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Editorial

World Tuberculosis Day 2021 Theme – ‘The Clock is Ticking’ – and the world is running out of time to deliver the United Nations General Assembly commitments to End TB due to the COVID-19 pandemic

On March 24th 1882 Koch's announcement in Berlin of the discovery of the microbial cause of tuberculosis (TB), *Mycobacterium tuberculosis*, heralded a major breakthrough, bringing hope for a devastating disease which at that time caused the death of one in seven people in Europe and the Americas. (Wallstedt and Maeurer, 2015). One hundred and twenty years later, and despite the availability of effective treatment for the past 6 decades, 1.4 million people die of TB annually (WHO, 2021a). Over the past 15 months, the unprecedented COVID-19 pandemic has disrupted health services globally (Cilloni et al., 2020) and has negatively impacted on gains being made in global TB control efforts to achieve End TB targets (Sahu et al., 2020; STOP TB, 2019).

The theme of this year's World TB Day March 24th, 2021, ‘**The Clock is Ticking**’ (WHO, 2021b), conveys the sense of urgency that the world is running out of time to deliver the commitments to End TB made by global leaders at the United Nations General Assembly high level meeting on TB (UNGA, 2018). This theme is particularly appropriate and critical in light of the devastating COVID-19 pandemic which is currently the top killer from an infectious disease globally, with TB now being shifted to second place (WHO, 2021a; WHO, 2021c). Since the end of December, 2019, when the WHO was made aware of several cases of atypical pneumonia in Wuhan, China, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as of March 15th 2021, there have been 119,603,761 confirmed COVID-19 cases, with 2,649,722 deaths, reported to WHO (WHO, 2021c).

In commemoration of World TB Day March 24th, 2021, the International Journal of Infectious Diseases is once again publishing a specific TB Theme issue of 18 articles covering a range of topics.

The October 2020 WHO Global TB report and the United Nations (UN) Secretary-General's 2020 progress report on TB, are reviewed by Chakaya et al. (2021). They reflect on current TB control strategies in light of the United Nations (UN) targets set in the political declaration at the September 2018 UN General Assembly high-level meeting on TB held in New York (UNGA, 2018). Progress in achieving TB control targets has been very slow. Globally, an estimated 10.0 million people developed TB disease in 2019, and there were an estimated 1.2 million TB deaths among HIV-negative people and an additional 208,000 deaths among people living with HIV. In addition, preliminary assessments of how the

unprecedented, devastating COVID-19 pandemic is affecting TB health services, interrupting and slowing down treatment and prevention efforts. It is anticipated that the End TB strategy target of ending TB by 2035 will not be met. The WHO 2020 TB Report (WHO, 2021a) states that a 50% drop in the number of people with TB detected, could result in up to 400,000 additional TB deaths in a year. Innovative plans are needed to maintain all TB services as well as access to these services, in the wake of the COVID-19 pandemic and investments in the development of low-cost rapid diagnostic tests for both COVID-19 and TB are urgently needed. There needs to be a rejuvenated, sustained, and concerted effort to identify and treat ‘missing people with TB’. Governments of high TB incidence countries need to ensure there are rapid TB diagnostic services available in every health facility, so all TB cases can be reached. Global health inequities that underlie differences in TB disease burden, as well as daunting environmental health challenges, need to be addressed by multiple approaches and sectors.

Fox et al. (2021) highlight that latent tuberculosis infection affects one quarter of the world's population and that despite effective oral treatment regimens being available, scale-up and rollout of TB preventive treatment (TPT) remains limited. They describe strategies to support scale-up of TPT in high-prevalence settings, where the potential benefit for affected individuals is considerable and emphasise that patients must be at the centre of TPT policies. Addressing health system requirements for scale-up will be important to ensure that programs can deliver treatment safely, efficiently and sustainably.

Nachega et al. (2021a) discuss the negative impact of COVID-19 on TB and HIV health services. They suggest approaches to mitigate the growing burden of these colliding epidemics in sub-Saharan Africa, which bear the highest proportions of TB and HIV cases worldwide. The COVID-19 pandemic has added an additional burden to already overstretched health systems, which, among many other things, were struggling to deal with the longstanding dual epidemics of TB and HIV.

