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# Clinical impact of COVID-19 on tuberculosis

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## SUMMARY

During COVID-19 pandemic, a lot of diseases suffered from a limited access to health care services, owing to the use of resources, both technical and financial, mainly directed towards such a dramatic outbreak.
Among these, tuberculosis (TB) has been one of the most penalized, with a huge delay both in diagnosis and in start of treatment, with a consequential dramatic increase in morbidity and mortality.
COVID-19 and tuberculosis share similar common pathogenetic pathways, and both diseases affect primarily the lungs.
About the impact of TB on COVID-19 severity and mortality, data are unclear and literature reports are often conflicting. Certainly, considering the management of coinfected patients, there are pharmacokinetic interactions between several drugs used for the therapy of SARS-CoV-2 infection and the treatment of TB.

*Keywords*: Covid, Tuberculosis, epidemiology, immunology, BCG vaccination

## INTRODUCTION

The SARS-CoV-2 infection, first reported in December 2019 in Wuhan, Hubei Province, China, rapidly spread worldwide, becoming a pandemic, as reported by the World Health Organization (WHO) on 11 March 2020 [1]. SARS-CoV-2, a positive single stranded RNA beta-coronavirus (betaCoV) belonging to Orthocoronaviridae subfamily of Coronaviridae family, was first isolated in a cohort of patient whit atypical pneumonia, and it is responsible of a disease characterized by fatigue, fever, cough and a progressive dyspnea often leading to acute respiratory failure called COVID-19. Nowadays, COVID-19 is still responsible for very high rates of morbidity and mortality, with a consequent dramatic socio-economic impact and a catastrophic effect on world demography with over 627.573.579 confirmed cases and 6.570.363 deaths worldwide (26 October 2022), emerging as the global health crisis with major repercussions from the 1918 Spanish pandemic [1].
Although COVID-19 continues to dominate both the scientific literature and media, other infective diseases including tuberculosis (TB) continues to affect people worldwide. Historically, tuberculosis has been one of the biggest human killer and it remains one of the foremost global infectious causes of death, the second leading cause of death from a single infectious agent after COVID-19 itself.

## EPIDEMIOLOGY

TB epidemiology has undergone substantial changes over the last decades, with a slow reduction of about a third of both incidence and mortality; globally 1.8 billion people are infected with

