Evidence and research gaps identified during development of policy guidelines for tuberculosis

Second edition

World Health Organization

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ISBN 978-92-4-008759-0 (electronic version)
ISBN 978-92-4-008760-6 (print version)

Contents

Acknowledgements

Acronyms and abbreviations

GDG	Guideline Development Group
LF-LAM	lateral flow urine lipoarabinomannan
MDR-TB	multidrug-resistant tuberculosis
NAAT	nucleic acid amplification test
NGS	Next Generation Sequencing
RR-TB	rifampicin-resistant tuberculosis
TPT	tuberculosis preventive treatment
TB	tuberculosis
TB-LAMP	loop-mediated isothermal amplification for detection of *M. tuberculosis*
WHO	World Health Organization

Glossary

- *Discovery*: Research and development of new biomedical interventions, such as vaccines, drugs and diagnostics.

- *Clinical research*: Research conducted with human subjects (or on material of human origin, such as tissues, specimens and cognitive phenomena) for which an investigator directly interacts with human subjects to understand the mechanisms of human disease and to study and evaluate interventions and technologies, including in clinical trials (1).

- *Epidemiological research*: Quantitative analysis of the circumstances under which disease processes occur in population groups, factors affecting their incidence, distribution, and the host response and use of this knowledge in prevention and control (2).

- *Implementation research*: Scientific study of methods to promote systematic integration of research findings and other evidence-based practices into routine practice and, hence, to improve the quality and effectiveness of health services (3).

- *Economic evaluation*: Systematic appraisal of the costs and benefits of projects, usually to determine the relative economic efficiency of programmes (4).

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Executive summary

Tuberculosis is one of the leading causes of death from an infectious agent worldwide. Provision of tuberculosis treatment to people with tuberculosis and antiretroviral therapy to people with tuberculosis and HIV coinfection has saved 75 million lives between 2000 and 2022. However, disruption caused by the COVID-19 pandemic compounded with an already inequitable and inadequate health service provision, adverse impacts of armed conflicts, climate change and disasters has derailed progress. Member States have adopted a new political declaration during the second United Nations high-level meeting on tuberculosis in September 2023, with a commitment to significantly expand access to tuberculosis services, boost investment, promote human rights and accelerate research and innovation.

Achievement of this goal requires innovative tools and strategies as well as rapid progress towards universal access to health care. It is critical that global policies remain firmly grounded in the best possible evidence in order to optimize the work of national tuberculosis programmes and governments. The World Health Organization issues recommendations to guide countries in choosing life-saving interventions and effective, efficient, sustainable models of care that have an impact. Experts convened by the World Health Organization to provide advice in guideline development also have an important role in identifying important gaps in research and implementation science that would overcome barriers to better care for people affected by tuberculosis.

This document serves as an update to a previously released report with an identical title. It provides a summary of the research gaps identified by guideline development groups in the context of new revisions made to tuberculosis guidelines since the previous report was published in 2021. Additionally, it provides information about recent advances in research and development. We have confidence that it will assist decision-makers responsible for funding and implementing research in directing their research agendas more effectively towards the priorities of tuberculosis programs and the populations affected by it.

Introduction

Background

Tuberculosis (TB) is one of the leading killers due to infectious diseases worldwide, the leading killer of people with HIV infection and a major cause of death from airborne antimicrobial-resistant infections, taking heavy tolls on communities and health systems. The World Health Organization (WHO) estimates that at least 10 million people fall ill with TB, and over 1 million die from the disease annually*(1)*. The COVID-19 pandemic had disrupted access to TB services in several countries, but access to and provision of TB services is showing significant signs of recovery.

The WHO End TB Strategy in the context of the 2030 Agenda for the Sustainable Development Goals sets ambitious goals and milestones to end the epidemic by reducing incidence and mortality by 80% and 90% in 2030 from those in 2015. Reaching the 2030 global TB targets will require the development and use of technological breakthroughs and strategies, together with the necessary financial resources. In 2021, global funding for TB research was estimated to amount to US$ 1 billion, which is significantly less than the annual US$ 5 billion target set in the 2023 political declaration of the high-level meeting of the General Assembly on the fight against tuberculosis *(2, 3)*.

National TB programmes are struggling with challenges both new and old: lingering impacts of the COVID-19 pandemic, challenges in finding people with TB, the HIV/AIDS pandemic and other comorbidities and the spread of drug resistance. Evidence for policy that is informed by country-led evaluations and data that are of high quality, accessible, timely and reliable are prerequisites for setting global and national policy.

Development of global TB policy guidance continues to be challenged by a shortage of good-quality evidence, due, for example, to the lack of sufficient clinical trials that provide direct evidence of clinical benefit or improvement in an established surrogate; inaccessible data, including programme experiences of the benefits and safety of interventions in real-world setting; and evidence that does not include broader values and priorities, beyond medical interventions, such as acceptability, feasibility and equitable resource distribution and health. Evidence from well-designed, large-scale, multidisciplinary studies with robust testing of interventions is therefore necessary to improve the quality and scope of future guidance.

This document, which is an update to a previously released report in 2021 *(4)*, summarizes evidence gaps in WHO TB policy guidance to steer innovation towards sustainable, desirable, acceptable, and feasible public health interventions. Its aim is to serve as a reference for research policymakers, funders, civil society and other relevant actors on the urgent priorities for research for setting TB policy.

Methodology

The Global TB Programme is mandated to provide global leadership in the TB response, including by setting norms and standards and shaping the TB research and innovation agenda, in line with pillar 3 of the End TB Strategy. WHO Global TB Programme therefore convenes guideline development groups (GDGs) to make recommendations to guide clinical practice and public health policy for TB prevention and care in response to demand from public health decision-makers.

GDGs include users of the guidelines, such as policymakers from government, professional associations and other constituencies, and also researchers, epidemiologists, health-care workers and civil society representatives. WHO TB GDGs provide recommendations by reviewing evidence according to the standard framework of population, intervention, comparator and outcomes (PICO) and the GRADE method

(Grading of Recommendations, Assessment, Development and Evaluation)[1] *(5-7)*. These tools permit systematic study of relevant evidence, formulation of recommendations and identification of gaps that must be addressed by high-quality research conducted in various epidemiological, demographic and geographical settings.

This document consolidates and analyses these gaps considered by successive GDGs to be critical to increase the certainty of existing recommendations or to stimulate the development or optimization of new technologies, approaches or methods of delivery that would improve patient health and welfare. In the following section, the research gaps are synthesized and analysed across the cascade of care, highlighting the main evidence needs they reflect, and taking into consideration the research domains they encompass, including discovery, economic evaluation, clinical, epidemiological, and implementation research. The source documents (TB guidelines) used for this exercise are listed in Table 1.

Table 1. TB guidelines in the different modules

Module	Guidelines	Year last updated
Module 1: Prevention	WHO consolidated guidelines on tuberculosis preventive treatment *(11)*	2020
	WHO guidelines on tuberculosis infection prevention and control *(12)*	2019
Module 2: Screening	WHO consolidated guidelines on systematic screening for tuberculosis disease *(13)*	2021
Module 3: Diagnosis	WHO consolidated guidelines on rapid diagnostics for tuberculosis detection *(14)*	2021
	WHO consolidated guidelines on tests for tuberculosis infection *(15)*	2022
	WHO consolidated guidelines on targeted next generation sequencing for the detection of drug-resistant tuberculosis *(16)*	2023
Module 4: Treatment	WHO consolidated guidelines on drug-resistant tuberculosis treatment *(17)*	2022
	WHO consolidated guidelines on drug-susceptible tuberculosis treatment *(18)*	2021
	WHO consolidated guidelines on tuberculosis care and support *(19)*	2022
Module 5: Management of TB in children and adolescents	WHO consolidated guidelines on management of tuberculosis in children and adolescents *(20)*	2022
Module 6: Comorbidities	Nutritional care and support for people with tuberculosis *(21)*	2013
	Integrating collaborative TB and HIV services within a comprehensive package of care for people who inject drugs *(22)*	2016
	WHO consolidated guidelines on the management of TB and comorbidities *(9)*	2023

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[1] The GRADE method is a tool for rating the quality of evidence and grading the strength of recommendations for use in summarizing evidence for systematic reviews and in clinical practice guidelines and health technology assessments.

Analyses of research questions from TB policy guidelines

The most recent WHO policy guidelines in TB screening, prevention, diagnosis, treatment and care are summarized by module in WHO's TB knowledge sharing platform (Box 1). Table 2 shows the 302 research questions extracted from relevant guidelines by module and research domain: 21 are related to screening, 76 to diagnosis, 42 to prevention, 85 to treatment, 40 to the management of children and adolescents and 38 to TB related comorbidities. Most of the gaps were on implementation research (52%), followed by clinical research (32 %).

