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Tuberculosis and COVID-19, the new cursed duet: what differs between Brazil and Europe?

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ABSTRACT

On April 1st, 2020, COVID-19 surpassed tuberculosis regarding the number of deaths per day worldwide. The combination of tuberculosis and COVID-19 has great potential for morbidity and mortality. In addition, the COVID-19 pandemic has had a significant impact on the diagnosis and treatment of tuberculosis. In this review article, we address concurrent tuberculosis and COVID-19, with particular regard to the differences between Brazil and Europe. In addition, we discuss priorities in clinical care, public health, and research.

Keywords: Tuberculosis; COVID-19; SARS-CoV-2; Coronavirus.

INTRODUCTION

Tuberculosis became the leading cause of death from infectious disease worldwide in 2015, when it surpassed HIV infection.[1] However, on April 1, 2020, COVID-19 surpassed tuberculosis in terms of the number of deaths per day.[2]

Since the beginning of the COVID-19 pandemic, cases of concurrent tuberculosis and COVID-19 have been reported.[3,4] The combination has great potential for morbidity and mortality. In addition, the COVID-19 pandemic has had a significant impact on the diagnosis and treatment of tuberculosis. The reduction in demand for the diagnosis and treatment of tuberculosis may be reflected in future incidence and mortality rates.[5]

In this review article, we address concurrent tuberculosis and COVID-19, with particular regard to the differences between Brazil and Europe. In addition, we discuss priorities in the management of clinical care and public health, as well as in research.

INTERACTIONS BETWEEN TUBERCULOSIS AND COVID-19

A review article published in 2021[6] summarized what is known on the interactions between tuberculosis and COVID-19. That review subdivided the topic into epidemiology, clinical presentation, prognosis, mortality, and impact on health care services.

CLINICAL PRESENTATION OF CONCURRENT TUBERCULOSIS AND COVID-19

The first obvious aspect of the clinical presentation of concurrent tuberculosis and COVID-19 is that the majority of patients with COVID-19 report signs and symptoms that largely correspond to those of tuberculosis, making the differential diagnosis difficult.[6-8]

Since the publication of the first cohort study of patients with tuberculosis and COVID-19,[9] it has been unclear whether and to what extent COVID-19 might increase the risk of the development of active tuberculosis in patients previously infected with *Mycobacterium tuberculosis*. Such a mechanism played a role when HIV infection boosted the tuberculosis epidemic. Preliminary data do not support that hypothesis for infection with SARS-CoV-2, although it remains an open question.[7]

PROGNOSIS AND MORTALITY

The real effect of COVID-19 as an additional risk factor for tuberculosis mortality (and vice-versa) has yet to be clearly established in different settings.[4] The main difficulty is to "clean" the interaction between the two diseases that form this "cursed duet" from the effect of age and, especially, of comorbidities (which, in turn, tend to increase with age), as well as of social determinants, such as poverty and malnutrition.[6,10] Similarly, the effect of COVID-19 in the probability

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of achieving a satisfactory outcome has yet to be described adequately.[7]

PREVENTION

Mycobacterium tuberculosis and SARS-CoV-2 are both spread through airborne transmission, although SARS-CoV-2 is much more infectious. In theory, the classical infection control measures,[11-13] including the use of personal protection equipment, environmental control, and administrative measures, should be effective. Physical distancing measures use concepts from tuberculosis infection control, adapting them to the context of the pandemic and the high transmissibility of SARS-CoV-2.[14]

Another major area of current debate concerns the role of vaccines. With regard to tuberculosis, we still rely on an old vaccine that has only relative/incomplete effectiveness (the BCG vaccine), whereas new, rapidly developed vaccines against SARS-CoV-2 are presently being used. The potential protective effect of the BCG vaccine against COVID-19 is still controversial.[15]

CLINICAL MANAGEMENT

Preliminary evidence suggests that there is a specific need for oxygen supply and invasive or noninvasive ventilation in patients with tuberculosis and COVID-19,[6,14] which further complicates the management of such patients. The subsequent waves of COVID-19 have differently burdened the ICUs in the affected countries, and the cadres traditionally involved in the clinical management of tuberculosis (pulmonologists and specialists in infectious diseases) seem to play a central role in the first-line response to the COVID-19 pandemic.[6,16,17]

