Review Article

National TB Elimination Programme—Can It End TB in India by 2025: An Appraisal

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Summary

India has the ambitious plan to End TB by 2025 which is five years ahead of the global strategy. To emphasise the point and not to be complaisant, the earlier Revised National Tuberculosis Control Programme (RNTCP) has been re-named as the National Tuberculosis Elimination Programme (NTEP) since January 2020. In this comprehensive review, various issues, weaknesses, strategies and their associated problems have been discussed. Starting with the problems of tuberculosis (TB) magnitude particularly latent TB infection, co-morbid conditions, like human immunodeficiency virus (HIV), diabetes mellitus, smoking, over-crowding, under-nutrition, immune-suppression, occupations like silicosis, etc have been reviewed and highlighted. Case notification, participation of private sector, diagnostic and treatment issues are discussed. Drug resistant TB (DR-TB) has also been described. Newer advances like molecular testing and treatment modalities including short course treatment and standardised longer regimens with injection free protocols are followed by the programme so that it will be possible in future for the patients to be diagnosed early, become more compliant and the treatment success will improve. Issues regarding prevention of TB in India with chemoprophylaxis, airborne infection control and future of vaccines are discussed in brief. National Strategic Plan (NSP) for 2017-25 and the Draft NSP for 2020-25 are also discussed with their possible impact to End TB by 2025. **[Indian J Chest Dis Allied Sci 2020;62:203-227]**

Key words: End-TB strategy, NTEP, RNTCP, NSP, NIKSHAY, Latent TB infection, Diabetes, Chemoprophylaxis, COVID, Epidemiology, Nutrition, Health-care workers.

Introduction

India has the highest number of tuberculosis (TB) cases in the world today with an estimated 2.88 million cases for the year 2018; 2.87 million for the year 2019 and a targeted estimate of 29,99,030 cases for 2020.[1] To control the disease, the country had, and has a TB control programme since 1962. However, because of inherent problems and lack of specific goals, the country failed to control the disease. Therefore, in 1997 the programme was re-named as Revised National TB Control Programme (RNTCP) with specific aims and goals. The entire country was covered under the RNTCP by March 31, 2006. However, TB still continued to be a major health problem[2-6] not only for India, but also for the whole world, and to achieve End TB, World Health Organization (WHO) passed a resolution in May 2014, the new post-2015 Global TB Strategy with ambitious targets.[7] The strategy aimed to end the global TB epidemic, with targets to reduce TB deaths by 95% and to cut new cases by 90% between 2015 and 2035, and to ensure that TB will not cause any family to be burdened with catastrophic expenses. Interim milestones were set for 2020, 2025 and 2030 (Tables 1 and 2). The resolution called on governments to adapt and implement the strategy with high-level commitment and financing. The focus of the strategy was to serve populations who are highly vulnerable to infection and those who are having poor health-care access, such as migrants. The other main strategy was to highlight the need to engage partners within the health-care sector and beyond, focusing on social protection, labour, immigration and justice. The WHO Secretariat was also to help Member States to adapt and operationalise the strategy with special emphasis on the importance of tackling the problem of multidrug-resistant TB (MDR-TB) and promoting collaboration across the countries. WHO was entrusted to monitor implementation and evaluation of progress towards the set milestones and the 2035 targets.

[Received: September 1, 2020; accepted September 28, 2020]

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India was a signatory to this resolution and developed its own National Strategic Plan (NSP) that proposed bold strategies so that decline of TB incidence and mortality by 2025, five years ahead of the global End TB targets and sustainable development goals to attain the vision of a TB-free India.[8] The vision of the strategy was a TB-Free India with zero deaths, disease and poverty due to TB. In fact the commitment

Table 1. Post-2015 global tuberculosis strategy framework

Vision	A world free of tuberculosis, zero deaths, disease and suffering due to tuberculosis
Goal	End the global tuberculosis epidemic
Milestones for 2025	75% reduction in tuberculosis deaths (compared with 2015) 50% reduction in tuberculosis incidence rate (less than 55 tuberculosis cases per 100 000 population) No affected families facing catastrophic costs due to tuberculosis
Targets for 2035	95% reduction in tuberculosis deaths (compared with 2015) 90% reduction in tuberculosis incidence rate (less than 10 tuberculosis cases per 100 000 population) No affected families facing catastrophic costs due to tuberculosis

Principles

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

Pillars and Components

1. ***Integrated, Patient-Centred Care and Prevention***
   - A. Early diagnosis of tuberculosis including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups
   - B. Treatment of all people with tuberculosis including drug-resistant tuberculosis, and patient support
   - C. Collaborative tuberculosis/HIV activities, and management of comorbidities
   - D. Preventive treatment of persons at high risk, and vaccination against tuberculosis
2. ***Bold Policies and Supportive Systems***
   - A. Political commitment with adequate resources for tuberculosis care and prevention
   - B. Engagement of communities, civil society organisations, and public and private care providers
   - C. Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control
   - D. Social protection, poverty alleviation and actions on other determinants of tuberculosis
3. **Intensified Research and Innovation**
   - A. Discovery, development and rapid uptake of new tools, interventions and strategies
   - B. Research to optimise implementation and impact, and promote innovations

Table 2. Key indicators, milestones and targets for the End TB strategy after 2015

Indicators with Baseline Values for 2015	Milestones			Targets
	2020	2025	2030	2035
Percentage reduction in deaths due to tuberculosis (projected 2015 baseline: 1.3 million deaths)	35%	75%	90%	95%
Percentage and absolute reduction in tuberculosis incidence rate (projected 2015 baseline 110/100 000)	20% (<85/100 000)	50% (<55/100 000)	80% (<20/100 000)	90% (<10/100 000)
Percentage of affected families facing catastrophic costs due to tuberculosis (projected 2015 baseline: not yet available)	0	0	0	0

for ending TB by 2025, five years ahead of the global strategy, was announced by none other than the Prime Minister of India, Shri Narendra Modi. The goal was to achieve a rapid decline in the burden of TB, morbidity and mortality while working towards elimination of TB in India by 2025. The core impact, outcome indicators and targets of the NSP are the four priority areas, such as private sector engagement, so that a seamless, efficient TB care cascade is ensured, active TB case-finding among the high-risk population, such as the socially and clinically vulnerable and to prevent progression from the latent TB infection (LTBI) to active TB in high risk groups. However, subsequently it was realised that the challenges are enormous and many complicated issues are involved to achieve these goals. Thus, to put thrust on such strategies, in January 2020, the central government re-named the RNTCP as the National Tuberculosis Elimination Programme (NTEP). In a letter to all the Chief Secretaries of States and Union Territories (UTs), the Union Government of India emphasised these commitments of achieving the sustainable development goal of ending TB by 2025, five years ahead of the global targets. The present review will focus on various challenges and possible solutions to overcome various hurdles that India as a country is facing to achieve End TB by 2025.

End–TB Strategy in India

The NSP sets out the strategic direction and key initiatives that will be undertaken from 2017 to 2025 for working towards achieving the goals of eliminating TB by 2025. There is an excellent commitment at the highest political level when the Prime Minister of India said "We have to defeat TB in India". This is an opportunity for the programme towards the goals of End TB in India. Further, progress achieved through the previous NSP period, indicates that it can be achievable. During the previous NSP period, RNTCP had tested more than 42 million people, put more than 7 million TB cases on treatment, saving an additional 1.5 million lives. The Central TB Division has achieved complete geographic coverage for the management of drug resistant TB (DR-TB) and more than 100,000 MDR-TB cases were diagnosed and treated. There are several landmark achievements of the previous NSP including policy and system preparedness for universal access to TB care including mandatory notification of TB cases, development of Standard for TB Care in India, case-based TB notification system—NIKSHAY, successful innovations in private sector engagement for TB care-UATBC, innovative use of immunochromatic test (ICT) platform for real-time monitoring of treatment adherence, etc. A considerable progress in addressing TB and co-morbidities, pediatric TB and urban TB control models has also been made and a major progress has been achieved in advocacy and communication areas.

The recently released Annual TB Report, 2020 by the Central TB Division, Government of India documented the journey on the excellent efforts and increased collaborations to end TB. More than 24 lakh TB patients were notified in 2019 (84% of the estimated cases) through the on-line notification system (NIKSHAY) addressing the problem of the "missing millions" so that the number of missing cases has now reduced to 2.9 lakhs against more than a million cases in 2017. Mandatory TB notifications, patient-provider support agency (PPSA) and incentives for private providers, are some of the key initiatives that have enabled the private health-care providers to play an important role in providing quality TB care. There are 48 PPSA through the Joint Effort for Elimination of Tuberculosis (JEET) consortium and 125 PPSA through domestic sources which support private sector engagement. With both collaborative and regulatory mechanisms, the country could register and notify 664,584 TB patients in 2019 from the private sector. This is an increase of 22% in TB notifications compared to the year 2018. As per WHO Global TB Report 2019, the incidence of TB is reduced from 300/lakh populations in 1990 to 199/lakh population in 2018 and the mortality is reduced to 32/lakh population in 2018 from 76/lakh in 1990. The aim is to provide universal access to treatment of all TB patients, free diagnostics and treatment including quality assured drugs has been provided to all patients whether in public or private sector. The death rate due to TB was 4% with 79,144 deaths occurring in 2019, which was way below the anticipated TB death projected earlier. Through *Ayushman Bharat*-Health and Wellness Centers, screening for TB, sputum collection, referral services are now being taken up. An accelerated campaign to NSP — "*TB Harega Desh Jitega*" has been launched on September 25, 2019. The campaign has seven pillars, *i.e.* advocacy and communication, health and wellness centers and TB, inter-ministerial collaboration on TB, private and corporate sector engagement, community participation and LTBI management. For the patient centric and community led response to TB, programme is successful in making National TB Forum to engage community with the representation from various stakeholders including cured patients, civil society, etc. Also, all State TB Forums and 700 (99%) District TB Forums have also been established. Over 90,000 TB survivors have been sensitised and more than 300 trained TB Champions are now supporting nearly 8,000 TB patients. Expansion of TB services has included professional societies of the country including the Academy of Pediatricians across the country. The programme is a forerunner in adopting

a Rights and Gender-based approach, a National Framework for Gender-Responsive approach to TB is developed and aimed at equitable, right-based TB services for women, men, and transgender persons and to mobilise, empower and engage them in TB response at the community level.

