

The COVID-19 and TB syndemic: the way forward

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SUMMARY

Together, SARS-CoV-2 and *M. tuberculosis* have killed approximately 5.7 million people worldwide over the past 2 years. The COVID-19 pandemic, and the non-pharmaceutical interventions to mitigate COVID-19 transmission (including social distancing regulations, partial lockdowns and quarantines), have disrupted healthcare services and led to a reallocation of resources to COVID-19 care. There has also been a tragic loss of healthcare workers who succumbed to the disease. This has had consequences for TB services, and the fear of contracting COVID-19 may also have contributed to reduced access to TB services. Altogether, this is projected

to have resulted in a 5-year setback in terms of mortality from TB and a 9-year setback in terms of TB detection. In addition, past and present TB disease has been reported to increase both COVID-19 fatality and incidence. Similarly, COVID-19 may adversely affect TB outcomes. From a more positive perspective, the pandemic has also created opportunities to improve TB care. In this review, we highlight similarities and differences between these two infectious diseases, describe gaps in our knowledge and discuss solutions and priorities for future research.

KEY WORDS: SARS-CoV-2; coronavirus; pandemic; mortality

COVID-19 is currently the leading cause of death from a single infectious agent, followed by TB, which has been the leading agent since 2014 (when it surpassed HIV/AIDS).¹ Since the first COVID-19 deaths were reported in Wuhan, China, in December 2019,¹ nearly 5.7 million deaths have been attributed to COVID-19 worldwide (as of 6 February 2022).² In 2020, the WHO estimated that TB killed over 1.5 million people (up from 1.4 million in 2019).³ COVID-19 has negatively impacted TB case notifications, which declined by 18% from 7.1 million in 2019 to 5.8 million in 2020, a 9-year setback in plans to End TB. Reduced case-finding are likely to result in a substantial increase in TB deaths over the coming years.

Previous viral pandemics have resulted in excessive deaths from TB.^{4,5} This may be due to service disruption, biological interaction between both agents and lung damage from both diseases.⁴ The non-pharmaceutical, public health interventions implemented in response to the COVID-19 pandemic (such as lockdown and social distancing, as well as public fear of infection in healthcare settings with

reduced healthcare workforce, either from disease or from reallocation)⁶ may have resulted in reduced access to health services and quality of TB care.^{7–9} The lack of protective equipment and prioritisation of laboratory services for COVID-19 may also have contributed to reduced TB diagnosis.⁷ The deterioration in living conditions of vulnerable populations may further worsen TB indicators.^{7,8,10} Modelling studies have predicted a catastrophic effect of the COVID-19 pandemic on TB and other infectious diseases,^{8,11} and the recent WHO Global TB report³ as well as other studies^{9,12} have confirmed these predictions. However, recovery measures and positive experiences reported in a few countries show that it is possible to reverse this situation – provided there is political will and financial investment.

Here we have critically summarised the evidence on the interplay of these two deadly pandemics from biological, clinical, epidemiological and public health perspectives, and highlighted the potential opportunities for strengthening TB control based on lessons learned from the COVID-19 response.

Table 1 Comparison of the main characteristics of TB and COVID-19.

