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Accelerating development of new shorter TB treatment regimens in anticipation of a resurgence of multi-drug resistant TB due to the COVID-19 pandemic



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ABSTRACT

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. The last decade has seen three new TB drugs being licensed; bedaquiline, delamanid and pretomanid, and combinations these new, existing and repurposed drugs are leading to improved cure rates. The all oral six month WHO regimen for MDR-TB is more tolerable, has higher treatment success rates and lower mortality. However, the unprecedented ongoing COVID-19 pandemic is having major direct and indirect negative impacts on health services overall, including national TB programs and TB services. This adds further to longstanding challenges for tackling MDR-TB such as cost, rollout of diagnostics and drugs, and implementation of latest WHO guidelines for MDR-TB. In light of COVID-19 disruption of TB services, it is anticipated the numbers of MDR-TB cases will rise in 2021 and 2022 and will affect 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. There is an urgent need for protecting current investments in TB services, sustaining gains being made in TB control and accelerating roll out of TB diagnostic and treatment services.

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Introduction

TB despite intense efforts remains a leading infectious disease cause of death worldwide. Following the 2018 United Nations General Assembly High-Level Meeting on TB (UNGA-HLMTB) declaration in New York to control the continuing global tuberculosis (TB) epidemic, investments into new TB drug and

regimen development are finally increasing after decades of cuts ([Report of the UN Secretary-General, 2020](#); [United Nations General Assembly, 2018](#)). Globally, an estimated 10.0 million (range, 8.9–11.0 million) people fell ill with TB in 2019 and 1.45 million died ([WHO, 2020a](#) Report). Of the 500,000 estimated cases of multi-drug resistant TB (MDR-TB) only 186,772 have actually been diagnosed and of these only 57% received treatment ([WHO, 2020a](#) Report). Whilst this is a steady increase over years, the data highlight the need for accelerating and improving MDR-TB screening, diagnostic, treatment and patient follow-up services ([WHO, 2020c](#) Consultation). Most high-TB endemic countries still fall below the minimum diagnostic and treatment targets success rates set by the World Health Organization (WHO). Tackling the growing global reservoir of latent tuberculosis infection (LTBI) caused by MDR strains of *Mycobacterium tuberculosis* (estimated to

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be 20 million) will also be important to reducing the global burden of MDR-TB (Knight et al., 2019). In addition, the ongoing unprecedented COVID-19 pandemic is having major direct and indirect negative impacts on health services, including national TB programmes and TB services (Ong et al., 2020; Vilbrun et al., 2020). This adds further to longstanding challenges in tackling MDR-TB such as cost, rollout of diagnostics and drugs, and implementation of the latest WHO guidelines for MDR-TB (Mirzayev et al., 2020; WHO, 2018b Latent TB infection).

Threats and challenges of COVID-19 pandemic to MDR-TB services and management

The COVID-19 pandemic poses a unique threat to healthcare delivery to patients with multidrug-resistant tuberculosis (MDR-TB) and threatens to undermine global control efforts. The 2020 WHO global TB Report states that fewer TB case notifications in more than 200 countries has resulted from reallocation of human, financial, and other resources from TB treatment and prevention to the COVID-19 response (WHO, 2020a Report). Three of the highest TB-burden countries, India, Indonesia, and the Philippines had TB notifications fall by up to 30% from January to June 2020, compared with the same period in 2019 because of health services disruptions caused by the COVID-19 pandemic. The impact of COVID-19 on TB services has been global (Migliori et al., 2020a,b; Visca et al., 2020; de Souza et al., 2020). The drop in notifications is significant because, if the number of TB patients detected falls by 25%–50% deaths from TB could rise by as much 400,000 in 2020 (Zumla et al., 2020).

Many high TB endemic countries have been reassigning personnel and budgetary resources from national TB programmes to COVID-19-related duties, resulting in fewer staff for TB healthcare services, decline in data collection, and re-assignment of TB laboratories for COVID-19 testing (Meneguim et al., 2020; Echeverría et al., 2020; Adewole, 2020). China's and South Africa's shift in focus to COVID-19 over the past year has led to diversion of both financial and staff resources away from TB and drug-resistant TB (DR-TB) management. This is the case with many high incidence TB endemic countries (Wu et al., 2020; Meneguim et al., 2020). Provision of direct services to TB patients has declined in high TB endemic countries. Frontline TB staff just like the communities they serve have also fell ill with COVID-19 further impacting overstretched services.

