebrae involved [28]. Multicentric tuberculosis meningitis – KIDS trial done in Chennai, Pune and Malawi showed that high dose rifampicin (R30mg/kg) improved neurocognitive outcomes in children with tuberculosis meningitis [29]. The recently concluded trial from Chennai showed that Ofloxacin containing four-month regimen was non-inferior and safe for adults with lymph node TB [30]. Optimal regimen and the duration of ATT in different forms of pulmonary TB is still an area to be explored.

Paediatric tuberculosis present status and current challenges

Paediatric tuberculosis remains a public health problem [31, 32]. Children younger than 5 years are particularly susceptible to this severe TB and can serve as reservoirs for future disease outbreaks and are important group for TPT (Tuberculosis Preventive therapy) as well [33–35]. Diagnostic issues, safety concerns ethically exclude paediatric population from very many trials that makes evidences

[7] Central TB Division M of H and FW. India TB Report 2023 [Internet]. New Delhi, India; 2023. Accessed August 6, 2024. https://tbcindia.gov.in/showfile.php?lid=3680

[8] Central TB Division, Ministry of Health and Family Welfare, Government of India. Index TB guidelines: Guidelines on extrapulmonary tuberculosis for India 2016. Central TB Division website. Accessed August 6, 2024. https://iris.who.int/bitstream/handle/10665/278953/IND-tb-guidelines- eng.pdf?sequence=5&isAllowed=y

[9] Central TB Division, Ministry of Health and Family Welfare, Government of India. Training module on extrapulmonary tuberculosis 2023. Central TB Division website. Accessed August 6, 2024. https://tbcindia.mohfw.gov.in/2023/06/06/training-module-on-extrapulmonary-tb/

[10] Indian Council of Medical Research, Ministry of Health and Family Welfare, Government of India. Training module on extrapulmonary tuberculosis: Standard treatment workflow. Central TB Division website. Accessed August 6, 2024. https://main.icmr.nic.in/sites/default/files/STWsDownload/Adult_Extr_Tuberculosis/Adult-Extrapulmonary-Tuberculosis-all.pdf

Sparse [35]. The recent Shorter Treatment for Non-severe TB in African and Indian Children (SHINE) trial was one of the few trials in children which showed a shorter four months regimen to be non-inferior to the conventional 6 months regimen among non-severe TB [36, 37].

Challenge in tuberculosis diagnosis in paediatric population

The paucibacillary nature of the disease, challenges in sample collection in young children, and the limitations of currently available microbiological tests restrict bacteriological confirmation of TB in children [38]. Recent WHO guidelines recommend the use of novel rapid molecular assays as initial diagnostic tests for TB and endorse alternative sample collection methods for children[11]. The poor reliability of current paediatric diagnostics has made clinicians rely heavily on clinical judgement and radiological evidence, both being non-specific. One of the ways to reduce reliability on expectoration in the paediatric population is to evaluate methods for *M.tb* detection in urine, stool and saliva collected from the children with presumptive TB and to compare the yield of *M.tb* detected which is now an ongoing study at ICMR-NIRT, the secondary outcome of interest is to determine the sensitivity of *M.tb* detection methods using stool and urine for screening the prevalence of TB disease among children with respiratory distress.

Nutrition and tuberculosis

Nutritional support has been an integral component of patient-centred care to improve TB treatment outcomes in the presence of disease-induced cachexia with undernutrition being a common comorbidity including India. The “RATIONS” (Reducing Activation of Tuberculosis by Improvement Of Nutritional status) study was a field-based, cluster-randomised controlled trial assessed the effects of nutritional support on tuberculosis mortality, treatment success, and other outcomes. Patients received nutritional support in the form of food rations (1200 kcal and 52 g of protein per day) and micronutrient pills for 6 months in the drug-susceptible tuberculosis and 12 months in the multidrug-resistant tuberculosis group. The median weight gain was 4.6 kg (IQR 2.8–6.8), but 1441 (54.8%) of 2630 patients remained underweight. At 2 months, 1444 (54.0%) of 2676 patients gained at least 5% of baseline weight. Weight gain, particularly in the first 2 months, was associated with a substantially decreased hazard of tuberculosis mortality. Nutritional support has been an integral component of patient-centred care to improve TB treatment outcomes [39].