SEQUELAE OF TUBERCULOSIS: EVALUATION AND REHABILITATION

The rehabilitation of individuals with sequelae of tuberculosis is an important area that has garnered more and more interest over time.[18-23] After completing antituberculosis treatment, patients often suffer from a variety of health problems, including difficulty engaging in physical exercise or even performing activities of daily living, resulting in deterioration of their quality of life.[24] A proportion of those patients can benefit from pulmonary rehabilitation, as recently demonstrated.[18-20] The core of the problem is how to evaluate the patients completing antituberculosis treatment by using simple, inexpensive tools, such as spirometry, oximetry, and the six-minute walk test, in order to identify those who are eligible for pulmonary rehabilitation.[25] Quality of life can also be evaluated with simple questionnaires.[24-26] Because COVID-19 can increase the number of sequelae, it is of utmost importance to evaluate patients with tuberculosis and COVID-19, as well as to determine their need for pulmonary rehabilitation.[23]

IMPACT ON HEALTH CARE SERVICES AND ON RESEARCH ACTIVITIES

The impact that the combination of tuberculosis and COVID-19 has had on health care services and research activities has been clearly highlighted in various studies, although the real overall economic impact is yet to be known.[27-35] A recent Global Tuberculosis Network study[5] clearly indicated that the rate at which active and latent tuberculosis are diagnosed has decreased during the COVID-19 pandemic in many countries, and that could have serious consequences for tuberculosis incidence and mortality in the future. One interesting study recently addressed aspects of the issue in Brazil.[36] The authors demonstrated that the cumulative number of new tuberculosis cases in the State of Bahia was 26.4% lower in the period from January to July of 2020 than in the same period in 2019.[36]

TUBERCULOSIS IN BRAZIL AND EUROPE

In Brazil, 73,864 cases of tuberculosis were diagnosed in 2019 (35.0 cases/100,000 population). In 2018, 4,490 tuberculosis-related deaths were reported in the country (2.2 deaths/100,000 population). Since 2010, the tuberculosis mortality rate has remained stable (2.2-2.3 deaths/100,000 population). The cure rates of new cases of pulmonary tuberculosis, retreatment of pulmonary tuberculosis, and rifampin-resistant/multidrug-resistant tuberculosis (MDR-TB) were 71.9%, 51.9%, and 55.7%, respectively. In general, there is a trend toward an improvement in the cure rates of new tuberculosis cases.[37]

In the WHO Region of the Americas, a gradual increase in the incidence of tuberculosis has been attributed to an upward trend observed in Brazil. Although a consistent trend toward a decrease was observed between 2010 and 2016, the tuberculosis incidence rate in the country increased in 2017 and 2018 when compared with the previous period.[37,38]

In 2018, 52,862 tuberculosis cases were reported in 30 countries in the European Union and European Economic Area. The joint European Centre for Disease Prevention and Control/WHO report[39] showed a decrease of 4% in the overall rate reported over the last five years in those countries. Of all of the tuberculosis cases reported, 40,625 (76.9%) were newly diagnosed, and 35.0% were of foreign origin. In 999 cases (3.7%), MDR-TB was detected (by drug susceptibility testing). Of those, 808 were tested for second-line drug susceptibility and extensively drug-resistant tuberculosis was detected in 19.6%. The rate of reported MDR-TB cases decreased from 0.3/100,000 population in the 2014-2016 period to 0.2/100,000 population in 2017 and remained unchanged in 2018. Among all of the reported cases of tuberculosis, the final outcome was cure in 67.6% and death in 6.9%, compared with 49.9% and 15.7%, respectively, among the reported cases of MDR-TB.[39]

In the WHO European Region, the mean annual decline in the tuberculosis incidence rate between 2014 and 2018 was 5.1%. The WHO European Region almost reached the 2020 End TB Strategy milestone (i.e., to reduce the tuberculosis incidence rate by 20% in 2020 against the 2015 baseline rate), with a reduction of 19% in the tuberculosis incidence rate, and is on track to reach the 2020 milestone for tuberculosis mortality (a 31% reduction). Although progress has been made in reducing the number of cases of tuberculosis and the mortality rate, treatment success rates in the region are still below regional and global targets.[38]

