

Evidence gaps and research needs identified during tuberculosis policy guideline development

Scoping reviews of policy guidelines published by the Global TB Programme were undertaken with a view to highlight research questions identified during guideline development process. The aim was to increase the uptake of research recommendations from policy guidance documents by relevant stakeholders, particularly by funders, research policy makers and implementers of TB research. The implementation of these research questions is expected to inform future policy guidance and subsequently clinical practice.

© World Health Organization 2018

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; <https://creativecommons.org/licenses/by-nc-sa/3.0/igo>).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO endorses any specific organization, products or services. The use of the WHO logo is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: "This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition".

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization.

Suggested citation. Evidence gaps and research needs identified during tuberculosis policy guideline development. Geneva: World Health Organization; 2018 (WHO/CDS/TB/2018.27). Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at <http://apps.who.int/iris>.

Sales, rights and licensing. To purchase WHO publications, see <http://apps.who.int/bookorders>. To submit requests for commercial use and queries on rights and licensing, see <http://www.who.int/about/licensing>.

Third-party materials. If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

General disclaimers. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

Table of Content

Introduction.....	1
Method	1
Research questions.....	2
1. Early detection of TB.....	2
<i>1.1 Systematic screening for active tuberculosis: Principles and recommendations</i> Research gaps documented in this guideline (2) include the following:.....	2
2. Diagnosing TB disease	2
<i>2.1 Xpert MTB/RIF and Ultra assays for the diagnosis of pulmonary and extrapulmonary TB in adults and children & WHO Meeting Report of a Technical Expert Consultation: Non-inferiority analysis of Xpert MTB/RIF Ultra compared to Xpert MTB/RIF.....</i>	<i>2</i>
<i>2.2 The use of loop-mediated isothermal amplification (TB-LAMP) for the diagnosis of pulmonary tuberculosis</i>	<i>3</i>
<i>2.3 The use of lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis and screening of active tuberculosis in people living with HIV Policy update</i>	<i>3</i>
<i>2.4 The use of molecular line probe assays for the detection of resistance to isoniazid and rifampicin.....</i>	<i>4</i>
<i>2.5 Molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs: Policy guidance</i>	<i>4</i>
3. Diagnosing and treating latent TB infection.....	4
4. Treating TB.....	7
<i>4.1 Treatment of drug-susceptible tuberculosis and patient care: 2017 update</i>	<i>7</i>
<i>4.2 WHO treatment guidelines for isoniazid-resistant TB</i>	<i>8</i>
<i>4.3 WHO treatment guidelines for drug-resistant tuberculosis 2016 update.....</i>	<i>9</i>
5. HIV infection and other comorbidities	10
<i>5.1 Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection.....</i>	<i>10</i>
<i>5.2 Integrating collaborative TB and HIV services within a comprehensive package of care for people who inject drugs (PWID): consolidated guidelines</i>	<i>11</i>

5.3 WHO policy on collaborative TB/HIV activities	12
5.4 Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy	12
5.5 Nutritional care and support for patients with tuberculosis	13
6. Managing TB in Children	14
6.1 Guidance for national tuberculosis programmes on the management of tuberculosis in children	14
Limitations	16
Ethical considerations	16
Conclusions	17
References	18

Introduction

The Global TB Programme (GTB) is mandated to produce recommendations to guide clinical practice and public health policy for Tuberculosis (TB) prevention and care. A compilation of the most up to date policy guidance from WHO has been published in *WHO's Compendium of TB Guidelines and Associated Standards (1)*. One of the major challenges facing global policy guidance in TB is the absence of good-quality evidence; suboptimal tools for preventing, diagnosing, and treating TB; and the issues around ensuring equitable access to new tools and interventions. Data and evidence obtained from well-designed, large-scale studies with robust testing of interventions are needed to improve the certainty of recommendations made during guideline development. WHO uses its guideline development process to identify research questions through systematic reviews, economic analyses and stakeholder consultations and publishes these research gaps within the policy guideline documents. In the present document, WHO secretariat has taken steps to compile these research gaps to facilitate their implementation.

Method

WHO guideline development groups (GDGs), which include researchers, health workforce, civil society, as well as end-users of the guidelines, such as policy makers from government, professional associations and other constituencies, have the role of supporting WHO to develop WHO policy guidelines. A GDG meets with the primary objective of agreeing on the scope of recommendations by reviewing evidence, structured according to the standard framework of population, intervention, control, outcomes (PICO). During the process of evidence review, the GDG identifies important gaps in knowledge that need to be addressed through high quality research conducted in various epidemiologic, demographic and geographic settings. The research questions highlighted in this document arose because the respective GDGs agreed they were critical for increasing the certainty of existing recommendation, and/or for stimulating the development or optimizations of new recommendations that can improve patient health and welfare. During this process, the GDGs also noted that for some research gaps there is planned or ongoing research. Since there is no certainty that the planned or ongoing research would give conclusive results, those research topics are still listed as evidence gaps in this document.

Research questions

1. Early detection of TB

1.1 Systematic screening for active tuberculosis: Principles and recommendations

Research gaps documented in this guideline (2) include the following:

- Investigate if shorter duration of cough, in combination with other signs, symptoms and TB risk markers, has sufficient sensitivity and specificity for use as initial TB screening;
- Investigate the feasibility, effectiveness and cost-effectiveness of screening people with previous episodes of TB for broader indications of TB symptoms, along the lines of recommendations for people living with HIV;
- Develop affordable non-sputum based diagnostic tests for pediatric TB, suited for use in low-resource settings¹.

