Introduction

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This timely and important *Monograph* provides a crucial update on recent changes, developments and setbacks in the field, and calls for a re-commitment to the achievement of the End TB Strategy and Sustainable Development Goals https://bit.ly/ERSM101intro

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Priorities to bend the TB epidemic curve towards elimination

The WHO Global End TB Strategy, launched in 2015, sets priorities and specific targets aimed at reducing TB incidence and mortality to end the TB epidemic and eliminate disease-associated economic hardship worldwide by 2030 [1]. Its three main pillars are: integrated patient-centred care and prevention; bold policies and supportive systems; and intensified research and innovation [1]. Regional and national elimination strategies have been developed to set targets and achieve these priorities. These enable region-specific TB control activities based on the local epidemiology and contextual factors. For example, the WHO TB action plan for the WHO European Region, provides strategies to allow Europe to reach the global End TB Strategy targets to reduce TB incidence by 80% and TB deaths by 90% by 2030 [2]. Resolutions adopted by member states at the first ever United Nations (UN) high level meeting (UNHLM) political declaration on TB in 2018 set the scene for bold policies and further sharpened the global focus on the priorities of the End TB Strategy, to accelerate adoption of specific strategies. Member states endorsed a declaration on TB that included targets to treat 40 million people with TB between 2018 and 2022, 3.5 million children with TB and 1.5 million people with DR-TB, and for ⩾30 million put on TPT during that period [3].

Recent advances in TB research

Innovative research is required to develop and assess new tools for the diagnosis, treatment and prevention of TB. To realise reductions in the burden of disease and reach the targets set by the international community (reduction in mortality, incidence and no households facing catastrophic costs), there is an urgent need to innovate. Specifically, we need acceleration of research and development in new effective TB vaccines, rapid and easy-to-use point-of-care diagnostics for TB, new drugs and shorter treatment regimens for both infection and disease, as

well as new tools to support prevention, care and implementation, including digital health technologies [4, 5]. Although there have been considerable challenges and shortcomings in the available funding for TB research and development (US$915 million in 2020, less than half of the intended target set by the international community) [6], the last decade has witnessed unprecedented efforts in the development of novel diagnostics, promising vaccine candidates, and medicines.

In the field of prevention, several milestones have been achieved. The development and roll out of short and ultra-short regimens for TB prevention, including weekly high-dose rifapentine and isoniazid for 3 months [6] and 1 month of daily rifapentine plus isoniazid to prevent HIV-related TB [7] have represented relevant advances, which have quickly translated into national and international policies [8]. In addition, several TB drug preventive trials for both drug-susceptible (DS)-TB and DR-TB are currently in progress, with the hope of increasing the preventive efficacy, improving safety in vulnerable populations, such as children or PLHIV, or further shortening the duration of these regimens [9].

Similarly, the field of TB vaccine development is experiencing a period of unprecedented optimism, mostly based on the promising results of two recent efficacy studies into prevention of disease and infection [10, 11]. The protein-subunit vaccine candidate M72/AS01E has shown an efficacy of ∼50% against progression from infection to disease in a large phase 2B study conducted in Kenya, South Africa and Zambia [10]. A large phase 3 registration trial is now in preparation and is expected to start enrolment during 2024. In addition, a study in South African adolescents has shown that BCG revaccination provides ∼45% protection against sustained IGRA conversion [11]. These findings are currently being followed-up with a further trial whose results are also expected in 2024. There has never been a time in history with more TB vaccine candidates being tested in large phase 3 trials (currently four at phase 3 and 17 in clinical development) [12]. Novel successful platforms used in the development of COVID-19 vaccines (using mRNA for TB antigen delivery) are already being tested in humans for TB [13]. We might be very close to adding a game-changing element to our tool kit in fight against TB.

The quest for improved point-of-care diagnostics continues to be a priority for TB research [5]. Importantly, novel, rapid molecular assays have been developed and recommended by the WHO for different levels of care [14]. Promising research is being conducted to develop sputum-free TB diagnostics, which are especially relevant for populations in whom TB laboratory confirmation continues to be suboptimal, such as children, PLHIV or in cases of EPTB [15]. Unfortunately, the only true point-of-care non-sputum-based TB diagnostic test continues to be TB-LAM, which is recommended for PLHIV under specific criteria [16]. Disappointingly, its uptake is low despite having evidence of its positive impact in reducing TB mortality [17, 18]. Thus, the quest for novel point-of-care tests that can accelerate TB diagnosis at decentralised levels of care remains.

Although the WHO recently included novel tools as part of the new TB-screening recommendations, such as C-reactive protein or artificial intelligence-based computer-aided detection to analyse digital CXR, there is a need for more specific assays for both screening or triage. New diagnostics capable of identifying individuals that are at high risk of TB progression are a priority target product profile in the field of TB diagnostics [19].