Key features	COVID-19	TB
Causative organism	Severe acute respiratory syndrome coronavirus-2	<i>Mycobacterium tuberculosis</i> complex (<i>M. tuberculosis</i> , <i>M. africanum</i> , <i>M. bovis</i> , <i>M. microti</i> , <i>M. canettii</i> , <i>M. caprae</i> , <i>M. pinnipedii</i> , <i>M. suricattae</i> , <i>M. mungi</i> , <i>M. dassie</i> and <i>M. orygis</i>)
Evolutionary changes	Rapid generation of variants due to mutations: alpha (UK, Sep 2020); beta (South Africa, May 2020); gamma (Brazil, Nov 2020); delta (India, Oct 2020); omicron (multiple countries, Nov 2021); lambda (Peru, Dec 2020); mu (Colombia, Jan 2021) ¹⁵	Gradual generation of resistance, compensatory and fitness mutations: rifampicin (<i>rpoB</i>); isoniazid (<i>katG</i> , <i>InhA</i> , <i>ahpC</i> , <i>kasA</i> , <i>ndh</i>); ethambutol (<i>embB</i>); pyrazinamide (<i>pncA</i>); streptomycin (<i>rpsL</i>); kanamycin (<i>rrs</i>); capreomycin (<i>tlyA</i>); fluoroquinolone (<i>gyrA</i> , <i>gyrB</i>); ethionamide (<i>inhA</i>)
Epidemiology	As of 6 February 2022, over 370 million confirmed cases and nearly 5.7 million deaths have been reported globally ²	In 2020, an estimated 10 million people fell ill with TB worldwide and 1.2 million died. TB is present in all countries and age groups ³
Immunopathological response	SARS-CoV-2 infects human respiratory epithelial cells through interactions between S proteins (spike glycoprotein) with ACE2 receptors. ACE2 receptor expression on lymphocytes, especially on T cells, promotes SARS-CoV-2 entry into lymphocytes. SARS-CoV-2 can also directly infect T-cells and macrophages (Figure) ⁷⁶	<i>M. tuberculosis</i> is phagocytised by macrophages and triggers granuloma formation during primary infection. Lung infection leads to cavitation, which is the development of large air-filled spaces within the lungs. Heparin-binding hemagglutinin adhesin is crucial for extrapulmonary dissemination of <i>M. tuberculosis</i> . ACE receptors have no role in <i>M. tuberculosis</i> infection
Incubation period	Incubation period is short (1–14 days)	Incubation period is long (2 weeks to several years before active TB develops)
Transmission	Aerosol and droplet transmission; ¹⁴ average number of people infected per person with COVID-19 highly variable according to variant (omicron more) and whether or not distancing and masks are used	Aerosol and droplet transmission. ¹³ Range from less than 1 to up to 4 people infected per person with TB
Clinical presentation	Cough, fever, dyspnoea, sore throat, anosmia/hyposmia, ageusia, diarrhoea, myalgia, fatigue; acute onset	Fever and night sweats, persistent productive cough, haemoptysis, loss of appetite, chest pain, fatigue. Insidious onset.
Comorbidities leading to severe presentation	HIV, chronic lung disease, chronic heart conditions, obesity, immunocompromised state, diabetes mellitus ^{17,18}	Diabetes mellitus, sickle cell disease, chronic lung disease, HIV and immunocompromised state
Sequelae	Long-term COVID may manifest as cognitive, mental health and respiratory disorders, ageusia and hypo/anosmia ¹⁹	Lung residual disease (bronchiectasis, scars, cavities) with reduced pulmonary function and repeated infections are common ^{20,77}
Diagnostics	RT-PCR (2 hours), rapid antigen test kits (a few minutes, point-of-care self-testing available)	Sputum microscopy, sputum RT-PCR and chest X-ray can detect active TB rapidly (same day technology), culture takes 2–8 weeks
Sample	Naso- and oropharyngeal swabs, saliva (easy-to-obtain specimens) ¹⁶	Sputum or extrapulmonary samples are necessary

ACE2 = angiotensin-converting enzyme 2; RT-PCR = real-time polymerase chain reaction.

SIMILARITIES AND DIFFERENCES BETWEEN TB AND COVID-19

TB and COVID-19 are droplet and airborne transmissible diseases,^{13,14} which typically attack the lungs, but virtually any organ can be affected. Both can present with cough, fever and fatigue. Although TB – a human disease for millennia – is caused by a complex, slow growing bacterium, COVID-19 is caused by a coronavirus, SARS-CoV-2, which has only recently caused disease in humans. Evolution has resulted in drug-resistant TB (DR-TB), whereas new variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have become highly transmissible.¹⁵ Both agents can be diagnosed in respiratory samples using molecular techniques, but sputum is not necessary for COVID-19 diagnosis and point-of-care self-tests quickly became available.¹⁶ Both conditions are more severe in patients with comorbidities,^{17,18} and can have long-term symptoms after cure.^{19,20} Despite

their similarities, huge investment and emergency approvals in regulatory agencies has led to rapid discoveries and development of control tools for COVID-19.^{21–23} In contrast, we still have a century-old vaccine for TB, which only prevents severe disease in children, and has no effect on incidence. The differences, similarities and interplay of both diseases are given in Table 1 and the Figure.

MATHEMATICAL MODELLING OF THE IMPACT OF COVID-19 ON TB

Early projections on the impact of COVID-19 on TB (and other infectious diseases) followed different scenarios and response strategies. In high HIV, TB and malaria burden settings, deaths due to these diseases were anticipated to increase by up to 10%, 20%, and 36%, respectively over 5 years, in response to the COVID-19 pandemic.⁸ The greatest increase in deaths due to TB was predicted to be due to