Table 2. Numbers and types of research gaps by WHO TB guideline module

TB guideline module	No. of research questions (N=302)	Characterization of research gaps by research domain (%) [a]				
		Discovery (3%)	Clinical research (32%)	Economic evaluation (8%)	Epidemiological research (5%)	Implementation research (52%)
Prevention	42	5%	31%	5%	12%	47%
Screening	21	5%	10%	14%	10%	62%
Diagnosis	76	5%	15%	11%	1%	68%
Treatment	85	2%	55%	6%	4 %	33%
Management of TB in children and adolescents	40	3%	33%	15%	-	50%
Comorbidities	38	-	26%	3%	8%	63%

[a] See Annex 1 for definitions of the research domains used in this document.

With regard to **prevention**, about one fifth of the research gaps are for clinical evidence on interventions that could significantly support national scaling-up of the provision of TB preventive therapy (TPT). These include specific, sensitive tests for TB infection, biomarkers of risk of progression to active disease and better treatment options for contacts of people with drug-resistant TB. The remaining gaps identified were for evidence on the best technologies and strategies for TB infection testing, treatment, and infection control.

Systematic screening is an important part of prevention and care. Most of the research gaps identified were for evaluation of the efficiency and impact of tools and strategies to increase confidence in existing recommendations and to inform future recommendations. In 2022, the WHO-recommended rapid molecular test was used as the initial diagnostic test in only 47% of the 7.5 million people newly diagnosed with TB. A considerable proportion of the gaps in **diagnosis** pertained to implementation research aimed at optimizing the utilization of diagnostic tools. This includes acquiring additional evidence on health impacts, exploring their use in various subpopulations, and evaluating the feasibility of alternative biospecimens for testing.

Most of the research gaps under **treatment** (55%) relate to the need for clinical evidence to optimize treatment of drug-resistant forms of TB. For example, stronger evidence on the efficacy, safety and tolerability of regimens; optimization of the composition, dosage and duration of regimens and drugs for various population groups; and the development of patient-friendly drug formulations. Others include identification and validation of biomarkers to monitor treatment response and better monitoring of adverse outcomes.

The gaps in research concerning the management of TB in **children and adolescents** were largely within the implementation (50%) and clinical research (33%) domains. The focus is on optimizing and expanding access to recommended treatment regimens, enhancing the health impact of diagnostic and treatment decision algorithms, and optimizing the utilization of healthcare resources. The list complements research gaps outlined in other documents and guidelines*(8, 9)*.

Evidence gaps related to management of TB related **comorbidities** such as mental health, HIV, diabetes, and substance use disorders, are listed across the relevant sections in prevention, screening, diagnosis and treatment of TB. Specific evidence needs on the best ways to provide care for people with undernutrition, people who inject drugs, as well as people with HIV are described separately under module 6. WHO is in the process of updating its consolidated guidelines and operational handbooks on TB and comorbidities to include HIV, diabetes and undernutrition, which will include research gaps for these comorbidities. Overall, a multisectoral approach is essential to conduct studies that examine and tackle the socio-economic determinants and repercussions of TB, including issues such as poverty, undernutrition, and drug use. In 2022, the burden of TB cases attributable to undernourishment was a staggering 2.2 million (one fifth of the total annual estimated incidence)*(1)*.

The demand for safer, more effective, affordable, people-centred tools for screening, diagnosis and treatment of TB, including for children and adolescents, was also reflected in the various guidelines. Requests for more evidence on the **costs and cost–effectiveness** of interventions was a cross-cutting issue in several guidelines. To complete the cycle of translating findings into "practice-ready" guidance, the socio-economic contexts within which an intervention is to be implemented must be considered. Guideline users and other stakeholders typically have additional questions, including on the **acceptability and feasibility** of interventions and the impacts of interventions on **equity** and human rights. Qualitative research questions on these topics appear in some guidelines, particularly on treatment for drug-resistant TB, in which patients face the compounded impact of long illness, stigmatization, catastrophic costs,

disability and death. Closing such evidence gaps requires input from many disciplines. Since 2020, the WHO Global TB Programme has been organizing an annual multistakeholder consultation on translation of research into policy *(10)* to identify the demands of Member States for policy and evidence and to discuss challenges in the fields of policy implementation and scale up (Box 2).

The research questions listed in the present document are those identified during the latest updating of guidelines and reflect evidence gaps at the policy and implementation interface. Addressing these gaps will thus significantly improve the effectiveness and efficiency of interventions. The research gaps were documented as they arose during the evidence review and were agreed by consensus of GDG members. For example, determination by the GDGs that the certainty of evidence was low or very low usually indicated that further research was necessary in the area.

Box 2. WHO consultation on translation of research into policy

WHO GDGs translate health research findings into policy recommendations based on the best available evidence. However, several factors slow or impede transfer of global TB policy guidance into practice. WHO has been organizing an annual consultation to discuss the most topical requirements of Member States for TB policy, including operational guidance to implement the recommendations within the national social, economic, cultural and capacity context. These exchanges between scientists, policymakers, funders, civil society and implementers, also highlight challenges in testing and evaluating interventions to provide the best available evidence and on the best strategies to enhance implementation and evaluation of global TB policy guidance.

WHO is committed to periodic updating and dissemination of the research gaps listed in this report to reflect new developments as they emerge. The research gaps are listed as they appear in the guidelines and not in any order of priority. The listing includes topics and questions that may be addressed by research that is already planned or advancing.

Research gaps

This section lists the research questions by TB guideline module. The guidelines and the year in which they were last updated are summarized in Table 1.

Module 1: Prevention

1.1   TB preventive treatment

- Risks for progression to active TB: Data on the likelihood of progression from infection to active TB in different at-risk populations will help in determining the potential benefits of TPT and for designing appropriate public health interventions. In particular, strong evidence from clinical trials is lacking, particularly for indigenous populations and people under the following circumstances: diabetes, harmful use of alcohol, tobacco smoking, underweight, silica exposure, on steroid treatment, rheumatological diseases and cancer. Both direct measurement of the incidence of active TB and methods for measuring the risk of active TB disease could be explored, such as use of genotyping to investigate reactivation. Evidence is also required on the differential harm and the acceptability of testing for TB infection and TPT in specific risk groups, including socially adverse effects such as stigmatization.
- Define the best screening and diagnostic algorithm for ruling out active TB: Operational and clinical studies should be conducted on how to exclude active TB before TPT is given. The performance and feasibility of the algorithms proposed in these guidelines should be assessed. In particular, few data are available on children and pregnant women. Better evidence is required to identify the best strategies for tracing contacts, reducing cost and improving feasibility (e.g., use of mobile chest radiography).
- Better diagnostic tests and performance of tests for TB infection in at-risk populations: Diagnostic tests with better performance and predictive value for progression to active TB are critical. In addition, the performance of TB infection tests should be evaluated in various risk groups to assess reinfection and to understand how best to use the available tools in each population (e.g., combination or sequential use of tuberculin skin test and interferon-γ release assay).
- *Treatment options for TB infection*: Research to find shorter, better-tolerated TPT regimens than those currently recommended remains a priority. Studies of efficacy and adverse events in certain risk groups (e.g., people who use drugs, people who engage in harmful use of alcohol and older people) are essential.
    - Very few data are available on the use of rifapentine in children < 2 years and in pregnant women. A trial on 1 month of rifapentine plus isoniazid given daily to children and adults not infected with HIV and in people living with HIV with low CD4 counts, in different settings, would also be desirable. A direct comparison of 1 month of rifapentine plus isoniazid given daily with 3 months of rifapentine plus isoniazid given weekly for safety, effectiveness and cost–effectiveness would be useful.
    - Studies of pharmacokinetics could help establish an optimal daily dosage of rifapentine in children under 13 years and interactions between rifamycin-containing regimens and other medicines, particularly antiretroviral therapy, in both adults and children. In addition, the durability of protection of different TPT regimens, including long acting injectables, should be evaluated in settings in which TB is endemic, including the efficacy of repeated TPT. Studies of the preferences for various regimens of people offered treatment and their caregivers would be helpful.
- *Monitoring of adverse events*: Prospective randomized studies are required to determine the incremental benefits of routine monitoring of liver enzyme levels as compared with education and clinical observation alone for preventing severe clinical adverse events, with stratification of the evidence by at-risk population.