Socio-behavioural component of tuberculosis control and elimination

Studies in India and globally point out to depression and unhealthy alcohol use as important socio-behavioural factors, determining non-adherence and leading to poor TB treatment outcomes. In recent studies, 48–59% of people starting TB treatment in India had probable moderate-to-severe depression, with more than one-quarter having persistent depression at the end of TB treatment [40, 41]. In a meta-analysis of global

[11] World Health Organization. Global Tuberculosis Report 2021. World Health Organization website. Published 2021. Accessed August 6, 2024. https://www.who.int/publications/i/item/9789240037021

studies [42] and in Indian studies [43–45]. Depression at TB diagnosis is strongly associated with medication nonadherence and unfavourable TB treatment outcomes (odds ratio 4.1, 95%CI 2.4–6.9, evident from the meta-analysis by Ruiz-Grosso P, 2020 [42]. Similarly, people with TB have high Unhealthy Alcohol Use prevalence globally has been reported as 30% by Necho M, 2021 and in India it ranges from 15–61% across six studies [46–52] and the odds ratio of an unfavorable TB treatment response has been 2.0, (95%CI 1.6–2.5) in a meta-analysis by Ragan EJ 2020 [46].

More intensive integration of mental and behavioral health services and scaling up of differential counselling and care services for persons with TB to address gaps in psycho- social needs of persons with TB, would help obviate this problem and ensure adherence to treatment [48].

Health economic evaluation of regimens and ways to reduce catastrophic cost – National Institute for Research in Tuberculosis

Towards achieving, zero catastrophic cost for tuberculosis affected families

Catastrophic Health expenditure (CHE) is defined as out-of-pocket expenditure for health care that exceeds a specified proportion of household income (10% to 40%), with the consequence that the household may have to sacrifice the consumption of other goods and services necessary for their wellbeing[12] [53, 54]. The India's National Strategic Plan (NSP) for elimination of TB 2017 to 2025 is committed to zero catastrophic cost for TB patients.

Catastrophic expenditure in tuberculosis

Study from ICMR-NIRT reported that on an average, a patient suffering from TB incurred out of pocket expenditure, while shopping for diagnosis and treatment, Rupees (Rs.) 2052 in terms of direct cost, Rs. 934 in terms of indirect cost and the collective total cost was Rs. 986 [55, 56]. When projected to the country with the current prevalence, the amount works out to Rs. 30 billion per year for the country, despite free diagnosis and treatment offered to patients. For daily wage labourers, the mean number of work-days lost due to TB was 83 days. Every year, more than 170 million workdays are lost to the national economy on account of TB, amounting to Rs billion. In addition, 67% of rural and 75% of urban patients borrowed money on account of the TB illness. The average debts incurred because of TB including treatment was Rs 405 for rural and Rs.762 for urban patients. The proportion of various costs to annual family income was for direct cost 13%, indirect cost 26%, total cost 40% and debts 14%. The pre-treatment direct cost incurred by patients was Rs.50.

Active case finding as a measure to reduce tuberculosis catastrophic expenditure

Currently active case finding is yet to be a strategy under the TB control programme. A study from ICMR-NIRT, of the 336 individuals, 110 were diagnosed through active case finding and 226 through passive case finding showed a total of 29% of patients diagnosed through passive case finding and 9% of patients diagnosed through active case finding experienced catastrophic costs due to TB [57]. Active Case Finding inter-

[12] World Health Organisation. The World Health Report 2000: Health Systems: Improving Performance. World Health Organization website. Published 2000 Jun 14. Accessed August 6, 2024. https://www.who.int/publications/i/item/924156198X

ventions for TB began in India a decade before and since than it has expanded and acquired importance in the national strategic plan for TB elimination in 2025. The WHO end TB strategy adopted a target of achieving 'no tuberculosis affected household face catastrophic costs due to tuberculosis' by 2020.

