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

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### Acronyms and abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>GDG</td>
<td>Guideline Development Group</td>
</tr>
<tr>
<td>LF-LAM</td>
<td>lateral flow urine lipoarabinomannan</td>
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<tr>
<td>MDR-TB</td>
<td>multidrug-resistant tuberculosis</td>
</tr>
<tr>
<td>NAAT</td>
<td>nucleic acid amplification test</td>
</tr>
<tr>
<td>TPT</td>
<td>tuberculosis preventive treatment</td>
</tr>
<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>TB-LAMP</td>
<td>loop-mediated isothermal amplification for detection of <em>M. tuberculosis</em></td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</table>
Executive summary

Tuberculosis (TB) is a communicable disease that is a major cause of ill health and one of the leading causes of death worldwide. Until the coronavirus pandemic, TB was the leading cause of death from a single infectious agent, ranking above HIV. Although it is a largely preventable, treatable and curable disease, it claims more than one million lives each year and affects millions more, with enormous impacts on families and communities. The End TB Strategy aspires for a 90% reduction in the number of TB deaths and an 80% reduction in TB incidence in 2030 from those in 2015.

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 TB programmes and governments. WHO issues recommendations to guide countries in choosing life-saving interventions and effective, efficient, sustainable models of care that have an impact. Experts convened by WHO 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 TB.

This document summarizes the research gaps compiled by guideline development groups during the latest updates of WHO guidelines on TB (2013–2021). It also provides information about advances in research and development. We trust that this document will guide decision-makers who fund and implement research to better focus their research agendas towards the priorities of TB programmes and affected populations.
INTRODUCTION

Background: Research on TB and a TB-free world are intertwined.

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. WHO estimates that TB affected 9.9 million people and claimed 1.5 million lives in 2020 (5). The situation is anticipated to worsen in the near future because of disruptions to TB services due to the COVID-19 response and indirect effects of the pandemic, such as greater poverty and undernutrition.

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 2019, global funding for TB research was estimated to amount to US$ 0.9 billion, which is less than half of the annual US$ 2 billion target set by Member States for the period 2018–2022 (6).

National TB programmes are struggling with challenges both new and old: adverse 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 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 policy-makers, funders, civil society and other relevant actors on the urgent priorities for research for setting TB policy.

Highlight: Impact of the COVID-19 pandemic on TB

Responses to the COVID-19 pandemic have adversely affected essential TB services in many countries, which is estimated to have reduced the global number of TB cases notified between 2019 and 2020 substantially, by 18%, from 7.1 million to 5.8 million; the global number of TB deaths increased from 1.4 million to 1.5 million in 2020. The COVID-19 pandemic has exacerbated the socio-economic determinants of TB, such as poverty and undernutrition, which will add to the burden of TB disease and death. Other effects include a decrease in the number of people initiated on TB preventive treatment (TPT) (from 3.6 million to 2.8 million); a reduction in spending on TB services (from US$ 5.8 billion to US$ 5.3 billion); a 15% decrease in the number of people treated for drug-resistant TB and a reduction in coverage of the bacille Calmette-Guérin (BCG) vaccine (≥ 5% in 31 countries).

WHO has been monitoring the impact of the COVID-19 response on TB notifications monthly, providing guidance and sharing lessons from case studies of programmatic innovations to address challenges in TB prevention and care. WHO at all three levels is working with countries, the Global Fund to Fight AIDS, Tuberculosis and Malaria, the STOP TB Partnership and other partners to mitigate the impact of the pandemic on TB services.
Overview of WHO policy development

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 policy-makers 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)\(^1\)(7-9). 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.

The research questions listed in this document are those 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.

Research questions from TB policy guidelines

The most recent WHO policy guidelines in TB prevention and care are summarized by guideline module along the cascade of care in WHO’s TB knowledge sharing platform (Box 1). Table 1 shows the 246 research questions extracted from relevant guidelines by module and research domain: 11 are related to screening, 48 to diagnosis, 42 to prevention, 79 to treatment and 66 to comorbidities and vulnerable groups. Most of the research questions were for implementation research (45%), followed by clinical research (35%).