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more than 10 million new cases (5.6 million men, 3.3 million women and 1.1 million children) and 2.5 million deaths every year [2].
This positive trend of reduction has been abruptly reversed by the COVID-19 pandemic outbreak, with all the consequences that can be determined by long lasting lockdowns, restrictions and reduced access to healthcare resulting in a drop in access to tuberculosis health services.
This reduction in tuberculosis testing is confirmed from the latest global tuberculosis report by WHO, showing a decline of 18% of TB cases notification in 2020 compared to 2019, from 7.1 million to 5.8 million, and a 24% reduction in the ten worst-affected countries with high tuberculosis burden, reducing by a decade the plan to eradicate TB [2].
Although in 2020 there was an overall reduction in TB case notification, sixteen countries responsible for 93% of the 1.3 million drop in TB case notifications in 2020 were India (41%), Indonesia (14%), the Philippines (12%) and China (8%), while the reduction was relatively modest in the African Region (2.5%) [2, 3].
South Africa's National Institute for Communicable Diseases (NICD) data show substantial reductions in tuberculosis testing alongside with each wave of COVID-19 and the subsequent limitations due to lockdown. Furthermore, this reduction in case-finding led to an increase of about 100.000 in the global number of TB deaths between 2019 and 2020, with a growth from 1.2 million to 1.3 million death per year [2].
According the forecast models of TB incidence and mortality until to 2025, it is believed that this impact will be much larger in 2022 and beyond, especially on TB mortality in 2022 and TB incidence in 2023. It is worth noting that these models may underestimate the actual data because projections don't take into account the impact of COVID-19 on the overall TB determinants, such as levels of poverty and undernutrition, both causes of reduction in health care seeking behavior, leading to delays in TB diagnosis and treatment. The reasons behind the more delayed impact on TB incidence compared with TB mortality are linked to the long time necessary for the development of symptomatology (usually between the infection and the disease it ranges from months to years) and the fact that limited access to health facilities mainly affects the pool of TB patients already infected, resulting in an increase in the number of deaths.
About one-third of the world's population is believed to harbour latent TB, which can be activated into active TB in immune-compromised people with comorbidities. Recent evidence suggests that the suppression of the cell-mediated immunity caused by SARS-CoV-2 induces the activation of latent TB, leading to a possible, severe hurdle to TB eradication by 2035 [4].
In the worst 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, determining an increase of 8-14% in cumulative TB deaths.
In his study Ergönül analyzed the influence of 16 different variables, including risk factors, health system settings and pandemic duration, in increasing COVID-19 case fatality deaths in 34 countries: TB incidence has proven to be one of the major determinants, given that each unit increase of TB incidence per 1.000 inhabitants raised COVID-19 fatality rates by 3.2% [5]. However, TB incidence may also be a proxy for uncontrolled variables such as poverty and malnutrition.
Although social isolation and the use of mask, responsible for reducing the outbreak of other respiratory infectious diseases as flu, may have reduced TB transmission outside, indeed prolonged stay in closed places could have increased the indoor transmission. It should be noted that the transmission of TB doesn't immediately generate new cases, requiring a period of latency varying from months to years to manifest the disease.
This dramatic reduction in TB incidence was especially noted in countries with a higher TB burden, even if nations with low TB incidence haven't remained unscathed (e.g., Italy, France and Spain) [6]. As expected, COVID-19 burden impacts more setting characterized by high TB prevalence and low health care system: in Jiangsu Province, China, TB notifications dropped as much as 52% in 2020 compared to 2015-2019 [7].
Disruption in healthcare and restrictions linked to COVID-19 pandemic have also had a serious impact on TB treatment: the reduction in the delivery of therapies has had repercussions in particular on the forms DR-TB (drug-resistant TB) and XDR-TB (extensively drug-resistant TB) with a decrease in 19% and 37%. The 2021 WHO global tuberculosis report estimated a decrease by 15%

in the number of people treated for XDR-TB and also a 21% reduction in people receiving preventing therapy for latent tuberculosis infection [1].
Data on the coinfection COVID-19/TB are very limited: first analyses suggested that Sars-CoV-2 doesn't play a determinant role in the progression from TB infection to TB disease. Also TB outcomes seems to be not influenced by hospital acquired COVID-19, as analyzed in a study of 20 patients among which only one died for respiratory insufficiency [8].
In contrast with those data, a recent meta-analysis showed that TB and COVID-19 common pathway in dysregulation of immune responses results in a dual risk to COVID-19 severity and TB disease progression [9].
Calculating the real impact of COVID-19 pandemic is complicated, both because the methods used to estimate TB mortality are based on indirect estimates, and because the weight of cases notification is weak in many countries with high tuberculosis burden. In addition, considering in this contest the high proportion of TB deaths without a diagnosis, even outside of a pandemic, the disruptions of TB diagnosis and prevention services with the consequent reduction in TB testing, are likely to result in under-reporting of tuberculosis deaths.
In that sense we have to interpretate the results of a small Italian study, that reported during COVID-19 outbreak a significantly deteriorations in TB follow-up (p=0.03) and mortality (p=0.04) [10].
Few data are present about the prevalence of TB and COVID-19 co-infection: it is thought that in countries with high level of TB the prevalence of this infection (past or current) range between about 2% and 8% in hospitalized COVID-19 patients. This is confirmed by the South African NCID data that found a percentage of 5.5% and 4% of current tuberculosis and previous tuberculosis respectively, among 3.217 COVID-19 hospitalized patients. In a similar way, among 22.308 COVID-19 patients from the Western Cape province of South Africa, in 10% of them previous tuberculosis or current active tuberculosis was diagnosed [11].
Another report of literature shows that among 219.265 COVID-19 hospitalized patients, 5.0% of those aged 20-39 years had concurrent active tuberculosis [12].