Economic aspects of shortening the duration of tuberculosis treatment

Consistent efforts to mitigate the burden of treatment for drug-resistant tuberculosis as well as reducing costs, has resulted in shorter regimens (STREAM stage 2) [58-60]. From the cost perspective, the study by Ryckman and colleagues suggests that shortened duration yielded the most savings for both rifampicin-sensitive and rifampicin-resistant TB in t three high burden countries [61]. It is important that the studies highlight that shortening TB treatment duration could be an important strategy to achieve the TB elimination goals together while also achieving sufficient economic gains [62-64].The shorter duration was the most important driver of medium term savings with novel regimens, followed by increased treatment adherence.

Post-tuberculosis lung diseases present status and current challenges

Though ATT drugs help to sterilize the lesions through bactericidal activity, Scarring is the rule and if extensive can derail the entire lung parenchyma, that could cripple even a cured patient, which has assumed center stage and termed Post TB Lung Diseases (PTLD), defined as "Evidence of chronic respiratory abnormality, with or without symptoms, attributable at least in part to previous tuberculosis" [65]. With mortality more than 4 times higher in TB patients compared to matched controls in general population, PTLD needs to be drastically reduced [66]. The first challenge is to have a succinct definition which is lacking currently. In recent days, Host directed therapies including anti-fibrotic agents are tried to prevent or reduce PTLD, by decreasing inflammatory cell death, matrix destruction and fibrosis of the lung [65, 67]. Standard guidelines have to be framed after overcoming the challenges stated so that we can appropriate prioritise PTLD and reduce on the catastrophic cost further creating recovery as a whole rather than merely achieving bacterial quiescence.

Challenges in tuberculosis preventive therapy

TB infection is present in over half of the population in India. But to convince a population of millions, especially when asymptomatic, without the certainty of breakdown of a disease pose major hurdles in initiating TPT therapy. The National TB elimination programme hence is using a tiered approach, initially dealing with the high-risk groups and slowly ramifying to cover other population based on available evidence.

Randomised controlled clinical trial for tuberculosis preventive therapy in human immunodeficiency virus

This trial was done among People living with HIV /AIDs who were screened for TB and were given either 36 months of daily Isoniazid alone or 6 months of a combination of Ethambutol and Isoniazid, with appropriate initiation of antiretroviral therapy as per prevailing guidelines. Both regimens were similarly effective in preventing TB, when compared to his-

torical incidence rates, but with a trend towards better control with the longer regimen with negligible emergence of Isoniazid resistance [68].

Accelerating testing for tuberculosis infection and initiating preventive therapy is critical to achieving the goal of END TB strategy envisioning a world free of tuberculosis by 2035. This will require constant innovation, locally driven solutions to address the diverse and dynamic tuberculosis epidemiology and persistent programme monitoring and evaluation. As new tools, regimens and approaches emerge, midcourse adjustments to policy and practice must be adopted. Key programmatic challenges regarding the TB preventive therapy includes the potential burden of latent tuberculosis infection, identifying persons for TB preventive therapy, development and adoption of new diagnostic tools and TB preventive therapy acceptance, adherence and completion [69].

The 3-month once-weekly isoniazid-rifapentine regimen recommended by WHO for tuberculosis preventive treatment is being rolled in countries including India. It has higher treatment completion rates and lower risk of hepatotoxicity than isoniazid preventive treatment. However, trials showed higher frequency of adverse drug reactions including flu-like syndromes and dizziness, and also uncommon Grade 3 or 4 adverse events like hypotension, syncope, bronchospasm [70] requiring further evaluation. It would also be prudent to rule out TB as much as possible before initiating TPT therapy.

Pragmatic trials have been initiated in ICMR-NIRT to evaluate the effectiveness of preventive regimens in drug resistant TB. Levofloxacin drug given daily for six months is planned to be studied as preventive treatment among MDR TB contacts. Similarly, delamanid is studied as a potential drug among contacts of pre-XDR (Extremely Drug Resistant) TB patients.