- Programmatic data collection and analysis on maternal and pregnancy outcomes, including post-natal follow-up of the child, could supplement current knowledge about the safety of different TPT regimens when used in pregnancy.
- *Drug resistance and TPT*: Programme-based surveillance systems and clinical studies are necessary to monitor the risk of resistance to the medicines used in TPT. Particular consideration should be given to rifamycin-containing regimens because of the dearth of data. In addition, studies should be conducted on the impact on preventive treatment of high levels of resistance to isoniazid and/or rifamycins among prevalent TB strains.
- *Adherence to and completion of treatment*: Carefully designed studies, including randomized controlled trials, are required to generate evidence on the effectiveness of context-specific interventions to enhance adherence and completion of treatment. The studies should include specific risk groups, depending on the available resources and the health system infrastructure, and address questions about integration of TPT into differentiated models of HIV service delivery. Use of digital technologies to improve adherence is an important area. Further research is required on the effectiveness of self-administration of the 3-month regimen of weekly rifapentine plus isoniazid.
- *Cost–effectiveness:* Although a number of studies of the cost-effectiveness of TPT are available, their wide heterogeneity obviates a comprehensive appraisal of the cost-effectiveness of TB infection management stratified by population group, type of regimen or intervention. Cost-effectiveness analysis with parameters from different resource settings could allow better planning for extension of national or local programmatic management of a TPT strategy.
- *Preventive treatment for contacts of people with multidrug-resistant TB*: The WHO recommendation on preventive treatment for multidrug-resistant TB (MDR-TB) should not discourage continued studies or raise ethical questions. Randomized controlled trials with adequate power are urgently required to update the recommendation on preventive treatment for contacts of people with MDR-TB or rifampicin-resistant TB. Trials should be performed with both adult and paediatric populations and with at-risk populations such as people living with HIV. The composition, dosage and duration of preventive treatment regimens for MDR-TB should be optimized, and the potential role of newer agents with good sterilization properties should be investigated. The effectiveness and safety of preventive treatment for contacts of people with MDR-TB should be evaluated under operational conditions. Further evidence on the risk of contacts of people with MDR-TB for progression to active TB will be important to understand the benefits of preventive treatment.
- *Improving TPT service delivery according to country context:* Continued epidemiological research should be conducted to determine the burden of TB infection in various geographical settings and risk groups and as a basis for nationally and locally tailored interventions, including integrated community approaches. Implementation research on context-specific barriers and facilitators should be conducted for different TPT regimens, to explore dimensions for which evidence is often sparse, such as acceptability, feasibility, equity and resource use. Research is also required on service delivery models to improve management, including the provision of additional interventions for smokers and harm-reduction services for people who use drugs or who engage in the harmful use of alcohol or are in prison. Household implementation models could increase the effectiveness and efficiency of delivery of interventions. Evidence from future trials could guide better optimization of contact-tracing strategies in households and elsewhere. Tools should be developed and assessed to facilitate monitoring and evaluation of programmatic management of TPT to improve future global guidance.

1.2   Infection prevention and control

The general research gaps listed below are to be prioritized for all infection prevention and control interventions:

- *Individual effect of interventions*: Most of the studies for this guideline addressed the effect of composite measures. Consequently, the effect of a single component of infection control could not be accurately

assessed. Further high-quality prospective studies (e.g., with randomized designs) should be conducted to evaluate the effect of single interventions.

- *Better-quality studies*: Most of the research on which these recommendations are based were uncontrolled before-and-after studies. This design is considered most useful in demonstrating the immediate impacts of short-term interventions but is less valuable for evaluating long-term interventions, as other temporal factors may obscure the effects of an intervention. Modelling may improve understanding of likely effects and cost–effectiveness, if appropriately parameterized. Alternative study designs such as randomized controlled trials should be considered to minimize bias. Experimental studies in which outcomes are measured in animals may also provide useful evidence of the effect of selected interventions on transmission – a particular advantage of these studies being that individual infection prevention and control interventions may be studied one at a time.

- *Cost–effectiveness*: Limited evidence is available on the cost–effectiveness of infection prevention and control measures, other than treatment of TB disease. Information from cost–effectiveness research is required to organize infection prevention and control at all levels of care and in other at-risk settings (e.g., congregate settings) in such a way that benefits can be optimized within available resources, especially in resource-limited and high-TB burden areas.

- *Feasibility and impact of infection prevention and control guidelines locally*: Countries are encouraged to apply implementation science to systematic evaluation of the introduction of TB infection prevention and control standards both nationally and sub-nationally.

- Further research is required to strengthen understanding of the incidence of *M. tuberculosis* infection and TB disease, including its drug-resistant forms, among health workers and other high-risk populations.

The GDG further identified research priorities for individual interventions, as outlined below.

- *Triage*: Evaluation of different approaches to triage in general, including requirements and priorities for specific individuals with comorbidities such as HIV and noncommunicable diseases (e.g., triage strategies in HIV facilities and in noncommunicable disease programmes).
- *Respiratory isolation*: Evaluation of the appropriate duration of respiratory isolation necessary to minimize the risk of infection to others.
- *Rapid diagnosis and initiation of effective treatment*: Determination of the effect of treatment on the duration of infectiousness of TB patients.
- *Respiratory hygiene*: High-quality studies of the effectiveness of surgical masks and non-mask respiratory hygiene interventions in a clinical setting.
- *Respiratory protection programmes*: Evaluation of the duration of effectiveness of filtering particulate respirators.
- *Upper-room germicidal ultraviolet light systems*: Direct evidence, including programme data, on the effectiveness of upper-room germicidal ultraviolet light on outcomes that are important to patients and health workers and further research on safe, effective upper-room germicidal ultraviolet light dosing by space volume (in cubic feet or metres) to guide implementation.
- Ventilation systems

  o effect of different air exchange rates in mechanical ventilation systems on transmission of *M. tuberculosis*.

  o effect of mechanical ventilation modes on the microclimate of mechanically ventilated settings.

  o high-quality research on the effect of portable room-air cleaners; and

  o further research on ventilation parameters for portable room-air cleaners and target product profiles for these devices.

Module 2: Screening

2.1 Screening for TB in targeted populations

The General population and high-risk groups

- Well-designed trials and rigorous quasi-experimental studies in various settings are required to investigate the effects of systematic, population-wide screening for TB on individual outcomes (diagnostic delay, treatment outcomes, costs to patients, social consequences) and population outcomes (TB prevalence, incidence, transmission) as well as to guide implementation choices, including the method of delivery, screening algorithms, the duration of screening intervals and frequency of screening and the mode of delivering intervention.

- Research on the longer-term impacts of screening, including whether morbidity or mortality is averted

- Research on the cost–effectiveness of screening, with longer time horizon to adequately capture all potential costs and longer-term effects, including potentially reduced future prevalence and incidence.

- Carefully designed observational research and programmatic evaluations of the impact of community-wide screening on TB case notification rates, which are an important source of evidence on the impacts of screening under programmatic conditions.

- Studies of screening interventions that incorporate both qualitative and quantitative assessment of the indirect effects of screening are necessary because of the significance of health-seeking behaviour in engagement in TB care (and the potential impact of population-wide screening to change it), as well as the importance of assessing any unintended mental, social or economic consequences of screening (including adverse effects, the burden of the test and downstream outcomes of clinical management guided by the outcomes of the test).

People living with HIV

- Well-designed clinical trials are necessary to strengthen the evidence on the accuracy, effectiveness (including the impact on patient-important outcomes such as mortality), feasibility and cost implications of using the WHO-recommended four-symptom screen, C-reactive protein, chest radiograph and molecular WHO-recommended rapid diagnostic test to screen for TB in all HIV subpopulations in settings with low, medium and high burdens of HIV and TB, with and without high antiretroviral therapy coverage. Subpopulations of people living with HIV for whom further investigation is required would include inpatients, people in acute care, patients for whom antiretroviral therapy have failed, patients newly diagnosed as HIV-positive enrolling in antiretroviral therapy clinics, stable patients established on antiretroviral therapy, pregnant women and children and adolescents living with HIV.

- More data are needed on the effectiveness, cost–effectiveness, feasibility, acceptability, frequency and optimal periodicity of routine, regular screening with the WHO-recommended four-symptom screen, C-reactive protein, chest radiograph and molecular WHO-recommended rapid diagnostic test among people living with HIV. Specifically, more studies should be conducted on the optimal placement of molecular WHO-recommended rapid diagnostic tests for screening: in antenatal care settings or in antiretroviral therapy clinics.

- Research should be conducted on the potential use of screening specimens other than sputum from people living with HIV in molecular WHO-recommended rapid diagnostic tests.

Children and adolescents

- The GDG considered data on use of molecular WHO-recommended rapid diagnostic tests for screening children and adolescents who access health care as outpatients. They concluded that the data, which comprised two studies with 787 participants, with substantially heterogeneous results, provided insufficient evidence to establish an accurate, reliable estimate of the diagnostic accuracy of molecular WHO-recommended rapid diagnostic tests. Thus, the GDG decided not to issue a recommendation on their use as a screening tool for children and adolescents. More rigorous studies should be conducted of the use of molecular WHO-recommended rapid diagnostic tests for screening this population.