### Table 1. Numbers and types of research gaps by WHO TB guideline module

<table>
<thead>
<tr>
<th>TB guideline module</th>
<th>No. of research questions (N=246)</th>
<th>Characterization of research gaps by research domain (%)(^a)</th>
<th>Implementation research (45%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention Screening</td>
<td>42</td>
<td>4.8% 31% 4.8% 11.8%</td>
<td>47.6%</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>48</td>
<td>6.3% 31.3% 10.4% -</td>
<td>52%</td>
</tr>
<tr>
<td>Treatment</td>
<td>79</td>
<td>2.5% 60.8% 7.6% 5.1%</td>
<td>24%</td>
</tr>
<tr>
<td>Comorbidities, vulnerable populations and people centred care</td>
<td>66</td>
<td>4.5% 19.7% 6.1% 9.1%</td>
<td>60.6%</td>
</tr>
</tbody>
</table>

\(^a\) See Annex for definitions of the research domains used in this document.

\(^1\) 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.
With regard to prevention, about one third 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 TB care, particularly in the context of the COVID-19 pandemic. 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 2020, the WHO-recommended rapid molecular test was used as the initial diagnostic test in only 33% of the 5.8 million people newly diagnosed with TB. Just over half of the gaps for diagnosis concerned implementation research to improve the use of diagnostic tools by obtaining additional evidence on health impacts, use for different subpopulations and testing use of alternative biospecimens.

Most of the research gaps under treatment (60.8%) are for clinical evidence to optimize treatment of drug-resistant forms of TB. They include 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 research gaps in comorbidities, vulnerable groups and people-centred care, including for HIV, show an overwhelming demand (60.6%) for implementation science to reduce gaps in research-to-policy and policy-to-practice. The gaps include evidence to optimize interventions for children and adolescents, who are often excluded from clinical trials, and on the best ways to provide care for people with undernutrition and people who inject drugs. Use of research findings to address socio-economic determinants and consequences of TB, such as undernutrition and drug use, must be addressed by multisectoral action. In 2020, the burden of TB cases attributable to undernourishment was a staggering 1.9 million (one fifth of the total annual incidence) (5).

The demand for safer, more effective, affordable, patient-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 and human systems 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, gender issues 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. Filling such evidence gaps requires input from many disciplines. In 2021, the WHO Global TB Programme organized a multistakeholder consultation on translation of research into
policy 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).

**Box 2. WHO consultation on translation of research into policy (I)**

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. The consultation discussed 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. Exchanges also highlighted 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.

The following issues were discussed:

- WHO’s short- and medium-term plans for policy review and other updates, derivative operational guidance and other normative documents to enhance implementation of global TB policy;
- upcoming research or implementation experience that could change global TB guidance;
- national challenges that could direct new areas for research;
- strategies that the Programme might use to encourage investment in TB research to improve global policies on TB care in areas in which there are significant gaps, such as in paediatrics;
- effective, efficient approaches to improve current policy for patient support and social protection; and
- approaches to enhance country-led and -owned implementation and scale-up of proven interventions.

This was the first of several planned annual meetings on the topic, to ensure coherence among scientists, policy-makers, funders, civil society and implementers.

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.

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. Further updates on relevant research may be found in WHO’s annual Global TB report (5).
**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 2.

**Table 2. TB guidelines in the different modules**

<table>
<thead>
<tr>
<th>Module</th>
<th>Guidelines</th>
<th>Year last updated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Module 1: Prevention</td>
<td>WHO consolidated guidelines on tuberculosis preventive treatment (10)</td>
<td>2020</td>
</tr>
<tr>
<td></td>
<td>WHO guidelines on tuberculosis infection prevention and control (11)</td>
<td>2019</td>
</tr>
<tr>
<td>Module 2: Screening</td>
<td>WHO consolidated guidelines on systematic screening for tuberculosis disease (12)</td>
<td>2021</td>
</tr>
<tr>
<td>Module 3: Diagnosis</td>
<td>WHO consolidated guidelines on rapid diagnostics for tuberculosis detection (13)</td>
<td>2021</td>
</tr>
<tr>
<td>Module 4: Treatment</td>
<td>WHO consolidated guidelines on drug-resistant tuberculosis treatment (14)</td>
<td>2020</td>
</tr>
<tr>
<td></td>
<td>WHO consolidated guidelines on drug-susceptible tuberculosis treatment (2)</td>
<td>2021</td>
</tr>
<tr>
<td></td>
<td>Guidelines for treatment of drug-susceptible tuberculosis and patient care (15)</td>
<td>2017</td>
</tr>
<tr>
<td>Module 5: Comorbidities, vulnerable populations and people-centred care</td>
<td>Nutritional care and support for people with tuberculosis (16)</td>
<td>2013</td>
</tr>
<tr>
<td></td>
<td>Integrating collaborative TB and HIV services within a comprehensive package of care for people who inject drugs (17)</td>
<td>2016</td>
</tr>
<tr>
<td></td>
<td>Guidance for national tuberculosis programmes on the management of tuberculosis in children (18-20)a</td>
<td>2013–2018</td>
</tr>
</tbody>
</table>

