OPINION ARTICLE

All eyes on COVID-19, let's not forget Tuberculosis [version 1; peer review: awaiting peer review]

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Abstract

Tuberculosis (TB) is a severe global threat killing more than one million people annually (WHO). With a successful TB control programme in place, there has been a decrease in the number of TB cases and deaths globally over recent years. The World Health Organisation (WHO) End TB Strategy has been momentarily shocked by the COVID-19 pandemic and it seems that any success made over recent years is likely to be reversed. We are now more than one year into the pandemic, and the effect COVID-19 has had on TB services is devastating. Hospitals typically dedicated to TB have been converted to COVID-19 hospitals and diagnostic laboratories focus on COVID-19 testing rather than TB. Delivery of TB care is being prioritised for people who have active TB disease whereas prevention and diagnosis of latent TB infection (LTBI) is being put on hold. This pause can lead to an increase in TB cases and transmission. Here, we discuss the connection between SARS-CoV-2 infection and latent TB and highlight the importance of TB prevention management in LTBI post-COVID-19 patients. Community engagement and contact tracing are of high importance in fighting TB in the post-COVID19 era. Getting back on track with TB progress is essential, thus further modelling on the COVID-19 impact on TB burden and its determinants is critical.

Keywords

covid-19, tuberculosis, latent TB infection, prevention, treatment, community engagement, contact tracing

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Introduction

As the COVID-19 pandemic continues to unfold, all eyes are on diagnostics, therapeutics, and vaccination programs to fight the virus and reduce cases, hospitalisations, and deaths. Heavy focus on a single pathogen has reshaped activities across the diagnostic landscape with basic health services and screening programmes being disrupted. What effect has this disruption had on a much older infectious and endemic disease – Tuberculosis (TB)? The focus on the COVID-19 pandemic has had a direct impact on the TB care cascade, with considerable delays in diagnosis and interruption to treatment, as well as a decrease in demand and access to treatment.¹ Mathematical modelling conducted by multiple research groups estimates the impact of the COVID-19 pandemic on TB incidence and mortality, suggesting an increase of around 5-15% over the next 5 years.¹⁻⁵ TB remains a global health emergency affecting mostly the poorest and most vulnerable, and we believe that now more than ever is the time to focus global efforts on the growing TB epidemic.

TB is caused by the bacillus *Mycobacterium tuberculosis*, which is spread when people who are infected expel bacteria into the air; for example, by coughing.⁶ TB infection exists in two phases: latent TB infection (LTBI) when people are asymptomatic and cannot pass it on to other people, and an active phase when they develop symptoms and become ill.⁶ Active TB can affect the lungs (pulmonary TB) with symptoms such as coughing blood or sputum, pain in the chest and fever; but it can also spread to other sites (extrapulmonary TB), in which case symptoms would be localised in those areas.⁶ TB remains the number one cause of death from a single infectious agent globally – killing approximately 4,000 people per day, and 1.4 million annually.⁶ This is a massive human and societal toll for a curable and preventable disease. Of the 10 million global cases of TB, South-East Asia has around 44%, Western Pacific 18%, and Africa around 25%, while America has 2.9% and Europe has the lowest number of cases at 2.5%.⁶ In the UK, there is a specific TB control programme in place, with tremendous TB control efforts which has led to a decline in the number of TB cases to approximately 4,500 new cases annually.⁷ However, according to Public Health England (PHE), the UK has the second highest mortality from TB in Western Europe, which is five times higher than in the US.

COVID-19 impact on TB services

One year on from the start of the pandemic, we are now seeing the catastrophic effect that COVID-19 has had on the global TB burden and TB services. Policies adopted in response to the pandemic have disrupted routine TB medical practices and converted designated TB wards to COVID-19 wards, and many respiratory specialists efforts have been diverted away from TB.⁸ In the UK, TB services have had to prioritise and focus on delivering care for TB disease rather than prevention (such as the management of latent, non-transmissible TB infection),⁹ and diagnostic laboratories are prioritising COVID-19 testing instead of TB testing. As a result, there has already been a drop in TB notifications, with a diagnostic delay for suspected TB patients; the substantial delays in TB diagnosis may increase community transmission of TB and development of drug-resistant TB. A decrease has also been observed in the number of TB patients seeking help due to fear of SARS-CoV-2 transmission in health facilities. Additionally, in paediatric TB, which progresses silently and needs to be reviewed regularly, routine clinics have been cancelled, and paediatric care beds moved to COVID-19 wards.⁹ Moreover, the reallocation of resources towards COVID-19 may lead to delays to innovative TB trials, which could halt the progress made towards new TB drugs, diagnostics, and vaccines.