Knipper et al. (2021) review the COVID-19 pandemic threat to derailing health services for forcibly displaced people and migrant populations, populations who face specific vulnerabilities placing them at increased risk of developing TB if they have LTBI, or not being diagnosed as having active TB. Highlighting three case studies as examples—from Peru, South Africa, and Syria—they

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illustrate the lived experience of forced migration and mobile populations, and the impact of COVID-19 on TB among these populations. They indicate that addressing TB, COVID-19 and migration from a syndemic perspective, not only draws systematic attention to comorbidity and the relevance of social and structural context, but also helps to find solutions. The true reality of syndemic interactions can only be fully understood by considering a particular population and bio-social context and ensuring that they receive the comprehensive care that they need. It also provides avenues for strengthening and expanding the existing infrastructure for TB care to tackle both COVID-19 and TB in migrants and refugees in an integrated and synergistic manner.

Over a quarter of the individuals diagnosed with TB in the European Union region are born outside the EU and the proportion has been increasing steadily. Over 50% of TB cases in Italy are foreign born migrants. [Gosce' et al. \(2021\)](#) describe the EDETECT-TB project in Italy which implemented and evaluated active TB screening in the migrant population and their study confirmed that early case detection is a cost-effective intervention and that targeted post-arrival early screening ensures that potential further transmission is averted.

Recurrent pulmonary TB is a growing, important and neglected problem affecting treated TB patients and TB health services across the world, particularly in sub-Saharan Africa and Asia. Analyses and identification of differences in clinical features between recurrent PTB and newly diagnosed PTB may lead to improved management recommendations. [Nagu et al. \(2021\)](#) performed a prospective case-controlled study of clinical and imaging features of patients with recurrent pulmonary TB (RPTB) and compared them with those of newly diagnosed PTB cases. They found that hemoptysis, lung parenchymal damage, and patients being older than 45 years of age are significant features of RPTB, suggesting that management of TB cases should focus on risk factors for recurrence, and design a more holistic model of care to prevent long term lung injury.

[Kizny Gordon et al. \(2021\)](#) review the clinical and public health utility benefits of *M. tuberculosis* whole genome sequencing (WGS), including provision of more rapid and complete information on drug-resistance, detection of transmission clusters, contamination events, mixed infections, and to differentiate between re-infection and relapse. They also discuss future advances that have the potential to change the landscape of TB diagnostics and management, such as culture-free sequencing and surveillance of antimicrobial resistance to guide precision medicine approaches, as well as some of the challenges involved. Whole genome sequencing-based differentiation between re-infection and relapse in TB cases has important implications for public health, especially in patients with human immunodeficiency virus (HIV) co-infection. [Shanmugam et al. \(2021\)](#) compared Mycobacterial Interspersed Repeat Unit (MIRU) typing and spoligotyping with WGS to differentiate between relapse and re-infection and assessed the value of WGS to track acquired drug resistance in those with relapse after successful treatment. Comparing *M. tuberculosis* genomes, they found that 95% of TB recurrences in the HIV-negative cohort were due to relapse, while the majority of TB recurrences in the HIV-positive cohort were due to re-infection, highlighting the need for effective infection control in HIV care setting.

WGS for *M. tuberculosis* drug resistance detection is now available in diagnostic and reference laboratories worldwide. Characterizing novel mutations and deletions associated with drug resistant *M. tuberculosis* could ultimately lead to better treatment outcomes. The additional value WGS provides in inferring drug resistance is discussed by [Lam et al. \(2021\)](#). They sequenced genomes from all *M. tuberculosis* isolates in NSW, Australia, collected between 2016 and 2019 and tracked the prevalence of drug resistance and circulation of predominant *M. tuberculosis*

lineages. They demonstrated that WGS was able to capture an additional 20% of drug resistance mutations not detected by commercial diagnostic assays, signaling the additional value that WGS offers over existing genotypic drug resistance assays in terms of sensitivity.

The Bandim TBscore is a clinical score that predicts treatment outcome in TB patients and may prove useful as an indicator of which healthcare-seeking adults to refer for sputum smear microscopy. [Rudolf et al. \(2021\)](#) conducted a stepped wedge cluster-randomized trial at six health centers in Bissau, Guinea-Bissau, and Gondar, Ethiopia. They conclude that it is an implementable approach and solution to an old and yet unresolved challenge. Using the TBscore for triage before smear microscopy may improve case detection and decrease mortality if there is sufficient laboratory capacity to increase sputum smears.