*a* These guidelines and their accompanying research questions will be updated and published in 2022 on WHO’s TB Knowledge-sharing Platform (2).

**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 care-givers 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**
  - effect of different air exchange rates in mechanical ventilation systems on transmission of *M. tuberculosis*;
  - effect of mechanical ventilation modes on the microclimate of mechanically ventilated settings;
  - high-quality research on the effect of portable room-air cleaners; and
  - further research on ventilation parameters for portable room-air cleaners and target product profiles for these devices.

### Module 2: Screening

#### 2.1 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).

2.2 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 has 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.

2.3 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.

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

• 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 (21) 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.

• Improve understanding of the correlation between detection of resistance-conferring mutations, phenotypic drug susceptibility testing results 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.

Module 4: Treatment

4.1 Drug-susceptible TB

Research gaps identified in the WHO guidelines on treatment of drug-susceptible TB (2, 15) 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, HIV-positive people with a CD4 count < 100 cells/mm³, 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 healthcare workers and indicators of quality of life. The research gaps identified by successive GDGs are grouped below.

4.2.1 Regimens for 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.

- 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);
- research on the potential benefits and risks of treatment with high-dose isoniazid;
- 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;
- modelling to estimate the number to be treated for empirical use of an isoniazid-resistant TB regimen, balancing risks and benefits;
- high-quality studies on treatment prolongation for HIV-positive individuals;

**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.
• high-quality studies evaluating regimens for extrapulmonary or disseminated TB;
• feasibility of fixed-dose combinations of rifampicin–ethambutol–pyrazinamide alone (with or without levofloxacin);
• monitoring of patient responses by isoniazid resistance genotype (e.g., katG versus inhA mutations), in individual patients or in a population;
• 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;
• 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; and
• 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 Shorter all-oral bedaquiline-containing regimen for MDR- and rifampicin-resistant TB

• research on the effectiveness and safety of variants of the shorter MDR-TB treatment regimen, in which the injectable agent is replaced by an oral agent (e.g., bedaquiline) and the total duration is reduced to ≤ 6 months;
• comparison of the effectiveness of variants of the shorter regimen in:
  o patient subgroups that are often systematically excluded from studies or country programme cohorts (e.g., children, patients with additional resistance, those with extrapulmonary TB and pregnant or breastfeeding women); and
  o settings with high background resistance to drugs other than fluoroquinolones and second-line injectable agents (e.g., pyrazinamide or high-level isoniazid resistance);
• additional randomized controlled trials on all-oral shorter MDR-TB treatment regimens, with comparison of shorter and longer all-oral regimens;
• collection and analysis of programme data from countries other than South Africa;
• collection and analysis of data on children, pregnant women, the elderly, patients with diabetes, patients presenting with extensive TB disease and other special populations;
• information on the frequency and mechanisms of the acquisition of bedaquiline resistance and the genetic markers that indicate probable resistance; and
• identification of optimal companion drugs that protect bedaquiline and limit acquisition of bedaquiline resistance, including consideration of protecting 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.

