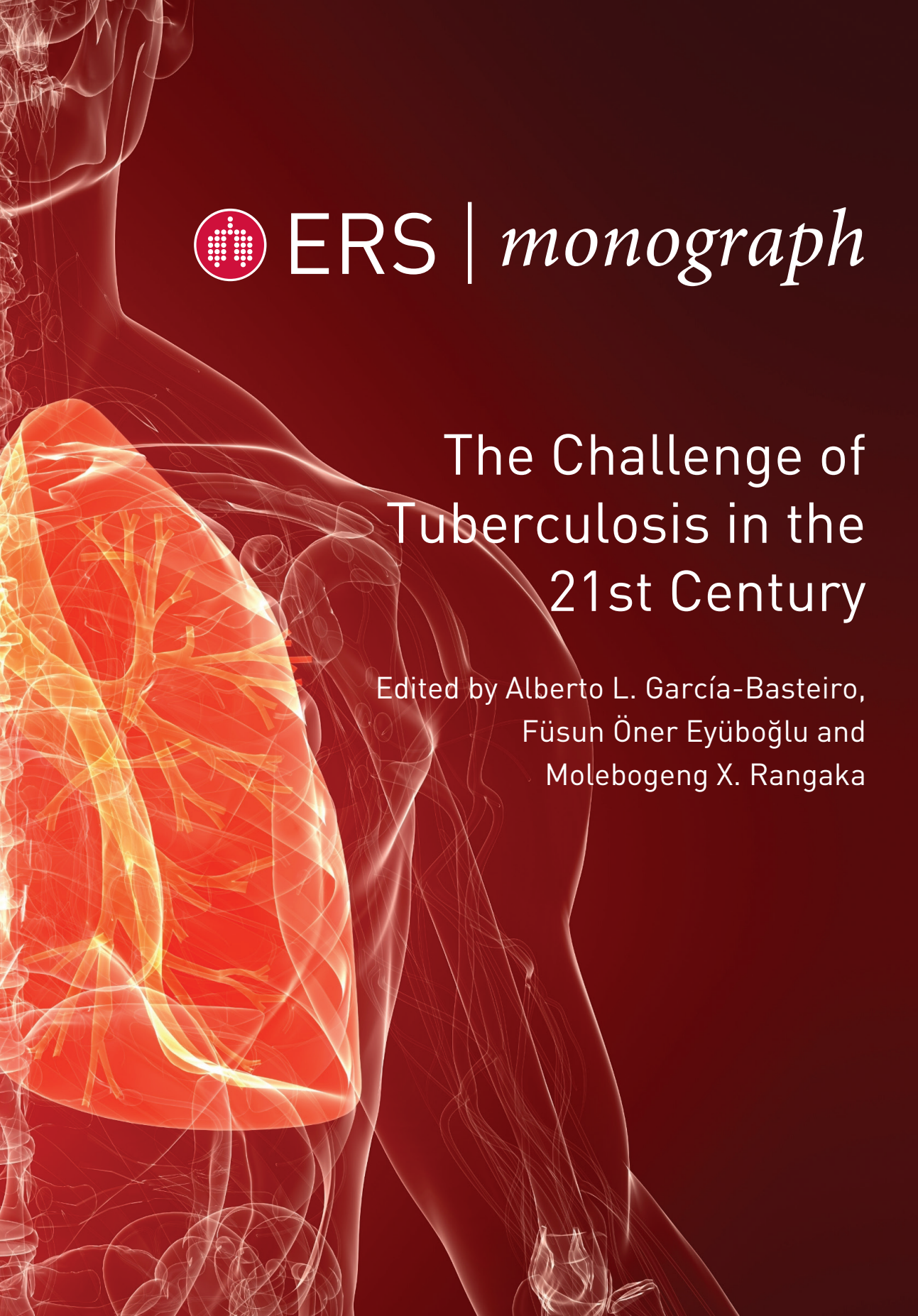

ERS | *monograph*

The Challenge of Tuberculosis in the 21st Century

Edited by Alberto L. García-Basteiro, Füsun Öner Eyüboğlu and Molebogeng X. Rangaka

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Editor in Chief
Peter M.A. Calverley

This book is one in a series of *ERS Monographs*. Each individual issue provides a comprehensive overview of one specific clinical area of respiratory health, communicating information about the most advanced techniques and systems required for its investigation. It provides factual and useful scientific detail, drawing on specific case studies and looking into the diagnosis and management of individual patients. Previously published titles in this series are listed at the back of this *Monograph*.

