

## COVID-19 and tuberculosis—threats and opportunities

RESPIRATORY TRACT INFECTIONS (RTIs) remain the top cause of morbidity and mortality from infectious diseases worldwide.<sup>1</sup> Until the end of December 2019, just three pathogens featured on the WHO Blueprint priority list for research and development: severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV) and *Mycobacterium tuberculosis*.<sup>2</sup> In January 2020, SARS-CoV-2, the cause of COVID-19, was added to the priority list. Since then, SARS-CoV-2 has spread outside China<sup>3</sup> to all continents causing death and economic disruption,<sup>4</sup> and considerable concern among national, regional and international communities. The social and psychological impact of the epidemic has been compounded by the need for strict social distancing, and the rapid spread of information and misinformation via both mainstream media and social media. This adds to the existing global burden of an estimated 4 million people who die from lower respiratory tract infections each year, with 1.4 million from tuberculosis (TB) alone.<sup>5</sup> Even more alarming is the disruption caused to global health services.

A priority for all governments during this difficult time should be to ensure continuity of essential health services, including national programmes to end HIV, TB and malaria. During the 2014–2015 Ebola outbreak in West Africa, additional deaths from HIV, TB and malaria (as an indirect consequence of the outbreak) exceeded deaths directly caused by Ebola.<sup>6–9</sup> Access to treatment for people with TB and HIV was interrupted because community health workers, doctors and laboratories devoted their energies and resources to the Ebola outbreak. The same is now likely to happen with the COVID-19 pandemic, but on a global scale. As the relatively weak health systems in high-burden settings struggle to respond to COVID-19, there is a significant risk that prevention and treatment programmes for the existing conditions will be disrupted.<sup>10</sup>

As pandemics become the focus of global attention, they should not merely be seen as a phenomenon of scientific interest until they are brought under control. They should be viewed in the light of the major socio-economic impacts, and their disruptive effects on routine health services and progress towards Sustainable Development Goals (SDGs). A modelling analysis commissioned by the Stop TB Partnership found that the global response to the COVID-19 pandemic is likely to have drastic

detrimental consequences for TB services.<sup>11</sup> Strict lockdown measures will place severe limitations on diagnostic, treatment and prevention services, which is expected to increase the annual number of TB cases and deaths over the next 5 years. It is estimated that at least 5 years of progress towards TB elimination could be lost.<sup>11</sup> The modelling was based on assumptions drawn from a rapid assessment on the impact of the COVID-19 pandemic and related measures on the TB response in 20 high-burden countries—representing 54% of the global TB burden. It shows that under a 3-month lockdown and a protracted 10-month restoration of services, the world could see an additional 6.3 million cases of TB between 2020 and 2025 and an additional 1.4 million TB deaths during that same period. The report evoked an appropriately sharp warning from the Stop TB Partnership:

We never learn from mistakes. For the past five years, TB, a respiratory disease, has remained the biggest infectious disease killer because the ‘TB agenda’ consistently became less visible in front of other priorities.

Today, governments face a torturous path, navigating between the imminent disaster of COVID-19 and the long-running plague of TB. But choosing to ignore TB again would erase at least half a decade of hard-earned progress against the world’s most deadly infection and make millions more people sick.

The fear of catching COVID-19 will deter people in need of timely diagnosis and treatment for TB from accessing health services. There is also a danger that the media focus, and hastily implemented public health measures to achieve “social distancing”, could exacerbate stigma and human rights-related barriers faced by marginalised communities and be detrimental to mental health.<sup>13,14</sup> The data indicate that the elderly (>70 years of age) and those with comorbidities are more likely to succumb to COVID-19,<sup>15–17</sup> and people with TB, TB-HIV co-infection or chronic lung disease will more likely develop sequelae,<sup>18</sup> which further highlights the importance of pulmonary rehabilitation and holistic care.<sup>19,20</sup> The poorest and most marginalised people across the world, who suffer most from TB and other RTIs, are therefore also likely to be the most affected by the COVID-19 epidemic.<sup>21</sup>