4.2.3 Longer regimens for MDR-TB and rifampicin-resistant TB

• 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;
• 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 end-points
chosen for these studies, which sometimes required additional, off-protocol analysis of data to determine the potential added value of the experimental interventions;

- 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;

- 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;

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

- 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:

- **levofloxacin**: optimization of the dose: the Opti-Q study will soon provide new information;

- **bedaquiline**: to determine optimal pharmacokinetics in children, revised cost–effectiveness analyses based on meta-analysis of individual patient data, optimization of the duration in both adults and children and use during pregnancy;

- **linezolid**: optimization of the dose and duration in both adults and children and predictors of adverse reactions in patients;

- **clofazimine**: optimization of the dose, especially for children, any added value of a loading dose and availability of drug-susceptibility testing methods;

- **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;

- **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;

- **pyrazinamide**: molecular testing for resistance (with either a line-probe assay or other approaches);

- **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;

- **amikacin**: safety and effectiveness of thrice-weekly administration at a higher dose (about 25 mg/kg per day);

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**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 (3).
identification of factors that determine the optimal duration of treatment (e.g., previous treatment, baseline resistance patterns, site of disease and age);

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

4.2.4 The BPaL regimen for MDR-TB with additional fluoroquinolone resistance

- the efficacy, safety and tolerability of the BPaL regimen comprised of bedaquiline, pretomanid and linezolid, as compared with those of other all-oral regimens;
- data from regions and countries other than South Africa;
- description of the mechanism and molecular markers of pretomanid resistance, and surveillance for the development of resistance, with adequate consideration of the impact of selected mutations;
- the full profile of adverse events associated with pretomanid and the frequency of relevant adverse events, especially hepatotoxicity and reproductive toxicity (the reproductive toxicity of pretomanid in experimental animals has been reported, but the effects of this medicine on human fertility have not been adequately evaluated);
- the relative efficacy (and added value in multi-drug regimens) of pretomanid and delamanid;
- optimal dose and duration of linezolid use in drug-resistant TB regimens (e.g., ZeNix study).

4.2.5 Monitoring patient responses to MDR-TB treatment in culture

- analysis of 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 assessment 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-TB treatment

- studies of decisions on when to operate and the appropriate type of surgical intervention and drug-resistance patterns;
- better collection, reporting and standardization of data on surgery, including long-term survival.

4.2.7 Care and support for patients with MDR-TB

- the patient support and treatment supervision that is best suited to different populations;
- the patient support interventions that are most effective in low- and middle-income countries;
- the cost–effectiveness of different types of patient support;
- the effectiveness of video-supported TB therapy in low- and middle-income countries, as the available data are only from high-income countries;
- the types of psychological support most appropriate for MDR-TB patients;
- the risk of TB transmission in different settings (i.e., those with higher risks of transmission, whether treatment be provided in hospitals or in outpatient clinics);
- additional cost–effectiveness studies of decentralized versus centralized care;
- systematic collection and publication of data on decentralized care.

Module 5: Comorbidities, vulnerable populations and people-centred care

5.1 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 (17)* are summarized below:

- 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;
- the confounders for TB disease risk among drug users, such as poverty, homelessness and mental health problems;
- 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;
- the overall impact of TB disease on drug users;
- the rates of MDR-TB and extensively drug-resistant TB;
- comparison of MDR-TB disease and treatment adherence among drug users inside and outside the prison system;
- specific barriers for women drug users to accessing TB care services in various settings, such as the criminal justice system;
- effective and cost-effective strategies to promote adherence to TB treatment among drug users in low-income and resource-limited settings;
- the overall impact of TB, TB/HIV and drug use on the prison system;
- 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;
- effective strategies for protecting health-care workers and other personnel in health care and criminal justice settings from TB;
- the most effective advocacy for addressing TB among drug users;
- the proportion of drug users who maintain treatment on entry to prison and on release or transfer;
- strategies to limit loss-to-follow up of drug users with TB who are released from prison while under TB treatment;
- best practices and strategies for caring for drug users with TB/HIV, other than in prisons;
- 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;

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.