Are we meeting the ambitious targets of the WHO End TB Strategy?

As part of the efforts to end the global TB epidemic, the WHO has set the END TB strategy to reduce TB incidence rate and deaths as well as catastrophic costs by 2035, with interim milestones set for 2020 and 2025. The strategy puts patients at the heart of service delivery, with strong participation from government, communities, and private stakeholders, and focuses on research and innovation.¹⁰ Prior to the COVID-19 pandemic many high TB burden countries were not on track to reach the 2020 milestones of the End TB Strategy. There was, however, clear progress in reducing the TB incidence rate as well as the number of deaths globally as shown in both the Global TB Report 2020⁶ and United Nations (UN) Political Declaration¹¹ on TB. COVID-19, however, is likely to cause a dramatic setback and reverse this progress. According to a modelling analysis commissioned by the Stop TB Partnership, a three-month lockdown and a ten-month restoration period could lead to an additional 6.3 million TB cases and 1.4 million TB deaths globally between 2020 and 2025.¹² There was a 25-50% drop in TB case detection over three months in several high TB burden countries including India and Indonesia in 2020. This would result in 200-400,000 additional TB deaths in 2020, which is equivalent to the annual mortality for 2012.⁶ One of the commitments of the global leaders at the UN high-level meeting on TB in 2018 was to ensure access to preventive TB treatment for 24 million contacts of active TB patients by 2022.¹¹ It seems that the COVID-19 pandemic could prove a major setback for such efforts. In 2018-2019 only 1 million people were treated for TB, which is only 35% of the 40 million target by 2022 and just over one-fifth of the five year target started TB preventive treatment.¹¹ These setbacks on TB control jeopardise our ability to meet the goals set by the End TB Strategy and getting the world back on track for TB control needs our attention more than ever in both adults and children.

Cursed duet

Both TB and COVID-19 are respiratory pathogens that are spread through the air and primarily attack the lungs with symptoms of cough, fever and difficulty breathing. The key question is whether coinfection with both TB and COVID-19 is more severe than individual infection with either one. A recent meta analysis suggested that the risk of death in COVID-19 and TB coinfecting patients is 2.17 times higher and the risk of recovery is 25% lower than in those without TB.¹³ Thus, coinfection with TB has shown poorer treatment outcomes and increased morbidity and mortality in COVID-19 patients.¹³ COVID-19 has also been shown to contribute to the deterioration of TB patients by worsening symptoms, in some cases leading to death.¹⁴ Another study, however, investigated 20 patients co-infected with TB and COVID-19 in Italy, and showed that active TB appears to be clinically manageable with only one death in the study.¹⁵ In immunocompromised patients with underlying comorbidities, COVID-19 leads to severe pneumonitis and long-term lung damage. One should also keep in mind that TB patients often have underlying comorbidities such as immunocompromised conditions like HIV/AIDS, diabetes, and lung damage. Whilst diabetics have a high risk of developing latent TB, diabetes has now emerged as a major co-morbidity for COVID-19 as well.¹⁶ It is of extreme importance to consider that such comorbidities could act as risk factors for developing severe COVID-19 or active TB, or both. Patients with active TB, or those who have previously recovered from it, are left with fibrotic, scarred lungs and compromised lung function. As such, the post-COVID-19 effects can be devastating in this patient population. Adversely, in most COVID-19 autopsy series published, diffuse alveolar damage (DAD) is the most common finding. *“This post-COVID pulmonary fibrosis, superimposed on the fibrosis caused by the sequelae of pulmonary TB, is likely to result in even more devastating disability”*.¹⁷ What is tremendously important now is to have a plan for managing patients with respiratory symptoms suspected for both TB and COVID-19.

