

# Impact of COVID-19 on tuberculosis: Turning challenges into opportunities

## Impacto de COVID-19 en tuberculosis: convertir los desafíos en oportunidades

Zoran Stojanovic<sup>1,2</sup>, Cristina Prat-Aymerich<sup>1,2,3</sup>

<sup>1</sup>Hospital Universitari Germans Trias i Pujol (Servei de Pneumologia, Servei de Microbiologia), Institut d'Investigació Germans Trias i Pujol, Universitat Autònoma de Barcelona, Barcelona, Spain. <sup>2</sup>CIBER Enfermedades Respiratorias, CIBERES, Instituto de Salud Carlos III, Madrid, Spain. <sup>3</sup>Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands.

### Impact of COVID on tuberculosis control

The COVID-19 pandemic is having a devastating effect in lives and economies worldwide. It has disrupted the continuity of essential services, partly because of overwhelmed healthcare systems but also because of interventions that promote social distancing. The most common cause of death from a single infectious pathogen already for years is, however, tuberculosis (TB). Although global TB control efforts were not on track even before the advent of the pandemic, diagnostic, prevention and treatment strategies have been further impacted<sup>1,2</sup>. In 2020, the COVID-19 apparently dislodged TB from the top infectious disease cause of mortality. However, according to the World Health Organization (WHO) report 2021, a reduced access to TB diagnosis and treatment has resulted in an increase in TB deaths. Best estimates for 2020 are 1.3 million TB deaths among HIV-negative people (up from 1.2 million in 2019) and an additional 214 000 among HIV-positive people (up from 209 000 in 2019), with the combined total back to the level of 2017<sup>2</sup>. Deaths due to TB over 5 years could increase by up to 20% compared with if there was no COVID-19<sup>2</sup>. At the same time, there are parallels and lessons learned that should contribute to minimize negative effects<sup>3</sup>. The disparity in the burden of TB in different countries and differences in the health system structure or the research resources affect differently but are becoming global.

The SARS-CoV-2 is unquestionably a one health disease and has highlighted the concept of syndemics: a synergistic effect

of the pandemic by overlapping with endemic diseases, both non communicable and neglected diseases and contextual determinants of health such as seasonal diseases, cultural and socio-economic factors and climate and environment<sup>4</sup>. TB policies need to be aligned with addressing these factors, close the gaps in diagnosis, treatment and prevention and optimize evidence-based interventions<sup>3,5</sup>. In our setting (Catalonia, Spain) in 2019, before the first COVID wave, TB incidence was reported as 14.1 cases per 100,000 inhabitants, being 5 times higher in newcomers than in native population. After the COVID outbreak the TB surveillance, prevention and control have been affected, as already highlighted by the public health reports and analyzed during the recent international TB meeting. In one survey around Spain, 70% of TB Units reported changes in the TB team usual operation<sup>6</sup>. In many occasions the staff normally dedicated to different aspects of TB control (eg. epidemiologists, microbiologists, pneumologists, infectious diseases specialists, nurses etc.) and also the infrastructure they used, were assigned to fight against the pandemic, decreasing the level of TB healthcare attention. During the upcoming winter season, despite vaccination achievements, the potential sixth wave may arrive together with seasonal influenza and additional consequences are still unknown.

### About the changes we were facing

In high-income settings, during the last two decades some epidemiological changes have impacted in TB control. The influence of non-communicable diseases such as diabetes or smoking are well known, but we are also facing a population

**Correspondence:** Cristina Prat Aymerich  
E-mail: cprata@igtp.cat

ageing as a new risk factor<sup>7</sup>. Due to higher life expectancy and lower rates of child birth, our population is getting older and therefore is more susceptible to new infections and reactivation of latent tuberculosis infection (LTBI). In the context of lower incidence, clinical suspicion gets also lower and leads to under-diagnosing, particularly in elderly people with comorbidities that justify the symptoms. Economical crisis arising within the pandemic, may affect some populations vulnerable to TB, an eminently social disease. We live in a connected world where people travel for several reasons, but at the same time we are witnessing changes in migration routes due to socio-economic conditions, globalization, armed conflicts, climate change and availability of resources<sup>8</sup>.

