

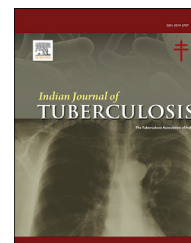


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## Correspondence - Post Graduate Corner

# White paper on challenges and opportunities for TB elimination with focus on COVID & Post-COVID era developed through scientific roundtable resolutions at NATCON 2020

## A B S T R A C T

## Keywords:

TB  
Elimination  
Challenges  
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Covid

A group of TB experts with vast clinical and epidemiological experience were drawn from a pool of doctors, epidemiologists and scientists participating in NATCON 2020 Conference in a closed-door session to discuss, highlight, and prioritize key resolutions that are most pertinent at present to eliminate TB from India and other developing countries in the Covid and post-COVID era. These Scientific experts were non-industry persons who met on 17th December, 2020 and used the prevailing scientific literature along with 2019 Joint Monitoring Mission document as a starting point of the discussion on this specific topic to build an agreement upon the resolutions. After the meeting on the virtual platform, all the attending doctors gave a set of recommendations on rebuilding TB Elimination programme in the Covid and Post-Covid era. Focused scientific roundtable discussion on rebuilding TB Elimination Post-Covid. Develop actionable recommendations for the scientific community and the government leadership to consider in moving forward. To prioritize the recommendations in the categories of *Build-Prevent-Detect-Treat*.

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## 1. Introduction

The 2019 novel corona virus or recently renamed as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) by the World Health Organization (WHO) was first notified from Wuhan City of Hubei Province of China in December 2019 in the form of unexplained pneumonia.<sup>1</sup> Disease associated with SARS-CoV-2 also termed as corona virus disease 2019 or COVID-19 has now become a potential threat to global health within a short span of time by spreading across 210 countries.<sup>1,2</sup>

Tuberculosis (TB) is existing as an unprecedented pandemic worldwide for the last three decades and it was declared a global health emergency by the WHO in 1993.<sup>3</sup> The causative agent of COVID-19 is the novel virus SARS-CoV-2, whereas for TB, it is bacteria *Mycobacterium tuberculosis*. Both can manifest with similar respiratory symptoms such as fever, cough, breathlessness, and weakness with varying

severity and are dealt by the same set of doctors (pulmonologists). It is the chronicity of symptoms in TB as compared to acute or rapid progression in case of COVID 19 that helps in differentiating the patients of these respective diseases. The estimated global burden of TB is 10 million, with nearly half of them having drug resistance in 2018.<sup>4</sup> Of 10 million cases, 3 million (30%) remain undiagnosed. Approximately 3 of 10 TB patients (27%) in the world belong to India. Around 1400 people die and 7500 people fall ill every day due to TB even in India.

Both the diseases are associated with huge social stigma and have created an unprecedented economic impact worldwide, hence it is imperative to have India specific recommendations to rebuild or re-strategize TB Elimination programme in the Covid and Post-Covid era. The objective of the round table was precisely that and participants believe that the set of recommendations which have been finalized will help in re-energizing the NTEP with an eye on elimination by 2025.

## 2. Recommendations

The recommendations are dealt under four sub-headings or categories: **Build-Prevent-Detect-Treat**.

The participants were very optimistic about the positives derived from the pandemic and the host of opportunities and possibilities which have emerged from it. “Nothing seems Impossible” was the chorus as this was reflected by overnight scaling up of well equipped modern molecular diagnostic laboratories with bio safety cabinets and overwhelming response from the administration, industry and public at large. The change that was seen in the society with respect to their health seeking behaviour using masks, social distancing and hand sanitisation which became the new normal. Media came out with plenty of information on a daily basis and kept the tempo up and the stigma (associated with COVID) down along with administration introducing “COVID warnings symptoms” on the **caller tunes** of the teeming millions. The biggest game changer was the launch of “**Aarogya Setu App**” (ASA); which was downloaded by 50 million users within days and now boasts of 100 million users. Such unprecedented measures ensured that India remained at the bottom of the COVID CFR list, which was the lowest in the world at 1.5%.

