

**Title:**

**COVID-19 and tuberculosis - threats and opportunities**

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## EDITORIAL

Respiratory tract infections remain the top cause of morbidity and mortality from infectious diseases worldwide.<sup>1</sup> Until the end of December 2019, three pathogens featured on the WHO Blueprint priority list for research and development: Severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV) and *Mycobacterium tuberculosis* (*Mtb*).<sup>2</sup> In January 2020, SARS-CoV-2, the cause of COVID-19, was added to the priority list. Since then, SARS-CoV-2 has spread outside China<sup>3</sup> to all continents causing death and economic disruption,<sup>4</sup> and considerable concern among national, regional, and international communities. The social and psychological impact of the epidemic has been compounded by the need for strict social distancing, and the rapid spread of information and misinformation via both mainstream media and social media. This adds to the existing global burden of an estimated 4 million people who die from lower respiratory tract infections each year, with 1.4 million from tuberculosis (TB) alone.<sup>5</sup> Even more alarming is the disruption caused to global health services.

A priority for all governments during this difficult time should be to ensure continuity of essential health services, including national programmes to end HIV, TB and malaria. During the 2014-2015 Ebola outbreak in West Africa, additional deaths from HIV, TB and malaria (as an indirect consequence of the outbreak) exceeded deaths directly caused by Ebola.<sup>6-9</sup> Access to treatment for people with TB and HIV was interrupted because community health workers, doctors and laboratories devoted their energies and resources to the Ebola outbreak. The same is now likely to happen with the COVID-19 pandemic, but on a global scale. As the relatively weak health systems in high-burden settings struggle to respond to COVID-19, there is a significant risk that prevention and treatment programmes for the existing conditions will be disrupted.<sup>10</sup> As pandemics become the focus of global attention, they should not merely be seen as a phenomenon of scientific interest until they are brought under control. They should be viewed in the light of the major socio-economic impacts, and their disruptive effects on routine health services and progress towards Sustainable Development Goals (SDGs). A modelling analysis commissioned by the Stop TB Partnership found that the global response to the COVID-19 pandemic is likely to have drastic detrimental consequences for TB services.<sup>11</sup> Strict lockdown measures will place severe limitations on diagnostic, treatment and prevention services, which is expected to increase the annual number of TB cases and deaths over the next 5 years. It is estimated that at least 5 years of progress towards TB elimination could be lost.<sup>11</sup>

The modelling was based on assumptions drawn from a rapid assessment on the impact of the COVID-19 pandemic and related measures on the TB response in 20 high-burden countries—representing 54% of the global TB burden. It shows that under a 3-month lockdown and a protracted 10-month restoration of services, the world could see an additional 6.3 million cases of TB between 2020 and 2025 and an additional 1.4 million TB deaths during that same period. The report evoked an appropriately sharp warning from the Stop TB Partnership:

*“We never learn from mistakes. For the past five years, TB, a respiratory disease, has remained the biggest infectious disease killer because the ‘TB agenda’ consistently became less visible in front of other priorities.”*

*Today, governments face a torturous path, navigating between the imminent disaster of COVID19 and the long-running plague of TB. But choosing to ignore TB again would erase at least half a decade of hard-earned progress against the world’s most deadly infection and make millions more people sick.”*

The fear of catching COVID-19 will deter people in need of timely diagnosis and treatment for TB from accessing health services. There is also a danger that the media focus, and hastily implemented public health measures to achieve “social distancing”, could exacerbate stigma and human rights-related barriers faced by marginalised communities and be detrimental to mental health.<sup>13,14</sup> The data indicate that the elderly (.70 years of age) and those with comorbidities are more likely to succumb to COVID-19,<sup>15-17</sup> and people with TB, TB-HIV co-infection or chronic lung disease will more likely develop sequelae,<sup>18</sup> which further highlights the importance of pulmonary rehabilitation and holistic care.<sup>19,20</sup> The poorest and most marginalised people across the world, who suffer most from TB and other RTIs, are therefore also likely to be the most affected by the COVID-19 epidemic.<sup>21</sup> Governments of high TB burden countries need to ensure the continuity of TB services in the time of COVID-19. This includes being proactive to protect the most vulnerable, including protection against economic hardship, isolation, stigma and discrimination. The global response needs to identify and mitigate potential risks to the critical mission of tackling TB (and other RTIs). This includes identifying how the capabilities and infrastructure can be adapted to strengthen the response to COVID-19 and allow flexibility in programmes to enable countries to respond at pace to the evolution of COVID-19.