Currently National TB Elimination Programme has rolled out adult Bacillus Calmette Gue'rin revaccination strategy for population with high risk like Elderly, malnourished, smokers, alcoholics and Diabetics is another step by the National TB Elimination Programme.

Pragmatic studies of national importance

The model directly observed therapy short course project – a game changer for programmatic implementation

The Governments of India and Tamil Nadu along with the world health organization and United States agency for international development conceptualized the idea of Model dots project between 1998 to 2002. They showed on the field that Directly Observed Therapy Short course with administration of the standard 4 drugs in intensive phase and isoniazid and rifampicin for four months, decreasing culture positive TB from 1.3% to 11.3%. The most salient feature was also the mortality survey which showed a four times higher risk among TB compared to matched controls of the same ages with incomplete treatment, failure and age above 45 years, proving to increase the risk of mortality due to TB[13].

National tuberculosis prevalence survey

The National TB Prevalence survey in India, conducted from 2019 to 2021, was a comprehensive endeavour to estimate the true burden of tu-

[13] National institute for research in Tuberculosis (ICMR). Genesis and achievements – A Monograph: Model Dots Project (1994-2014). September 2014. Accessed August 6, 2024. https://www.nirt.res.in/pdf/AR/MDP_GENESIS%20AND%20ACHIEVEMENTS_A%20MONOGRAPH_2014.pdf

berculosis at the national level. This robust survey funded by the Central TB Division and supported by technical assistance from the WHO and various Indian research institutions, utilized a cluster sampling design to cover a population of over 3.54 million across the country. The findings revealed a prevalence of microbiologically confirmed pulmonary TB among individuals aged 15 and above at 316 per 100,000 population, with notable variations among the 20 surveyed states/state groups for the year 2021. The prevalence to notification ratio was observed as 2.84 highlighting a significant gap in case detection and notification. The prevalence of TB infection among the surveyed participants was 21.6%. Additionally, the survey informed that 64% of the symptomatic population did not seek healthcare services. These insights have significantly informed India's efforts to combat tuberculosis through evidence-based interventions [71].

Reporting adverse drug reaction during tuberculosis management in India

Adverse drug reactions can lead to cryptic non-adherence contributing unfavourable response to TB therapy through cryptic non-adherence[14] [72]. The increasing use of complex regimens for drug-resistant TB globally, the concomitant use of antiretroviral therapy in patients with HIV-associated TB, and the imminent release of new classes of medicines to treat TB on the market make the requirement for pharmacovigilance in TB even stronger. Understanding the need, WHO has come out with a framework namely active TB drug-safety monitoring and management[14] in 2015, that refers to active and systematic clinical and laboratory assessment of patients on treatment with new anti-TB drugs, novel MDR-TB regimens or XDR-TB regimens to detect, manage and report suspected or confirmed drug toxicities[14]. The National TB Elimination Programme prioritizes pharmacovigilance at Drug Resistant TB Centres and the Adverse Drug Reactions Monitoring Centres established under Pharmacovigilance programme of India are linked with the Drug Resistant TB centres, so as to improvise adverse drug reactions management and appropriate reporting[15].

Capacity building

Therapeutic anti-tuberculosis therapy drug monitoring

Though not routinely required, therapeutic anti-TB drug monitoring help in dose optimization to improvise success rates [73, 74]. This is especially true in pulmonary TB when sensitive bacilli persist despite adherence to ATT and comorbidities where malabsorption is inevitable [75]. There is a need for expansion in the programme as it plays a critical role in diagnosing and differentiating simple malabsorption from emergence of Drug resistance.

