

Tackling drug-resistant tuberculosis is central to global efforts to combat antimicrobial resistance

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Tuberculosis (TB) kills more people annually than any other infectious disease. The global emergence of resistance to antituberculosis agents is a serious problem, hampering the progress made to tackle a long-standing public health threat. Drug-resistant TB is far more difficult to cure than susceptible disease and requires longer, more toxic and costly treatment. Drug-resistant TB is the most common form of antimicrobial resistance (AMR) globally. An accelerated global response to end TB and to curb drug resistance will not only achieve the End TB Strategy targets but will contribute to ending the threat posed by AMR worldwide.

Tuberculosis (TB) is the top infectious killer in the world today (1). Drug-resistant TB is a major driver of antimicrobial resistance (AMR) worldwide, it threatens hard-earned gains made in the global TB response over the past two decades and leads to an emergency situation. From a public health standpoint, the emergence and spread of drug-resistant TB have the potential to bring us back into an era when minimal options were available to effectively treat TB patients and reduce their suffering. From an economic standpoint, depending on the country and model of care, the cost of treating a single case of drug-resistant TB, especially multidrug-/rifampicin-resistant TB (MDR-/RR-TB) or extensively drug-resistant TB (XDR-TB) can be significantly higher than treating a case of drug-susceptible TB. This places a major burden on the healthcare systems of affected countries and contributes to the impoverishing, catastrophic impact of the disease on TB-affected households. The global community under the leadership of the World Health Organization (WHO) has taken a number of important steps to address this problem.

The political declaration of the 2018 United Nations (UN) High-Level Meeting on TB includes commitments by Heads of State to overcome the global public health crisis of MDR-TB and reach 1.5 million people with MDR-TB by 2022 to close gaps in care. (1) In 2018, the WHO released new consolidated treatment guidelines for MDR-TB to improve treatment outcomes and quality of life of patients and recommended a shift to more effective and fully oral regimens that are less likely to provoke adverse side effects.

Currently, the number of new TB cases is falling by approximately 2% per year (1). WHO has estimated that in order to achieve the global targets to end TB, an annual decline of at least 4–5% per year is needed until 2020, followed by a 10% annual decline until 2025, and a 17% annual decline from 2025 to 2035 (1, 2). This entails closing the large case-detection gap and improving treatment outcomes through improvements in overall TB detection, better diagnostic coverage, and novel treatment and care approaches. To address the TB epidemic, the global community must synergistically

tackle multiple factors that lead to the development of TB and drug resistance. Achievement of the desired targets for tackling drug-resistant TB will rely upon converging global strategies and frameworks to end the epidemic, fostered by increased political commitment, optimal investment for TB programmes, and research and development of new tools for prevention and treatment of TB, particularly new vaccines and medicines.

Drug-resistant TB and the evolving political context

Bringing an end to TB, including drug-resistant TB, has never been so much in the political spotlight as during the past two years. The momentum started building in early 2017 with the G20 Leaders' Declaration, "Shaping an interconnected world". This declaration highlighted the importance of combatting antimicrobial resistance, including TB, within a section on "Building Resilience". Additionally, TB was prioritized among priority bacterial pathogens identified by WHO for which there is a critical need for fostering research and development (http://europa.eu/rapid/press-release_STATEMENT-17-1960_en.htm). This was followed by commitments made by BRICS leaders in the Xiamen Declaration on prioritizing TB (<http://pibphoto.nic.in/documents/rlink/2017/sep/p20179401.pdf>). In November 2017, over 1000 participants, including 80 ministers and leaders from 120 countries, came together at the first WHO Global Ministerial Conference on Ending TB. The conference resulted in the "Moscow Declaration to End TB", the commitments of which were supported by all Member States in a resolution during the seventy-first World Health Assembly in May 2018. In September 2018, the fight to end TB was elevated to the highest level, with Heads of State coming together at the first UN High-Level Meeting on TB to commit to accelerating the response. The UN High-Level Meeting political declaration includes bold targets on closing gaps in care by finding and treating 40 million people with TB, including 1.5 million people with drug-resistant TB, by 2022. This is well-aligned with WHO's overall strategic priorities in its thirteenth General Programme of Work (2019 – 2023), including the triple billion targets, as well as the End TB Strategy (2016–2035), which was adopted by Member States at the World Health Assembly in 2014. The End TB Strategy is framed within the United Nation's Sustainable Development Goals – SDGs – (2016–2030), which focus on the three dimensions of sustainable development – economic, social and environmental protection for all populations across the globe – and support a framework of multisectoral interventions that jointly address issues of health and poverty. Within the framework of the SDGs, governments have been called upon to provide concerted global action to end the TB epidemic, including drug-resistant forms, by 2030. As the

global community races to end TB, sustaining commitment to accelerate the appropriate implementation and scale-up of current tools and to support the development of innovations is vital. To support this development, WHO has been tasked by Member States to develop a Global Strategy for TB Research and Innovation, working in close cooperation with partners, researchers and other key stakeholders.