COVID-19 disruption of implementing new MDR-TB regimens

The last decade has seen three new TB drugs being licensed; bedaquiline, delamanid and pretomanid, and combinations of these new, as well as existing and repurposed drugs are leading to improved cure rates (Migliori et al., 2020a,b; Abidi et al., 2019; Ahmad et al., 2018; Borisov et al., 2019). Recent progress in the TB drug-developmental pipeline, with several ongoing clinical trials, aimed at shortening TB treatment, improving treatment outcomes in MDR-TB, and treating people with latent TB infection (LTBI) provide much needed hope for improved treatment outcomes (CDC Truncate Trial, 2020; V-Quin MDR investigators, 2019). The all oral six month WHO regimen for MDR-TB is more tolerable, has higher treatment success rates and lower mortality (WHO operational Handbook on tuberculosis, 2020b). In light of COVID-19 disruption of TB services (Ong and Goletti, 2020), it is anticipated that numbers of MDR-TB cases will rise in 2021 and 2022 and will affect treatment outcomes further. There is an urgent need for ring fencing current investments in TB services, sustaining gains made in TB control and accelerating roll out of TB diagnostic and treatment services and investing more in development of new TB drugs and treatment regimens in

anticipation of emerging drug resistance to new TB drug regimens.

Treatment of MDR-TB with drug therapy requires five drugs during the intensive phase and follow up of MDR-TB patients in the TB clinic to provide medications, check adherence, monitor for toxicity and track progress. Plans to implement a shorter, all-oral TB treatment for MDR-TB patients have been disrupted by the lockdowns, despite rollout of mobile technologies to familiarize patients on their MDR-TB regimens (Ong et al., 2020) The WHO recommended MDR-TB treatment regimens include bedaquiline, linezolid, and fluoroquinolone with addition of clofazimine or cycloserine (WHO operational Handbook on tuberculosis, 2020b). Best practice models of community-based ambulatory MDR-TB care have been affected to the detriment of patients, families, and the TB services. TB hospitals and healthcare facilities face major challenges since they are not designed to isolate so many patients with COVID-19 as well as protect vulnerable MDR-TB patients.

Thus COVID-19 lockdown and other mitigation efforts are substantially impacting TB services and will further delay achieving WHO END TB targets for elimination (WHO Assembly 67, 2018a). There is an urgent need for new safe, potent, durable TB drugs with few drug interactions, to shorten the treatment for all forms of tuberculosis. Inadequately treated and undiagnosed and untreated cases of TB create conditions for development of increased drug resistance, continuing spread of MDR-TB, and creating lung co-morbidities which lead to poor COVID-19 treatment outcomes. MDR-TB patients furthermore are likelier to suffer from sequelae at the end of their treatment, this can be further aggravated by COVID-19. It is important to identify which patient may benefit from pulmonary rehabilitation early on (Visca et al., 2020a, 2020b, 2021; Muñoz-Torrico et al., 2020). TB patients appear particularly vulnerable and should be prioritised to receive vaccination for COVID-19.

Need for development and evaluation of new drugs and treatment regimens for MDR-TB

There are several trials underway for new MDR-TB treatment regimens. The new drugs under investigation can be further categorised into their respective classes; the diarylquinolines (bedaquiline, TBAJ-587, TBAJ-876), nitroimidazoles (delamanid, pretomanid), oxazolidinones (sutezolid, delpazolid, OTB-658, TBI-223), DrpE1 inhibitors (including benzothiazones BTZ-043 and macozinone – PBTZ-169), imidazopyridine amide (telacebec (Q203)), beta-lactam (sanfetrinem) and nine other unique classes. There are 21 TB drugs from fifteen different classes in clinical or pre-clinical development for the treatment of drug-susceptible, MDR-TB or latent TB infection, of which twelve drugs are new (phase 1 (six): TBI-223, SPR720, BTZ-043, TBA-7371, macozinone (PBTZ-169), TBI-166, phase 2 (=six): telacebec (Q203), GSK 3036656, OPC-167832, SQ109, sutezolid, delpazolid), and four are already approved (bedaquiline, delamanid, pretomanid, rifapentine), repurposed (clofazimine, auranofin, nitazoxanide) or re-dosed (rifampicin, rifapentine, and levofloxacin). Of these there are only 6 agents in pre-clinical (GLP) studies, sanfetrinem, GSK-286, OTB-658, TBAJ-587, TBAJ-876, and spectinamide 1810, several of these agents are in the same drug class, precluding use in the same regimen and in the event of toxicity we may risk losing several agents during the development phase. Other novel agents include the oxazolidinones sutezolid and delpazolid. Another class of new agents includes the DrpE1 inhibitors that inhibit mycobacterial cell wall synthesis. Whilst the current TB drug pipeline is the most robust it has ever been, further trials and evidence base is required to select the most effective regimens. This will require further political commitments, funding, and

Table 1

List of priorities for improving MDR-TB services in light of the COVID-19 pandemic.

