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Article

The ancient Tuberculosis in the novel COVID-19 scenario

Jean Eduardo Meneguello[1,3], Paula Aline Zanetti Campanerut-Sá[2,4], Luciana Dias Ghiraldi-Lopes[3,5], Dennis Armando Bertolini[2,5], Rosilene Fressatti Cardoso[1,2,3*]

[1]Postgraduate Program in Biosciences and Physiopathology, State University of Maringá, Maringá, PR, Brazil, [2]Postgraduate Program in Health Sciences, State University of Maringá, Maringá, PR, Brazil, [3]Laboratory of Medical Bacteriology, Department of Clinical Analysis and Biomedicine, State University of Maringá, Maringá, PR, Brazil, [4]Laboratory of Food Microbiology, Department of Clinical Analysis and Biomedicine, State University of Maringá, Maringá, PR, Brazil, [5]Laboratory of Clinical Virology, Department of Clinical Analysis and Biomedicine, State University of Maringá, Maringá, PR, Brazil

Recently, the world has coped with the challenge of the novel SARS-CoV-2 rapid spreading, causing COVID-19. This scenario has overburdened health systems, forced social isolation, and interrupted some services, changing the way how health assistance is provided. The management of chronic infectious diseases such as tuberculosis is a sensitive matter in times when the control strategies are at risk. In this sense, how could a high burden disease such as tuberculosis affect or be affected when combined with the COVID-19 pandemic? Patients with tuberculosis have a social background and lung impairment that represent risks in the pandemic scenario of another widely transmitted respiratory disease. Thus, even with several questions remaining unanswered, research and public policies should be addressed to control the effects of the current highly contagious COVID-19 without forgetting how it will affect the natural progression of patients suffering from tuberculosis.

Keywords: Tuberculosis. COVID-19. Pandemic.

Recently, the world has coped with the challenging and rapid spread of the novel SARS-CoV-2, causing COVID-19. The clinical characteristics of COVID-19 range from asymptomatic status to acute respiratory distress syndrome and multiple organ dysfunctions. The rapid transmissibility and mortality caused by COVID-19 has overburdened staff of health services all around the world. To control the consequences of this health crisis that extends to a pandemic level, social isolation was forced with the maintenance of only essential services, which, in fact, has challenged health providers and the global economy. Given this scenario, it is worth remembering that historically, tuberculosis (TB) has been implied in high rates of morbidity and mortality, killing more than any other infectious disease, being a long-standing public health problem (Alagna *et al*., 2020). Since the early discovery of antimicrobial therapy, TB has been associated with drug resistance, suffering from the rise of multidrug-resistant *Mycobacterium tuberculosis* isolates (World Health Organization, 2019). Now, we are still in the middle of COVID-19 pandemic; however, in times like these, how could a high burden disease such as TB affect or be affected when combined with the COVID-19 pandemic?

In general, patient retention and the accomplishment of the treatment schema are fundamental to cure TB. However, they are sensitive matters in times of overwhelmed health facilities that could expose fragilities in health systems (Saunders, Evans, 2020). Patients with TB diagnosis should finish the treatment schema unless in exceptional cases this is not possible. If the treatment stops in high burden

***Correspondence:** R. F. Cardoso. Laboratório de Bacteriologia Médica. Departamento de Análises Clínicas e Biomedicina. Universidade Estadual de Maringá. Avenida Colombo 5790, Bloco T20 sala 212. CEP 87020-900, Maringá, PR, Brasil. Phone: +55 44 3011 5375. Email: rfressatticardoso@gmail.com. ORCID: https://orcid.org/0000-0001-6228-4780. Jean Eduardo Meneguello – ORCID: https://orcid.org/0000-0003-1836-2950

areas, it could cause further transmission of TB. Mainly in less-developed parts of the world, it is important that public health authorities keep active policies driven to directly observed therapy (DOTs), as recommended by the World Health Organization. Under these circumstances, alternatives for medication provision and patient following might be guaranteed by taking advantage of teleconsultation and a warranted aid of drug supply, supported by all necessary public health nursing, staffing, and appropriate facilities, to avoid losing patient compliance. One of the essential topics associated with TB control is the rapid laboratory diagnosis to deliver the correct identification and drug susceptibility profile of clinical isolates (World Health Organization, 2015). However, the current situation of overburden staff and facilities, the slow replenishing supplies, and sometimes the lack of investments, could lead to a reallocation of resources that compromise TB diagnosis (Louie *et al.*, 2020). Initially, this may reflect in delays in test results or unavailable services, which means risks in increasing cases of untreated disease or in numbers associated with multi and extensively resistant TB. In addition, to keep TB stable, public policies should address the social protection of the vulnerable population, because poverty is the main social determinant influencing the background of increases in TB cases (Saunders, Evans, 2020). For example, the impacts of the pandemic in health services are already experienced by slum communities (Ahmed *et al.*, 2020) and maybe by those from remote areas. Together, all these events challenge the Sustainable Development Goals, which part of the targets figures in TB control. However, now this becomes a sensitive matter with potential decrease in cure rates and consequently the increased spread of resistant TB.