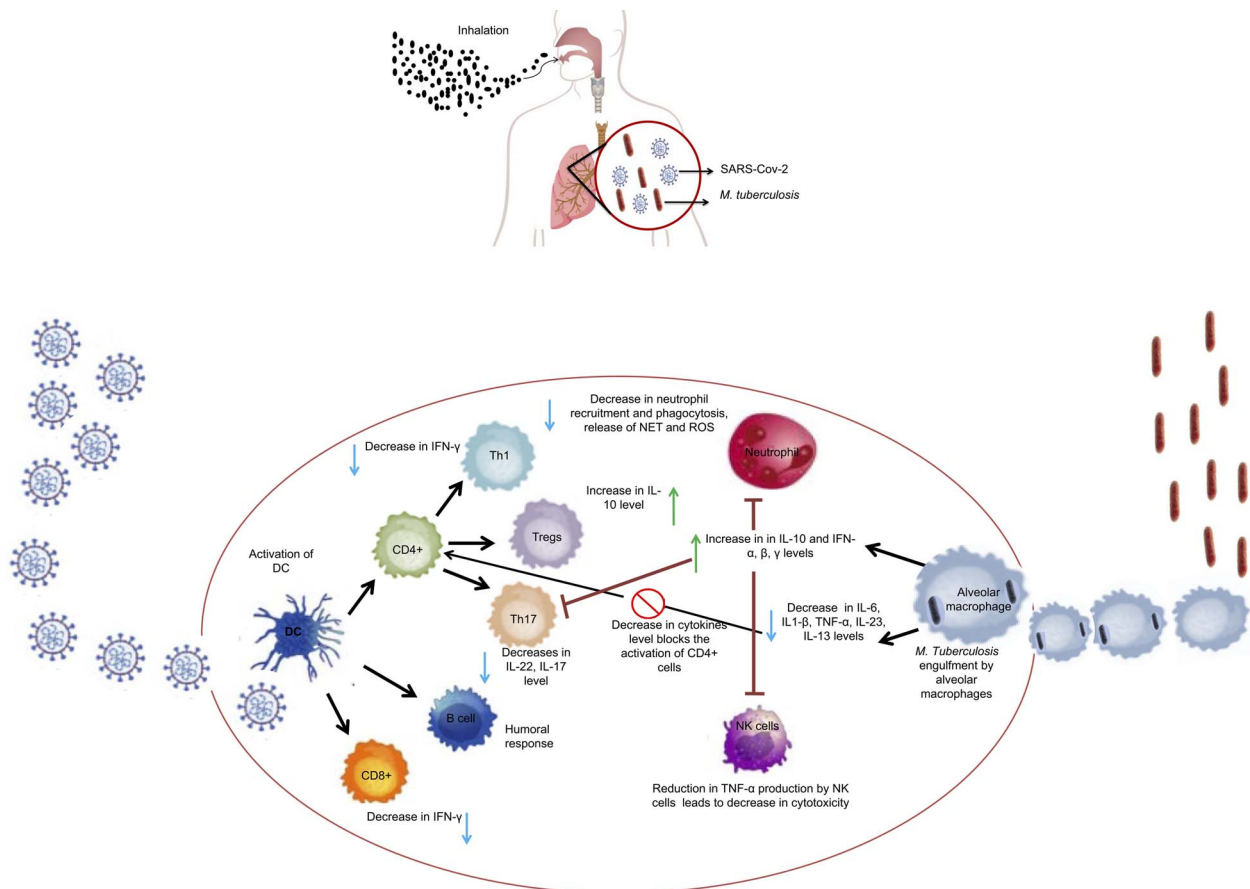


Figure Illustrative mechanism of SARS-COV-2 and TB interplay inside the host. Immunological response to *M. tuberculosis* and SARS-COV-2 includes role of both innate and adaptive immunity. SARS-COV-2 virus first activates dendritic cells resulting in the stimulation of lymphocytes such as B-cell, CD4⁺ and CD8⁺ cells; CD4⁺ and CD8⁺ cells in turn stimulate the Th1, Treg as well as, Th17 cells, resulting in an increase in IL-10 and decrease in cytokines IL-22, IL-17 and IFN- γ level. Reduced level of IFN- γ increases the susceptibility to bacterial infections and TB. The bacteria engulfed by the alveolar macrophages lead to an increase in IL-10, TNF- α , IFN- α , β and γ which further suppresses neutrophils, NK cells and Th17 cells. Suppression of neutrophils leads to the decrease in phagocytosis, release of NET and ROS, while suppression of NK cells reduces their cytotoxic activity. Activated macrophages also decreases IL-6, IL-13, IL-23 and IL-1 β that further blocks the activation of CD4⁺ cells and subsequent stimulation of Th1, Treg and Th17 cells. SARS-Cov-2 = severe acute respiratory syndrome coronavirus 2; NET = neutrophil extracellular trap; ROS = reactive oxygen species; IFN- γ = interferon-gamma; Th = T-helper cells; DC = dendritic cells; CD4⁺ = cluster of differentiation 4; Treg = regulatory T-cells; T-cells = T-lymphocytes; B-cells = B-lymphocytes; IL = interleukin; TNF- α = tumour necrosis factor alpha; NK = natural killer; CD8⁺ = cluster of differentiation 8.