2. Diagnosing TB disease

Current recommendations on the commercial use of the following tests (3-8) should not prevent or restrict further research on new TB diagnostics, especially point-of-care assays that can be used as close as possible to where patients access TB treatment. Research gaps documented during the evaluation of these tests are listed below.

2.1 Xpert MTB/RIF and Ultra assays for the diagnosis of pulmonary and extrapulmonary TB in adults and children & WHO Meeting Report of a Technical Expert Consultation: Non-inferiority analysis of Xpert MTB/RIF Ultra compared to Xpert MTB/RIF

- Diagnostic accuracy of Xpert MTB/RIF Ultra;
- Comparative assessment of diagnostic algorithms involving Xpert MTB/RIF and Ultra in different epidemiological and geographical settings, and patient populations;
- Country-specific cost-effectiveness and cost-benefit analyses of Xpert MTB/RIF and Ultra in different programmatic settings;
- Impact assessment of performing a second Xpert Ultra assay when the initial test was *MTB not detected*, as a way to improve the sensitivity of the testing algorithm;
- Evaluate the role of repeat testing of a fresh specimen with Xpert Ultra from a patient with signs and symptoms of TB whose initial specimen was “trace call” positive, as a way to improve the specificity of the testing algorithm;
- Prospective evaluation using Xpert MTB/RIF and Ultra for the detection of pulmonary TB in children (including urine and stool samples);
- Prospective evaluation using Xpert MTB/RIF and Ultra for the detection of extra-pulmonary TB in adults and children (including urine and stool samples);
- Evaluation of the use of “trace call” result when Xpert Ultra is used for systematic screening, active case finding and for prevalence surveys;

¹ See section 6, Managing TB in children

- Assess the performance of Xpert MTB/RIF and Ultra as a reference standard method for rifampicin resistance detection;
- Evaluation of the impact of Xpert MTB/RIF and Ultra in reducing the diagnostic delay and the time until appropriate treatment is initiated;
- Evaluation of the impact of Xpert MTB/RIF and Ultra on case-detection, treatment access, treatment outcomes and mortality in hard-to-reach populations;
- Meeting the Standards for reporting Diagnostic Accuracy Studies (known as STARD) for future studies (see <http://www.equator-network.org/reporting-guidelines/stard/>).

2.2 The use of loop-mediated isothermal amplification (TB-LAMP) for the diagnosis of pulmonary tuberculosis

- Diagnostic accuracy studies using standardized protocols that include a high-quality culture reference standard (liquid culture results on at least two samples) in order to evaluate relative performance of TB-LAMP compared with the Xpert MTB/RIF assay.
- Comparative evaluation of diagnostic algorithms in different epidemiological and geographical settings and patient populations;
- Impact assessment of TB-LAMP use on TB treatment initiation, morbidity and mortality;
- Country-specific cost-effectiveness and cost-benefit analyses of targeted TB-LAMP use in different programmatic settings;
- Meeting the Standards for reporting Diagnostic Accuracy Studies (known as STARD) for future studies (see <http://www.equator-network.org/reporting-guidelines/stard/>).

2.3 The use of lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis and screening of active tuberculosis in people living with HIV Policy update

- Comparative evaluation of diagnostic algorithms in different epidemiological and geographical settings and patient populations;
- Performance evaluation of LF-LAM in different patient groups of people living with HIV (with signs and symptoms of TB vs without signs and symptoms of TB; CD4 less than 200 vs CD4 more than 200; CD4 less than 100 vs CD4 more than 100; inpatients vs outpatients; adults, adolescents and older children vs children ≤ 5 years);
- Conduct more rigorous studies with higher quality reference standards (including multiple specimen types, also extrapulmonary) to improve confidence in specificity estimates.
- Determine training, competency, and quality assessment needed for maximum impact of LF-LAM;
- Impact of LF-LAM use on TB treatment initiation and mortality;
- Country-specific cost-effectiveness and cost-benefit analyses of targeted LF-LAM use in different programmatic settings;
- Meet the Standards for reporting Diagnostic Accuracy Studies (known as STARD) for future studies (see <http://www.equator-network.org/reporting-guidelines/stard/>).

2.4 The use of molecular line probe assays for the detection of resistance to isoniazid and rifampicin

- Determine the correlation between the detection of resistance-conferring mutations to isoniazid and rifampicin using culture-based DST and patients' treatment outcomes;
- Determine the detection limit of LPA in detecting hetero-resistance to isoniazid and rifampicin;
- Impact of LPA use on appropriate treatment initiation for RR-TB, HR-TB or MDR-TB and treatment outcome (mortality);
- Country-specific cost– effectiveness and cost–benefit analyses of LPA use in different programmatic settings;
- Meet the Standards for reporting Diagnostic Accuracy studies (known as STARD) for future diagnostic studies (see <http://www.equator-network.org/reporting-guidelines/stard/>).

2.5 Molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs: Policy guidance

- Determine the correlation between the detection of resistance- conferring mutations with phenotypic DST results and patient outcomes;
- Develop improved knowledge of the presence of specific mutations detected with the assay, correlated with minimum inhibitory concentrations for individual drugs within the class of fluoroquinolones and group of second-line injectable drugs (SLIDs);
- Determine the limit of detection of LPA for the detection of hetero-resistance;
- Impact assessment of SL-LPA use on appropriate MDR-TB treatment initiation and mortality;
- Country-specific cost-effectiveness and cost-benefit analyses of the use of SL-LPA in different programmatic settings;
- Follow the recommendations in the Standards for Reporting Diagnostic Accuracy (STARD) statement to improve the quality of reporting.