- The GDG also highlighted the urgent requirement for more research and better screening tools and approaches for use in this population, including more data on screening approaches that target specific and distinct age ranges, including infants < 12 months, children < 5 years, children ≤ 10 years and those aged 10–19 years.

- More data are needed to determine the frequency with which screening should be conducted among the subpopulations of children at highest risk of TB, and well-designed clinical trials are necessary to provide evidence on patient-important outcomes for TB screening in children.

2.2 Tools for screening TB

Computer-aided detection

- Develop additional evidence about the performance of computer-aided detection software stratified according to the characteristics of the individual being evaluated (e.g., by smear status, HIV status, age cohort, history of TB, smoking status, and sex) to allow for better setting-specific and patient-specific calibration of computer-aided detection programmes.
- Assess users' perspectives about computer-aided detection technologies in TB screening and triage, including their perceived acceptability to patients, providers and other stakeholders.
- Develop and evaluate computer-aided detection programmes for automated detection of TB in children, considering that chest radiograph is an important tool for detecting pulmonary TB in children and adolescents, given the difficulty of bacteriological testing and diagnosis.

C-reactive protein

Evaluate the accuracy and predictive value of measuring C-reactive protein above any cut-off higher than 5 mg/L (alone or in combination with other screening tests) for screening TB among people living with HIV in different TB prevalence settings.

Screening algorithms

Across all populations and tools, more research is needed to evaluate the accuracy and effectiveness of complete screening and diagnostic algorithms, including symptom screening, chest radiograph, C-reactive protein and molecular WHO-recommended rapid diagnostic tests used in various combinations with diagnostic evaluation. Research into their effectiveness should include measures of the impacts on patient-important outcomes, such as mortality and treatment success.

Standard monitoring and evaluation procedures may be complemented by operational research aimed at improving the performance of screening in the local setting as well as research aimed at improving the global evidence base for screening. Topics that may be explored include:

- Assess the accuracy and performance of different algorithms for screening and diagnosis.
- Identify operational challenges and solutions.
- Identify the best ways to improve acceptability and minimize the harms of screening.
- Establish the effectiveness and cost–effectiveness of screening in different risk groups and in different epidemiological situations.
- Establish local calibration of computer-aided detection software for the specific case of a programmatic use.

Overall, there is a need for larger and better randomized trials to assess the short-term and long-term effectiveness and cost–effectiveness of screening.

Module 3: Diagnosis

Priorities for further research on diagnostics are listed below, grouped for each technology. These should not discourage or restrict further research on new, rapid molecular tests for TB and detection of drug resistance, especially on assays that can be used as close as possible to where patients with a presumptive diagnosis of TB are identified and where treatment can be initiated.

3.1   Initial molecular tests for diagnosis of TB, including drug resistance

- Evaluation of the impact of Xpert MTB/RIF Ultra, Truenat assays and moderate-complexity, automated nucleic acid amplification testing (NAAT) on outcomes that are important for patients (cure, mortality, time to diagnosis and time to starting treatment).

- Evaluation of the benefit of testing several types of specimens. Limited data suggest that testing of a combination of non-invasive specimens is comparable to traditional testing of gastric or induced-sputum specimens.

- Additional operational and qualitative research to determine the best approach to less invasive specimen collection.

- Implementation studies on a method of suction for nasopharyngeal aspiration that is appropriate for low-skill or low-resource environments.

- Extensive operational research on use of stool as a diagnostic specimen in terms of integration into usual diagnostic clinical pathways, definition of laboratory protocols that balance ease of implementation and diagnostic performance and the impact on outcomes important for patients. Little qualitative research is available on the preferences of children and families for and the acceptability of different diagnostic approaches.

- Identification of an improved reference standard to accurately define TB disease in children and in paucibacillary specimens, as the sensitivity of all the available diagnostics is suboptimal.

- Development of new tools for correct diagnosis of a higher proportion of child TB cases. Ideally, the new tools will be rapid, affordable, feasible and acceptable to children and their parents.

- Comparison of NAATs to determine which tests (or strategies) have better diagnostic accuracy. The preferred study design is one in which all participants receive all available diagnostic tests or are randomly assigned to receive a particular test. Studies should include children and HIV-positive people. Future research should acknowledge the concern about use of culture as a reference standard and should consider ways to address this limitation.

- Development of rapid point-of-care diagnostic tests for pulmonary and extrapulmonary TB, applicable to all individuals with presumptive TB. Research should focus on developing diagnostic tests and strategies in which readily available clinical specimens are used, such as urine, rather than specimens that require invasive procedures for collection.

- Operational research to ensure that tests are used optimally in the settings of their intended use.

- Evaluation of the diagnostic accuracy of Truenat (MTB, MTB Plus and MTB-RIF) and moderate-complexity, automated NAATs in specific patient populations, such as people living with HIV and former TB patients, for pulmonary and extrapulmonary TB in adults and children.

- Impact of specific mutations on treatment outcomes among people with drug-resistant TB.

- Use, integration and optimization of diagnostic technologies in overall testing and care and in diagnostic pathways and algorithms.

- Economic studies of the costs, cost–effectiveness and cost–benefit ratio of different NAATs.

- Qualitative studies of equity, acceptability, feasibility and end-user values of different diagnostic technologies.

- Effect of indeterminate, non-determinate or invalid results on diagnostic accuracy and outcomes that are important to patients.

- Operational research on the advantages and disadvantages of individual moderate-complexity, automated NAATs.

- Effect of moderate-complexity, automated NAATs in fostering collaboration among and integration of disease programmes.

- Studies of the potential utility of detecting *katG* resistance to identify MDR-TB clones that may be missed if they do not have an *RRDR* mutation (e.g., the Eswatini MDR-TB clone, which has both the *katG* S315T and the non-RRDR *rpoB* I491F mutation).

3.2 Initial biomarker tests for the diagnosis of TB but not drug resistance

3.2.1 Lateral flow lipoarabinomannan (LF-LAM) assay in urine

- Development of simple, more accurate tests based on lipoarabinomannan detection, which could be used in HIV-negative populations.

- Evaluation of the use of the LF-LAM assay in people living with HIV without signs or symptoms of TB.

- Evaluation of the use of the LF-LAM assay in children and adolescents with HIV.

- Evaluation of parallel use of the LF-LAM assay and a rapid qualitative CD4 cell count.

- Implementation research on the acceptance, scaling-up and impact of use of the LF-LAM assay in routine clinical settings.

- Qualitative research on user perspectives of the LF-LAM assay for feasibility, accessibility and equity.

- Implementation research on use of the LF-LAM assay integrated into HIV care packages.

- Evaluation of the performance of the LF-LAM assay as the HIV epidemic evolves and more people on treatment with viral load suppression are hospitalized.

- Evaluation of the cost–effectiveness of the LF-LAM assay.

- Evaluation of other rapid LAM-based tests, such as Fujifilm SILVAMP TB LAM.

- Diagnostic accuracy of the LF-LAM assay in specific patient populations (e.g., children, people living with HIV and patients with signs and symptoms of extrapulmonary TB) and in non-sputum samples.

- Impact of diagnostic technologies on clinical decision-making and outcomes that are important to patients (e.g., time to diagnosis, time to treatment initiation, cure and mortality) in all patient populations.

- Evaluation of means to improve the overall use, integration and optimization of diagnostic technologies in overall testing and care and in diagnostic pathways and algorithms.

- Study of the effect of indeterminate, non-determinate or invalid results on diagnostic accuracy and outcomes that are important to patients.

- Evaluation of low-complexity, automated NAATs for initial TB detection, in addition to its use as a follow-on test, in all people with signs and symptoms of TB, including children and people living with HIV; and interpretation of the results of a high-complexity, hybridization-based NAAT assay as compared with sequencing and newer evidence on genotypic and phenotypic associations.

3.2.2 *Loop-mediated isothermal amplification for detection of* M. tuberculosis *(TB-LAMP)*

- Evaluation of diagnostic algorithms in different epidemiological and geographical settings and patient populations, including among people living with HIV.

- Rigorous studies on TB-LAMP, with higher-quality reference standards (including various specimen types and extrapulmonary specimens) to improve confidence in estimates of its specificity.

- Determination of training needs and assessment of competence and quality.

- Studies on the impact of TB-LAMP on TB treatment initiation and on morbidity and mortality.

- Assessment of performance in analyses of cost–effectiveness and cost–benefit of targeted TB-LAMP use in specific countries.

- Use of the Standards for Reporting Diagnostic Accuracy Studies statement *(23)* in diagnostic research to improve the quality of reporting.

3.3   Follow-on diagnostic tests for detection of additional drug resistance

- Improve understanding of the correlation between detection of resistance-conferring mutations, culture-based drug susceptibility testing and patient outcomes.

- Review evidence to confirm or revise the critical concentrations used in culture-based drug susceptibility testing.

- Improve knowledge about the correlation between specific mutations detected with follow-on NAATs and the minimum inhibitory concentrations of individual drugs.

