COVID-19 and Tuberculosis: A Meeting of Two Pandemics!

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Abstract
Coronavirus disease 2019 (COVID-19), causes serious respiratory illness manifesting as pneumonia, adult respiratory distress syndrome and respiratory failure. Amidst the rising number of cases and deaths, it is imperative to not forget Tuberculosis (TB) which is another pandemic existing since centuries. There could be dire consequences for tuberculosis patients globally especially in low and middle income countries with a high burden of disease and overwhelmed health care systems. Tuberculosis is still the leading infectious killer worldwide, and therefore, it is crucial to reflect on the interaction between the two diseases. Evidence suggests that both COVID-19 and tuberculosis have a synergistic relationship, boosting detrimental effect of each other, disrupting existing health care models, and also worsening the clinical outcomes in terms of morbidity and mortality. This review aims to draw attention towards this pertinent clinical issue, and tries to unravel the intricate relationship between COVID-19 and tuberculosis, as also the role of BCG vaccination to combat the COVID-19 pandemic.

Introduction
It has been less than a year since the first novel coronavirus (SARS-CoV-2) case was described in Wuhan, China, and yet it has quickly escalated the ladder and COVID-19 has become a pandemic, arguably the largest outbreak world has witnessed in more than a century. But, one should not forget tuberculosis (TB), which is an already existing pandemic, declared as a global health emergency by WHO in 1993. One-quarter of the world’s population is infected by Mycobacterium tuberculosis and half of this population is concentrated in merely 8 countries- China, India, Pakistan, Bangladesh, Indonesia, Philippines, Nigeria, and South Africa.¹ The superimposition of the coronavirus pandemic over tuberculosis is bound to have a significant impact, especially in emerging economies. Glaziou used predictive models to estimate the impact of COVID-19 pandemic on tuberculosis and has estimated a 13% increase in tuberculosis deaths in 2020, mainly due to a 25% decrease in case detection rate.² In 2018, tuberculosis was responsible for 1.5 million deaths¹ making it the topmost infectious disease.
killer, and now coronavirus is just slightly behind. Data about concurrent COVID-19 and tuberculosis infection is scarce, hence we sought to provide a brief review of available literature on the same.

**Prevalence of COVID-19 disease in tuberculosis patients**

Tuberculosis and COVID-19 are both primarily respiratory illnesses, the difference being the insidious onset of tuberculosis compared to the acute viral illness that COVID-19 is. Both diseases notoriously spread through droplet nuclei, and respiratory symptoms such as fever, cough, breathlessness, and malaise are also very similar in the two. Simultaneous tuberculosis and COVID-19 can also exist in the same person and there exists the possibility of one disease augmenting the other as a transient decrease in cellular immunity may lead to new infection (COVID-19) or lead to reactivation of latent infection (tuberculosis). Importantly, tuberculosis and COVID-19 share common social predispositions viz., overcrowding, poverty and pollution as well as similar risk factors such as advanced age, diabetes, malnutrition, immunosuppression, and other chronic respiratory illnesses. A meta-analysis showed that patients with pre-existing chronic respiratory disease had more than two times likelihood of getting infected (odds ratio of 2.46). Since, tuberculosis is known to have varied presentations, it is imperative to anticipate important interactions between the two diseases and understand the same. A diagnosis of COVID-19 does not exclude underlying tuberculosis, and in tuberculosis-endemic settings, if the acute COVID-19 illness extends beyond two weeks, it is imperative to consider tuberculosis as a concomitant infection. Otherwise, national tuberculosis guidelines in India do state that any fever and cough that extends beyond 2 weeks should be investigated for tuberculosis. Hence, in the COVID era, it is more pertinent that COVID patients who demonstrate delayed or slow recovery, possibility of co-infection with tuberculosis should be entertained and promptly ruled out.

Tadolini et al described a cohort of 49 patients with concurrent tuberculosis and COVID-19 infection. 26 (53.0%) had tuberculosis before COVID-19, 14 (28.5%) had COVID-19 first and nine (18.3%) had both diseases diagnosed within the same week. Although this study had its limitations, it proved the association between tuberculosis and COVID-19. The three subgroups can be put under the umbrella of old/active TB cases, which were probably unmasked by COVID-19 infection.

Another observational case-control study conducted by Liu et al in China with 36 confirmed COVID-19 cases reiterated the above findings. Controls were selected from another case-control study on bacterial/viral pneumonia and tuberculosis infection data for them was sought and comparisons made. Cases were grouped according to the severity of COVID-19 infection (mild/moderate, severe/critical) and the status of Mycobacterium tuberculosis infection was sought in these patients using IGRA (interferon-gamma release assay). The prevalence of tuberculosis infection in COVID-19 patients was found to be 36.11%, which was higher compared to the control arm which consisted of two groups with bacterial (20%) and viral pneumonia patients (16.13%). Notably, tuberculosis infection (36.11%) was found to be more common than other comorbidities viz. diabetes (25%), hypertension (22.2%), coronary heart disease (8.3%), COPD (5.6%). This is an important observation as tuberculosis has not been studied as a comorbidity for COVID-19 infection compared to the extensive research about the effect of non-communicable diseases such as hypertension, diabetes, and coronary artery disease on COVID-19 outcomes.

