WHO consolidated guidelines on tuberculosis

Module 4: treatment and care

Second edition

World Health Organization

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Contents

Acknowledgements v

Abbreviations and acronyms vi

Definitions ix

Executive summary xi

Chapter 1 Drug-susceptible TB treatment 1

Introduction 3

Structure of the chapter 4

Summary of WHO recommendations on drug-susceptible TB treatment 4

Recommendations 7

A1. Treatment of drug-susceptible TB using a 6-month regimen 7

A2. Treatment of drug-susceptible TB using 4-month regimens 15

A3. Drug-susceptible TB treatment and ART in people living with HIV 24

A4. The use of adjuvant steroids in the treatment of TB meningitis and pericarditis 26

A5. Treatment regimens for extrapulmonary TB in children and adolescents 27

A6. Monitoring and evaluation 32

Research gaps 33

References (Chapter 1) 35

Chapter 2 Drug-resistant TB treatment 41

Introduction 43

Summary of WHO recommendations on DR-TB treatment 50

Recommendations 55

B1. Treatment of drug-resistant TB using 6-month regimens 55

B2. Treatment of drug-resistant TB using 9-month regimens 112

B3. Treatment of drug-resistant TB using longer regimens 147

B4. Treatment of rifampicin-susceptible and isoniazid-resistant TB (Hr-TB) 168

B5. Monitoring and management strategies for MDR/RR-TB treatment 176
B6. Starting antiretroviral therapy in patients on MDR/RR-TB regimens 181
B7. Surgery for patients on MDR/RR-TB treatment 182
B8. Hepatitis C virus (HCV) and MDR/RR-TB treatment co-administration 184

Research gaps 191

References (Chapter 2) 197

Chapter 3 Tuberculosis care and support 209

Introduction 211

Summary of WHO recommendations on TB care and support 211

Recommendations 215

C1. Care and support interventions for all people with TB 215
C2. Models of care for people with drug-resistant TB 224
C3. Models of care for children and adolescents exposed to TB or with TB disease 226
C4. Palliative care interventions for MDR/RR-TB patients 233

Research gaps 239

References (Chapter 3) 241

Annex 1. Summary of recommendations 253

Annex 2. Expert panels 298

Annex 3. Declarations of interest 318

Annex 4. PICO questions 346

Annex 5. Summary of evidence, GRADE evidence profiles and evidence-to-decision tables 377

Annex 6. Reports of the systematic reviews for tuberculosis care and support 512

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The details on the members of the Guideline Development Group and other groups and partners who contributed to all the related policy updates can be found in **Annex 2**.

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Abbreviations and acronyms

AE	Adverse event
AFB	acid-fast bacilli
AIDS	acquired immunodeficiency syndrome
aOR	adjusted odds ratio
aRR	adjusted risk ratio
ART	antiretroviral therapy
BMI	body mass index
CI	confidence interval
CL	confidence limits
CNS	central nervous system
DALY	disability-adjusted life year
DELIBERATE	DELamanId Bedaquiline for ResistAnt TubErculosis (trial)
DR-TB	drug-resistant tuberculosis
DSD	differentiated service delivery
DS-TB	drug-susceptible tuberculosis
DST	drug susceptibility testing
ECG	electrocardiogram
EDRWeb	Electronic Drug-Resistant Tuberculosis Register (South Africa)
FDC	fixed-dose combination (medicines)
GDF	Global Drug Facility
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRC	Guidelines Review Committee
HIV	human immunodeficiency virus
Hr-TB	rifampicin-susceptible, isoniazid-resistant tuberculosis
HTH	Department for HIV, Tuberculosis, Hepatitis and Sexually Transmitted Infections (HTH)
iCCM	integrated community case management
IMCI	integrated management of childhood illness
IPD	individual patient data (or dataset)
IQR	interquartile range
LTFU	loss to follow-up
LPA	line probe assay
M. tuberculosis	*Mycobacterium tuberculosis*
MDR-TB	multidrug-resistant tuberculosis
MDR/RR-TB	multidrug- or rifampicin-resistant tuberculosis

MIC	minimum inhibitory concentration
MSF	Médecins Sans Frontières
NExT	Newer and Emerging Treatment for MDR/RR-TB (trial)
NGO	non-government organization
NTP	national TB programme
PHC	primary health care
PK	pharmacokinetic
PICO	population, intervention, comparator and outcomes
pre-XDR-TB	pre-extensively drug-resistant tuberculosis
QTcF	corrected QT interval by Fredericia
RCT	randomized controlled trial
RD	risk difference
REZ	rifampicin–ethambutol–pyrazinamide
RR	risk ratio
RR-TB	rifampicin-resistant tuberculosis
SAT	self-administered therapy (also meaning unsupervised treatment)
SMD	standardized mean difference
SMS	short message service or text message
SoC	standard of care
SRL	TB supranational reference laboratory
STREAM	Standard Treatment Regimen of Anti-tuberculosis Drugs for Patients with MDR-TB (trial)
TB	tuberculosis
TBM	tuberculous meningitis
The Union	International Union Against Tuberculosis and Lung Disease
TPT	TB preventive treatment
VST	video-supported treatment
USA	United States of America
WHO	World Health Organization
WHO/HTH	Department for HIV, Tuberculosis, Hepatitis and Sexually Transmitted Infections (HTH)
XDR-TB	extensively drug-resistant tuberculosis

TB medicines

B or Bdq	bedaquiline
C or Cfz	clofazimine
Cs	cycloserine
D or Dlm	delamanid
E	ethambutol
Eto	ethionamide
FQ	fluoroquinolones
H	isoniazid
Hh	isoniazid high dose
Ipm–Cln	imipenem–cilastatin
L or Lzd	linezolid
Lfx	levofloxacin
M or Mfx	moxifloxacin
Mpm	meropenem
P or Rpt	rifapentine
Pa	pretomanid
PAS	*p*-aminosalicylic acid
Pto	prothionamide
R	rifampicin
Z or PZA	pyrazinamide

TB treatment regimens

BDLC	bedaquiline, delamanid, linezolid and clofazimine
BDLLfx	bedaquiline, delamanid, linezolid and levofloxacin
BDLLfxC	bedaquiline, delamanid, linezolid, levofloxacin and clofazimine
BPaL	bedaquiline, pretomanid and linezolid
BPaLC	bedaquiline, pretomanid, linezolid and clofazimine
BPaLM	bedaquiline, pretomanid, linezolid and moxifloxacin
BLLfxCZ	bedaquiline, linezolid, levofloxacin, clofazimine and pyrazinamide
BDLLfxZ	bedaquiline, delamanid, linezolid, levofloxacin and pyrazinamide
BLMZ	bedaquiline, linezolid, moxifloxacin and pyrazinamide
HPMZ	isoniazid, rifapentine, moxifloxacin and pyrazinamide
HRZE	isoniazid, rifampicin, pyrazinamide and ethambutol
HRZEto	isoniazid, rifampicin, pyrazinamide, ethambutol and ethionamide
(H)REZ–Lfx	(isoniazid optional) – rifampicin, ethambutol, pyrazinamide and levofloxacin
(H)RZE	rifampicin–ethambutol–pyrazinamide

Definitions

Adverse event: any untoward medical occurrence that may present in a person with tuberculosis (TB) during treatment with a pharmaceutical product but that does not necessarily have a causal relationship with the treatment.

Bacteriologically confirmed: a person from whom a biological specimen is positive by a World Health Organization (WHO) recommended rapid diagnostic test, culture, or smear microscopy.

Clinically diagnosed: a person who does not fulfil the criteria for bacteriological confirmation but has been diagnosed with TB disease by a medical practitioner who has decided to give the person a full course of TB treatment. This definition includes pulmonary cases diagnosed based on radiographic abnormalities and extrapulmonary cases diagnosed based on suggestive clinical presentation or histology. Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

Drug-resistant TB (DR-TB): a person with TB disease who is infected with a strain of *M. tuberculosis* complex that is resistant to any TB medicines tested. When available, drug susceptibility testing (DST) results for individual drugs should be recorded.

Drug-susceptible TB (DS-TB): a person with TB disease for whom there is no evidence of infection with a strain of *M. tuberculosis* complex that is resistant to rifampicin or isoniazid. This includes people for whom DST was not done or for whom DST shows a strain of *M. tuberculosis complex* that is susceptible to both rifampicin and isoniazid.

Drug susceptibility testing (DST): in vitro testing of a strain of *M. tuberculosis* complex using either molecular, genotypic techniques to detect resistance-conferring mutations; or phenotypic methods to determine susceptibility to a medicine.

Extensive (or advanced) pulmonary TB disease: presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged below 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest radiography.

Extensively drug-resistant TB (XDR-TB): a person with TB disease who is infected with a strain of *M. tuberculosis* complex that is resistant to rifampicin (and which may also be resistant to isoniazid), as well as resistant to at least one fluoroquinolone (levofloxacin or moxifloxacin) and at least one other "Group A" drug (bedaquiline or linezolid).

Extrapulmonary TB: a person with TB disease involving organs other than the lung parenchyma or tracheobronchial tree (e.g. pleura, lymph nodes, digestive track, genitourinary tract, skin, joints and bones, meninges).

Isoniazid-resistant, rifampicin-susceptible TB (Hr-TB): a person with TB disease who is infected with TB disease caused by a strain of *M. tuberculosis* complex that is resistant to isoniazid but susceptible to rifampicin.

Multidrug-resistant TB (MDR-TB): a person with TB disease who is infected with a strain of *M. tuberculosis* complex that is resistant to both rifampicin and isoniazid.

MDR/RR-TB: MDR-TB is a subset of rifampicin-resistant TB (RR-TB), and the two are often grouped together using the term MDR/RR-TB.

New case: a person with TB disease who has never been treated for TB or has only previously ever taken TB drugs for less than 1 month.

New episode: a person with TB disease who is classified as a new case, a recurrent case or a case with unknown previous treatment history (i.e. any case apart from a re-registered case).

Palliative care: the prevention and relief of the physical, psychological, social and spiritual suffering of adults and children with serious illnesses, and psychosocial support for their families. Palliative care enhances quality of life, promotes dignity and comfort, and may also positively influence the course of illness. It provides accompaniment for the patient and family throughout the course of illness and should be integrated with and complement prevention, early diagnosis and treatment of serious health problems such as TB.

Pre-extensively drug-resistant TB (pre-XDR-TB): a person with TB disease who is infected with TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (either levofloxacin or moxifloxacin).

Pulmonary TB: a person with TB disease involving the lung parenchyma or the tracheobronchial tree. *Note: A case with both pulmonary and extrapulmonary TB should be recorded and counted as a pulmonary TB case for surveillance purposes. Miliary TB is classified as pulmonary TB.*

Rifampicin-resistant TB (RR-TB): a person with TB disease who is infected with a strain of *M. tuberculosis* complex that is resistant to rifampicin. *Note: these strains may be susceptible or resistant to isoniazid (i.e. MDR-TB) or resistant to other first-line or second-line TB medicines.*

Serious adverse event: an adverse event that leads to death or a life-threatening experience, to hospitalization or prolongation of hospitalization, to persistent or significant disability, or to a congenital anomaly. It includes adverse events that do not immediately result in one of these outcomes but that require an intervention to prevent such an outcome from happening. Serious adverse events may require a drastic intervention, such as termination of the drug suspected of having caused the event.

Severe extrapulmonary TB: the presence of miliary TB, TB meningitis, osteoarticular or pericardial TB. In children aged below 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are considered severe.

Social support: in this document the term is defined as support to TB patients that includes informational and educational support (health education and counselling), psychological or emotional support, material support and companion support.

TB patient: a person who is receiving care for TB disease.

Tuberculosis (TB) disease: A disease in humans caused by the *M. tuberculosis* complex, which includes closely related organisms – *M. africanum, M. bovis, M. canetti, M. caprae, M. microti, M. mungi, M. orygis, M. pinnipedii, M. suricattae and M. tuberculosis*. The most common and important agent of human disease is *M. tuberculosis*.

Treatment adherence interventions: these include social support such as: patient education or information support and counselling; material support (e.g. food, financial enablers and transport fees); psychological support; tracers, such as home visits or digital health communications (e.g. short message service [SMS], telephone calls); medication monitors; and staff education. The interventions should be selected on the basis of the assessment of the individual patient's needs, values and beliefs, and the provider's resources and conditions for implementation.

Treatment administration options: these include various suitable forms of treatment support, such as regular community- or home-based treatment support and video-supported treatment. The options also include less preferable forms of treatment administration such as health facility-based treatment support and self-administered or unsupervised treatment.

Treatment support: is used in this document to describe an approach to supporting patients who are taking prescribed doses of TB medicines to help ensure adherence to treatment and maximize its efficacy. Treatment support needs to be provided in the context of person-centred care and should be based on the individual patient's needs and preferences, and the acceptability of the support. It includes aspects of support, motivation and understanding of patients without coercion. Historically, this group of interventions were labelled as "directly observed treatment" or DOT.

Executive summary

The World Health Organization (WHO) Department for HIV, Tuberculosis, Hepatitis and Sexually Transmitted Infections (HTH) maintains all current recommendations on tuberculosis (TB) treatment and care in one overall set of consolidated guidelines. The guidelines contain recommendations pertaining to all areas related to the programmatic management of TB; for example, screening, preventive treatment, diagnostics, patient support, and the treatment of drug-susceptible TB (DS-TB) and drug-resistant TB (DR-TB) in all patients. The consolidated guidelines contain modules specific to each programmatic area.

The first edition of *WHO consolidated guidelines on tuberculosis. Module 4: treatment and care (1)* was published in 2025. In this updated and consolidated second edition, stakeholders will be able to distinguish between:

- previous recommendations that remain valid (referred to as "Unchanged");
- previous recommendations that have been updated (referred to as "UPDATED"); and
- new recommendations that have been developed based on additional studies, considering the range of known benefits and potential harms, modelling exercises and other data to inform the decision-making process (referred to as "NEW").

The methods used to develop and formulate the recommendations complied with WHO standards for guideline development. They were based on up-to-date evidence reviews, complemented with additional information on values and preferences, feasibility and acceptability, and cost. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to rate the certainty in the estimate of effect as high, moderate, low or very low; it was also used to determine the strength of the recommendations, rating them as strong or conditional.

Objectives

The objectives of these updated guidelines are to:

- provide updated, evidence-based recommendations on the treatment and care of people with DS-TB and DR-TB, including children and adolescents, people living with HIV and people with hepatitis C virus (HCV) coinfection;
- consolidate, in a single reference document, all valid WHO recommendations on TB treatment regimens, monitoring, models of care and patient support, with clear labelling of recommendations that are new, updated or unchanged in this edition;
- support the alignment of national TB policies and programmes with the WHO End TB Strategy *(2)* by promoting safer, shorter, more effective and more people-centred treatment regimens; and
- identify priority research gaps to inform the next generation of evidence on TB treatment and care.

Target audience

These guidelines are primarily targeted at policy-makers in ministries of health or managers of national TB programmes (NTPs) who formulate country-specific TB treatment guidelines or are involved in the planning of TB treatment programmes.

The recommendations are also intended for use by:

- health professionals, including doctors, nurses, pharmacists and educators working in governmental and nongovernmental organizations involved in TB care;
- technical agencies and partners supporting the planning, implementation and monitoring of TB treatment services;
- clinicians, researchers and academic institutions involved in TB clinical care, training and research;
- civil society, community organizations, TB-affected communities and TB survivors engaged in advocacy, service delivery and accountability.

Methods

Since 2007, the guideline development process within the WHO has been overseen by the WHO Guidelines Review Committee (GRC), which follows internationally recognized standards (e.g. the GRADE approach) to support a structured and transparent methodology for policy-making. The policy recommendations presented in this guideline document were developed following the standards and updated procedures as described in the *WHO handbook for guideline development (3)*.

A WHO Guideline Steering Group was first established to determine specific areas requiring up-to-date evidence and to carry out arrangements to bring together experts to synthesize and independently review new evidence and develop recommendations. An external review group was also assembled to review the updated recommendations based on the inputs of the Guideline Development Group (GDG). The GDG comprises researchers, epidemiologists, end-users (clinicians and NTP officers), community representatives and experts in evidence synthesis. In compliance with the procedures and practices established by the GRC, declarations of interest (DOI) *(4)* were managed according to WHO requirements *(4)*, which include a review of curriculum vitae and critical evaluation of DOI. Additionally, contingent on the assessment of competing interests, the full list of members of the GDG and their biographies were published on the WHO website. This was followed by a public notice and comment period, during which WHO allowed members of the public to provide comments pertinent to any interests that may have gone unnoticed or not reported during earlier assessments.

During the virtual GDG meeting, the members of the group reached decisions through a process of discussion and consensus. Where consensus through discussion could not be reached, the GDG members voted on decisions, and decisions were made based on the vote of the majority.

Preparation for evidence assessment

The GRADE approach was used to rate the certainty in the estimate of effect (certainty of evidence) as high, moderate, low or very low, and to determine the strength of the recommendations as strong or conditional. A scoping proposal was submitted and approved by the WHO GRC. Details about the preparatory work ahead of the update were released to the public through public comment, focusing on the following:

- rationale for providing up-to-date guidance, including the scope of the updates;
- prioritization and formulation of key questions; and
- the list, affiliations and constituencies of potential members of the GDG undergoing conflict of interest assessments, as per the WHO Office of Compliance, Risk Management and Ethics policies.

In preparation for the GDG meeting, four webinars (via Zoom®) were held with members of the group to finalize the scoping and PICO (population, intervention, comparator and outcomes) questions, score outcomes of interest and discuss preliminary results of data analysis. The PICO questions – including subpopulations, treatment regimen composition, duration and outcomes – were agreed upon by members of the GDG. The questions were framed to capture the effect of novel treatment regimens

for specific populations and the values, in terms of effectiveness and safety, of adding, prolonging and combining specific anti-TB agents.

The PICO questions looked at six distinct outcomes: sustained treatment success; treatment failure and recurrence; death (due to any cause); loss to follow-up; serious adverse event or adverse events of special interest; and amplification (acquisition) of drug resistance.

Members of the GDG were invited to score the outcomes as "critical", "important" or "not important" for making recommendations on the use of specific regimens under evaluation.

Certainty of evidence and strength of recommendations

In assessing the certainty of evidence, several factors can increase or decrease it. The highest certainty rating is usually assigned to evidence gathered from randomized control trials, while evidence from observational studies, including programmatic data, may usually be assigned a low or very low certainty value. The higher the certainty of evidence, the more likely it is that a strong recommendation can be made (Table A). The criteria used by the GDG to determine the quality of available evidence are summarized in the summary of evidence tables (Annex 5). The certainty in the estimates of effect (certainty of evidence) was assessed and either rated down or up based on considerations such as risk of bias, inconsistency or heterogeneity, indirectness and imprecision.

Table A. Certainty of evidence and its impact on the estimate of effect

Certainty of evidence	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

Through the GRADE approach, the strength of a recommendation is classified as "strong" or "conditional". The strength of a recommendation is determined by the balance between desirable and undesirable effects, values and preferences, resource use, equity considerations, acceptability and feasibility to implement the intervention. For strong recommendations, the GDG is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects. For conditional recommendations, the GDG considers that desirable effects probably outweigh the undesirable effects. The strength of a recommendation has different implications for the individuals affected by these guidelines (Table B).

Table B. Perspective taken and description of strength and conditionality of recommendations

Perspective	Strong recommendation	Conditional recommendation
From patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
From clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guidelines could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients, and that patients must be helped to arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
From policy-makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

The full GRADE evidence profiles and evidence-to-decision tables are provided in Annex 5.

Assessment of the quality of the evidence

The WHO guideline development process uses specific criteria to assess the characteristics of a body of evidence. Examples of these criteria are within-study bias (methodological quality), consistency, precision, directness or applicability of the evidence.

Publication, implementation and evaluation

These guidelines were prepared in accordance with the requirements of the GRC. They will be published on the WHO website for free download as part of the. comprehensive WHO consolidated guidelines on TB, and will be communicated widely at international and regional conferences and meetings of programme managers in all regions. In parallel with the guidelines, WHO will also release an operational handbook with more practical details to support the programmatic implementation of the new or revised recommendations. NTPs will be supported by WHO and technical and funding partners to prepare a national plan for the programmatic management of DR-TB.

Implementers should create a conducive policy and programmatic environment – including national and local policies and standard operating procedures – to facilitate the implementation of the recommendations in these guidelines. This should include promoting universal health coverage and offering public financing for DR-TB management. Furthermore, dedicated resources should be allocated, including for staff development and service delivery in the community. It is important that frontline health care staff and students are trained on critical areas such as diagnosis, designing a regimen, patient support, monitoring response to treatment and management of adverse reactions. NTPs should ensure meaningful engagement with affected populations, their communities, the private sector, and other relevant health programmes and ministries in both planning and implementing the

recommendations. The uptake of these WHO recommendations will be monitored in the annual data collection of WHO global TB data monitoring.

What is new in this edition

This second edition (2026) of the consolidated treatment and care guidelines carries forward all valid recommendations from the first edition *(5)*, merges recommendations from the WHO consolidated guidelines on the management of TB in children and adolescents *(6)*, and adds new and updated recommendations developed by the GDG at its November 2025 meeting.

Drug-susceptible TB treatment (Chapter 1)

The following recommendations related to the management of TB in children and adolescents have been consolidated:

- **A1.6a–c (Unchanged):** detailing the use of ethambutol as the fourth drug in the standard treatment regimen for children with pulmonary TB or tuberculous peripheral lymphadenitis, depending on the setting, and the management of TB in infants aged 0–3 months with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis.
- **A5.1 (Unchanged):** the 2HRZE/10HR regimen for children with suspected or confirmed tuberculous meningitis or osteoarticular TB.
- **A5.2 (Unchanged):** the 6-month intensive regimen (6HRZEto) as an alternative to the standard 12-month regimen in children and adolescents with TB meningitis (TBM).