Currently, a refreshed NSP to End TB in India 2020–2025 is being developed[9] which is an update of the NSP 2017–2025 and was necessitated by the rapidly changing environment within which NTEP operates. Knowledge and insights generated from the Joint Monitoring Mission in 2019, 16 large scale programme evaluations (Central Internal Evaluations) during 2017–2019; implementation of the past NSP, especially scale up of private sector involvement strategies, roll out of rapid molecular tests, LTBI treatment rollout; and updated recommendations from WHO sets the direction for this NSP. As in the past, the NSP 2020–2025 is a framework to guide the activities of all stakeholders including the national and the state governments, development partners, civil society organisations, international agencies, research institutions, private sector, and many others whose work is relevant to TB elimination in India. This NSP is a five-year proposed strategy document that provides goals, strategies and interventions for the country's response to the disease and aims to direct the attention of all stakeholders to the most important interventions that the NTEP believes will bring about significant changes in the incidence, prevalence and mortality of TB. These strategies and interventions are in addition to the processes and activities already ongoing in the country.

As a strategic document, the subsequent operational plans will necessarily follow. The NSP will guide the development of the national project implementation plan (PIP) and state PIPs, as well as District Health Action Plans (DHAP) under the National Health Mission (NHM). This NSP replaces previous strategies, and will inform and guide for updating of technical and operational guidelines and associated programme tools.

This proposed new NSP 2020–2025[9] takes into account the sustainable development goals, and global direction to END TB as is enunciated in the END TB strategy, and the United Nations High Level Meeting (UNHLM) in addition to the National Health Policy. It also takes into account the guidance provided by WHO in setting its course to end TB. Since the last NSP 2017– 2025, many new WHO policy documents has been developed which provide guidance for the national programmes. This NSP adapts the recommendations of these new and updated recommendations in the national context and incorporates them for the use in the country that incorporates **Diagnostic guidelines like** Lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis of active TB in people living with humon immunodeficiency virus (HIV); technical manual for drug susceptibility testing of medicines used in the treatment of TB (2018) (WHO); the use of next-generation sequencing technologies for the detection of mutations associated with drug resistance in *Mycobacterium tuberculosis* complex: technical guide (2018) (WHO); Global Fund`s Empowered Review Panel for Diagnostics (ERPD) recommendations; **Adult treatment guidelines, like** WHO consolidated guidelines on DR-TB treatment (2019), Rapid Communication: key changes to the treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) (Dec 2019) (WHO), WHO position statement on the continued use of the shorter MDR-TB regimen following an expedited review of the Standradised Treatment Regimen of Anti-TB Drugs for Patients with MDR-TB (STREAM) Stage 1 preliminary results (2018), WHO treatment guidelines for isoniazid-resistant tuberculosis: supplement to the WHO treatment guidelines for drug-resistant tuberculosis (2018), Handbook for the use of digital technologies to support tuberculosis medication adherence (2018), WHO position statement on the use of delamanid for multidrug-resistant tuberculosis (2018), Compendium of WHO guidelines and associated standards: ensuring optimum delivery of the cascade of care for the patients with tuberculosis (2017); **Prevention guidelines like** WHO consolidated guidelines on tuberculosis: module 1: prevention: tuberculosis preventive treatment (2020); WHO operational handbook on tuberculosis: module 1: prevention: tuberculosis preventive treatment (2020); Rapid Communication on forthcoming changes to the programmatic management of tuberculosis preventive treatment (2020), South-East Asia Regional Action Plan on Programmatic Management of Latent TB Infection (2019), WHO guidelines on TB infection prevention and control (2019); **Programme management including** People-centered framework for tuberculosis programme planning and prioritisation, User guide (2018), Multisectoral Accountability Framework to Accelerate Progress to end Tuberculosis by 2030 (2019) and Roadmap towards ending TB in children and adolescents (2020).

This new NSP adapts the WHO's post-2015 End TB Strategy, adopted by the World Health Assembly in 2014, that aims to end the global TB epidemic as part of the Sustainable Development Goals. The document includes END TB Strategy framework for designing its national strategic framework. The WHO End TB Strategy and the United Nations (UN) Agenda for Sustainable Development share the common aim of

ending the TB epidemic; the former includes ambitious milestones (2020, 2025) and targets (2030, 2035) for reductions in TB cases and deaths.

On September 26, 2018, the first ever UN General Assembly (UNGA) High-Level Meeting on Tuberculosis (UNGA-HLM-TB), with more than 1000 participants from across the world, assembled in New York. The meeting resulted in the adoption of a Political Declaration on Tuberculosis, which re-affirmed the commitment to end the TB epidemic globally by 2030 and included ambitious and bold targets for scale-up of TB care and prevention services, as well as commitments on research for new tools, principles of equity and human rights, and resource needs targets for both implementation and research. A follow-up WHO Executive Board meeting focused on ending TB re-affirmed targets set for 2022. India being a signatory is committed to attain the targets. The India NSP targets are more ambitious than the UNHLM targets and highlight the country's resolve to END TB earlier than the stipulated timeline. The UNHLM Targets for India envisage diagnosing and treating 1,19,00,000; 4,06,600 MDR-TB diagnosis and treatment; total preventive therapy for 69,97,400; 8,44,200 childhood TB diagnosis and treatment between 2018 and 2022 in a cumulative manner.

Further, the National Health Policy 2017 comes after 15 years of the last health policy in 2002. It aims at providing health-care in an "assured manner" to all by addressing the current and emerging challenges arising from the ever changing socio-economic, epidemiological and technological scenarios. It aims to raise public health-care expenditure to 2.5% of GDP by 2025 from current 1.4%, with more than two-thirds of those resources going towards primary health. The policy also calls for retaining a certain excess capacity in the public sector to meet the needs of health security and in times of crisis as is being felt during the COVID-19 pandemic. The articulation of goals, key policy principles and objectives in the National Health Policy 2017 is in tune with India's commitment towards Universal Health Coverage (UHC). The suggested architecture for achieving UHC is free primary care provision by the public sector, supplemented by strategic purchase of secondary and tertiary care services from both public and from non-government sector to fill critical gaps to assure health-care services. With an objective to achieve UHC by 2030, the Government of India has initiated significant reforms to improve citizens' access to good quality, affordable health-care. It too has innovated in its journey towards achieving universal health coverage – *"Ayushmaan Bharat"* and the NTEP proposes to utilise the *"Ayushman Bharat"* scheme to benefit TB patients. These key policy shifts in the National Health Policy that have a potential for the NTEP to leverage for expanding and deepening programme impact relate to (1) assured comprehensive care with linkages to referral hospitals; (2) assured free drugs, diagnostic and emergency services to all; (3) inter-sectoral preventive and promotive action leading to a social movement of health — the *Swasth Nagrik Abhiyan* or Health in All; (4) health and wellness centers; (5) retention of doctors and specialists in remote areas in public services; (6) creation of a multi-disciplinary public health management cadre; and (7) access, pricing, regulation and manufacture of technologies.

The TB control programme in the country has undergone a paradigm shift in recent times and is a glowing success story on many fronts. There is substantial visible commitment not only at the highest political levels, but also among other ministries and stakeholders. Are these achievements enough to achieve End TB Strategy? The answer is "NO" and much more is required to be done to accelerate the march towards a TB free India. The coming years are critical and would require a holistic approach and intensive efforts to expand access and improving the quality of services to achieve the ambitious aspirations to End TB by 2025 in the country.

The targets of End TB are to reduce the estimated TB incidence from 217 per 100,000 population in 2015 to 44 per 100,000 population; to reduce the prevalence from 320 to 65 per 100,000 population during the same periods; to reduce the mortality from 32 to 3 per 100,000 population between 2015 to 2025 and to ensure no family should suffer catastrophic cost due to TB by 2020 and to be maintained till 2025. During this period total TB notification is to be increased, there should be increased involvement of the private sector, there should be increased notification and treatment of more number of MDR/RR-TB cases; offering of DST (Drug Susceptibility Testing) to almost all cases (Universal DST); to achieve a treatment success rate of 92% for the drug sensitive cases and 75% for the DR-TB cases; 100% of identified targeted key affected population undergoing active case finding; 90% of the notified TB patients receiving financial support through Direct Benefit Transfers (DBT); and 95% of the identified/ eligible individuals for preventive therapy/LTBIs to be initiated on therapy.

With all these strategies in place, the question is, can we end TB by 2025? What are the challenges? TB elimination is defined as achieving an incidence of less than 1 case of infectious TB per million populations or a prevalence of LTBI infection of less than 1%. Several countries have already reached the TB elimination phase; others are expected to do so in the foreseeable

future. We need to distinguish between the words End TB and TB Elimination. **End TB** is the reduction of TB deaths and incidence rate by 90% and by 80%, respectively by the year 2030 (in India it is pre-dated to 2025) in comparison to 2015.[6] The same figures should be 95% and 90% respectively by 2035 (India has no commitment/clarification regarding 2035, presumably the target will be by 2025). Moreover, TB affected families should not face catastrophic cost due to the disease (0% starting from 2020). Currently, the TB incidence is declining only by 1%-2% per year and to achieve the NSP goal by 2025, we need to have an accelerated annual decline in TB incidence by about 10%. For this, the country need to optimise the existing strategies with the proposed new one and to ensure universal access through free diagnosis, treatment, active engagement of the private sector, utilisation of digital technologies and solutions that reaches the last man.

Are there any constraints in achieving this goal of Ending TB by 2025? We do not have the exact epidemiological data about TB prevalence in India. We are working on estimated numbers only based on periodic sub-national data (Guessing estimates). After the 1955-58 TB epidemiology study by Indian Council of Medical Research (ICMR) we do not have a nation-wide data although there are several sub-national studies. After about 60 years, the RNTCP and ICMR are undertaking a prevalence survey at the national level and it will take some time to get the exact results. Although there are several estimates based on these sub-national studies, as per the NIKSHAY reporting system, the programme can only diagnose/notify 75%, 73% and 84% of the target for the years 2017, 2018 and 2019, respectively, thus missing a large number of cases.[1] Therefore, case finding and notification and treating these cases with success are the key to achieve the strategy. As per the 2020 Annual TB Report, out of the 24 lakh notified TB cases in 2019, 94.4% (N=2,272,518) were initiated on treatment. The remaining 5.6% (N=132,297) of cases were not initiated on treatment, thus a sizable number of over one lakh cases were not treated by the programme despite notification. Other lapses of the programme was that of the reported 21 lakh cases in 2018, treatment success was 80% (N=16.79 lakhs), which is not a very good figure. Death rate was 4%, lost to follow-up after treatment initiation was 4%, treatment failure and regimen change was together about 2%, and an overall of 7% cases were not evaluated after the notification. With these figures, if we make a calculation of 100 cases of TB in the country; 84 are notified to the programme; 94.4% are initiated on the treatment, thus 79 patients of these 100 are put on treatment. If the treatment success rate is 80%, then 63.4 cases out of the 100 cases in the community are cured by the programme. This is an unsatisfactory figure for our goal of End TB.