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The Challenge of Tuberculosis in the 21st Century

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Foreword

Tereza Kasaeva

Tereza Kasaeva
Director, WHO Global Tuberculosis Programme

We live in a world of global and local challenges: new threats, pandemics like COVID-19, climate change and natural disasters, armed conflicts and socioeconomic crises. These challenges affect many different regions and countries, and heavily impact on people's life, health and wellbeing. However, the world today is also very dynamic, with many new opportunities and unprecedented advances in science and technology – and, of course, medicine.

This is the backdrop that inspired world-renowned experts to come together as a team to develop this new issue of the *ERS Monograph*, The Challenge of Tuberculosis in the 21st Century. This *Monograph* is a consolidated, comprehensive guide to all key aspects of TB management and care, based on the latest data and WHO guidelines. It includes an overview of the progress made towards ending TB, and includes information on the latest evidence-based approaches to TB prevention, diagnosis and treatment. It also considers management of the TB response following the principles of people-centred care to address the specific needs of vulnerable groups and those with comorbidities. It places a spotlight on the importance for multisectoral engagement to address social determinants and drivers of the disease.

In recent years, TB diagnosis has expanded considerably. Methods include: molecular tests for the detection of TB disease and drug resistance; IGRAs and new antigen-based skin tests for the detection of TB infection; computer-aided detection in TB screening using digital chest radiography. Clinical trials have evaluated: new drugs and regimens for TB treatment, including MDR-TB; management of TB in children and adolescents; and preventive treatment of TB infection. These advances have informed important updates of core WHO guidelines and have resulted in improved access to the latest diagnostic tests, treatment of both drug-susceptible TB and DR-TB, and development of TPT. It is now possible to achieve treatment with a shorter administration, that is fully oral and more effective.

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Research and innovation, alongside use of the latest tools and guidelines, are essential in the mission to save millions of lives. These tools will help us realise the targets of reduced TB incidence and TB death outlined in the WHO's End TB Strategy and the *Global Strategy for TB Research and Innovation*.

This *Monograph's* authors and Guest Editors highlight that, while being a preventable and curable disease, TB remains one of the world's top infectious killers, affecting millions every year, especially in low- and middle-income countries. Progress towards achieving the global target of ending TB is lagging behind and has been pushed back by the impact of the COVID-19 pandemic. Access to WHO-recommended rapid molecular diagnostics, and new, effective and shorter TB regimens (including DR-TB treatment) remains limited. Only 60% of people with TB disease accessed treatment in 2021, according to the WHO's *Global Tuberculosis Report*. We need to do better. This *Monograph* provides clear answers on what should be done to fast-track the TB response and reach targets, saving lives.

I would like to specifically acknowledge the focus on accelerating the development of new, effective TB vaccines as a game changer in the fight against TB, and on strengthening the meaningful engagement of civil society and TB-affected communities in the TB response. I would also like to express my special appreciation of the international team of Guest Editors who brought this Monograph together – Alberto L. García-Basteiro from Spain, Füsun Öner Eyüboğlu from Turkey and Molebogeng X. Rangaka from South Africa.

In September 2023, Heads of State will come together at the second United Nations high-level meeting on TB, to deliberate on and reinvigorate commitments to end TB. This presents a landmark opportunity to strengthen global cooperation and solidarity required to recover from the COVID-19 pandemic and accelerate efforts towards ending TB. The launch of this *Monograph* is timely and can help inform stakeholders on the challenges and priorities to end this ancient disease once and for all. We have the tools, and with commitment, unity and dedication we can end TB.

T. Kasaeva is a staff member of the WHO. The author alone is responsible for the views expressed in this Foreword and they do not necessarily represent the views, decisions or policies of the WHO. This Foreword is published with the permission of the WHO.

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Preface

Peter M.A. Calverley

TB has variously been described as the "Captain of the Men of Death" and the "White Plague". Although known to the ancient Egyptians, TB cases grew exponentially in the poverty-stricken, over-crowded conditions that characterised the Industrial Revolution of the 19th century. Sadly, it continues to cause death and suffering in developing economies across the Global South.

TB is the foundational illness that respiratory medicine came into being to address by developing specialist treatments, accurate epidemiology and better systems for the delivery of care, ultimately leading to its eclipse in the Western world. One of the main reasons I became a pulmonary physician was because of the time I spent working for the late Sir John Crofton, the modest man who devised the triple therapy treatment regime that showed that TB could be cured rather than contained.