- Determine the limit of detection of follow-on NAATs for heteroresistance.

- Determine the requirements for training, assessment of competence and ensuring quality assurance.
- Collect more evidence on the impact on mortality of initiating appropriate treatment for MDR-TB.
- Use the Standards for Reporting Diagnostic Accuracy *(19)* in future diagnostic studies.
- Perform cost–effectiveness and cost–benefit analyses of use of follow-on NAATs in specific countries.

3.4 Targeted next generation sequencing for the detection of drug-resistant tuberculosis

3.4.1. Clinical research:
- Conduct clinical trials to assess the impact of targeted next generation sequencing (NGS) on patient-important outcomes.
- Evaluate the accuracy and effectiveness of targeted NGS among populations composed of individuals diagnosed with TB, without enrichment for rifampicin or other drug resistance.
- Assess the accuracy and effectiveness of targeted NGS for detecting resistance to new and repurposed drugs, including pretomanid, across varied geographic and epidemiologic settings.
- Assess the accuracy and effectiveness of targeted NGS for analysing extra-pulmonary samples, including cerebrospinal fluid for meningitis, non-sputum samples (such as nasopharyngeal aspirate, gastric aspirate, stool) for children, and alternative sample types (e.g., tongue swabs) in both adults and children.
- Undertake additional qualitative and quantitative research to further understand the perspectives of end-users and clinicians regarding the acceptability and feasibility of using targeted NGS.

3.4.2. Implementation research priorities:

- Develop and evaluate effective and efficient implementation models by integrating targeted NGS into laboratory networks and optimising algorithms, aiming to enhance timely access to testing, treatment initiation and improve patient outcomes.
- Develop strategies to enhance the efficiency of targeted NGS testing, including sample processing and concentration techniques, determining optimal thresholds of bacterial load from initial tests before performing targeted NGS, and employing molecular transport medium for ambient storage and transfer of samples to testing sites.
- Explore technological advancements to simplify the testing process, automate steps (especially library preparation), develop decentralised targeted NGS solutions, and investigate potential synergies with existing initial tests (e.g., utilising leftover DNA or smear-positive slides).
- Conduct comprehensive mapping of sequencing capacity within countries and perform diagnostic network optimisation exercises. Placement of the technology should consider the demand for sequencing across multiple diseases, facilitating cross-disciplinary use of the machines and shared costs.
- Compile and utilise lessons learned from applying targeted NGS technology in other diseases (e.g., from the response to the COVID-19 pandemic-19) to guide implementation strategies for TB effectively.

3.4.2. Monitoring and evaluation needs
- Regularly monitor performance data, including overall resistance rates, resistance rates by specific drugs or targets and turnaround times (both total and in-laboratory).
- Incorporate quality monitoring measures, such as tracking indeterminate rates, sequencing coverage and depth, and participation in external quality assurance programs.
- Establish an external quality assurance program for sequencing that covers all relevant targets of interest.

- Integrate the sequencing data generated into existing surveillance systems to monitor the prevalence and trends in drug resistance effectively. Share the data to update the WHO mutation catalogue.
- Collect cost data to address important questions, such as the costs associated with introducing and scaling up targeted NGS in different settings, the trade-offs between turnaround time and batching, and the optimal balance in various settings.
  - Assess the impact of multi-disease testing on program operations and costs, including disease-specific testing volumes, turnaround times, costing, resource sharing, and resource requirements.
  - Evaluate the impact of time to treatment initiation/modification, treatment outcomes, and overall cost-effectiveness of targeted NGS implementation.

3.5   Tests for TB infection

3.5.1. Use of Mycobacterium tuberculosis antigen-based skin tests for the diagnosis of TB infection

- Improve knowledge of specificity of Diaskintest and C-TST in populations with a low prevalence of TB infection and implement direct head-to-head comparisons across all three antigen-based skin tests.
- Characterize the barriers for implementation of TB infection tests, including barriers faced by patients when seeking access.
- Conduct studies to measure of accuracy of these tests among high-risk groups, including children and adolescents, HIV-positive people, prisoners and migrants.
- Evaluate the health and economic impact of TB antigen-based skin tests in the context of TB infection diagnosis, as well as in the context of linkage to TB preventive treatment.
- Measure the potential of TB antigen-based skin tests in predicting active TB disease compared with current tests, through longitudinal studies.
- Conduct economic studies (e.g., cost and cost–effectiveness of TB antigen-based skin tests under different scenarios).
- Evaluate the potential of digital technologies for reading results, to avoid return patient visits.

3.5.2. Use of the TST and IGRAs for the diagnosis of TB infection
- Develop or optimize diagnostic tests to attain improved performance and predictive value to measure progression to active TB.

3.5.3. Use of the TST and IGRAs for the diagnosis of TB disease
- Develop IGRAs with improved accuracy to diagnose TB disease through robust study design and quality principles such as inclusion of relevant risk groups in studies, prospective follow-up, and adequate blinding.
- Follow up promising proof-of-principle studies by developing additional evidence through prospectively implemented and well-designed evaluation and demonstration studies, including with respect to impact on patient health.

Module 4: Treatment

4.1   Drug-susceptible TB

Research gaps identified in the WHO guidelines on treatment of drug-susceptible TB *(18, 24)* are summarized below.

4.1.1 Comparison of the effectiveness of fixed-dose combination TB treatment with separate drug formulations in patients with drug-susceptible TB disease

- Conduct additional research on why fixed-dose combination formulations do not show a clear benefit over separate drug formulations.
- Conduct pharmacokinetics studies of the bioavailability of fixed-dose combinations and of separate drug formulations and develop better weight-banding categories for drug dosing.
- Establish the optimal dose of rifampicin, including in different drug formulations, for all age groups.
- Conduct additional qualitative studies on adherence to medication.
- Conduct additional work on fixed-dose combination formulations to further decrease the pill burden, especially among patients with comorbidities.

4.1.2 Use of steroids in the treatment of extrapulmonary TB disease

- Establish the optimal dose of steroids for TB meningitis (in various drug formulations).
- Determine the optimal duration of steroids for TB meningitis and whether the duration differs according to the grade of meningitis.
- Investigate the different effects of steroids in people who are or are not HIV-positive and who are or are not receiving antiretroviral therapy.
- Investigate the relation between steroid treatment and cancer risk.

4.1.3 Four-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide for drug-susceptible pulmonary TB

- Study the acquisition of drug resistance to *M. tuberculosis* and other bacteria during treatment with a 4-month regimen.
- Determine the efficacy of the regimen for patients with extrapulmonary TB.
- Conduct studies of pharmacokinetics, safety and tolerability in young adolescents and children. A pharmacokinetics study in adults has been initiated within a trial, and the results are expected shortly.
- Determine the cost–effectiveness of the shorter regimen.
- Establish the impact of the 4-month regimen on equity.
- Determine the acceptability of the shorter, 4-month regimen, particularly by patients.
- Study use of this regimen in subgroups including pregnant and lactating women, children < 12 years, people living with HIV with a CD4 count < 100 cells/mm^3, people living with HIV who are on non-efavirenz based ART, people with diabetes mellitus and people with a body weight < 40 kg.
- Consider dosing for people who weigh < 40 kg.
- Study the use and acceptability of fixed-dose combination formulations for the shorter, 4-month regimen.
- Conduct operational research on the relative advantages of directly observed treatment and of self-administered therapy.
- Study treatment adherence and completion in operational settings.

4.1.4 Effectiveness of various interventions to improve treatment adherence

- Determine the types of supervision of patient support and treatment that are most suitable for various populations.

- Determine the patient support interventions that are most effective in low-and middle-income countries.

- Analyse the cost–effectiveness of different types of incentives.
- Conduct research on the effectiveness of video-supported TB therapy in low- and middle-income countries, as the available data are from high-income countries.

- Improve understanding of the psychological support that is most appropriate in this context.

4.2   Drug-resistant TB

Most of the recommendations in these guidelines are conditional, because the estimates of effect in studies of patients were usually assigned a low or very low-certainty rating. The group identified lack of studies of how patients, caregivers and other stakeholders value different treatment options and outcomes (e.g., time to sputum conversion, cure, treatment failure and relapse, death and serious adverse events). Areas of study that would be relevant to many priority questions in programmatic management of drug-resistant TB are implementation research on resource use, incremental costs, acceptability, feasibility, equity, the values and preferences of patients and health-care workers and indicators of quality of life. The research gaps identified by successive GDGs are grouped below.