Post COVID-19 patients: From LTBI to active TB

A number of people with LTBI get ill when their immune system becomes weak for another reason. There is a worrisome connection between SARS-CoV-2 infection and latent TB. Clinical studies have shown that co-infection with SARS-CoV-2 accelerates TB progression by weakening host immunity.^{18,19} Inflammation is the major driving pathology for severe disease in COVID-19 patients, and anti-inflammatory drugs such as corticosteroids (CST) are used to treat severe COVID-19 cases.²⁰ However, CSTs work by suppressing the immune system, and as such treatment with CST poses a significant risk for acquiring opportunistic infections, reactivating LTBI or exacerbating existing TB among COVID-19 cases.²⁰ In addition, SARS-CoV-2 infection can cause severe immune dysregulation, with a reduction of lymphocyte subsets including CD4 and CD8 T cells, in COVID-19 patients.^{21,22} Together, the significant depletion of CD4 T cells caused by COVID-19 coinfection and the concurrent administration of CSTs for COVID-19 treatment might promote reactivation of LTBI.^{17,23} At present, most COVID-19 cases are not screened or monitored for LTBI before and during immunosuppressive therapy. This situation could delay the diagnosis of TB and increase the number of undiagnosed cases contributing to the overall global TB burden. Therefore, it is important to identify these patients early on and perform LTBI testing during and post-COVID. PHE addressed the need *“to improve latent TB infection (LTBI) testing and treatment to prevent reactivation of TB and transmission, a service that has been greatly affected by COVID-19”* in its 2020 TB report.⁶

Massachusetts General Hospital health emergency guidelines recommend a detailed documentation of the TB history of the patient is required for COVID-19 patients and a LTBI reactivation risk mitigation for steroids should be considered when screening high risk patients. As part of the TB elimination strategy, ending the global TB epidemic requires a focus on treating LTBI to prevent future cases and transmission. LTBI reactivation risk mitigation for steroids and immunomodulation could become part of a universal management practice to improve the cascade of TB care. Such a strategy should be shared and considered globally for better management of both TB and COVID-19 cases.

A global model to end TB

A global effort has been put in place in order to handle the urgent need to defeat COVID-19 through the “Swiss Cheese” model.²⁴ This metaphor is based on multiple interventions where each intervention (cheese layer) has imperfections (holes in cheese). Due to the “slice gaps”, COVID-19 will always get through. Thus, multiple layers need to be combined in order to block SARS-CoV-2, reduce risk and improve success.²⁴ Such protective layers include social distancing, isolation, mask wearing, contact tracing, vaccinations, and medical care. The Swiss Cheese Model has now been adapted for ending TB and categorises interventions into societal and personal, whilst focusing on a person-centric healthcare system.²⁵ It highlights the need to challenge societal issues that make people vulnerable to TB such as poverty and malnutrition, and emphasises the need for development of better vaccines. TB needs to be de-stigmatised and early care should be encouraged along with personalised quality care for all forms of TB.²⁵

The WHO has provided key guidance and support for the TB response including maximising remote care by expanding digital technologies, utilising the existing infrastructure and expertise in rapid testing and contact tracing for COVID-19

and expanding it to TB management, ensuring basic infection prevention and control for health staff and patients, providing simultaneous testing for TB and COVID-19 by leveraging TB laboratory networks and platforms; and proactive planning and budgeting for both conditions.^{7,26} Innovation is the key in re-imagining TB diagnosis and developing an integrated and comprehensive TB care model.²⁶ Further modelling on the COVID-19 impact on TB burden and its determinants could help implement better infection control measures.

To get back on track with TB progress, we need to have measures and resources to reduce the accumulated pool of undetected people with latent TB. Such measures could be rigorous community engagement and wide-reaching contact tracing to maintain awareness of TB symptoms. The bottom line is that it is crucial to sustain and reinforce the cascade of TB care. Allocating existing TB resources and advocating for additional resources will ease the impact of COVID-19 on the global TB burden. Dealing with COVID-19 is important, but let's not forget TB, which is meeting us on the other side of this crisis.

Data availability

No data are associated with this article.

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