Unsurprisingly, the *ERS Monograph* has visited the topic of TB before. In 2018, G.B. Migliori and colleagues presented a masterful summary of our knowledge of this condition. However, in the short time since then there have been important developments in the diagnosis and treatment of this old foe, and this merited a further volume that summaries the new approaches to the management of TB available in the 21st century. The present volume, ably edited by Alberto L. García-Basteiro, Füsun Öner Eyüboğlu and Molebogeng X. Rangaka, meets this need and provides a wider perspective on the impact and management of TB globally. Despite many challenges and setbacks, TB remains a disease that we can defeat, if we work together. This volume offers us important insights into how we can do that.

Disclosures: P.M.A. Calverley reports receiving grants, personal fees and non-financial support from pharmaceutical companies that make medicines to treat respiratory disease. This includes reimbursement for educational activities and advisory work, and support to attend meetings.

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Guest Editors

Alberto L. García-Basteiro

Alberto L. García-Basteiro is Associate Research Professor at the Barcelona Institute for Global Health (ISGlobal) – Hospital Clínic in Barcelona (Spain) and coordinates the TB research area at the Centro de Investigação em Saúde de Manhiça (CISM) in Manhica (Mozambique). He trained as a physician at the University of Santiago de Compostela (USC) (Santiago, Spain), and finished his residency on preventive medicine and public health at Hospital Clínic in Barcelona. He completed an MSc in epidemiology at the London School of Hygiene and Tropical Medicine (LSHTM) (London, UK), and a PhD at the University of Amsterdam (Amsterdam, the Netherlands).

Alberto currently leads research focused on the study of TB in high TB-burden and high HIV-burden settings in sub-Saharan Africa, including field epidemiological assessments, novel sputum-free diagnostic evaluations, and drug and vaccine clinical trials. His interests include the burden of TB disease in different vulnerable populations and the characterisation of TB at a clinical, microbiological and social level.

Alberto has published over 170 manuscripts in peer-reviewed biomedical journals, and has attracted international funding from the European and Developing Countries Clinical Trial Partnership (EDCTP), the National Institute for Health (NIH), the Stop TB Partnership, the United States Agency for International Development (USAID), and the Bill & Melinda Gates Medical Research Institute, among others. His scientific contributions have been recognised by several international organisations. In 2017, he received the Young Investigator Prize, awarded by the International Union against Tuberculosis and Lung Disease (The Union). He also received the Early Career Member Award from the European Respiratory Society (ERS) in 2020, and the Stephen Lawn TB-HIV Research Leadership Prize from the LSHTM, the Desmond Tutu HIV Centre at the University of Cape Town (Cape Town, South Africa) and The Union in 2021.

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Füsun Öner Eyüboğlu

Füsun Öner Eyüboğlu currently practices at her private clinic and holds adjunct teaching positions at private medical schools.

She trained as a physician at the Medical School of Ankara University (Ankara, Turkey) and completed her residency on pulmonolgy at the Atatürk Chest Diseases and Surgery Center (Ankara). She was a research fellow at the Hospital of the University of Pennsylvania (Philadelphia, PA, USA) and was involved in several projects and clinical trials relating to the immunology of TB. She started work as a specialist at the Başkent University Faculty of Medicine (Ankara) in 1997 and became a professor at the same division in 2007. During this time, she established the Pulmonary Division at Başkent University and was Chair of the division from 2000 to 2016.

Füsun was a member of the Tuberculosis Advisory Board of the Turkish Ministry of Health National. Throughout her academic career, she has made a notable contribution to the education and training of medical students, as well as specialists in the field of pulmonology.

Füsun's research focuses on pulmonary infection in immunocompromised patients (solid organ transplant patients and other immunosuppressed conditions) and the immunology/diagnosis of TB. She also has expertise in the diagnosis and management of TB among immunocompromised patients.

Füsun has participated in several national and international research projects and clinical trials as principal investigator or co-investigator of the diagnosis of latent TBI in renal failure and solid organ transplant patients. She has collaborated in several TB-NET/European Respiratory Society (ERS) research projects and produced a number of peer-reviewed publications. Füsun has been the Secretary of the ERS Group "Tuberculosis and non-tuberculosis mycobacterial diseases" since 2021.