National tuberculosis biorepository

ICMR-NIRT has set up a large TB Biorepository in its Thiruvallur campus, inaugurated by the honourable Prime minister of India on 25th

[14] World Health Organisation. Active TB drug-safety monitoring and management (aDSM). World Health Organization website. Accessed August 6, 2024. https://www.who.int/teams/global-tuberculosis-programme/diagnosis-treatment/treatment-of-drug-resistant-tb/active-tb-drug-safety-monitoring-and-management-(adsm)

[15] Central TB Division, Directorate General of Health Services, Ministry of Health with Family Welfare. Technical and Operational guidelines for TB Control in India 2016. Central TB Division website. Accessed August 6, 2024. https://tbcindia.mohfw.gov.in/wp-content/uploads/2023/05/5585665076Index-TB-Guidelines.pdf

February 2024. The Biorepository stores large numbers of various types of biological specimens including whole blood, DNA, RNA, urine, saliva, sputum, *M.tb* isolates and peripheral blood mononuclear cells collected from well-characterized cohorts of TB patients, their household contacts, as well as community controls, enrolled and followed-up in various clinical trials, multicentric cohort studies and research projects of ICMR-NIRT, thus serving as an extremely valuable and much needed resource for the TB research community to support advances in diagnostics and biomarker research. The samples are stored appropriately in -80° freezers and liquid nitrogen storage tanks. All the storage equipment is equipped with temperature monitors capable of real time temperature logging and alerting users via SMS as well as emails when temperature deviations are noticed. The specimen inventory is managed through a cloud- based software. The Biorepository is manned by skilled staff who are trained in Good clinical and laboratory Practice and International Air transport Association guidelines. The Biorepository has all safeguards and safety devices including access control, Closed circuit cameras, smoke detectors, oxygen monitors, fire extinguishers and backup generators. This facility will be a boon to the TB research community within and outside the country to accelerate basic and translational research to support global TB elimination efforts.

Other collaborative activities spear headed by Indian Council of Medical Research

ICMR along with WHO South East Asian Region (SEAR) office collaborated with 10 SEAR member states to implement a common platform titled 'Regional Enabler for the South-East Asia Research Collaboration for Health'. This SEAR RESEARCH Platform has been established to formulate and implement public health research projects and conduct capacity-building activities based on common national health priority areas. The other activity for capacity building in the same platform with regard to diagnosis is the "Capacity building for Advanced TB diagnostics in SEAR countries" organised by ICMR-NIRT and McGill's University for effective application of diagnostics in TB care.

Future technologies and strategies proposed for implication

Research: clustered regularly interspaced short palindromic repeats system. CRISPR-Cas technology

Among the many technologies evolving in a rapid manner to address these gaps, CRISPR-Cas is one of the promising technologies. It uses the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) system. For diagnostic tool development, the CRISPR-Cas system, particularly Cas 12/Cas 13 enzyme is used to detect specific genetic signature from mycobacteria. The methodology as such involves designing a CRISPR RNA (crRNA) that guides the Cas enzyme to the target DNA or RNA sequence and upon recognition of the site, the Cas enzyme gets activated and cleaves the reporter molecule producing a detectable signal such as Florescence signal that can be read on a plate reader or captured as a band immune-chromatogram strip. ICMR-NIRT is in the early stages of developing a CRISPR-Cas based mycobacterial detection tool and has submitted for process patent. This tool is being developed for detection of TB in sputum and urine samples.

Research: direct drug susceptibility testing – commercial version

The microscopic observation drug susceptibility (MODS) assay is the only WHO approved non-commercial direct susceptibility testing method which is a growth-based assay system proven to be an in-house low-cost assay which simultaneously detects M. tb and their susceptibility to first-line anti-TB drugs. Bob Gilman and Luz Caviedes introduced the MODS assay at the Universidad Peruana Cayetano Heredia in Lima [76] and WHO recommends this assay as a non-commercial and direct drug susceptibility testing technique [76, 77]. An attempt was made to miniaturize the conventional MODS into a 96-well plate method (M-MODS). This effort created an avenue to reduce the quantity of liquid media used to ten times lower and the data showed almost identical sensitivity of over 95% to that of the conventional methods used (MODS, MGIT960) in determining the presence of M. tb in sputum sediments (n=20).The turnaround time was again identical between M-MODS and MODS. Furthermore, this assay method M-MODS has the advantage of including more drugs and a greater number of specimens tested in a single plate with ten times lesser volume of reagents. In addition, the commercialization of this format (M-MODS) is plausible, and the optimal quantity re-hydrant was also determined in the preliminary work.