Governments of high TB burden countries need to ensure the continuity of TB services in the time of

COVID-19. This includes being proactive to protect the most vulnerable, including protection against economic hardship, isolation, stigma and discrimination. The global response needs to identify and mitigate potential risks to the critical mission of tackling TB (and other RTIs). This includes identifying how the capabilities and infrastructure can be adapted to strengthen the response to COVID-19 and allow flexibility in programmes to enable countries to respond at pace to the evolution of COVID-19. All stakeholders with an interest in TB must remain closely engaged with the WHO to ensure close coordination in response to COVID-19, and to sustain the progress made towards the SDG target of health and well-being for all.

As the COVID-19 pandemic spreads into high TB burden settings, countries must put in place strategies to ease pressure on health systems and to mitigate disruption in routine health services. The current social distancing and stay-at-home measures make it particularly challenging for TB programmes to provide diagnosis, treatment and care for communities affected by TB. To ensure no disruption to TB services, the TB programmes will have to identify and rely on alternative options, such as virtual care, digital health and community-monitoring solutions to bring the required services as close as possible to the people and communities affected by TB.

COVID-19 disease presentation can range from no symptoms (asymptomatic) to severe pneumonia and death. A review of COVID-19 cases indicates that typical signs and symptoms include fever, dry cough, fatigue, sputum production, shortness of breath, sore throat, headache, myalgia or arthralgia, chills, nausea or vomiting, nasal congestion, diarrhoea and haemoptysis, and conjunctivitis.<sup>15</sup> Thus, at first clinical presentation a wide range of differential diagnoses need to be considered, including TB.<sup>15</sup> Importantly, the same universal precautions for all infectious causes of RTIs are needed for safety and the prevention of further transmission on wards and to health care workers. The use of masks may also reduce transmission in the community and workplace; however, this has not been supported to date by the WHO.<sup>22–24</sup> Thus, a major opportunity arises from the current COVID-19 outbreak for ensuring TB control targets are not delayed. The overlap and commonalities for surveillance, screening, diagnosis, and management should be exploited.

Although long-term pulmonary sequelae for patients with post-TB are well known, an integration of biological therapy concepts taking pathophysiology into account has not been taken forward. For example, promising research on the use of autologous bone-marrow derived stem/stromal cells in patients with multidrug- and extensively drug-resistant TB demonstrated the potential for new therapeutic interventions targeting the host rather

than the pathogen.<sup>25</sup> There is also a different, cross-fertilising aspect in regard to advanced treatment options. While anti-viral drugs targeting the pathogen SARS-CoV-2 are being actively evaluated in clinical trials, host-directed therapies (HDTs) targeting the host's immune system are now attracting attention. These include an array of Phase I and Phase II clinical trials of anti-interleukin (IL) 1, anti-IL-6R, and cellular therapies using allogeneic mesenchymal stromal cells (MSCs) (<https://clinicaltrials.gov/ct2/results?cond=COVID-19>). The concept of using adjunct cellular therapies for improving outcomes could be a significant development because the major target organ for both pathogens is pulmonary tissue. Safe and clinically relevant treatment modalities for COVID-19, which curb damaging inflammation and restore lung tissue may well have relevance for patients with TB.<sup>26</sup> A global consortium of HDTs has been formed, which is open to all and provides opportunities to take forward the HDT portfolio for research into all respiratory tract conditions.