COVID-19 IN BRAZIL AND EUROPE

The incidence of SARS-CoV-2 infection and the number of deaths due to COVID-19 between January of 2020 and January of 2021 are shown in Figures 1 and 2, respectively, for Brazil and for five major European countries (France, Germany, Italy, Spain, and the United Kingdom). The first wave was more pronounced in Brazil than in those European countries (Figure 1). In Brazil and in the United Kingdom, the peaks of new infections were highest between the end of 2020 and the beginning of 2021. The situation is similar in terms of mortality, the United Kingdom reporting the highest peak. With the exception of Germany, two peaks in the number of deaths were observed in all countries, those peaks being more prolonged in Brazil (Figure 2). The epidemiological patterns described in the various countries result from specific features of the pandemic, the response by health care facilities, and the preventive measures adopted.[40] Figure 3 summarizes the information available, by WHO Region.

PRIORITIES FOR CLINICAL MANAGEMENT

Diagnosing tuberculosis during the COVID-19 pandemic requires a high degree of clinical suspicion, because the two diseases have similar characteristics, such as fever and respiratory symptoms. In addition, tuberculosis and COVID-19 can present simultaneously, as previously demonstrated in the first cohort study of patients with tuberculosis and COVID-19.[9] Often, the investigation carried out for the diagnosis of COVID-19, such as a CT of the chest, detects an undiagnosed pre-existing tuberculosis infection.[3]

In settings with a high tuberculosis burden, the possibility of a concomitant diagnosis of tuberculosis and COVID-19 should always be considered in order to ensure the appropriate management of both diseases.[41] It has been suggested that the development of algorithms for the management of the tuberculosis/COVID-19 combination could improve outcomes.[42]

Some of the drugs used in the treatment of COVID-19 (such as hydroxychloroquine, remdesivir, dexamethasone, and anticoagulants) may interfere with the treatment of tuberculosis. Although the short-term use of corticosteroids is indicated in some