prolonged periods of reduced diagnosis and treatment of new TB cases, assumed to occur in the suppression (both well managed and unmanaged) scenarios. The period of extremely high demand on the health system was predicted to have a small effect on increasing TB deaths because it was short, and the effects would be overcome during the recovery phase. This disruption was nonetheless predicted to lead to an increase in TB deaths for several years as the disruptions leave individuals untreated for longer, leading to more transmission and more cases in later years.⁸ Well-designed models have projected the same effect in China, India, South Africa, Kenya and Ukraine.^{24,25} In the absence of public health interventions, the number of TB/COVID-19 patients would be 1.3 times higher compared to the scenario with interventions.²⁶ In scenarios with substantial health service disruption, an increase in both TB cases

and deaths was projected regardless of the level of social distancing.²⁴ In the worst case scenario, an additional 201,595 TB deaths (with a range of 123,523–301,553) are expected in China, India and South Africa between 2020–2024. This represents an increase of 8–14% in cumulative TB deaths. However, if these countries could minimise the impact on TB health service delivery, major reductions in social contacts could keep the number of additional TB deaths comparatively low.

The contribution of 16 variables (including risk factors, health system settings and pandemic duration) to COVID-19 case fatality death was estimated in 34 countries. TB incidence had one of the highest impacts: each unit increase of TB incidence per 1,000 inhabitants raised COVID-19 fatality rates by 3.2% (95% confidence interval [CI] 1.09–5.22; $P = 0.004$).²⁷ However, TB incidence may also be a proxy

for uncontrolled variables such as poverty and malnutrition. The effect of COVID-19 and TB co-infection was also modelled. Among different combinations of five control measures, COVID-19 prevention, treatment and control of co-infection yielded the better outcome in terms of the number of COVID-19 cases prevented at a lower percentage of the total cost of this strategy.²⁸

The effect of the reduction of TB notifications on future deaths has been a matter of debate for modellers.^{29–33} The preceding models attributed the increased number of deaths to the reduced case detection due to global lockdowns and health service disruptions. Reduced TB transmission from social isolation has been proposed,²⁹ but the potential benefit of social distancing is thought to be more significant for TB disease incidence than for TB deaths. However, it has been argued that delays in TB notification may not express a real decrease in TB detection. On the other hand, lockdowns and the use of masks and respirators have resulted in the suppression of other respiratory disease outbreaks (such as influenza) and could have resulted in less TB transmission outside the household. However, lockdowns may have increased household transmission. Furthermore, TB transmission does not result in immediate new cases, as there can be a variable latency period, which can last up to decades. Finally, TB affects mainly the poor, and these individuals may not have been able to follow the social distancing rules. Indeed, most sharp decreases in TB notification were followed by an increase that did not attain the previous levels. Interpreting this finding is difficult, as it may represent actual reduced transmission of the disease, or an insufficient recovery program to detect the missed cases during the first waves of the pandemic, when restrictive measures were stricter.

OBSERVED EFFECTS OF THE PANDEMIC ON TB SERVICES AND INDICATORS

Health services have been disrupted and most settings described a decrease in TB testing, treatment and prevention coverage. Reports covering multiple TB centres in different countries,^{9,34} comparing indicators in 2020 with the pre-pandemic year 2019, consistently show that the overall number of TB patients (including DR-TB) substantially decreased in the first year of the pandemic. This was especially noted in countries with a higher TB burden but was also observed in low TB incidence settings (e.g., Italy, France and Spain).⁹ Subsequent studies have shown the indirect impact of COVID-19 on TB care in low-resource, high TB burden settings as well.^{35–38} In Jiangsu Province, China, TB notifications dropped as much as 52% in 2020 compared to 2015–2019. Treatment completion and screening for drug resistance decreased continuously in 2020.³⁹ In countries

where the private sector plays a significant role in TB services, this sector might have been more affected than the public sector.⁴⁰ A review of the data in June 2021, suggested that delays in reporting rather than detection might have occurred, with most reductions in TB in the first half of 2020 expected to recover in the second half of 2020 or early part of 2021.¹² The WHO Global Report 2021 captured some recovery after the first wave of the COVID-19 pandemic, but by the end of 2020, the total number of TB cases was back to 2012 levels of incidence.³ All six WHO regions documented a decrease in reported TB between 2019 and 2020, although the reduction in the African Region was relatively modest (2.5%). Sixteen countries accounted for 93% of the 1.3 million drop in TB case notifications in 2020 and the greatest shortfalls were reported for India (41%), Indonesia (14%), the Philippines (12%) and China (8%).³ Deficits in case-finding have persisted, and monthly and quarterly TB notifications in the first half of 2021 remained substantially below the average for 2019 in most of the high TB burden countries.³ Likewise, the Global Fund Results Report across 502 facilities in 32 countries revealed the catastrophic impact of the COVID-19 pandemic on the fight against TB. In 2020, the number of people treated for DR-TB dropped by 19%, extensively drug-resistant TB by 37%, while the number of HIV-positive TB patients on antiretroviral treatment fell by 16%.⁴¹