[Marais et al. \(2021\)](#) discuss new advances to close persistent gaps in the prevention and diagnosis of childhood TB. Almost all children estimated in the Global TB Report 2020 to have died from TB were never diagnosed or offered TB treatment. Thus new approaches are required to ensure that effective TB prevention strategies are implemented and to improve the accuracy of current and new diagnostic (rule-in and rule-out) tests. Reducing the major gaps in TB preventive treatment (TPT) will require strong political commitment and concerted effort, with major upscaling of household contact investigation. While widespread roll-out of Xpert MTB/RIF Ultra[®] should be supported and could improve case detection in young children, they caution that specimen collection remains difficult and test sensitivity low. The use of non-sputum specimens are essential to improve diagnostic access, but given the limited accuracy of all available tests and the excellent tolerance of TB drugs in children the global community may have to accept some over-treatment using the most feasible approaches available; if we are serious about closing the persistent case detection gap in young children.

Zoonotic TB is evolving in an everchanging global landscape. Despite slow reductions in the annual burden of active TB cases, Zoonotic TB (zTB) remains a poorly monitored and poorly addressed global burden. [Kock et al. \(2021\)](#) in their zoonotic TB review highlight the higher incidence in some specific regions and countries, especially where close association exists between growing numbers of cattle (the major source of *Mycobacterium bovis* (*M. bovis*) and people, many suffering from poverty and where milk or dairy products are consumed un-pasteurized. Attention needs to be refocused to prevent a rapid increase in zTB disease along with growing intensification of dairy production. Evidence of new zoonotic mycobacterial strains such as *M. orygis*, especially in South Asia and Africa warrants rapid assessment of drivers and risk, and the development of appropriate interventions. Control of *M. bovis* in cattle through early detection of infection and disease, as well as pasteurization of dairy products, remains the mainstay of reducing zTB risk to humans, while new point of care diagnostics will help to detect and appropriately treat human cases.

[Lipman et al. \(2021\)](#) highlight that pulmonary disease caused by non-tuberculous mycobacteria (NTM) is often missed, is difficult to treat successfully in an often frail population with other chronic conditions such as bronchiectasis and COPD, is on the rise globally, and results in significant morbidity and even mortality. They identify and discuss key issues in NTM management. In addition to the need for research into epidemiology, immunology and treatment, they recommend an 8-point plan including greater use of patient and clinician networks to educate primary and secondary care clinicians and promote a multidisciplinary team approach with shared patient-clinician decision making throughout care. They also call for co-ordinated patient-focused research to improve what is often a limited evidence base to guide management.

Nacheha et al. (2021b) re-ignite the century old controversies on the Bacille Calmette–Guérin (BCG) vaccine, which is yet again a focus of global attention—this time due to the global COVID-19 pandemic caused by SARS-CoV-2. Their viewpoint focusses on the assumptions, knowns, unknowns and need for developing an accurate scientific evidence base for suggestions of potential cross-protection against SARS-CoV-2 infection. Recent studies have shown that human CD4+ and CD8+ T-cells primed with a BCG-derived peptide developed high reactivity to its corresponding SARS-CoV-2-derived peptide. Furthermore, BCG vaccine has been shown to substantially increase interferon-gamma (IFN- γ) production and its effects on CD4+ T-cells and these nonspecific immune responses could be harnessed as cross protection against severe forms of COVID-19. They highlight that there are numerous clinical trials in progress to determine the effectiveness of BCG vaccination for prevention of SARS-CoV-2 infection or to reduce morbidity and mortality associated with COVID-19. Data from ongoing BCG trials may shed light on the mechanisms underlying BCG-mediated immunity and could lead to improved efficacy, increased tolerance of treatment, and identification of benefits combining BCG and COVID-19 vaccines, or other adjunct immunotherapies.

There are several ongoing studies which are defining the interactions between COVID-19 and TB. Petrone et al. (2021) evaluated IFN- γ levels in whole blood after stimulation with *Mtb* antigens in the Quantiferon-Plus format or with peptides derived from SARS-CoV-2 spike protein, Wuhan-Hu-1 isolate (CD4-S). They demonstrated for the first time that COVID-19 patients, either with TB or LTBI, have a low ability to build an immune response to SARS-CoV-2 while retaining the ability to respond to *Mtb*-specific antigens. These results may have important implications for the clinical management of COVID-19 individuals coinfecting with *Mtb*.