The TB experts were of the opinion that if the same gusto is put in early diagnosis, aggressive treatment and contact tracing of TB patients, then we can achieve the elimination plan by 2025.

## 3. Build

Both diseases require contact tracing and infection control measures that include hand washing, cough etiquette, social distancing, regular cleaning of surfaces, isolation, prolonged quarantine, and respiratory protection by using barriers like masks and gloves. There is no doubt that these measures have been prioritized to prevent COVID-19 but still remain underutilized for TB. Both are transmitted mainly through close contacts. Hence the first recommendation was centred at the active education, surveillance of active TB cases and their contacts. The experts believed that this participatory approach between the care givers and recipients is a win-win strategy and the gains achieved in the war on COVID shouldn't be diluted. On the contrary these efforts should be converted into TB Elimination by 2025.

**1<sup>st</sup> Recommendation:** Resources and notification system used in COVID like “**Aarogya Setu App**”; **Caller tunes & Advertorials in print/broadcasting media** can be used for active education and surveillance of current cases of TB on treatment & their contacts.

“**Aarogya Setu App**” can be used for *active Surveillance of all chest symptomatic* in NTEP in the *family or work place* at the time of “*Sputum testing*” of the patient in NTEP (**To assess their dual status of COVID and TB**).

Digital paperless reporting tool for TB and COVID along with NIKSHAY.

Some participants were of the opinion that a similar APP for TB can be developed or some modifications in the

NIKSHAY may be enough to achieve the above goal of surveillance of active TB cases and their household contacts. When the user types cough, he/she should be directed to the nearest testing centre. Another suggestion was that instead of piggybacking on ASA, we could incorporate the features of **Aarogya Setu APP** into NIKSHAY for the sake of patient confidentiality and to avoid the stigma associated with neighbourhood surveillance and patient policing. Self surveillance by the patient may be more appropriate in TB. .

As COVID is still not over in India and is likely to impact the healthcare system for at least next one and a half years, we must be prepared to diagnose and treat both the diseases together in this COVID and Post COVID era by the same set of doctors. TB programme was pushed back due to COVID and the “lost cases” can be retrieved through the gains in the form of new infrastructure and increased funding in COVID care. We must take help from the Ministry of Health, State departments; STOs, Medical Institutions and other stake holders for there could be state to state variations and challenges in implementing these recommendations.

## 4. Prevent

Success of a Covid-19 vaccine reignites hopes that a New TB vaccine is imminent if sufficient financial resources are deployed by governments, industry, and academic institutions. ICMR is involved in the development of new more effective TB vaccines for our country, which may fructify before 2022. This fact was also highlighted by some experts. These vaccines may be a potential game changer in our fight against TB.

**2<sup>nd</sup> Recommendation:** The Governments and private foundations must *fast tract and prioritize the development of a TB vaccine by 2022* as an end game for TB disease. National and international scientists need to pivot from COVID to TB as their first priority for disease elimination with the same set of financing, rigor, and support.

Diagnosis and treatment for LTBI are important for TB, especially in high-risk populations especially in high prevalent country like India. TB can exist in active or latent form depending on the immune status, whereas the latent period is not defined for COVID-19.

The Indian TB National Strategic Plan (NSP) 2017–2025 is the plan produced by the government of India (GoI) which sets out what the government believes is needed to eliminate TB in India. One of the four main “thrust” or priority areas is preventing the development of active TB in people with latent TB for people in “high risk” groups. The high risk groups are the one containing immunocompromised population. Currently, India carries a huge TB burden, and therefore the burden of LTBI is proportionately large, estimated at 33–40% of the population. A huge proportion of the Indian population is amenable to progression to active TB disease from LTBI.

Japan has made the notification of LTBI mandatory since 2006. Patients detected with LTBI are offered treatment based on risk factors for progression of disease.<sup>5</sup> The risk factors chosen were HIV/AIDS; organ transplant; Silicosis; recent infection; poorly controlled DM and use of corticosteroids.

This approach followed by Japan has resulted in the decrease in TB burden over the years, with total number of TB cases detected falling drastically. Japanese targets for 85% treatment of all LTBI patients with requisite risk factors have been met and this has resulted in ameliorating the TB scenario in the country.