Drug-resistant TB treatment (Chapter 2)

Pooled evidence from the BEAT Tuberculosis and endTB-Q trials, with extended follow-up data from TB-PRACTECAL, supported a more stratified treatment approach for pulmonary pre-extensively drug-resistant TB (pre-XDR-TB), in which regimen choice now depends on disease severity:

- **B1.1 (UPDATED):** the 6-month BPaL/M/C regimen. The BPaLM regimen continues to be suggested for most patients with multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB). The recommendation has been restructured to incorporate two new sub-recommendations for pulmonary pre-XDR-TB: **B1.1a (NEW)** suggests the 6-month BPaL regimen in non-severe disease, and **B1.1b (NEW)** suggests the 6-month BPaLC regimen (with clofazimine) in severe disease.
- **B1.2 (UPDATED):** the 6-month BDLLfx/C regimen. The BDLLfx/C regimen is retained as an option for patients who cannot receive BPaLM. Two new sub-recommendations have been added on the use of the BDLC variant in pulmonary pre-XDR-TB: **B1.2a (NEW)** suggests the 6-month BDLC regimen in non-severe pulmonary pre-XDR-TB, while **B1.2b (NEW)** suggests against using BDLC in severe pulmonary pre-XDR-TB, where amplification of resistance is more likely.

Tuberculosis care and support (Chapter 3)

C4.1 (NEW): palliative care interventions for people with pulmonary MDR/RR-TB. Drawing on a randomized trial of nurse-led palliative care in Uganda, WHO now recommends integrating palliative care assessment and interventions, delivered by trained providers, alongside effective MDR/RR-TB treatment. The recommendation introduces a new section (C4) in the chapter on TB care and support and is the first WHO recommendation to address the palliative care needs of people on TB treatment.

What has not changed

All other recommendations from the 2025 first edition remain valid in this edition without modification, including all recommendations on DS-TB treatment (Chapter 1); the 9-month all-oral regimens, longer regimens, the Hr-TB (rifampicin-susceptible, isoniazid-resistant TB) regimen, monitoring of MDR/RR-TB treatment, antiretroviral therapy (ART), surgery and HCV co-administration in Chapter 2; and the existing care and support recommendations C1–C3.

Chapters and sections

The consolidated guidelines document is divided into three chapters and relevant sections as shown below. Each section presents the series of recommendations with the justifications, evidence, subgroups and implementation considerations.

Chapter 1. Drug-susceptible TB treatment

A1. Treatment of drug-susceptible TB using a 6-month regimen

A2. Treatment of drug-susceptible TB using 4-month regimens

A3. Drug-susceptible TB treatment and antiretroviral therapy (ART) in people living with HIV

A4. The use of adjuvant steroids in the treatment of TB meningitis and pericarditis

A5. Treatment regimens for extrapulmonary TB in children and adolescents

Chapter 2. Drug-resistant TB treatment

B1. Treatment of drug-resistant TB using 6-month regimens (UPDATED and NEW)

B2. Treatment of drug-resistant TB using 9-month regimens

B3. Treatment of drug-resistant TB using longer regimens

B4. Treatment of rifampicin-susceptible and isoniazid-resistant TB (Hr-TB)

B5. Monitoring and management strategies for MDR/RR-TB treatment

B6. Starting ART in patients on MDR/RR-TB regimens

B7. Surgery for patients on MDR/RR-TB treatment

B8. Hepatitis C virus (HCV) and MDR/RR-TB treatment co-administration

Chapter 3. Tuberculosis care and support

C1. Care and support interventions for all people with TB

C2. Models of care for people with drug-resistant TB

C3. Models of care for children and adolescents exposed to TB or with TB disease

C4. Palliative care interventions for MDR/RR-TB patients (NEW)

Summary of recommendations

All recommendations consolidated in this second edition (2026) are listed below in Table C. Each recommendation carries the identifier used in this edition (Annex 1); the recommendation text; the recommendation's strength and the certainty of the supporting evidence (in italics); and a short status entry indicating whether it is new in this edition, was updated in this edition, or remains unchanged from a previous WHO guideline (with the year in which it was first issued or last substantively updated).

Note on the labelling of recommendations

In this second edition, recommendations are labelled as follows:

- **NEW** indicates a recommendation issued for the first time at the November 2025 GDG meeting and published in this edition – these are shown with a green background;
- **UPDATED** indicates a recommendation whose wording, scope, strength or certainty rating has been substantively revised in this edition – these are shown with a pink background; and
- **Unchanged** indicates a recommendation carried forward, in its current wording, from a previous WHO TB guideline (the year shown in parentheses indicates the year in which the recommendation was first issued or, where applicable, last substantively updated) – these are shown with a grey background.

The complete history of changes to each recommendation is provided in Annex 1.

Table C. Summary of recommendations

Chapter 1. Drug-susceptible TB treatment

ID	Recommendation	Strength / certainty	Status (year)
A1. Treatment of DS-TB using a 6-month regimen			
A1.1	New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR.	*Strong / high*	**Unchanged (2010)**
A1.2	Wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy.	*Strong / high*	**Unchanged (2010)**
A1.3	In all patients with drug-susceptible pulmonary TB, the use of thrice-weekly dosing is not recommended in either the intensive or continuation phase; daily dosing remains the recommended dosing frequency.	*Conditional / very low*	**Unchanged (2017)**
A1.4	The use of fixed-dose combination tablets is recommended over separate drug formulations in the treatment of patients with drug-susceptible TB.	*Conditional / low*	**Unchanged (2017)**
A1.5	In new pulmonary TB patients treated with the regimen containing rifampicin throughout treatment, if a positive sputum smear is found at completion of the intensive phase, extension of the intensive phase is not recommended.	*Strong / high*	**Unchanged (2010)**

ID	Recommendation	Strength / certainty	Status (year)
A1.6a	Children with pulmonary TB or tuberculous peripheral lymphadenitis who live in settings with low HIV prevalence and/or low prevalence of isoniazid resistance, and children who are HIV-negative, can be treated with a three-drug regimen (HRZ) for 2 months followed by a two-drug regimen (HR) for 4 months at standard dosages.	*Strong / moderate*	**Unchanged (2010/2014/2022)**
A1.6b	Children and adolescents with severe pulmonary disease should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 4 months at standard dosages.	*Strong / moderate*	**Unchanged (2010/2014/2022)**
A1.6c	Infants aged 0–3 months with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis should be promptly treated with the 6-month treatment regimen (2HRZ(E)/4HR). Treatment may require dose adjustment to reconcile the effect of age and possible toxicity in young infants. The decision to adjust doses should be taken by a clinician experienced in managing paediatric TB.	*Strong / low*	**Unchanged (2010/2014/2022)**
A2. Treatment of DS-TB using 4-month regimens			
A2.1	People aged 12 years or older with drug-susceptible pulmonary TB may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide	*Conditional / moderate*	**Unchanged (2022)**
A2.2	In children and adolescents between 3 months and 16 years of age with non-severe TB (without suspicion or evidence of MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used.	*Strong / moderate*	**Unchanged (2022)**
A3. DS-TB treatment and ART in people living with HIV			
A3.1	TB patients who are living with HIV should receive at least the same duration of daily TB treatment as HIV-negative TB patients.	*Strong / high*	**Unchanged (2012)**
A3.2	ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV (adults and adolescents – strong recommendation, low to moderate certainty of evidence; children and infants – strong recommendation, very low certainty of evidence).	*Strong / low to moderate (adults & adolescents). Strong / very low (children & infants)*	**Unchanged (2021)**

ID	Recommendation	Strength / certainty	Status (year)
A4. Adjuvant steroids in TB meningitis and pericarditis			
A4.1	In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks should be used.	*Strong / moderate*	**Unchanged (2017)**
A4.2	In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used.	*Conditional / very low*	**Unchanged (2017)**
A5. Treatment regimens for extrapulmonary TB in children and adolescents			
A5.1	Children with suspected or confirmed tuberculous meningitis or osteoarticular tuberculosis should be treated with a four-drug regimen (HRZE) for 2 months, followed by a two-drug regimen (HR) for 10 months; the total duration of treatment should be 12 months.	*Strong / low*	**Unchanged (2010/2014/2022)**
A5.2	In children and adolescents with bacteriologically confirmed or clinically diagnosed TB meningitis (without suspicion or evidence of MDR/RR-TB), a 6-month intensive regimen (6HRZEto) may be used as an alternative option to the 12-month regimen (2HRZE/10HR).	*Conditional / very low*	**Unchanged (2022)**

Chapter 2. Drug-resistant TB treatment

ID	Recommendation	Strength / certainty	Status (year)
B1. Treatment of DR-TB using 6-month regimens			
B1.1	WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) rather than the 9-month or longer (18-month) regimens in MDR/RR-TB patients.	*Conditional / very low*	**UPDATED (2026)**
B1.1a	WHO suggests the use of a 6-month regimen composed of bedaquiline, pretomanid and linezolid (BPaL) in patients with non-severe pulmonary pre-XDR-TB rather than the BPaLC regimen.	*Conditional / very low*	**NEW (2026)**
B1.1b	WHO suggests the use of a 6-month regimen composed of bedaquiline, pretomanid, linezolid and clofazimine (BPaLC) in patients with severe pulmonary pre-XDR-TB rather than the BPaL regimen.	*Conditional / very low*	**NEW (2026)**
B1.2	WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, delamanid, linezolid (600 mg), levofloxacin and clofazimine (BDLLfx/C) in MDR/RR-TB patients with or without fluoroquinolone resistance.	*Conditional / very low*	**UPDATED (2026)**
B1.2a	WHO suggests the use of a 6-month BDLC regimen in patients with non-severe pulmonary pre-XDR-TB over the currently recommended longer (18 months or longer) regimens.	*Conditional / very low*	**NEW (2026)**
B1.2b	WHO suggests against using the 6-month BDLC regimen in patients with severe pulmonary pre-XDR-TB compared to the currently recommended longer regimens (18 months or longer).	*Conditional / very low*	**NEW (2026)**
B2. Treatment of DR-TB using 9-month regimens			
B2.1	WHO suggests the use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded.	*Conditional / very low*	**Unchanged (2022)**
B2.2	WHO suggests using the 9-month all-oral regimens (BLMZ, BLLfxCZ and BDLLfxZ) over currently recommended longer (>18 months) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. Among these regimens, BLMZ is suggested over BLLfxCZ, and BLLfxCZ is suggested over BDLLfxZ.	*Conditional / very low*	**Unchanged (2025)**

ID	Recommendation	Strength / certainty	Status (year)
B2.3	WHO suggests against using the 9-month DCLLfxZ or DCMZ regimen compared with currently recommended longer (>18 months) regimens in patients with fluoroquinolone-susceptible MDR/RR-TB.	*Conditional / very low*	**Unchanged (2025)**
B2.4	In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used.	*Conditional / very low*	**Unchanged (2022)**
B3. Treatment of DR-TB using longer regimens			
B3.1	In MDR/RR-TB patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it.	*Conditional / very low*	**Unchanged (2019)**
B3.2	Kanamycin and capreomycin are not to be included in the treatment of MDR/RR-TB patients on longer regimens.	*Conditional / very low*	**Unchanged (2019)**
B3.3	Levofloxacin or moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens.	*Strong / moderate*	**Unchanged (2019)**
B3.4	Bedaquiline should be included in longer MDR-TB regimens for patients aged 18 years or more (strong recommendation, moderate certainty). Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years (conditional recommendation, very low certainty). In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used (conditional recommendation, very low certainty).	*Strong / moderate (≥18 y). Conditional / very low (6–17 y; <6 y)*	**Unchanged (2019/2022)**
B3.5	Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens.	*Strong / moderate*	**Unchanged (2019)**
B3.6	Clofazimine and cycloserine or terizidone may be included in the treatment of MDR/RR-TB patients on longer regimens.	*Conditional / very low*	**Unchanged (2019)**
B3.7	Ethambutol may be included in the treatment of MDR/RR-TB patients on longer regimens.	*Conditional / very low*	**Unchanged (2019)**

ID	Recommendation	Strength / certainty	Status (year)
B3.8	Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens (conditional recommendation, moderate certainty). In children with MDR/RR-TB aged below 3 years, delamanid may be used as part of longer regimens (conditional recommendation, very low certainty).	*Conditional / moderate (≥3 y). Conditional / very low (<3 y)*	**Unchanged (2019/2022)**
B3.9	Pyrazinamide may be included in the treatment of MDR/RR-TB patients on longer regimens.	*Conditional / very low*	**Unchanged (2019)**
B3.10	Imipenem–cilastatin or meropenem may be included in the treatment of MDR/RR-TB patients on longer regimens.	*Conditional / very low*	**Unchanged (2019)**
B3.11	Amikacin may be included in the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions.	*Conditional / very low*	**Unchanged (2019)**
B3.12	Ethionamide or prothionamide may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible.	*Conditional / very low*	**Unchanged (2019)**
B3.13	*P*-aminosalicylic acid may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible.	*Conditional / very low*	**Unchanged (2019)**
B3.14	Clavulanic acid should not be included in the treatment of MDR/RR-TB patients on longer regimens.	*Strong / low*	**Unchanged (2019)**
B3.15	In MDR/RR-TB patients on longer regimens, a total treatment duration of 18–20 months is suggested for most patients; the duration may be modified according to the patient's response to therapy.	*Conditional / very low*	**Unchanged (2019)**
B3.16	In MDR/RR-TB patients on longer regimens, a treatment duration of 15–17 months after culture conversion is suggested for most patients; the duration may be modified according to the patient's response to therapy.	*Conditional / very low*	**Unchanged (2019)**

ID	Recommendation	Strength / certainty	Status (year)
B3.17	In MDR/RR-TB patients on longer regimens that contain amikacin or streptomycin, an intensive phase of 6–7 months is suggested for most patients; the duration may be modified according to the patient's response to therapy.	*Conditional / very low*	**Unchanged (2019)**
B4. Treatment of rifampicin-susceptible, isoniazid-resistant TB (Hr-TB)			
B4.1	In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis (Hr-TB), treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months.	*Conditional / very low*	**Unchanged (2018)**
B4.2	In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen.	*Conditional / very low*	**Unchanged (2018)**
B5. Monitoring and management strategies for MDR/RR-TB treatment			
B5.1	In MDR/RR-TB patients on longer regimens, the performance of sputum culture in addition to sputum smear microscopy is recommended to monitor treatment response. It is desirable for sputum culture to be repeated at monthly intervals.	*Strong / moderate (test accuracy)*	**Unchanged (2018)**
B6. Starting ART in patients on MDR/RR-TB regimens			
B6.1	Antiretroviral therapy is recommended for all patients with HIV and drug-resistant tuberculosis requiring second-line antituberculosis drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of antituberculosis treatment.	*Strong / very low*	**Unchanged (2011)**
B7. Surgery for patients on MDR/RR-TB treatment			
B7.1	In patients with rifampicin-resistant tuberculosis (RR-TB) or multidrug-resistant TB (MDR-TB), elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen.	*Conditional / very low*	**Unchanged (2016)**
B8. Hepatitis C virus (HCV) and MDR/RR-TB treatment co-administration			
B8.1	In patients with MDR/RR-TB and HCV coinfection, WHO suggests the co-administration of HCV and TB treatment over delaying HCV treatment until after treatment of MDR/RR-TB is completed.	*Conditional / very low*	**Unchanged (2025)**

Chapter 3. Tuberculosis care and support

ID	Recommendation	Strength / certainty	Status (year)
C1. Care and support interventions for all people with TB			
C1.1	Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment.	*Strong / moderate*	**Unchanged (2017)**
C1.2	A package of treatment adherence interventions may be offered to patients on TB treatment in conjunction with the selection of a suitable treatment administration option.	*Conditional / low*	**Unchanged (2017)**
C1.3	One or more of the following treatment adherence interventions (complementary and not mutually exclusive) may be offered to patients on TB treatment or to health care providers: (a) tracers and/or digital medication monitor (conditional recommendation, very low certainty); (b) material support to patient (conditional recommendation, moderate certainty); (c) psychological support to patient (conditional recommendation, low certainty); (d) staff education (conditional recommendation, low certainty).	*Conditional / very low to moderate (varies by intervention)*	**Unchanged (2017)**
C1.4	The following treatment administration options may be offered to patients on TB treatment: (a) Community- or home-based treatment support is recommended over health facility-based treatment support or unsupervised treatment (conditional recommendation, moderate certainty); (b) Treatment support administered by trained lay providers or health care workers is recommended over treatment support administered by family members or unsupported treatment (conditional recommendation, very low certainty); (c) Video-supported treatment (VST) can replace in-person treatment support when the video communication technology is available and can be appropriately organized and operated by health care providers and patients (conditional recommendation, very low certainty).	*Conditional / very low to moderate (varies by option)*	**Unchanged (2017)**
C2. Models of care for people with drug-resistant TB			
C2.1	Patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalization.	*Conditional / very low*	**Unchanged (2011)**
C2.2	A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment.	*Conditional / very low*	**Unchanged (2017)**

ID	Recommendation	Strength / certainty	Status (year)
C3. Models of care for children and adolescents exposed to TB or with TB disease			
C3.1	In TB high burden settings, decentralized models of care may be used to deliver TB services to children and adolescents with signs and symptoms of TB and/or those exposed to TB.	*Conditional / very low*	**Unchanged (2022)**
C3.2	Family-centred, integrated models of care to deliver TB services may be used in children and adolescents with signs and symptoms of TB and/or those exposed to TB, in addition to standard models of care.	*Conditional / very low*	**Unchanged (2022)**
C4. Palliative care interventions for MDR/RR-TB patients			
C4.1	In patients with pulmonary MDR/RR-TB, in addition to effective treatment, WHO recommends integrating palliative care assessment and interventions by trained providers, as described in WHO palliative care guidance documents.	*Conditional / moderate*	**NEW (2026)**

B: bedaquiline; C: clofazimine; D: delamanid; DR-TB: drug-resistant TB; DS-TB: drug-susceptible TB; E: ethambutol; H: isoniazid; HCV: hepatitis C virus; HIV: human immunodeficiency virus; Hr-TB: rifampicin-susceptible, isoniazid-resistant TB; L: linezolid; Lfx: levofloxacin; M: moxifloxacin; MDR-TB: multidrug-resistant TB; MDR/RR-TB: multidrug- or rifampicin-resistant TB; P: rifapentine; Pa: pretomanid; pre-XDR-TB: pre-extensively drug-resistant TB; R: rifampicin; RR-TB: rifampicin-resistant TB; TB: tuberculosis; VST: video-supported treatment; WHO: World Health Organization; Z: pyrazinamide.

References for Executive summary

1. WHO consolidated guidelines on tuberculosis. Module 4: Treatment and care. Geneva: World Health Organization; 2025 (https://iris.who.int/handle/10665/380799). Licence: CC BY-NC-SA 3.0 IGO.
2. The End TB Strategy. Geneva: World Health Organization; 2015 (https://iris.who.int/handle/10665/331326).
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Chapter 1
Drug-susceptible TB treatment

Introduction

For several decades, the World Health Organization (WHO) has developed and issued recommendations on the treatment of tuberculosis (TB). The WHO recommendations for treating people affected by drug-susceptible TB (DS-TB) have been defined in WHO's *Guidelines for treatment of drug-susceptible tuberculosis and patient care*, 2010 and 2017 updates *(1, 2)*. These guidelines focused on the 6-month treatment regimen composed of four first-line TB medicines – isoniazid, rifampicin, ethambutol and pyrazinamide – recommended for the treatment of DS-TB. This regimen is well known and has been widely adopted worldwide for decades; when used, about 85% of patients achieve a successful treatment outcome. This regimen is based on seminal TB treatment studies conducted by the British Medical Research Council in the second half of the 20th century *(3)*. In addition to the recommendation on the treatment regimen, the 2010 and 2017 guideline updates included a number of recommendations on the modalities and formulations used for treatment, frequency of treatment administration, special situations and patient care during treatment. The consolidated and updated guidelines chapter on DS-TB treatment in this edition brings together, without modifications, all valid and evidence-based recommendations from the 2010 and 2017 guidelines; it then adds a new section based on the subsequent round of guidelines development in 2021 – the recommendations for 4-month treatments of DS-TB.

This chapter of the consolidated guidelines includes recommendations for the treatment of DS-TB across all age groups. All recommendations on patient care and support during treatment for both DS-TB and drug-resistant TB (DR-TB) have been merged into a dedicated chapter: *Tuberculosis care and support*. The recommendations specific to children and adolescents also featured in the module on management of tuberculosis in children and adolescents *(4)* are also included in this chapter.

The update of the guidelines for treatment of DS-TB is important in the context of the End TB Strategy *(5)*, which recommends treatment and patient support for all people with TB.

The objectives of these updated guidelines are to:

- provide updated recommendations based on newly emerged evidence on the treatment of DS-TB; and
- provide a summary of changes in the new guidelines, together with all existing and valid WHO recommendations on the treatment of DS-TB.

The guidance provided in this chapter outlines specific WHO recommendations on the overall treatment, management, care and monitoring of patients with DS-TB. It presents recommendations developed by various WHO-convened guideline development groups (GDGs), using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to summarize the evidence and formulate policy recommendations and accompanying remarks. The recommendations and remarks in the current chapter on the treatment of DS-TB are the result of collaborative efforts of professionals from a range of specialties who have broad expertise and experience in public health policy, TB programme management, the care and management of patients with TB, members of affected communities and TB survivors.

The recommendations included herein are part of WHO's consolidated guidelines on TB and are primarily intended for use by NTPs, public health agencies and other key constituencies involved in the planning, implementation and monitoring of activities for the programmatic management of DS-TB.

These recommendations have been developed through several meetings of the GDGs (2009, 2016 and 2021) and have then been consolidated in the present chapter. The recommendation on the use of the 4-month regimens stem from the GDG meetings that took place in 2021. The remainder of the recommendations have been consolidated from the GDGs that took place in 2009, 2016 and 2021, as expressed in the guidelines updates in 2010, 2017 and 2022 and from *Rapid advice – on treatment of tuberculosis in children* (2010) *(6)* and *Guidance for national tuberculosis programmes on the management of tuberculosis in children* (2014) *(7)*.

Structure of the chapter

The recommendations part of this chapter has five main sections on treatment of DS-TB. The elements covered are:

- treatment of DS-TB using a 6-month regimen;
- treatment of DS-TB using 4-month regimens;
- DS-TB treatment and antiretroviral therapy (ART) in people living with HIV;
- the use of adjuvant steroids in the treatment of TB meningitis (TBM) and pericarditis; and
- treatment regimens for extrapulmonary TB in children and adolescents.