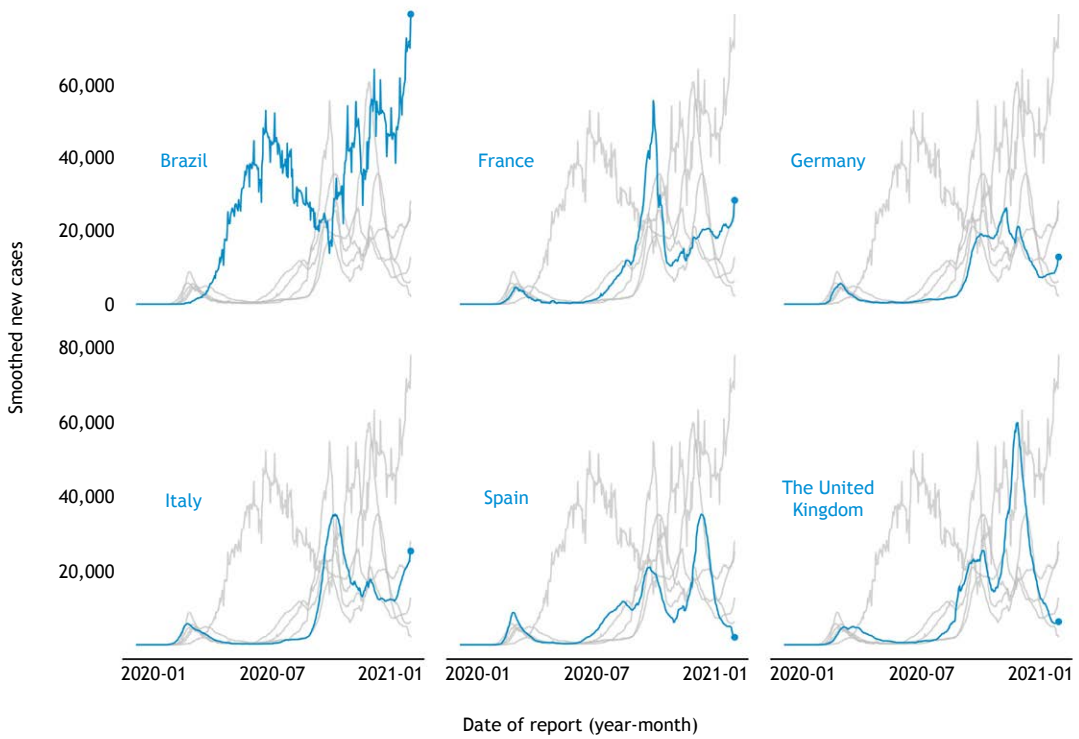

Figure 1. Number of new COVID-19 cases in six countries between January of 2020 and January of 2021. Source: COVID Intel database; data retrieved on March 15, 2021.

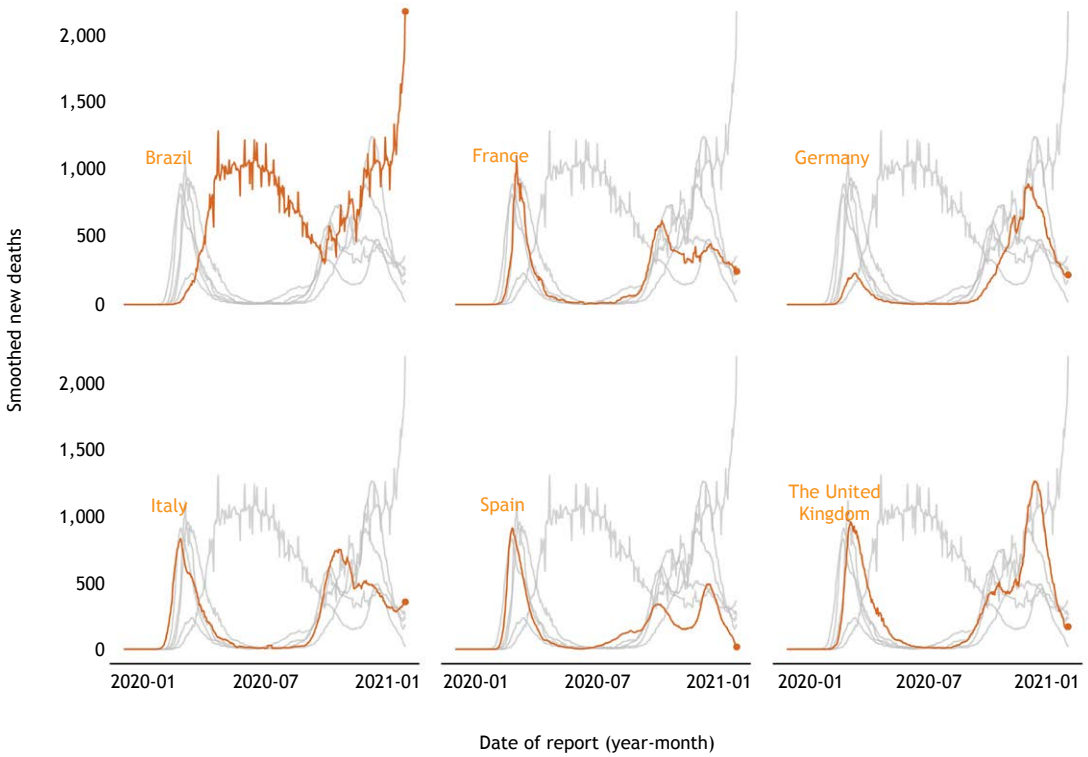

Figure 2. Number of new deaths in six countries between January of 2020 and January of 2021. Source: COVID Intel database; data retrieved on March 15, 2021.