This means that without the elimination of latent TB, India's efforts to eliminate TB by 2025 will not bear fruit. Therefore pragmatism dictates that India must actively treat LTBI patients who are at risk of progression to active TB.

**3<sup>rd</sup> Recommendation:** An unequivocal policy of diagnosis, treatment and screening of LTBI in “high risk” groups to be developed for the country (India). **India can make the notification of LTBI in the contacts mandatory put in the NIKSHAY at the time of DBT** to the patient in RNTCP.

Clinical trials can be undertaken to study the efficacy of BCG in protection of adolescents and elderly population against *M. Tuberculosis* reactivation. A study from China is the first to assess the potential impact of new tuberculosis vaccines targeting older adults and to provide a comparison with adolescent vaccination, which has been a strategic focus over the past 5–10 years.<sup>6</sup> They match results of a study by Huynh and colleagues, which showed the importance of controlling reactivation disease in people aged 65 years or older.<sup>7,8</sup>

**4<sup>th</sup> Recommendation:** Consider clinical trials of re-vaccination of Mantoux negative adult population in two age targets between the Age of 15–19 years and 60–64 years in the Country in the post-COVID era to provide dual CD4 protection against TB & other respiratory viral infections. Such an exercise may help in the goal of TB elimination by 2025.

In developing countries like India; BCG revaccination practices, particularly in the elderly age group, may provide additional protection against severe COVID-19. BCG is the only vaccine available for TB that prevents dissemination, whereas for COVID-19, vaccines are still under development. Data from few epidemiological studies reported reduced morbidity and mortality (CFR) for COVID-19 in Asian and African counties where BCG vaccination policy is adopted universally in contrast to Europe and the USA with low vaccination coverage.<sup>9</sup> WHO does not recommend BCG vaccination for the prevention of COVID-19. WHO continues to recommend reserving BCG for neonatal vaccination in settings with a high risk of tuberculosis.

**5<sup>th</sup> Recommendation:** N-95 masks can be made mandatory for all healthcare workers who are actively involved in RNTCP henceforth by notification from the health ministry.

Many experts pointed out that masking is an important exercise in especially the highly infectious sputum positive pulmonary TB patients as the source of infection needs to be capped. The masks will have a great impact in breaking the chain of transmission especially in aerosol generating procedures undertaken by HCWs. But this exercise may have some challenges in its implementation on a Pan India basis. Some experts pointed out that current guidelines include this practise and only reinforcement needs to be done with more emphasis on surveillance, infection control and biomedical waste management.

May be a subset of serious immunocompromised TB patients with drug resistant TB who are under institutional care can be provided with these masks. They may not be mandatory for drug sensitive TB patients. But as masks have become more acceptable in society among HCWs and patients, it is practise which can be encouraged voluntarily as seen in some more developed countries.

## 5. Detect

Estimation of TB and COVID-19 coinfection is not possible at this moment but could not be underestimated in India. Malnutrition, social diversity, poverty, and overcrowding in unauthorized colonies, especially slums, are also rampant in our densely populated country (1.34 million) and this can create a significant hindrance to containment plan. All these factors will be responsible for delay in diagnosis and treatment of both TB and COVID-19, which may lead to a spike in both diseases and increased transmission of infection in community. The impact of lockdown can be perceived as only 34 566 TB patients were notified nationwide during the past 3 weeks in comparison to 1, 14, 460 patients in early March 2020 (pre-lockdown phase).<sup>10</sup> **Between 2020 and 2025 an additional 1.4 million TB deaths could be registered as a direct consequence of the COVID-19 pandemic.**

COVID-19 pandemic led to a global reduction of 25% in expected TB detection for 3 months – a realistic possibility given the levels of disruption in TB services being observed in multiple countries – then we could expect a 13% increase in TB deaths, bringing us back to the levels of TB mortality that we had 5 years ago. India will need to manage 232 665 excess TB cases for every month of lockdown and 71 290 excess TB deaths.

What we have built recently for COVID-19 pandemic like effective notification (Aarogya Setu App), promotion of active surveillance, contact tracing (active local administration), and effective infection control measures (masks, disinfectants) may provide an opportunity in future to end TB.

Community volunteers may be appointed for awareness raising, prevention, and early notification for Active TB, Latent TB and COVID-19. Molecular testing is the currently recommended method for the identification of infectious COVID-19 and just as for TB. Amongst these is the Xpert Xpress SARS-CoV-2 cartridge for use on GeneXpert machines, which are machines used in TB diagnosis. WHO is currently evaluating this cartridge as well as other tests for dual testing.

**6<sup>th</sup> Recommendation:** Developing a test kit to simultaneously test the same patient for both tuberculosis (TB) and COVID-19. Research in next-generation sequencing and pooling for large scale testing needs to be implemented.

**Integrated TB & COVID laboratories** based on molecular testing will pave the way for tackling TB and any other future pandemics with point of care common testing platforms. Need to take care of transmission risks to the patients in such set ups with good airborne infection control measures. COPD clinics at the periphery can be clubbed well with screening both TB & COVID along with tobacco cessation. **We need to protect the TB staff so that they are not all reassigned to COVID-19.**

## 6. Treat

Unlike Covid-19, TB has good treatment options for both DSTB and DRTB are available.

**7<sup>th</sup> Recommendation:** Digital platforms such as *Teleconsultation OPD or video-observed therapy, smart pill boxes, and other mobile phone-supported adherence strategies* in the form of teleconsult like 99DOTS must be *enhanced and strengthened*.

99DOTS is a pharmaco-economic approach for monitoring and improving adherence to TB medication. 99DOTS introduces anti-TB blister pack wrapped in a custom envelope, which includes hidden phone numbers that are visible only when doses are dispensed. After taking daily medication, patients make a free call to the popped up phone number which is hidden till then, yielding high confidence that the dose was “in-hand” and has been taken. As a very high success rate (of about 99%) is expected by this remote in-built techno-supervision, it is termed as 99DOTS. Mobile phones can cover all these areas and be a boon in bringing compliance and thus TB cure for patients. Andrew et al in his study on Using Mobile Phones to Monitor Adherence to Tuberculosis Medications found that Over 90% of all doses were reported correctly using 99DOTS.<sup>11</sup>

*During lockdown these technologies proved a boon* in many places in India along with smart pill boxes and *e-pharmacies*. Many participants highlighted the *successful models of door step delivery of drugs and sample collection along with Video assisted DOTS and tele-consultations* during these months of the pandemic. *E-Sanjivini* in Tamil Nadu and *e-pharmacy model* in Madhya Pradesh with door step delivery of TB drugs were live examples given by the panellists. *The need of the hour is to scale up this model along with virtual clinics with telemedicine and VOT for DS and DR TB patients.*

The *integrated dashboard* in NIKSHAY will ensure a *digital paperless platform for uniform implementation with seamless integration* in the future.

**8<sup>th</sup> Recommendation:** Drug Resistance TB treatment should be prioritized so as to prevent DRTB from becoming an endemic disease. A *universal regime* needs to be *formulated for both DS and DR TB patients preferably without an injectable drug* to simplify the therapy.

Regimens that could treat both rifampin-resistant (RR) and rifampin-susceptible tuberculosis (TB) while shortening the treatment duration have reached late-stage clinical trials. A Markov state-transition model of 100 000 representative South African adults with TB was used to simulate implementation of the regimen BPamZ (*bedaquiline, pretomanid, moxifloxacin, and pyrazinamide*), either for RR-TB only or universally for all patients. Using BPamZ exclusively for RR-TB increased the proportion of all RR-TB that was cured by initial treatment from  $60 \pm 1\%$  to  $67 \pm 1\%$ . Expanding use of BPamZ to all patients increased cure of RR-TB to  $89 \pm 1\%$  and cure of all TB from  $87.3 \pm 0.1\%$  to  $89.5 \pm 0.1\%$ , while shortening treatment by 1.9 months/person.

Novel regimens such as BPamZ could improve RR-TB outcomes and shorten treatment for all patients, particularly with universal use and may be the need of the hour in India to eliminate TB by 2025.

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