Regarding immunosuppression as a risk factor, a clear recent change was the reduction on the TB/HIV co-infections in the European region as effect of the wide use of HAART (highly active antiretroviral therapy). However, European Center Disease Control (ECDC) warned about an increase in the number of TB/HIV co-infections during the period from 2007 to 2016 and trends need to be carefully analysed and followed-up. On the other hand, novel risk groups are appearing because, for example, the increased use of immunosuppressive therapies including biological response modifiers for a wide range of medical conditions. Biological therapies targeting TNF- $\alpha$ , but also other cytokines and even cell subsets have become essential for the treatment of several immune-mediated diseases and have affected the risk of TB reactivation in patients with LTBI. Patients who are candidates for this therapy, already at risk because of comorbidities and additional therapies, need to be properly screened for LTBI and, when confirmed, properly assessed for the indication of treatment. Effects of individual therapies have been reviewed elsewhere<sup>9</sup>.

In addition, during the COVID pandemic, several immunomodulators were introduced (including corticosteroids and anti IL6 but also some others) in order to control the pathological immune response to the virus. The use of these drugs has the potential risk of facilitating the emergence of other illnesses. Epidemiological data for the impact of steroid therapy on LTBI cases, particularly in reactivating to symptomatic TB, is lacking<sup>10</sup>.

Finally, TB related complications (acute, subacute or chronic) are well studied and are attributable, despite successful cure, to structural damage (anatomic alterations at disease sites) or vascular compromise caused by *Mycobacterium tuberculosis*. Examples include mycetomas and the emergence of environmental mycobacteria developing within residual TB cavities, impaired pulmonary function, or focal neurologic deficits from tuberculomas<sup>11</sup>. Similarly, the acute multi-organic complications of COVID-19 are relatively well documented being the acute

respiratory distress syndrome (ARDS) one of the major ones, followed by the acute venous thromboembolism. The potential long-term implications of these manifestations remain to be better understood, although it is certain that affects different organ systems (eg. respiratory, nervous, cardiovascular) and survivors may have risks for all-cause mortality<sup>12,13</sup>.

Within the last two decades, several technological advances in diagnostic methods have become available on the different stages of disease: i) Regarding LTBI, appearance of interferon gamma release assays (IGRA) clearly improved screening, although there is a lack of consensus of cost-effectiveness from global perspective. The IGRA are more accurate in *Bacillus Calmette-Guérin* (BCG) vaccinated population, require a single visit, and results are easily retrieved electronically. On the other the tuberculin skin test (TST) has a lower price and logistical advantages under certain conditions, such as testing large groups in a field setting. The pool of latently infected has been re-estimated but the targeted TB preventive therapy needs refining. Improved approaches are under investigation. LTBI testing and treatment is of great importance in prevention of TB and as reflected in recent guidelines for both drug sensitive and MDR/XDR TB<sup>14</sup>. ii) Regarding the diagnosis of the disease, targeted molecular methods or mass spectrometry have reached the clinical labs. Simultaneously, Next Generation Sequencing (NGS) is rapidly gaining interest as an affordable all-in-one diagnostic solution that allows for individualised treatment and in the future could even substitute phenotypical testing and iii) advances in radiology and interventional pulmonology (e.g. endobronchial ultrasonography) are providing new tools for advanced diagnosis and follow up. However, despite advances in big data management, underreporting, suboptimal disease surveillance and insufficient patient information is still present, together with a fear of stigma and discrimination.