3. Diagnosing and treating latent TB infection

Latent tuberculosis infection: Updated and consolidated guidelines for programmatic management

Overall, the review of evidence for formulating the recommendations in the above-mentioned policy guidance (9) exposed a number of upstream research gaps for effectively preventing, diagnosing and treating LTBI. These include basic and clinical research for the development of affordable diagnostic tests with improved performance and predictive value for progression to active TB; and safer and shorter duration treatments that can cure LTBI. It is imperative that donors and the scientific research community respond equally to all the priorities listed here to improve patient health and save lives.

- Treatment options for LTBI: Research to develop shorter, better-tolerated treatment regimens than those currently recommended is a priority. Studies of efficacy and adverse events in certain risk groups (e.g. people who use drugs, people with alcohol use disorder and elderly people) are essential. In particular, there is little or no data on the use of rifapentine in children < 2 years of age and pregnant women. Drug interactions and pharmacokinetics between rifamycin-containing regimens and other drugs, particularly antiretroviral drugs should be explored. In addition, the durability of protection by preventive treatment should be evaluated in high TB and high MDR TB prevalent areas, and the efficacy of repeated courses of preventive treatment needs to also be evaluated.
- Improved diagnostic tests and performance of LTBI tests in at-risk populations: Diagnostic tests with improved performance and predictive ability to measure reactivation of LTBI to active disease are critically needed. The performance of new and existing LTBI diagnostic tests should be evaluated in various at-risk populations, (e.g. combination or sequential use of TST and IGRA) in each at-risk population.
- Potential of at-risk populations to develop active disease once latently infected Evidence on the potential of at-risk populations to progress from LTBI to active disease with a view to assess the wider public health benefits of preventive treatment and for designing alternative public health interventions. *In particular, strong evidence from clinical trials is lacking for the following groups: patients with diabetes, people with harmful use of alcohol, tobacco smokers, underweight people, patients receiving steroid treatment, patients with rheumatological conditions, indigenous populations and cancer patients.* Both direct measurement of the incidence of active TB and methods for measuring the risk for active TB disease could be explored, such as use of genotyping to measure the risk for reactivation. Evidence is also required on differential harm and the acceptability of testing and treatment for LTBI in specific risk groups, including social adverse events such as stigmatization.
- Adherence to and completion of treatment: Carefully designed studies, including RCTs, are required to generate evidence on the effectiveness of context-specific interventions for enhancing adherence and completion of treatment.
- Preventive treatment for contacts of people with MDR-TB: RCTs with adequate power are urgently needed to stimulate policy recommendation on preventive treatment for contacts of people with MDR-TB. Trials should be performed with both adult and pediatric 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 drugs 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 to develop active disease will be important for understanding the benefits of preventive treatment.

- Risk of drug resistance following LTBI treatment: Programme-based epidemiologic and clinical surveillance is needed to monitor the risk for bacterial resistance to the drugs used in LTBI treatment. Particular consideration should be given to rifamycin-containing regimens because of the dearth of data.
- Cost-effectiveness: Although a number of studies on the cost-effectiveness of TB preventive treatments are available, their wide heterogeneity obviates a comprehensive appraisal of the cost-effectiveness of LTBI management stratified by population group and types of interventions. Direct measurement of cost-effectiveness in certain settings and populations would allow extension of the LTBI strategy at national or local level.
- Programme management: Epidemiological research should be conducted to determine the burden of LTBI in various geographical settings and risk groups and be used as a basis for nationally and locally tailored interventions, including integrated community-based approaches. Research is also needed on service delivery models to ensure that patients are properly managed including the provision of additional interventions for tobacco smokers, illicit drug users, and people with harmful use of alcohol. Household implementation models could improve the effectiveness and efficiency of service delivery. Tools should be developed and assessed to facilitate monitoring and evaluation of programmatic management of LTBI.
- Monitoring of adverse events: Prospective randomized studies are required among various populations at risk of developing active TB to determine the comparative benefit of laboratory monitoring versus patient education and clinical observation, for preventing treatment related severe clinical adverse events.
- Defining the best algorithm for ruling out active TB: Research to determine how to exclude asymptomatic active TB before administering preventive treatment. The performance and feasibility of the algorithms proposed in these guidelines should also be assessed in various at-risk populations, particularly among children and pregnant women. Strategies to save cost and improve feasibility (e.g. use of mobile chest radiography) should also be explored.

4. Treating TB

4.1 Treatment of drug-susceptible tuberculosis and patient care: 2017 update

Research gaps documented in this guideline(10) are summarized below.