After many decades of struggling to get global attention for TB control, the turning point in the fight against TB occurred in September 2018 at the unprecedented United Nations General Assembly (UNGA) High Level meeting on TB. This resulted in a Political Declaration with bold and ambitious targets to achieve global TB control (UNGA-HLM Ref 2018).<sup>27</sup> The adoption was a significant milestone, providing the key political change that set wide-ranging targets, including specific numbers of people to be treated and funding to be mobilised.<sup>28</sup> While implementation of the three critical components—funding, action and accountability has been initiated in the right direction, there remains an urgent need to restore momentum. To do so, we must overcome the challenges that COVID-19 presents and use the opportunities it affords us to achieve a paradigm shift in TB treatment and care.<sup>29</sup>

ALIMUDDIN ZUMLA<sup>1</sup>  
 B. J. MARAIS<sup>2</sup>  
 T. D. MCHUGH<sup>1</sup>  
 M. MAEURER<sup>3,4</sup>  
 ADAM ZUMLA<sup>5</sup>  
 N. KAPATA<sup>6</sup>  
 F. NTOUMI<sup>7,8</sup>  
 P. CHANDA-KAPATA<sup>9</sup>  
 S. MFINANGA<sup>10</sup>  
 R. CENTIS<sup>11</sup>  
 D. M. CIRILLO<sup>12</sup>  
 E. PETERSEN<sup>13,14</sup>  
 D. S HUI<sup>15</sup>  
 G. IPPOLITO<sup>16</sup>  
 C. C. LEUNG<sup>17</sup>  
 G. B. MIGLIORI<sup>9</sup>  
 S. TIBERI<sup>18,19</sup>

<sup>1</sup>Center for Clinical Microbiology  
Division of Infection and Immunity  
University College London  
Royal Free Hospital Campus  
London, UK

<sup>2</sup>Marie Bashir Institute for Emerging Infectious  
Diseases and Biosecurity  
University of Sydney  
Sydney NSW, Australia;

<sup>3</sup>Immunotherapy Programme  
Champalimaud Centre for the Unknown  
Lisbon, Portugal

<sup>4</sup>I Med Clinic  
University of Mainz  
Mainz, Germany

<sup>5</sup>Barts and The London School of Medicine and  
Dentistry  
Queen Mary University of London  
London, UK

<sup>6</sup>Zambia National Public Health Institute  
Ministry of Health  
Lusaka, Zambia

<sup>7</sup>Foundation Congolaise pour la Recherche Médicale/  
University Marien Ngouabi Brazzaville  
Congo

<sup>8</sup>Institute for Tropical Medicine/University of  
Tübingen  
Germany

<sup>9</sup>Ministry of Health  
Lusaka, Zambia

<sup>10</sup>National Institute of Medical Research  
Dar es Salaam, Tanzania

<sup>11</sup>Servizio di Epidemiologia Clinica delle Malattie  
Respiratorie

Istituti Clinici Scientifici Maugeri Istituto di Ricovero  
e Cura a Carattere Scientifico (IRCCS)  
Tradate, Varese,

<sup>12</sup>Emerging Bacterial Pathogens Unit  
IRCCS San Raffaele Scientific Institute  
Milan, Italy

<sup>13</sup>Institute for Clinical Medicine  
Faculty of Health Sciences  
University of Aarhus  
Denmark

<sup>14</sup>Department of Molecular Medicine  
University of Pavia  
Italy

<sup>15</sup>Department of Medicine & Therapeutics  
Chinese University of Hong Kong  
Prince of Wales Hospital  
Shatin, New Territories, Hong Kong, China

<sup>16</sup>Lazzaro Spallanzani  
National Institute for Infectious Diseases IRCCS  
Rome, Italy

<sup>17</sup>Hong Kong Tuberculosis  
Chest and Heart Diseases Association  
Hong Kong, China

<sup>18</sup>Blizard Institute

Barts and The London School of Medicine and  
Dentistry  
Queen Mary University of London  
London

<sup>19</sup>Division of Infection  
Royal London Hospital  
Barts Health NHS Trust  
London, UK

e-mail: [simon.tiberi@nhs.net](mailto:simon.tiberi@nhs.net)

#### Acknowledgments

AZ, TDM, SM, FN, GI and NK are members of the Pan-African Network on Emerging and Re-emerging Infections (PANDORA-ID-NET - <https://www.unza-uclms.org/pandora-id-net>) funded by the European and Developing Countries Clinical Trials Partnership the EU Horizon 2020 Framework Programme for Research and Innovation. This article is part of the scientific activities of the Global Tuberculosis Network (GTN); and of the WHO Collaborating Centre for Tuberculosis and Lung Diseases, Tradate, Italy (ITA-80, 2017-2020- GBM/RC/LDA).