Latent TB Infection

Latent tuberculosis infection is defined as a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without the evidence of clinically manifested active TB disease. Individuals with LTBI represent a reservoir for active TB cases. According to recent estimates, approximately one-quarter of the global population is infected with LTBI.[15] The duration of latency is variable, and healthy individuals can harbor LTBI for a lifetime. In a small fraction (~5%–15%), reactivation occurs, often within the first 2 to 5 years following infection.[16,17] Reactivation is the process by which a sub-clinical latent infection transitions into active TB disease. Thus, individuals with LTBI represent a major reservoir for new active TB cases.[18-20] In 2014, the global burden of LTBI was 23.0% (95% uncertainty interval: 20.4%–26.4%), amounting to approximately 1.7 billion people. WHO South-East Asia, Western-Pacific, and Africa regions had the highest prevalence and accounted for around 80% of those with LTBI. Prevalence of recent infection was 0.8% of the global population, amounting to 55.5 million individuals currently at high risk of TB disease, of which 10.9% was isoniazid-resistant. Current LTBI alone, assuming no additional infections from 2015 onwards, would be expected to generate TB incidences in the region of 16.5 per 100,000 per year in 2035 and 8.3 per 100,000 per year in 2050. In 2014, India had 354,000,000 (range of 339,000,000 – 377, 000,000) LTBI cases, thus, having a huge pool with a potential to develop into active TB.[15] Other studies have reported the prevalence of LTBI to be 48% (Quantiferon test) and 42% by TST (tuberculin skin test) and an overall positvity of 37.5% by both the tests.[16-20] Thus, there are a huge number of infected persons in the country those can progress to active TB cases. Therefore, an important strategy/goal have to be to treat these cases of LTBI. The contact screening is one of the ways for intensified case finding activity which RNTCP has implemented since its inception. Under RNTCP all children less than six years of age and contacts of the family member suffering with active TB are screened for active TB and provided isoniazid (INH) chemoprophylaxis once active TB has been ruled out. However, only 30% of the eligible households were visited and 68% of the identified contacts were screened for TB by the programme. Out of more than 2.5 lakh children contacts of less than six years of age who were screened for TB as part of household contact investigation in 2018, only 83,000 contacts (23% of eligible) of adult index TB cases offered preventive

therapy in 2018, which is a grossly inadequate coverage for the chemoprophylaxis.[21] In 2019 among the child household contacts, nearly 4.2 lakhs contacts (78%) of TB cases aged less than six years were offered preventive therapy.[21] The country has not yet started prophylaxis for other infected cases except people living with HIV. Even if the country will be able to do that, it has not yet been planned and the programme has not conducted any trial on the regimen yet, even though it wishes to use chemoprophylaxis as a strategy.

Various risk factors are known to perpetuate and are known to be responsible for progression to active TB.[22-26] These include close contacts of a person with infectious TB disease, persons who have immigrated from areas of the world with high rates of TB, children less than five years of age who have a positive TB infection test, groups with high rates of TB transmission, such as homeless persons, injection drug users, and persons with HIV/AIDS (acquired immunodeficiency syndrome) infection, persons who work or reside with people who are at high risk for TB in facilities or institutions, such as hospitals, homeless shelters, correctional facilities, nursing homes, and residential homes for those with HIV, persons with medical conditions that weaken the immune system, and babies and young children often have weak immune systems. Other people can have weak immune systems too, especially people with any of these conditions: HIV infection, substance abuse, silicosis, diabetes mellitus, severe kidney disease, malnutrition with low body weight, organ transplants, cancer, medical treatments, such as corticosteroids or immunosuppressive therapy and specialised treatment for rheumatoid arthritis or Crohn's disease, smoking, over-crowding like slum dwellers, prisons, homeless and shelter homes and migrants.[22-26] Many of these risk factors are there in plenty in India. A brief description of some of these risks will be discussed.

HIV and Other Immunosuppressive States

The total number of people living with HIV (PLHIV) in India is estimated at 21.40 lakhs (15.90 lakhs–28.39 lakhs) in 2017, with a prevalence of 0.2% (0.16% – 0.30%) amongst persons aged 15-49 years of age.[27] Although the risk of developing TB in HIV will depend upon several factors like antiretroviral treatment (ART) therapy, CD4 counts, INH prophylaxis and HIV prevalence, the risk has been very high.[28-31] Despite free ART being available, uptake remains low as many people face difficulty in accessing the clinics. PLHIV are 21 times at higher risk of developing TB. It is estimated that India is to have around 87.58 (36.45 – 172.90) thousand new cases every year. The epidemic is concentrated among key affected populations, including sex workers and men who have sex with men. The National AIDS Control Programme (NACP) has made particular efforts to reach these two high-risk groups with HIV interventions. Compared to neighbouring countries, India has made good progress in reducing new HIV infections by half since 2001. Only 56% of adults are on anti-retroviral treatment. TB is the leading cause of morbidity and mortality among PLHIV. India has the third-highest number of HIV cases in the world. TB-HIV co-infection results in higher mortality rates and nearly 25% of all deaths among PLHIV are estimated to be due to TB. The TB-HIV collaborative framework is being successfully implemented since 2001 and learning from the success of this initiative has been expanded to form TB co-morbidity committees at all levels. The HIV co-infection rate among incident TB patients is estimated to be 3.4%. Total 92,000 HIV-associated TB patients have been estimated annually. By numbers, India ranks second in the world and accounts for about 9% of the global burden of HIV-associated TB. The mortality in this group is very high and 9,700 people die every year among TB/HIV co-infection. The single window delivery of TB and HIV services is being successfully implemented for all PLHIV in the ART centers, where in intensified case-finding through screening all ART centre attendees for TB, offering rapid molecular testing to symptomatic and ICT adherence-based daily fixed dose combination (FDC) anti-TB treatment, tuberculosis therapy for TB prevention and airborne infection control activities in HIV care settings are being carried out. These interventions along with the joint collaborative activities helped in reducing TB related fatalities by 85% (baseline 2010) among PLHIV, thereby meeting the 2020 END TB target. The single window delivery of TB and HIV services for all PLHIV receiving care in the ART centres have been streamlined with improved coverage. Over 90% of PLHIV are being screened in ART centres for TB symptoms, and nearly six lakh PLHIV have been given access to rapid molecular testing via Cartridge Based Nucleic Acid Amplification Test (CBNAAT) for TB diagnosis. Nearly one lakh TB/HIV patients were initiated on daily drug regimen, nearly five lakh PLHIV were initiated on TB preventive therapy till December 2018. These interventions along with the joint collaborative activities helped in reducing TB related fatalities by 82% (from baseline 2010). Over 94% of PLHIV are being screened in ART centres for TB symptoms. Although there is a good coordination between the two programmes, (NACO and RNTCP/NTEP), the basic fact is that many PLHIV are still uncovered and the activities need to be scaled up in a sustained manner.

Diabetes Mellitus

Once named as the Diabetes capital of the world, the number of people with diabetes mellitus (DM) in India

increased from 26 million in 1990 to 65 million in 2016. The prevalence of diabetes in adults aged 20 years or more in India increased from 5.5% in 1990 to 7.7% in 2016.[32] Until recently, according to the International Diabetes Foundation, India had more diabetics than any other country in the world, although the country has now been surpassed in the top spot by China.[33] India will see the greatest increase in people diagnosed with diabetes by 2030. The high incidence is attributed to a combination of genetic susceptibility plus adoption of a high-calorie, low-activity lifestyle by India's growing middle class population. Projections for the whole of India would be 62.4 million people with diabetes and 77.2 million people with pre-diabetes. India is projected to be home to 109 million individuals with diabetes by 2035. In a recent study by ICMR, it was found that the overall prevalence of diabetes in 15 states of India was 7.3%, and the overall prevalence of pre-diabetes was 10.3% and there were large differences in its prevalence between the States. Thus, diabetes as a risk factor for TB will be another important challenge for End TB by 2025.[34] Individuals with DM have three times more the risk of developing TB and there are now more individuals with TB-DM co-morbidity than TB-HIV co-infection and the prevalence of TB-DM is higher in low- and middle-income countries where TB and DM are most prevalent.[35-38] Therefore, patients with DM need to be screened for TB. Evidence and modelling studies indicate that nearly 20% of all TB cases in India also suffer from DM. Diabetes can worsen the clinical course of TB, and TB can worsen blood sugar control in people with diabetes. The NTEP and the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) have jointly developed a 'National Framework for Joint TB-Diabetes Collaborative Activities' in 2017. The framework aims to reduce the morbidity and mortality due to TB and diabetes through prevention, bi-directional screening for early diagnosis and prompt management of TB and diabetes. Accordingly, all TB patients need to be screened for diabetes by testing for blood sugar, and diabetic patients attending diabetic clinics should be asked for symptoms of TB during each visit. As a result of the implementation of TB-Diabetes collaborative framework, nearly 72% of the designated microscopy centers under NTEP are now co-located in diabetes screening facility. Between April 2019 and September 2019, 11% of the non-communicable disease (NCD) clinic attendees under NPCDCS have been screened for TB, as compared to 6% in April 2018—March 2019. Among those screened for TB, referral for TB testing has increased from 13% in April 2018-March 2019 to 14% in April-September 2019. The performance has improved across most States. In 2019, among the notified TB patients under RNTCP, 64% had their blood sugar screened. Among all TB patients screened, 7% were TB-diabetes co-morbid and 52% among these were linked to diabetic treatment. Despite improvements in the TB-diabetes collaboration, it is perhaps not being pursued vigorously.