> **Highlight: Global individual patient data platform for drug-resistant TB treatment**
>
> A combination of longitudinal individual data and aggregated epidemiological and public health data are critical for policy development and to catalyse translational health research. The WHO Global Tuberculosis Programme has established a global platform of individual patient data for drug-resistant TB. The platform allows pooling of individual data from researchers and local and national databases on treatment of drug-resistant TB treatment for use in policy updates and public health research. It will ensure scientific advances and potential public benefits with the informed consent of research participants while protecting their privacy. The WHO Global TB Programme will establish an oversight body to coordinate requests for data access from the public.
>
> *For more information: Launch of global individual patient data platform for tuberculosis treatment. World Health Organization; 2023 (https://www.who.int/news/item/31-01-2023-launch-of-global-individual-patient-data-platform-for-tuberculosis-treatment).*

4.2.1 Regimens for rifampicin-susceptible, isoniazid-resistant TB

All the recommendations on isoniazid-resistant TB were conditional, as they were based on very low-certainty estimates of effect. Thus, further research is necessary to refine policies to optimize treatment of isoniazid-resistant TB. The GDG identified the following research priorities:

- Conduct randomized controlled trials of the efficacy, safety and tolerability of regimens for isoniazid-resistant TB and for cases with additional resistance to other medicines, such as ethambutol or pyrazinamide (polydrug resistance).

- Conduct research on the potential benefits and risks of treatment with high-dose isoniazid.

- Implement high-quality studies on optimizing the composition and duration of regimens for children and adults, particularly of high-dose isoniazid, fluoroquinolones and other second-line medicines, and on reducing the duration of pyrazinamide treatment.

- Estimate the number to be treated for empirical use of an isoniazid-resistant TB regimen, balancing risks and benefits.

- Conduct high-quality studies on treatment prolongation for HIV-positive individuals.

- Conduct high-quality studies evaluating regimens for extrapulmonary or disseminated TB.

- Assess feasibility of fixed-dose combinations of rifampicin–ethambutol–pyrazinamide alone (with or without levofloxacin).

- Perform monitoring of patient responses by isoniazid resistance genotype (e.g., *katG* versus *inhA* mutations), in individual patients or in a population.

- Assess the cost–effectiveness of different approaches to drug susceptibility testing, including rapid testing of all TB patients for both isoniazid and rifampicin resistance before the start of treatment.

- Conduct research on participatory action of communities and other stakeholders (e.g., field practitioners and community workers) to explore sociocultural factors that facilitate treatment adherence and influence outcomes.

- Identify effect of underlying polydrug resistance to fluoroquinolones–isoniazid on treatment outcomes and diagnostic accuracy of second-line line-probe assays in rifampicin-sensitive patients.

4.2.2. The 6-month BPaLM regimen for treatment of rifampicin-resistant, multidrug-resistant TB (MDR/RR-TB)or pre-extensively drug-resistant TB

- Assess the efficacy, safety and tolerability of the BPaLM/BPaL regimen across regions, countries, as well as subpopulations for whom current data are limited or missing, including children aged below 14 years of age, people with extrapulmonary TB, HIV-positive people with CD4 count < 100 cells/mm^3, and pregnant and lactating women.

- Identify the mechanism and molecular markers of pretomanid resistance to support the development of drug-susceptibility test; the clinical implications of the lineage 1 effect on efficacy of pretomanid and cross-resistance with delamanid; and conduct surveillance to monitor the development of resistance against pretomanid, with adequate consideration paid to the impact of selected mutations.

- Record and analyse the adverse event profile of pretomanid, including their frequency, with a focus on hepatotoxicity and reproductive toxicity in humans.

- Explore the relative efficacy (and added value in multidrug regimens) of pretomanid and delamanid.

- Strengthen the evidence base on comprehensive health impact of this regimen, particularly in areas evidence is scarce (e.g., acquisition of drug resistance and quality of life).

- Investigate geographical differences in the frequency and severity of linezolid-related adverse events and the underlying cause, considering that large and unexplained differences in linezolid-related adverse events were previously observed in post-hoc analyses between different geographic sites.

- Investigate opportunities to further optimize the regimen by replacing moxifloxacin with levofloxacin.

- Investigate the extent of cross-resistance between bedaquiline and clofazimine.

- Monitor resistance to new and repurposed medicines.

- Explore approaches to improve treatment adherence.

- Optimize regimen composition when the new generation of component medicines are available and investigate the efficacy of other 6-month regimens.

4.2.3. The 9-month all-oral regimen for MDR/RR-TB treatment

- Measure the effectiveness and safety of shorter MDR-TB treatment regimen variants, in which the injectable agent is replaced by an oral agent (e.g., bedaquiline) and the total duration is reduced to 6 months or less.
- Compare the effectiveness of these variants in:
    - patient subgroups that have often been systematically excluded from studies or country programme cohorts (e.g., children, people with additional resistance, people with extrapulmonary TB, and pregnant or breastfeeding women).
    - settings where background resistance to drugs other than fluoroquinolones and second-line injectable agents is high (e.g., pyrazinamide or high-level isoniazid resistance).
- Conduct randomized controlled trials and operational research projects to measure and compare the impact of all-oral shorter MDR-TB treatment regimens to all-oral longer regimens.
- Monitor the safety, efficacy and tolerability of this regimen using programmatic data from countries other than South Africa.
- Research the safety, efficacy and tolerability of this regimen from subpopulations for whom current data are limited or missing such as children, pregnant women, older people, people with diabetes, people presenting with extensive TB disease, and other vulnerable populations.
- Identify the frequency and mechanisms of bedaquiline resistance acquisition, and the genetic markers that indicate probable resistance.
- Identify optimal companion drugs that protect bedaquiline and limit the acquisition of bedaquiline resistance, including consideration of the need to protect the long "tail" of potential single drug exposure (given its exceptionally long half-life) if bedaquiline is stopped at the same time as companion drugs.

> **Highlight: Ethical considerations**
>
> Compilation of research gaps in WHO policy guidelines was an opportunity to highlight the principles of "protecting human rights, ethics and equity", one of the four principles of the WHO End TB Strategy. Health research should be guided by international and national principles for ethical conduct of research, including the Nuremberg Code, the World Medical Association's Declaration of Helsinki and WHO's Ethical standards and procedures for research with human beings. WHO has also published Ethics guidance for implementation of the End TB Strategy *to* ensure that due attention is given to equity, human rights and ethics in all aspects of TB service provision.
>
> *For more information: Ethics guidance for the implementation of the End TB Strategy. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/handle/10665/254820).*

4.2.4 Longer regimens for MDR/RR-TB treatment

- Conduct additional research on the optimal combination of medicines and regimen design for adults and children with MDR- or rifampicin-resistant TB, with or without additional resistance to other agents.

- Conduct randomized controlled trials, especially on new drugs and regimens: release of results from the first phase-III trials on MDR-TB has led to debate about the clinical relevance of the design and endpoints chosen for these studies, which sometimes required additional, off-protocol analysis of data to determine the potential added value of the experimental interventions.

- Approaches to strengthen inclusion and separate reporting of outcomes for subgroups in randomized controlled trials, especially children, pregnant and breastfeeding women and HIV-positive individuals on treatment.

- studies of pharmacokinetics and safety to determine optimal drug dosing (especially in pregnancy) and the effect of extemporaneous manipulation of existing dosing.

- Strengthen approaches to enable complete recording and analysis of adverse events and standardized data on organ class, seriousness, severity and certainty of association to allow meaningful comparisons of associations between adverse events and exposure to various medicines between studies, patient subgroups and regimens.

- Optimize the minimum number of drugs and treatment duration (especially in patients previously treated for MDR-TB).

- Develop improved diagnostics and drug susceptibility testing methods (e.g., for resistance to pyrazinamide), especially for medicines for which no rapid molecular methods are currently available.

- Further research and development would be particularly helpful for the following agents:
    a. levofloxacin: optimization of the dose – the Opti-Q study will soon provide new information on this.
    b. bedaquiline: optimization of the duration in both adults and children and use during pregnancy.
    c. linezolid: optimization of the dose and duration in both adults and children and predictors of adverse reactions in patients.
    d. *clofazimine*: optimization of the dose, especially for children, any added value of a loading dose and availability of drug-susceptibility testing methods.
    e. *cycloserine* and *terizidone*: differences in the efficacy of the two medicines, approaches to test for susceptibility and best practices in psychiatric care for people on these medicines.
    f. *delamanid*: better understanding of its role in MDR-TB regimens, including in children (pharmacokinetics and pharmacodynamics), people living with HIV and pregnant women; mechanisms of development of drug resistance; and optimization of the duration for both adults and children.
    g. pyrazinamide: molecular testing for resistance (pursuing either a line-probe assay or other approaches).
    h. *carbapenems*: given their effectiveness, further research on their role in MDR-TB regimens, including the potential role and cost–effectiveness of ertapenem (which can be given intramuscularly) as a substitute for meropenem and imipenem–cilastatin.
    i. *amikacin*: safety and effectiveness of thrice-weekly administration at a higher dose (about 25 mg/kg per day).