Each section starts with the current WHO recommendations for that element. It then gives information on the evidence used to inform the recommendations, summarizes the analyses that were carried out based on the evidence, and describes considerations for specific subgroups, for monitoring and evaluation, and implementation. Research gaps that were identified for each of the sections are presented at the end of the document; annexes provide more details on the methods, the GDGs (2009, 2016 and 2021), the reports of systematic reviews and data analyses, evidence profiles, unpublished data and statistical analysis plans. Each section reflects discussions held at GDG meetings. Additional information on implementing patient care interventions is presented in the relevant chapter of the WHO consolidated operational handbook on TB treatment and care *(8)*, which is a separate document that is designed to aid implementation efforts.

Summary of WHO recommendations on drug-susceptible TB treatment

The recommendations for the treatment of DR-TB presented in Table 1.1 below are reprinted from the previous edition of the current guidelines (where no new evidence was available or searched for in the review) or WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents.

Table 1.1. List of recommendations on drug-susceptible TB treatment

A1. Treatment of drug-susceptible TB using a 6-month regimen	
A1.1	New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR. *(Strong recommendation, high certainty of evidence)*
A1.2	Wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy. *(Strong recommendation, high certainty of evidence)*

A1.3	In all patients with drug-susceptible pulmonary TB, the use of thrice-weekly dosing is not recommended in both the intensive and continuation phases of therapy, and daily dosing remains the recommended dosing frequency. *(Conditional recommendation, very low certainty of evidence)*
A1.4	The use of fixed-dose combination (FDC) tablets is recommended over separate drug formulations in treatment of patients with drug-susceptible TB. *(Conditional recommendation, low certainty of evidence)*
A1.5	In new pulmonary TB patients treated with the regimen containing rifampicin throughout treatment, if a positive sputum smear is found at completion of the intensive phase, the extension of the intensive phase is not recommended. *(Strong recommendation, high certainty of evidence)*
A1.6a	Children with pulmonary TB or tuberculous peripheral lymphadenitis who live in settings with low HIV prevalence and/or low prevalence of isoniazid resistance and children who are HIV-negative, can be treated with a three-drug regimen (HRZ) for 2 months followed by a two-drug (HR) regimen for 4 months at standard dosages. *(Strong recommendation, moderate certainty of evidence)*
A1.6b	Children and adolescents with severe pulmonary disease should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 4 months at standard dosages. *(Strong recommendation, moderate certainty of evidence)*
A1.6c	Infants aged 0–3 months with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis should be promptly treated with the 6-month treatment regimen (2HRZ(E)/4HR). Treatment may require dose adjustment to reconcile the effect of age and possible toxicity in young infants. The decision to adjust doses should be taken by a clinician experienced in managing paediatric TB. *(Strong recommendation, low certainty of evidence)*
A2. Treatment of drug-susceptible TB using 4-month regimens	
A2.1	People aged 12 years or older with drug-susceptible pulmonary TB may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide (2HPMZ/2HPM). *(Conditional recommendation, moderate certainty of evidence)*
A2.2	In children and adolescents between 3 months and 16 years of age with non-severe TB (without suspicion or evidence of MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used. *(Strong recommendation, moderate certainty of evidence)*
A3. Drug-susceptible TB treatment and antiretroviral therapy (ART) in people living with HIV	
A3.1	It is recommended that TB patients who are living with HIV should receive at least the same duration of daily TB treatment as HIV-negative TB patients. *(Strong recommendation, high certainty of evidence)*
A3.2	ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV. *Adults and adolescents (strong recommendation, low to moderate certainty of evidence);* *Children and infants (strong recommendation, very low certainty of evidence)*

A4. The use of adjuvant steroids in the treatment of TB meningitis and pericarditis	
A4.1	In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks should be used. *(Strong recommendation, moderate certainty of evidence)*
A4.2	In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used. *(Conditional recommendation, very low certainty of evidence)*
A5. Treatment regimens for extrapulmonary TB in children and adolescents	
A5.1	Children with suspected or confirmed tuberculous meningitis or osteoarticular tuberculosis should be treated with a four-drug regimen (HRZE) for 2 months, followed by a two-drug regimen (HR) for 10 months. The total duration of treatment should be 12 months. *(Strong recommendation, low certainty of evidence)*
A5.2	In children and adolescents with bacteriologically confirmed or clinically diagnosed TB meningitis (without suspicion or evidence of MDR/RR-TB), a 6-month intensive regimen (6HRZEto) may be used as an alternative option to the 12-month regimen (2HRZE/10HR). *(Conditional recommendation, very low certainty of evidence)*

ART: antiretroviral therapy; E: ethambutol; Eto: ethionamide; FDC: fixed-dose combination; H: isoniazid; HIV: human immunodeficiency virus; M: moxifloxacin; MDR/RR-TB: multidrug- or rifampicin-resistant TB; P: rifapentine; R: rifampicin; TB: tuberculosis; Z: pyrazinamide.

Recommendations

A1. Treatment of drug-susceptible TB using a 6-month regimen

Recommendation A1.1

No.	Recommendation
A1.1	New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR. *(Strong recommendation, high certainty of evidence)*

Remarks

- The recommendation also applies to extrapulmonary TB – except TB of the central nervous system, bone or joint, for which some expert groups suggest longer therapy.
- WHO recommends that national TB control programmes (NTPs) provide supervision and support for all TB patients, to ensure completion of the full course of therapy.
- WHO recommends drug-resistance surveys (or surveillance) for monitoring the impact of the treatment programme, and for designing standard regimens.

Source of recommendation

This recommendation was first put forward in 2010 and was considered valid in the 2017 guidelines update (see summary of recommendations in Annex 1). The recommendation is copied without modification into this consolidated document and appears exactly as in the 2010 guidelines.

Justification and evidence

A systematic review and meta-analysis included 21 472 participants in 312 arms of 57 randomized controlled trials (RCTs) conducted in various regions of the world since 1965 *(9)*. In three of the 57 trials, patients were randomly assigned to either a 2-month rifampicin or a 6-month rifampicin arm; rates of failure, relapse and acquired drug resistance were compared "head-to-head" across the two study arms. In a multivariate regression analysis, each arm of the 57 trials was treated as a separate cohort and results were adjusted for potentially confounding patient and treatment factors.

The three studies with head-to-head comparisons showed that the risk of relapse after a 6-month rifampicin regimen was significantly lower than that after a 2-month rifampicin regimen. If a country were to change from a 2-month to a 6-month rifampicin regimen, the benefit would be an estimated 112 relapses averted per 1000 TB patients.

Regression analysis suggests that changing to a 6-month regimen would significantly reduce failure and acquired drug resistance rates, in addition to relapse rates.[1] This analysis found that regimens with 5–7 months of rifampicin have 0.43 times the failure rate, and 0.32 times the relapse rate of regimens with 1–2 months of rifampicin. Among the failures and relapses from regimens with 5–7 months of rifampicin, the rate of acquired drug resistance is 0.28 times that of the regimens with 1–2 months of rifampicin.

Patients with isoniazid resistance would realize major benefits if the 2-month rifampicin regimen were replaced with a 6-month regimen. Among patients with isoniazid monoresistance at the start of treatment, 38% relapsed after treatment with 2-month rifampicin regimens, which is significantly higher than the 5.5% relapse rate after treatment with 6-month rifampicin regimens. Thus, changing to the 6-month rifampicin regimen would avert 325 relapses per 1000 patients who start treatment with isoniazid resistance.

Even for patients with pansusceptible TB, the proportion who relapsed after the 2-month rifampicin regimen was 8.2%, which was significantly higher than the 3.1% for the 6-month rifampicin regimen.

When the first course of therapy is considered along with retreatment for patients who fail or relapse, it is estimated that the 6-month rifampicin regimen would avert between 3 and 12 deaths per 1000 compared with the 2-month rifampicin regimen across seven countries modelled with a range of drug resistance among new patients. In addition, 0.6–4.4 failures and relapses with drug resistance other than MDR-TB would be averted per 1000 TB patients, but an additional 0.6–1.3 MDR-TB cases would be generated.

Among patients who failed or relapsed after their first course of treatment containing 6 months of rifampicin, regression analysis found a reduction in overall acquired drug resistance; however, the pattern of acquired drug resistance was different from that in patients who received the 2-month rifampicin regimen. The risk of acquiring drug resistance other than MDR-TB is higher with the 2-month rifampicin regimen, but the risk of acquiring MDR-TB is higher with the 6-month rifampicin regimen. Among failures, the proportion with MDR-TB is predicted to be 4–56% after initial treatment with the 2-month rifampicin regimen but 50–94% after initial treatment with the regimen containing 6 months of rifampicin.

Subgroup considerations

The interactions of rifampicin with antiretroviral therapy (ART) are of concern. Switching to the 6-month rifampicin regimen means that these drug interactions must be taken into account for the full 6 months rather than for just the first 2 months of therapy. However, the 6-month rifampicin regimen has marked benefits for persons living with HIV, and the drug interactions can be managed *(10)*.

Implementation considerations

To help minimize the acquisition of MDR-TB, it is critically important that national TB control programmes ensure adequate supervision of rifampicin. Implementing patient supervision for the 4-month continuation phase will require additional resources in areas where the continuation phase has been self-administered – an investment that may be offset by the savings from relapses (and therefore retreatments) averted. In 2008, 23 countries (including four that are considered high burden) still used the 2-month rifampicin regimen for their new patients. These countries reported 706 905 new cases in 2007, or 13% of the global new TB notifications that year.

[1] The difference in failure and acquired drug resistance was not statistically significant in these three randomized controlled trials.

Recommendation A1.2

No.	Recommendation
A1.2	Wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy. *(Strong recommendation, high certainty of evidence)*

Source of recommendation

This recommendation was first put forward in 2010 and considered valid in the 2017 guidelines update (see summary of recommendations in Annex 1). The recommendation is copied without modification into this consolidated document and appears exactly as in the 2010 guidelines.

Justification and evidence

A systematic review and meta-analysis included 21 472 participants in 312 arms of 57 RCTs conducted in various regions of the world since 1965 *(9)*. In a multivariate regression analysis, each arm of the 57 RCTs was treated as a separate cohort, and results were adjusted for potentially confounding patient and treatment factors. Only one study of 223 patients evaluated a rifampicin-containing regimen administered twice weekly throughout therapy; this study was not included in the meta-analyses.

No significant increase in failure, relapse or acquired drug resistance was found when daily dosing throughout therapy was compared with the following intermittent regimens in new TB patients overall, namely: daily then thrice weekly; daily then twice weekly; or thrice weekly throughout therapy.

However, the regression analysis showed that patients being treated thrice weekly throughout therapy had rates of acquired drug resistance that were 3.3 times higher than those in patients who received daily drug administration throughout treatment.

The meta-analysis revealed no difference in rates of failure, relapse or acquired drug resistance in pansusceptible new patients being treated with these dosing schedules. However, the use of a three times weekly intensive phase schedule in patients with pretreatment isoniazid resistance was associated in another meta-analysis with a significantly higher risk of failure and acquired drug resistance *(11)*.

Implementation considerations

When based in a health facility, daily administration of therapy places a larger burden on TB programmes and patients than does intermittent therapy. Intermittent regimens require stronger programmes with higher-quality patient supervision, but all regimens should be provided with full patient supervision and support.

Studies of patients' preferences for dosing schedules were not systematically reviewed. The higher isoniazid dose used in intermittent therapy was not considered to have an increased incidence of adverse effects. The rifampicin dosage was unchanged when using intermittent therapy.

In an international, multicentre, randomized trial (Union Study A), Jindani, Nunn & Enarson found thrice weekly dosing resulted in significantly lower culture conversion rates at 2 months *(12)*. In developing recommendations, this endpoint was ranked by the GDG (2009) as important but not critical for decision-making and was not part of the systematic review.

For new patients without HIV infection, high- certainty of evidence demonstrated no significant difference between regimens that were administered daily throughout treatment, daily initially and then intermittently in the continuation phase, or thrice weekly throughout treatment.

Daily dosing is optimal because it probably achieves better adherence under programme conditions. While the definition of the term varies across countries, "daily" is considered to mean at least five times per week. In addition, meta-analyses showed the superiority of daily (compared with thrice weekly) intensive-phase dosing for patients with pretreatment isoniazid resistance and for preventing acquired drug resistance in patients overall.

Recommendation A1.3

No.	Recommendation
A1.3	In all patients with drug-susceptible pulmonary TB, the use of thrice-weekly dosing is not recommended in both the intensive and continuation phases of therapy and daily dosing remains the recommended dosing frequency. *(Conditional recommendation, very low certainty of evidence)*

Source of recommendation

This recommendation was first put forward in 2010 and then updated in the 2017 guidelines (see summary of recommendations in Annex 1). It is copied without modification into this consolidated document and appears exactly as in the 2010 guidelines.

Justification and evidence

The use of intermittent dosing of TB medications has been adopted in some geographical settings in an effort to improve treatment adherence and to reduce the burden on the health care system due to daily treatment support. However, it was unclear how this intermittent dosing might affect treatment outcomes. In addition to the evidence from a systematic review conducted in 2009 of treatment regimens with intermittent dosing schedules *(9)*, this systematic review was updated in 2016 with the most recent RCTs *(13–18)*.

Evidence showed that when thrice-weekly dosing throughout therapy was compared to daily dosing throughout therapy, patients who received thrice-weekly dosing had a higher risk of treatment failure, disease relapse and acquired drug resistance in both drug-susceptible disease and when the strain susceptibility was unknown. Consequently, thrice-weekly dosing in the intensive phase should never be used.

Likewise, when thrice-weekly dosing during the continuation phase only is compared to daily dosing throughout, there were higher rates of treatment failure and relapse in the patients that received thrice-weekly treatment during the continuation phase. In this case, acquired drug resistance rates did not differ. If thrice-weekly dosing during the continuation phase is used, it is essential to make sure that patients do not miss any dose of the medications and that treatment support is used.

In this review, the use of twice-weekly dosing in the continuation phase only was also reviewed. Twice-weekly dosing in the continuation phase only had higher rates of treatment failure, disease relapse and drug resistance than thrice-weekly dosing in the continuation phase only. As a result, twice-weekly dosing should never be used during any part of TB therapy.

Adherence to treatment was not adequately addressed in the reviewed studies to be included as an outcome. However, in most studies included in the systematic review, intermittent dosing used treatment support, while the use of treatment support during daily dosing was variable.

The GDG (2016) also considered that health equity would be adversely affected with intermittent dosing because more vulnerable populations would receive inferior treatment if intermittent dosing were used. This is because people living in more resource-constrained settings would be at greater

risk of missing doses of medication, not only because of their difficulty in reaching a clinic but also because of the risk of medication stock-outs in clinics. Additionally, patients who are coinfected with HIV or have other comorbidities may not absorb TB medications well and therefore they may receive less medication than they are ingesting. In order for TB medication to be used as part of a treatment regimen, no doses may be missed with thrice-weekly intermittent dosing during the continuation phase because the rates of unfavourable outcomes may rise. Consequently, populations that are more vulnerable are at risk of missing doses of medication or of not absorbing the doses well, and intermittent dosing puts them in a situation where there is an increased risk of unfavourable outcomes.

Intermittent dosing may also create problems at national and international levels by resulting in requirements for different drug manufacturing and packaging and a reduced drug supply buffer, leading to an increased risk of TB medication stock-outs.

Given the findings in this review, all countries are encouraged to use daily dosing exclusively in both the intensive and the continuation phases of treatment. Although two separate evidence assessments were conducted on thrice-weekly dosing in the intensive phase and the continuation phase, both the formulated recommendations were conditional and there was very low certainty in the evidence. A combined recommendation for both intensive and continuation phases was formulated to make it more convenient for use by the end-users.

Subgroup considerations

This recommendation is the same for HIV-negative people and for people living with HIV.

The data used in this review examined only patients with drug-susceptible pulmonary TB who had no extenuating circumstances – such as adverse reactions which might require modification of the dosing schedule.

Children were not considered specifically in this review. However, there is no biologically plausible reason why this recommendation should not also apply to children. It is recommended that all children receive daily dosing of TB medications during the intensive and continuation phases of therapy for the same reason as adults.

Implementation considerations

There are no new implementation considerations as the recommended daily treatment is already widespread practice. However, intermittent dosing is still used in some countries. In such exceptional cases, implementation of the recommendation to use exclusively daily dosing in the intensive and continuation phases of TB therapy is likely to have implications for medication procurement, practitioner training, change of programme practice and patient support.

Recommendation A1.4

No.	Recommendation
A1.4	The use of fixed-dose combination tablets is recommended over separate drug formulations in treatment of patients with drug-susceptible TB. *(Conditional recommendation, low certainty of evidence)*

Source of recommendation

This recommendation was first put forward in the 2017 guidelines update (see summary of recommendations in Annex 1). It is copied without modification into this consolidated document and appears exactly as in the 2017 guidelines.

Justification and evidence

The evidence presented to the GDG (2016) was based on a systematic review of randomized controlled trials done by Albanna et al. *(19)* and by a recent Cochrane review *(20)*. This evidence showed that the fixed-dose combination (FDC) tablets are non-inferior and equally effective as separate drug formulations in terms of treatment failure, death, treatment adherence and adverse events. There was a small increase in 2-month culture conversion with FDC treatment; however, there was no difference in culture conversion rates by the end of treatment. Patient satisfaction was higher among persons treated with FDCs. A slightly higher rate of disease relapse and acquired drug resistance among patients treated with FDCs compared with those treated with separate drug formulations was not statistically significant.

Patient treatment satisfaction with FDCs was considered the most important factor for making decisions on this recommendation.

Studies in these reviews did not evaluate bioavailability of the drugs in the FDCs, but previous studies did not indicate that the FDC formulations used had significant bioavailability issues *(19)*. As no pharmacokinetic studies were done on these FDC formulations, the bioavailability of drugs within the FDCs versus the separate drug formulations remains an important consideration that indicates the need to procure FDCs of demonstrated bioavailability *(21–23)*. This area requires further research.

FDCs may provide programme benefits by making the ordering of medication easier, simplifying supply chain management, reducing the occurrence of stock-outs, and facilitating drug delivery and prescription preparation. FDCs may also provide benefits – especially in settings with a large number of TB patients and a limited number of health care workers – by reducing the need for additional health care staff and training in the dosing and dispensing of medications, as well as by contributing to a lower pill burden for patients. Nevertheless, national TB programmes are advised to have a quantity of separate drug formulations available for certain treatment conditions. Having single drug formulations available would be beneficial to national TB programmes when designing MDR-TB regimens that include some first-line drugs (i.e. pyrazinamide, EMB, high-dose isoniazid), when providing preventive therapy, and in cases of adverse reactions to TB medications when drugs must be reintroduced one at a time.

The GDG acknowledged that greater patient satisfaction is an advantage of FDCs over separate drug formulations.

Subgroup considerations

The reduced pill burden as a result of using FDCs may be especially valuable in patients with comorbidities (notably HIV infection) and paediatric patients (who may have some difficulty in swallowing large amounts of medications).

Patients with some specific medical conditions (e.g. intolerance to certain TB drugs, liver or renal function impairment) are likely to require individual medication dose adjustment which can be done only with separate drug formulations.

Implementation considerations

There are no specific implementation considerations as the use of FDC formulations is already widespread.

Recommendation A1.5

No.	Recommendation
A1.5	In new pulmonary TB patients treated with the regimen containing rifampicin throughout treatment, if a positive sputum smear is found at completion of the intensive phase, the extension of the intensive phase is not recommended. *(Strong recommendation, high certainty of evidence)*

Source of recommendation

This recommendation was first put forward in 2010 and considered valid in the 2017 guidelines update (see summary of recommendations in Annex 1). It is copied without modification into this consolidated document and appears exactly as in the 2010 guidelines.

Justification and evidence

The systematic review identified only one relevant study (with results published in 2012). A study still underway (at moment of review) in Bangladesh of a 6-month rifampicin-containing regimen randomized 3775 new smear-positive patients who remained positive at 2 months to either the 1-month extension arm (extension of the intensive phase by 1 month) or the no-extension arm *(24)*.

Preliminary results at 1 year of follow-up showed that patients in the 1-month extension arm had a significantly lower relapse rate (relative risk 0.37, 95% confidence interval [CI]: 0.21, 0.66) than patients in the no-extension arm. A smaller decrease in failure in the 1-month extension arm was not statistically significant. Given the preliminary nature of the results and the passive follow-up of patients, the evidence from the Bangladesh study was graded with moderate certainty.

In 1000 TB patients with a 7% risk of relapse, the Bangladesh study predicts that extending the treatment of 183 patients who are smear-positive at 2 months would avert 16 of the 70 expected relapses. However, to achieve this 23% reduction in relapses, 158 patients per 1000 would be incorrectly predicted to relapse; consequently their treatment would be extended unnecessarily.

While extending rifampicin beyond 6 months reduces the risk of relapse, there is insufficient evidence to determine which patients are most likely to benefit. Historically, when the new patient regimen included only 2 months of rifampicin, the extension of the intensive phase meant an extra month of supervised rifampicin. This extra month is less important now as the current recommended regimen is 6 months of supervised rifampicin. Given these considerations, together with preliminary results from one moderate-certainty study that showed only modest benefit, a conditional recommendation was made not to extend treatment on the basis of a positive smear at 2 months.

Recommendations A1.6a to A1.6c

Source of recommendation

These three recommendations were included in the 2010 publication *Rapid advice: treatment of tuberculosis in children (6)* and the 2014 publication *Guidance for national tuberculosis programmes on the management of tuberculosis in children, second edition (7)*; they are considered valid in the 2022 consolidated guidelines on the management of TB in children and adolescents *(4)* (see summary of recommendations in Annex 1). They are copied without modification into this consolidated document and appear exactly as in Annex 2 (supplementary table) of the 2022 guidelines.

Recommendations A1.6a and A1.6b

No.	Recommendation
A1.6a	Children with pulmonary TB or tuberculous peripheral lymphadenitis who live in settings with low HIV prevalence and/or low prevalence of isoniazid resistance, and children who are HIV-negative, can be treated with a three-drug regimen (HRZ) for 2 months followed by a two-drug (HR) regimen for 4 months at standard dosages. *(Strong recommendation, moderate certainty of evidence)*
A1.6b	Children and adolescents with severe pulmonary disease should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 4 months at standard dosages. *(Strong recommendation, moderate certainty of evidence)*

Justification and evidence: recommendations A1.6a and A1.6b

The 2010 publication *Rapid advice: treatment of tuberculosis in children (6)* established the recommendation for the choice between a three-drug versus a four-drug intensive-phase regimen for children with pulmonary TB or tuberculous peripheral lymphadenitis. Accordingly, the recommendation is retained as longstanding WHO policy (with the original strength and certainty rating preserved).

