

Review Article

The potential impact of COVID-19 infection on tuberculosis: a literature review

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ABSTRACT

Tuberculosis is among the oldest endemic conditions affecting humans; however, it remains a significant health issue around the globe. As with previous outbreaks/epidemics, the COVID-19 impact on TB control efforts and outcomes should raise concerns; however, the extent of this impact is currently unknown. In the current study, we aim to review the literature to provide an overview of the available evidence discussing the impact of coronavirus disease-2019 (COVID-19) on TB infections. On one hand, many of the existing reports showed that having TB infection may contribute to developing severe forms of acute respiratory syndrome in patients co-infected with COVID-19, and the presence of underlying TB infection was identified as a risk factor for COVID-19 infection. However, other reports showed that patients with present TB were not more vulnerable to get infected with COVID-19 or to higher mortality rates. In the same context, COVID-19 may have an impact on the late reactivation of TB, which could be mediated through its effects on the immune system functionality and subsequent development of active TB. Moreover, TB preventive treatment programs, awareness campaigns, and anti-TB funding were also affected by COVID-19. Accordingly, the global strategy to end the TB by 2035 may be affected by the COVID-19 pandemic. Hospital admission for TB patients should be restricted to severe cases, to prevent the transmission of COVID-19 in those cases. Due to scarce evidence, more studies are needed to guide management plans in this particular context.

Keywords: COVID-19, Tuberculosis, Co-infection, Burden

INTRODUCTION

Tuberculosis (TB) is among the oldest endemic conditions affecting humans; however, it remains a significant health issue around the globe.^{1,2} The latent TB infection is estimated to be affecting one-quarter of the

world's population (TB dormant form).³ It is estimated, by the world health organization (WHO), that ten million individuals develop active TB and more than one million ones pass away due to TB, every year.⁴ The burden of TB has declined rapidly following the development of TB medications and improvement in the population's socioeconomic status, with subsequent control in high-

income countries.^{5,6} Nevertheless, TB re-emerged in the 1980s, with the appearance of the human immunodeficiency virus (HIV) pandemic; leading to high mortality in millions worldwide.⁷ Accordingly, the morbidity and mortality of TB started to decrease, over the past decades, as a result of using antiretroviral therapy (ART) in managing HIV.⁸

Recently, different viral outbreaks emerged in several spots of the world; posing new difficulties for efforts of TB control, whether on the national or global scales. For instance, the TB programs in West African countries were majorly damaged following the Ebola outbreak.^{9,10} Similarly, TB control efforts in Saudi Arabia have compromised following the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreaks.¹¹ Accordingly, there was an increase in the TB burden among the countries affected by viral outbreaks over the following years. Ending the TB epidemic, by 2030, is among the United Nations sustainable development goals (SDGs) and the WHO ambitious targeting a 90% TB reduction (compared to 2015 rates), by 2035.^{12,13} Before the COVID-19 pandemic, the deaths from TB were over 4000 individuals daily.⁴ As with previous outbreaks/epidemics, the COVID-19 impact on TB control efforts and outcomes should raise concerns; however, the extent of this impact is currently unknown.^{14,15} Driven by the high load of COVID-19 cases and measures to control its transmission, there is an obvious reduction in the availability of health services needed for the diagnosis and management of TB cases.¹⁶ Although COVID-19 related social distancing may limit *Mycobacterium tuberculosis* (MTB) non-household transmission, it is not clear if this can compensate for the shortage in TB health services.¹⁷ In the current study, we aim to review the literature to provide an overview of the available evidence discussing the impact of COVID-19 on TB infections.

An extensive literature search of the Medline, Cochrane, and EMBASE databases was performed on 20 November 2020 using the medical subject headings (MeSH) or a combination of all possible related terms. Papers discussing the impact of COVID-19 on TB infections were screened for relevant information. We did not pose any limits on date, language, age of participants, or publication type.

LESSONS FROM PAST EPIDEMICS/PANDEMICS

To improve understanding of the management of the novel coronavirus pandemic, understanding the experience is needed. Since the emergence of the coronaviruses in 1960, three human types were identified with their ability to cause fatal respiratory conditions. In 2002, a global epidemic was caused by the severe acute respiratory syndrome (SARS) coronavirus, followed by the Middle-East respiratory syndrome coronavirus (MERS-CoV) in 2012, which has been identified in 27 countries so far.^{18,19} Recently, COVID-19 has emerged; causing an ongoing pandemic with growing daily

numbers of new cases and deaths around worldwide.²⁰ COVID-19 has high transmissibility similar to that of the 1918-1919 pandemic; the one-third of the world population was estimated to be affected, with a 2.5% mortality rate.²¹ Moreover, the COVID-19-induced acute respiratory distress syndrome (ARDS) showed pathological similarities with H7N9-associated ARDS.²² However, the influenza pandemics showed lower fatality among healthcare workers, compared to SARS, MERS, and COVID-19 infections.²³