- Identify factors that determine the optimal duration of treatment (e.g., previous treatment, baseline resistance patterns, site of disease and age).

- Explore strategies to optimize the balance of benefits and harm of regimen duration through risk-stratification approaches.

4.2.5 Monitoring patient response to MDR/RR-TB treatment using culture

- Identify the predictors and biomarkers of treatment failure (related to strain, regimen and host) and of the bacteriological response in the following subgroups, to identify more resource-saving options and reduce the time to make decisions:
  – patients aged < 15 years;

– patients with extrapulmonary disease (various forms);
– patients on shorter MDR-TB regimens (standardized or all-oral variants).

- Continued evaluation of the potential role of future rapid molecular testing to monitor not only diagnostic testing but also the treatment response.

- Evaluation of the engineering challenges to finding more affordable liquid culture systems.

4.2.6 Surgery for patients on MDR/RR-TB treatment

- Conduct studies of decisions on when to operate and the appropriate type of surgical intervention and drug-resistance patterns.

- Implement better collection, reporting and standardization of data on surgery, including long-term survival.

4.3   Tuberculosis care and support

Research gaps identified in the WHO consolidated guidelines on tuberculosis care and support TB *(25)* are summarized below.

The effectiveness of different forms of interventions to improve treatment adherence

- Identify interventions for patient support and treatment supervision that are best suited to different risk groups.
- Identify interventions for patient support that are most effective in low- and middle-income countries.
- Analyze the cost-effectiveness of different types of incentives to improve treatment adherence.
- Research into the effectiveness of video supported therapy in low- and middle-income countries, as the current available data are from high-income countries.
- The types of psychological support that are most appropriate to improve treatment adherence and health outcomes.

Models of care for all people with TB

- Evaluate the risk of TB transmission in different settings, for example to explore if treatment centred on hospital care or outpatient clinics pose a higher risk of transmission.
- Conduct additional cost-effectiveness studies to compare decentralized versus centralized care.
- Systematic programmatic data collection and analysis on decentralized care, could supplement current knowledge about models of care.

Module 5: Management of tuberculosis in children and adolescents

Research gaps documented in the WHO consolidated guidelines on management of tuberculosis in children and adolescents *(26)*are summarized below.

5.1 The use of integrated treatment decision algorithms in children with presumptive pulmonary TB attending health care facilities

- Implement external validation of the integrated treatment decision algorithms included in the 2022 Operational handbook on the management of TB in children and adolescents, including for specific subpopulations such as children under 2 years of age, children with HIV, malnutrition, and across various geographic settings.
- Conduct implementation/operational research on the use and impact of the integrated treatment decision algorithms, including how to tailor them to local epidemiological settings (such as settings with differing burdens of TB, different health care settings, including settings with limited access to chest radiography).
- Conduct modelling studies to determine the potential impact of treatment decision algorithms on case detection and treatment initiation.
- Conduct qualitative studies on the feasibility and acceptability of the newly developed integrated treatment decision algorithms among relevant stakeholders in various settings.
- Conduct diagnostic test accuracy studies and effectiveness studies of algorithms for the diagnosis of extrapulmonary TB.

5.2 The use of Xpert Ultra in gastric aspirate or stool to diagnose pulmonary tuberculosis in children

- Evaluate the benefits and incremental yield of combining multiple specimen types. Limited data suggest that combining multiple non-invasive specimens performs comparably with gastric aspirate or induced sputum specimens.
- Conduct additional operational and qualitative research to determine the best approach to less invasive specimen collection in children, including: implementation studies on a method of suction for nasopharyngeal aspiration that is appropriate for low-skill or low-resource environments; research on the use of stool as a diagnostic specimen as part of treatment decision algorithms; definition of laboratory protocols that successfully balance the ease of implementation and diagnostic performance; and the impact of stool testing on patient-important outcomes.
- Identify, evaluate and validate host and pathogen associated biomarkers in paediatric populations as potential novel tests for TB infection, TB disease, risk of disease progression and response to treatment among children, ideally requiring non-invasive samples and for use at the point of care.
- Optimize current microbiological reference standard by improving and harmonizing specimen collection; supporting laboratory research to improve specimen processing to optimize diagnostic yield using current assays; and to improve phenotypic and genotypic drug-susceptibility testing on paediatric clinical specimens, including on stool samples.
- Qualitative research on equity, acceptability and feasibility aspects of diagnostic approaches, including specimen types and diagnostic tools.

5.3 A 4-month treatment regimen for children and adolescents with non-severe drug-susceptible tuberculosis

- Develop stronger evidence on the feasibility of assessing the severity of TB in children and adolescents in settings where there is limited or no access to diagnostic tools, in particular to chest radiography.

- Evaluate societal costs, including direct and indirect patient costs such as transportation costs and loss of family income in the context of implementation of shorter treatment regimens for drug-susceptible TB.
- Build evidence to optimize the use of automated software for chest radiography reading in children, including for differentiating severe from non-severe forms of intrathoracic TB disease among children.

5.4. MDR/RR-TB treatment regimens for children

Bedaquiline

- Evaluate treatment outcomes of children of all ages with MDR/RR-TB, treated with shorter and longer all-oral, bedaquiline containing regimens.
- Conduct studies aimed at optimizing dosing of bedaquiline in children.
- Assess the cost-effectiveness of using bedaquiline containing regiments in children.
- Optimize the duration of bedaquiline use in children related to PK and safety.
- Studies exploring the concomitant use of bedaquiline and delamanid in children related to PK and safety.
- Assess the acceptability, equity and feasibility of bedaquiline containing MDR/RR-TB treatment regimens in children.

Delamanid

- Assess the long-term safety and side-effects of delamanid, especially related to neuropsychiatric safety signals.
- Optimize the dosing of delamanid in children (some studies are already ongoing, such as IMPAACT P2005, "A phase I/II open-label, single-arm study to evaluate the PK, safety, and tolerability of delamanid in combination with optimized multidrug background regimen for multidrug-resistant tuberculosis (MDR-TB) in HIV-infected and HIV-uninfected children with MDR-TB)".
- Specific cost-effectiveness studies on the use of delamanid in children.
- Identify mechanisms of acquisition of resistance and genetic markers to identify resistance.
- Optimize the duration of delamanid use in children related to PK and safety.

5.5. Treatment of presumed or bacteriologically confirmed drug-susceptible TB meningitis in children and adolescents

- Implement studies to explore the comparative efficacy and safety of short intensive treatment regimens, compared to standard treatment regimens.
- Optimize dosing for the shorter intensive regimen and for alternative regimens under research, including regimens that include higher doses of medicines than are currently recommended.
- Conduct studies to improve equity in care, including equitable access to medicines in the short intensive regimen.
- Assess the cost-effectiveness of shorter regimens compared to the current standard of care.
- Assess the feasibility and acceptability of regimens used for the treatment of TB meningitis.
- Research on the sequelae of TB meningitis (including the type and severity of sequelae and the ability to prevent or manage them) as well as objective measures of quality of life/functionality post-treatment.
- Explore the added benefit of co-administering anti-inflammatory agents during the treatment of children and adolescents with TB meningitis.
- Develop optimal regimens to treat TB meningitis among children and adolescents living with HIV.

5.6 Models of TB care for children and adolescents

- Assess the cost effectiveness of decentralization/integration for case detection and provision of TB preventive treatment and its impact on health equity.
- Assess acceptability and feasibility of decentralized approaches to child and adolescent TB care for case detection and for provision of TB preventive treatment.

    - Map currently operating family-centred and integrated services; associated costs and cost-effectiveness and associated catastrophic costs[2].
    - Conduct implementation research on the components of these interventions; assessment of real-world implementation of these programmes.
    - Assess feasibility and acceptability of family-centred, integrated and/or decentralized approaches to child and adolescent TB care for case detection and provision of TB preventive treatment in different settings, from person with TB, caregiver and provider perspectives.
    - Conduct cost-effectiveness evaluations of family-centred, integrated and/or decentralized approaches, considering currently available resources (some models assume that these interventions are built upon existing structures that may not be available).
    - Evaluate of outcomes of interest using randomized/non-randomized designs and qualitative designs. Outcomes of interest: initiation of TB preventive treatment; number of additional children and adolescents diagnosed; delay, retention in care, treatment completion, clinical outcomes (such as treatment success); qualitative research related stigma, mental health outcome, school interruption, equity.
    - Characterize the baseline needs and perceptions of the community regarding TB prevention and care for children and adolescents.
    - Conduct studies to improve the quality of TB diagnosis in children - addressing both under-diagnosis and over-diagnosis.

Module 6: TB related comorbidities

6.1   WHO consolidated guidelines on the management of TB and comorbidities

Section on management of TB/HIV co-infection

A selection of research gaps relevant for reducing the burden of HIV in people with presumptive or diagnosed TB are listed below. A full list of the TB/HIV research gaps is included in the WHO consolidated TB/HIV guidelines*(9)*.