Preventive TB services were also affected by the pandemic. At three centres in Montreal and Toronto, Canada,⁴² data from 10,833 patients (8,685 with latent TB infection, 2,148 with active TB) were compared in the pre-pandemic period with data from after the pandemic period. Reductions in TB infection treatment initiation rates ranged from 30% to 66%. In a survey of 50 out of the 61 state programmes for TB elimination funded by the US Centers for Disease Control and Prevention, 68% of services reported partial (26%) or high impact (46%) of the pandemic on TB prevention services. The effect was a consequence of diverted human resources from TB activities.⁴³

The quality of laboratory services has also been disrupted, as reported by the WHO European Laboratory Initiative. Training and research activities, sample turnaround times, access to external quality assessment and the availability of selected diagnostic services were affected, resulting in lower sample numbers, reagent shortages and the need to support SARS-CoV-2 testing through reallocation of human and infrastructural resources.^{44,45} In low-resource settings, such as South Africa, significant reductions in samples were reported.³⁵

Biological and clinical direct effects of COVID-19 on TB
There is limited data on the direct effects of COVID-

19 on the progression of TB infection to TB disease or TB outcomes. A multi-country TB/COVID-19 individual-level co-infected patient database suggested that COVID-19 does not play a major role in progression from TB infection to TB disease.⁴⁶ In a series of 20 patients with TB with nosocomially acquired SARS-CoV-2, only one patient died with respiratory insufficiency.⁴⁷ In contrast, a systematic review and patient-level meta-analysis on the transcriptomic risk of overlapping diagnostic biomarkers of COVID-19 and TB identified shared dysregulation of immune responses to be a dual risk to COVID-19 severity and TB disease progression. The authors conclude that COVID-19 patients should be followed up for TB in the months subsequent to COVID-19 diagnosis.⁴⁸ The long treatment times for TB, and even longer time for qualified reported data to be released, explains the paucity of studies currently available. An analyses of linked individual patient databases in Brazil and India is currently underway to better understand the direct implications of COVID-19 disease on TB outcomes.

Direct biological and clinical effects of TB on COVID-19

Evidence about the impact of past or present TB on COVID-19 in patients with COVID-19/TB comorbidity is limited and conflicting. The best current evidence is available from two large cohort studies in South Africa^{17,18} and a Global Report on TB/COVID-19 co-infected patients from 34 countries.⁴⁶ For the purposes of this review, a cohort is defined as consecutive patients with TB and COVID-19 compared with consecutive patients without co-infection (exposed and unexposed). Case series refers to reports of co-infection cases (consecutive or not). Both South African cohorts analysed current or past TB among other risk factors for death and concluded that TB is an independent risk factor for increased mortality due to COVID-19. One used a cohort of in- and outpatients¹⁸ and linked data from 3,460,932 adult patients (16% living with HIV) attending public sector health facilities in the Western Cape, South Africa. Of these, 22,308 were diagnosed with COVID-19, of whom 625 died (2.8% case-fatality ratio). Models were adjusted for age, sex, location, and comorbidities to examine the associations between HIV, TB and COVID-19 death. COVID-19 death was associated with male sex, increasing age, diabetes, hypertension and chronic kidney disease. The chance of COVID-19 death in patients with current TB was 2.7 times higher and 1.5 times higher with past TB. HIV was also independently associated with COVID-19 deaths (adjusted hazard ratio 2.14), regardless of viral loads and degree of immunosuppression. There was residual confounding, indicating overestimation of the modifying effect of both HIV and TB, but the findings are striking.¹⁸ The other study used a retrospective cohort of almost 220,000

hospital admissions of individuals with confirmed COVID-19 in South Africa.¹⁷ Increasing age was the strongest predictor of COVID-19 in-hospital mortality. Other factors associated were HIV infection (adjusted odds ratio [aOR] 1.34, 95% CI 1.27–1.43), past TB (aOR 1.26, 95% CI 1.15–1.38), current TB (aOR 1.42, 95% CI 1.22–1.64), as well as other described risk factors for COVID-19, such as male sex and non-communicable comorbidities (hypertension, diabetes, chronic cardiac disease, chronic renal disease and malignancy in the past 5 years). After adjusting for other factors, people with HIV not on antiretroviral therapy (aOR 1.45, 95% CI 1.22–1.72) were more likely to die in hospital than people with HIV on ART.¹⁷