Conflicts of interest: none declared.

#### References

- Zumla A, Niederman M S. The explosive epidemic outbreak of novel coronavirus disease 2019 (COVID-19) and the persistent threat of respiratory tract infectious diseases to global health security, *Curr Opin Pulm Med* 2020; doi: 10.1097/MCP.0000000000000676.
- World Health Organization. List of Blueprint priority diseases. Geneva, Switzerland: WHO, 2020. <http://origin.who.int/blueprint/priority-diseases/en/> Accessed April 2020.
- World Health Organization. Coronavirus disease (COVID-19) pandemic. Geneva, Switzerland: WHO, 2020. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>.
- World Health Organization. Coronavirus diseases (COVID-19) situation reports. Geneva, Switzerland: WHO, 2020. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports> Accessed May 2020.
- World Health Organization. Global tuberculosis report, 2019. Geneva, Switzerland: WHO, 2019. [https://www.who.int/tb/publications/global\\_report/en/](https://www.who.int/tb/publications/global_report/en/) Accessed May 2020.
- Hoffman S J, Silverberg S L. Delays in global disease outbreak responses: lessons from H1N1, Ebola, and Zika. *Am J Public Health* 2018; 108(3): 329–333.
- McCloskey B, Dar O, Zumla A, et al. Emerging infectious diseases and pandemic potential: status quo and reducing risk of global spread. *Lancet Infect Dis* 2014; 14(10): 1001–1010.
- Hui D S, Memish Z A, Zumla A. Severe acute respiratory syndrome vs. the Middle East respiratory syndrome. *Curr Opin Pulm Med* 2014; 20: 233–241.
- Zumla A, Hui D S C. Emerging and reemerging infectious diseases: global overview. *Infect Dis Clin North Am* 2019; 33(4): xiii–xix.
- World Health Organization. World Tuberculosis Day 2020. Geneva, Switzerland: WHO, 2020. <https://www.who.int/news-room/events/detail/2020/03/24/default-calendar/world-tuberculosis-day-2020> Accessed February 2020.
- Stop TB Partnership. We did a rapid assessment: the TB response is heavily impacted by the COVID-19 pandemic. Geneva, Switzerland: Stop TB Partnership, 2020. [http://stoptb.org/news/stories/2020/ns20\\_014.html](http://stoptb.org/news/stories/2020/ns20_014.html) Accessed May 2020.
- Hill-Cawthorne G A, Negin J, Capon T, et al. Advancing planetary health in Australia—focus on emerging infections and antimicrobial resistance. *BMJ Glob Health* 2019; 4(2): e001283.
- Leung C C, Cheng K K, Lam T H, et al. Mask wearing to