Management of HIV in people with TB:
- Evaluate how initiating antiretroviral therapy among people with TB symptoms (excluding those with signs and symptoms of meningitis) affects mortality, TB and HIV outcomes, adverse events, immune reconstitution inflammatory syndrome, retention in care and antiretroviral therapy adherence.

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[2] Defined by the WHO standardized survey protocol as costs faced by households affected by tuberculosis, including direct medical expenditures, direct non-medical payments, and indirect costs such as lost income, which exceeded 20% of annual household income.

- Explore the role of administering prophylactic corticosteroids (and the initiation timeline) to reduce the incidence of immune reconstitution inflammatory syndrome among people with TB and HIV co-infection in public health settings.
- Assess the safety and tolerability of earlier antiretroviral therapy initiation among children, pregnant and breastfeeding women living with HIV and TB co-infection, and for people living with HIV who have drug-resistant TB.
- Evaluate the long-term safety and tolerability of newer antiretroviral drugs used in first, second- or third-line regimens in the context of TB and HIV coinfection.
- Close the data gap on the impact of corticosteroids use in preventing immune reconstitution inflammatory syndrome among people living with HIV who have low CD4 cell counts.
- Conduct longitudinal studies to evaluate viral load suppression among people with HIV on formulations containing efavirenz 400 mg, particularly for pregnant women and individuals receiving TB co-treatment and particularly when the TB treatment regimen contains rifampicin.
- Evaluate the pharmacokinetics and safety of alternative dosing of tenofovir alafenamide when co-administered with TB treatment.
- Measure health outcomes of people being treated for TB and histoplasmosis coinfection.

6.2   Nutritional care and support for patients with TB

Research gaps documented in this guideline are:

- Measure the effect of macronutrient intake and food supplementation in addition to treatment on TB treatment outcomes.
- Measure the effect of macronutrient supplementation or routine supplementation with micronutrients at the recommended nutrient intake in pregnant women with active TB and on neonatal complications.
- Assess benefits of macro- or micronutrient supplementation on growth and development of young people aged 5–19 with active TB as compared with those without TB.
- Define nutritional parameters and TB-specific outcomes that can be measured in trials of nutritional supplementation.
- Measure the effect of implementing WHO nutrition and TB recommendations on nutritional recovery and TB treatment outcomes.
- Evaluate the relative importance of food assistance as compared with other enablers of adherence to TB treatment.
- Explore aspects of nutritional counselling that enhance the effectiveness and uptake of advice on nutritional outcomes.
- Define the best measure of nutritional status in pregnant women with and without TB, and both maternal and infant outcomes.
- Study the optimal range of body mass index for healthy maternal and infant outcomes in pregnant women with TB.
- Assess energy requirements of TB patients and of people without TB (including protein and fat requirements) with consideration of TB treatment, coexistent HIV, phase of treatment and MDR-TB.
- Determine the risk of micronutrient deficiencies in people with active TB as compared with people without TB.
- Explore the proportional causes of malnutrition in people with TB.
- Evaluate the natural course of weight change during the intensive phase of TB treatment in people with drug-sensitive TB and MDR-TB and various degrees of malnutrition and in settings with different levels of food security.

6.3 People who inject drugs

Research gaps documented in the consolidated guidelines for *Integrating collaborative TB and HIV within a comprehensive package of care for people who inject drugs (22)* are summarized below:

- Measure the relative risks for developing TB of non-injecting drug users; crack, cocaine and opiate smokers, people living with HIV and those who are HIV-negative.

- Identify the confounders for TB disease risk among drug users, such as poverty, homelessness and mental health problems.

- Identify country-specific contexts and risks for TB among drug users, particularly in India, Nepal, Pakistan and other large Asian countries with a high prevalence of TB/HIV and growing injecting drug use.

- Investigate the overall impact of TB disease on drug users.

- Characterize the rates of MDR-TB and extensively drug-resistant TB among drug users.

- Compare MDR-TB disease and treatment adherence among drug users inside and outside the prison system.

- Identify the specific barriers for women drug users to accessing TB care services in various settings, such as the criminal justice system.

- Identify effective and cost-effective strategies to promote adherence to TB treatment among drug users in low-income and resource-limited settings.

- Assess the overall impact of TB, TB/HIV and drug use on the prison system.

- Assess the frequency of reinfection during re-exposure among drug users in congregate settings such as prisons and in non-prison settings and the implications on the cascade of care.

- Explore effective strategies for protecting health-care workers and other personnel in health care and criminal justice settings from TB.

- Identify the most effective advocacy strategy for addressing TB among drug users.

- Assess the proportion of drug users who maintain treatment on entry to prison and on release or transfer.

- Identify strategies to limit loss-to-follow up of drug users with TB who are released from prison while under TB treatment.

- Identify best practices and strategies for caring for drug users with TB/HIV, other than in prisons.

- Determine the proportion of TB detection and treatment outcomes among drug users in prisons.

- In the context of the continuum of care, the best prison release practices for people who inject drugs and the relation to and integration with TB/HIV programmes and services.

- Map current general practices for caring for prisoners who are terminally ill, such as an incentive for discharge from prison, and if mortality rates are monitored.

Accelerating research towards public health impact

The aim of this compilation of research gaps, based on WHO TB guidelines, is to increase the impact of TB research by addressing the requirements of national policymakers and implementers. It is aligned with several resolutions, recommendations and strategies at the highest level. These include the End TB Strategy, the 2018 and 2023 political declaration of the High-level Meeting of the General Assembly on the fight against tuberculosis, the Moscow Declaration to End TB, and the Global Strategy for TB research and innovation, which affirms that research and development should be based on need and evidence, guided by the principles of affordability, effectiveness, efficiency and equity, and be considered a shared responsibility*(3, 27-30)*.

The global strategy for TB research and innovation was adopted by the World Health Assembly in August 2020 *(29)* to provide strategic guidance for accelerating research and innovation aligned to the requirements of Member States. The strategy calls for an enabling environment for research, mobilization of increased domestic and international investments in TB research, leveraging the potential of data-sharing and global collective action to improve equitable access to the benefits of research and innovation. In 2021, WHO launched a situational assessment checklist *(19)* to help countries to contextualize implementation of the global strategy through changes in policies, programmes and interventions.

> **Box 3. TB vaccine accelerator council**
>
> In January 2023, WHO convened a high-level event during the World Economic Forum, to highlight the role of new TB vaccines in the fight against TB. The importance of strategic partnerships and investments to boost the development, testing and manufacturing of safe and effective TB vaccines and equitable access to their use once available was highlighted, drawing on lessons learned during the COVID-19 pandemic. During the meeting, WHO's Director-General announced plans to establish an "accelerator Council" on new TB vaccines. The Council was launched in September 2023, in the margins of the second UN high-level meeting on TB. The aim of the Council is to boost the TB vaccine pipeline and facilitate the licensing and use of safe TB vaccines that will have a substantive impact on the TB epidemic, through catalysing high-level alignment among funders, global agencies, governments and communities on both the important challenges in TB vaccine development and the actions to address them.
>
> *For more information:*
> *WHO announces plans to establish a TB Vaccine Accelerator council Geneva: World Health Organization; 2023 (https://www.who.int/news/item/17-01-2023-who-announces-plans-to-establish-a-tb-vaccine-accelerator-council#:~:text=Speaking%20earlier%20today%20at%20a,new%20TB%20Vaccine%20Accelerator%20Council).*

In line with these United Nations initiatives, many intergovernmental forums have noted that greater cooperation and joint action are necessary on TB research. In 2016, the ministers of health of the BRICS countries agreed to set up a "network on TB research". In 2023, the WHO Director-General established an accelerator Council to facilitate the development and access to new TB vaccines (Box 3).

Conclusions

Research is central to guideline development, as it provides the evidence necessary to solve the wide-ranging problems faced by TB policymakers globally and nationally. All the research gaps documented in the most recent WHO TB policy guidelines are summarized in this report in order to stimulate large, well-funded, well-coordinated research executed by skilled research teams in partnership with clinicians, patients and policymakers, including, when possible, WHO. The Treatment Action Group reported that investment in research and development in 2021 was US$ 1 billion, which is far below the target of US$ 5 billion per year set at the 2023 UN high-level meeting of the General Assembly*(2, 3, 28)*. In view of this significant funding gap for TB research, this report may help direct time and resources to some of the most urgent evidence required by policymakers. As stated in the Global Strategy for TB research and innovation, research is a political choice – to invest, implement, use and share findings, guided by principles of affordability, effectiveness, efficiency and equity. To End TB by 2030, Member States must significantly increase their investment in TB research to ensure the development and uptake of new technologies and innovative approaches.

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