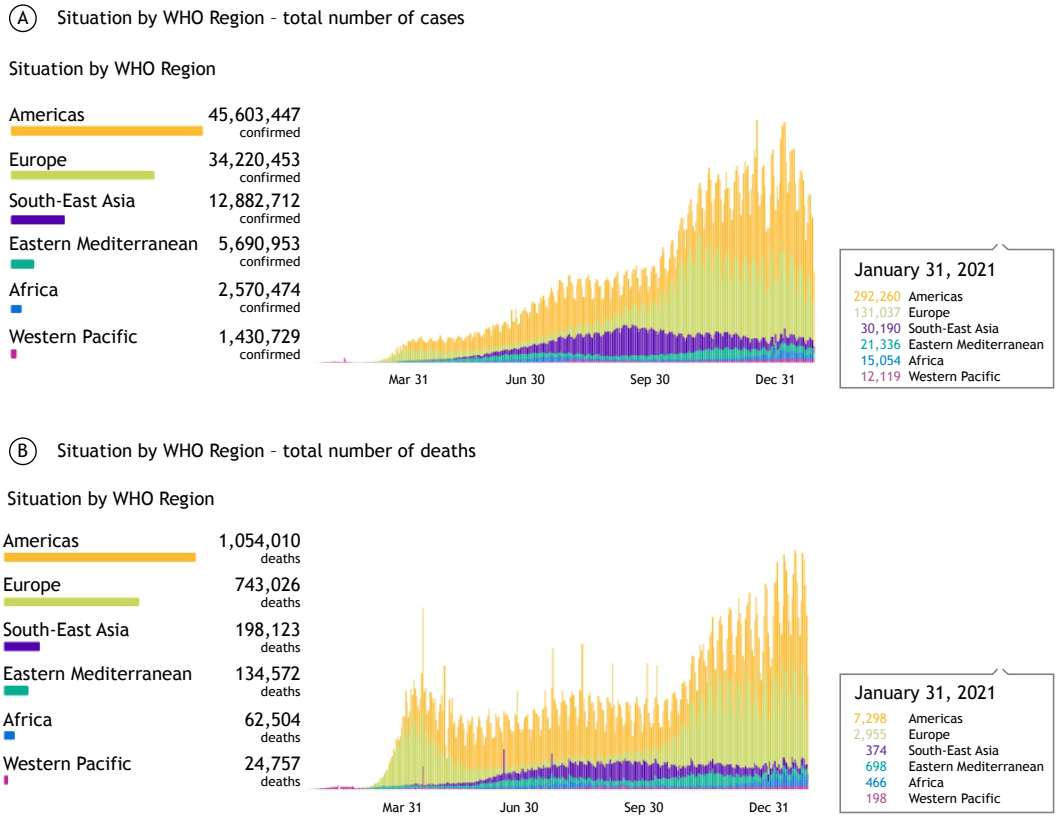

Figure 3. Total number of cases (in A) and total number of deaths (in B), by WHO Region, from the beginning of the COVID-19 pandemic to January 31, 2021. Source: World Health Organization. https://covid19.who.int/

situations in COVID-19 patients, their prolonged use for the treatment of post-COVID-19 organizing pneumonia may result in tuberculosis reactivation. In addition, the doses of antituberculosis drugs that have hepatotoxic or nephrotoxic potential should be adjusted in cases of patients with severe COVID-19 who show changes in liver and kidney function.[42,43] It is also important to bear in mind that COVID-19 can lead to sequelae, such as pulmonary fibrosis, which can reduce the penetration of antituberculosis drugs in the lungs, thus contributing to poor outcomes, especially in patients with MDR-TB.[42]

Patients with tuberculosis and COVID-19 may be at a greater risk of poor outcomes and death than are those with COVID-19 alone.[3,4,44,45] One study showed that the risk of death was 2.17 times higher in patients with tuberculosis and COVID-19 than in those with COVID-19 only.[44] Therefore, early detection of the combination is important for the proper management of both diseases. In addition, adequate isolation of tuberculosis patients, thus minimizing their exposure to SARS-CoV-2, can prevent coinfection.[46] It has been demonstrated that patients with tuberculosis and COVID-19 are 25% less likely to recover from the latter.[44] In addition, patients with pulmonary sequelae due to COVID-19 may have a higher risk of developing tuberculosis in the future.[42]