5.2 Nutritional care and support for patients with TB

Research gaps documented in this guideline are:

- effect of macronutrient intake and food supplementation in addition to treatment on TB treatment outcomes;
- effect of macronutrient supplementation or routine supplementation with micronutrients at the recommended nutrient intake in pregnant women with active TB and on neonatal complications;
- 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;
- nutritional parameters and TB-specific outcomes in trials of nutritional supplementation;
- effect of implementing WHO nutrition and TB recommendations on nutritional recovery and TB treatment outcomes;
- relative importance of food assistance as compared with other enablers of adherence to TB treatment;
- aspects of nutritional counselling that enhance the effectiveness and uptake of advice on nutritional outcomes;
- the best measure of nutritional status in pregnant women with and without TB, and both maternal and infant outcomes;
- optimal range of body mass index for healthy maternal and infant outcomes in pregnant women with TB;
- 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;
- risk of micronutrient deficiencies in people with active TB as compared with people without TB;
- the proportional causes of malnutrition in people with TB;
- 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.

5.3 Managing TB in children and adolescents

Research gaps documented in the guidance for national TB programmes on the management of tuberculosis in children (18) and in the accompanying road maps (19, 20) are summarized below.

The guideline for the management of TB in children and adolescents is currently under review, and updated guidance with accompanying research questions will be published in 2022 on WHO’s knowledge sharing platform (2).
5.3.1 Screening and diagnosis

- strategies for obtaining specimens for increasing diagnostic yield, including non-respiratory samples;
- new diagnostic tools for use in children, including young, malnourished children, HIV-positive children and children with MDR–TB;
- diagnostic algorithms for children and adolescents in different epidemiological settings and identification of the most effective (and cost–effective) strategies for implementation of current and novel diagnostics;
- efficient, reliable systems for specimen collection, transport and laboratory evaluation, especially for following up children with bacteriologically negative, paucibacillary specimens;
- identification, evaluation and validation of new, more effective diagnostics to be used as highly sensitive, “rule-out” screening tests (requiring non-invasive samples and for use at points of care); identification, evaluation and validation (as necessary) of novel pathogen-associated biomarkers in paediatric populations (e.g., DNA, mRNA expression profiles, micro-RNA, next-generation LAM-based assays) and host biomarkers for paediatric populations as potential novel tests for TB infection, TB disease, risk of disease progression and response to treatment in children.

5.3.2 Prevention

- Evaluate shorter, simpler drug treatment regimens for TB infection in children, including those to prevent TB among contacts of children with drug-resistant TB;
- Evaluate symptom-based screening tools for screening HIV-positive and -negative child contacts;
- Identify operational challenges to contact-tracing for eventual wide-scale implementation of preventive treatment;
- Identify strategies for enhancing adherence to preventive treatment by children and adolescents;
- development and evaluation of cost–effective, child-friendly preventive drug regimens for children to determine optimal dosing, particularly for children co-infected with HIV and < 12 months of age;
- pragmatic, scalable, decentralized, community-based strategies (e.g., family-centred models) for TB screening and provision of TPT and TB treatment to enhance early entry and retention in the cascade of care;
- qualitative research to better understand facilitators of and barriers to provision of preventive treatment, diagnostic access, treatment adherence and effective management for families affected by TB;
- Characterize the immune response to TB infection and disease in children by age, nutritional status, co-infections, disease phenotype and mycobacterial and host genotype, in multi-centre, longitudinal paediatric cohort studies; support discovery, evaluation and validation of novel biomarkers (including those for accurate differentiation between children with TB disease from those presenting with similar symptoms, to distinguish between infection and disease, to predict risk of disease progression and vaccine efficacy) among children with a broad spectrum of disease presentations;
- strategies for effective management of child contacts of parents and caregivers with drug-resistant TB in the intensive phase of treatment;
- new vaccines that provide greater protection than BCG; prevent all forms of TB, including drug-resistant forms, and reactivation of TB; would be effective in all age groups and in HIV-infected people; would improve safety and would perform consistently in all populations;
• additional research requirements included in the updated WHO position paper on BCG published in February 2018 (22):
  o the safety and effectiveness of BCG vaccination of HIV-infected children, including those receiving antiretroviral therapy;
  o strategies to improve the timeliness of BCG vaccination and to limit wastages of vaccine in multi-dose preparations;
  o long-term strategic studies to explore the effectiveness of BCG vaccine, the duration of BCG-derived protection, particularly in temperate settings, and the effect of BCG vaccination on morbidity and mortality from all causes.