## Opportunities

In the context of the already suboptimal TB control, socio-economical crisis linked to the pandemic may appear as a devastating scenario but there is a chance to turn challenges into opportunities. Reflections on the TB report 2020<sup>1</sup> highlighted the major advances in the development of new oral regimens both for MDRTB and for preventive therapy. In the meantime, unprecedented milestones have been achieved during the pandemic by improving and applying latest technologies in key aspects such as epidemiology, contact tracing, diagnostics and vaccine development. Several authors have underlined how overlap and commonalities for surveillance, screening, diagnosis, and

management should be exploited<sup>15</sup>. We have summarized the opportunities as follows:

*Opportunity 1:* The social and political awareness and the public health importance of transmissible diseases and in particular the role of air dropped transmission is unprecedented. Non pharmaceutical interventions such as social distancing or the use of masks, have reached every level of the community and contributes to reduce the usually associated stigma. On the other hand, TB contact tracing by concentric center approach is almost ancestral, but we have also faced a digital transformation and everyone got familiar with household and non-household contact tracing and clinical epidemiology. Parallels, lessons and resources from existing public health programs identify the value of contact identification and evaluation<sup>3</sup>. Newly trained personnel and resources can be reallocated once the COVID incidence decreases as well as for treatment follow up.

*Opportunity 2:* Interdisciplinary technological impulse. There are at least two players in the infectious disease, the host (human or animal) and the pathogen, and this interaction is a dynamic phenomenon. Recent advances have allowed the identification of both human and pathogen genomic features that may influence the course of diseases. The progress on the tracing of variants of concern (including full genome accessible databases, and bio-banking regulations) may allow the technologies to reach faster the bedside for other pathogens. When the usual pathogens come back to circulation, differential diagnosis must be clearly addressed. The value of rapid and accurate diagnostics has never been so well known by the general public and the unprecedented development of diagnostic tests can also be translated to TB. The objectives for TB control need from: i) early diagnosis of active cases to improve prognosis and prevent transmission, and ii) early diagnosis of LTBI cases that are at risk of progression. These objectives require from interdisciplinary communication clinical-radiology-microbiology-pathology-epidemiology-farmacology but also basic and translational research.

*Opportunity 3:* Vaccine development together with deeper study of the immune response was unprecedented and necessary in the context of urgent response to the pandemic. It is also urgent to focus efforts on TB vaccines pipeline<sup>16</sup>, where we are still using a hundred years old vaccine. Awareness has been reached on how necessary are the well designed clinical trials to ensure robust conclusions and the need of global leadership and coordination at the administrative, regulatory and logistical levels. Some steps are in progress within national and international settings. On the other hand, more than 20 trials evaluate efficacy of BCG vaccine in COVID-19 with the premise of the described beneficial non-specific (heterologous) effects in immune system<sup>17</sup>. In absence

of evidence WHO did not recommend BCG vaccination outside the clinical trials and the COVID specific vaccines appeared soon after. However, because of the trials we will have the opportunity to further learn on the mystery of the BCG response, now also in adult population and low TB incidence settings.

*Opportunity 4:* Handle the long-term effects. TB involves in some cases severe lung damage and long term functional disability. The focus on the long term effects of COVID recently raised may allow the setting up of a better structured follow up of lung sequelae.

*Opportunity 5:* The one health perspective has become more evident. Despite the fact that the world became global, there are contextual determinants that seem to contribute to poorer health and accumulating social disadvantages and global health inequities need to be addressed. Syndemic- informed approaches can lead to impactful multilevel prevention strategies<sup>4</sup>.

*Opportunity 6:* Although we may have fallen into an infodemic, defined as too much information including false or misleading information in digital and physical environments during a disease outbreak, we have incurred into a digital transformation of health that needs to be wisely used and with critical spirit on the communication channels.

In summary, the pandemic brought back to the forefront the need for an integrated approach for handling infectious diseases and contextual determinants of health. It is mandatory to align this momentum with the fight against TB. It is unlikely that a single strategy/package will be effective for all situations, but some common approaches and engagement of local leaders, community and civil society, private and public partnership could guide policy-making.

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