Molebogeng X. Rangaka

Molebogeng X Rangaka is a Professor in Infectious Disease Epidemiology and Public Health at the Institute of Global Health and the MRC Clinical Trials Unit, University College London (London, UK). She holds the position of honorary Associate Professor at the University of Cape Town (Cape Town, South Africa) where she has contributed to global health research in infectious diseases within the School of Public Health and the Wellcome Centre for Clinical Infectious Disease Research Institute in Africa (CIDRIAFRICA) since 2005. She is the co-Director of the Clinical Research Platform of the Wellcome-funded Discovery Platform Award.

Lele held a position at the WHO Global TB Programme as the consultant lead for TB prevention, responsible for policy development on the programmatic management of LTBI testing and treatment, with particular focus on under-resourced high-burden contexts. She is the Director of the WHO Collaborating Centre on TB Research and Innovation and the lead for the WHO global TB-IPD platform for TB treatment and outcomes at University College London.

Her research spans the epidemiology of poverty-related diseases, randomised assessment of public health technology, digital health innovation and implementation science. Her team conducts clinical trials into TB prevention across a range of multimorbidities, people at risk and world regions.

Lele sits on a number of international working groups, including TB-LEAP, the Collaboration for TB Vaccine Discovery (CTVD), the Cross-Network TB Vaccine Working Group (TB Vaccine WG), the Maternal and Child Working Group of The Union (the International Union Against Tuberculosis and Lung Disease) and the LTBI Task Force of the Stop TB New Diagnostic Working Group. She is also a member of The Lancet Digital Health International Advisory Board and UCL-TB Leadership.

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Introduction

Alberto L. García-Basteiro[1,2,3], Füsun Öner Eyüboğlu[4] and Molebogeng X. Rangaka[5,6,7]

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@ERSpublications
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.

References

1 Uplekar M, Weil D, Lonnroth K, *et al.* WHO's new End TB Strategy. *Lancet* 2015; 385: 1799–1801.
2 World Health Organization. Tuberculosis Action Plan for the WHO European Region 2023–2030: Draft for the Seventy-second Regional Committee for Europe. https://apps.who.int/iris/bitstream/handle/10665/361921/72bg06e-AP-TB.pdf Date last updated: 14 September 2022. Date last accessed: 19 July 2023.
3 Stop TB Partnership. UNHLM on TB Key Targets and Commitments. https://www.stoptb.org/advocacy-and-communications/unhlm-tb-key-targets-and-commitments Date last accessed 19 July 2023.
4 World Health Organization. Multisectoral Accountability Framework to Accelerate Progress to End Tuberculosis by 2030. Geneva, World Health Organization, 2019.
5 World Health Organization. The End TB Strategy. Geneva, World Health Organization, 2015.
6 World Health Organization. Global Tuberculosis Report 2022. Geneva, World Health Organization, 2022.
7 Swindells S, Ramchandani R, Gupta A, *et al.* One month of rifapentine plus isoniazid to prevent HIV-related tuberculosis. *N Engl J Med* 2019; 380: 1001–1011.
8 World Health Organization. WHO Consolidated Guidelines on Tuberculosis: Module 1: Prevention: Tuberculosis Preventive Treatment. Geneva, World Health Organization, 2020.
9 World Health Organization. Research and development for tuberculosis. www.who.int/observatories/global-observatory-on-health-research-and-development/analyses-and-syntheses/tuberculosis/analysis-of-tb-r-d-pipeline Date last accessed: 19 June 2023.
10 Tait DR, Hatherill M, Van Der Meeren O, *et al.* Final analysis of a trial of M72/AS01E vaccine to prevent tuberculosis. *N Engl J Med* 2019; 381: 2429–2439.
11 Nemes E, Geldenhuys H, Rozot V, *et al.* Prevention of *M. tuberculosis* infection with H4:IC31 vaccine or BCG revaccination. *N Engl J Med* 2018; 379: 138–149.
12 Tuberculosis Vaccine Initiative. Pipeline of vaccines. www.tbvi.eu/what-we-do/pipeline-of-vaccines/ Date last accessed: 19 June 2023.
13 Bagcchi S. Can mRNA vaccine tech take on tuberculosis? www.gavi.org/vaccineswork/can-mrna-vaccine-tech-take-tuberculosis Date last updated: 14 April 2022.