Fatima et al. (2021) focus on TB control in Pakistan and discuss the importance of a multi-pronged approach for building better TB control systems to cope with the effects of COVID-19. As in all high-TB endemic countries, COVID-19 is impacting negatively in Pakistan. The COVID-19 has provided an opportunity in country to introduce some adaptations to bring TB care closer to communities, increased investments in human resources and addressing stigma, and implementation of telemedicine systems for follow-up and consultations. Global health inequities driving TB epidemiology, including the environment and climate control, gender, age, socio-economic status, and wealth as well as resource distribution, need to be addressed by multiple approaches and sectors.

The WHO 2020 global TB Report estimates that in 2019 there were an estimated 500,000 cases of multi-drug resistant TB (MDR-TB) of which only 186,772 MDR-TB cases were diagnosed, and positive treatment outcomes were achieved in 57% of them. These data highlight the need for accelerating and improving MDR-TB screening, diagnostic, treatment and patient follow-up services. Issayeva et al. (2021) present the first study from Kazakhstan on culture conversion at six months in patients receiving bedaquiline- and delamanid-containing regimens for the treatment of MDR-TB.

Tiberi et al. (2021) emphasize that the direct and indirect negative impacts of COVID-19 on health services overall, including national TB programs and TB services add further to longstanding challenges for tackling MDR-TB such as availability of budgets, rollout of TB diagnostics and TB drugs. Implementation of latest WHO guidelines for MDR-TB, in light of COVID-19 disruption of TB services will be difficult and, it is anticipated the numbers of MDR-TB cases will rise in 2021 and 2022 and will affect MDR-TB treatment outcomes further. Investing more in development of new TB drugs and shorter MDR-TB treatment regimens is required in anticipation of emerging drug resistance to new TB drug regimens. These include closely aligning and optimizing COVID-19 and MDR-TB algorithms and improving clinical capacity to offer

rapid diagnosis, quality treatment and follow up, and ensuring availability of quality, regular supply of cost-free TB drugs (for both DS-TB and MDR-TB) through improved procurement and distribution of TB drugs.

Sahu et al. (2021) remind us that it has been over two years since global leaders signed the UN General Assembly high level meeting on TB (UNGA-HLM-TB) declaration which committed to mobilize 15 billion USD per annum for TB, 13 billion USD for TB care and 2 billion USD per annum for TB R&D (UNGA, 2018). They point out that the follow up October 21, 2020 UN Secretary-General report (UNGA, 2020) on progress towards implementation of the UNHLM political declaration on TB stresses that although high-level commitments and targets had galvanized global and national progress towards ending TB, urgent and more ambitious investments and actions were required, especially in lieu of the COVID-19 pandemic where associated public health measures and travel restrictions, have disrupted health services universally. The report sets out 10 priority recommendations to get the world on track to reach agreed targets by 2022. Importantly, all countries should sign up to these ten priority recommendations and the Global Fund needs to increase its current commitment to mitigating the impact of COVID-19 on TB services (Global Fund, 2020). Additional supplementary measures and resources are required to reduce the accumulating pool of undetected people with TB. These should include ramped-up active case-finding with intensive community engagement and contact tracing to sustain awareness of recognizing and responding to symptoms suggestive of TB, using digital technology and other diagnostic tools, and an uninterrupted supply of quality TB drugs and care for all people with TB (Stop TB Partnership, 2020).

On World TB Day 2021, every political and community leader, and funding agency must get the message that it is time to reduce global inequities as we work towards a TB free world. While there is a continued need to develop new prevention and treatment tools for TB, obtaining the resources required for implementation of current TB diagnostic and management tools could significantly advance TB control efforts. World leaders need to urgently address and reverse the socio-economic and health services impact of the COVID-19 pandemic. As COVID-19 vaccines and public health measures start to have an effect on slowing down the COVID-19 outbreak, every effort must be made by to ensure that health services and prevention programs for TB are not compromised. The commitment of western governments to the rapid development and rollout of COVID-19 vaccines is commendable, but it is important to ensure that no-one is 'left behind'. It's now time for them to invest with equal commitment to ending the TB epidemic. Reality showed us that it can be achieved, if there is serious political will which is translated into measurable, tangible actions resulting in impactful deliverables.

Conflicts of interest

All authors have a specific interest in Tuberculosis and have contributed to articles in this special IJID issue for World TB Day 2021. All authors declare no other conflicts of interest

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