- Pharmacokinetic studies of the bioavailability of fixed dose combinations (FDCs) versus separate drug formulations and better development of weight banding categories for drug dosing.
 - The optimal dose of rifampicin, including the use of different drug formulations.
 - Additional qualitative studies detailing medication adherence.
 - Additional work on FDC formulations to further decrease the pill burden, especially among patients with co-morbidities.
- The effectiveness of a TB treatment period greater than 8 months compared to the standard 6-month treatment period for HIV co-infected patients with drug-susceptible pulmonary tuberculosis
 - What are the factors that may cause people, especially people living with HIV, to not respond well to TB treatment (e.g. starting ART late, low CD4 cell counts, TB drug resistance, cumulative drug toxicity, drug-drug interaction with newer ARV drugs)?
 - Explore and describe etiological factors leading to higher death rates and rates of adverse events in HIV-positive TB patients.
- Research on the use of steroids in the treatment regimen of extrapulmonary TB disease
 - The optimal steroid dose for TB meningitis (including different drug formulations).
 - The optimal steroid duration for TB meningitis, and if this duration differs between different grades of meningitis.
 - The different effects of steroids on people who are HIV-positive or HIV-negative, or who are being treated with ART or not.
 - The relationship between steroid treatment and cancer risk – with reference to the study on pericarditis
- More qualitative research and systematic reviews are required on patient values and preferences with regard to TB treatment regimens.
 - The effectiveness of fixed-dose combination TB treatment when compared to separate drug formulations in patients with drug-susceptible TB disease
 - Additional research on the reasons why FDC formulations did not show a clear benefit over separate drug formulations.
- Assess the benefits of treating MDR-TB patients within a decentralized compared to centralized model of care
 - Evaluating the risk of TB transmission in different settings – i.e. does treatment centered on hospital care or outpatient clinics pose a higher risk of transmission?
 - Additional cost-effectiveness studies of decentralized versus centralized care.
 - Many programmes are providing decentralized care, but very few have published the data. Programmes should be encouraged to publish or even just systematically collect their data.

- The effectiveness of different forms of interventions to improve treatment adherence
 - The patient support and treatment supervision interventions that are best suited to populations
 - The patient support interventions that are most effective in low- and middle-income countries.
 - Analysis of the cost-effectiveness of different types of incentives
 - Research into the effectiveness of VOT in low- and middle-income countries, as the available data is from high income countries.
 - Which types of psychological support are most appropriate.
- The effectiveness of intermittent dosing of TB medications, both in the intensive phase and in the continuation phase of treatment, when compared to daily treatment
 - The utility and efficacy of 5 days of treatment per week versus 7 days of treatment per week in the intensive phase of therapy (i.e. sparing weekend dosing).
 - The optimal duration of the intensive phase of therapy.
 - Additional research on the benefit of thrice-weekly dosing in the continuation phase, as effect differences seen in this review between the thrice-weekly dosing in the continuation phase and daily dosing during the continuation phase are small.
- The effectiveness of 4-month fluoroquinolone-containing regimen when compared to the standard 6-month treatment regimen of 2HRZE/4HR in patients with drug-susceptible pulmonary TB disease
 - Certain subgroups may do equally well with a 4-month fluoroquinolone-containing regimen (i.e. people with body mass index (BMI) greater than 18, people with non-severe, non-cavitary disease). Therefore, further research to assess if a 4-month fluoroquinolone-containing regimen could be non-inferior to the standard regimen in these populations may be warranted.
 - The optimal dosing of fluoroquinolone needs to be determined. Higher doses may affect outcomes.
 - To determine why certain groups are more likely to do worse with a 4-month fluoroquinolone-containing regimen.
 - To explore biological mechanisms behind *Mycobacterium TB* persistence and the recurrence of disease despite more rapid culture conversion with certain regimens.

4.2 WHO treatment guidelines for isoniazid-resistant TB

The development of the recommendations in the above mentioned guideline (11) was made possible by the availability of a global, Hr-TB (rifampicin-susceptible, isoniazid-resistant TB), individual patient dataset (IPD). As in other IPD analyses conducted to inform WHO treatment guidelines in recent years, the Hr-TB IPD analysis facilitated the comparison of different patient groups, some adjustment for covariates and better interpretation of the results. It is important for researchers and national programmes to continue contributing patient records to the Hr-TB IPD to increase its value as a source of information for future treatment policy. All recommendations in this guideline were conditional and were based on very low certainty. Thus, further research is needed to inform the refinement of policies to optimize treatment of Hr-TB. The GDG identified various research priorities, including:

- The need for randomized trials evaluating the efficacy, safety and tolerability of regimens for Hr-TB, and for cases with additional resistance to other medicines such as ethambutol or pyrazinamide (e.g. polydrug resistance);
- Evidence to clarify the potential benefits and risks of treatment with high-dose isoniazid;
- High-quality studies on the optimization of the regimen composition (e.g. reducing duration of pyrazinamide) and duration in children and adults, particularly the role of high-dose isoniazid, fluoroquinolones, and other second-line medicines;
- Modelling studies measuring the number-needed-to-treat for empirical use of an Hr-TB regimen, balancing risk to benefit;
- High-quality studies on treatment prolongation among HIV-positive individuals
- High-quality studies evaluating regimens in which especial emphasis is placed on extrapulmonary or disseminated TB;
- Feasibility of Developing FDCs for REZ alone (with or without integrating levofloxacin);
- Monitoring of patient response by isoniazid resistance genotype (e.g. katG vs. inhA mutations), either in an individual-patient or distribution of genotypes in a population;
- Cost-effectiveness of different approaches to DST, including the rapid testing of all TB patients for both isoniazid and rifampicin resistance before start of treatment;
- Participatory action research within communities and other stakeholders (e.g. field practitioners, community workers) to explore and implement socio-cultural factors that can facilitate treatment adherence and influence outcomes;
- Effect of underlying fluoroquinolones/isoniazid polydrug resistance on treatment outcomes;
- Diagnostic accuracy of second-line line probe assays in rifampicin-sensitive patient.