The above commitments and efforts to tackle all forms of TB, including drug-resistant TB, come at the time of heightened awareness on antimicrobial resistance, given the potential for this threat to outpace the world's capacity for antibiotic discovery. Concerns about the potential lack of effective antibiotics to treat drug-resistant TB have been discussed since the discovery of the first anti-TB drugs, more than 60 years ago. Today's response cannot rely on the development of new medicines alone, but on synergistic and stepwise approaches that ensure the rational use and stewardship of antimicrobials, a stronger body of evidence on drug resistance patterns, and the rapid adoption of novel diagnostic tools and treatment regimens. This approach is clearly incorporated into WHO's new guidelines on MDR-TB treatment, which could be a game changer for improving treatment outcomes for those ill with MDR-TB. The new WHO recommendations, based on the most recent available evidence, signal an important departure from previous approaches to treating MDR/RR-TB. Injectable agents are no longer among the priority medicines when designing longer MDR-TB regimens and fully oral regimens are thus the preferred option for most patients. Fluoroquinolones (levofloxacin or moxifloxacin), bedaquiline and linezolid are strongly recommended for use in longer regimens, which are completed by additional medicines ranked by their relative balance of effectiveness to potential toxicity. WHO also recommends supporting treatment with active monitoring of drug safety and providing counselling support to help patients complete their course of treatment. Equally important to successful implementation of these new developments is sustainable investment, both to build resilient and sustainable healthcare systems as well as research and development to mitigate additional antimicrobial resistance.

Within the broader context of antimicrobial resistance, drug-resistant TB exemplifies not only the ripple effect that occurs when antibiotics are no longer effective, but it also exposes systematic and multifaceted factors that jeopardise the health and well-being of entire populations. While TB may be perceived as a condition that mostly affects low-income countries with fragile healthcare systems, experiencing socio-economic crises or with large HIV epidemics, drug-resistant TB disproportionately affects middle- and upper-middle income countries, which account for more than 80% of the global estimated MDR-TB burden (11). Global efforts

to reduce the burden of drug-resistant TB provide a key opportunity to combat AMR and are also relevant to countries with well-resourced health systems. The Global Action Plan on Antimicrobial Resistance (GAP) endorsed by Member States and recognized by Heads of State and Government at the UN General Assembly's high-level meeting on antimicrobial resistance in 2016 has further laid out responsibilities for national governments to respond to the antimicrobial resistance crisis. The principles and actions underpinned in the GAP, which are also embedded within the End TB Strategy, are framed within a broader context of ensuring healthy lives and promoting well-being for everyone at all ages. The GAP continues to urge governments and key stakeholders to strengthen cross-sectoral coordination and collaboration at all levels, improve access to essential healthcare services, and ensure access to safe, effective, high quality and affordable essential medicines and innovative tools for prevention and care. The complementarity of these two strategies (GAP and WHO's End TB Strategy) converges on the actions required to: increase engagement of a wide range of collaborators across and beyond government; improve delivery of TB prevention services, including infection prevention and control; achieve universal access to patient-centred quality healthcare and health outcomes; increase commitment of governments and funding agencies to provide adequate and sustainable resources for intensified research and innovation efforts; and to pursue incremental targets for implementation as the response capacity of health systems is improved.