Despite decades of limited progress in global efforts to establish shorter treatment regimens for DS-TB (including several unsuccessful phase 3 treatment-shortening trials) [20–22], the field has been invigorated by exciting results demonstrating the effectiveness of a 4-month regimen against

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DS-TB (including high-dose rifapentine and moxifloxacin) [23]. 8 weeks of daily treatment with high-dose rifapentine (1200 mg), isoniazid, pyrazinamide and moxifloxacin, followed by 9 weeks of daily treatment with high-dose rifapentine, isoniazid and moxifloxacin was shown to be non-inferior to the standard 6-month regimen [23]. These results show that shorter, efficacious and safe treatments are possible and thus, further late-stage trials, including new and repurposed drugs, are warranted. Similarly, recent studies have shown that shorter MDR-TB oral regimens can achieve high cure rates. Combinations of 6 weeks of bedaquiline, pretomanid and linezolid (with or without moxifloxacin) have shown favourable outcomes and an improved safety profile compared with the previous standard of care [24, 25]. Importantly, results have immediately translated into policy and the new 6-month MDR-TB treatment regimens are already recommended by the WHO [26]. Shorter regimens are likely to improve patient adherence and reduce adverse events; they may also decrease overall treatment costs in the long term.

Current priorities of TB research focus not only on the development of new tools but also on the factors associated with their successful implementation and on improving our understanding of the natural history of TB, especially the early stages of the spectrum infection–disease. Several studies suggest that asymptomatic TB disease, also referred to as subclinical TB, might be associated with a large proportion of global TB transmission [27, 28]. (See chapter 2 of this *Monograph* [29]). Large prevalence surveys in both African and Asian countries report that ~50% of TB patients in whom *Mycobacterium tuberculosis* was isolated in sputum, were subclinical [30]. There is therefore a need to understand and measure its contribution to global TB transmission, given its immediate implications for control and research.

Re-prioritisation of control strategies

Globally, challenges remain in reducing the burden of disease. Specifically, DR-TB and TB-associated HIV co-infection continue to cause premature mortality in many world regions. Future threats include emerging and re-emerging pandemics, and disruption as a result of war and climate change.

The recent COVID-19 pandemic eroded gains toward TB control and target achievement. The shift in focus towards public health interventions to control COVID-19 contributed to service disruptions and barriers in accessing TB care, significantly reducing both the number of people notified with TB, those enrolled to treatment – especially for MDR/RR-TB – and those put on TPT, worldwide.

Wars (such as those ongoing in the Middle East, Africa and Europe in 2023) can trigger humanitarian crises, worsen the broader determinants of TB, and have a damaging impact on TB control, thereby reducing progress towards TB targets.

Re-prioritisation is essential for future impact on the TB epidemic. On the eve of the second UNHLM political declaration on TB in 2023, it is hoped that member states will steady and increase their resolve to eliminate TB by re-committing to the End TB Strategy pillars, setting bold disease burden targets and closing the funding gap.

Patient and provider-centred care is crucial to realising the desired declines in TB incidence, which can only be achieved if both patients and providers are made central to policies. This involves early diagnosis of TB with relevant tests, prompt treatment (for both DS-TB and DR-TB), investigation and appropriate evaluation, treatment of contacts of people with infectious TB disease, and prevention of further transmission through infection control.

Everyone, regardless of socioeconomic or geographical context, should receive appropriate and effective care. All people diagnosed with TB should have an equal opportunity to access standard diagnostic tools and treatment options, and should benefit from new modalities. New treatment options provide an opportunity for personalised and patient-centred care that considers individual factors such as drug resistance, comorbidities and treatment preferences – this should be prioritised.

Moreover, success in TB control is not realistic without preventive treatment of those at high risk, vaccination against TB, and management of comorbidities and TB-associated impairment and disability. BCG vaccination offers protective effects against TB. Priorities for the future should not only expand BCG vaccination to wider populations and strengthen vaccination programmes, they should also invest in research for new and effective vaccines against TB.

Decisive and accountable global, regional and national leadership is important, and this should include regular UN reporting and review. Following the 2018 UNHLM on TB, WHO developed the Multisectoral Accountability Framework for Tuberculosis [4], as a monitoring and accountability tool to track progress in the fight against TB in global, regional and country profiles. Member states declared that they would strengthen collaborations between global and national public health authorities, patient groups, researchers and the private sector, providing a framework for action and a roadmap for accelerating efforts to end the TB epidemic [4]. National TB programmes and synergies with other strategies would improve TB control.

The UNHLM on TB 2023 [3] will provide an opportunity for all stakeholders to contribute to the ongoing preparatory process for the high-level meetings, with a focus on current efforts and requirements to accelerate the response among TB survivors, people affected by TB, communities and civil society, and other TB stakeholders, including UN agencies, high-burden TB countries, donors and the private sector.

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