All stakeholders with an interest in TB must remain closely engaged with the WHO to ensure close coordination in response to COVID-19, and to sustain the progress made towards the SDG target of health and well-being for all. As the COVID-19 pandemic spreads into high TB burden settings, countries must put in place strategies to ease pressure on health systems and to mitigate disruption in routine health services. The current social distancing and stay-at-home measures make it particularly challenging for TB programmes to provide diagnosis, treatment and care for communities affected by TB. To ensure no disruption to TB services, the TB programmes will have to identify and rely on alternative options, such as virtual care, digital health and community-monitoring solutions to bring the required services as close as possible to the people and communities affected by TB. COVID-19 disease presentation can range from no symptoms (asymptomatic) to severe pneumonia and death. A review of COVID-19 cases show typical signs and symptoms, including fever, dry cough, fatigue, sputum production, shortness of breath, sore throat, headache, myalgia or arthralgia, chills, nausea or vomiting, nasal congestion, diarrhoea and haemoptysis, and conjunctivitis.<sup>15</sup> Thus at first clinical presentation a wide range of differential diagnoses need to be considered, including TB.<sup>15</sup> Importantly, the same universal precautions for all infectious causes of RTIs are needed for safety and the prevention of further transmission on wards and to health care workers. The use of masks may also reduce transmission in the community and workplace; however, this has not been supported to date by the WHO.<sup>22-24</sup>

Thus, a major opportunity arises from the current COVID-19 outbreak for ensuring TB control targets are not delayed. The overlap and commonalities for surveillance, screening, diagnosis, and management should be exploited. Although long-term pulmonary sequelae for patients with post-TB are well known, an integration of biological therapy concepts taking pathophysiology into account has not been taken forward. For example, promising research on the use of autologous bone-marrow derived stem/stromal cells in patients with multidrug- and extensively drug-resistant TB demonstrated the potential for new therapeutic interventions targeting the host rather than the pathogen.<sup>25</sup> There is also a different, crossfertilising aspect in regard to advanced treatment options. While anti-viral drugs targeting the pathogen SARS-CoV-2 are being actively evaluated in clinical trials, host-directed therapies (HDTs) targeting the host’s immune system are now attracting attention. These include an array of Phase 1 and Phase II clinical trials of anti-interleukin (IL) 1, antiIL-6R, and cellular therapies using allogeneic mesenchymal stromal cells (MSCs) (<https://>

clinicaltrials.gov/ct2/results?cond¼COVID-19). The concept of using adjunct cellular therapies for improving outcomes could be a significant development because the major target organ for both pathogens is pulmonary tissue. Safe and clinically relevant treatment modalities for COVID-19, which curb damaging inflammation and restore lung tissue may well have relevance for patients with TB.<sup>26</sup> A global consortium of HDTs has been formed, which is open to all and provides opportunities to take forward the HDT portfolio for research into all respiratory tract conditions. After many decades of struggling to get global attention for TB control, the turning point in the fight against TB occurred on September 2018 at the unprecedented United Nations General Assembly (UNGA) High Level meeting on TB. This resulted in a Political Declaration with bold and ambitious targets to achieve global TB control (UNGA-HLM Ref 2018).<sup>27</sup> The adoption was a significant milestone, providing the key political change that set wide-ranging targets, including specific numbers of people to be treated and funding to be mobilised.<sup>28</sup> While implementation of the three critical components—funding, action and accountability has been initiated in the right direction, there remains an urgent need to restore momentum. To do so, we must overcome the challenges that COVID-19 presents and use the opportunities it affords us to achieve a paradigm shift in TB treatment and care.<sup>29</sup>

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