Smoking

There is a strong association between tobacco smoking and TB. Smoking substantially increases the risk of TB and death. More than 20% of global TB incidence may be attributable to smoking.[39,40] Controlling the tobacco epidemic will help control the TB epidemic. Smoking is a risk factor for TB, independent of alcohol use and other socio-economic risk factors and 40% of the TB burden in India may be attributed to smoking. Smoking increases the risk of TB disease by more than two-and-a-half time. About 28.6% of the population consume tobacco in any form, 10.7% smoke. Nearly 275 millions of adults smoke tobacco in India.[39,40] India is the second-largest tobacco consumer country in the world and the third-largest producer of tobacco after China and Brazil (FAO, 2005). As per Global Adult Tobacco Survey-2 (GATS-2), nearly 28 % of the adult population in 2017-18, *i.e.* nearly 275 million adults consume tobacco in some form or the other and this adversely impacts TB case management due to the strong association between tobacco use and TB treatment outcomes. The use of smokeless tobacco is much more prevalent than smoking tobacco. Prevalence of smokeless tobacco use (26%) is almost twice the prevalence of smoking tobacco (14%). Five percent of adults use both, smoking as well as smokeless tobacco. The prevalence of tobacco use (both smoking and smokeless forms) is higher in rural areas as compared to urban areas. The women use mainly the chewing forms of tobacco (smokeless). A study conducted in 2004 using health-care data from the National Sample Survey Organization (NSSO), estimated that the tobacco–attributable cost of TB was three times higher than the expenditure on overall TB control in the country. Therefore, WHO recommended policies to combat tobacco and TB with control tobacco everywhere, but especially where people are at risk of TB infection, coordinate national TB and tobacco control programmes, cross-train TB and tobacco control health workers, register TB patients' tobacco use and offer them counseling and treatment, promote and enforce smoke-free policies, particularly where TB services are delivered, integrate brief tobacco interventions (5 'A's and the 5 'R's) [**5 A's** — Brief intervention method that is effective: (1) Ask about tobacco use, (2) Advise to quit, (3) Assess willingness to make a quit attempt, (4) Assist in quit attempt and (5) Arrange follow-up. **5 R's** — Use for a client who is unwilling to quit at this time: (1) Determine the relevance of quitting to client,

(2) Discuss the risks of client's continued tobacco use, (3) Explore rewards of quitting, (4) Examine possible roadblocks to quitting and (5) Continue repetition of the discussion.] into TB control programme activities, implement smoking cessation procedures through PAL (the Practical Approach to Lung Health).[41] The National Framework for Joint TB-Tobacco Collaborative Activities has been developed for India and the Framework provides guidelines for the programme managers of RNTCP and the National Tobacco Control Programme (NTCP).[42] The NTEP and NTCP have jointly developed the 'National Framework for Joint TB-Tobacco Collaborative Activities' in 2017 to reduce the burden of co-morbidity due to TB and tobacco use. The strategies of the framework include the establishment of collaboration mechanism, identification of tobacco users among TB patients and the provision of brief advice, TB symptom screening among all tobacco cessation set-ups and linkage to the services and awareness generation activities. Such pilot ventures showed that 67.3% patients and 75% TB patients respectively quit tobacco use after offer of 'Brief Advice' to TB patients registered for the Directly Observed Treatment, Short-course (DOTS). The programme has set up TB comorbidity committee at National, State and District levels on the lines of TB-HIV committee to build the capacity of all stakeholders, to establish and streamline recording and reporting mechanisms and to strengthen the collaboration. Under NTEP nearly 57% of the notified TB patients had their tobacco usage status known and 14% were found to be tobacco users. Among those using tobacco, 24% were linked to Tobacco Cessation Centres (TCCs),[42] in addition to brief advice being provided to all TB patients. The TB Tobacco cessation service programme is being implemented in all States/UTs of the country with focussed activities in 2 districts in each of the 8 States. In these districts, 83% of the TCCs attendees were screened for TB symptoms and 9% were referred for TB testing.

Although RNTCP has expanded its collaboration with diabetes and tobacco control programmes and is being further strengthened with cross linkage of services, nearly 36% and 27% of the TB patients in public sector have been screened for diabetes and tobacco usage, respectively and linked to appropriate services through the NCD programme and the Tobacco Control Programme. However, a lot more need to be done in this area.

Over-crowded Places (Slum Dwellers, Prisons, etc)

People living in over-crowded places, like slums, prisons, shelter homes, etc are more prone for developing active TB. Slums are those residential areas where dwellings are unfit for human habitation by reasons of dilapidation, over-crowding, faulty arrangements and designs of such buildings, narrowness or faulty arrangements of streets, lack of ventilation, light or sanitation facilities or any combination of these factors which are detrimental to safety, health and morals. A total of 52.4 million people were living in the slums, According to the 2001 Census of India, it was about 5.09% of the total population. The slum dwellers were 18.3% of the total urban population. The report of the Committee on Slum Statistics/Census 2011 had projected that in 2017 the total slum population will be 104. 7 million. According to a United Nations (UN) report, the share of urban Indians living in slums is 24%—about 100 million people. Because of over-crowding and poor ventilation, cases of TB of either type (drug sensitive or drug-resistant forms) are much higher than in the general population.[43] In a recent review[44] it was found that compared with national TB incidence rates, the combined odds ratio (OR) of smear-positive TB within slums was 2.96 (2.84–3.09; p<0.01). The combined OR for smear-positive TB with active case finding across 15 studies was 2.85 (2.71–2.99; p<0.01). Among the 11 studies that reported incidence of smear-positive TB with prevalent TB-HIV co-infection in the community, the combined OR for slum residents with the random effects model was 2.48 (2.34–2.63; p<0.01). The findings indicated that the odds of developing TB are almost five times more in urban slums.[44] Reaching the most vulnerable and often overlooked groups in the slums is crucial to achieve the Sustainable Development Goals (SDGs) and End TB Strategy by 2035. A survey was carried out to estimate the point prevalence of bacteriologically positive pulmonary tuberculosis (PTB) among persons ≥15 years of age residing in *Jhuggi-Jhopri* (JJ) colonies, urban slums in Delhi. Among 12 *JJ* colonies selected through simple random sampling, persons having persistent cough for more than 2 weeks at the time of the survey or cough of any duration along with a history of contact/currently on ant-TB treatment/known HIV positive were subjected to sputum examination– 2 specimens, by smear microscopy for acid-fast bacilli and culture for *Mycobacterium tuberculosis*. Persons with at least one specimen positive were labeled as bacteriologically confirmed PTB. Prevalence was estimated after imputing missing values to correct bias introduced by incompleteness of data and corrected for non-screening by x-ray by a multiplication factor derived from recently conducted surveys.[45] Of 40,756 persons registered, 40,529 (99.4%) were screened. Of them, 691 (2%) were eligible for sputum examination and spot specimens were collected from 659 (99.2%) and early morning sputum specimens from 647 (98.1%).

Using screening by interview alone, prevalence of bacteriological positive PTB in persons ≥15 years of age was estimated at 160.4 (Confidence interval (CI) 123.7-197.1) per 100,000 populations and 210.0 (CI: 162.5-258.2) after correcting for non-screening by x-ray.[45] The observed prevalence suggests further strengthening of TB control programme in urban slums. The 2020 TB report of India shows that National Urban Health Mission (NUHM) frontline workers to carry out TB screening, referral and treatment adherence support, reaching 140,000 households in urban slum pockets, identifying 15,604 presumptive TB cases, and contributing to 1535 TB patients being diagnosed and linked with TB treatment. However, slum areas need special attention of the programme.

Prisons

Prisons are other TB hot spots. In 2018, in India there were 466,084 prisoners in 1412 Jails against a capacity of 380,876 (occupancy rate of 117.6%). Indian prisons are always having inmates which are more than the sanctioned capacity, so that they are often over-crowded.[46,47] It is estimated that the world's prisons hold 8-10 million prisoners any day and 4-6 times this number pass through prisons each year, because of the high turnover of the population. A disproportionate number of prisoners come from socio-economically disadvantaged populations where the burden of the disease may be already high and access to medical care is limited, *e.g.* substance users, homeless, mentally ill, ethnic minorities, asylum seekers, immigrants. Prison conditions can facilitate the spread of the disease through over-crowding, poor ventilation, weak nutrition, inadequate or inaccessible medical care, etc. The level of TB in prisons has been reported to be up to 100 times higher than that of the civilian population. Cases of TB in prisons may account for up to 25% of a country's burden of TB. Late diagnosis, inadequate treatment, over-crowding, poor ventilation and repeated prison transfers encourage the transmission of TB infection. HIV infection and other pathology more common in prisons (*e.g.*, malnutrition, substance abuse) encourage the development of active disease and further transmission of the infection. High levels of MDR-TB cases have been reported from some prisons with up to 24% of TB cases suffering from MDR forms of the disease. Factors that encourage the spread of TB in prisons also promote the spread of MDR forms. Prisoners may self-treat because of barriers to access to medical care with supplies of anti-TB drugs available through visitors or internal markets. However, such supplies are usually erratic and unregulated and promote further development of MDR-TB. As prisons act as a reservoir for TB, pumping the disease into the civilian community through staff, visitors and inadequately treated former inmates is common. TB does not respect prison walls. Improving TB control in prisons benefits the community at large. Community TB control efforts cannot afford to ignore prison TB. Prisoners have the right to at least the same level of medical care as that of the general community. Catching TB is not a part of a prisoner's sentence. Therefore, the priority strategy must be the widespread implementation of the End TB Strategy in the incarcerated population. Every prisoner should have unrestricted access to the correct diagnosis and treatment of TB. Delays in the detection and treatment of TB cases must be minimised to reduce further transmission of the infection and pressures to self-treat TB. Unregulated, erratic treatment of TB in prisons should cease. Urgent action is needed to integrate prison and civilian TB services to ensure treatment completion for prisoners released during treatment. Measures to reduce over-crowding and to improve living conditions for all prisoners should be implemented to reduce the transmission of the TB.[48-52]

Although the Annual TB Report 2020 of Government of India does not give any specific figures about TB in prisons in India, it emphasises that NTEP is collaborating with the Department of Home for HIV-TB interventions in prisons and other closed settings. Nonetheless, there are many studies from different parts of the country which highlights the increased risk of TB, and HIV in our prisons that need special attention. Prasad *et al*[53] conducted a study in 157 prisons across 300 districts between July to December 2013. Information on services available and practices followed for screening, diagnosis and treatment of TB was collected. Additionally, the inmates and prison staff were sensitised on TB using inter-personal communication materials. The inmates were screened for cough ≥2 weeks as a symptom of TB. Those identified as presumptive TB patients (PTBP) were linked with free diagnostic and treatment services. The study found that diagnostic and treatment services for TB were available in 18% and 54% of the prisons, respectively. Only half of the prisons screened inmates for TB on entry, while nearly 60% practised periodic screening of inmates. District level prisons (OR, 6.0; 95% CI, 1.6-22.1), prisons with more than 500 inmates (OR, 52; 95% CI, 1.4-19.2), and prisons practising periodic screening of inmates (OR, 2.7; 95% CI, 1.0-7.2) were more likely to diagnose TB cases. About 19% of the inmates screened had symptoms of TB (cough ≥2 weeks) and 8% of the PTBP were diagnosed with TB on smear microscopy. The authors concluded that TB screening, diagnostic and treatment services are sub-optimal in prisons in India and need to be strengthened urgently. Similar such studies are available from other parts of the country like Mizoram, Chhatisgarh and South India.