## IMMUNOLOGY OF SARS-CoV-2 AND MTB CO-INFECTION

Sars-CoV-2 and MTB (Mycobacterium tuberculosis) share many common pathogenetic pathways. Although both pathogens can invade several organs with a systemic spread, they affect primarily the lungs as initial site of infection, owing to the airborne. Like MTB, SARS-CoV-2 infects and replicates inside ciliated mucus-secreting cells of bronchial epithelium, type-II alveolar cells and macrophages in the lungs. Once settled in the lungs, both pathogens induce a dysregulated production of pro-inflammatory cytokines leading to a cytokine storm driven by monocytes mainly, cause of the neutrophilic recruitment, exacerbating lung damage. Also, T-helper cells 1 (Th1) are triggered by initial lung damage, further increasing the share of cells infiltrating the lungs and leading to a systemic lymphopenia, which ends in excessive reactive oxygen species production and protease secretion, altering the vascular permeability and leading in pulmonary oedema, with reduced oxygen diffusion capacity and higher vulnerability to secondary infections. Beyond lung cells, both SARS-CoV-2 and MTB tend to infect immune cells, leading to aberrant cytokine production and disrupting the host's ability to regular immune system [13].
The infection process is facilitated by the ability, common to both these pathogens, to escape immunity responses, with strategies as hindering interferon responses, regulating cytokine signaling, hampering antigen presentation and modulating cell-death pathways. However, several studies pointed out a balance between detrimental and protective Th1-cells responses, due to the protection capacity of this kind of cells against SARS-CoV-2 [13]. The severe decrease in CD4+ T-cell-mediated immunity due to Sars-CoV-2, leads to a drop in cytokines production, including interleukin (IL)-2, IL-4, IL-5 and IL-13, responsible to promote latent TB progression into active disease [4]. This T-cell quantitative and functional alteration, both CD4+ and CD8+ cells, is confirmed by a Chinese study, in which 76% of 522 COVID-19 patients had significantly reduced T-cell lymphocytes with functional exhaustion of the remaining share [4, 5].
Furthermore, MTB infection increases the expression of angiotensin-converting enzyme 2, the en-

try receptor for SARS-CoV-2, increasing dramatically the chance of COVID-19 infection [16].

## POSSIBLE ROLE OF BCG VACCINATION ON COVID-19

Bacillus Calmette-Guérin (BCG) vaccination, is a live-attenuated vaccine effective for nearly a century against TB, with more than 4 billion people vaccinated with BCG worldwide and another 100 million newborn children vaccinated with BCG each year, providing over 50% protection against lung respiratory diseases and over 80% protection against disseminated TB [17].

The mechanisms by which BCG induces a cross-protection against other respiratory diseases is linked to innate immune system cells. A recent case cohort study by Aaby et al. reported a better survival rates and lower mortality (adjusted hazard ratio of 0.54) in Denmark associated to smallpox and tuberculosis vaccination during childhood, after more than 30 years since BCG vaccination [18].

The BCG non-specific and heterologous ability of protection against respiratory tract infection, both viral and bacterial, as widely demonstrated by literature, could also concern SARS-CoV-2 [19]. It's supposed that this effect is linked to the "trained immunity" imparted by BCG vaccines that protects against non-specific infections [20].

As reported by many studies, COVID-19 mortality and morbidity are significantly lower in countries with mandatory BCG vaccination programs [21]. It is worth noting that, after COVID-19 outbreak, was recorded a dramatic drop in BCG neonatal vaccination, due to the vaccines fear, that will affect pediatric TB morbidity and mortality.

