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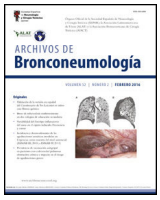

Editorial

TB/Covid-19: An Underestimated Risk?

After almost three years from the detection of the first Covid-19 cases in the Chinese province of Hubei, a highest toll of deaths caused by SARS-CoV-2 has been recorded worldwide. The highest morbidity, hospitalization, and mortality rates have dramatically affected the resilience of the national healthcare, social, and economic systems. The daily life of millions of people has been changed following the implementation and scale-up of different community-based lockdown measures, while adhering to individual infection control and preventative recommendations.

Unfortunately, the high burden of disease has affected the healthcare activities, interrupting the delivery of diagnostic, therapeutic, rehabilitative, and preventive interventions for communicable and non-communicable diseases. Several experts have warned about the clinical short- and long-term consequences of healthcare delays: higher incidence and severity (with difficult-to-treat conditions) of several diseases, with a dramatic increase of deaths and a reduction of life expectancy.[1–3]

Infectious diseases and pulmonary medicine, as well as public health specialists, have described the impact of the Covid-19 pandemic on tuberculosis (TB).[1–3] Apart from the biological hazardous risk of the TB/Covid-19 co-infection, a disruption of the activities of TB services has occurred worldwide.[3,4]

A detailed estimation of the role of SARS-Co-2 infection on the incidence and mortality of drug-susceptible and -resistant TB is impossible to perform because of the heterogeneity of the national and subnational information systems, as well as of the poor scientific evidence on the biological relationship between *Mycobacterium tuberculosis* and SARS-CoV-2.[3–5] However, several research studies, based on an ecological design, have demonstrated national negative changes in the diagnosis of TB disease and infection.[1,2,4–6] In some geographical areas policy makers and public health specialists have tried to address Covid-19-related challenges implementing the digital technology, mainly the telemedicine to monitor treatment follow-up (e.g., adherence to anti-TB drugs, careful assessment and management of therapy-related adverse events, etc.).[7,8] It was described a reduction of TB notifications in several countries during the solar year 2020, with the only exception of Australia, Singapore, and Virginia (USA).[7] A systematic review on TB and Covid-19 proved a prevalence of TB in Covid-19 patients of 0.47–4.47%, which was significantly higher in those with severe Covid-19 (i.e., 1.47% VS. 0.59); furthermore, the risk of death was 1.4 times higher in patients with concomitant Covid-19.[9] More recently, a mean overall and in-hospital fatality rates of coinfection of 13.9% and 17.5% was reported, respectively.[10]

The reason behind the estimated decreased incidence of TB cases might be attributed to the reduction of social contacts, social distancing, and the long-term implementation of community-based restrictive lockdown measures, to the use of surgical or FF2 masks, and to the natural or artificial ventilation of congregate settings.[2,7,11] Similar epidemiological trends were showed for influenza viruses: during the winter in the Southern (2020) and Northern (2020–2021) hemispheres no or few culture-confirmed cases were found, and the agreed-upon explanation highlighted the corner role of infection and preventative control measures.[7] Similar changes were described for drug-resistant TB, including countries where the incidence of new and treatment-experienced patients is usually high.[3,4,7] The biological and public health elements behind this change of the TB landscape should not be prevalent over an hypothesized under-reporting associated to patient and/or healthcare delays: fear of SARS-CoV-2 infection could have hindered medical visits of patients with non-severe respiratory symptoms[7,8]; on the other side, healthcare workers focused on virological diagnosis or shortages of healthcare professionals devoted to TB could have favoured the under-diagnosis and -reporting of new incident cases.[11] Indeed, a decrease in treatment initiation for both TB infection and disease, mirroring reduced access to non-Covid-19-related healthcare services, was recently demonstrated in a large multicentre Canadian study.[12]

The decreased incidence of TB disease following the implementation of individual and community-based measures coupled with the decreased incidence of TB infection, although a decreased number of immunological tests were recorded in several geographical areas.[12,13] The hard outcome mortality was in line with the epidemiological indicator incidence of TB infection and disease. The number of TB-attributable deaths in 2020 was significantly lower if compared with the 2019 figures, with the only exception of the months May and July 2020, when misinterpretation between Covid-19 and TB probably occurred.[7,12,13]

Unfortunately, multi-centre studies did not always provide a comprehensive epidemiological assessment: underserved geographical areas, peripheral centres, and low-income countries with poor surveillance and healthcare systems did show only a partial overview of this complicated puzzle.[7] African countries and TB centres frequently decline the invitation to take part to those epidemiological studies.[3,4,14] The African continent, where

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the TB incidence is high, was significantly affected by several Covid-19 waves during the years 2020 and 2021 with subsequent detrimental consequences on TB services indicators (e.g., detection, treatment success, community participation, notification of rifampin-resistance cases).[7,15] It would be interesting to compare their trends with those of other geographical areas to better understand the biological interaction between SARS-CoV-2 and *Mycobacterium tuberculosis*.

The complexity of the immunological response in SARS-CoV-2 co-infected patients deserves experimental and clinical attention. The cytokine storm after the viral peak in the blood has been treated with several immunosuppressive and anti-inflammatory drugs. The exposure to immune-modulating drugs can impair the immunity against *Mycobacterium tuberculosis* strains which latently infect the lungs and could trigger an increase of the bacterial load and, then, the occurrence of TB disease.[5,7] The enrolment of African and other TB reference and peripheral centres located in low-income countries and where TB infection incidence and prevalence are high could help understand the role of SARS-CoV-2 in the natural history of *Mycobacterium tuberculosis* infection.

Another important field of research is related to the issue of vaccinations: unresolved doubts on the dual protective role of BCG vaccines against TB disease and Covid-19 have been raised during the pandemic.[7] Observational studies did show scientific uncertainties, which are technically difficult to address. BCG vaccine can protect against biological agents other than *Mycobacterium tuberculosis* during the childhood period; however, it is unclear if it could prime the immune system against SARS-CoV-2 and its circulating variants.[7]

The availability of effective and safe Covid-19 vaccines has changed the epidemiology of Covid-19 in several high-income and low TB incidence countries, reducing disease, hospitalization, and mortality rates; a longer period of follow-up and its broad distribution in low-income and high TB incidence countries could help understand if they could indirectly change TB epidemiology.

Political attention focused on both TB and Covid-19 challenges is needed. The heterogeneous distribution of disease and healthcare resources highlights missing equity worldwide. Collaborative efforts should be immediately implemented to reduce the burden of avoidable cases of diseases and deaths.

Authorship

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