A large prospective, anonymised, multi-country individual register-based database in 34 countries identified 767 TB/COVID-19 co-infected patients, of whom 74% had TB before COVID-19, 9.5% had COVID-19 first and 16.5% were diagnosed with both conditions at the same time. Overall mortality was high (11.1%), despite the relatively young age (median age 44 years), but a high proportion of the reported cases were hospitalised at the time of reporting. As there were no comparison groups, conclusions are limited. Not surprisingly, death was associated with previously identified risk factors for COVID-19 mortality: need for ventilation (aOR 28.22, 95% CI 1.37–64.39), male sex (aOR 2.92, 95% CI 1.38–6.16) and older age (OR 1.93, 95% CI 1.60–2.32). Out of the 85 patients who died, 42 (49.4%) deaths were reported to be from COVID-19, 31 (36.5%) from COVID-19 and TB, 1 (1.2%) from TB and 11 from other causes. The authors concluded that TB should be considered a risk factor for severe COVID-19 disease, and patients with TB should be prioritised for COVID-19 preventive efforts, including vaccination.^{9,46} Other smaller cohorts,^{49–51} and one case-control study,⁵² also compared the outcomes of COVID-19 patients with and without TB (Supplementary Data). Although most suggest a worse prognosis (with longer course of disease and higher morbimortality) among patients with current or past TB,^{49,52} some suggest no effect⁵⁰ or even better outcomes.⁵¹ Some of these cohort studies also reported a higher incidence of COVID-19 in TB or TB infection (TBI) patients than those without TB.^{51,52} In an early meta-analysis of six Chinese studies (including 2,765 patients), there was no evidence to suggest higher SARS-CoV-2 incidence or more severe disease among those with TB.⁵³ In one large series reporting 526 patients with COVID-19, HIV and TB at a single centre,⁵⁴ case fatality was 8.9% higher than in historical controls, although not as high as in other smaller series. The severity of their condition was determined mainly by HIV stage (100% in Stages IVA and IVB), TB and other secondary or intercurrent diseases. The fatality rates

depend, of course, on the setting and context where the series is reported (hospitalised vs. outpatients, and whether or not there was health system overload at the time of reporting). Many small case report series of COVID-19/TB co-infected patients were published, some of which underwent meta-analyses in a non-systematic review, with high rates of adverse outcomes reported, including high fatality rates (up to 23%).^{55,56} A large study of high-resolution chest computed tomography scans found signs of past TB to be half as frequent (4.8%) in the pandemic period than in the pre-pandemic period (9.8%), but indications for the scans were different in the two periods, hampering relationship conclusions.⁵⁷ An ecological study in Peru also found more COVID-19 cases in TB hot spots, independent of socio-economic characteristics or morbidity rates from other diseases.⁵⁸

TBI has also been reported to interact with SARS-CoV-2. TBI is associated with heightened levels of humoral, cytokine and acute phase responses in seropositive SARS-CoV-2 infection.⁵⁹ Early anecdotal reports have also suggested that TBI may increase susceptibility to SARS-CoV-2 infection⁵² and to increase COVID-19 severity.^{52,60} In contrast, a mathematical model based on ecological data suggests that TBI might have a protective effect on COVID-19. However, protection from confounding variables need to be taken into account, and confirmation from individual data is lacking.⁶¹

OPPORTUNITIES TO LEARN FROM THE COVID-19 RESPONSE

Although the COVID-19 pandemic has negatively impacted TB services globally, it has also created numerous opportunities for strengthening TB control.^{31,62–64} It is important that we use the knowledge gained and investments in COVID-19 to strengthen public health programmes.⁶⁵ COVID-19 has highlighted the vulnerabilities in healthcare systems. As this will not be the last pandemic, COVID-19 provides an opportunity for governments to reconceptualise healthcare in a more holistic manner, one that addresses health risks beyond the health sector and integrates policies, programmes and systems to address health emergencies and create healthy populations.⁶⁶ We cannot fight COVID-19 as a stand-alone disease, we need an integrated system that addresses both COVID-19 and TB case-finding, treatment and prevention simultaneously. The COVID-19 pandemic has shown the world that political will is vital in responding to epidemics. The United Nations General Assembly high-level meeting on TB (September 2018)⁶⁷ was an important step to accelerate efforts to end TB, but it did not deliver the immediate action required to actually end TB. The COVID-19 pandemic has shown that governments are capable of the kind of action needed.

Accelerated responses from governments to COVID-19 enabled countries to rapidly put public health measures in place, start vaccine research and develop surveillance systems to mitigate the impact of COVID-19.^{62,63,68}