Recommendation A1.6c

No.	Recommendation
A1.6c	Infants aged 0–3 months with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis should be promptly treated with the 6-month treatment regimen (2HRZ(E)/4HR). Treatment may require dose adjustment to reconcile the effect of age and possible toxicity in young infants. The decision to adjust doses should be taken by a clinician experienced in managing paediatric TB. *(Strong recommendation, low certainty of evidence)*

Justification and evidence

Treatment may require adjustment of dosages to reconcile the effect of age and possible toxicity in young infants. The decision to adjust dosages should be taken by a clinician experienced in managing paediatric TB.

The panel noted the very limited systematic clinical data describing treatment and outcomes of the treatment of TB in this age group, and took into account:

- the importance of treating TB in infants as a serious infectious disease with high morbidity and mortality in this age group;
- the importance of commencing treatment with an effective treatment regimen as soon as the diagnosis of TB is suspected; and
- the need for simplified treatment instructions for programmes dealing with these children.

A2. Treatment of drug-susceptible TB using 4-month regimens

Recommendation A2.1

No.	Recommendation
A2.1	People aged 12 years or older with drug-susceptible pulmonary TB, may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide.[2] *(Conditional recommendation, moderate certainty of evidence)*

Source of recommendation

This recommendation was developed following the advice of the GDG convened in April 2021 to review data from a randomized controlled trial that assessed the safety and effectiveness of 4-month regimens for the treatment of DS-TB.

Justification and evidence

Since 2010, the WHO guidelines have recommended treating persons with DS-TB with a 6-month regimen composed of four first-line TB medicines – isoniazid, rifampicin, ethambutol and pyrazinamide – where rifampicin is used for 6 months (2HRZE/4HR) *(2)*. This regimen is based on seminal TB treatment studies conducted by the British Medical Research Council in the 1980s *(3)* and has been widely adopted worldwide. Using it, approximately 85% of patients will have a successful treatment outcome *(25)*. Despite its familiarity, safety and efficacy, many patients find the 6-month regimen difficult to complete due to its length. In fact, long treatment regimens present serious challenges both to patients and to the programmatic management of TB globally.

Since the discovery of first-line anti-TB medicines and treatment regimens, there has been a search for shorter and more effective treatments for TB disease. This has resulted in various trials and other studies designed to assess whether treatment can be shortened, while remaining highly effective. Three phase III trials (i.e. REMoxTB, OFLOTUB, RIFAQUIN) failed to demonstrate non-inferiority of shorter regimens to treat DS-TB *(13, 14, 26)*. A recent phase III trial (TBTC study 31/ACTG A5349, or S31/A5349, referred to below as "Study 31") assessed the safety and efficacy of two 4-month regimens for the treatment of DS-TB *(27)*. Study 31 was the first and only phase III trial to demonstrate the non-inferiority of the 4-month regimen for treatment of DS-TB when compared to the standard of care. The dedicated Cochrane review *(28)* in 2019 and the literature search for the period 2019–2021 performed prior to the GDG (2021) failed to identify any studies other than Study 31; therefore this was the only trial to provide evidence for this GDG review.

Study 31 was an international, multicentre, randomized, open-label, controlled, three-arm non-inferiority trial among adolescents and adults (aged 12 years and above) with smear-positive[3] and culture-positive pulmonary DS-TB *[27]*. Study participants were recruited from 13 countries. The study objectives were to evaluate the efficacy of: 1) a rifapentine-containing regimen to determine whether the single substitution of rifapentine for rifampicin makes it possible to reduce the duration of treatment for drug-susceptible pulmonary TB to four months; and 2) a rifapentine-containing regimen that additionally substitutes moxifloxacin for ethambutol and continues moxifloxacin throughout treatment, to determine whether the duration of treatment can be reduced, compared with the currently recommended 6-month regimen using a non-inferiority margin of 6.6 percentage points *(27)*.

[2] Two months of isoniazid, rifapentine, moxifloxacin, and pyrazinamide, followed by two months of isoniazid, rifapentine, and moxifloxacin

[3] Smear-positive for acid-fast bacilli on smear microscopy or smear-positive for *M. tuberculosis* by GeneXpert MTB/RIF® ("Xpert", Cepheid Inc., Sunnyvale, CA) testing with semi-quantitative result of "medium" or "high".

The rifapentine-moxifloxacin arm was the only arm to demonstrate non-inferiority when compared to the standard of care (the WHO-recommended regimen of six months of treatment with rifampicin, isoniazid, pyrazinamide and ethambutol) and thus the regimen was the one reviewed by the GDG. This regimen consisted of eight weeks of daily isoniazid (H), rifapentine (P), moxifloxacin (M) and pyrazinamide (Z), followed by nine weeks of daily isoniazid, rifapentine, and moxifloxacin (2PHZM/2PHM). The dose of rifapentine used was 1 200 mg daily. The primary efficacy end point of Study 31 was TB disease-free survival at 12 months after randomization, while the primary safety end point was the proportion of participants with grade 3 or higher adverse events during the study drug treatment.

In the trial, a total of 2 516 patients from 34 sites (in Brazil, China, Haiti, India, Kenya, Malawi, Peru, South Africa, Thailand, Uganda, the United States of America (USA), Viet Nam and Zimbabwe) were randomly assigned to a treatment group. The microbiologically-eligible population[4] included 791 patients with TB in the rifapentine-moxifloxacin arm and 768 in the standard of care control arm. The GDG accepted the outcomes used by the Study 31 for analysis, using the microbiologically-eligible population as defined by the study to minimize bias, and using the safety analysis population (as defined by the study protocol) for the review of all-cause mortality and adverse events. The proportion of patients who were cured[5] was similar in both arms (84.5% in the rifapentine-moxifloxacin arm versus 85.4% for the standard of care, relative risk (RR) 0.99, 95% CI: 0.95–1.03). Retention on treatment was high for both arms, namely: 99.7% for the rifapentine-moxifloxacin arm and 99.0% for the standard of care arm (RR: 1.01, 95% CI: 1.00–1.02). All-cause mortality recorded within 14 days after the end of treatment was reported for 0.4% of patients in the rifapentine-moxifloxacin arm versus 0.8% in the standard of care (RR 0.42, 95% CI: 0.11–1.61); and grade 3 or higher adverse events were noted in 18.8% of participants in the rifapentine-moxifloxacin arm versus 19.3% in the standard of care arm (RR 0.97, 95% CI: 0.76–1.24). There were no statistically significant differences in the proportion of patients who were cured when comparing the rifapentine-moxifloxacin arm to the standard of care arm for all four subgroups that were analysed (persons living with HIV infection; persons with extensive disease, based on extent of disease on chest radiography, persons with diabetes mellitus; and persons with a low body weight, less than 17.9 kg/m3). There was little or no difference in all-cause mortality and adverse events during treatment – a slight increase in retention on treatment was noted in the rifapentine-moxifloxacin arm (RR 1.01, 95% CI: 1–1.02) and the evidence was uncertain with regard to acquisition of drug resistance.

The GDG judged that the benefits of a shorter, 4-month regimen that is as effective as the currently recommended 6-month regimen would justify the introduction of the shorter regimen as an option for treating patients with DS-TB.

Certain contextual issues were discussed that resulted in a conditional recommendation, rather than a strong one. These included:

Resources: The costs related to the use of this regimen are currently high and further research is needed on resource implications (e.g. patient and health system savings) and cost–effectiveness of the 4-month regimen. In all, 90% of the cost of medicines for the 2HPMZ/2HPM regimen comes from the rifapentine component.

Equity: Shorter-term and longer term equity considerations were raised by GDG members. The GDG considered that in the short term, issues such as access to rifapentine, the costs of rifapentine and increased pill burden (due to the lack of fixed-dose combinations for the 4-month regimen and the fact that rifapentine was dosed at 1 200 mg) may decrease equity. However, in the longer term as costs reduce and access to rifapentine (including 300 mg tablets) increases, the shorter regimen is

[4] The microbiologically eligible population excludes persons with resistance to the medicines used for treatment; those with no baseline positive TB culture and others that were not eligible to participate in the trial. The choice of a microbiologically eligible population for the analyses minimizes the chance of underestimating the effect of the rifapentine-moxifloxacin in view of the non-inferiority trial design.

[5] The outcome, named 'cure' or 'favourable' outcome in the Study 31, was chosen as it was prioritized by the GDG. The definition of the favourable outcome is detailed in the Study 31 protocol and the evidence-to decisions tables for this GDG review.

considered likely to increase equity for patients who will have a shorter period of time engaged with the health system, potentially reducing costs associated with TB treatment, and who would be able to return to work sooner.

Acceptability and feasibility: Although patients and health care workers may prefer a regimen of shorter duration, GDG members were concerned at the pill burden relative to the standard 6-month regimen and the potential need for fluoroquinolone DST in some settings with a high background prevalence of fluoroquinolone resistance.

Subgroup considerations

Subgroup analyses were conducted for four patient groups in order to inform the GDG discussions. The subgroup analyses presented to the GDG included people living with HIV infection, people with diabetes mellitus, people with a low body weight (body mass index < 17.9 kg/m2) and people with extensive disease (using a cut-off of >50% lung area affected) on chest radiography. The reported risk differences for these subpopulations indicated no statistically significant differences when comparing the shorter regimen to the current standard of care; however, in some subgroups the overall numbers were small in both intervention and control groups (persons with HIV and those with diabetes mellitus).

Additional pharmacokinetic analyses being undertaken by the trial investigators will be available in the future and may provide more nuanced information on drug exposures in these groups. Other subgroup analyses that were part of the trial included analyses by age group, sex, presence of cavities on chest radiography, cavity size, WHO sputum smear grade, smoking history, Xpert Ct value and Mycobacterial Growth Indicator Tube liquid culture automated system TTP (days).

Subgroups included in the recommendation

The panel suggested that the shorter regimen can be used in the subgroups for which evidence was available for review (people living with HIV infection, persons with diabetes mellitus, those with a low body weight and those with extensive disease). However, the panel also emphasized that additional research on the use of the shorter regimen in these subgroups is desirable.

People living with HIV infection: The proportion of patients living with HIV infection in the intervention and control regimen arms was 8% and only patients with CD4 count above 100 cells/mm^3 were enrolled. Of all the persons with HIV who participated in the trial (in all three arms), 95.4% were receiving antiretroviral therapy (ART). HIV-positive persons not on ART at enrolment, had planned initiation of efavirenz-based ART before or at study week 8. Persons with HIV were excluded from enrolment in the trial if, at the time of enrolment, their CD4-T cell count was known to be <100 cells/mm^3. Overall, there were nine patients who were not on ART throughout the trial follow-up in the microbiologically eligible analysis population (4.6%); the reasons for non-initiation of ART were not clear.

People with diabetes mellitus: Additional information from pharmacokinetic analyses will be available for this population in the future which may provide more nuanced evidence on the use of the intervention and control regimens in persons with diabetes mellitus.

People with extensive TB disease: The trial reported on the presence of cavitation on chest radiograph (CXR), the extent of disease on CXR as a percentage, and cavity size (absent, < or > = 4cm).

For patients with less severe and minimal forms of TB, such as lymph node TB there was limited or no evidence on the use of the shorter regimen. However, GDG members felt that the use of the shorter regimen could be considered because favourable outcomes were reported using the shorter regimen in patients with extensive disease.

Subgroups excluded from the recommendation

However, there were also subgroups for which there was no evidence (as they were not eligible for inclusion in the trial) and therefore the use of the shorter regimen outside the research environment is not indicated in these populations. These groups include:

- people weighing less than 40 kg;
- people with certain forms of extrapulmonary TB (such as TB meningitis, disseminated TB, osteoarticular TB, abdominal TB);
- persons living with HIV infection with a CD4 count less than 100 cells/mm^3 (NB: The trial did not include persons living with HIV infection if they had a CD4 count of less than 100 cells/mm^3 and the GDG panel expressed concerns at an increased risk of relapse in this group (also because this group is at a higher risk of disseminated TB);
- children less than 12 years of age (NB: The trial aimed to recruit people aged 12 years and above. The youngest participant was 13 years of age. Therefore, no children were included in the trial. In the microbiologically eligible population, there were 70 and 56 participants who were under 20 years of age in the rifapentine-moxifloxacin and control arms respectively); and
- pregnant, breastfeeding and postpartum women (NB: Pregnant or breastfeeding women were excluded from the study because of uncertainties about the safety of rifapentine, moxifloxacin, and pyrazinamide in these groups. Women who became pregnant while receiving study regimens were deregistered from the study and were treated according to national TB programme or local guidelines. The women continued to receive scheduled study follow-up, were classified as being on a non-study regimen, and did not receive study radiographs. Women who became pregnant while on study follow-up (but not on study treatment) continued to receive scheduled study follow-up and did not receive study radiographs. In all cases – i.e. whether pregnant during treatment or during follow-up – the outcome of the pregnancy was reported on study forms).

Implementation considerations

A number of implementation considerations were discussed by the GDG. These included the following:

Drug susceptibility testing: The panel agreed that national TB programmes should strive for universal DST. The panel also acknowledged that universal DST is not always available but rapid DST for key medicines, including rifampicin, isoniazid and the fluoroquinolones is available and is expanding at an accelerated pace. Rapid genotypic testing for TB and rifampicin resistance is recommended by WHO as an initial test for TB and, if the same sputum sample can be tested for drug susceptibility for the fluoroquinolones and isoniazid, this can facilitate assignment of the most effective regimen. This would clearly have implications in terms of logistics, laboratory workload and cost. Balancing the desired situation of having the universal DST with reality, the panel considered that although desirable, baseline DST for fluoroquinolones would not be essential when patients with TB receive a WHO-recommended rapid molecular diagnostic test to detect rifampicin resistance. Fluoroquinolone resistance in new patients with DS-TB can reach up to 15% *(25)*, although it is significantly lower in most settings *(29–33)*. In countries with high prevalence of resistance to fluoroquinolones in new patients DST for the fluoroquinolones would be highly recommended at baseline.

Directly observed treatment: Patients in the trial received daily treatment that was directly observed at least five days per week. However, this may not be possible in programmatic settings. Directly observed treatment may be important in view of the pill burden and the lack of a fixed-dose combination formulation, and also as a measure to prevent potential amplification of drug resistance. Current WHO recommendations support the use of directly observed treatment and also other forms of patient support and, overall, even though this regimen is a 4-month one and shorter than the current standard of care, patient support remains an important element of TB programming.

Pill burden: At present, the overall pill burden will be higher for patients who will receive this 4-month regimen[6] because no fixed-dose combination tablet exists for the regimen and the dose of rifapentine is high (1 200 mg). This may affect acceptability by patients currently, however this situation may change in future as uptake of this regimen improves, creating a demand for the regimen and its component medicines. Wider availability of rifapentine formulation of 300 mg[7] may decrease the pill burden and facilitate the implementation of this new regimen until the FDC tablet becomes available.

Cost of medicines: The current cost of the shorter regimen is substantially[8] higher than the standard of care, mainly due to the inclusion of rifapentine. Again, this situation may change in future as uptake of the regimen improves, creating a demand for the regimen and for the medicines in it.

Administration of the shorter regimen with food may present a challenge in some settings. In the trial, a flat dose of 1 200 mg of rifapentine was dosed daily, with food. This was based on: 1) demonstration of the safety of rifapentine at 1 200 mg in phase I and phase II trials; 2) demonstration that body weight does not significantly affect rifapentine clearance; 3) recognition of an effect of food in increasing rifapentine absorption *(34)*; and 4) modelling predictions that the target rifapentine exposure (area under the curve [AUC] of approximately 500–600 mcg*h/L) is achievable using this strategy – see the supplementary appendix to *(13)*).

As described in the trial's statistical analysis plan, pharmacokinetic/pharmacodynamic modelling predicted that a rifapentine dose of 1 200 mg without food would yield an AUC approximately the same as that of a rifapentine dose of 900 mg with a very high fat meal. Since the target rifapentine AUC lies somewhere between that achieved with a very high fat meal and a rifapentine dose of 900–1 200 mg, the strategy proposed was a rifapentine dose of 1 200 mg with a modest food requirement. The rationale was that a very high fat meal may not be feasible under trial or routine TB care conditions, whereas dosing with food may be feasible.

Training of health care workers was another implementation consideration that the panel discussed. Training will be necessary when introducing the shorter regimen into a programmatic setting. However, this is a requirement for any new programmatic intervention and the ability to shorten treatment and potentially treat more patients may offset initial training investments.

Another implementation consideration discussed by the GDG concerned the choice of regimen to treat DS-TB. The GDG considered that, when choosing between the shorter 4-month regimen or the 6-month regimen, clinicians should consider eligibility criteria for the regimen and patient preference as well as local factors such as the availability of rifapentine.

Recommendation A2.2

No.	Recommendation
A2.2	In children and adolescents between 3 months and 16 years of age with non-severe TB (without suspicion or evidence of MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used. *(Strong recommendation, moderate certainty of evidence)*

[6] Based on estimates by the Global Drug Facility for an average weight of 55–70 kg: 1358 tablets versus 728 for whole course of treatment.

[7] Rifapentine 150 mg and 300 mg are both included in the WHO Model list of essential medicines: 22nd list (2021). See: https://iris.who.int/handle/10665/345533 (accessed 29 September 2021).

[8] Approximately five times (US$ 225–233 versus US$ 343), based on current estimates using weighted average prices of the Global Drug Facility.

Remarks

- Non-severe TB is defined as: Peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary, non-cavitary disease, confined to one lobe of the lungs, and without a miliary pattern;
- Children and adolescents who do not meet the criteria for non-severe TB should receive the standard six-month treatment regimen (2HRZE/4HR), or recommended treatment regimens for severe forms of extrapulmonary TB.
- The use of ethambutol in the first 2 months of treatment is recommended in settings with a high prevalence of HIV,[9] or of isoniazid resistance.[10]

Source of recommendation

This recommendation has been developed following advice from the Guidelines Development Group convened by the WHO in May-June 2021 on the topic of the management of TB in children and adolescents. The recommendation is also featured in the consolidated guidelines module on management of tuberculosis in children and adolescents.

Justification and evidence

The majority of children with TB have less severe forms of the disease than adults. Treatment regimens that are shorter than those for adults may be effective in treating children with TB, however solid evidence to substantiate this has been lacking to date. Shorter treatment regimens can result in lower costs to families and health services, potentially less toxicity, lower risks of drug–drug interactions in children living with HIV, and fewer problems with adherence. Shorter, safe and effective treatment regimens for children with both drug-susceptible and DR-TB benefit children with TB and their families and are a key intervention to achieve the WHO's End TB Strategy targets, as well as targets related to children set during the UNGA HLM on TB in 2018. New evidence from a recently completed trial on the shortened treatment of drug-susceptible TB in children and adolescents has paved the way for new recommendations on shorter regimens for this group.

The SHINE trial (Shorter Treatment for Minimal Tuberculosis in Children) was the first and only large phase three trial to evaluate the duration of TB treatment in children with non-severe drug-susceptible TB. Therefore, evidence from the trial rather than a systematic review, was used to answer this PICO question *(35)*. The SHINE trial was a multicentre, open-label, parallel-group, non-inferiority, randomized, controlled, two-arm trial comparing four-month (16 weeks) versus the standard six-month (24 weeks) treatment durations in children under 16 years of age with symptomatic non-severe TB. Children and young adolescents aged below 16 years were treated with rifampicin, isoniazid, pyrazinamide with or without ethambutol using WHO-recommended doses, appropriate for paediatric dosing *(36)*.

PICO question: In children and adolescents with non-severe TB, should a four-month intervention regimen versus the standard six-month regimen conforming to WHO guidelines be used?

Evidence: In the SHINE trial, the primary efficacy outcome was a composite of treatment failure (including an extension of treatment beyond the replacement of missed doses, TB treatment drug changes or restarts due to suspected treatment failure), on-treatment loss-to-follow-up, TB recurrence or death by 72 weeks (from randomization), excluding children not reaching 16 weeks follow-up (modified-intention-to-treat). The non-inferiority margin for the primary efficacy outcome was 6%. The primary safety outcome was grade 3–5 adverse events recorded while on TB treatment.

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[9] Defined as countries, subnational administrative units, or selected facilities, where the HIV prevalence among adult pregnant women is ≥1% or among TB patients is ≥5% in the *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition)* 2014.

[10] WHO does not intend to establish thresholds for low, moderate or high levels of prevalence of isoniazid resistance: NTPs will establish definitions for their own countries.

The SHINE trial definition of non-severe TB was: peripheral lymph node TB or respiratory TB (including uncomplicated intrathoracic lymph node disease) confined to one lobe without cavities, no significant airway obstruction, uncomplicated pleural effusion, and no miliary TB.

The SHINE trial inclusion criteria were: children and young adolescents aged <16 years; weight ≥3 kg; no known drug-resistance; symptomatic but non-severe TB; smear negative on gastric aspirate or other respiratory sample (an Xpert MTB/RIF positive, rifampicin-susceptible result was allowed);[11] clinician's decision to treat with a standard first-line regimen; not treated for TB in the previous two years; known HIV status (positive or negative). Trial exclusion criteria were: respiratory sample acid-fast bacilli smear-positive (a smear-positive peripheral lymph node sample was allowed); premature birth (<37 weeks) and aged below 3 months; miliary TB, spinal TB, TBM, osteoarticular TB, abdominal TB, congenital TB; pre-existing, non-tuberculous disease likely to prejudice the response to, or assessment of, treatment (such as liver or kidney disease, peripheral neuropathy or cavitation); any known contraindication to taking TB drugs; known contact with a drug-resistant adult source case (including mono-resistant TB); known drug-resistance in the child; being severely ill; pregnancy.