Future developments in paediatric tuberculosis in India

Drug trials focusing on shorter regimen for both DS-TB and DR-TB are underway. In addition, PK studies looking at the optimal dosage of anti TB drugs are also being conducted. Increased funding from the public and private sectors, improved stakeholder collaboration, and increased investment in paediatric TB-specific basic science, vaccine, diagnostic, and implementation research are all essential to improve the health of children with TB [78, 79].

Zoonotic and zoo-anthroponotic tuberculosis

Tuberculosis is one of the important Zoonotic disease with Bovine TB not amenable to either vaccines or any other treatment. Culling or slaughtering of the concerned animal, is the only way to eliminate transmission, which the poor farmer cannot afford. Diagnosis is by using.

Tuberculin skin test for detecting the presence or exposure of the pathogen. The Institute was the first to report Mycobacterium Orygis in India among the wild ungulates. The One Heath approach is globally gaining momentum as well due to possibility of reverse Zoonosis.

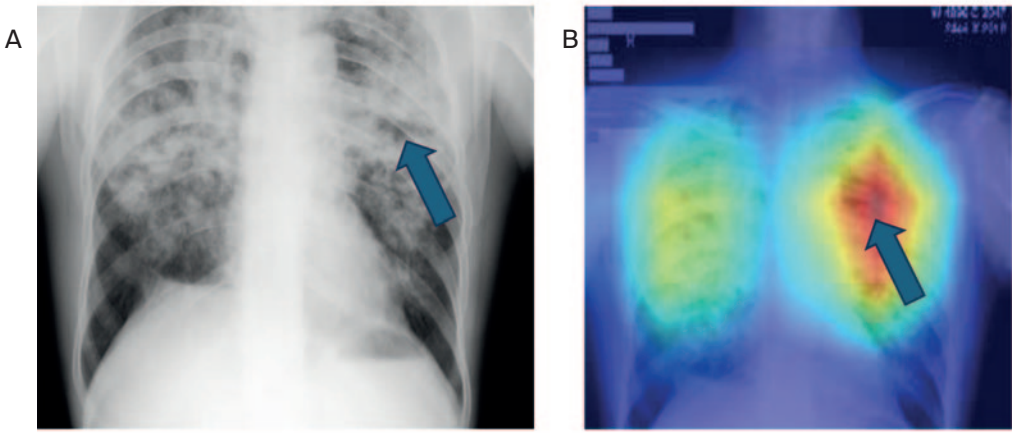
Artificial intelligence incorporation for early detection

Innovative TB health technology sharing platform is a periodical scientific exercise and exploration conducted at the ICMR headquarters with Central TB Division that brings the stakeholders for a first-hand information about the status of these products to facilitate validation and apply in field conditions. The two artificial intelligence tools currently explored are the Xray Computed aided Detection in Chest X-ray (fig. 5) and Cough artificial intelligence tool for prompt detection and early initiation of therapy working to prevent secondary transmission.

Evaluation of the artificial intelligence model performance for line probe assay first line and 2nd line reporting

LPA is used to diagnose drug resistant TB cases. There are two types of LPA: First Line (FL) and Second Line (SL). FL-LPA picks up drug resistance to First Line Anti TB Drugs (Isoniazid and Rifampicin) while SL-LPA

FIG. 5. Xray of the lungs (A) and heat mapping (B)



Note: Heat mapping to reveal the extent of severity of lesion showing the increased activity on the left side where the infiltration is breaking into a cavity, suggesting a more ominous lesion compared to the right – tool indigenously being developed by Indian Council of medical research with Centre for development of advanced computing courtesy CDAC and ICMR-NIRT.

detects drug resistance to Second line Anti TB drugs (Fluoroquinolones and second line injectable). The LPA testing process is an output of a complex interaction between a series of probes (reagents) and specific segments of TB bacterial DNA called genotypes (wild types and mutations) which are visible as dark bands of varying intensities against a white background. Each individual patient's LPA test result is captured over a special slender paper strip with 27 bands, which is interpreted by lab technicians and microbiologists to infer sensitivity to various drugs. Multiple LPA test strips are serially pasted on to an LPA Hain's sheet and are interpreted manually in the laboratory using a reference paper card.