The WHO's pulse survey on the continuity of services during the COVID-19 pandemic⁶⁹ highlighted seven approaches to mitigate the impact of COVID-19 on routine services: triaging to identify priorities; using telemedicine as a substitute for in-person consultation; task shifting; supplying medicines through non-medical facilities; providing information to communities on possible service changes; redirecting patients to health facilities that are open; and removing user fees (Table 2). Many of these strategies have been implemented successfully. In South Africa, the centralised chronic disease dispensing and distribution system and the use of telephone consultation was expanded³⁵ and TB treatment practices were modified to limit visits to health facilities.⁶³ In Mumbai, India, continuity of services was ensured by focusing on measures to protect healthcare workers and patients. These included improved infection prevention and control measures, screening, linkage to COVID-19 care and the avoidance of non-essential visits.⁷⁰ In Portugal, decentralisation of services increased diagnostic capacity of extrapulmonary TB, although treatment delays were observed.⁷¹ The need to reduce health facility visits presents the opportunity to shift to people-centred models with home-based care, strengthened community and self-administered TB therapy accompanied by virtual support and further decentralisation of medication pick-up.^{40,72} These TB mitigation strategies can also be used to reduce the spread of COVID-19.^{10,70,73} Appointments via online portals, even in low-income countries, have helped reduce the number of patients at facilities, thereby addressing overcrowding, reducing the risk of cross infection between patients and ultimately improving the standard of healthcare.³¹ Contact investigation during the pandemic was successful in many parts of the world and should leverage the same practice for TB patients.^{62,68} Table 2 provides further details of opportunities for TB service improvement. Because TB and COVID-19 are both respiratory diseases, COVID-19 has increased awareness of and improved behavioural practises around respiratory infection prevention and control and cough etiquette. The wearing of masks has been normalised (destigmatised) and this should be capitalised on.⁶³ In addition, given the overlap of clinical signs and symptoms for TB and COVID-19, those who screen positive for either TB or COVID-19 should be tested for both pathogens at the same time. Finally, contact investigation during the pandemic was successful in many parts of the world and should leverage the same practice for TB patients.^{62,68} The COVID-19 pandemic created significant awareness among the general population around infectious diseases and how to reduce their transmission, as well

Table 2 Lessons learned and opportunities for TB services.

Lessons/practices	Description
Digital innovations	
Digital system for data management ⁶²	Real-time COVID-19 dashboards are widely available, and governments respond immediately to new data, allocating sufficient funds Digital data system could make TB data more visible and accessible. During the pandemic, the WHO offered modelling estimates to guide countries' recovery efforts. Rapid TB data reporting should become the new routine standard and real-time TB data should be available everywhere
Telemedicine and other digital adherence technologies ^{46,62,63,78-81}	Remote support through video-supported therapy helps to guide TB patients through their clinical management, identify and monitor comorbidities, including food insecurity, and encourage treatment adherence
Artificial intelligence-based systems to support image diagnosis ^{82,83}	Adoption of artificial intelligence imaging systems for TB and other respiratory infections. Systems for automated interpretation of chest X-ray images with computer-aided design software have been under development for TB for a decade and were quickly reconfigured for COVID-19 within the first months of the pandemic This technology can be used throughout the healthcare system and offer promise for high-throughput screening and integrated COVID-19 and TB testing
Diagnostics	
Increase the availability of TB testing and the coverage by TB tests in risk groups ^{84,85}	Better integration of TB and COVID-19 testing is necessary in combination with validation of simpler, non-sputum samples. Improved and affordable swabs and new approaches to sampling using saliva, mouthwash, oral swabs, and absorbent strips in face masks have shown promise for COVID-19 sample collection and are now being tried for TB Some countries have leveraged automated, cartridge-based molecular technologies (e.g., GeneXpert®, Cepheid, Sunnyvale, CA, USA; and Truenat®, Molbio Diagnostics, Verna, India) for TB and COVID-19. Wide use of molecular technologies and bi-directional testing will improve the TB diagnosis. Also, exploiting multi-disease molecular platforms will increase the coverage by TB tests in the most vulnerable populations
Contact investigation of TB and COVID-19 ^{62,63,86,87}	Both diseases can present with respiratory symptoms and fever. Geographic information systems mapping could be used for direct contact and delivery of test results and health information especially reaching at-risk communities
Treatment	
Decreasing the time to review and introduce new medication or drug regimen and practises ^{10,78,88}	Operational research should be used as the instrument to examine the efficacy of shorter and fully oral WHO-recommended MDR-TB treatment regimens to assess influence of social determinants of health on TB, vaccine effectiveness and community acceptability
Service organisation	
Integrated services of TB and COVID-19 ^{66,70,71,89}	As part of the Zero TB activities in Karachi, Pakistan, TB and COVID-19 activities were integrated. The following activities were successfully implemented: 1) integrated COVID-19 screening and testing within existing TB programme activities, along with the use of an artificial intelligence software reader on digital chest X-rays; 2) home delivery of medication; 3) use of telehealth and mental health counselling; 4) provision of personal protective equipment; 5) burnout monitoring of health workers; and 6) patient safety and disinfectant protocol. The case notifications in six districts in Karachi were over 80% of the trend-adjusted expected notifications with three districts having over 90% of the expected case notifications. Collaborative efforts with private sector partners facilitated the reduced loss in case notifications
Research and capacity building	
eLearning for capacity building ⁹⁰⁻⁹²	Sustained use of digital tools for education about TB is crucial for community engagement and support
Research into TB vaccines, new diagnostic tools, anti-TB drugs ⁶²	Increasing investment in the development of new TB diagnostic tools, using scientific advances that rapidly produced Covid-19 vaccines, diagnostics, and drugs. Development of a simple, point-of-care TB test, more effective and safe TB vaccine is critical

as education of basic epidemiological terminology. In South Africa, there were regular public addresses by the South African President and Minister of Health.⁶³ This level of public awareness should not be underestimated and should be leveraged for TB. The benefit of empowering of communities and individuals around public health issues should not be underestimated.