A total of 1204 children were enrolled in the trial between July 2016 and July 2018. The median age of enrolled children was 3.5 years (range: 2 months – 15 years), 52% were male, 11% had HIV infection, and 14% had bacteriologically confirmed TB. Retention in the trial by 72 weeks and adherence[12] to allocated TB treatment were 95% and 94%, respectively. Sixteen (2.8%) versus 18 (3.1%) children reached the primary efficacy outcome (treatment failure) in the 16- versus 24-week arms respectively, with an unadjusted difference of -0.3% (95% CI: -2.3, 1.6). Treatment success was reported in 97.1% of participants receiving the 16-week regimen versus 96.9% in those receiving the 24-week regimen (relative risk (RR): 1.00, 95% CI: 0.98–1.02). Non-inferiority of the 16-week regimen was consistent across all intention-to-treat, per-protocol and key secondary analyses. This included restricting the analysis to the 958 (80%) children that were independently adjudicated to have TB at baseline by the trial Endpoint Review Committee. A total of 7.8% of children experienced a grade 3–5 adverse event in the 16-week arm, versus 8.0% in the 24-week arm (RR: 0.98, 95% CI: 0.67–1.44). There were 115 on-treatment grade ≥3 adverse events in 95 (8%) children, 47 (8%) in the 16-week and 48 (8%) in the 24-week arm, most common being pneumonia or other chest infections (29 (25%)) or liver-related events (11 (10%)) across both arms. There were 17 grade 3 or 4 adverse reactions (considered possibly, probably or definitely) related to trial drugs, including 11 hepatic events; all adverse reactions except three occurred in the first eight weeks of treatment.

GDG considerations: The GDG (2021) judged that while the desirable effects related to this PICO question are related to treatment outcomes, shortening the duration of treatment is also important and desirable (as reducing the length of treatment could make treatment easier for children and caregivers as well as reduce cost for families and the health system). The GDG discussed that since the SHINE trial was a non-inferiority trial, no difference in unfavourable outcomes between the two arms is what the trial aimed to detect. Therefore, both desirable and undesirable effects were judged by most GDG members as trivial. Since non-inferiority of the 4-month regimen was demonstrated in the trial, the balance of effects was judged to not favour either the shorter or the longer duration of treatment. However, the GDG noted that treatment duration is a critical issue which was further considered in the context of issues such as cost, acceptability and feasibility.

The GDG also discussed that presumably, a shorter duration of treatment will reduce costs to both the health care system and to children with TB and their families. The GDG ultimately agreed on 'moderate savings' despite the varying views of the level of these savings. The GDG judged that equity was probably increased with a shorter duration of treatment. Despite no direct evidence on acceptability, the GDG judged that the shorter regimen was acceptable to stakeholders.

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[11] In the SHINE trial, children with Xpert MTB/RIF results had very low or low semi-quantitative results, or a negative result. Xpert Ultra was not used in the SHINE trial.

[12] In the SHINE trial, adherence was defined as the proportion of children who received an adequate amount of treatment (as defined in the statistical analysis plan for both the intervention and control regimens; generally, a cut off of 80% of the allocated doses was used, within a certain time frame of starting each phase of treatment (i.e. intensive phase versus continuation phase).

In addition, the GDG felt that, in the absence of exposure to DR-TB, access to CXR would help distinguish between non-severe and severe disease. However, the panel recognized that access to CXR is often limited or quality of CXR and capacity for interpretation is insufficient at lower levels of the health care system, which may have equity implications. Therefore, feasibility was judged to vary by setting. The GDG noted that it is critically important to clearly define "non-severe" disease and that NTPs be encouraged to scale up access to quality CXR and train health care providers in its interpretation. Overall, the GDG judged that if the severity of TB disease in children can be adequately determined under programmatic conditions, then implementation of a four-month regimen is highly feasible.

Subgroup considerations

Children with peripheral lymph node TB: Although the number of children with peripheral lymph node TB in the SHINE trial were small (*n*=19 in the 16-week arm and *n*=21 in the 24-week arm), there was no difference in the proportion of unfavourable outcomes between the two arms. The SHINE trial also found that 16 weeks of treatment was non-inferior compared to 24 weeks of treatment among children with both peripheral lymph node disease and pulmonary disease (*n*=182 in the 16-week arm and *n*=171 in the 24-week arm). These results may provide reassurance to clinicians regarding a seemingly delayed clinical response to TB treatment, frequently seen in children with peripheral lymph node TB (where lymph nodes remain enlarged even after treatment).

Children and adolescents living with HIV infection (CALHIV): CALHIV were eligible for enrolment in the SHINE trial; 65 (11%) CALHIV were enrolled in the 16-week arm and 62 (10%) in the 24-week arm. 49% of CALHIV in the 16-week arm and 43% in the 24-week arm were on antiretroviral therapy at the time of enrolment. 20% of CALHIV in both arms had a CD4 count of less than 200 cells per mm^3. 51% of CALHIV in the 16-week arm and 63% in the 24-week arm were classified as severe as per the WHO immunological classification for established HIV infection *(37)*. In this subgroup, the 16-week regimen was non-inferior as compared to the 24-week regimen as well, although the 95% confidence interval for the difference in the unfavourable rate compared to the control arm was wide (risk difference -4.3, 95% CI -14.9 to 6.2).

In view of the limited evidence, clinicians may consider treating CALHIV with non-severe TB for four months, depending on the degree of immunosuppression and ART status, as well as the presence of other opportunistic infections. These children and adolescents will need to be monitored closely, especially at four months of treatment, and treatment extended to 6 months if there is insufficient progress.

Children with severe acute malnutrition (SAM): In the SHINE trial, SAM was defined as weight-for-height Z-score (WHZ) <−3 or MUAC <115 mm *(38)*. Thirty children with SAM (5%) were included in the 16-week arm and 33 (5%) in the 24-week arm. No separate subgroup analysis was therefore conducted for children with SAM. In view of the insufficient evidence on this subgroup, and as SAM is defined as a danger sign, children with SAM and non-severe TB should preferably receive 6 months of TB treatment.

Infants <3 months of age and/or weighing < 3 kg: Infants <3 months of age and infants weighing <3 kg (including premature birth (<37 weeks) were not eligible for inclusion in the SHINE trial. No new data on the treatment of congenital TB and very young infants (aged 0–3 months) with TB disease was received following a call for data. Therefore, infants aged 0–3 months with suspected or confirmed PTB or tuberculous peripheral lymphadenitis should be promptly treated with the six-month treatment regimen (2HRZ(E)/4HR), as per the existing recommendation from the 2014 *Guidance for national tuberculosis programmes on the management of tuberculosis in children (7)*. Treatment may require dose adjustment to reconcile the effect of age and possible toxicity in young infants. The decision to adjust doses should be taken by a clinician experienced in the management of paediatric TB.

Children treated for TB in the past two years: Given the increased risk of treatment failure and of drug resistance, children and adolescents treated in the preceding two years were not eligible for inclusion in the SHINE trial; they should be treated with the six-month treatment regimen (2HRZ(E)/4HR).

Implementation considerations

Assessing severity of disease: The feasibility of assessing the severity of TB disease, particularly in settings without access to CXR or capacity for CXR interpretation and WHO-recommended diagnostic tests was identified as a major implementation consideration. CXR was identified by the GDG as a critical tool to evaluate the severity of intrathoracic disease. As indicated under the recommendation remarks, non-severe intrathoracic or PTB disease refers to: intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary, non-cavitary disease confined to one lobe of the lungs and without a miliary pattern. Extensive or advanced disease in children under 15 years of age is usually defined by the presence of cavities or bilateral disease on CXR *(39)*. NTPs are encouraged to scale up access to quality CXR and provide training to health care providers in its interpretation. Out-of-pocket expenses for CXR pose a potential barrier to TB diagnosis and access to shorter regimen for eligible children and young adolescents. In the SHINE trial, children who were Xpert MTB/RIF positive, but sputum smear-negative were eligible for inclusion. The 85 children (7%) who were Xpert MTB/RIF positive (45 in the four-month arm and 40 in the six-month arm), had very low or low semi-quantitative Xpert MTB/RIF results.

Detailed implementation guidance is provided in the *Operational handbook on the management of tuberculosis in children and adolescents*, taking into consideration differences in the health care system and country context, including the availability of diagnostic tools to make a diagnosis and to assess disease severity. While access to CXR is an important implementation consideration, it should not be a barrier for children and adolescents in lower resourced settings to benefit from the shorter regimen. The implementation guidance in the operational handbook comprises criteria for assessing disease severity, including clinical criteria in the absence of CXR or rapid diagnostics or other bacteriological tests, to determine eligibility for the shorter regimen. Children with Xpert MTB/RIF or Ultra results that are trace, very low or low, who meet radiographical or clinical criteria for non-severe TB, can be treated with the four-month regimen.

Continuum between TB infection and disease: An additional implementation consideration is the concept that a continuum exists between TB infection, non-severe and more severe forms of TB disease in children. Shorter treatment regimens for drug-susceptible TB are now very similar to recently recommended shorter regimens for the treatment of TB infection, in terms of duration and composition, in particular the regimen that consists of three months of daily isoniazid and rifampicin (3HR) *(40)*. This implies that incorrectly diagnosing a child who has TB infection as having non-severe TB disease may not have severe consequences.

Contact investigation: Another implementation consideration is the scale-up contact investigation approaches, which can improve early case detection of children with non-severe disease who may benefit from the 4-month regimen.

Use of ethambutol in the intensive phase of treatment: Children and young adolescents with non-severe TB who live in settings with low HIV prevalence or a low prevalence of isoniazid resistance and those who are HIV-negative can be treated with a three-drug regimen (HRZ) for two months, followed by two months of HR. Children and young adolescents with non-severe TB who are living in settings where the prevalence of HIV is high[13] and/or the prevalence of isoniazid resistance is high[14] should

[13] This level of resistance was defined as countries, subnational administrative units, or selected facilities, where the HIV prevalence among adult pregnant women is ≥1% or among TB patients is ≥5% in the Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition) 2014.

[14] WHO does not intend to establish thresholds for low, moderate or high levels of prevalence of isoniazid resistance; instead NTPs will establish definitions for their own countries.

be treated with HRZE for two months followed by HR for two months. In the SHINE trial, ethambutol was used in line with these recommendations as per national guidelines and all CALHIV received ethambutol as part of their treatment. For the six-month regimen used to treat more severe forms of TB, it is recommended to add ethambutol to the regimen (i.e. 4HRZE/2HR).

Child-friendly formulations: NTPs are encouraged to prioritize the use of child-friendly fixed-dose combination (FDC) formulations for TB treatment in children up to 25 kg body weight, such as: the 3-FDC HRZ 50/75/150 mg with or without the addition of dispersible ethambutol, and the 2-FDC HR 50/75 mg (available from the Stop TB Partnership's Global Drug Facility (GDF)). Capacity-building of health care workers at all levels of the health system on diagnostic approaches (including treatment decision algorithms), eligibility for the four-month regimen and monitoring of children on first-line TB treatment will also be critical factors in the successful implementation of the shorter regimen.

Treatment of severe pulmonary TB in children and young adolescents: Children and young adolescents with forms of PTB that do not meet the eligibility criteria for the four-month regimen should be treated with a standard six-month regimen that includes a fourth drug (ethambutol) in the intensive phase (such as 2HRZE/4HR).

Treatment options for adolescents from 12 years of age: Another implementation consideration is that adolescents aged 12 years and above with TB can benefit from the four-month regimen that consists of isoniazid, rifapentine, moxifloxacin and pyrazinamide (HPMZ), which is now conditionally recommended by WHO (see Recommendation A2.1 in the current document). Adolescents aged between 12 and 16 years therefore have three options for treatment: the four-month HPMZ regimen, the four-month 2HRZ(E)/2HR regimen, and the standard six-month 2HRZ(E)/4HR regimen. Adolescents from 16 years of age were not included in the SHINE trial and therefore have two options: the four-month HPMZ regimen and the standard six-month 2HRZE/4HR regimen.

Choosing an appropriate regimen for this age group will depend on clinical factors (such as the presence of severe disease or if living with HIV, ART status and CD4 count) as well as contextual factors (including the availability of the HPMZ regimen in the country).

A3. Drug-susceptible TB treatment and ART in people living with HIV

Recommendation A3.1

No.	Recommendation
A3.1	It is recommended that TB patients who are living with HIV should receive at least the same duration of daily TB treatment as HIV-negative TB patients. *(Strong recommendation, high certainty of evidence)*

Source of recommendation

This recommendation was first put forward in 2010 and considered valid in the guidelines update of 2017 (see summary of recommendations in Annex 1). The recommendation is copied without modification into this consolidated document and appears exactly as in the 2010 guidelines.

Justification and evidence

A systematic review and meta-analysis of six randomized controlled trials and 21 cohort studies provided pooled estimates of failure, relapse and death by duration of rifampicin, and daily intensive phase versus intermittent throughout *(41)*. The systematic review revealed a marked and significant

reduction in failure and relapse in the arms where some or all patients received ART. In a regression model, treatment failure or relapse was 1.8–2.5 times more likely with intermittent rather than daily dosing in the intensive phase. Compared with 8 or more months of rifampicin, 2-month rifampicin regimens carried a 3-fold higher risk of relapse and 6-month regimens carried a 2.2 -fold higher risk. Extending treatment beyond 6 months is recommended by some expert groups in certain persons living with HIV and the meta-analysis showed that this is associated with significantly lower relapse rates. However, several other considerations were given greater weight. Separate regimens for TB patients living with or without HIV would be very challenging in operational terms and could create stigma. Other potential harms of extending treatment are acquired resistance to rifampicin, and a longer period during which ART options are limited (because of ART–rifampicin interactions).

Recommendation A3.2

No.	Recommendation
A3.2	ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV.[a] Adults and adolescents *(Strong recommendation, low to moderate certainty of evidence)*; Children and infants *(Strong recommendation, very low certainty of evidence)*

[a] Except when signs and symptoms of meningitis are present.

Source of recommendation

This recommendation is from WHO's Consolidated guidelines on HIV infection, testing, treatment, service delivery and monitoring: recommendations for a public health approach *(42)*. The background and history of this recommendation is provided below, while the detailed rationale and supporting evidence can be found in the source document.

The recommendation applies to both children and adults but the strength of the recommendation and certainty of the evidence differ for each group because of the difference in the available data for the reviews. One specific exception that is highlighted in this recommendation relates to situations in which signs and symptoms of meningitis are present. Caution is needed regarding people who are living with HIV and who have TB meningitis because immediate ART is significantly associated with more severe adverse events. Thus, it might be a consideration to delay ART for 4–8 weeks after TB treatment is initiated in such situations.

The use of corticosteroids as adjuvant treatment for TB meningitis still applies in these situations.

Background

Since 2010, WHO has recommended that ART be started as soon as possible within eight weeks of initiating TB treatment (strong recommendation, high certainty of evidence) *(43)*. In 2012, WHO added a recommendation to initiate ART within two weeks among those with a CD4 count less than or equal to 50 cells/mm^3 (except for children for whom previous recommendations remained unchanged because of the lack of specific evidence) *(44)*. In 2017, on the basis of a systematic review of evidence that earlier ART initiation resulted in reduced morbidity and mortality *(45)*, WHO-recommended offering rapid ART initiation within one week, and on the same day if ready, for all people diagnosed with HIV – including adults, adolescents and children *(45)* – with stated cautions for those with signs and symptoms of TB meningitis.

A4. The use of adjuvant steroids in the treatment of TB meningitis and pericarditis

Recommendation A4.1

No.	Recommendation
A4.1	In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks should be used. *(Strong recommendation, moderate certainty of evidence)*

Recommendation A4.2

No.	Recommendation
A4.2	In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used *(Conditional recommendation, very low certainty of evidence)*

Source of recommendation

These recommendations were first put forward in the guidelines update of 2017 (see summary of recommendations in the Annex 1). They are copied without modification into this consolidated document and appear exactly as in the 2017 guidelines.

Justification

In patients with tuberculous meningitis, evidence from randomized controlled trials in the systematic review *(46–50)* showed lower rates of mortality, death or severe disability, and disease relapse when patients were treated with steroids in addition to anti-TB treatment. The benefits in terms of mortality increased with the increasing TB meningitis stage (i.e. increasing severity of disease). Additionally, rates of adverse events and severe adverse events, including severe hepatitis, were lower in the patients receiving steroids.

In patients with tuberculous pericarditis, evidence from studies in the systematic review *(51–57)* showed a benefit to steroid treatment with regard to death, constrictive pericarditis and treatment adherence. When the studies were considered individually, the largest (1400 patients) and most recent study – the IMPI study *(53)* – showed no benefit with steroids. However, a complicating factor in these findings is HIV infection. In the IMPI study, 67% of subjects were HIV-positive and only 14% were on ART. This raises the question as to whether immunosuppressed patients may have had a different benefit from steroids when compared to HIV-negative people or persons living with HIV who are on ART. In the IMPI study, a supplemental analysis was done of the HIV-negative patients only and a small mortality benefit was shown with steroid treatment. However, the relationship between HIV infection and steroids is complex. In another smaller study of 58 subjects, all of whom were HIV-positive, steroids were found to reduce mortality *(52)*. It is of note that the other studies in the review did not address HIV and mortality.

The panel considered that the benefit in preventing constrictive pericarditis outweighed the potential harms of corticosteroid therapy.

Subgroup considerations

Steroids should be given regardless of the severity of meningitis. With regard to the use of steroids in tuberculous pericarditis, in one study an increase in HIV-related cancers (non-Hodgkins' lymphoma and Kaposi sarcoma) was observed *(53)*. However, this increase appears to be caused by co-administration of immunotherapy (*M. indicus pranii*).

Implementation considerations

Practitioners should give oral steroids if intravenous formulations are not available.

A5. Treatment regimens for extrapulmonary TB in children and adolescents

Recommendation A5.1

No.	Recommendation
A5.1	Children with suspected or confirmed tuberculous meningitis or osteoarticular tuberculosis should be treated with a four-drug regimen (HRZE) for 2 months, followed by a two-drug regimen (HR) for 10 months. The total duration of treatment should be 12 months. *(Strong recommendation, low certainty of evidence)*

Source of recommendation

This recommendation was first put forward in the 2010 publication *Rapid advice: treatment of tuberculosis in children (6)* (see summary of recommendations in Annex 1). It is copied without modification into this consolidated document and appears exactly as in the 2010 document.

Justification

In 2010, the GDG panel noted that the evidence base for both conditions relied largely on observational studies and was of low or very low quality. For tuberculous meningitis, available studies are heterogeneous and outcomes remain poor, with high mortality and long-term morbidity, particularly in children with grade 2 or grade 3 disease. The panel also noted that several existing guidelines recommend treatment durations longer than those used for pulmonary TB, ranging from 9 months to 2 years. In addition, about 30% of children with a miliary pattern on chest radiography have CNS involvement, supporting the use of a 12-month regimen. Because penetration of anti-TB medicines into the CNS is uncertain, the panel recommended considering doses at the upper end of the recommended range for tuberculous meningitis.

For osteoarticular TB, the panel noted that treatment durations of at least 12 months were commonly used in published studies in children. These studies most often reported relapse-free survival as the primary outcome, although follow-up was often short or poorly documented. The panel considered pharmacological arguments supporting longer treatment durations for bone and joint infections, the difficulty of confidently determining cure in osteoarticular disease, and the lack of evidence indicating an increased risk of toxicity with longer treatment. These considerations supported alignment with a 12-month regimen, consistent with the approach recommended for tuberculous meningitis.

Recommendation A5.2

No.	Recommendation
A5.2	In children and adolescents with bacteriologically confirmed or clinically diagnosed TB meningitis (without suspicion or evidence of MDR/RR-TB), a 6-month intensive regimen (6HRZEto) may be used as an alternative option to the 12-month regimen (2HRZE/10HR). *(Conditional recommendation, very low certainty of evidence)*

Remarks

- The shorter intensive regimen is suitable for children and adolescents who have no evidence of drug resistance and in children and adolescents who have a low likelihood of drug-resistant TB, e.g. those without risk factors for any form of drug-resistant TB.
- The recommendation from the *Guidance for national tuberculosis programmes on the management of tuberculosis in children (7) (second edition, 2014)* remains an option for the treatment of children and adolescents with suspected or confirmed TB meningitis (TBM): Children and adolescents with suspected or confirmed tuberculous meningitis should be treated with a four-drug regimen (HRZE) for 2 months, followed by a two-drug regimen (HR) for 10 months, the total duration of treatment being 12 months *(Strong recommendation, low certainty of evidence)*.
- Due to a lack of data, the shorter intensive treatment regimen recommendation should not be used in children and adolescents living with HIV who are diagnosed with TB meningitis.

Source of recommendation

This recommendation was developed following advice from the GDG convened by WHO in May–June 2021 on the topic of the management of TB in children and adolescents. It is featured in the 2022 *WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents*.

Justification and evidence

Following *M. tuberculosis* infection, young children are at high risk of developing the most severe forms of the disease, of which the most devastating form is TBM. This predominantly affects young children, with a peak age of onset of 2–4 years *(58)*. Up to 15% of childhood TB may present as TBM *(59)*; with a decreasing incidence of bacterial meningitis attributed to other causes, TB is the leading cause of bacterial meningitis in many settings *(60)*. TBM is associated with significant mortality and morbidity; for example, in a systematic review and meta-analysis published in 2014, the risk of death among children aged 0–14 years with TBM was estimated at 19.3% and the risk of neurological sequelae among TBM survivors was estimated at 36.7% *(61)*. Even among children without severe neurological sequelae, attention deficit and behavioural disorders are common, and the human cost and financial burden for families and society are high. Diagnosis in the most advanced clinical stage, which occurred in almost 50% of children with TBM, was associated with worse outcomes based on the findings of the review. WHO currently recommends a regimen of 12 months duration to treat TBM, comprising isoniazid, rifampicin, ethambutol and pyrazinamide given daily for the first 2 months, followed by isoniazid and rifampicin given daily for 10 additional months (2HRZE/10HR) *(6, 7)*. Recommended doses to be used in this regimen are the same as those for the treatment of pulmonary TB *(7)*.

The recommendation on the use of the 12-month regimen was based on a literature review *(62)* and was first included in the 2010 *Rapid advice: treatment of tuberculosis in children (6)*. The review included 46 studies with information on the efficacy of different regimens and dosages for the management of TBM (25 studies included paediatric data, and 21 included data on both adults and children). Most of these studies were nonrandomized, noncomparative studies. The quality of the studies ranged from

low to very low, and no clear conclusions could be drawn from the efficacy studies, given that they differed widely in terms of design, drugs used and patient populations. None of the studies from this review were entered into GRADE, given the lack of comparative data.