4.3 WHO treatment guidelines for drug-resistant tuberculosis 2016 update

The reviews undertaken during the 2016 update of WHO treatment guideline for drug-resistant TB revealed a number of gaps in current knowledge about critical areas for the treatment of MDR/RR-TB(12). Where evidence was available it was usually assigned a very low-quality rating during evidence grading. This was one of the main reasons why all the recommendations made in this guidelines revision are conditional. The GDG discussed research priorities and highlighted several them.

- The optimal combination of medicines and approach towards regimen-design for patients (both adults and children) with isoniazid-resistant TB, RR-TB, MDR-TB and XDR-TB, as well as for patients with *M. bovis* disease. More randomized controlled trials, especially involving the new drugs and regimens, but also for patients with isoniazid-resistant forms of TB who are placed on fluoroquinolone-containing regimens;
- Inclusion and separate reporting of outcomes for key subgroups, especially children and HIV-positive individuals on treatment, in randomized controlled studies;
- Complete recording of adverse events and standardized data recording on organ class, seriousness, severity, and certainty of association, to allow reliable comparison of the association between adverse events and exposure to different medicines;
- Identification of factors that determine the optimal duration of treatment (e.g. previous treatment history, baseline resistance patterns, site of disease, child/adult);

- Determination of the minimum number of drugs and treatment duration (especially in patients previously treated for MDR-TB);
- Determination of conditions under which injectable-sparing regimens can be used in both children and adults (e.g. surrogates for severity / extent of disease, alternative medication);
- Pharmacokinetic studies to determine optimal drug dosing and safety (especially in pregnancy);
- Develop/identify improved diagnostics and drug-susceptibility testing methods (e.g. a test for pyrazinamide);
- Randomized controlled trials to define the benefits and harms of chemoprophylaxis for child and adult contacts of MDR/RR-TB (with and without additional resistance patterns);
- The composition, dosages and duration of the latent TB infection (LTBI) regimen for MDR-TB needs to be optimized and the potential role of newer drugs with good sterilization properties investigated. Studies are needed to examine the adverse reactions of the long-term use of fluoroquinolones in preventive treatment;
- Impact of palliative and end-of-life care in patients with very advanced resistance patterns;
- The effectiveness and safety of standardized regimens lasting up to 12 months for the treatment of patients with MDR-TB (“shorter regimens”) when compared with longer treatment;
- The effectiveness/safety of the shorter MDR-TB treatment regimen in subgroups which have been systematically excluded from study protocols (e.g. children, patients with different forms of extrapulmonary TB) and in settings where background resistance to drugs other than fluoroquinolones and second-line injectable agents is high (e.g. pyrazinamide or high-level isoniazid resistance);
- Implementation research on the introduction of the shorter MDR-TB regimen;
- More studies on cost effectiveness and health-related quality of life;
- The effect of surgical interventions on treatment outcomes for patients with drug-resistant TB;
- Better definition of the role of surgery (i.e. decisions about when to operate and the type of surgical intervention, drug-resistance patterns), needs to be better examined;
- Improved collection, reporting, standardization of data on surgery including long-term survival post-surgery.

5. HIV infection and other comorbidities

5.1 Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection

Research gaps documented in this guideline(13) are summarized below.

- The optimal timing of initiation of ART in children living with HIV being treated for TB and patients with drug-resistant TB. There is also a need for studies that compare the effect of starting ART within 2 weeks and from 2 weeks but within 8 weeks of TB

treatment. More research is also needed into the optimal timing of initiation of ART in adults and children with TB meningitis.

- Further research is required to determine the safety of DTG and the efficacy of EFV 400 mg/day in people with HIV/TB coinfection and in pregnant and breastfeeding women. EFV exhibits significant genetic-based interindividual pharmacokinetic variability, which can make it challenging to undertake accurate pharmacokinetic/pharmacodynamic (pK/pD) analysis. There is a need to conduct this modelling in African and non-African populations and in people without the CYP2B6 genotype.

5.2 Integrating collaborative TB and HIV services within a comprehensive package of care for people who inject drugs (PWID): consolidated guidelines

Research gaps documented in this guideline(14) are summarized below. In addition, Several priority research questions have previously been identified that can guide the research agenda relating to PWID (15).The Guideline Group also generated the questions below for further research.

- Assess the relative risks for developing TB among non-injecting drug users; crack, cocaine and opiate smokers and people who are living with HIV and those who are HIV-negative;
- Investigate the confounders for TB disease risk among drug-users, for example, poverty, homelessness, mental health problems, etc.;
- Assess country specific contexts and risks for TB among drug-users, particularly in India, Pakistan, Nepal, and other large Asian countries with high prevalence TB/HIV, as well as growing injecting drug use;
- Assess the overall impact of TB disease on drug users;
- Establish numbers for the denominator for injecting drug users: baseline population of drug users; baseline rates of injecting drug use; and TB and HIV rates in background population and in drug users;
- Determine the rate of multidrug-resistant TB and extensively drug-resistant TB (resistance to isoniazid and rifampicin plus any fluoroquinolone and at least one of three injectable second-line drugs (capreomycin, kanamycin and amikacin)) among drug users;
- Comparative assessment of MDR-TB disease and treatment adherence among drug-users inside and outside the prison system;
- What are specific barriers for women drug-users accessing TB care services in different settings, such as in the criminal justice systems;
- Identify impactful and cost-effective strategies to promote TB treatment adherence 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
- Determine the frequency of reinfection during re-exposure among drug users in congregate settings like prison, as well as in non-prison settings, and identify the implication of this on the cascade of care;
- Determine effective strategies for protecting health care workers and other personnel in health care and criminal justice settings from TB;

- What are the most effective advocacy interventions for addressing TB among drug users
- Determine the proportion of drug users maintains treatment on entry to prison and on release or transfer
- Identify strategies to limit lost-to-follow ups among drug-users with TB released from prison while under TB treatment;
- Identify best practices and strategies, alternatives to prisons, for caring for drug users with TB/HIV;
- Determine the proportion of TB detection and treatment outcome among drug users in prisons;
- In the context of the continuum of care, determine the best prison release practices for PWIDs, and on how should this should relate/integrate with TB/HIV programmes and services;
- Assess current general practices for caring for prisoners who are terminally ill. For example, is there an incentive for prisons to discharge if they are monitored on mortality rates?