Other exploratory objectives in the near future include:

- Markers of recurrence and predictors of paradoxical reaction in immunocompromised;
- Markers for detection of extrapulmonary TB;
- Point of care tests for drug resistance testing for newer drugs and expanding mutation catalogues;
- climatic influence on TB (fig. 6).

Programmatic initiatives on tuberculosis elimination

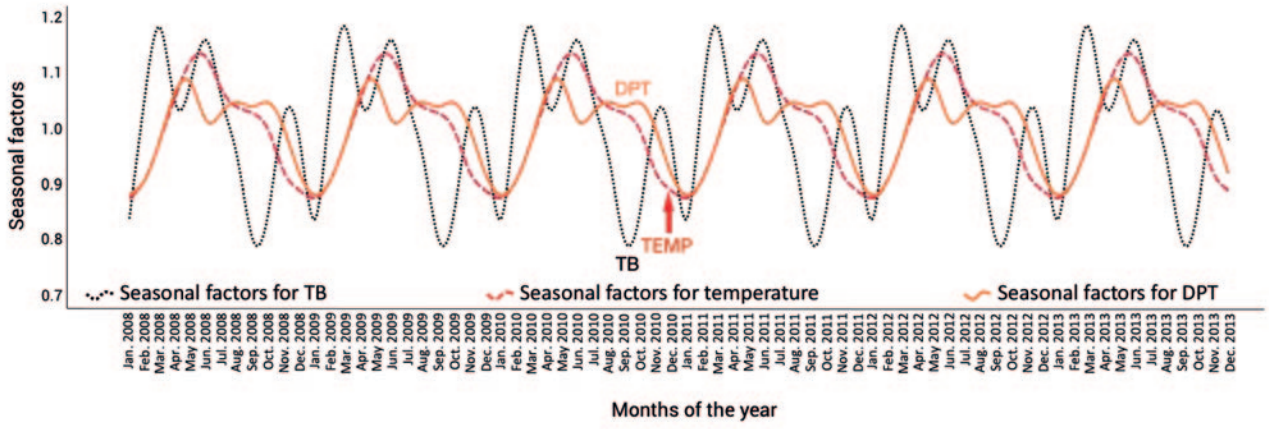
Pradhan Mantri Tuberculosis Mukt Bharat Abhiyaan

This is a unique community engagement program that adopts TB patients, providing support in various forms, from nutritional support, vocational assistance to support for diagnostics etc., for a period of six months to three years while the patient is on treatment for TB, aiming to create awareness and reduce stigma by involving the community in the treatment cascade[16].

Jan Andolan – A People's Movement. This movement envisage reaching out to the population at large, focusing on improved active/passive case finding efforts for early diagnosis, prompt treatment initiation, and ensuring successful treatment across both public and private sectors.

[16] Pradhan Mantri TB Mukt Bharat Abhiyaan. Central TB Division website. Accessed August 6, 2024. https://tbcindia.mohfw.gov.in/pradhan-mantri-tb-mukt-bharat-abhiyaan/

FIG. 6. Influence of climate on tuberculosis transmission (adapted from [80])



Note: The role of temperature, dew point temperature (DPT), and relative humidity have bearing on the survival on the *M.tb* and may influence tuberculosis (TB) disease's progression from latent stage infection to active, supported by higher dew point temperature and moderate temperature in summer and monsoon season.

Support for the patients come from own family caregivers introduced in 2023, from TB vijeta or TB champions who share their struggle and success stories, how hey overcome the obstacle of TB disease and Ni-kshay Mitras – The Donors, which has substantially supported the TB programme with nearly 1 lakh 60 thousand Ni-kshay Mitras committing to assist around a million patients, raising an estimated $146 million per year.