Shorter regimens to treat paediatric TBM are used in some settings. The national TB guidelines from South Africa recommend a regimen composed of daily isoniazid, rifampicin, pyrazinamide and ethionamide, given for 6 months (6HRZEto) *(63)*. The recommendations in South Africa are based on expert opinion; in particular, with regards to replacing ethambutol with a drug (ethionamide) that has more efficient blood–brain barrier penetration *(62)*. A clinical trial is underway to compare a regimen that, compared with the WHO-recommended regimen, comprises higher dose isoniazid, higher dose rifampicin, pyrazinamide and levofloxacin given daily for 6 months, but the results are not expected until 2026 (SURE trial, ISRCTN40829906). Shorter regimens may be as effective and safe, and may improve adherence and reduce the burden on both people with TBM and health care systems; however, it is not known how outcomes compare between the shorter regimens and the WHO-recommended 12-month regimen.

PICO question: In children and adolescents with presumed or bacteriologically confirmed drug-susceptible TB meningitis, should a 6-month intensive regimen, compared to the 12-month regimen that conforms to WHO guidelines, be used?

Evidence: To inform recommendations on the treatment for child and adolescent TBM, a systematic review and meta-analysis was conducted to compare the effectiveness of shorter regimens versus the current WHO-recommended 12-month regimen *(7)*. The primary intervention of interest was the regimen currently used in South Africa *(63)*; in secondary analyses, outcomes associated with other shorter regimens were examined. The search criteria from an earlier systematic review and meta-analysis conducted in 2014 were updated and the search was run in February 2021 *(61)*. Studies with available information on at least the composition and duration of treatment regimens were included. Ineligible regimens included those without rifampicin, treatment regimens with a duration over 12 months (other than the WHO regimen), intermittent regimens and nonintensive short regimens. Pooled proportions were estimated across studies and within regimens through aggregate-level meta-analysis using generalized linear mixed models (with Gauss-Hermite quadrature for the following outcomes: death by end of treatment; loss to follow-up; treatment success; neurological sequelae [among survivors]; and survival without neurological sequelae [among those starting treatment]). Subgroup analyses were planned but were not feasible, owing to insufficient data.

Of the 1820 unique citations screened, 149 full-text papers were evaluated. Of these, five met inclusion criteria for the systematic review. In addition, two unpublished cohorts were eligible for inclusion. In total, four studies of intervention regimens (three published and one unpublished) *(64–67)*, and three studies of the comparator regimen (two published and one unpublished) *(68–70)* were identified. No studies performing head-to-head comparisons of regimens were identified. Three of the four studies of intervention regimens were conducted in a single referral centre in South Africa. Given that only one study reported on outcomes from an 8-month regimen in Viet Nam *(66)*, it was excluded from the meta-analysis. The two published studies of the comparator regimen were conducted at different sites in India *(68, 69)*, although data for the unpublished study were collected in various centres in Europe through the Pediatric Tuberculosis Network European Trials Group *(70, 71)*. A total of 837 patients with TBM received intervention regimens, with the median age in each study ranging from 2.3 to 5.5 years (age range: 2 months to 15 years). Among the 282 patients treated with the comparator regimen, the median age in the European study was 3.3 years; summary data on age were not reported in the studies from India.

The cumulative number of deaths was recorded at the end of treatment for each regimen (i.e. at 6 months after treatment initiation in studies of the intervention regimen and at 12 months after treatment initiation in studies of the comparator regimen). Among studies of the intervention regimen, 0.0–9.6% of patients died within 6 months; most deaths occurred early after hospital admission and primarily involved patients diagnosed in stage 3 at baseline. Among studies of the comparator

regimen (i.e. the standard of care), 7.1–30.0% of patients died. In one of these studies, diagnosis at stage 3 was most strongly associated with mortality, although stage-specific outcome data were not reported. In a random-effects meta-analysis, the pooled proportions of deaths were 6.0% (95% CI: 2.0–13.0) and 24.0% (95% CI: 18.0–32.0) for children and adolescents who received the intervention and comparator regimens, respectively. The percentage of patients with treatment success were 78.5–100.0%, with a random-effects pooled proportion of 95.0% (95% CI: 74.0–99.0) among studies of the intervention regimen, and 70–85.7%, with a random-effects pooled proportion of 75.0% (95% CI: 69.0–81.0) among studies of the comparator regimen.

Neurological sequelae were defined and assessed differently across studies. Among patients treated with the intervention regimen, 50.0–66.7% had neurological sequelae, mostly categorized as mild, and being among patients diagnosed at stage 2 or 3. Among patients treated with the comparator regimen, 31.9–50.0% had neurological sequelae. In one study on the comparator regimen from India, 17 of 29 (58.6%) cases were categorized as mild. The random-effects pooled proportions of neurological sequelae among survivors were 66.0% (95% CI: 55.0–75.0) and 36.0% (95% CI: 30.0–43.0) for the intervention and comparator regimens, respectively. Among the 135 HIV-negative and 13 HIV-positive patients who received the intervention regimen in South Africa, none relapsed within 2 years of treatment. Other studies did not report on relapse.

Because of the noncomparative nature of the studies, which were all observational, narrative descriptions reporting pooled proportions were provided rather than estimated measures of effect. The certainty of evidence was deemed to be very low for all outcomes owing to very serious risk of bias, serious or very serious inconsistency within regimens, and very serious indirectness. Imprecision could not be assessed owing to the lack of comparative data.

The reviewers concluded that pooled estimates need to be interpreted with caution considering the small number of studies, the potential for confounding by indication, other potential residual confounding and between-study heterogeneity regarding the assessment of neurological sequelae.

The GDG convened in 2021 considered a range of factors. Although the GDG members discussed evidence of benefits of the intervention regimen and biological plausibility, they noted the very low certainty of the data. Members decided to choose that the balance of effects "does not favour either the intervention or the comparison". This decision reflects variation in both the desirable and undesirable effects, as well as the very low certainty of the evidence overall. Recognizing how quickly the condition of children with TBM can deteriorate, GDG members were not comfortable favouring one regimen over the other, based on the very low certainty of the data.

The GDG members also noted that the feasibility of introducing the shorter intensive regimen depends on the setting. Acceptability, affordability and access to the component medicines (including the child-friendly ethionamide formulation, a 125 mg dispersible tablet) are important contextual factors, as well as any other factors such as the necessity and availability of monitoring tests that are needed with the shorter regimen. GDG members thought that the short intensive regimen would probably be acceptable because it includes medicines that have been in use for many years, including first-line medicines and ethionamide. The intervention regimen is more costly than the comparator regimen, but this refers to the costs of medicines only; GDG members noted that other costs (including to patients, families and the health system) were important.

The GDG acknowledged the limited data on alternative regimens to treat TBM and the need for continued efforts to optimize and better understand treatment options for TBM, including implementation considerations such as dosing.

Subgroup considerations

Children living with HIV infection: most studies in the review were restricted to children who were HIV-negative. Children who were HIV-positive represented a small proportion of children with TBM

overall, and all received the intervention regimen. In the three studies using the intervention regimen included in the evidence review, 11 children were identified as having HIV infection (of a total of 724 children). Therefore, it was not possible to undertake analyses stratified by HIV infection. An additional small study of 13 children from South Africa used an extended duration of the intervention regimen (i.e. 9 months of HRZEto). Therefore, the recommendation on the 6-month regimen does not apply to children who are HIV-infected and are diagnosed with TBM.

Adolescents: the population in the PICO question included both children (aged 0–9 years) and adolescents (aged 10–19 years). Based on the available information in the studies, the median ages of patients in the three studies using the intervention regimen were 35 months (range: 2 months to 14 years), 28 months (range: 2 months to 15 years) and 30 months (5–82 months). In the studies using the comparator regimen, the age structure reported in two of the three studies was aged below 18 years and 3.3 years (range: 1–16 years). This recommendation, therefore, applies to both adolescents and children.

Other subgroup analyses: several subgroup analyses were preplanned by the systematic reviewers (including subgroup analyses by age group, for patients with DR-TB [including isoniazid-resistant TB]), for patients who were microbiologically confirmed versus those clinically diagnosed, by Medical Research Council stage at diagnosis, and for patients with complications including tuberculoma and hydrocephalus. However, these analyses could not be conducted owing to insufficient data.

Implementation considerations

One key implementation consideration is the administration of the intervention regimen with the correct dosages of the included medicines, using currently available child-friendly formulations, including FDC formulations when possible. The regimen includes isoniazid, rifampicin, pyrazinamide and ethionamide, and is dosed as follows:

- isoniazid: 20 mg per kg, maximum 400 mg daily;
- rifampicin: 20 mg per kg, maximum 600 mg daily;
- pyrazinamide: 40 mg per kg, maximum 2 000 mg daily; and
- ethionamide: 20 mg per kg, maximum 750 mg daily.

Historically, the regimen was dosed using a child-friendly FDC (dispersible tablet) of isoniazid and rifampicin (60 mg/60 mg), with pyrazinamide and ethionamide added as single medicines. This 60/60 mg FDC has limited availability globally, whereas a 50/75 mg isoniazid/rifampicin dispersible tablet is widely available through the Stop TB Partnership GDF in over 100 countries (at the time of the GDG meeting). Using this formulation, rifampicin is dosed at slightly higher mg per kg doses because the drug ratio between isoniazid and rifampicin is 1:1.5 in the formulation. Higher doses of rifampicin are being used in several other trials, including the SURE trial, TBM-KIDS and OptiRif Kids. Results from the SURE trial and TBM-KIDS are expected in the coming years, while the results from the OptiRif Kids trial *(72)* were published after the GDG meeting. The dosing of the shorter intensive regimen was the subject of an expert consultation convened by the WHO after the GDG meeting, and information on dosing for this regimen is included in the operational handbook *(73)*.

A dispersible paediatric formulation of ethionamide (125 mg) has been available from the Stop TB Partnership GDF since March 2018. Although orders for ethionamide are received from high MDR-TB burden countries consistently (this formulation was supplied by GDF to 41 countries between 2019 and 2021 at the time of the GDG meeting), the GDG members discussed that the paediatric formulation of ethionamide may not be available in all countries or health care levels where it is needed. Ethionamide is a component of the shorter all-oral bedaquiline-containing regimens to treat MDR/RR-TB; however, at the time that the GDG meeting was held (May–June 2021), the shorter regimen was only recommended for children aged 6 years and above.

The GDG members also noted that this regimen should ideally be used in children with TBM that is bacteriologically confirmed as drug susceptible. However, it can also be used for children who are clinically diagnosed, but there should be no suspicion of DR-TB, such as in children or adolescents who have a history of contact with a patient with confirmed DR-TB (including isoniazid resistance, rifampicin resistance or multidrug resistance). In countries or areas with a high background prevalence of DR-TB and where ethionamide is in use to treat DR-TB, programmes and clinicians need to consider the risks and benefits of using this regimen. The current recommendation for the diagnosis of TBM is that in adults or children with signs and symptoms of TBM, Xpert MTB/RIF or Xpert Ultra should be used in cerebrospinal fluid as the initial diagnostic test rather than smear microscopy/culture (strong recommendation, moderate certainty of evidence for test accuracy for Xpert MTB/RIF; low certainty of evidence for test accuracy for Xpert Ultra) *(74)*.

A6. Monitoring and evaluation

All recommended regimens for drug-susceptible TB should be implemented within standard programmatic monitoring frameworks. National TB programmes should document baseline clinical and bacteriological status, monitor clinical response during treatment, and assign treatment outcomes using standard definitions. Treatment supervision remains essential to reduce the risk of acquired drug resistance. At the national level, periodic drug-resistance surveys or continuous surveillance systems are required to assess the impact of rifampicin-based regimens and detect emerging resistance patterns.

For the standard 6-month regimen (2HRZE/4HR), daily dosing, and the use of fixed-dose combinations, no additional monitoring measures are required beyond routine TB programme practice.

For the 4-month regimen in people aged 12 years or older that includes isoniazid, rifapentine, moxifloxacin, and pyrazinamide, clinical and laboratory monitoring remains the same as for the 6-month regimen. Routine baseline ECG is not required unless clinically indicated. Liver function testing should follow national policies, including any additional requirements related to the safety warnings for moxifloxacin.

For children and adolescents with non-severe TB receiving the 4-month regimen (2HRZ(E)/2HR), clinical monitoring is unchanged, but treatment outcomes are determined at 4 months. In cases of insufficient clinical improvement, programmes should reassess for alternative diagnoses, including drug-resistant TB, and consider extending treatment to 6 months. Follow-up for up to 12 months after treatment completion is important to detect relapse, particularly when shorter regimens are introduced.

For children and adolescents with TB meningitis receiving the 6-month intensive regimen as an alternative to the 12-month regimen, implementation should include strengthened monitoring of uptake and treatment outcomes. Programmes should also monitor the incidence of TB meningitis in children and adolescents, as this reflects ongoing transmission and delays in diagnosis.

Research gaps

The GDGs (2016 and 2021) discussed future research and highlighted a number of priorities.

The effectiveness of fixed-dose combination TB treatment when compared to separate drug formulations in patients with DS-TB disease

- Additional research on the reasons why FDC formulations did not show a clear benefit over separate drug formulations.
- Pharmacokinetic studies of the bioavailability of FDCs versus separate drug formulations and better development of weight band categories for drug dosing.
- The optimal dose of rifampicin, including the use of different drug formulations in all age groups.
- Additional qualitative studies detailing adherence to medication.
- Additional work on FDC formulations to further decrease the pill burden, especially among patients with comorbidities.

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 (or not) with ART.
- The relationship between steroid treatment and cancer risk, with reference to the Mayosi et al. study on pericarditis *(54)*.

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

- Acquisition of drug resistance for Mycobacterium tuberculosis and for other bacteria while on treatment with a 4-month regimen.
- The efficacy of the regimen for patients with extrapulmonary TB.
- Pharmacokinetic, safety and tolerability studies in younger adolescents and children. A pharmacokinetic sub-study in adults was initiated alongside the trial, and the results were expected within months of the GDG meeting.
- The cost–effectiveness of the shorter regimen.
- Considerations regarding the impact of the 4-month regimen on equity.
- The acceptability of the shorter 4-month regimen, particularly for patients.
- The use of this regimen in specific subgroups – including pregnant and breastfeeding women, children aged less than 12 years, HIV-positive individuals with a CD4 count lower than 100 cells/mm^3, people with diabetes mellitus and people with a body weight less than 40 kg.
- Dosing considerations for people weighing less than 40 kg.

- The use and acceptability of FDC formulations for the shorter 4-month regimen.
- Operational research on directly observed treatment versus self-administered therapy.
- Treatment adherence and completion in operational settings.

Treatment of extrapulmonary TB

- Comparative efficacy and safety data on the short intensive and standard treatment regimens.
- Dosing for the shorter intensive regimen and for alternative regimens under research, including regimens that include higher doses of medicines than are currently recommended.
- Considerations regarding equity, including equitable access to medicines in the short intensive regimen.
- Cost–effectiveness of shorter regimens versus the current standard of care.
- Feasibility and acceptability of regimens for the treatment of TBM.
- Research on the sequelae of TBM (including the type and severity of sequelae and the ability to prevent or manage them) as well as objective measures of quality of life/functionality post-treatment.
- Co-administration of anti-inflammatory agents in the treatment of children and adolescents with TBM.
- Optimal regimens to treat TBM among CALHIV.

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Chapter 2
Drug-resistant TB treatment

Introduction

Tuberculosis (TB) strains that are resistant to TB medicines are more difficult to treat than drug-susceptible strains, and present a major challenge for patients, health care workers and health care services. In addition, the increase of drug-resistant TB (DR-TB) threatens global progress towards the targets set by the End TB Strategy *(1)* of the World Health Organization (WHO). Thus, there is a critical need for the continual development of evidence-based policy recommendations on the treatment and care of patients with DR-TB, based on the most recent and comprehensive evidence available.

In the past decade, WHO has developed and issued evidence-based policy recommendations for the treatment and care of patients with DR-TB, published in a range of documents (see **Box 2.1**). WHO has consolidated guidelines in response to requests from Member States to facilitate policy transfer at the country level. The first integrated recommendations for the management and care of multidrug- or rifampicin-resistant TB (MDR/RR-TB) were released in 2019, as the *WHO consolidated guidelines on drug-resistant tuberculosis treatment (2)* with an update released in 2022 *(3)*. The consolidation of WHO recommendations on TB and DR-TB has been expanded to better outline the path that a patient will take following exposure to resistant strains of *Mycobacterium tuberculosis*, once infection has progressed to TB disease, and the patient has been identified by the health system and referred for DR-TB treatment.

The guidance provided in this chapter outlines specific WHO recommendations on the overall treatment management, care and monitoring of patients with MDR/RR-TB. It brings forward recommendations developed by various Guideline Development Groups (GDGs) convened by WHO in 2011, 2018, 2019, 2021, 2022, 2024 and 2025. The GDGs use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to summarize the evidence and formulate policy recommendations and accompanying remarks. This chapter incorporates recommendations that were made in 2022, based on new evidence that was available to WHO on the following: the use of the bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for patients with MDR/RR-TB; and the use of 9-month all-oral bedaquiline-containing regimens for patients with MDR/RR-TB. It also includes new recommendations developed in June 2024, based on new evidence from the BEAT Tuberculosis and endTB-Q trials. The inclusion of new recommendations in the update of the consolidated guidelines was communicated to the public via a rapid communication in August 2024 *(4)*. This rapid communication was released in advance of updated WHO consolidated guidelines, to inform national TB programmes (NTPs) and other stakeholders of key changes in the treatment of DR-TB, and to allow for rapid transition and planning at the country level. The update of this chapter in the second edition of consolidated guidelines follows the GDG meeting in November 2025. It includes several new recommendations stemming from the review and meta-analysis of evidence from the BEAT Tuberculosis and endTB-Q trials.

Overall, this chapter focuses on recommendations for the use of effective treatment regimens for people with DR-TB; specifically, regimens for rifampicin-susceptible, isoniazid-resistant TB (Hr-TB), all-oral shorter regimens for MDR/RR-TB, longer regimens for MDR/RR-TB, monitoring of the patient response to MDR/RR-TB treatment, starting antiretroviral therapy (ART) in patients on second-line anti-TB regimens, providing surgery for patients on multidrug-resistant TB (MDR-TB) treatment, and co-administering treatment for hepatitis C virus (HCV) and MDR/RR-TB. To inform the global community of the major gaps and research areas to be addressed and to support the development of evidence-based recommendations, this document also outlines the research priorities that will help to generate knowledge on evidence-based, attainable standards of health.

The recommendations included herein are a component of the WHO consolidated guidelines on TB and are primarily intended for use by NTPs, public health agencies and other key constituencies involved in the planning, implementation and monitoring of activities for the programmatic management of DR-TB.

DR-TB remains a significant public health challenge, having a profound impact on patients, communities and health care systems. In 2024, global estimates suggest there were about 390 000 new cases of MDR/RR-TB, yet less than half of these cases were officially reported and started on treatment *(5)*. Treatment success rates have improved, rising from 50% in 2012 to 71% in 2022; nevertheless, almost 15% of those with MDR/RR-TB still succumb to the disease *(6)*. Before 2022, treatment options for MDR/RR-TB were suboptimal, involving prolonged treatment durations, a higher number of pills and the use of drugs with more severe side-effects, leading to significant adverse events (AEs) and less favourable outcomes. However, a breakthrough came in 2022 with the introduction of the first 6-month treatment regimen using three or four medications.

This chapter concerns TB treatment and care; it presents newly developed WHO recommendations published here for the first time, and existing recommendations from other WHO guidelines that applied the GRADE approach.

Structure of the chapter

The recommendations part of this chapter has eight sections that cover aspects of the treatment of DR-TB. The aspects covered are:

- treatment of DR-TB using 6-month regimens:
  - the 6-month bedaquiline, pretomanid, linezolid and moxifloxacin or clofazimine (BPaL/M/C) regimen;
  - the 6-month bedaquiline, delamanid, linezolid, levofloxacin and/or clofazimine (BDLLfx/C) regimen;
- treatment of DR-TB using 9-month regimens:
  - the 9-month all-oral regimens;
  - the modified 9-month all-oral regimens;
- treatment of DR-TB using longer regimens;
- treatment of rifampicin-susceptible and isoniazid-resistant TB (Hr-TB);
- monitoring and management strategies for MDR/RR-TB treatment;
- starting ART for people on MDR/RR-TB regimens;
- surgery for people on MDR/RR-TB treatment; and
- HCV and MDR/RR-TB treatment co-administration.

Each section starts with the current WHO recommendations for that aspect, then gives information on the evidence used to inform that recommendation, a summary of the analyses that were carried out based on the evidence, considerations for specific subgroups and considerations for implementation. Annexes provide more details on the methods, the GDGs (from 2011, 2018, 2019, 2021, 2022, 2024 and 2025), PICO (population, intervention, comparator and outcome) questions, evidence profiles and evidence-to-decision (EtD) analyses, unpublished data and statistical analysis plans. Additional information on the management of MDR/RR-TB is presented in the relevant chapter of the *WHO operational handbook on tuberculosis treatment and care*, a separate document that is designed to aid implementation efforts *(7, 8)*.

Background

Effective treatment of TB, including its drug-resistant forms, relies on the use of several medicines administered in combination for an adequate duration. Significant progress has been made in recent years in identifying more efficacious, safer medicines and shorter treatment regimens. Since the 1990s,

WHO has regularly evaluated evidence on the use of specific drug compositions and combinations of regimens of different durations *(2, 9–16)*. Historically, patients with certain drug-resistance patterns were often treated for 20 months or longer. In 2016, a standardized, shorter treatment regimen (9–12 months) was recommended for patients with MDR/RR-TB strains not resistant to fluoroquinolones or second-line injectable agents, although longer regimens (18–20 months) remained an option for patients who were not eligible for the shorter regimen. Subsequent modifications to these treatment regimens led WHO to reassess the evidence, which in turn resulted in revised recommendations that balance the effectiveness and harms of new regimens or modifications of recommended regimens.

Interest in reducing the duration of treatment for MDR/RR-TB has driven several initiatives in recent years to treat patients with shorter regimens under programmatic and trial conditions *(17–22)*. When used in carefully selected patients with MDR/RR-TB who have not been previously exposed to second-line medicines or do not have additional resistance to those medicines, these regimens can achieve relapse-free cure in about 80% of cases or more, even under programmatic conditions *(17, 21)*. In 2016, on the basis of data from observational studies of the standardized shorter regimens in various countries in Africa and Asia, WHO for the first time recommended a standardized 9–12-month shorter MDR-TB regimen for eligible patients *(16)*. In 2018, following the results of a trial – the Standard Treatment Regimen of Anti-tuberculosis Drugs for Patients with MDR-TB (STREAM) Stage 1 trial – a revised recommendation on the use of a shorter MDR-TB regimen was released, following an evidence assessment and a ranking of benefits and harms attributed to specific drugs; the revision included a recommendation to replace the injectable agent kanamycin (or capreomycin) with amikacin *(2)*.