COVID-19 can also have a negative impact on latent tuberculosis infection (LTBI). The immune dysregulation caused by COVID-19 can affect the diagnosis and management of LTBI.[47] In that sense, many questions remain open. It is unknown, for example, whether there is a need to screen patients with severe COVID-19 with a tuberculin skin test/IFN-γ release assay before prescribing immunosuppressant drugs and, in the case of a positive result on the tuberculin skin test/IFN-γ release assay, whether immunosuppressant drugs currently in use should be discontinued. Additional studies are also needed in order to understand the role of SARS-CoV-2 in the progression from LTBI to active tuberculosis and to plan the post-COVID-19 follow-up of such patients.[3] Chart 1 summarizes the priorities for clinical management.

PRIORITIES FOR PUBLIC HEALTH MANAGEMENT

Given that tuberculosis is a major public health problem in Brazil and that COVID-19 is a health emergency with increasing numbers of cases in our country, we need to identify strategies for the best management of these two infectious diseases of the respiratory tract in our country.

The control of COVID-19 is based on the same strategies as those of tuberculosis control: early detection of infectious cases, infection prevention, and contact tracing.[48] Therefore, by adapting and integrating existing control programs, we can reduce the spread of COVID-19 and improve tuberculosis control.[48,49] However, to achieve this goal, some priorities should be addressed.

Regarding patient care, physicians and nurses should be trained in COVID-19 diagnosis and control.[48] Patients with respiratory symptoms can be tested for both pathogens, depending on clinical presentation. In addition, close contacts can be screened for *M. tuberculosis* and SARS-CoV-2 infection in order to control the spread of disease.[50]

The tuberculosis control program can share its laboratory network to support the diagnosis of COVID-19 efficiently if microbiological safety cabinets become widely available in our country. In addition, the implementation of automated molecular tests, such as the Xpert Xpress SARS-CoV-2 assay (Cepheid, Sunnyvale, CA, USA), could be an alternative for our laboratories, because the Xpert MTB/RIF Ultra

Chart 1. Priorities for clinical management.

• High degree of clinical suspicion for the diagnosis of tuberculosis due to the similarity of symptoms with those of COVID-19.
• In settings with a high tuberculosis burden, the possibility of a concomitant diagnosis of tuberculosis and COVID-19 should always be considered.
• Development of algorithms for the management of the tuberculosis/COVID-19 combination can improve outcomes.
• The doses of antituberculosis drugs with hepatotoxic or nephrotoxic potential should be adjusted in patients with severe COVID-19 who show changes in liver and kidney function.
• Remember that the prolonged use of corticosteroids for the treatment of post-COVID-19 organizing pneumonia may result in tuberculosis reactivation.
• Remember that COVID-19 can lead to sequelae, such as pulmonary fibrosis, which can reduce the penetration of antituberculosis drugs in the lungs, contributing to poor outcomes, as well as to the development of multidrug-resistant tuberculosis.
• Patients with tuberculosis and COVID-19 may be at a greater risk of poor outcomes and death than are those with COVID-19 alone. Therefore, early detection of the combination is important for the proper management of both diseases.
• Adequate isolation of tuberculosis patients, thus minimizing their exposure to SARS-CoV-2, can prevent coinfection.
• Remember that patients with pulmonary sequelae due to COVID-19 may have a higher risk of developing tuberculosis in the future.
• The diagnosis and management of latent tuberculosis infection can be affected by the immune dysregulation caused by COVID-19.

assay (Cepheid) has already been incorporated for the diagnosis of tuberculosis and both tests use the same equipment.

The community also has an important role to play, and community-wide education on behavioral practices, such as the use of masks, may be reinforced to reduce the transmission of *M. tuberculosis* and SARS-CoV-2.[48,50]

The integration of tuberculosis into the geospatial mapping system set up to report cases of COVID-19 could be useful to improve the tracing of tuberculosis cases and their contacts.[50] In addition, COVID-19 has necessitated the use of virtual tools for the in-home management of cases. These tools can help increase adherence to tuberculosis treatment and should be incorporated into tuberculosis control programs. Finally, the economic support provided during the

Chart 2. Main research questions on COVID-19 and tuberculosis, by field of study.