Among TB patients, it has been shown that inducing type I interferons (IFNs), as mediated by influenza infection, can affect the ability of competent individuals to control MTB replication.²⁴ Accordingly, promoting the infection and increasing TB mortality; it was noted that the mortality rate caused by pneumonia and influenza amidst the age group most affected by TB was higher during the 1918 pandemic, compared to death rates before and following it.^{25,26} During winter months, in coincidence with seasonal influenza, TB-related deaths were higher, which may suggest that pulmonary TB is a risk factor for mortality among influenza patients.²⁷ In contrast, some studies reported the absence of a significant association between the pulmonary TB severity and influenza co-infection.^{28,29} Also, an animal study showed that the influenza-induced IFN- γ increase had little effect on the bacterial load in BCG-infected murine model.²⁹ Furthermore, a recent systematic review did not show a significant impact of influenza on pulmonary TB clinical picture or outcomes, and vice versa.³⁰

In china TB patients infected with SARS from the exposure to patients admitted within the same hospital wards, which could have been prevented.³¹ Although, most of those patients recovered with no serious complication, the SARS-TB co-infection was accompanied by a significant reduction in average CD4+, CD8+, and low antibody levels following recovery from SARS.³¹ A possible higher spread of SARS may be associated with the presence of TB since the viral excretion was for longer durations in stool of TB-SARS co-infected patients, compared to those with SARS infection alone.³¹ In Taiwan, during a screening related to SARS infection, 60 healthcare workers were found to have TB.³² Moreover, during the SARS epidemic, SARS cases developed active pulmonary TB following the recovery from SARS, which is consistent with previous animal models showing a cellular immunity attenuation following viral infection.^{24,31} Similarly, the MERS-CoV infection was found to augment the TB infection through the immunosuppression, and accordingly, discovering the coexisting TB should be always done in SARS and MERS-CoV patients.¹¹

PATHOLOGICAL ASSOCIATION BETWEEN TB AND COVID-19

The pathophysiology of COVID-19 is not fully digested; however, it seems to be similar to the one of SARS infection. The COVID-19 infection can induce severe inflammation by enhancing cytokine release; resulting in

the so-called “cytokine storm”, which may explain the severe disease in young patients.³³ Noteworthy, cytokines have an important role in the resistance of the host to the TB infection, which was confirmed by the findings of severe MTB disease in individuals with IFN- γ and IL-12 signaling pathway mutations or those with Crohn’s disease or rheumatoid arthritis and receiving TNF- α blockers.^{25,34} Established and possible interactions between MTB and coronaviruses is shown in (Figure 1).³⁵

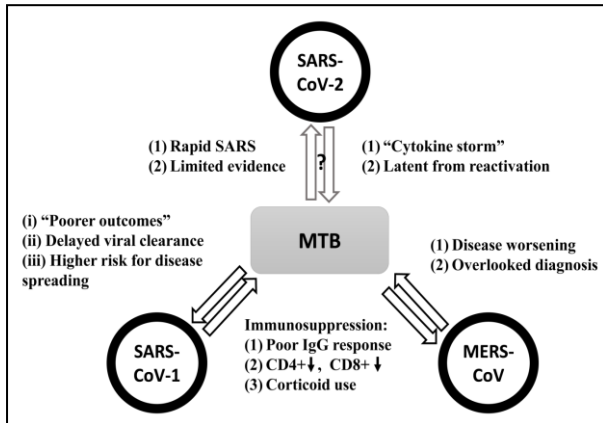


Figure 1: Established and possible interactions between MTB and coronaviruses.

IMPACT OF COVID-19 ON TB PATIENTS

There is limited evidence on the COVID-19-TB co-infection, nevertheless, existing reports showed that having TB infection may contribute to developing severe forms of acute respiratory syndrome in patients co-infected with COVID-19.^{33,36,37} According to a recent meta-analysis, the presence of underlying TB infection was identified as a risk factor for COVID-19 infection, increasing its severity and mortality rates, and decreasing disease recovery.³⁸ In contrast, another meta-analysis showed that patients with present TB were not more vulnerable to get infected with COVID-19 or to higher mortality rates; however, the same study acknowledged that there was a 2.1-fold increase in the risk of developing severe forms of COVID-19 disease, with no statistical significance.³⁹ It should be mentioned that the latter study included a small number of TB patients with COVID-19 co-infection and the risk of bias was not assessed in a rigorous way.³⁹ In the same context, a cohort study of 69 COVID-19-TB co-infection, the COVID-19 worsened the prognosis of TB patients; nevertheless, TB was not a significant predictor of mortality.⁴⁰ In case series of 20 patients with COVID-19-TB co-infection, except for one patient who died, there was no major impact of COVID-19 on active TB infection, with no obvious clinical deterioration, no intensive care unit admissions, no new-onset pneumonia and no worsening of TB lesions in chest X-ray.⁴¹ However, this study was limited by small number of patients, the young age of most of the included individuals, and low frequency of significant co-

morbidities and multidrug-resistant TB.⁴¹ In the same context, COVID-19 may have an impact on the late reactivation of TB, which could be mediated through its effects on the immune system functionality and subsequent development of active TB.^{42,43} COVID-19-related pneumonia and respiratory failure may inflict long-standing respiratory system damage, which would result in enhancing TB risk.⁴⁴ Furthermore, the evidence shows that viral infections (as HIV and influenza) can take a part in developing active TB, either directly the following exposure to TB or indirectly by re-activating a latent TB infection.⁴⁵⁻⁴⁷