To ensure the ethical and scientific quality and outcomes of proposed research, its relevance to the affected community, and its acceptance by the affected community, researchers should consult communities through a transparent and meaningful participatory process. This process should involve communities in an early and sustained manner in research design, development, implementation, monitoring, analysis and dissemination of results(16).

5.3 WHO policy on collaborative TB/HIV activities

Cultural and system-wide differences between HIV and TB care providers and operational difficulties for providing effective and appropriate interventions have contributed to a lack of progress in expanding collaborative TB/ HIV activities(17). Operational research is needed to define how best to provide high-quality integrated TB and HIV interventions at facility and community levels to inform global and national policy and strategy development. Priority research questions for TB/HIV in HIV-prevalent and resource-limited settings, including for operational research, have been identified and need to be urgently answered (15).

5.4 Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy

Research gaps documented in this guideline (18) are summarized below.

- Identify the optimal timing of initiation of ART in children living with HIV being treated for TB and patients with drug-resistant TB. There is also a need for studies that compare the effect of starting ART within 2 weeks and from 2 weeks but within 8 weeks of TB treatment. More research is also needed into the optimal timing of initiation of ART in adults and children with TB meningitis;
- Determine the safety of DTG and the efficacy of EFV 400 mg/day in people with HIV/TB coinfection and in pregnant and breastfeeding women;

- Research to better understand choice and sequencing strategies for PI options in second- and third-line ART. Several ongoing studies comparing various drugs and ARV classes will provide more data on appropriate second-line regimens, including NRTI-sparing and NRTI-limiting approaches. The different drug toxicity profiles of ATV/r, DRV/r and LPV/r, the contraindication of using ATV/r and DRV/r with rifampicin and the lack of WHO approval for the use of ATV/r and DRV/r in younger children is noted in this policy guidance. Further investigation is needed of the role of boosted DRV in second- and third-line regimens, including optimal dosing in adults and children, FDCs with other boosting agents and INSTIs, and sequencing strategies. Several trials are under way to examine induction and maintenance using PI/r monotherapy or in combination with 3TC as maintenance therapy. The potential of including rifabutin as part of FDCs for TB treatment also needs to be explored.
- Pharmacovigilance research is needed, including studies on the long-term safety of and potential interactions between drugs used for TB, malaria, hepatitis opioid substitution therapy, and third-line ART drugs.

5.5 Nutritional care and support for patients with tuberculosis

Research gaps documented in this guideline(19) are summarized below.

- The effect of macronutrient intake/food supplementation in addition to treatment alone, on TB treatment outcomes;
- The effect of macronutrient supplementation or routine supplementation with micronutrients at 1× recommended nutrient intake in pregnant women with active TB, and on neonatal complications;
- Benefits of macro- or micronutrient supplementation on growth and development in the 5–19-year age groups with active TB, compared to those without TB;
- Assessment of nutritional parameters/TB-specific outcomes in nutritional supplementation trials;
- The effect of implementing WHO nutrition and TB recommendations on nutritional recovery/TB treatment outcomes;
- The relative importance of food assistance (compared with other enablers) as an enabler to adherence to TB treatment;
- Identify aspects of nutritional counselling that enhance the effectiveness and uptake of advice on nutritional outcomes;
- Identify the best measure of nutritional status in pregnant women, with and without TB, considering both maternal and infant outcomes;
- Identify optimal body mass index ranges for healthy maternal and infant outcomes in pregnant women with TB;
- Identify energy requirements in TB patients compared with persons without TB (including proteins, as well as fat requirements), considering TB treatment, coexistent HIV, phase of treatment and multidrug-resistant tuberculosis (MDR-TB);
- Assess the risk of micronutrient deficiencies in people with active TB in relation to people without TB;
- Identify the proportional causes of malnutrition in people with TB;

- Identify natural course of weight change during the intensive phase of TB treatment in drug-sensitive TB and MDR-TB, in people with different levels of malnutrition, and in settings with varying levels of food security.

6. Managing TB in Children

6.1 Guidance for national tuberculosis programmes on the management of tuberculosis in children

Research gaps documented in this guideline (20) are summarized below.