Evidence of permanent effects attributed to the toxicity of injectable agents has prompted further advances in the development of new treatments (e.g. shorter injectable-sparing regimens). Bedaquiline was the first new medicine to be added to the group of available second-line TB medicines. In 2013, WHO issued interim guidance for using bedaquiline with other WHO-recommended MDR-TB treatments. Bedaquiline gradually became a staple drug in the treatment of DR-TB, initially featuring as an add-on agent in the longer regimens for MDR/RR-TB and then becoming a Group A medicine along with fluoroquinolones and linezolid. In 2019, South Africa's Department of Health shared with WHO observational data on an all-oral bedaquiline-containing shorter regimen of 9 months duration. That regimen was reviewed and has been recommended by WHO since 2019, with the following combination of medicines: bedaquiline (used for 6 months), in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high-dose), pyrazinamide and clofazimine for 4 months (with the possibility of extending to 6 months if the patient remains sputum smear-positive at the end of 4 months); followed by 5 months of treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide (4–6 Bdq[6]-Lfx[Mfx]-Eto-E-Z-Hh-Cfz / 5 Lfx[Mfx]-Cfz-Z-E).

The pressing need for more effective treatment regimens for patients with extensive drug resistance (including fluoroquinolone resistance and more complex drug-resistance profiles) has driven several studies and initiatives to test novel and repurposed treatments, including newer and repurposed medicines. One of the first studies was the Nix-TB study, conducted by the TB Alliance. The Nix-TB study was a one-arm, Phase 3, open-label observational cohort study that assessed the safety, efficacy, tolerability and pharmacokinetic properties of a 6-month bedaquiline, pretomanid and linezolid (BPaL) treatment regimen, extendable to 9 months for those who missed doses, or remained culture positive, or reverted from culture negative to positive between months 4 and 6 of treatment *(23)*. The study was conducted between 2014 and 2019 at three study sites, all in South Africa, with the first patient enrolled in April 2015. The Nix-TB study contributed evidence to WHO that was reviewed by the GDG in November 2019 and gave rise to the recommendation for the use of the BPaL regimen in patients with pre-extensively drug-resistant TB (pre-XDR-TB), under operational research conditions.

In preparation for the 2022 guidelines update, WHO received data from another trial – the Newer and Emerging Treatment for MDR/RR-TB (NExT) trial – which was a Phase 2–3 open-label randomized controlled trial (RCT) evaluating the effectiveness of an all-oral 6–9-month regimen for the treatment of MDR-TB in South Africa *(24)* in comparison with a local standard of care (SoC) regimen at the

time. Sharing of the data by the principal investigator and colleagues at the University of Cape Town and the South African Medical Research Council is gratefully acknowledged. However, during the GDG meeting, the panel decided that the data from this study could not be used to complement the discussion on the PICO question designed for that study, owing to early termination of the trial and variability of the components in the intervention regimen. This does not undermine the high value of the trial results, which reiterate the inferiority and significantly worse safety profile of the DR-TB regimens based on injectable medicines and fluoroquinolones (but not including new and repurposed drugs). Importantly, the trial showed that better outcomes could be achieved with a 6-month all-oral regimen than with the traditional 9-month or longer injectable-based regimens, supporting the concept of a 6-month all-oral regimen for MDR/RR-TB.

Two RCTs that concluded in 2021 (TB-PRACTECAL and ZeNix) provided new evidence and prompted assessment by WHO to develop new or updated recommendations for wide programmatic use of the BPaL/M regimen for treatment of MDR/RR-TB and pre-XDR-TB. The latest evidence-based guidelines for the treatment of DR-TB, including MDR/RR-TB and pre-XDR-TB, were published by WHO in December 2022 as the *WHO consolidated guidelines on tuberculosis. Module 4: treatment and care – drug-resistant tuberculosis treatment (25)*.

In 2024, two clinical trials, BEAT Tuberculosis and endTB, shared new evidence on the use of the novel 6-month regimen and several modified 9-month regimens for the treatment of MDR/RR-TB. This evidence contributed to the 2025 guidelines update, which included new recommendations for a 6-month and several modified 9-month regimens.

In 2025, WHO shared and assessed extended follow-up data from TB-PRACTECAL, including 108-week outcomes and whole-genome sequencing (WGS) of isolates from participants with failure or recurrence. New data from the endTB-Q trial enabled a meta-analysis across the endTB-Q and BEAT Tuberculosis trials. These analyses informed a more stratified treatment approach for patients with different severities of pulmonary pre-XDR-TB. The pooled results indicated that in patients with severe pulmonary pre-XDR-TB, the efficacy of the BDLC regimen may be suboptimal and associated with an increased risk of amplification of resistance to core medicines. For this subgroup, the use of BPaLC or longer 18-month WHO-recommended regimens, according to age-based eligibility, was suggested to optimize outcomes and limit the development of further resistance.

Scope of the guidelines update and available evidence

This chapter provides specific recommendations on the treatment of DR-TB, including the use of regimens for Hr-TB, shorter and longer regimens for MDR/RR-TB, monitoring of the patient response to MDR/RR-TB treatment, initiation of ART in patients on second-line anti-TB regimens, undertaking surgery for patients on DR-TB treatment, and co-administration of MDR/RR-TB and HCV therapies.

Table 2.1 describes the evidence that was generously shared by researchers and NTPs with WHO for DR-TB treatment guideline updates in 2019, 2021, 2024 and 2025.

Table 2.1. Evidence available for the guidelines updates

Trial (setting)	Population	Intervention regimen(s)	Comparator regimen(s)
BEAT Tuberculosis trial **(South Africa)**	6 years and older: • participants between the ages of 6 and 12 years with either confirmed pulmonary RR-TB or probable pulmonary RR-TB, and the referring clinician or investigator has decided to treat the child for RR-TB • participants above the age of 12 years with confirmed pulmonary TB with initial laboratory results of resistance to at least rifampicin	6-month BDL_{600}LfxC	Multiple – local standards of care, including: • 9–12-month all-oral regimen with L_{600} for 2 months (for fluoroquinolone-susceptible) • 18–20-month all-oral individualized regimen (for fluoroquinolone-resistant)
endTB trial **(Georgia, India, Kazakhstan, Lesotho, Pakistan, Peru, South Africa)**	Patients aged 15 years and older with documented pulmonary TB due to strains of *M. tuberculosis* resistant to rifampicin and susceptible to fluoroquinolones, diagnosed by validated rapid molecular test	9-month regimens BL_{600}MZ BL_{600}LfxCZ BDL_{600}LfxZ DCL_{600}LfxZ DCMZ (at 16 weeks, participants were randomized to a linezolid dose of 300 mg daily or 600 mg three times a week)	Multiple – local standards of care, including: • 18–20-month all-oral individualized regimen
TB-PRACTECAL trial **(South Africa, Belarus, Uzbekistan)**	Microbiologically confirmed *M. tuberculosis* in sputum and resistance to rifampicin *The primary analysis population is followed up at 72 weeks.* The number of people reaching 24, 72 and 108 weeks differs because the study was terminated early	Stage 2 (Phase 3 trial) 24 weeks BPaLM (B-Pa-$Lzd_{600->300}$-Mfx) Stage 1 (Phase 2 trial) 24 weeks BPaLC (B-Pa-$Lzd_{600->300}$-Cfz) 24 weeks BPaL (B-Pa-$Lzd_{600->300}$)	Multiple – local standard of care, including: • 9–12-month injectable-containing regimen • 18–24-month WHO-recommended regimen (pre-2019) • 9–12-month all-oral regimen • 18–20-month all-oral regimen

Trial (setting)	Population	Intervention regimen(s)	Comparator regimen(s)
Nix-TB **(South Africa)**	14 years and older pre-XDR-TB (pre-2021 definition) or treatment intolerant nonresponsive MDR-TB	6–9 month $BPaL_{1200–26\ weeks}$ Including linezolid 1 200 mg daily for 6 months (option of 9 months for subjects who remain culture positive at month 4)[a]	No standard of care control group
ZeNix (South Africa, Georgia, the Republic of Moldova and the Russian Federation) ***(26)***	Patients aged 14 years and older pre-XDR-TB (pre-2021 definition) or intolerant/ nonresponsive MDR/RR-TB Stratified by HIV status and type of TB Phase 3 partially blinded	6–9 month BPaL 4 arms with varying linezolid dosing $BPaL_{1200–26\ weeks}$ $BPaL_{1200–9\ weeks}$ $BPaL_{600–26\ weeks}$ $BPaL_{600–9\ weeks}$	No standard of care control group
South African TB Program 2019 cohort, EDRWeb **(South Africa)**	Confirmed rifampicin resistance, based on GeneXpert MTB/RIF or line probe assay	Longer regimen: ≥18 months including bedaquiline, levofloxacin, linezolid, terizidone and clofazimine Shorter regimen including 9–12 months of bedaquiline, linezolid (2 months), levofloxacin, clofazimine, high-dose isoniazid, pyrazinamide and ethambutol	No comparator group
South African TB Program 2017 cohort, EDRWeb dataset **(South Africa)**	Confirmed rifampicin resistance, based on GeneXpert MTB/RIF or line probe assay	Not applicable	Shorter regimen: 9–12 months; 4–6Bdq-Lfx/ Mfx-Eto-E-Z-Hh-Cfz, with <1% receiving linezolid

Trial (setting)	Population	Intervention regimen(s)	Comparator regimen(s)
2021 WHO IPD (multiple cohorts following a public call for data by WHO)	Confirmed rifampicin resistance, based upon molecular or culture-based drug susceptibility testing	Not applicable	The WHO IPD was used as an external comparator regimen. Included participants who received 9–12-month all-oral regimens using at least bedaquiline and linezolid; OR used WHO (2019) all-oral bedaquiline-containing regimen (9–12 months) in the combination: 4–6 Bdq(6 m)-Lfx/Mfx-Cfz-Z-E-Hh-Eto / 5 Lfx/Mfx-Cfz-Z-E; OR ≥18-month all-oral treatment regimen containing at least bedaliquine and linezolid (WHO long)
NExT trial *(24)* (South Africa)	GeneXpert positive MTB and rifampicin resistance on at least two drug susceptibility tests No resistance to fluoroquinolones or second-line injectables	6–9-month Lzd-Bdq-Lfx-PZA-Eto/high-dose isoniazid/Trd (gene-directed individualized)	**2015–16:** 21–24-month regimen of Km-Mox-PZA-Eto/Hh-Trd for 6–8 months then Mox-PZA-Eth-Trd for 18 months after 2 negative sputum cultures **2016 onwards:** 9–11 Km (6–8)-Mfx-Cfz-Trd-Z-Eto/Hh And longer regimen: 18–20 Km (6–8)-Mfx-Cfz-Trd-Z-Eto/Hh
endTB-Q trial	Participants aged 15 or older with pre-XDR-TB	6-month $BDL_{600}C$	18–20-month all-oral individualized regimen (for fluoroquinolone-resistant)

BDLC: bedaliquine, delamanid, linezolid and clofazimine; BDLLfxC: bedaquiline, delamanid, linezolid, levofloxacin and clofazimine; BDLLfxZ: bedaquiline, delamanid, linezolid, levofloxacin and pyrazinamide; BLLfxCZ: bedaquiline, linezolid, levofloxacin, clofazimine and pyrazinamide; BLMZ: bedaquiline, linezolid, moxifloxacin and pyrazinamide; BPaL: bedaquiline, pretomanid and linezolid; BPaLC: bedaquiline, pretomanid, linezolid and clofazimine; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; DCLLfxZ: delamanid, clofazimine, linezolid, levofloxacin and pyrazinamide; DCMZ: delamanid, clofazimine, moxifloxacin and pyrazinamide; HIV: human immunodeficiency virus; IPD: individual patient dataset; *M. tuberculosis*: *Mycobacterium tuberculosis*; MDR/RR-TB: multidrug- or rifampicin-resistant TB; MDR-TB: multidrug-resistant TB; pre-XDR-TB: pre-extensively drug-resistant TB; RCT: randomized controlled trial; RR-TB: rifampicin-resistant TB; TB: tuberculosis; WHO: World Health Organization.
[a] Twenty-one patients in the Nix-TB study received linezolid 600 mg per day, at the beginning of the recruitment period.

Summary of WHO recommendations on DR-TB treatment

The recommendations for the treatment of DR-TB that are presented in this document have been derived from earlier WHO guideline documents (**Box 2.1**), and a recent WHO GDG meeting conducted in November 2025. These recommendations supersede the *WHO consolidated guidelines on tuberculosis. Module 4: Treatment and care* that were published in 2025 *(3)* and *the WHO consolidated guidelines on tuberculosis. Module 5: Management of tuberculosis in children and adolescents in 2022 (27)*.

Box 2.1. WHO treatment guidelines containing recommendations that are incorporated into the present chapter on DR-TB treatment

- Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Geneva: World Health Organization; 2011 (WHO/HTM/TB/2011.6) *(13)*
- The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance. Geneva: World Health Organization; 2013 (WHO/HTM/TB/2013.6) *(14)*
- The use of delamanid in the treatment of multidrug-resistant tuberculosis: interim policy guidance. Geneva: World Health Organization; 2014 (WHO/HTM/TB/2014.23) *(15)*
- The use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents: interim policy guidance. Geneva: World Health Organization; 2016 (WHO/HTM/TB/2016.14) *(28)*
- WHO treatment guidelines for drug-resistant tuberculosis: 2016 update. Geneva: World Health Organization; 2016 (WHO/HTM/TB/2016.4) *(16)*
- WHO treatment guidelines for isoniazid-resistant tuberculosis. Supplement to the WHO treatment guidelines for drug-resistant tuberculosis. Geneva: World Health Organization; 2018 (WHO/CDS/TB/2018.7) *(29)*
- WHO treatment guidelines for rifampicin- and multidrug-resistant tuberculosis, 2018 update. Geneva: World Health Organization; 2018 (WHO/CDS/TB/2018.15) *(30)*
- WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019 (WHO/CDS/TB/2019.7) *(2)*
- WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020 (ISBN 978–92–4–000704–8) *(31)*
- WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO *(27)*
- WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2022 update (ISBN 978–92–4–006312–9). Licence: CC BY-NC-SA 3.0 IGO *(25)*
- WHO consolidated guidelines on tuberculosis. Module 4: treatment and care. Geneva: World Health Organization; 2025 (ISBN 978–92–4–010724–3). Licence: CC BY-NC-SA 3.0 IGO *(32)*

The recommendations are presented in Table 2.2 below and labelled as either NEW or UPDATED, where based on a review of new evidence. Recommendations without these labels are unchanged; that is, they are reprinted from existing guidelines (where no new evidence was available or searched for in the review).

Table 2.2. List of recommendations on drug-resistant TB treatment, where NEW or UPDATED recommendations based on review of the new evidence are highlighted in red

B1. Treatment of drug-resistant TB using 6-month regimens	
B1.1	**The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin or clofazimine (BPaL/M/C) regimen for MDR/RR-TB and pre-XDR-TB (UPDATED)** WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients. *(Conditional recommendation, very low certainty of evidence)*
B1.1a	WHO suggests the use of a 6-month regimen composed of bedaquiline, pretomanid and linezolid (BPaL) in patients with non-severe pulmonary pre-XDR-TB[15] rather than the BPaLC regimen (**NEW**). *(Conditional recommendation, very low certainty of evidence)*
B1.1b	WHO suggests the use of a 6-month regimen composed of bedaquiline, pretomanid, linezolid, and clofazimine (BPaLC) in patients with severe pulmonary pre-XDR-TB[16] rather than the BPaL regimen (**NEW**). *(Conditional recommendation, very low certainty of evidence)*
B1.2	**The 6-month bedaquiline, delamanid, linezolid, levofloxacin and clofazimine (BDLLfx/C) regimen (UPDATED)** WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, delamanid, linezolid (600 mg), levofloxacin, and clofazimine (BDLLfx/C) in MDR/RR-TB patients with or without fluoroquinolone resistance. *(Conditional recommendation, very low certainty of evidence)*
B1.2a	WHO suggests the use of a 6-month BDLC regimen in patients with non-severe pulmonary pre-XDR-TB[17] over the currently recommended longer (18 months or longer) regimens (**NEW**). *(Conditional recommendation, very low certainty of evidence)*
B1.2b	WHO suggests against using the 6-month BDLC regimen in patients with severe pulmonary pre-XDR-TB[18] compared to the currently recommended longer regimens (18 months or longer) (**NEW**). *(Conditional recommendation, very low certainty of evidence)*

[15] See recommendation remarks.

[16] See recommendation remarks

[17] See recommendation remarks

[18] See recommendation remarks

B2. Treatment of drug-resistant TB using 9-month regimens

B2.1 **The 9-month all-oral regimen for MDR/RR-TB**

WHO suggests the use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded.

(Conditional recommendation, very low certainty of evidence)

B2.2 **The modified 9-month all-oral regimens for MDR/RR-TB**

WHO suggests using the 9-month all-oral regimens (**BLMZ, BLLfxCZ and BDLLfxZ**) over currently recommended longer (>18 months) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. Among these regimens, using BLMZ is suggested over using BLLfxCZ, and BLLfxCZ is suggested over BDLLfxZ.

(Conditional recommendation, very low certainty of evidence)

B2.3 WHO suggests against using 9-month DCLLfxZ or DCMZ regimen compared with currently recommended longer (>18 months) regimens in patients with fluoroquinolone-susceptible MDR/RR-TB.

(Conditional recommendation, very low certainty of evidence)

B2.4 In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used

(Conditional recommendation, very low certainty of the evidence)

B3. Treatment of drug-resistant TB using longer regimens

B3.1 In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of the treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it.

(Conditional recommendation, very low certainty of evidence)[19]

B3.2 **Kanamycin and capreomycin** are not to be included in the treatment of MDR/RR-TB patients on longer regimens.

(Conditional recommendation, very low certainty of evidence)

B3.3 **Levofloxacin or moxifloxacin** should be included in the treatment of MDR/RR-TB patients on longer regimens.

(Strong recommendation, moderate certainty of evidence)

B3.4 **Bedaquiline** should be included in longer multidrug-resistant TB (MDR-TB) regimens for patients aged 18 years or more.

(Strong recommendation, moderate certainty of evidence)

Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years.

(Conditional recommendation, very low certainty of evidence)

In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing **bedaquiline** may be used.

(Conditional recommendation, very low certainty of evidence)

[19] Group A = levofloxacin or moxifloxacin, bedaquiline and linezolid; Group B = clofazimine, and cycloserine or terizidone; and Group C = ethambutol, delamanid, pyrazinamide, imipenem–cilastatin or meropenem, amikacin (or streptomycin), ethionamide or prothionamide, and *p*-aminosalicylic acid. See more details on grouping of medicines in Table 2.20.

B3.5	**Linezolid** should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)*
B3.6	**Clofazimine and cycloserine or terizidone** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
B3.7	**Ethambutol** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
B3.8	**Delamanid** may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens. *(Conditional recommendation, moderate certainty of evidence)* In children with MDR/RR-TB aged below 3 years **delamanid** may be used as part of longer regimens. *(Conditional recommendation, very low certainty of evidence)*
B3.9	**Pyrazinamide** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
B3.10	**Imipenem–cilastatin or meropenem** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*[20]
B3.11	**Amikacin** may be included in the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions. *(Conditional recommendation, very low certainty of evidence)*
B3.12	**Ethionamide or prothionamide** may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. *(Conditional recommendation, very low certainty of evidence)*
B3.13	***P*-aminosalicylic acid** may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. *(Conditional recommendation, very low certainty of evidence)*
B3.14	**Clavulanic acid** should not be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, low certainty of evidence)*[1]
B3.15	In MDR/RR-TB patients on longer regimens, a **total treatment duration of 18–20 months** is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)*

[20] Imipenem–cilastatin and meropenem are administered with clavulanic acid, which is available only in formulations combined with amoxicillin. Amoxicillin–clavulanic acid is not counted as an additional effective TB agent, and it should not be used without imipenem–cilastatin or meropenem.

B3.16	In MDR/RR-TB patients on longer regimens, a **treatment duration of 15–17 months after culture conversion** is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)*
B3.17	In MDR/RR-TB patients on longer regimens containing amikacin or streptomycin, **an intensive phase of 6–7 months** is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)*
B4. Treatment of rifampicin-susceptible and isoniazid-resistant TB (Hr-TB)	
B4.1	In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis (Hr-TB), treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months. *(Conditional recommendation, very low certainty of evidence)*
B4.2	In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen. *(Conditional recommendation, very low certainty of evidence)*
B5. Monitoring and management strategies for MDR/RR-TB treatment	
B5.1	In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, the performance of sputum culture in addition to sputum smear microscopy is recommended to monitor treatment response. It is desirable for sputum culture to be repeated at monthly intervals. *(Strong recommendation, moderate certainty in the estimates of test accuracy)*
B6. Starting ART in patients on MDR/RR-TB regimens	
B6.1	Antiretroviral therapy is recommended for all patients with HIV and drug-resistant tuberculosis requiring second-line antituberculosis drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of antituberculosis treatment. *(Strong recommendation, very low certainty of evidence)*
B7. Surgery for patients on MDR/RR-TB treatment	
B7.1	In patients with rifampicin-resistant tuberculosis (RR-TB) or multidrug-resistant TB (MDR-TB), elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen. *(Conditional recommendation, very low certainty of evidence)*
B8. Hepatitis C virus (HCV) and MDR/RR-TB treatment co-administration	
B8.1	In patients with MDR/RR-TB and HCV coinfection, the WHO suggests the co-administration of HCV and TB treatment over delaying HCV treatment until after treatment of MDR/RR-TB is completed. *(Conditional recommendation, very low certainty of evidence)*

Recommendations

B1. Treatment of drug-resistant TB using 6-month regimens

Recommendation B1.1 The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin or clofazimine (BPaL/M/C) regimen

No.	Recommendations
B1.1	WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) rather than the 9-month or longer (18-month) regimens in MDR/RR-TB patients (**UPDATED**). *(Conditional recommendation, very low certainty of evidence)*
B1.1a	WHO suggests the use of a 6-month regimen composed of bedaquiline, pretomanid and linezolid (BPaL) in patients with non-severe pulmonary pre-XDR-TB (see remarks) rather than the BPaLC regimen (**NEW**). *(Conditional recommendation, very low certainty of evidence)*
B1.1b	WHO suggests the use of a 6-month regimen composed of bedaquiline, pretomanid, linezolid and clofazimine (BPaLC) in patients with severe pulmonary pre-XDR-TB (see remarks) rather than the BPaL regimen (**NEW**). *(Conditional recommendation, very low certainty of evidence)*

Remarks

- Drug susceptibility testing (DST) for fluoroquinolones is strongly encouraged in people with MDR/RR-TB, although it should not delay initiation of the BPaL/M/C regimen. Results of the test should guide the decision on whether moxifloxacin can be retained or should be dropped from the regimen. In cases of documented resistance to fluoroquinolones, BPaL or BPaLC would be initiated or continued, depending on disease severity (BPaL for non-severe and BPaLC for severe pulmonary pre-XDR-TB).
- This recommendation applies to the following:
  - people with MDR/RR-TB or with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR-TB);
  - people with confirmed pulmonary TB and all forms of extrapulmonary TB except for TB involving the central nervous system (CNS), osteoarticular or disseminated forms of TB with multiorgan involvement;[21]
  - adults and adolescents aged 14 years and older;
  - all people regardless of HIV status; and
  - patients with less than 1 month of previous exposure to bedaquiline, linezolid, pretomanid, delamanid or clofazimine. When exposure is greater than 1 month, these patients may still

[21] See subgroup considerations.

receive these regimens if resistance to the specific medicines with such exposure has been ruled out.