Poverty and Other Social Determinants of TB

Other social elements, like poverty, are a powerful determinant of TB. Crowded and poorly ventilated living and working environments are often associated with poverty which constitutes direct risk factor for the transmission of TB. Under-nutrition is an important risk factor for developing the active disease. Poverty is also associated with poor general health knowledge and a lack of empowerment to act on health knowledge, which leads to the risk of exposure to several risk factors of TB, such as HIV, smoking and alcohol abuse. Poverty alleviation reduces the risk of TB transmission and the risk of progression from infection to disease. It also helps to improve access to health services and adherence to the recommended treatment. Actions on the determinants of ill health through "health-in-all-policies" approach will immensely benefit TB care and prevention. The required social, economic and public health policies include those that pursue overarching poverty reduction strategies and expanding social protection; reduce food insecurity; improve living and working conditions; improve environment and living conditions in prisons and other congregate settings; address the social, financial, and health situation of migrants; and promote healthy diets and lifestyles, including reduction of smoking and harmful use of alcohol and drugs. Addressing the social determinants of health is a shared responsibility across the disease programmes and other stakeholders within and beyond the health sector. Gender issues are also important. In most of the world, more men than women are diagnosed with TB and die from it. TB is nevertheless a leading infectious cause of death among women. As TB affects women mainly in their economically and reproductively active years, the impact of the disease is also strongly felt by their children and families. Stigmatising and discriminating attitudes towards TB patients remain high among the general population in India.[54,55] Since these attitudes were independent of the knowledge regarding TB, it is possible that the current disseminated knowledge regarding TB which is mainly from a medical perspective may not be adequately addressing the factors that lead to stigma and discrimination towards TB patients. Therefore, there is an urgent need to review the messages and strategies currently used for disseminating knowledge regarding TB among general population and revise them appropriately. The disseminated knowledge should include medical, psycho-social and economic aspects of TB that not only informs people about medical aspects of TB disease, but also removes stigma and discrimination. There are other individuals, groups or communities who are marginalised, such as women, children, scheduled castes (SC), scheduled tribes (ST), persons with disabilities, migrants and also the aged population whose interest needed to be taken care of.[56,57] The SC/ST population constitutes about 22.5% of the Indian population and these communities are considered as the marginalised groups. The tribal populations, in particular, are constrained by the structural and cultural barriers in accessing health services. The magnitude of TB disease among vulnerable population and the changes over time are useful indicators for understanding the extent of TB transmission and for monitoring the effectiveness of TB control in the area. Information on these aspects is not available in tribal areas as it is difficult to obtain such information at the community level, especially in a large country like India with limited resources. In India, the tribal population is 104 million constituting 8.6% of the total population. The Saharia tribe is one among these groups and live in geographically isolated locations, working mainly as agriculture labours with very low socio-economic living conditions. A very high prevalence of infection (20.4%) and TB disease (1518 per 100,000) has been reported among them.[58-60] A recently conducted TB disease prevalence survey in Gwalior district showed alarmingly high TB prevalence of 3294 per 100,000 in this community.[59] The high prevalence of PTB was found to be associated with malnutrition, poor housing conditions, alcoholism, tobacco smoking and history of asthma. Health literacy on TB among these vulnerable tribal groups was very poor. Equal benefits from the programme are available to all the sections of the society irrespective of caste, gender, religion, etc. However, in large proportion of tribal and hard to reach areas the norms are relaxed. These include provision of additional Designated Microscopy Centres (DMCs) and TB Units, travel facilities, higher rates of salary and enhanced vehicle maintenance, etc. These need further strengthening.[61,62]

Nutrition

Under-nutrition and TB are closely linked co-epidemics in India.[63,64] In TB, as in many other infectious diseases, there is a bi-directional interaction between the nutritional status and the active disease.[65] Under-nutrition is associated with an increased frequency, severity and fatality of infections, including TB; while infections in turn lead to under-nutrition. Under-nutrition affects a third of the adult population. It increases the risk of LTBI progressing to active TB.[66] At the population level in India, under-nutrition is the most widely prevalent risk factor for TB. An estimated 55% of TB incidence in India (or more than 1 million new cases annually) are attributable to the effect of under-nutrition,[67] which is significantly greater than those

attributable to other risk factors, like HIV (5%), diabetes (9%) or smoking (11%).[68] Malnutrition was the primary reason behind 69% of deaths of children below the age of five years in India, according to a United Nations International Education Fund (UNICEF's), The State of the World's Children 2019 report. The report further says that every second child in India, belonging to that age group is affected by some form of malnutrition. This includes stunting (low height for age) with 35% of the children, wasting (low weight for height) with 17% and 2% over-weight. Malnutrition is not an issue that is new rather it has been a major cause of concern for Indians for decades. The UN's Sustainable Development Goal 2 wants to ensure Zero Hunger, while Goal 3 is good health and well-being for all; these goals are expected to be met by India by 2030.[69-72] The Global Nutrition Report 2018 also reaffirmed[71] the crisis of malnutrition in the nation by concluding that India topped the list of the maximum number of stunted children with 46.6 million cases being recorded as having low height for their age. India was followed by Nigeria (13.9 million) and Pakistan (10.7 million). The report further stated that India was also accounted for 25.5 million children who are wasted. According to the National Family Health Survey-4 (NFHS-4), India has unacceptably high levels of stunting, despite marginal improvement over the years. In 2015-16, 38.4% of children below five years were stunted and 35.8% were under-weight. India ranks 158 out of 195 countries on the human capital index.[72] 194 million Indians are undernourished. Recently out of 117 countries, India ranked at 104 at the Global Hunger Index. India is home to 46.6 million stunted children, a third of world's total as per Global Nutrition Report 2018. Nearly half of the under-5 child mortality in India is attributable to under-nutrition. Any country cannot aim to attain economic and social development goals without addressing the issue of malnutrition. Malnutrition was the predominant risk factor for death in children younger than five year of age in every state of India in 2017, accounting for 68.2% of the total under-5 deaths, translating into 706,000 deaths (due to malnutrition). It was also the leading risk factor of loss of health among all age groups. This was revealed in the state-wide data on malnutrition presented by the ICMR, Public Health Foundation of India (PHFI) and National Institute of Nutrition (NIN).

According to the Global Malnutrition Report 2020, India will miss targets for all four nutritional indicators for which data is available. These indicators include– stunting among under-5 children, anaemia among women of reproductive age, childhood overweight and exclusive breast-feeding. According to the data available on stunting and wasting among children in the country, 37.9% of children below the age of five years are stunted and 20.8% are wasted, compared to the Asia average of 22.7% and 9.4%, respectively. Additionally, stunting prevalence is 10.1% higher in the rural areas compared to urban areas.[69-72] In India, one in two women of reproductive age is anaemic, one in three children under five years of age is stunted, and one in five children under five years is wasted. Inequalities are evident for stunting, with stunting prevalence being 10.1% higher in rural *versus* urban areas. Rates of over-weight or obesity reach 20.7% in adult women and 18.9% in adult men. With this coexistence of under-nutrition and overweight or obesity, India faces the double burden of malnutrition.

Organ Transplantation

Organ transplantation programmes are rapidly progressing in India over the last few years. The most common transplantation is kidney, liver, heart, lung, pancreas and bone-marrow.[73,74] Use of immunosuppressive drugs is frequently used for these conditions and organ transplantation itself is an immunosuppressed state. The incidence of TB in organ transplant recipients worldwide ranges from 0.35% to 15%.[74-83] So far a total of 21,395 kidney and liver transplants have been carried out according to the Indian Transplant Registry maintained by the Indian Society of Organ Transplantation. Tuberculosis is an important infection encountered after renal transplantation in third-world countries. Tuberculosis incidence in kidney transplanted recipients was 28 times higher than in the general population in a study from Brazil.[80] Over an 8-year period, 36 cases of TB were encountered in 305 renal transplant recipients (11.8%) with grafts functioning for more than three months followed up at the PGIMER, Chandigarh.[79] The infection was limited to the thoracic cavity in 41.7% and a single extra-pulmonary site in 11.1%, and it was disseminated in 27.8% cases. In 19.4% of cases, the disease appeared as pyrexia of unknown aetiology and the diagnosis was confirmed by a good therapeutic response to anti-tubercular therapy. Tuberculosis was diagnosed within one year of transplantation in 58.3% of cases. There was no significant difference in the incidence of TB in patients on different immunosuppressive regimens. A review of BMT (Bone Marrow Transplant) patients in large US centers revealed an incidence rate of 0.5%-1% and the scant data available in countries with a high incidence of TB referred frequencies ranging from <1% to 5.5% and 16% in Pakistan.[74-83] Thus, it is imperative that the RNTCP programme should be in touch with the transplant programmes undertaken in different Institutions to diagnose TB. It is estimated that a transplanted patient has a risk of developing TB

50 times higher than the general population. The chance of developing TB in dialysed patients is considerably high due to uremia-induced immunosuppression, this risk is 10-25 times higher in these patients compared to the general population, and is independent of the status of tuberculin test. Furthermore, patients on dialysis are generally the candidates for transplantation and latent disease can progress to the disease during immunosuppression imposed during kidney transplantation, *i.e* patients on hemodialysis have a high risk of TB reactivation. Tuberculosis in these patients can be difficult to diagnose and frequently presents in the extra-pulmonary form. Previous studies suggest that there are high rates of purified protein derivative (PPD) energy in patients in the final stage of renal disease and in dialysates.[76] The risk is increased between chronic renal failures, and increased even more when these patients undergoing transplantation are placed under immunosuppressive therapy. Most cases are found in the first year after transplantation, so they are likely to represent the progression from latent infection to active disease. Identifying these cases has a positive impact on the morbidity and mortality associated with this infection. Nosocomial transmission of TB has also been reported in long-term dialysis patients. Studies report an 8-fold increase in the incidence of TB in dialysis patients compared to the general population. Detection of LTBI in this population is, thus, an important issue, to prevent the progression to active TB and secondary contamination to other patients and health-care professionals.[75-83]

Immunosuppressive States Other Than HIV

Corticosteroids and other immunosuppressive drugs including anti-tumour necrosis factor (TNF) drugs (infliximab, etanercept, etc) are commonly used for a variety of conditions.[84-99] Tuberculosis is one of the most significant infection in patients receiving these drugs. The clinical expression of TB in immunosuppressed patients is conditioned by the patient's degree of immunosuppression. It is important to keep this peculiarity in mind so as not to delay the diagnosis of suspected TB. Current available data show an association between systemic corticosteroid therapy and an increased risk of reactivation of LTBI. In relation to inhaled corticosteroids, Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines 2019 state that it is not possible to draw definitive conclusions, although observational studies and a meta-analysis of randomised controlled trials describe a possible association. It is worth noting that in the cited meta-analysis, both follow-up and number of incident cases of TB were limited.