- Identify, evaluate, and validate new and more effective diagnostics tools to be used as a highly sensitive “rule-out” screening test (requiring non-invasive samples and for use at the point of care). To facilitate this, identify, evaluate and validate (as needed);
 - novel pathogen-associated biomarkers in pediatric populations (e.g. DNA, mRNA expression profiles, micro-RNA, next-generation LAM-based assays)
 - host biomarkers derived from pediatric populations as potential novel test for TB infection, TB disease, risk of disease progression, and response to treatment in children.
- Identify strategies for obtaining specimens effective for increasing diagnostic yield, including non- respiratory samples;
- Evaluate new diagnostic tools in children, including in young, malnourished children, HIV- positive children and children with MDR-TB;
- Evaluation of diagnostic algorithms in different epidemiological settings and identification of the most effective (and cost-effective) strategies for implementation of current and novel diagnostics;
- Determine efficient and reliable systems for specimen collection, transport and laboratory evaluation, especially important for following up children with bacteriologically-negative, paucibacillary specimens.
- Determine the most appropriate and cost-effective service delivery models for children of all ages (0-18) among the maternal and child health continuum of care,
- Evaluate programme integration strategies for pediatric TB, including with HIV; maternal, neonatal and child health, nutrition, and other relevant programmes in order to find missing children and adolescents with TB;
- Assess health system needs, including human resources and cost, for scaling up evidence-based interventions and programme integration for TB prevention and treatment at national level;
- Investigate barriers and opportunities in providing integrated services and develop indicators for assessing quality of care;
- Develop new vaccines that would provide greater protection than BCG, preventing all forms of TB including drug-resistant TB, as well as reactivation of TB, and that would be

effective in all age groups including HIV-infected persons, improves on the safety and perform consistently in all populations

- Below additional research needs as included in the updated WHO position paper on BCG published in February 2018:
 - Assess the safety and effectiveness of BCG vaccination of HIV-infected children, including those receiving ART;
 - Studies on strategies to improve the timeliness of BCG vaccination, and on limiting wastages of vaccine in multi-dose preparations;
 - Long term studies to strategically explore BCG vaccine effectiveness, the duration of BCG-derived protection, particularly in temperate climate settings, and the effect of BCG vaccination on all cause morbidity and mortality.
- Evaluate shorter and simplified drug treatment regimens for TB infection in children including those that can be used to prevent TB among contacts of drug-resistant TB;
 - Evaluate symptom-based screening tools in the screening of child contacts (HIV-positive and -negative);
 - Identify operational challenges to the contact-tracing process for eventual implementation of wide-scale preventive treatment;
 - Identify strategies for enhancing adherence to preventive treatment in children and adolescents;
 - Develop and evaluate cost-effective and child-friendly preventive drug regimens in children to inform optimal dosing, particularly for children co-infected with HIV and younger than 12 months of age;
 - Identify pragmatic and scalable decentralized community-based strategies (e.g. family-centered models) for TB screening and provision of preventive treatment and TB treatment to enhance early entry and retention in the cascade of care;
 - Conduct 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, considering variability by age, nutritional status, co-infections, disease phenotype, as well as mycobacterial and host genotype;
 - Through multi-center longitudinal pediatric cohort studies, support the discovery, evaluation and validation of novel biomarkers (including those that can: accurately distinguish children with TB disease from those presenting with similar symptoms; distinguish between infection and disease; predict risk of disease progression and vaccine efficacy) among children with a broad spectrum of disease presentations.
 - Identify strategies for effective management of child contacts of parents/caregivers with drug-resistant TB in the intensive phase of treatment;
 - Conduct social research to better understand the impact of stigma and TB on education among school-aged children and adolescents.
-
- Pharmacokinetic trials to determine optimal dosages of second-line and novel anti-TB drugs, including in HIV-positive children and especially in children under 2 years of age.
 - Pharmacokinetic trials to determine optimal dosages of anti-TB drugs in newborn, including preterm, infants in the first week of life.

- Clinical trials to determine the efficacy and safety of new regimens of anti-TB drugs in children.
- Determination of the optimal duration of anti-TB treatment in different 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, and ensuring the inclusion of children and adolescents in late stage clinical trials of new TB drugs, regimens, and treatment strategies.
- Develop/evaluate strategies that can shorten and simplify treatment, and reduce treatment-related toxicities for children with all forms of TB, including TB meningitis
- Describe and monitor the burden of TB infection and disease (including drug-resistant TB) and treatment outcomes among children and adolescents at national level;
- Describe and monitor the burden of TB infection and disease (including drug-resistant TB), socio-economic impact and treatment issues for children and adolescents living with HIV;
- Describe the occurrence of residual morbidity after cure or completion of TB treatment (both in HIV-negative and positive children and adolescents), including long-term adverse effects and socio-economic impacts of TB treatment;
- Evaluate completeness of routine recording and reporting of childhood TB along the care cascade, including how to strengthen and standardize reporting of child contact management and the provision of preventive treatment.

Limitations

The compilation of research questions in the present document is limited in scope by research gaps identified during guideline development processes. Consequently, exclusively research questions articulated within WHO TB policy guidelines are reported. Research gaps were documented as they arose during evidence review through decisions based on consensus amongst GDG members. Individuals with significant professional, intellectual, scientific or financial conflicts of interest were not included in GDG decision making as per WHO procedures (21). The WHO Secretariat is committed to periodically update and disseminate the research gaps documented in this report to reflect new developments as they emerge. Feedback on this document is welcome: please contact the WHO Secretariat at gebreselassien@who.int.

Ethical considerations

Compiling the research gaps from WHO policy guidelines presents an opportunity to highlight the principles of “protecting human rights, ethics and equity”, one of the four key principles of the WHO End TB Strategy. Health research should be guided by international and national principles on 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 the implementation of the End TB Strategy (22) to ensure that due attention to equity, human rights and ethics is given in all aspects of TB prevention and care services.