CONCLUSION

The COVID-19 pandemic substantially affected the TB care cascade with reductions in TB tests and notifications of TB, mainly because of disrupted TB services and restricted movement of patients. This has resulted in an increased number of TB deaths. More

preventable TB deaths are expected if the missed cases are not quickly recovered. It is therefore important that national TB programmes increase their efforts and governments and donors invest in recovery measures.^{62,65} The pandemic has created opportunities to better understand how to improve access to health, accelerate discoveries and expedite the use of approved technologies and systems.⁷⁴ Modelling studies were carried out at the start of the pandemic; new modelling studies should now include vaccination, SARS-COV-2 variants and recovery measures to guide health policy makers. TB can also have a direct clinical adverse effect on COVID-19 outcomes.^{17,18,46} Large cohort studies suggest a harmful impact of past and current TB on COVID-19 prognosis, with higher fatality

rates.^{17,18,46} The incidence of COVID-19 may also be higher in TB patients, but longitudinal prospective cohorts are necessary to confirm this hypothesis. The interplay between these two diseases will be further clarified with studies currently underway.

Our review has limitations. We did not pre-establish criteria for study selection, and did not use formal tools for critical appraisal of the literature, as our goal was to rapidly discuss the state of the art concerning the syndemic. We acknowledge a global vulnerability to TB through a decrease in healthcare access and increase in poverty, as well as COVID-19-related lung damage, making patients more vulnerable to TB.⁷⁵ Our review is limited in terms of exploring vulnerabilities and highlight this as an area for future research.

The COVID-19 pandemic has highlighted the need for political will, adequate finance and an accelerated response, as well as effective global health governance.⁶² Lessons learnt from the pandemic should be applied to strengthen TB programmes and discovery. More research is needed to understand the clinical effect of TB/COVID-19 coinfection, the effect of the non-pharmaceutical interventions to contain the pandemic in different steps of the cascade of TB care, and the long-term effects on quality of life from the intersection between both diseases.

Acknowledgements

The authors thank S Verma and M Chaudhari for their assistance with the Figure.

This review was supported by grants from the following agencies in the context of the BRICS STI Framework Programme: Brazilian Ministry of Science, Technology and Innovation, Conselho Nacional de Desenvolvimento e Pesquisa (CNPq-441048/2020-0); Republic of South Africa, Department of Science and Innovation (DSI) and the South African Medical Research Council (SAMRC) under the BRICS JAF #2020/101; Government of India, Ministry of Science & Technology, Department of Biotechnology; FSBI Russian Foundation for Basic Research (project number 20-515-80006). The content and findings reported herein are the sole deduction, view and responsibility of the researcher/s and do not reflect the official position and sentiments of any funder.

Conflicts of interest: none declared.

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R É S U M É

À eux deux, le SARS-CoV-2 et *M. tuberculosis* ont été responsables d'environ 5,7 millions de décès à travers le monde au cours des deux dernières années. La pandémie de COVID-19, et les interventions non pharmacologiques mises en place pour réduire la transmission du virus (dont distanciation sociale, confinements partiels et isolement), ont perturbé les services de soins et entraîné l'allocation des ressources à la prise en charge de la COVID-19. Un pourcentage significatif de soignants est également décédé des suites de la maladie. Cela a entraîné des conséquences sur les services de lutte contre la TB, et la peur de contracter la COVID-19 a aussi pu contribuer au moindre accès aux services antituberculeux. On estime en effet que

cela a entraîné un recul de 5 ans en matière de mortalité due à la TB et de 9 ans pour la détection de la TB. Par ailleurs, des antécédents de TB ou une TB active augmentent le risque de décès dû à la COVID-19, ainsi que l'incidence de cette dernière. De même, la COVID-19 peut avoir un impact négatif sur les résultats du traitement anti-tuberculeux. Toutefois, la pandémie a également créé des opportunités d'amélioration des soins antituberculeux. Dans cette revue, nous soulignons les similarités et les différences entre ces deux maladies infectieuses. Nous détaillons également les lacunes en matière de connaissances et évoquons des solutions et priorités pour les recherches futures.