Health-Care Workers

Health-care workers (HCWs) are at an increased risk of acquiring TB compared to the general population, regardless of economic setting and local TB incidence.[100-107] However, the risk is higher in low-resource, high-TB-burden settings, where HCWs are in more frequent and prolonged contact with the people in an infectious stage of active TB.[100-105] Health-care facilities in low- and middle-income countries, where TB is more likely to be endemic, lack the resources to implement effective TB infection control, placing HCWs at serious risk.[102-104] An estimated 81% of TB cases among HCWs are attributable to occupational exposure.[100] In India, therefore, HCWs are a more vulnerable group requiring constant watch.

Occupation and Tuberculosis

Occupational lung diseases, especially silicosis, are well established risk factors for the development of active TB.[108-113] Silicosis occurs most commonly as an occupational disease in people working in the quarrying, manufacturing and building construction industries. It is also reported from population with non-occupational exposure to silica dust from industrial as well as non-industrial sources. In 1999, the ICMR reported that around three million workers are at high risk of exposure to silica; of these, 1.7 million work in mining or quarrying activities, 0.6 million in the manufacture of non-metallic products (such as, refractory products, structural clay, glass and mica) and 0.7 million in the metals industry. There are also around 5.3 million construction workers at the risk of silica exposure. In India silicosis is prevalent in Gujarat, Rajasthan, Pondicherry, Haryana, Uttar Pradesh, Bihar, Chhattisgarh, Jharkhand, Odisha and West Bengal. Prevalence of silicosis in India ranges widely from 3.5% in ordnance factory to 54.6% in the slate-pencil industry and this variation in the prevalence is due to the silica concentrations in different work environments, duration of exposure and the job demands.[114-122] Tuberculosis is a common complication reported in Indian studies. Therefore, silica workers are another group of workers need special attention by the programme.

Other Issues

While the programme is marching ahead to end TB by 2025, the above discussed factors, like HIV and other immunodeficiency states, diabetes mellitus, malnutrition, over-crowded areas (slums, prisons), chronic kidney diseases, chronic liver diseases, organ transplantation, alcoholism, drug abuse, homelessness, occupations (silicosis) are to be taken care of. A population's nutritional profile is an important determinant of its

TB incidence. Ultimately, reduction of TB burden in India and its elimination will require improving the nutritional status of the community as a whole. General improvement of the socio-economic conditions, better housing, are important parameters that are linked to the political system of the country. That is how and why TB is a very uncommon problem in developed countries. Thus, End TB will have a direct link to the overall socio-economic development of the country.

Private Sector and TB Control Programme

The RNTCP/NTEP has taken many new initiatives and policy changes over the last few years as discussed earlier under the NSP 2017–25 and proposed NSP 2020–25. Involving the private sector is one of the key factors to achieve universal health coverage for TB care services. Currently, the incidence of TB is declining by about 1%–2% per year and to achieve the END TB strategy by 2025, we need to have an accelerated annual decline in TB incidence by about 10%. For this, there is a need to catch all TB patients in the country, register them under the programme, diagnose them and to see that treatment is completed hassle free. The estimated TB incidence in India is around 28.8 lakh. In 2018, RNTCP was able to achieve a notification of 21.5 lakh. This is a 16% increase as compared to 2017 and the highest so far. Of the total notification, 25% (5.4 lakh) cases was from the private sector; a 40% increase from the last year. Among the notified, treatment was initiated for about 19.1 lakh cases (~90%), across both public and private sectors. This indicates an increased engagement with private sector providers and patients seeking care from them. However, the notification rate for that year was 73%. The same for the year 2017 was 75% and for 2019 was 84%. This indicates a gap of 16% to 25% and needs further improvement. During 2017, 1,364,562 patients were notified as drug sensitive TB cases with a treatment success rate of 79%, which was achieved by the use of standardised treatment regimens, although the situation is little better in 2019 as regards TB notification, mortality and treatment success. The treatment success rate of drug sensitive TB patients needs further improvement. Extra-pulmonary TB is the another area of concern. Almost all specialities of medicines deal with this form of TB. Unfortunately not all are on board although involvement of medical colleges is a success story into the programme. Still different specialists believe in different drug combinations, although guidelines for these diseases are developed by the programme.[123]

Drug Resistant Tuberculosis (DR-TB)

Another area of concern is the diagnosis and management of DR-TB. Tuberculosis strains with DR-TB are more difficult to treat than drug-susceptible TB. This is considered to be one of the major challenges to progress towards the country's targets to End TB by 2025. After introduction of Programatic Management of DR-TB (PMDT) to manage DR-TB in India, and after the upgradation and implementation of guidelines for the same in 2017, major steps were taken to improve molecular diagnostics and detection of DR-TB, CBNAAT was scaled up to 1180 laboratories at the district level with additional 345 TrueNAT machines, the number of tests performed doubled to 22.5 lakhs in 2018 against 10.7 lakh in 2017. Another 1500 machines are planned at sub-district level facilities in the coming years. The programme for the first time in the country developed a laboratory network of National Reference Laboratories (NRLs), Intermediate reference laboratories (IRLs), etc with the facility of DST, both solid and liquid mycobacteria growth indicator tube (MGIT) culture and line probe assay (LPA) laboratories. As of today there are 6 NRLs, 50 liquid culture (LC) laboratories and 64 LPA laboratories in the states; 19 LC and LPA facilities in the private and corporate sector; and 20,356 microscopy centres in the periphery available for TB diagnosis under the programme. DR-TB centres were increased from 197 to 509 in the past two years that has resulted in a 52% increase in DR-TB cases. By the end of 2018, 509 DR-TB centres have been made functional which include 149 Nodal DR-TB centres, and 360 District DR-TB centres.[21] This decentralisation will empower districts to enable the "test and treat approach" to minimise the delays in diagnostic and treatment initiation pathways for all MDR/RR-TB patients within their respective district. During 2007–2018, India tested 2,798,599 patients using CBNAAT and LPAs. These tests detected 236,725 DR-TB patients.

Patients at risk of developing MDR-TB as defined by the programme are diagnosed using WHO endorsed rapid diagnostics (WRD), like CBNAAT/LPA/TrueNAT. Response to treatment for MDR-TB is monitored by the follow up on LC (MGIT) system. Identification of *Mycobacterial* species is performed by the commercial immunochromatic test (ICT). In 2019, a total of 73,771 cases of RR-TB were diagnosed through CBNAAT. Of the 346,282 first-line LPA tests done in 2019, 20,329 (5.9%) cases of H-resistance, 2247 (0.65%) cases of rifampicin resistance and 10,837 (3.1%) cases of MDR-TB could be diagnosed. Of the 72,748, 39,931 (54.8%) second-line LPA performed in the same year, 19,984 (27.4%) cases of flouroquinolone resistance, 1007 (1.3%) cases of second-line injectable resistance; 487 (0.66%) low level kanamycin resistance and 3882 (5.3%) of extremely drug resistant TB (XDR-TB). Even if, these are improved figures compared to that from the earlier years; a large number of DR-TB cases

remain undiagnosed and untreated. India had an estimated 130,000 DR-TB cases of various types in 2018. Fifty-six percent of the estimated MDR-TB patients were undiagnosed and 64% of the estimated MDR-TB patients were untreated! Further, starting from 2007 when the PMDT was started in India, during this period of 12 years, the total new MDR-TB cases will be over 12 lakhs if one takes an average of one lakh cases per year. One important milestone was the National Anti-TB Drug Resistance Survey (NDRS) of India that studied drug susceptibility testing (DST) for 13 anti-TB drugs using the automated LC system, MGIT-960. MDR-TB was 6.2% among all TB patients with 2.8% among the new and 11.6% among the previously treated TB patients. This is the largest DR-TB survey in the world.[124] Among MDR-TB patients, additional resistance to any fluoroquinolones was 21.8%, and 3.6% to any second-line injectable drugs. Among MDR-TB patients, additional resistance to at least one drug from each of the two classes, *i.e.* fluoroquinolone and second-line injectable drugs (XDR-TB) was 1.3%. In 2018, the estimated incidence of MDR/RR-TB was about 130,000 cases (range 77–198), with 9.6 (5.7–15) per 100,000 population and India had the highest number of these cases of the world with 27% of the burden. But in that year the programme could diagnose 58,347 cases of MDR/RR-TB and 2724 XDR-TB, thus more than half of these cases could not be included in the programme. Moreover, of this number about 46,559 (79.5% of the detected cases; and 35.8% of the estimated cases) were put on treatment. Out of the 3400 XDR-TB cases, 2724 could be put on treatment. Still 20% of the diagnosed cases of XDR-TB were not put on treatment. Forty-six percent of the bacteriologically confirmed new TB cases and 91% of the previously treated cases could be tested for rifampicin resistance. A total of 38,236 MDR/RR-TB cases were tested for resistance to second-line drugs to find out Pre-XDR and XDR-TB (66%) only. The success rate for MDR/RR-TB cases (n=33,197) started in 2016 was only 48% and 30% for XDR-TB (n=2464). Death rate was about 20%. To improve these results, on the occasion of World TB Day 2018, the programme introduced shorter MDR-TB regimen for the country for the wider implementation. As per the current programme guidelines, shorter MDR-TB regimen (9-11 months duration) is the first choice of the treatment for the patients diagnosed with rifampicin resistance that would be continued or switched to longer regimen, based on second-line LPA results. In addition to pulmonary MDR/RR-TB patients, extra-pulmonary diseases, like lymph node TB and plural TB are also eligible for shorter MDR-TB regimen. In 2018, more than 16,488 MDR/RR-TB patients were initiated on shorter MDR-TB regimen in India. After successful expansion in initially selected five states during 2016-17, the access to the bedaquiline containing regimen was expanded to the rest of India in 2018. Introduction of second-line LPA during 2018 have reduced the time required to detect additional resistance to fluroquinolones and/or second-line injectable drugs at the baseline. This resulted in the early identification of the patients eligible for the newer drug containing regimen. Since December 2017, based on the guidelines on PMDT in India (2017), ground level preparatory activities and trainings for the state and district level staff were completed by majority of the states during 1Q18. With concerted efforts, 2827 patients have been initiated on bedaquiline containing regimen during 2018, marking three times improvement compared to 2017. There would be significant increase in uptake once the RNTCP will update its policy as per the recommendations of the recently released WHO guidelines for the management of DR-TB (December 2019). Delamanid is one of two drugs developed specifically for the treatment of MDR/ RR-TB in the last 40 years. The programme has implemented delamanid containing regimen in seven states as per the guidelines for the treatment of DR-TB under RNTCP (2018). In these states, delamanid is indicated for the use as a part of an appropriate combination regimen for pulmonary MDR-TB in adult and adolescent (6-17 years) patients, when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. Recently, a decision has been taken to expand the access of delamanid to the entire country, for all the eligible patients among children and adolescents (6 to 17 years). The programme has received donation of 400 courses of delamanid from the manufacturer (Otsuka Pharmaceutical, Japan). The first patient was put on delamanid containing regimen in October 2018 at Chandigarh. Till end of 2018, 41 MDR/RR-TB patients were initiated on the regimen containing delamanid including five children. As required by the Drug Controller General of India (DCGI), each patient initiated on delamanid containing-regimen is being followed up as per the Delamanid guidelines for monitoring of drug safety parameters in the prescribed format on a regular basis. There has been an increase in the proportion of the patients on injection free regimens which went up from 67% in 2017 to 98.5% in 2018. During December 2018, RNTCP has introduced all six oral levofloxacin, rifampicin, ethambutol and pyrizinamide (LfxREZ) regimen for H mono/poly patients based on recommendations of the National Technical Expert Group on Treatment of TB. Both pulmonary as well as extra-pulmonary TB patients are given the same regimen. After introduction of all oral H mono/poly regimens, more than 95% of all TB patients