Conclusions

Research can have a central role in supporting guideline development by providing the evidence base needed to alleviate the range and extent of problems that TB policy makers face. All research gaps documented within the most recent WHO TB policy guidelines are summarized in this report. This is the first time these research gaps have been compiled by WHO as a means to stimulate large-scale well-funded, and coordinated research executed by skilled research teams working in partnership with clinicians, patients and policy makers, including where possible, WHO.

Future work will include developing a methodological framework for research gap identification and prioritization for GDGs to ensure the appropriate need for evidence in TB prevention and care is documented systematically. Future work will also consider qualifying the research questions in terms of how long it potentially takes to answer each research question taking into account the stage the research area has reached, and the relative complexity, scale and length of time it might take to undertake it. Considering the significant funding gap for TB research, we hope this report will help direct time and resources to the most urgent evidence needs faced by policy makers.

References

- 1 WHO Compendium of TB Guidelines and Associated Standards. Geneva: World Health Organization. Geneva: World Health Organization; 2018 (http://www.who.int/tb/features_archive/TB_guidelines_associated_standards/en/ accessed 25 June 2018).
- 2 Systematic screening for active tuberculosis: Principles and recommendations. Geneva: World Health Organization; 2013 (<http://www.who.int/tb/publications/tbscreening/en/>, accessed 25 June 2018).
- 3 Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children : policy update. Geneva: World Health Organization; 2013 (<http://www.who.int/tb/publications/xpert-mtb-rif-assay-diagnosis-policy-update/en/>, accessed 25 June 2018).
- 4 WHO meeting report of a technical expert consultation: non-inferiority analysis of Xpert MTB/RIF Ultra compared to Xpert MTB/RIF. Geneva: World Health Organization; 2017 (<http://apps.who.int/iris/bitstream/10665/254792/1/WHO-HTM-TB-2017.04-eng.pdf>, accessed 25 June 2018).
- 5 The use of loop-mediated isothermal amplification (TB-LAMP) for the diagnosis of pulmonary tuberculosis. Geneva: World Health Organization; 2016 (<http://www.who.int/tb/publications/lamp-diagnosis-molecular/en/>, accessed 25 June 2018).
- 6 The use of lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis and screening of active tuberculosis in people living with HIV. Geneva: World Health Organization; 2015 (<http://www.who.int/tb/publications/use-of-lf-lam-tb-hiv/en/>, accessed 25 June 2018).
- 7 The use of molecular line probe assays for the detection of resistance to isoniazid and rifampicin. Geneva: World Health Organization; 2016 (<http://www.who.int/tb/publications/molecular-test-resistance/en>, accessed 15 June 2018).
- 8 The use of molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs: policy guidance. Geneva: World Health Organization; 2016 (<http://apps.who.int/iris/bitstream/10665/246131/1/9789241510561-eng.pdf?ua=1> accessed 15 June 2018).
- 9 Latent TB Infection : Updated and consolidated guidelines for programmatic management. Geneva: World Health Organization; 2018 (<http://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/>, accessed 25 June 2018).
- 10 WHO treatment guidelines for isoniazid-resistant tuberculosis. Geneva: World Health Organization; 2018 (http://www.who.int/tb/publications/2018/WHO_guidelines_isoniazid_resistant_TB/en/ accessed 25 June 2018).
- 11 WHO treatment guidelines for drug-resistant tuberculosis-2016 update. Geneva: World Health Organization; 2016 (<http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/resources/en/>, accessed 25 June 2018).

- 12 Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection Recommendations for a public health approach Geneva: World Health Organization; (<http://www.who.int/hiv/pub/arv/arv-2016/en/>, accessed 20 June 2018).
- 13 Integrating collaborative TB and HIV services within a comprehensive package of care for people who inject drugs: consolidated guidelines Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/10665/204484/1/9789241510226_eng.pdf?ua=1, accessed 20 June 2018).
- 14 Priority research questions for TB/HIV in HIV-prevalent and resource-limited settings. Geneva: World Health Organization; 2010 (http://apps.who.int/iris/bitstream/10665/44431/1/9789241500302_eng.pdf, accessed 08 September 2018).
- 15 Ethical considerations in biomedical HIV prevention trials. Geneva, Joint United Nations Programme on HIV/AIDS. Geneva: 2012 (http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2012/jc1399_ethical_considerations_en.pdf, accessed 05 July 2018).
- 16 WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders. Geneva: World Health Organization; 2012 (http://www.who.int/tb/publications/2012/tb_hiv_policy_9789241503006/en/, accessed 25 June 2018).
- 17 Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy. Geneva: World Health Organization; 2017 (<http://www.who.int/hiv/pub/guidelines/advanced-HIV-disease/en/>, accessed 25 June 2018).
- 18 Nutritional care and support for patients with tuberculosis. Geneva: World Health Organization; 2013 (http://www.who.int/nutrition/publications/guidelines/nutcare_support_patients_with_tb/en/, accessed 25 June 2018).
- 19 Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2nd ed. Geneva: World Health Organization. Geneva, World Health Organization. 2014 (http://apps.who.int/iris/bitstream/10665/112360/1/9789241548748_eng.pdf?ua=1, accessed).
- 20 Handbook for Guideline Development. Geneva: World Health Organization; 2014 (http://www.who.int/publications/guidelines/handbook_2nd_ed.pdf?ua=1, accessed 24 June 2018).
- 21 Ethics guidance for the implementation of the End TB Strategy. Geneva: World Health Organization; 2017 (<http://www.who.int/tb/publications/2017/ethics-guidance/en/>, accessed 25 June 2018).