A case series of 4 COVID-19 patients from Singapore with atypical radiographic features was reported. Ground glass opacities, multifocal patchy consolidation and peripheral interstitial changes are considered typical radiographic findings in COVID-19 patients. In spite of a confirmed COVID-19 diagnosis, the pulmonary radiologic findings in these four patients appeared to be more consistent with those of tuberculosis. This highlights the importance of entertaining a differential of other pulmonary pathologic conditions such as tuberculosis causing atypical radiographic features in patients of COVID-19.

Diagnostic uncertainty due to non-specific clinical features and radiological findings for tuberculosis can lead to missing of the diagnosis. Tuberculin skin tests and IGRA have been widely used for screening of tuberculosis, although it is not a sure-shot diagnostic tool. The results are influenced by host’s immune response after Mycobacterium tuberculosis (or BCG) exposure and this increases the possibility of diagnostic errors. Increasing age, low blood lymphocyte count, high body mass index and immunosuppressive therapies can be associated with false negative results. Further, an excess of inflammatory markers is known to affect the sensitivity of IGRA and the high value of C-reactive protein (CRP) might be a confounder for false negative results. Moreover, high CRP and low peripheral blood lymphocyte counts have been observed within a few days of exposure to SARS-CoV-2, and this may contribute to false negativity of IGRA.

**Impact of tuberculosis on COVID-19 severity**

Tuberculosis and COVID-19 are linked bi-directionally; the temporary immunosuppression induced by tuberculosis may increase the susceptibility of patients to COVID-19, and COVID may, in turn, also increase susceptibility to tuberculosis.

According to a modelling analysis by STOP-TB partnership in collaboration with John Hopkins University and USAIDS, a 3-month lockdown and a protracted 10-month restoration could lead to an additional 6.3 million cases of tuberculosis and an additional 1.4 million tuberculosis deaths during 2020-2025, implying a setback of 5-8 years due to the COVID-19 pandemic. Each month taken to return to normal tuberculosis services would incur, in India, an additional 40,685 deaths between 2020 and 2025.

Pre-existing tuberculosis disease and underlying lung condition will affect the clinical categorization (for severity) of COVID-19. The severity of COVID-19 in patients with tuberculosis was also studied by Liu et al in 31 patients with 78% patients being in the severe/critical category, while mild/moderate cases were just 22% of the total (p=0.0049). Similarly, the rate of disease progression was significantly faster, i.e; the time period between infection and development of symptoms in patients with concurrent tuberculosis and COVID was less (6.5±4.2 days) compared to patients
without tuberculosis (8.9±5.2 days), and between symptom development and being diagnosed as severe disease was 3.4±2.0 days in concurrent infection vs 5±0.5 days in SARS-COV-2 alone.3

Motta et al described 2 cohorts with a total of 69 patients with tuberculosis (including post-tuberculosis sequelae) and COVID-19. In all cases, COVID-19 worsened the prognosis of tuberculosis patients and/or resulted in death. Mortality is likely to occur in elderly individuals specially if they have comorbidities. Higher mortality rates can be expected in settings where advanced forms of tuberculosis frequently occur and are caused by drug-resistant strains of Mycobacterium tuberculosis.

The long-term effect of this virus on lung function will be discerned only in the times to come. SARS-CoV-2 infection is known to initiate an aggressive inflammatory response, called the “cytokine storm”. Cytokines such as interleukin-1β, interferon-γ, tumor necrosis factor-α, interleukin-2, interleukin-4, interleukin-10 increase significantly and contribute to disease severity.10

The potential impact of COVID-19 on tuberculosis

The Ministry of Health and Family Welfare, India have released an advisory on 26th August 2020,3 stating that prevalence of tuberculosis among COVID-19 patients is 0.37% - 4.47% and recommended bi-directional screening for COVID-19 and tuberculosis. It has also advised for tuberculosis screening in all cases of influenza-like illnesses (ILI) and severe acute respiratory illness (SARI). Tuberculosis is reportedly associated with a 2.1-fold increased risk of severe COVID-19 disease. In the period from January to June 2020 compared to previous year, an overall decline in tuberculosis notification by 26% has been observed due to the COVID-19 pandemic.

Similarly, Hogan et al used established transmission models to estimate the potential additional impact of COVID-19 on tuberculosis, human immunodeficiency virus (HIV) and malaria epidemics. It is estimated that in high-burden settings, deaths due to HIV, tuberculosis, and malaria could increase by up to 10%, 20%, and 36%, respectively over the next 5 years. Due to COVID-19 suppression strategies, the major impact for tuberculosis is likely to be from reductions in timely diagnosis and its subsequent treatment.4

A retrospective study was done by Buensono et al in Sierra Leone, a small town of Africa, to study the impact of COVID-19 in a high tuberculosis burden setting, wherein tuberculosis incidence and directly observed therapy (DOT) administration was compared to previous years. A significant drop of confirmed tuberculosis cases was noted. The number of presumptive cases of tuberculosis, that might have other respiratory diseases, decreased in March and April 2020. Moreover, no DOT was presumably administered in April 2020.