- complement social distancing and save lives during COVID-19. *Int J Tuberc Lung Dis* 2020; 24(6): 556–558. <https://www.theunion.org/news-centre/news/mask-wearing-to-complement-social-distancing-and-save-lives-during-covid-19>. Accessed May 2020.
- 14 Moukaddam N *Psychiatric Times*: 2020: <https://www.psychiatrictimes.com/psychiatrists-beware-impact-coronavirus-pandemics-mental-health/page/0/1> Accessed May 2020.
  - 15 Tucci V, Moukaddam N, Meadows J, et al. The Forgotten Plague: Psychiatric Manifestations of Ebola, Zika, and Emerging Infectious Diseases. *J Glob Infect Dis* 2017; 9(4): 151–156.
  - 16 Tadolini M, Codecasa LR, García-García Jé-Mía, et al. Active tuberculosis, sequelae and COVID-19 co-infection: first cohort of 49 cases. *Eur Respir J* 2020; <https://doi.org/10.1183/13993003.01398-2020>.
  - 17 Motta I, Centis D, D'Ambrosio L, et al. Tuberculosis, COVID-19 and migrants: preliminary analysis of deaths occurring in 69 patients from two cohorts. *Pulmonology* 2020; <https://doi.org/10.1016/j.pulmoe.2020.05.002>
  - 18 Vitacca M, Nava S, Santus P, et al. Early consensus management for non-ICU ARF SARS-CoV-2 emergency in Italy: from ward to trenches. *Eur Respir J* 2020; <https://doi.org/10.1183/13993003.00632-2020>.
  - 19 Visca D, Centis R, D'Ambrosio L et al. The need for pulmonary rehabilitation following tuberculosis treatment. *IJTLD* 2020; 24(7): 720–722.
  - 20 Hsu D, Irfan M, Jabeen K, et al. Post TB treatment infectious complications. *Int J Infect Dis* 2020; doi:10.1016/j.ijid.2020.02.032.
  - 21 Zumla A, Ippolito G, Ntoumi F, et al. Host-directed therapies and holistic care for tuberculosis. *Lancet Respir Med* 2020; doi:10.1016/S2213-2600(20)30078-3.
  - 22 Quaresima V, Naldini M M, Cirillo D M. The prospects for the SARS-CoV-2 pandemic in Africa. *EMBO Mol Med* 2020; doi:10.15252/emmm.202012488.
  - 23 Leung C C, Lam T H, Cheng K K. Mass masking in the COVID-19 epidemic: people need guidance. *Lancet* 2020; 395(10228): 945.
  - 24 World Health Organization. Advice on the use of masks in the context of COVID-19. Geneva, Switzerland: WHO, 2020. [https://www.who.int/publications-detail/advice-on-the-use-of-masks-in-the-community-during-home-care-and-in-healthcare-settings-in-the-context-of-the-novel-coronavirus-\(2019-ncov\)-outbreak](https://www.who.int/publications-detail/advice-on-the-use-of-masks-in-the-community-during-home-care-and-in-healthcare-settings-in-the-context-of-the-novel-coronavirus-(2019-ncov)-outbreak). Accessed May 2020.
  - 25 Cheng K K, Lam T H, Leung C C. Wearing face masks in the community during the COVID-19 pandemic: altruism and solidarity. *Lancet* 2020; S0140-6736(20)30918-1. doi: 10.1016/S0140-6736(20)30918-1
  - 26 Skrahin A, Ahmed R K, Ferrara G, et al. Autologous mesenchymal stromal cell infusion as adjunct treatment in patients with multidrug and extensively drug-resistant tuberculosis: an open-label phase 1 safety trial. *Lancet Respir Med* 2014; 2(2): 108–122.
  - 27 Zumla A, Wang F S, Ippolito G, et al. Reducing mortality and morbidity in patients with severe COVID-19 disease by advancing ongoing trials of Mesenchymal Stromal (stem) Cell (MSC) therapy - achieving global consensus and visibility for cellular host-directed therapies. *Int J Infect Dis* 2020; doi:10.1016/j.ijid.2020.05.040.
  - 28 World Health Organization. 2018 UN General Assembly adopts modalities resolution for the UN High-Level Meeting on TB, 26 September 2018. Geneva, Switzerland: WHO, 2018. [https://www.who.int/tb/features\\_archive/UN-General-Assembly-resolution-HLM-TB/en/](https://www.who.int/tb/features_archive/UN-General-Assembly-resolution-HLM-TB/en/) Accessed February 2020.
  - 29 Zumla A, Dar O, Kock R, et al. Taking forward a 'One Health' approach for turning the tide against the Middle East respiratory syndrome coronavirus and other zoonotic pathogens with epidemic potential. *Int J Infect Dis* 2016; 47: 5–9.
  - 30 WHO End TB strategy. Geneva, Switzerland: WHO, 2015. [https://www.who.int/tb/post2015\\_strategy/en/](https://www.who.int/tb/post2015_strategy/en/). Accessed May 2020.