The phase III randomized clinical trial ACTIVATE (NCT03296423) confirmed that recent vaccination with BCG in elderly (>65 years) protects against new infections, reducing the incidence of new infections among 198 elderly participants (25.0% vs 42.3), prolongs the reinfections time (16 weeks vs 11 weeks) and decreases of 79% the risk of acquiring one new respiratory infection in a 12 months period. It suggested that this protection is inducted by trained immunity due to pro-inflammatory cytokines as IL-10 TNFα and IL1-β [22].

Anyway, based on its immunomodulate effect on respiratory viral infection, the protective effect of BCG vaccination against COVID-19 has to be proven, although early studies, as the BCG-PRIME (Prevention of Respiratory Tract Infection and COVID-19 through BCG Vaccination in Vulnerable Older Adults) didn't suggest any benefit [23].

About the duration of the protection, a Norwegian study suggested that BCG vaccine remains effective after several decades following vaccination, with an effectiveness against pulmonary tuberculosis of 40% after 30-40 years [24]. Consistent with this view, Mayda and Ishan Gursel hypothesized that countries with stable BCG immunization programs better contain the spread of SARS-CoV-2, reporting statistical differences between 5 European countries after 11-22 years and 8 European countries after 30-45 years since last BCG vaccination [25].

On the other hand, other studies demonstrated the absence of correlation between a decrease of SARS-CoV-2 infections and BCG-vaccinated adults, suggesting that the BCG vaccine does not interfere with infection in young adults [26].

A recent retrospective observational study carried out in healthcare workers in Los Angeles demonstrated that history of BCG vaccination was associated with a lower COVID-19 related symptoms and a significantly lower positive serology against SARS-CoV-2 (IgG) [27].

BCG vaccine has strong "self-adjuvant" properties that stimulate multiple innate immune sensors or PRRs, including TLR2, TLR4, TLR8, C-type lectin receptors Dectin-1, and Mincle that enhance vaccine induced immunity [28].

## TB IMPACT ON COVID-19 PROGNOSIS

Unlike comorbidities as chronic obstructive pulmonary disease (COPD), cerebrovascular disease, hypertension, diabetes, and cardiovascular disease that represent risk factors for disease progression in COVID-19, leading to a mortality rate of 4.6%, is unclear the impact of TB on COVID-19 severity and mortality [1].

A huge meta-analysis that included 6 Chinese studies, tried to assess the impact of TB among 2.765 COVID-19 patients, in facilitating disease progression or increasing death rate. This meta-analysis indicated that TB was not associated with an increased risk of mortality in COVID-19 patients (OR=1.40, 95%CI), although was associated with a 2.10 - fold increased risk of progression in severe COVID-19 disease. This can be

justified by chronic lung impairment due to TB, a lower resistance to viruses and a frequent trend to develop ARDS in response to COVID-19 infection [29].
Following Tadolini's and Stochino's studies, concerning the first Italian COVID-19 outbreak among 20 TB patients, which didn't find a significant clinical deterioration in TB/COVID-19 cases (5% case fatality rate), an Italian observational retrospective study conducted during the first wave of pandemic (from March 2020 to September 2020) tried to analyze clinical and imaging features, outcomes and risk factors of this coinfection [7, 30]. In another Italian study by Canetti et al. 254 TB patients were enrolled in the study, 37 with latent infection (14.6%) and 217 with active disease (85.4%), with high prevalence of TB-associated risk factors (active smoking and alcoholism recorded in 18.9% and 21.4%, respectively) and low rate of severe or complicated TB presentation. In most cases, chest x-ray TB lesions didn't worsen and only 9 patients showed typical HRCT COVID-19 pattern [31].

## CONCLUSIONS

In conclusion, with the outbreak of the pandemic COVID-19 multiple diseases, both infectious but also those with different etiology such as neoplastic, have been penalized by reduced access to hospital facilities, leading to a consequent reduction in diagnosis and therapy.
This is especially true for TB, whose increased morbidity and mortality had mainly affected low socio-economic contexts where the disease is endemic, characterized by extreme levels of poverty and undernutrition, supplementary causes of reduction in health care seeking behavior.

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**Conflicts of interest**
The authors declare no conflict of interest.

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