IMPACT OF COVID-19 ON TB CONTROL AND BURDEN

As mentioned before, the strategies for TB prevention and control are always compromised at times of outbreaks, which applies to the current COVID-19 pandemic. For instance, on March 24 every year, the world tuberculosis day is celebrated to enhance disease-related awareness and to raise funding; it was canceled in many countries due to the COVID-19 situation.¹⁵ Moreover, the BCG vaccination programs, administered to prevent TB in children, were negatively influenced by COVID-19 infection.⁴⁸ Moreover, programs of preventive treatment targeting the high-risk groups, to prevent the progression of latent TB to the active one, were also affected by COVID-19.⁴⁹ Accordingly, the global strategy to end the TB by 2035 may be affected by the COVID-19 pandemic. McQuaid et al constructed mathematical modeling to measure the combined effect of COVID-19 related shortage in TB control measures and the possible benefit of COVID-19-associated social distancing on TB burden.⁵⁰ Their results showed an 8-14% increase in the cumulative TB mortality between 2020-2024, with a total of 201,595 deaths in China, India, and South Africa alone.⁵⁰ They concluded that this damaging spike in mortality can be minimized by the impact of COVID-19 on the delivery of TB health services along with a strict reduction in social contacting.⁵⁰ They also anticipated that external factors like poverty rates increase and decline in the access to antiretroviral therapy within a country with high HIV prevalence; could increase the incidence of TB infection.⁵⁰ Noteworthy, the effect of social distancing was more favorable on TB incidence rather than TB death rates.⁵⁰ The COVID-19 pandemic would cause severe economic damage in national and global aspects. This crisis will have a negative impact on the less fortunate people with fewer jobs, reduced remittances, high prices, and changes in the services provided; including education and health care sectors.⁵¹ As per the World Bank, driven by the COVID-19 crisis, 2020 will have an increase in the extreme poverty rate (0.3-0.07 percent points) and 40-60 million populations will be in the extreme poverty category, which will have a long-lasting impact on the TB burden.⁵² The reason for that is the poverty being recognized as an impending risk factor for TB infections, whether new or re-activated one.⁵²⁻⁵⁴

Table 1: Strategies to Mitigate the Impact of COVID-19 on TB Control.⁴²

Impact of COVID-19 on TB	Strategies to mitigate the impact of COVID-19 on TB control
Increased household transmission of TB	Apply infection prevention and control measures (e.g., cough etiquette, personal protective equipment).
	Consider using upper-room germicidal ultraviolet (GUV) where indicated.
	Apply room ventilation (including natural, mixed-mode, mechanical ventilation, and recirculated air through high-efficiency particulate air (HEPA) filters).
	Separate or isolate people with presumed or demonstrated infectious TB.
	Provide TB preventive treatment for high-risk groups.
Delayed TB diagnosis and treatment services	Initiate TB treatment early.
	Maintain supports to essential TB services during and after the COVID-19 pandemic.
	Provide information to patients about COVID-19 and TB so they can protect themselves and continue their TB treatment.
	Apply patient-centred delivery of TB prevention, diagnosis, treatment, and care services.
	Decentralise TB treatment to community health workers and increase access to TB treatment for home-based TB care.
	Provide adequate supply of TB medication to patients for safe storage at home.
	Design mechanisms to deliver medicines and to collect specimens for follow-up testing at home.
	Integrate TB and COVID-19 services for infection control, contact tracing, community-based care, surveillance and monitoring.
	Provide short-term training for students and health professionals and recruit additional staff to work on TB programs.
	Change policy if required and support private hospitals, and academic or research centres, to provide TB testing and treatment.
Affecting TB prevention and control strategies	Use virtual care and digital health technologies (e.g., video observed therapy) for adherence support, early initiation of treatment, remote monitoring of TB patients, counselling, and follow-up consultations.
	Organize virtual conferences, seminars, workshops and fundraising.
	Design strategies to deliver BCG and TB preventive therapy at home.
Reactivation of TB	Create community awareness of the importance of TB services.
	Plan additional support and resources to reduce the burden of TB.
	Conduct research to identify the impact of COVID-19 on reactivation of TB and to design interventions mitigating this problem.

Alene et al proposed some possible strategies to “mitigate the impact of COVID-19 on TB control”, which are represented in (Table 1).⁴⁸

CONCLUSION

COVID-19 and TB attenuate the host’s immune responses; this fatal synergism can contribute to higher severity and clinical deterioration. Coinfection with COVID-19 and TB most probably affecting both sides of the patients: causing severe acute respiratory syndrome through cytokine-dependent immune response and enhancing TB reactivation risk. Hospital admission for TB patients should be restricted to severe cases, to prevent the transmission of COVID-19 in those cases. In spite of the increasing number of COVID-19 cases, there are not enough data to accurately measure the impact of

the COVID-19 pandemic on patients with TB. More studies are needed to guide management plans in this particular context.

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