 https://doi.org/10.1183/2312508X.10025822

14 World Health Organization. WHO Consolidated Guidelines on Tuberculosis: Module 2: Screening: Systematic Screening for Tuberculosis Disease. Geneva, World Health Organization, 2021.
15 Nathavitharana RR, Garcia-Basteiro AL, Ruhwald M, *et al.* Reimagining the status quo: how close are we to rapid sputum-free tuberculosis diagnostics for all? *EBioMedicine* 2022; 78: 103939.
16 Broger T, Koeppel L, Huerga H, *et al.* Diagnostic yield of urine lipoarabinomannan and sputum tuberculosis tests in people living with HIV: a systematic review and meta-analysis of individual participant data. *Lancet Glob Heal* 2023; 11: e903–e916.
17 World Health Organization. Global Tuberculosis Report 2021. Geneva, World Health Organization, 2021.
18 Peter JG, Zijenah LS, Chanda D, *et al.* Effect on mortality of point-of-care, urine-based lipoarabinomannan testing to guide tuberculosis treatment initiation in HIV-positive hospital inpatients: a pragmatic, parallel-group, multicountry, open-label, randomised controlled trial. *Lancet* 2016; 387: 1187–1197.
19 World Health Organization. Consensus Meeting Report: Development of a Target Product Profile (TPP) and a Framework for Evaluation for a Test for Predicting Progression from Tuberculosis Infection to Active Disease. Geneva, World Health Organization, 2017.
20 Jindani A, Harrison TS, Nunn AJ, *et al.* High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. *N Engl J Med* 2014; 371: 1599–1608.
21 Merle CS, Fielding K, Sow OB, *et al.* A four-month gatifloxacin-containing regimen for treating tuberculosis. *N Engl J Med* 2014; 371: 1588–1598.
22 Gillespie SH, Crook AM, McHugh TD, *et al.* Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *N Engl J Med* 2014; 371: 1577–1587.
23 Dorman SE, Nahid P, Kurbatova EV, *et al.* Four-month rifapentine regimens with or without moxifloxacin for tuberculosis. *N Engl J Med* 2021; 384: 1705–1718.
24 Nyang'wa B-T, Berry C, Kazounis E, *et al.* A 24-week, all-oral regimen for rifampin-resistant tuberculosis. *N Engl J Med* 2022; 387: 2331–2343.
25 Conradie F, Bagdasaryan TR, Borisov S, *et al.* Bedaquiline-pretomanid-linezolid regimens for drug-resistant tuberculosis. *N Engl J Med* 2022; 387: 810–823.
26 World Health Organization. WHO Consolidated Guidelines on Tuberculosis: Module 4: Treatment: Drug-resistant tuberculosis treatment. 2022 Update. Geneva, World Health Organization, 2022.
27 Ryckman TS, Dowdy DW, Kendall EA. Infectious and clinical tuberculosis trajectories: Bayesian modeling with case finding implications. *Proc Natl Acad Sci USA* 2022; 119: e2211045119.
28 Emery JC, Dodd PJ, Banu S, *et al.* Estimating the contribution of subclinical tuberculosis disease to transmission – an individual patient data analysis from prevalence surveys. *medRxiv* 2022; pre-print [DOI: https://doi.org/10.1101/2022.06.09.22276188].
29 Verstraeten R, Cossa M, Martinez L, *et al.* Epidemiology: the current burden of tuberculosis and its determinants. *In*: García-Basteiro AL, Öner Eyüboğlu F, Rangaka MX, eds. The Challenge of Tuberculosis in the 21st Century (ERS Monograph). Sheffield, European Respiratory Society, 2023; pp. 18–33.
30 Frascella B, Richards AS, Sossen B, *et al.* Subclinical tuberculosis disease - a review and analysis of prevalence surveys to inform definitions, burden, associations, and screening methodology. *Clin Infect Dis* 2021; 73: e830–e841.

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List of abbreviations

ART	antiretroviral therapy
BCG	bacille Calmette–Guérin
COVID-19	coronavirus disease 2019
CXR	chest X-ray
DOTS	directly observed treatment, short course
DR-TB	drug-resistant tuberculosis
DST	drug-susceptibility testing
EPTB	extrapulmonary tuberculosis
IFN	interferon
IGRA	interferon-γ release assay
IL	interleukin
LTBI	latent tuberculosis infection
MDR-TB	multidrug-resistant tuberculosis
PLHIV	people living with HIV
PTB	pulmonary tuberculosis
RR-TB	rifampicin-resistant tuberculosis
TB	tuberculosis
TBI	tuberculosis infection
TNF	tumour necrosis factor
TPT	tuberculosis preventive treatment
TST	tuberculin skin test
WGS	whole-genome sequencing
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis