The impact of COVID-19 on tuberculosis: challenges and opportunities

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***Abstract*:** The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from a seafood market in Wuhan, China, has ushered in a new era. It transformed into a pandemic, seized global attention, and was the biggest highlight of the year 2020. The SARS-CoV-2 outbreak has jeopardized health systems and greatly affected socioeconomic parameters. With global focus on fighting this unpredictable fight with this new virus, the biggest chronic infectious killer, mycobacterium tuberculosis (M. tb), was hugely affected from this shift in attention. Due to certain similarities in the behavior of the two infectious agents, there have been inevitable consequences. On one hand, administrative measures to contain SARS-CoV-2 have simultaneously led to a breaking in the chain of tuberculosis (TB) management. Consequently, a regression occurred in the milestones achieved in the battle against TB. On the other hand, the same measures and heightened hygiene awareness has helped to decrease the spread of the TB bacilli. With an improved understanding of the interrelations and the outcomes noticed in 2020, we can better gear ourselves to develop a more sophisticated and robust strategy to tilt the balance against TB. Keeping this in mind, in this review we aim to discuss in detail the implications of SARS-CoV-2 on an already unwavering health hazard: TB.

Keywords: tuberculosis control, COVID-19, SARS-CoV-2 impact, chronic respiratory diseases

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Introduction

The history of tuberculosis (TB) is nearly as old as humanity. Evidence of bony TB has been found in the skeletons of Egyptian mummies.[1,2] The first written records of TB trace back to ancient India and China. In the Vedas, TB has been described as 'Rajyakshama' which means 'to waste away' in Sanskrit.[3,4] No part of the world has been spared from the impact of TB.[5] In Europe, the 'King's touch' was practiced for several decades.[6] During the middle ages, extrapulmonary TB gained recognition, a pathological description of lesions including tubercles and abscesses, was developed and surgical removal of the diseased gland, the scrofula, was recommended. Commendable epidemiological associations were made when it was noticed that soldiers who stayed indoors in barracks developed TB compared with those who spent more time on the battlefields. As a result, a link between overcrowding and disease-spread was established. Later, TB was referred to as 'consumption', 'phthisis', and 'white plague', as the disease seemed to consume the afflicted person, leaving them emaciated and severely anemic.[7,8] These descriptions are similar to 'Rajayakshma', the oldest description of TB.

Our understanding of TB was revolutionized by the isolation of the TB mycobacteria by Robert Koch on the 24 March, 1882.[9] As a result, 24 March is celebrated as World TB Day. Robert Koch not only identified but also cultivated M. tb, and demonstrated its growth on re-inoculation. Years later, streptomycin was the first antitubercular drug to be developed, followed by isoniazid and several other drugs.[10] Later, the Bacillus of Calmette and Guerin (BCG) vaccine was

developed and conferred protection from severe forms of TB.[11] With the development of treatment and vaccinations, TB was considered a manageable disease. However, in 1993 the World Health Organization (WHO) declared a global emergency due to a rise in cases secondary to an outbreak of human immunodeficiency virus (HIV) and inflation in multi-drug resistant cases.[12]

TB continues to pose a threat to the world. The mycobacterium tends to lie dormant within macrophages and resists death by preventing the formation of the phagosome-lysosome complex.[13,14] The disease runs a chronic course and requires prolonged treatment. Due to the increased propensity of the TB mycobacterium to become drug-resistant, the WHO recommends multidrug therapy (MDT). Failure of compliance is also responsible for relapse and the development of resistance. In 2019, nearly 10 million people developed TB across the globe, a number that has been diminishing gradually over several years.[15] The problem is more profound in developing countries, where overcrowding, undernutrition, and poverty are common.[16–18] The largest TB burden is found in India and China. India accounts for a quarter of all drug-sensitive and multidrug-resistant TB (MDR-TB) cases. While the WHO and Sustainable Development Goals (SDG) aim to eliminate TB by 2035, and 2030, respectively, India's prime minister set an ambitious goal of eliminating TB by 2025 at the End TB summit held in New Delhi on 13 March 2018. Strong measures were immediately taken to achieve this target. TB notification was made mandatory; failure to comply with these measures was made a punishable act on 16 March 2018. Active case finding has also begun in susceptible populations. A District Tuberculosis Officer (DTO) was posted in every single district of India. Now, incentives are being given to private providers in addition to patients and care providers. Separate financial support for nutritional supplementation was introduced on 1 April 2018. New technology has been utilized by the government program; most notably, the Medication Event Reminder Monitor System (MERM) and 99-DOTS to further ensure compliance.[19–21] Despite all these measures, TB affected 2.64 million people, claiming 450,000 lives in 2019 that is, more than 1000 deaths every single day.[15]

All efforts to contain TB were severely impacted by the SARS-CoV-2 pandemic. SARS-CoV-2 is caused by the β-coronavirus genus from the Coronaviridae family. Prior to this, the viruses that caused Severe Acute Respiratory Syndrome (SARS) in 2003 and Middle East Respiratory Syndrome (MERS) in 2012 originated from the same family. SARS-CoV-2 is a positive-sense RNA virus that attaches to cells *via* angiotensin coverting enzyme-2 (ACE-2) receptors in order to gain entry to the cell. Once inside, the virus replicates generating virions that utilize the host cell's endoplasmic reticulum and golgi apparatus, before being released into the blood stream.[22] The host immune system is activated and is responsible for most of the disease manifestation.

The first case of SARS-Cov-2 was identified in the Wuhan district of China on 29 December 2019. The SARS-CoV-2 virus was believed to be zoonotic disease with bats and pangolins as intermediary hosts.[23] The virus was named 2019nCov (2019 novel corona virus). Later, nearly 80% genomic similarity with SARS corona virus was seen.[24] Subsequently, the WHO declared it an emergency on 30 January 2020 and then a pandemic on 11 March 2020 and renamed the virus as SARS-CoV-2 while the disease was called COVID-19.[25] The disease has a high infectivity with basic reproduction number varying between 3 and 5.[26] The transmission occurs *via* aerosol and infected fomites. This deadly virus has been responsible for over a hundred million infections and a mortality of more than 2 million, a figure that continues to rise.[27] The outbreak seized global attention; almost entire health care services were utilized to cope with the outbreak, blurring the focus on other chronic diseases, especially TB.

India, a densely-populated country with the largest number of TB patients in the world, is currently witnessing a second surge in COVID-19 cases with greater severity. Perhaps the timely nation-wide lockdown helped to curb the spread of the virus last year and the country was not harshly-scathed. The ramifications of this second peak remain to be seen, as more than 200,000 people are being infected each day.[27] Meanwhile, based on the experience of 2020, in this article, we aim to bring out the key inter-linkages between COVID-19 and TB.

COVID-19 and tuberculosis: interactions

Both TB and COVID-19 are infectious diseases that primarily involve the lungs. TB spreads *via* droplet infection; SARS-CoV-2 too fans out *via* aerosol.[28] Overcrowding promotes further propagation of both diseases.[29,30] Those who are elderly, malnourished, diabetics, or who have some other chronic disease or are immunocompromised are more prone to contract these infections.[31,32] Both infectious agents involve cell-mediated immunity in their pathogenesis.[33,34] It is possible that one infection increases the probability of contraction of the other; possibly due to a weakening of the host immune system. The acquisition of COVID-19, as well as the use of corticosteroids for its management may also carry the risk of exogenous TB infection, or reactivation of old endogenous infection. Likewise, those with active TB or who have structural lung disease secondary to healed pulmonary Koch's disease are probably at a greater risk of developing COVID-19. The interactions between the two agents are reported in a meta-analysis by Sheerin D *et al.*, in which an overlapping of genetic signatures between TB and COVID-19 were identified.[35] They concluded that patients with latent/active TB or post-TB sequelae are at a higher risk for severe COVID-19 and those diagnosed with SARS-Cov-2, should be followed up for development of TB. There was also speculation that the BCG vaccination might confer protection from SARS-Cov-2; however, nothing conclusive could be ascertained.[36,37]

As far as clinical manifestations are concerned, symptoms such as cough, fever, weakness, malaise and hemoptysis can be seen in both conditions. Similar presentations can pose a diagnostic challenge. Tadolini *et al* reported facilitation of TB diagnosis while investigating for SARS-CoV-19 infection in a small number of patients in their study; it was the first study conducted on a cohort of active TB or post-TB sequelae patients with COVID-19 co-infection.[38] They called for larger studies to evaluate the impact of one agent on disease development of the other. In another study, indoor patients with active TB were screened and 20 patients were found positive out of a total of 24, indicating a possible higher susceptibility. Although they reported an overall benign course, a remark for further studies to ascertain the bilateral impact was made.[39] Several clinical studies which indicate an increased propensity of TB patients to acquire corona infection and run through a severe course have been made.[39–44] However, most of these studies suffer from a serious limitation: a small sample size and a lack of knowledge of prior comorbidities.

Nevertheless, further studies will clarify the association and long-term implications of these coexistent conditions.

The impact of SARS-Cov-2 on tuberculosis: challenges faced

In order to contain SARS-Cov-2, lockdowns were imposed by countries worldwide.[45] People were forced to stay indoors, resulting in a number of effects. The symptom similarity between TB and COVID-19 probably resulted in a delay in suspecting TB, as most people could have attributed similar symptoms to COVID-19 and preferred to wait it out. Also, pre-existing stigma around TB and the added stigma of COVID-19 might have discouraged people from getting tested, even after experiencing symptoms common to both diseases. These were mostly people of lower socioeconomic strata, who were already struggling with their daily earnings and food. As a result, the additional fear of isolation or quarantine would have be an added misery to their prevailing life concerns. Spread among household contacts is also an important concern due to close interactions fostered by home confinement. Among those who wished to seek medical advice, the diagnosis of novel TB was delayed, as most non-emergency services were suspended. Access to private sector healthcare was also reduced.[46] This resulted in an overall fall in disease detection and notification. This is evident from the 2020 Global TB report which featured reduced notification of TB. The notification rate was reduced by approximately 25% in three countries with the highest burden of TB: India, Philippines, and Indonesia during a six month period from January to June 2020 as compared to the same period in the year 2019. Similar findings were reported by Milgliory *et al.*[47] In the long run, deaths from TB could rise significantly in the coming years; an about 13% increase in mortality is expected in the coming years.[15] This is certainly a major setback to the global progress made so far to combat TB.

Already diagnosed patients have also suffered. Outpatient departments have not been functional,

while laboratories have mostly been dedicated to the processing of samples of COVID-19 patients. The follow-up and response evaluation of pulmonary TB patients is chiefly done by sputum microscopy and culture growth. This assessment was lost during lockdown. Hence, those who had treatment failure, relapse, or who had developed drug resistance could not be timely identified and may have continued to deteriorate. Furthermore, extensive counseling and motivation is needed for patients to deal with this disease, its side effects, the stigma associated with it, and the long duration of treatment. The entire process came to a standstill with the implementation of lockdown. In India, where drug treatments are dispersed under direct observation and the patient or caretaker must frequently collect the drugs from the DOTS centre, the drug supply was suddenly halted. There was no prior planning to ensure uninterrupted supply in case of an emergency; however, announcements regarding delivery of ATT drugs at the doorstep of patients were made. There is no record of its application and effectiveness.[48] Premature discontinuation of drugs for long periods may have possible lead to disease relapse and the development of resistance among many patients. Financial constraints also developed, as the WHO directed all funds towards combating COVID-19.[15] Presently, India is dealing with the second wave of SARS-CoV-2. This time curfews have been restrained.[49,50] The absence of complete lockdown has allowed patients with TB to seek medical care; however, this approach it may pose a challenge in containing SARS-CoV-2, which is currently rampant. The effect of these experiences on TB patients and the impact on their management remain to be elucidated.

The opportunities revealed

With numerous emerging challenges, there are also several opportunities. Lockdown and physical distancing have been practiced globally and this has helped to contain the person-to-person spread of SARS-CoV-2 infection. Mask wearing, the maintenance of a safe distance, and the avoidance of unnecessary physical contact has become a regular practice. This has helped not just to control COVID-19, but also M. tb, which remains suspended in the air for 10 days once a person releases infected droplets.[51] In general, air quality has shown remarkable improvement due to a smaller number of vehicles on road and shut down factories.[52] This might have indirectly helped respiratory patients, including those with TB. Bidirectional screening of patients has been recommended by the Ministry of Health and Family Welfare in India, which helped in the early diagnosis of so many cases of pulmonary TB, as well as COVID-19.[53]

Since the dawn of this pandemic, health services are in a constant state of improvisation. Most funds provided by health organizations are being allocated to the health sector.[54,55] Medical facilities have been upgraded for facilitate the better management of respiratory failure and ARDS; these are the hallmarks of severe COVID-19 disease. Level one and level two hospitals were also provided with newer equipment, such as high flow nasal cannula and non-invasive ventilation.[56,57] The upgradation that has occured is there to last and will be utilized for better patient care long after the end of the COVID-19 pandemic. After lifting lockdown, an appraisal of the situation and its impact on other diseases was conducted worldwide. Loopholes in healthcare systems were identified, and aggressive measures were taken to tackle setbacks in the management of other health conditions. Networking between the laboratories and clinical departments has been improved. The frequency of aerosol generating procedures was reduced in order to minimize iatrogenic COVID-19 spread.[58–60] Reduced aerosol production also helps to control pulmonary TB spread. It is quite likely that administrative, laboratory, and environmental factors applicable for TB can be utilized for COVID-19 management as well.

TB patients are now provided drugs for a prolonged duration in order to minimize visits. Online and telephonic consultation gained favor for minor conditions.[61,62] Appointments for non-emergency conditions are provided *via* online portals, even in developing countries such as India. This helps to space the patients outdoors with respect to time slot and place; thereby reducing the odds of cross infection among patients. These practices have brought about an order and structure in overcrowded health care facilities. The health sector has gained global attention and governments have channeled a considerable percentage of their gross domestic product (GDP) towards it.[63,64] These changes have improved the standard of health care in general worldwide.

Conclusion

The COVID-19 pandemic has affected the world in unpredictable ways and caused massive damage. There has been a great increase in morbidity and mortality; not just in those who were infected by SARS-Cov-2 but also those who had pre-existing ill health conditions. The pandemic has revealed the existing gaps in healthcare and offers an opportunity to bridge them and gain a better understanding of our priorities. Now, there is the regular use of masks among the general population as well as patients. The importance of cough etiquettes, physical distancing, and general hygiene has been realized. Strengthening of peripheral health institutions has been conducted, which has resulted in the decreased movement of TB patients and better provision of care. The adequate utilization of digital consultations and appointments has refined the process of health care delivery. The efforts and resources put in over the last year are now proving worthwhile as the cases numbers rise again.[65] It is now up to us to make effective use of existing resources and use the opportunity in order to be better prepared tomorrow.

Authors contributions

Surya Kant: conceptualization, manuscript editing, and approval of final version.

Richa Tyagi: manuscript preparation and revision.

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The authors declare that there is no conflict of interest.

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