Coinfection with tuberculosis and SARS CoV-2 is of particular concern due to several reasons. COVID-19 itself or use of immunomodulators in moderate to severe COVID-19 may lead to reactivation of latent tuberculosis in high endemic areas like India as demonstrated by Pathak et al in mouse models by activation of a stem cell defense mechanism that accelerates activation of dormant tuberculosis. Their findings point to a potential increase of tuberculosis post-COVID. Mandal et al in their review highlighted that characteristics of COVID-19 progression are similar to fatal central nervous system tuberculosis, and suggested that some anti-tubercular therapeutic strategies can be helpful for SARS-CoV-2 treatment.17

Use of immunosuppressive agents for COVID-19 remains an area of concern, as it can potentially increase the risk of reactivation of latent tuberculosis. Also, possibility of drug-drug interactions (e.g., Rifampicin and Lopinavir/ritonavir) and additive hepatotoxicity due to simultaneous use of antitubercular drugs with agents for COVID-19 cannot be overlooked.18

Is BCG vaccine protective against COVID-19?

Another hypothesis which has generated widespread interest is the role of Bacille Calmette-Guerin (BCG) vaccine for protection against COVID-19. As on date, the status of BCG vaccine remains to prevent serious tuberculosis infection when administered in infants. It confers protection from tuberculosis by enhancing cellular immunity. IFN-γ is a key cytokine produced by CD4+ T cells and mediates macrophage activation and resistance to Mycobacterium tuberculosis via cellular immune mechanisms.19 However, the NSE (nonspecific effects) of the vaccine are the ones which are considered to confer protection against coronavirus, and one of these NSE is trained immunity. Trained immunity is defined as the enhancement in the innate immune responses to subsequent infections, which is different from the cellular immunity important for prevention against tuberculosis. It is believed to be achieved through epigenetic and metabolic programming of immune cells (monocytes and/or natural killer cells) which allows them to mount an enhanced response to pathogen-associated molecular patterns (PAMPs- from bacteria or viruses) and to activate adaptive responses efficiently which is non-specific, thus promoting host defence.20 This is the plausible mechanism why a vaccine for tuberculosis can lead to protection against multiple pathogens, like the protection conferred by the BCG vaccine to salmonella, and its use in bladder cancer.21

A study that involved both BCG vaccination at birth and delayed vaccination showed a reduced mortality rate in the birth vaccinated group. This effect is attributable to the BCG-based prevention of a range of conditions, including respiratory infections, neonatal sepsis, and fevers.22 Similarly, BCG vaccination of elderly patients over a period of three months was observed to result in a reduction in the incidence of acute upper respiratory tract infections.23

In another interesting study done by Escobar et al, a correlation between the BCG index, and COVID-19 mortality in different socially similar European countries was observed. Every 10% increase in the BCG index was associated with a 10.4% reduction in COVID-19 mortality. Moreover, COVID-19–related deaths were significantly higher in countries with higher quality of life when compared to developing countries even after correcting for confounding factors. This is in contrast to the general expectation that higher income countries would have lower mortality rates due to better healthcare systems. An inverse relation has been demonstrated with the ‘BCG
vaccine coverage and COVID-19 mortality, even after adjusting for morbidity, PCR-tests, age, universal health coverage, numbers of medical doctors, elevated total cholesterol and healthy life expectancy. But no such relation of BCG vaccination was evident with COVID-19 morbidity.[25]

Clinical trials are ongoing to evaluate the effect of BCG vaccination on COVID-19 outcomes. BCG vaccination of health-care workers is being conducted in several countries to see if it can offer protection against COVID-19. A study in Germany is also evaluating VPM1002, a recombinant vaccine strain derived from BCG, if it can protect health-care workers and elderly from COVID-19.[26] It is important to note that, since BCG is a live attenuated vaccine, there is limited data on the safety of its administration to elderly people and it should also be avoided in immunocompromised individuals.[27]

**Conclusion**

Co-infection with tuberculosis in patients with COVID-19 should always be suspected especially in patients with severe features, prolonged clinical course and atypical radiographic findings. Timely initiation of treatment should be our priority in these subsets of patients, especially in high tuberculosis burden settings. Large scale prospective studies are required to study the actual impact of COVID-19 on the already existing tuberculosis pandemic on all fronts including health, social and economic fronts. Not only this, it is important to initiate randomized controlled trials to ascertain the interactions of the various drugs used for COVID-19 and tuberculosis, so as to prevent deleterious side effects and manage post- tuberculosis as well as post-COVID sequelae.

**References**