are now eligible to receive an injection-free oral regimen for the treatment of TB and H mono/poly DR-TB.[125,126] The initial bedaquiline was tried in six centers of the country in 620 patients under the Conditional Access Programme (CAP) to gain experience on the drug in India.[127] In more complex cases a salvage regimen with both bedaquiline and delemanid has been used.[128]

During 2019, 66,255 MDR/RR-TB cases were diagnosed and 56,569 (85%) of them were put on treatment, of which, 40,397 (71%) were initiated on shorter MDR-TB regimen at the time of diagnosis of MDR or RR. National TB Elimination Programme has seen improvement over 2018 (79% were put on treatment and only 35% were initiated on shorter MDR-TB regimen). H mono/poly patients diagnosed were 16,067 and 13,231 (82%) were put on treatment. Based on the second-line DST results and other eligibility criteria, 5774 (39%) were initiated on newer drug containing regimen out of 14,911 MDR-TB patients, majority were initiated on bedaquiline (5513 patients) while 264 on delamanid containing regimen. Till the end of 2019, Guidelines for PMDT in India 2019 (pre-final text) has been rolled out in eight states where 1738 patients were enrolled on all oral longer regimen. Smear negative status at 4th month for the patients initiated on shorter regimen during (3Q18 to 2Q19) was reported up to 59%, while for patients on H mono/poly regimen it was 78% for the same period.[21] Treatment outcomes of the patient initiated on various therapies are shown in table 3.

The treatment outcome of MDR/RR-TB cases (conventional regimen) has been dismal being less than 50% starting from 2007 till the second quarter of 2017, which was just 52% for the year 2007. The results were around 44%, 50%, 48%, 50%, 46%, 47%, 45%, 47%, 48% and 48% respectively for the years 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016 and till 2nd Quarter of 2017, respectively. Around 20% of the patients died and similar percentage of the patients were lost to follow-up. The treatment outcomes for XDR-TB is still low, being 28% to 37% since 2012. These results indicate a poor handling of DR-TB cases by the programme. With newer regimens using bedaquiline the results might show better outcomes. Use of newer drugs and regimens may imrove treatment outcomes.

Even if significant improvement has taken place in the diagnosis and management of DR-TB patients, not all cases could be diagnosed, and not all those who are diagnosed could be put on treatment. Laboratory network needs further expansion with faster availability of the results. However, quality maintenance of the laboratories will be another challenge. Short-course DR-TB treatment and newer drug regimens containing bedaquiline and delemanid and injection-free regimens will increase patient compliance with better outcomes. There was some initial reluctance by the treating doctors for the use of new drugs as they had no first-hand experience, but that could be overcome by the confidence building and training. The programme should procure these new drugs of its own rather than depending upon donations from the manufacturers.

Operational Research

Intensified operational research is one of the important pillars and components of End TB Strategy. Although the programme has a well built structure, like National/Zonal/State Operational Research Committees, these do not function in a regular and robust way. For a country like India with enormous TB cases, only 11 research proposals were presented, 4 were approved by the National Operational Research Committee and only 2 were started in 2018. However, a major progress has been made in the form of a National TB prevalence study along with ICMR. The other priorities identified by the NTEP are:

1. TB prevalence survey in special groups, such as, tribal, migrants, slums, paediatric population, etc and to study of its unique dynamics (epidemiological factors).
2. Point of care diagnostic tests to confirm extra-pulmonary TB.
3. Non-tuberculous *Mycobacterium* (NTM) diagnosis. Proportion of NTM disease among treatment non-responders. Studies that assess the diagnostic algorithms and treatment regimens for NTM.
4. Studies on biomarkers of TB for diagnosis; prognosis and cure or its attribution to cell mediated immune status.
5. Identify hot-spots for TB transmission–using molecular epidemiological methods.
6. Cost effective technologies to disinfect hospitals/OPDs ambient airborne TB infection and its monitoring and control.

Table 3. Treatment outcomes of patients receiving various therapies to treat TB

Type of Case/ Regimen	No. of Patients Enrolled on Treatment in 2018	Success Rate	Death Rate	Lost to Follow- up	Failure Rate	Regimen Changed	Not Evaluated
Shorter MDR-TB	16311	60%	11%	13%	2%	12%	2%
H mono/poly	6189	76%	7%	12%	2%	2%	1%

7. Drug resistance (hospital or community) surveillance and monitoring. Conventional (INH; rifampicin) as well as newer (bedaquiline, delamanid etc). Multicentric study to be preferred.
8. Studies on baseline INH resistance in community and its relevance in relation to INH prophylaxis.
9. *Yoga-Ayurveda* intervention studies to see if there is any beneficial effects of *Yoga/Ayurvedic* regimen along with conventional drug treatment for better – earlier treatment outcomes and amelioration of drug induced effects.

TB Research Consortium of the ICMR is another important platform for TB research that works on TB control issues in the country. In order to maximise India's response to TB elimination, the Ministry of Health and Family Welfare and ICMR decided to create India TB Research Consortium (ITRC). The aim of the consortium is to advance technology by harnessing inter-disciplinary expertise, focus on building and strengthening scientific capabilities to accelerate development of new diagnostics, new and improved vaccines, immunotherapy and drugs for TB. ITRC is collaborating with all the relevant stakeholders in TB research including other Ministries from the Government of India, non-governmental national and international organisations, trusts and industries as funding and non-funding partners. ITRC activities are mainly focused in four thematic areas: therapeutics, diagnostics, vaccines and implementation research to develop efficacious and cost-effective new tools as per national priorities, ensure proper and efficient spending and channelisation to the most promising leads, and minimise duplication of efforts.

BRICS countries (Brazil, India, China, Russia and South Africa) have established a collaborative TB Research Network. The network promotes and conducts collaborative scientific and operational research along with development and innovations on diagnostics, vaccines, drugs, regimens, infection control and patient service delivery mechanisms commonly applicable in all these countries for effective TB control and management. NTEP is working closely with the other BRICS countries.

Budget and Financing

Budget or financial requirements are key to the management and smooth running of the programme. During the past five years (2014-2018), a total of 9973 crore of rupees were asked for, but 6970.15 crores were sanctioned by the Government of India (~70%). For this five-year (2014-18), the programme could spend only 71.3% of the allocated budget. In a recent review meeting, many states had very poor expenditure capacity.

Human Resource

To manage and sustain such a large programme and to achieve the targets, huge manpower, both technical and otherwise is a very essential component. Although the annual TB reports do not specifically mention about the total number of human employees working in the programme, it is common knowledge that attrition rates and retention rates are highly unsatisfactory. Even if there are sanctioned posts, whether medical or para-medical, many such posts are either vacant or people leave the job very frequently. This is a big problem for the programme. The situation becomes complicated further as health is in the concurrent list, and hence, the programme is implanted through the State health machinery and with contribution and engagement of the programme staff through the States. In the NSP, more posts and manpower are asked for and this will help improve the performance.

Programme and Emergency Situations

Performance of the programme is further complicated in situations, like flood, strikes, closures, and holidays, etc. COVID-19 pandemic has created a lot of problems for the health-care delivery in the country for the management of non-COVID cases including TB.[129] Due to lock-down, hospitals are closed and the RNTCP (NTEP) has also suffered a lot. The case notification through the NIKSHYA portal shows a dismal and disastrous figure. Till August 30, 2020, a total of 11,41,088 cases (38% of the targeted number of 29,99,030 for the year) were notified over these eight months, public sector could register only 43% and private sector only 30% of their target numbers. From 2020 onwards, there is a precipitous fall in the number of cases: January–1, 96,112; February–2,11,021; March–1,62,038; April–7,5,789; May–96,601 and so on. Thus, it is expected that the case notification in this year will have a drastic fall. Because of lock-down and many hospitals being closed, new registrations has come down and even patients who are on treatment from the Directly Observed Treatment, short-course (DOTS) centre are suffering. Many hospitals are converted to COVID care centers and hospitals. Technicians and CBNAAT machines are being used for COVID testing, jeopardising TB testing. Many medical officers are put on COVID duty. If some patient is lucky and he could contact the DOTS center, he is given drugs for about a month or so. The Central TB Division has issued advisory to the State TB Officers how to go about the patients, but understandably they are constrained. Supervisory visits are not possible. In earlier months, there was travel restrictions and movement of patients/ symptomatic cases as well as health-care workers

affecting the services. Gene-x-pert machines are being used for COVID testing, which are over busy and molecular testing for TB is a big causality. Specimen transport and drug delivery to State Stores also face problems, even if there is no ban for the essential medicine transport. Because many hospitals and DR-TB Centres are converted into COVID hospitals, DR-TB patients are not being admitted as expected. It is not yet clear how patients on any form of the therapy for DR-TB, are getting their drugs. Interruption of treatment even for few days/weeks, will affect the results of the treatment, and in particular, the short-course chemotherapy. TB research is also a big causality with issues, like patient enrolment and follow-up.