Ni-kshay Poshan Yojana (Nutritional Support Scheme through Direct Benefit Transfer)

The National TB Elimination Programme (NTEP) in India has been providing Rs.500/- per month to all notified TB patients from the day of notification until the time treatment outcome is achieved in India since 2018[17]. Currently, NTEP provides Rs.3000/- at Rs.1500 at two different instances during the treatment – at notification and 84 days later till 6m duration. Rs.500/- per month will be added in case someone needs an additional amount. As on date, the NPY incentives have been disbursed to ~9.8 million beneficiaries, amounting to more than Rs. 28,120 million i.e., approx. USD 336,315,200.

Ayushman Arogya Mandir Health and Wellness Centres (HWCs) (integration of health services) integrating TB services with the various platforms of National Health Mission, Ministry of Health and Family Welfare is one of the key strategies proposed in the National Strategic Plan (2017–2025) of NTEP.

The NTEP framework in collaboration with the HWCs aims to integrating and strengthening TB services like TB case finding, Referral for Testing, Case management, advocacy, counselling, Treatment support and monitoring, TB preventive treatment and interventions to ensure community participation. Multiple batches of Community Health officers were trained by Central TB Division, State TB cells and District TB office on how to integrate TB services in HWC and about how to efficiently exercise the same.

[17] Ministry of Health and Family Welfare. Nikshay Poshan Yojana (Nutritional Support to TB Patients). myScheme website. Accessed August 6, 2024. https://www.myscheme.gov.in/schemes/npy

Operational challenges and their rectification

NTEP aims to eliminate TB as a public health problem in India[18]. Despite significant progress, several challenges impede the programme's success. One of the primary challenges is in detecting TB, particularly regarding diagnosis. According to the National TB Prevalence Survey, 60% of symptomatic individuals do not seek care, indicating a significant gap in awareness and accessibility to TB diagnostic services. Additionally, the timely and adequate supply of NAAT consumables, crucial for rapid and accurate TB diagnosis, is essential for effective case detection. Community engagement for active case finding also remains a challenge, necessitating effective strategies to improve case detection rates.

In terms of treatment modalities, interrupted supplies of drugs are a significant issue. Continuous and reliable drug supply chains are vital for uninterrupted treatment. Many TB cases remain undiagnosed or untreated, highlighting the need for strengthened surveillance and follow-up mechanisms. Timely direct benefit transfer disbursements to patients are often delayed, and timely financial support is necessary to ensure patients adhere to their treatment regimens.

Preventing TB within the programme also faces challenges, particularly in identifying and motivating the eligible population for adult Bacillus Calmette Gue'rin vaccination and TB preventive therapy. Efforts must be intensified to expand coverage and acceptance of these preventive interventions.

Capacity building of NTEP staff is another significant challenge. Continuous training and capacity building are required to enhance their skills and knowledge in TB management and ensuring regular and comprehensive training programs is essential for the effective implementation of NTEP. Additionally, strong advocacy and sustained engagement with various government and non-government departments are necessary for a coordinated response to TB. Collaborative efforts can help address the multifaceted challenges of TB elimination.

Differentiated tuberculosis care-prioritization in preventing deaths among tuberculosis cases

NTEP has implemented a range of measures to address factors contributing to increased morbidity and mortality among individuals with TB[19] [81]. One notable initiative is the adoption of a differentiated TB care approach in 2021, which involves the provision of comprehensive evaluation and supportive treatment services at various healthcare levels. It aims to reduce death among TB patients by prioritizing patients who are high risk of death for special care including hospitalization currently being practiced in 20 states.

Conclusion

Research and implementation, Governmental and non-governmental organisations, patients and health staff require to work like Hand and glove to achieve this task of TB elimination. End TB task is achievable with countries and organisations coming together to work for the welfare of the TB community. This kind of philanthropic collaboration for ending TB knows no boundaries. A multidisciplinary approach with innovations centered around patients perception of disease would make the earth breath freely, bereft of TB.

[18] Central TB division. National TB Elimination Programme. Central TB Division website. Accessed August 6, 2024. https://tbcindia.mohfw.gov.in/

[19] Ministry of Health and Family Welfare. Nikshay Poshan Yojana (Nutritional Support to TB Patients). mySCheme website. Accessed August 6, 2024. https://www.myscheme.gov.in/schemes/npy

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