Part of the risks related to severe disease in COVID-19 are advanced age, hypertension, diabetes, cardiopathies and previous lung impairment. TB manifests as active disease, latent infection, or as sequelae of past disease (World Health Organization, 2018). Considering one of the biggest risks, which is previous lung injury, the presence of cases of MDR-TB and XDR-TB should be evaluated. Usually, this group of patients suffers from TB for longer periods. Resistance represents an element for chronification and sequelae, turning the medicines available into a more burdensome administration, with fewer options and more side effects (Datta, Evans, 2019). On the other hand, SARS-CoV-2 potentially evolve as viral sepsis and inflammatory-induced lung injury, leading to other complications, which in the case of TB represents a risk of progression from latent infection to active disease. In this sense, research should provide sufficient clinical evidence to point out prognosis and therapeutic strategies in these cases, as little is known about COVID-19 immunology. When considered the severity of the convergence TB/COVID-19, the risk of death could be 2.17 times higher with shorter time-to-death and longer time-to-recovery (Sy *et al.*, 2020), but a limited body of evidence has been presented until this moment (Liu et al., 2020; Motta *et al.*, 2020; Tadolini *et al.*, 2020). From that perspective, epidemiological data collection could answer if lung impairment caused by TB compromise patients recovering from SARS-CoV-2 infection or what are the best options to manage patients co-infected with TB. Regarding co-infection, the impact of antiviral therapy proposed against SARS-CoV-2 should be assessed over the anti-TB schema, because usually, anti-TB drugs are inactivated or have increased toxicity when co-administered with the drugs purposed to treat COVID-19 (Ong *et al.*, 2020).

Although it has been controversial, initial observations suggest that there may be a link between vaccination with bacillus Calmette-Guérin (BCG) and a likely decrease in severe outcomes due to infection with SARS-CoV-2 (Miller *et al.*, 2020). While studies are being conducted, BCG has arisen discussions on its role as a booster to the immune system, preparing it for other infections than those caused by *M. tuberculosis* (Belicchi-Ferrari *et al.*, 2010). Apparently, after BCG vaccination, a trained non-specific immunostimulatory response by monocytes and NK cells is prepared to deal with infectious diseases other than TB, sounding like a "memory" from innate immunological cells, crucial for the antiviral immune response (Maheshwari, Jain, 2020; Yitbarek *et al.*, 2020). In this sense, some countries which have left the BCG vaccination have started clinical studies to evaluate the potential of BCG protecting against SARS-CoV-2. Even not being an effective strategy in TB combat, now BCG gains credit as an alternative to prepare the immune system against infectious diseases

other than TB, so, its role as a compulsory vaccination has once again been discussed.

Another important point applied to TB management that could be suggested to COVID-19 diagnosis is the implantation of the GeneXpert platform. GeneXpert has been used in TB diagnosis detecting not only the presence of *M. tuberculosis* but also resistance to rifampicin for the presumptive detection of MDR-TB. The molecular basis of the method provides high sensitivity and specificity, and it is an easy performance tool for TB diagnosis. Using GeneXpert to detect SARS-CoV-2 could provide the availability of rapid results within a few hours, while the symptoms and radiological findings of COVID-19 are non-specific and could induce misdiagnosis. Moreover, it is a safe device to manage the high transmissibility of SARS-CoV-2. Due to the pandemic, in cases of severe complications of TB, the testing for COVID-19 should be endorsed as a precaution to the correct management of the case when both conditions are present (World Health Organization, 2020).

The rapid evolution of respiratory diseases such as COVID-19 in some cases associated with misinformation could trigger social stigma and panic that individually and collectively jeopardize the measures of control proposed for the disease. In this sense, it could be learned from TB control strategies that correct information about etiology transmission/prevention, diagnosis, and treatment, which will certainly have a positive impact on the population, improving their comprehension and acting to help in the process of dealing with the pandemic.

In sum, due to the chronic evolution of TB, at this moment, it is early to measure the effects of pandemic on its epidemiology. Indeed, the world has currently suffered from the economic slowdown and the impacts of pandemic in health systems, which could compromise diagnostic, treatment, and, hence, threaten the TB-focused strategies to control spreading and drug-resistance. Additionally, patients with TB have a social background and lung impairment that represents risks in the pandemic scenario of another widely transmitted respiratory disease. Thus, even with several questions remaining unanswered, research and public policies should be addressed to control the effects of the current highly contagious COVID-19 without forgetting how it will affect the natural progression of patients suffering from TB, as the rise/decline of TB depends on economic and social transformations related to health care.

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