Challenges and Way Forward

The programme has made much and impressive progress since its inception in 1997. In-spite of a lot of advances in the diagnosis and treatment, the country continues to face major challenges in ending TB. With more than 1/4th of the world's DS-TB and DR-TB burden and a slow rate of decline, there is much work for the country to do. Case detection in the vulnerable group including children as discussed earlier as well as in the population as a whole, will be a major issue. Active case finding amongst the vulnerable group will be one step forward in the right direction in addition to the currently adopted method of passive case detection. Ensuring availability of diagnostics and drugs for the patient being managed in private sector along with other services identified under the public health action would be one of the major challenges. A major hindrance in detection of DS/DR-TB patients is poorly established specimen collection and transportation systems, which adversely affects the RNTCP's UDST (Universal Drug Susceptibility Testing) coverage as well as first-and second-line DST. Efforts are being made to link sputum transport with India Postal services and other private courier services and road transport by human carriers in difficult areas, with more number of laboratories and molecular testing facilities. Ensuring patient adherence for the treatment of DS-TB or DR-TB cases is essential for the programme success. DOTS, which was the corner-stone of our programme is perhaps not being strictly implemented as supervision by DOT-providers has come down.[99] DOTS by using technology with mobile phones is being advocated by the programme, but its universal use and utilisation needs to be seen and evaluated. Fatigue has set into the programme. Human resource is a big problem. Health is in the concurrent list in India, thereby having a dual responsibility, although the central Government spends the major portion for the programme. But the implementation is done through the state machinery. National/State Health Mission is responsible for handling the financial matters, but many believe that the system needs improvement. Every state has its own problem and performs through its own system; therefore uniformity is not maintained as this depends upon the public-health care system of that particular state. As emphasised, human resource is a big challenge with variable number of positions, which are key posts, are lying vacant throughout the country despite the budget being available. Recruitment and retention of trained manpower is a big challenge occurring across the country. There are frequent transfers and replacements of Programme Managers in the State depending on the policy, over which the programme has no control. There are occasions when the State TB Officers are either not TB specialists/public health specialists or they are changed very often before he/she understands the programme. Similar things do happen with District TB Officers. Technical issues are very simple and clear — diagnosis and treatment which are not complicated nor these are rocket sciences — and these are fairly standardised and do not need frequent changes except recent guidelines for DR-TB. The only issue is managerial — the human resource management and implementation issues which we need to address. Even the Central TB Division is understaffed with so many functions being done by handful of officers. This also needs strengthening. An independent supervisory and advisory committee consisting of subject and management experts with finance persons need and should to supervise and decide various implementation issues. Adequate manpower will take care of major treatment issues even for longer duration of the treatment protocols. Identifying and managing adverse drug reactions (ADRs) and establishing robust linkages with higher referral centres to manage them continue to be sub-optimal. Linkages with the Pharmacovigilance Programme of India (PvPI) and active Drug Safety Monitoring and Management (aDSM), will improve the programme to build its capacity in managing and reporting ADRs. Strengthening this systems at the district and block levels will be required. Regular and repeated training of the staff including the medical personnel managing DR-TB cases should include detailed sessions on ADR management, a DSM and causality assessment to strengthen the RNTCP's pharmacovigilance activities. Better ADR management would also lead to better adherence to the long and complex DR-TB treatment regimen. Home-based counselling services by the counsellors have been useful. Expansion of such counselling services is required to be extended to all states. Addressing social determinants of TB, like poverty, malnutrition, ventilation (infection control),

stigma and belief and linkages with social schemes will be beneficial to promote patient adherence to treatment and completion of the treatment. More efforts are needed to systematically bridge the gap between estimated and actual initiated on treatment through establishing NIKSHAY system for patient tracking. Decentralisation of DR-TB treatment services under the "test and treat" approach within the districts would facilitate further reducing the gap in the treatment initiation of DR-TB patients. Procurement and supply chain should be streamlined and maintained so that there is no shortage of drugs or any material related to the programme. Laboratories and CBNAAT need to be expanded with improvement in reporting system so that reports are given to the treating team at the earliest. If the test takes less than two hours, then why the report should take days to reach the clinician or treating centre? Simple use of e-technology will help to solve this problem.

Although the programme is encouraging various NGOs and other groups, the programme management need to be looked after by programme managers and periodic review of their performances and activities. Medical college involvement in the programme is a novel initiative by the RNTCP/NTEP and is the only such model of involvement in the whole world. By such involvement, the programme gets a huge number of trained and technical hands. Nearly 20% of the total TB cases are reported from medical colleges. Management of difficult cases like DR-TB and use of new drugs and research will be the areas which the medical colleges will help.[130] Diagnosis and management of extra-pulmonary TB cases are better handled at the medical colleges. Medical College teachers teach medical students at all levels about TB and the programme, who are the future health-care providers in the country. Curriculum change/modifications are required at the Medical Council level so that the Medical students are oriented and trained about TB in all its aspects. Research on TB, particularly the operational research, is very poor in the country. Easy and smooth review of projects, timely sanction and release of funds will encourage researchers to take up operational research. The operational research wing should be independent of the Central TB Division, as the programme managers are too busy to handle research issues. Finance needs to be sufficient and money handling should be smooth and easy. Good and effective collaboration with the ICMR TB Reseearch Consortium will be of immense help. Medical colleges have contributed immensely to the programme and the involvement needs to be continued with more vigour.[129]

Air-borne infection control (AIC) practices is again very poor in the country, particularly in health-care settings and because of over-crowding everywhere in the country.[131,132] Tuberculosis transmission in health-care settings represents a major public health problem. In 2010, national AIC guidelines were adopted in India. These guidelines included specific policies for TB prevention and control in health-care settings,[133] which need to be followed strictly. While COVID pandemic has forced people to adopt preventive measures, such acceptability for TB was not there. The lessons from COVID can be fully utilised for the prevention of TB.

Chemoprophylaxis is another important requirement for the prevention of TB. The performance of the programme is very poor in this regard as discussed earlier. It may be difficult to convince an otherwise healthy individual to take potentially hepatotoxic drugs with INH or other combinations for varying periods of time. Shorter forms of prophylaxis for LTBI cases with rifapentin where only 12 doses will be taken can be a welcome step. But the drug is not available in the country at present. The programme should make all attempts to get this drug and introduce it as soon as possible.[134,135]

Another preventive strategy is the use of vaccination. The Bacille Calmette-Guerin (BCG) vaccine has been used globally since 1921 for the prevention of TB in humans, and was derived from an attenuated strain of *Mycobacterium bovis*. Worldwide, BCG is the most widely used vaccine with approximately 100 million vaccinations given to the newborn children per annum. In children under five years, immunisation with BCG is thought to reduce hematogenous spread of *Mycobacterium* TB from the site of the primary infection which may result in severe disease, such as milliary TB and TB meningitis; and BCG vaccination is beneficial to prevent these. Studies conducted in the past showed that its efficacy varies ranging from 0 to 80% against pulmonary TB, and over 70% against TB meningitis. Other systematic reviews in the past found substantial variation between trials on the protective efficacy of BCG against pulmonary TB, and in one review 50% average protective efficacy was estimated.[136] India should actively participate in new vaccine trials. The country continues to use this vaccine and as a part of universal vaccination policy every child gets it at birth. There are trials on the efficacy of other vaccines in the country, but we have to wait for the results to arrive at a conclusion whether the new vaccine(s) is better or not.[137]

Although India is a diverse country geographically, the number of epidemiological studies available does not do justice to the reported type of strains circulating in the country. In addition, the number of isolates included in most of the studies is only a few.[138] Moreover, though the relapse rate of TB in India is 10%, there are no data on whether the relapse is due to reactivation of

a previous infection or due to re-infection. The need of the hour is large multi-site studies that include strains from large parts of India. Given the recent increase in travel related to work and leisure, a continuous vigil is required to be able to arrest the spread of TB and the emergence of new clones. In addition, it is now widely clear that missed diagnostic opportunities, particularly that of drug-resistant *M. tuberculosis*, can lead to the evolution of more transmissible organisms that may become increasingly drug resistant. Molecular typing tools can help public health officials to identify transmission links with confidence. In the future, we may see powerful high throughput technologies, such as next generation sequencing (NGS) being used for complete strain characterisation, detection of drug resistance, monitoring emergence of new drug resistance mutations and mechanisms and outbreak investigation through identification of classes and lineages that will transform disease management and target interventions and resources for TB control more appropriately.[138]

Advocacy, communication and social mobilisation (ACSM) is important in this disease and its associated problems in this country. ACSM activities need to be more effective, particularly making awareness amongst people, specifically the vulnerable group, identification of symptomatics, and letting the people to know that diagnosis and treatment facilities are available free of cost and bringing awareness amongst general public, patient groups and the involvement of society at large. There is enough scope for the programme to improve in its performance as regards ACSM.[139,140]

Care of the post-TB sequel cases will be an issue of rehabilitation like other chronic respiratory diseases. The programme should take care of these sequel.[141-148] Managing post-TB complications, like haemoptysis, pneumonia, empyema, chronic pulmonary aspergillosis, chronic obstructive pulmonary disease following TB, bronchiectasis and other complications need to be managed through the programme. More surgical centers and thoracic surgeons are also a necessity, as there is deficit of these services in India. More dedicated TB institutes like the existing ones (NITRD, New Delhi, NIRT, Chennai, and NTI, Bengaluru) need to be established to take care of some of these immediate and specific needs of the TB Elimination Programme.

Thus, Ending TB by 2025 is achievable, and may be possible but the country and the programme need to work very hard. It may be difficult but still feasible if some of the correct measures and steps are followed. TB free India will not be just a dream, but can be a reality.

Conclusions

It may be seen that there are numerous challenges for TB control in India. The country is trying to overcome some of them in a very effective manner. Lot of progress has been made in this direction. However, many more are still there to be overcome. Current COVID epidemic in the country has come as a major setback for the End TB in India by 2025.[149] The programme in particular and the nation as a whole has to walk extra miles to achieve this goal. The targets are difficult but achievable with sincere efforts.

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