5.3.3 Treatment

• pharmacokinetic studies to determine the optimal dosages of second-line and novel anti-TB drugs, including in HIV-positive children and especially in children < 2 years;
• pharmacokinetic studies to determine optimal dosages of anti-TB drugs for newborn infants, including preterm, in the first week of life;
• clinical trials to determine the efficacy and safety of new regimens of anti-TB drugs in children;
• the optimal duration of treatment for various forms of TB, including in HIV-positive children;
• clinical trials to determine the optimal treatment regimens and duration of treatment of children with drug-resistant TB, including for isoniazid-mono-resistant TB and MDR-TB, ensuring the inclusion of children and adolescents in late-stage clinical trials of new TB drugs, regimens and treatment strategies;
• development and evaluation of strategies to shorten and simplify treatment and reduce treatment-related toxicity in children with any form of TB, including TB meningitis.

5.3.4 Recording, monitoring and evaluation

• description and monitoring of the burden of TB infection and disease (including drug-resistant TB) and treatment outcomes among children and adolescents at national level;
• description and monitoring of the burden of TB infection and disease (including drug-resistant TB), socio-economic impact and treatment issues for children and adolescents living with HIV;
• description of the occurrence of residual morbidity after cure or completion of TB treatment (in both HIV-negative and -positive children and adolescents), including long-term adverse effects and socioeconomic impacts of TB treatment;
• completeness of recording and reporting of childhood TB along the cascade of care, including how to strengthen and standardize reporting of child contact management and the provision of preventive treatment.

5.3.5 Service delivery

• the most appropriate, cost-effective service delivery models for children of all ages;
• evaluate programme integration strategies for pediatric TB, including with HIV, and maternal, neonatal and child health, nutrition and other relevant programmes in order to find children and adolescents with TB;
• health system requirements, including human resources and cost, for scaling up evidence-based interventions and programme integration for TB prevention and treatment at national level;
• barriers to and opportunities for providing integrated services and developing indicators for assessing the quality of care;
• determinants of TB and key barriers faced by adolescents to accessing TB diagnostic and treatment services;
• social research to better understand the impact of stigmatization and TB on education among school-aged children and adolescents.

ACCELERATING RESEARCH TO ENSURE AN 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 policy-makers and implementers. It is aligned with several resolutions, recommendations and strategies at the highest level. These include the End TB Strategy, the political declaration of the High-level Meeting of the General Assembly on the fight against tuberculosis, the Moscow Declaration to End TB, the United Nations Secretary-General’s report on progress towards achievement of global TB targets, United Nations General Assembly resolution 73/3 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(4, 23-26).

The global strategy for TB research and innovation was adopted by the World Health Assembly in August 2020 (27) 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 (28) to help countries to contextualize implementation of the global strategy through changes in policies, programmes and interventions.

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” (Box 3).

Box 3. BRICS TB research network

Health ministers in Brazil, the Russian Federation, India, China and South Africa (BRICS) have long been committed to working together to advance TB research and have agreed to several resolutions. Their commitments were reiterated by their heads of states when they met in Xiamen, China, in September 2017. In their declaration, the countries agreed to “foster the development and improve the availability of innovative medical products through promotion of research and development”. Importantly, the declaration specifically referred to establishment of new global network to advance TB research in line with the Sustainable Development Goals. The network was officially launched during the First WHO Global Ministerial Conference on Ending Tuberculosis in the Sustainable Development Era: A Multisectoral Response, Moscow, 2017 (4).

The Global TB Programme was officially asked to support the network during the Seventy-second World Health Assembly and the ninth meeting of BRICS health ministers, and WHO has since been supporting the secretariat of the network, when requested.
CONCLUSIONS

Research is central to guideline development, as it provides the evidence necessary to solve the wide-ranging problems faced by TB policy-makers 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 policy-makers, including, when possible, WHO. The Treatment Action Group reported that investment in research and development in 2019 was US$ 901 million, which is far below the target of at least US$ 2 billion per year set at the high-level meeting of the General Assembly (6, 24). 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 policy-makers. 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 double their investment in TB research to ensure the development and uptake of new technologies and innovative approaches to integrated care.
REFERENCES


Annex: Definitions of research domains used in this document

- **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)

References