1. Protecting and safeguarding existing TB services, resources and infrastructure.
2. Closely aligning COVID-19 diagnostics and treatment services with common WHO approved protocols.
3. Optimizing COVID-19 and MDR-TB algorithms and improving clinical capacity to offer rapid diagnosis, quality treatment and follow-up.
4. 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.
5. Enhancing community based and home care including use of new technologies.
6. Provide minimal levels of universal access and social protection all patients.
7. Reducing poverty, improving the quality of housing and sanitation, resolution of conflicts.
8. Increased political commitment and financing is required to increase MDR-TB case detection and rendering treatment to bridge the implementation gap and access to adequate therapy.
9. Potential interactions between MDR-TB and COVID-19 need to be accurately defined and solutions found.
10. Greater communication, transparency, and cooperation between research groups, to achieve consensus on research priorities and new MDR-TB regimen development.
11. All countries should sign up to the ten priority recommendations in the October 2020 UN Secretary-General report on progress towards implementation of the UNHLM political declaration

development of further clinical trial and laboratory infrastructures (Table 1).

Challenges

In light of COVID-19 and the rapidly changing landscape of TB drug development and treatment guidelines, it is now challenging to carry out drug trials with appropriate comparator arms. The full oral regimen for treatment of DR-TB which excludes ototoxic injectables now requires a safer alternative to Linezolid. Greater communication, transparency, and cooperation between research groups, to achieve consensus on research priorities and regimen development. Whilst TB programmes endeavor to provide adequate diagnosis, treatment, and management for drug-susceptible TB, attention should be paid to increasing the proportion of diagnosed cases, provide wider access to resistance testing, improve access to new TB drug regimens through improved procurement and distribution of new TB drugs, as well as prevent stock outs of both first- and second-line drugs.

Since TB thrives in conditions of poverty, and the current negative economic impacts of the COVID-19 pandemic, lost income and unemployment, an increased number of TB, including MDR-TB cases worldwide is anticipated. Moreover, inadequate funding for TB prevention, diagnosis, and treatment services remains a major issue. The \$13 billion a year pledged by member states at the UNGA-HLM-TB in 2018, for TB prevention and care by 2022, had only reached half that target (\$6.5 billion) at the end of 2020 (UNHLM, 2018). Most funding for TB services still comes from domestic sources, much of which are now being directed to the COVID-19 response.

Other new challenges are represented by the possibility to offer universal access and social protection to patients in need, while ensuring availability of quality and free of charge drugs for all cases, while optimizing COVID-19 and MDR-TB algorithms and improving clinical capacity to offer rapid diagnosis and quality treatment.

Increased resources, reducing poverty, improving the quality of housing and sanitation, resolution of conflicts as well as providing minimum levels of free essential universal healthcare to all including refugees and displaced populations, is now more critical than ever if we to eliminating TB by 2050 (less than 1 case per 1 million people per year) (The END TB Strategy). Increased political commitment and financing is required to bridge the implementation gap to provide rapid detection of MDR-TB and access to adequate therapy. High TB burden countries have a huge number of patients with post TB lung sequelae which may be further worsened by COVID-19. Any potential interaction between TB and COVID-19 needs to be accurately defined and solutions found.

Conclusions

Tackling the many challenges of MDR-TB will require rollout of better point of care diagnostics, effective shorter course safe treatment drug regimens, with rapid implementation and upscaling into national programmes, and aligning TB services with HIV and COVID-19, so that they can make a difference to patient lives through holistic community oriented patient care. All countries should sign up to the ten priority recommendations in the October 2020 UN Secretary-General report on progress towards implementation of the UNHLM political declaration to get the world on track to reach agreed targets by 2022.

Transparency declaration

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Authors' contributions

Dr Simon Tiberi, Mr. Adam Zumla, Miss Jessica Galvin, Dr Michael Vjecha, Prof. GB Migliori and Sir Alimuddin Zumla, initiated the idea and developed initial and several subsequent drafts. All authors contributed to finalisation of the manuscript.

Conflict of interest

The authors declare no conflicts of interest.

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