Field of study	Research question
Human exposure and immunology	When and where did COVID-19 first appear? What are the main immunological consequences of exposure to *Mycobacterium tuberculosis* and SARS-CoV-2?
Epidemiology	What is the real impact of COVID-19 on the epidemiology of tuberculosis and vice-versa? To what extent can SARS-CoV-2 trigger latent tuberculosis to evolve into active tuberculosis?
Transmission	What is the relevance of COVID-19 transmission via surface contamination, fecal-oral route, and aerosols versus droplet transmission? What is the relevance of transmission occurring from asymptomatic individuals? What are the implications for the prevention of transmission?
Signs and symptoms	What are the signs and symptoms possibly supporting the initial differential diagnosis between the two diseases?
Comorbidities	What is the role of different comorbidities on the incidence and mortality of the two diseases separately and when they are combined?
Vaccine	What is the real effectiveness and epidemiological impact of the COVID-19 vaccination program that has recently begun? What about vaccination of specific groups, such as the elderly and immunocompromised individuals? Is the BCG vaccine protective against COVID-19?
Other preventive measures	What are the most effective prevention measures (hand washing, use of personal protection equipment, physical distancing, other mitigation measures such as curfews and lockdowns, etc.) in different COVID-19 epidemiological scenarios?
Rapid diagnostics	What are the feasibility, importance, and potential impact of combined rapid diagnostics?
Treatment	What treatment is effective against COVID-19? Are corticosteroids necessary? Is there a relevant drug-to-drug interaction to monitor specifically? What is the importance of providing oxygen supplementation or invasive/noninvasive ventilation, and when should they be initiated? Are treatment outcomes different in patients with the tuberculosis/COVID-19 combination? What is the need for pulmonary rehabilitation following tuberculosis or COVID-19? Is pulmonary rehabilitation effective?
Case definition	What is the final case definition and associated criteria for classification of COVID-19, which are still subject to updates?
Stigma	What types of stigma are associated with the two diseases, and what can be done to prevent that?
Policy development	What have we learned in terms of policy development, risk communication, rapid implementation of travel policies, and quarantine restrictions, etc., one year after the beginning of the COVID-19 pandemic?
Resource mobilization	Can the rapid but sometimes chaotic resource mobilization experienced during the COVID-19 pandemic be used in order to prepare rational, comprehensive epidemic prevention/control plans for the future? Can this resource mobilization include benefits for tuberculosis prevention as well?
Economic impact	What is the overall cost of the COVID-19 pandemic to the global economy? To what extent will the COVID-19 epidemic create an additional economic burden that will impact the tuberculosis epidemic in the future?
Stress on health care systems	What is the real stress imposed by the two diseases on health care systems presently and in the coming future?
Data availability	How can we improve surveillance data to make evidence-based decisions?

COVID-19 pandemic should continue for patients with tuberculosis, prioritizing those living in poverty.[50]

PRIORITIES FOR RESEARCH

Although much has been written on the topic of tuberculosis and COVID-19, the quantity of evidence in the literature is still modest. An international study has recently been initiated with the objective of describing the interactions between the two diseases using a large individual cohort (over 600 patients) in approximately 40 countries in all continents.[7]

As summarized in Chart 2, important research questions can be derived from the studies available.[4-7,9,11,15,42,44-46,49,51,52] Those questions are related to the following major areas of interest: human exposure and immunology; epidemiology; transmission; signs and symptoms; comorbidities; vaccines and other preventive measures; rapid diagnostics; treatment; case definition; stigma; policy development; resource mobilization; economic impact; stress on health care systems; and data availability.

FINAL CONSIDERATIONS

This review article describes specific features of tuberculosis and COVID-19 according to what is known in Brazil and in Europe to date. Because the COVID-19 pandemic is still in progress, much needs to be known in order to maximize the impact of new discoveries and the implementation of best practices.

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AUTHOR CONTRIBUTIONS

DRS and GBM: conception and planning of the study; drafting and revision of preliminary and final versions; and approval of the final version. FCQM, LD, RC, and MPD: drafting and revision of preliminary and final versions; and approval of the final version.

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