As the global community continues to observe poor TB treatment outcomes and significant health service challenges, compounded by a large pool of "missing" TB cases, targeted scaling-up of specific areas can help accelerate achievement of global targets, and contribute to the overall fight against antimicrobial threats. As an example, strengthening national surveillance and health systems would help to address under-reporting, under-diagnosis and misdiagnosis and, in turn, rapidly provide countries with a better understanding of their epidemics and allow the development of appropriate strategies. Contributing to these efforts is the Global Project on Anti-tuberculosis Drug Resistance Surveillance, hosted by WHO, which is the largest and oldest antimicrobial surveillance project globally. Since 1994, data from WHO Member States have been systematically collected and analysed to determine the burden of drug-resistant TB (12). Data are currently available from 160 countries, which collectively account for more than 97% of the world's TB cases. Among these, 91 countries have continuous surveillance systems based on routine drug-susceptibility testing of TB patients, while 69 rely on periodic surveys conducted on average every five years. Sequencing is playing an increasingly important role in

the surveillance of drug-resistant TB. It allows a more rapid assessment of the resistance profile to a range of drugs than conventional phenotypic methods, while also providing other information regarding the genotypic profile of circulating TB strains. To expand the body of knowledge on the interpretation and clinical relevance of specific mutations, a large-scale drug resistance surveillance database, the Relational Sequencing TB Knowledgebase (ReSeqTB) platform has been established to collect, analyse and safeguard sequencing data. These data may inform the development of new diagnostic tools and, in future, guide clinical decision-making for the management of patients with drug resistance (13).

A salient component of all strategies, including the GAP, is that of infection prevention. Effective infection prevention and control practices (IPC) reduce the need for antibiotics. From a TB perspective, prevention measures focus not only on the effective implementation of administrative, environmental and respiratory protection aimed at reducing the risk of exposure and transmission, but also on the prevention of disease progression among individuals exposed to, and latently infected with, *M. tuberculosis*. WHO's recommendations on the core components of building effective IPC programmes (14) in 2016, as well as TB-specific IPC guidelines launched in 2019 (15), are intended to help establish and strengthen existing services. In the context of preventive treatment for TB infection, although services are expanding, the majority of at-risk populations cannot access them. To better guide relevant policy decisions for the management of drug-resistant TB, WHO continues to assess clinical and programmatic data to inform the development of relevant and up-to-date treatment and care recommendations for the benefit of global public health.

Conclusions

The risk of emerging, resistant microbial infections is increasing, and as inappropriate use of antimicrobials to treat TB and other infectious conditions continue to fuel the global spread of drug-resistant disease, the availability of effective antibiotics is decreasing. Unquestionably, while the global TB community, with the leadership of WHO, champions efforts to gather momentum and harness major political commitment, the emergence of drug-resistant TB cannot be fully addressed without all stakeholders coming together to promote and rapidly implement existing and novel evidence-based solutions. More importantly, as new tools become available, countries will be in continued need of support to keep pace with the adoption of novel technologies, medicines and vaccines. There are still major gaps in implementing current tools and delivering preventive services as well as effective treatment to patients suffering from TB and drug resistance. Preventive treatment of latent TB is such a case in point. With

23% of the world's population having latent TB infection, the provision of preventive therapy for high-risk groups, including contacts of MDR/RR-TB cases, is lagging behind. Prevention represents an important entry point not only to bring down the incidence of TB, but also to curb drug-resistant forms. Although a number of methods and assays have been developed for the detection of *M. tuberculosis*, with or without detection of drug resistance, high TB burden countries do not possess adequate and sustainable resources for building laboratory infrastructure and fully reaching all communities in need. Countries must expedite the transition to replacing microscopy as the initial diagnostic test with rapid molecular tests that simultaneously detect TB and rifampicin resistance. The use of WHO-recommended rapid diagnostics, including the Xpert MTB/RIF® is yet to be systematically adopted as the initial diagnostic test for all individuals suspected of having pulmonary TB. Ongoing delays in the full implementation of currently available rapid tests for early detection of TB and drug resistance will continue to fuel the suffering of patients. Moreover, as antibiotics resistance is bound to occur for as long as antibiotics are used, the global TB drug pipeline will also need to be rapidly assessed and expanded to meet needs of treatment, as drug-resistant mutations developed.

Efforts to combat drug resistance in TB, such as dedicated programmatic approaches embedded within global strategies, a long history of surveillance and antimicrobial stewardship, make a significant contribution and provide a pathway to address antimicrobial threats globally. However, as the search for improved, shorter and more feasible treatment options continues and the potential of novel diagnostic technologies is unveiled, the global community must focus on accelerating the implementation of existing tools, without losing sight of economic, social and other local concerns that fuel the epidemic. The political declaration of the UN High-Level Meeting on TB offers a significant opportunity to keep the spotlight on ending TB and MDR-TB, ensuring high-level commitments are translated into actions which are backed by investments. This can be the turning point for the fight to end TB and drug-resistant TB, saving millions of lives. ■

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