- This recommendation does not apply to pregnant and breastfeeding women owing to limited evidence on the safety of pretomanid.[22]
- The recommended dose of linezolid is 600 mg once daily, for all the BPaLM, BPaL and BPaLC regimens.[23]
- When resistance to fluoroquinolones is unknown, the regimen should be started as BPaLM and then adjusted based on the DST results. In case of fluoroquinolone susceptibility, the regimen can be continued as BPaLM, regardless of disease severity. In people with pre-XDR-TB and severe pulmonary TB, moxifloxacin should be replaced by clofazimine (C) and the regimen initiated or continued as BPaLC. In people with pre-XDR-TB and non-severe forms of pulmonary TB, the regimen can be initiated or continued as BPaL.
- Severity in pulmonary pre-XDR-TB for this regimen selection is defined by the presence of cavitary lesions on chest radiography and high bacillary load shown by sputum smear results of 1+ or higher positivity, or smear results of 2+ or higher (or an equivalent result on WHO-recommended molecular tests) even when cavities are not present. Non-severe, in this context, refers to all situations not covered by the definition of severe pulmonary pre-XDR-TB.

Rationale

The rationale for this recommendation is based on the evidence and considerations described in detail in the subsections below. Briefly, data from an RCT (stage 2 of TB-PRACTECAL, which corresponds to a Phase 3 trial) showed much improved sustained treatment success rates with the BPaLM regimen (89%) of 6 months duration compared with the multiple local SoC regimens recommended by WHO at the time the trial was conducted (52%), as well as lower levels of treatment failure, death and loss to follow-up (LTFU) over the post-treatment follow up period. Data from two trials (TB-PRACTECAL and ZeNix) suggested fewer AEs with a linezolid dose of 600 mg while maintaining high efficacy. It was judged that implementing this regimen was probably feasible and acceptable, with cost–effectiveness and equity probably improved. The comparison of patient groups receiving this regimen with those receiving recommended regimens lasting 9 months or longer has favoured the 6-month BPaLM regimen, suggesting it to be the regimen of choice for eligible patient groups.

Additional evidence from the TB-PRACTECAL trial was provided to WHO in 2025; this included an extended follow-up period to 108 weeks and WGS of cultures from participants with failure or recurrence. The evidence was reviewed during the GDG meeting in November 2025 and a more nuanced treatment strategy for patients with different severities of pulmonary pre-XDR-TB was suggested.

Summary of evidence

This section provides the PICO questions posed; the data and studies considered to answer the questions; the methods used for analysis and data synthesis; a summary of evidence on desirable and undesirable effects, and certainty of evidence; and a summary of other evidence considered during the recommendation's development. Additional detail on the evidence is available in the annexes containing the GRADE evidence summary tables and GRADE EtD tables (**Annex 5**).

[22] Data on the use of pretomanid in pregnant women are limited. Animal studies do not indicate direct or indirect harmful effects with respect to embryo-fetal development.

[23] Additional details on linezolid dosing and possible dose reductions are given in the implementation considerations.

PICO questions

The recommendations in this section are a result of assessments of the PICO questions listed below. Because of the different intervention and comparator groups used, PICO questions 3, 5 and 6 have been split into several sub-PICO questions (details are given in the text and in Table 2.5).

PICO question 3–2022 (MDR/RR-TB, 2022): *Should BPaL regimens with lower linezolid exposure (dose or duration) be used instead of the original BPaL regimen in patients who are eligible for the BPaL regimen?*

PICO question 4–2022 (MDR/RR-TB, 2022): *Should a 6-month regimen using bedaquiline, pretomanid and linezolid be used in patients with pulmonary pre-XDR-TB (MDR/RR-TB with fluoroquinolone resistance)?*

PICO question 5–2022 (MDR/RR-TB, 2022): *Should a 6-month regimen using bedaquiline, pretomanid and linezolid be used in patients with pulmonary MDR/RR-TB and without fluoroquinolone resistance?*

PICO question 6–2022 (MDR/RR-TB, 2022): *Should a 6-month regimen using bedaquiline, pretomanid and linezolid with or without addition of moxifloxacin (BPaLM) or clofazimine (BPaLC) be used in patients with pulmonary MDR/RR-TB (with or without fluoroquinolone resistance)?*

PICO question 2–2025 (pre-XDR-TB 2025): *Should a BPaL regimen be used in patients with pulmonary pre-XDR-TB over the TB-PRACTECAL comparator regimens?*

PICO question 3–2025 (pre-XDR-TB 2025): *Should a BPaLC regimen be used in patients with pulmonary pre-XDR-TB over the TB-PRACTECAL comparator regimens?*

PICO question 6 (a; b)–2025 (pre-XDR-TB 2025): *Should a BPaLC regimen be used in patients with pulmonary pre-XDR-TB over the BPaL regimen?*

Data and studies considered

The review of PICO questions 3–2022, 4–2022, 5–2022 and 6–2022 during the GDG meeting convened by WHO in February–March 2022 was based on new evidence provided by Médecins Sans Frontières (MSF) from the TB-PRACTECAL clinical trial and by the TB Alliance from the ZeNix trial. For several assessments, the data from the 2021 WHO individual patient dataset (IPD) were used. Patient populations in two trials were recruited according to strict inclusion and exclusion criteria; the populations shared many similarities and few notable differences. The highlights of the criteria used by these trials are presented in Table 2.3; a complete list of the exclusion criteria can be found in published trial protocols.[24]

[24] Available at https://clinicaltrials.gov/ct2/home.

Table 2.3. High-level summary of main inclusion and exclusion criteria: TB-PRACTECAL and ZeNix trials

	TB-PRACTECAL	ZeNix *(26)*
Inclusion	• Aged 15 years and older • Confirmed TB and RR-TB • Regardless of HIV status	• Aged 14 years and older • Confirmed MDR/RR-TB or pre-XDR-TB • Regardless of HIV status
Exclusion	• Known resistance to Bdq, Pa, Dlm or Lzd • More than 1 month prior use of Bdq, Pa, Dlm or Lzd • Pregnant or breastfeeding • Liver enzymes 3 times the upper limit of normal • QTcF >450 ms and other risk factors for QT prolongation (excluding age and gender) or other risk factors for tdp • History of cardiac disease, syncopal episodes, significant symptomatic or asymptomatic arrhythmias (except sinus arrhythmia) • Moribund • Taking any medications contraindicated with the medicines in the trial • Any baseline laboratory value consistent with Grade 4 toxicity • TB meningoencephalitis, brain abscesses, osteomyelitis or arthritis	• Documented resistance to Bdq, Pa, Dlm or Lzd • More than 2 weeks of Bdq, Dlm or Lzd • Pregnant • Liver enzymes 3 times the upper limit of normal • BMI <17 • QTcF interval on ECG >500 ms, history of congenital QT prolongation, history of tdp, bradyarrhythmia • Karnofsky score <60 • Peripheral neuropathy of Grade 3–4 • Not expected to survive for more than 6 months • Uncontrolled diabetes or cardiomyopathy, extrapulmonary TB requiring extended treatment, cancer that could affect survival • Abuse of alcohol or illegal drugs • CD4+ count <100 • Use of zidovudine, stavudine or didanosine, use of MAOIs

Bdq: bedaquiline; BMI: body mass index; Dlm: delamanid; ECG: electrocardiogram; HIV: human immunodeficiency virus; Lzd: linezolid; MAOI: monoamine oxidase inhibitor; MDR/RR-TB: multidrug- or rifampicin-resistant TB; Pa: pretomanid; pre-XDR-TB: pre-extensively drug-resistant TB; QTcF: corrected QT interval by Fredericia; RR-TB: rifampicin-resistant TB; TB: tuberculosis; tdp: torsades de pointes.

TB-PRACTECAL

TB-PRACTECAL was a multicentre, open-label, multi-arm, randomized, controlled, multistage, Phase 2–3 trial evaluating short treatment regimens containing bedaquiline and pretomanid in combination with existing and repurposed anti-TB drugs (e.g. linezolid and clofazimine) for the treatment of microbiologically confirmed pulmonary MDR/RR-TB.[25]

The study was divided into two stages, with a seamless transition between the stages, meaning that recruitment into an arm would only stop after a decision had been taken following stage 1 primary endpoint data analysis. In the first stage – equivalent to a Phase 2B trial of safety and preliminary efficacy – patients were randomly assigned one of four regimens, stratified by site. Investigational regimens included oral bedaquiline, pretomanid and linezolid. Two of the regimens also included moxifloxacin (arm 1) and clofazimine (arm 2). The main objective of stage 1 was to select drug regimens for evaluation in stage 2, based on 8-week safety and efficacy endpoints. Investigational arms that did not meet predefined safety and efficacy criteria were not considered for further evaluation.

[25] Trial protocol available at https://trialsjournal.biomedcentral.com/articles/10.1186/s13063–022–06331–8

The second stage of the study was equivalent to a Phase 3 trial investigating the safety and efficacy of the most promising regimen. As intended in the study protocol, the regimen was evaluated for safety and efficacy in comparison with the SoC arm at 72 weeks after randomization. Stage 2 of the trial included an intervention arm of BPaLM compared with the locally approved SoC, consistent with WHO recommendations for the treatment of MDR/RR-TB or pre-XDR-TB at the time of trial conduct (including a 9–12-month injectable-containing regimen; 18–24-month WHO-recommended regimen [pre-2019]; 9–12-month all-oral regimen; and 18–20-month all-oral regimen). The TB-PRACTECAL trial stopped enrolling patients soon after its independent data safety and monitoring board indicated that the BPaLM regimen is superior to the SoC, because it was considered that more data were extremely unlikely to change the results of the trial. This trial was not designed to compare the investigational regimens against each other.

Eligible patients were aged 15 years or older and had bacteriologically (molecular or phenotypic) confirmed TB and resistance to at least rifampicin by a molecular or phenotypic drug susceptibility test. The primary efficacy outcome was the composite endpoint of unfavourable outcomes (failure, death, treatment discontinuation, recurrence or LTFU) at 72 weeks after randomization. Relevant secondary efficacy outcomes included culture conversion at 12 and 24 weeks, unfavourable outcomes at 24 weeks after randomization, unfavourable outcomes at 108 weeks after randomization, median time to culture conversion and recurrence by week 48 in the investigational arms. Participants were randomized in a 1:1:1:1 ratio into either the SoC or one of the following three intervention arms:

- Arm 1: 24 weeks of B-Pa-Lzd-Mfx (BPaLM);
- Arm 2: 24 weeks of B-Pa-Lzd-Cfz (BPaLC); and
- Arm 3: 24 weeks of B-Pa-Lzd (BPaL).

In all intervention arms, linezolid was given at 600 mg daily for 16 weeks then 300 mg daily for the remaining 8 weeks (or earlier when moderately tolerated). Bedaquiline was given at 400 mg once daily for 2 weeks followed by 200 mg three times per week for 22 weeks. Safety monitoring for most participants included multiple electrocardiograms (ECGs) at baseline, then weekly until week 8, every 4 weeks up to week 24 and then every 8 weeks thereafter. Microbiological monitoring included smear microscopy and culture at baseline and day 7, then every 4 weeks up until week 24 and every 8 weeks thereafter.

ZeNix

ZeNix was a Phase 3 partially blinded, randomized trial assessing the safety and efficacy of various doses and treatment durations of linezolid plus bedaquiline and pretomanid in individuals with pulmonary MDR/RR-TB and additional resistance to fluoroquinolones (with or without resistance to injectable agents) or those with treatment-intolerant or nonresponsive MDR/RR-TB. Eligible patients were aged 14 years or older, weighed at least 35 kg, had a documented HIV result and had bacteriologically confirmed sputum culture positive XDR-TB (pre-2021 definition) or bacteriologically confirmed MDR/RR-TB, but were treatment intolerant or nonresponsive to previous MDR/RR-TB treatment. The primary study outcome was the incidence of bacteriological failure or relapse, or clinical failure through follow-up until 26 weeks after the end of treatment. The secondary outcomes included incidence of bacteriological failure or relapse, or clinical failure through follow-up until 78 weeks after the end of treatment. Participants received 26 weeks of treatment with BPaL. Each of the four arms varied the dose and duration of linezolid: 1 200 mg 26 weeks, 1 200 mg 9 weeks, 600 mg 26 weeks or 600 mg 9 weeks. Bedaquiline was given at 200 mg once daily for 8 weeks then 100 mg once daily for 18 weeks. This off-label dosing schedule is supported by pharmacokinetic simulations for an alternative bedaquiline dosing schedule that provides comparable exposures and was developed to support adherence and facilitate treatment administration (all medicines daily throughout the regimen) *(33)*. Safety monitoring included scheduled testing and assessments of laboratory parameters, ECG, vital signs and other physical examinations *(34)*. Microbiological monitoring included smear microscopy, molecular testing and liquid culture from sputum at baseline and liquid culture at all patient visits thereafter *(34)*.

Table 2.4. Dosing, treatment administration and toxicity-related treatment modification tolerances

TB-PRACTECAL	ZeNix (linezolid 600 mg/26-week arm)
24 weeks	26 weeks, extendable to 39 weeks
Bedaquiline 400 mg once daily for the first 2 weeks of treatment followed by 200 mg 3 times per week for 22 weeks (on-label)	Bedaquiline 200 mg once daily for the first 8 weeks of treatment followed by 100 mg once daily for 18 weeks (off-label)
Pretomanid 200 mg once daily for 24 weeks	Pretomanid 200 mg once daily for 26 weeks
Linezolid 600 mg daily for 16 weeks then 300 mg daily for the remaining 8 weeks	Linezolid 600 mg daily for 26 weeks (could be reduced to 300 mg)
Treatment administered 7 days a week under direct observation or video-supported therapy	Treatment administered 7 days a week. Adherence was monitored by direct observation or by checking medication cards during site visits
Maximum allowed 2 consecutive weeks of treatment interruption	Maximum allowed total of treatment interruptions – 5 weeks (if 26 weeks duration) and 8 weeks (if 39 weeks duration). All treatment interruptions above 7 consecutive days should have been made up by extending treatment duration. Minimum taken total doses of linezolid – at least 9 weeks

A pharmacokinetic simulation study assessed whether a bedaquiline dosing scheme could be devised that would permit daily dosing while maintaining drug exposure levels of the labelled dosing scheme. The key findings from the simulations of the proposed dosing scheme for ZeNix of bedaquiline administered 200 mg daily over 8 weeks followed by 100 mg daily for an additional 16 weeks were as follows *(33)*:

- The exposures (Cmax, mean or trough) of the proposed dosing scheme were not expected to exceed the exposures associated with the labelled scheme on day 14 at the end of the 400 mg daily dose. With the labelled dosing scheme, the highest exposures were on day 14, at the end of the 400 mg daily loading dose.
- The average daily exposures with the proposed dosing scheme over 6 months were within (or were not substantially different from) the range of exposures over 6 months of the labelled dosing scheme.
- The cumulative exposure, in terms of area under the curve (AUC) over time, is similar between the proposed dosing scheme and the labelled scheme.

2021 WHO IPD

In 2021, WHO issued a public call for data to serve as a comparator group (SoC) against which 6–9-month regimens could be compared. These cohorts received treatment conforming to the WHO DR-TB guidelines of 2020 with bedaquiline and linezolid for a duration ranging from 6 to 24 months. Patients receiving injectable antibiotics were excluded. Included datasets comprised individuals using one of the following regimens:

- 6–12-month all-oral regimens using at least bedaquiline and linezolid; or
- 9–12-month WHO (2019) all-oral bedaquiline-containing regimen in the combination, such as 4–6 Bdq(6m)-Lfx/Mfx-Cfz-Z-E-Hh-Eto / 5m Lfx/Mfx-Cfz-Z-E; or

- 18-month or more WHO (2018) all-oral treatment regimen containing at least bedaquiline and linezolid.

To be eligible for inclusion in a short comparator regimen (target 9–12 months at treatment commencement), patients must have fulfilled each of the following conditions:

- had a treatment duration not exceeding 12 months;
- received six or more drugs during treatment, including bedaquiline; and
- if given an outcome of cure or completed, had a treatment duration of 8.5 months or more.

To be eligible for inclusion in a longer comparator regimen (target 18–24 months), patients must have fulfilled each of the following:

- be classified in the dataset as having received a longer regimen (if stated);
- had a treatment duration not longer than 24 months;
- received four or more drugs (regardless of drug susceptibility; i.e. regardless of whether they were likely to be effective), including bedaquiline; and
- if given an outcome of cure or complete, had a treatment duration of 17.5 months or more.

2025 WHO IPD

In 2025, WHO issued a public call for IPD from clinical trials or cohorts of patients treated for MDR/RR-TB within programmatic settings. As a result of the call, three completed clinical trial datasets were submitted to WHO, including the endTB-Q trial (247 participants, using the BDLC regimen), the BEAT Tuberculosis trial (403 participants, using the BDLLfx/C regimen) and the TB-PRACTECAL trial updated dataset (507 participants, using the BPaLM, BPaL and BPaLC regimens). In addition, datasets of three cohorts (without comparators) of MDR/RR-TB patients received either BPaL or BPaLC regimen from Belarus (722 participants), Uzbekistan (425 participants) and Italy (25 participants) were submitted. Data from clinical trials were used to assess the performance of the BDLC, BPaL and BPaLC regimens for the treatment of pre-XDR-TB (PICOs 1–6, 2025). The analyses of observational data provided supporting evidence on the performance of the BPaL and BPaLC regimens in the programmatic settings.

Methods used for analysis and data synthesis

Descriptive analyses of the baseline characteristics of participants in all included studies were performed; characteristics included demographics, diagnostic test results, treatment regimens and treatment outcomes.

Comparative analyses were performed within individual studies and between multiple studies:

- Within-study comparisons – for studies in which both a short-course (6 months in duration) regimen and a relevant comparator are used, pairwise comparisons were conducted between each of the short-course regimens and the comparator. For included RCTs (e.g. the TB-PRACTECAL trial and NExT trial), the primary outcome of the prespecified analysis was also calculated and reported.
- Pairwise comparisons between studies – comparisons addressing each PICO question were conducted by comparing outcomes among cohorts in which participants received either the intervention or the control regimen relevant to that question.

Statistical models

For comparisons between datasets or cohorts, outcomes were presented as unadjusted and adjusted risk ratios (RRs). Adjusted risk ratios (aRRs) were calculated using a log-binomial generalized linear regression (binomial error distribution with log link function). Prespecified potential confounders were adjusted for using inverse probability propensity score weighting. No convergence issues arose with the log-binomial model. When outcome rates were close to the boundary, aRRs were not calculated

and unadjusted RRs were presented. For outcomes where the number of outcome events was zero, an unadjusted risk difference (RD) was calculated. For unadjusted RDs or RRs, 95% confidence intervals (CIs) were calculated using the score method. Covariate selection for calculation of propensity scores was based on data availability and clinical knowledge. The covariates considered for inclusion in the propensity scores analysis included age, gender, baseline smear result, HIV status (including ART status), prior treatment history (including whether previous infection was drug resistant), body mass index (BMI), smoking status, diabetes diagnosis, cavitation at baseline, presence of bilateral disease and fluroquinolone resistance. For the calculation of aRRs, multiple imputation by chain equations using the "within" propensity score approach was used to account for missing data in potential confounders when the proportion of missing values for a confounder was less than 45%.

Timing of follow-up for comparisons between regimens

The analyses undertaken for this evidence review combined results from cohorts with differing follow-up times after initiation of treatment. There were differences in the follow-up time between cohorts (from 5.5 months to 24 months) and within single cohorts (e.g. the WHO IPD 2021 dataset combined multiple cohorts with variable follow-up times). Follow-up time was separated into the time between commencement of treatment and treatment completion, and the period from treatment completion until the end of follow-up. For shorter regimens, post-treatment follow-up was particularly important because higher relapse rates may be a consequence of shorter treatments that do not completely remove *M. tuberculosis*. Where possible, an equivalent follow-up time between two groups in a comparison was used, so that participants had an equivalent likelihood of death or relapse. In these analyses, the follow-up time was measured from the start date of treatment rather than after the date of treatment completion, to minimize the effect of differences in total follow-up time.

The principles for accounting for time periods of follow-up were as follows:

- Where possible, follow up participants in the intervention and control groups for the same total time, so that the likelihood of unsuccessful outcomes (e.g. death) is the same in both groups.
- Limit follow-up to 24 months after treatment initiation for all cohorts. There were no analyses in which both intervention and comparator cohorts had more than 24 months of follow-up available. The evidence accumulated from TB treatment trials demonstrates that a high proportion of recurrences are likely to occur within 12 or even 6 months of stopping treatment *(35)*.
- Select a primary analysis that optimizes the number of participants included in both groups. For shorter (6–9-month regimens), follow-up time in the comparison was included so that relapse could be captured.

Additional sensitivity analyses were performed, where possible, evaluating the effect of follow-up time upon treatment outcomes.

Decision thresholds

A more structured method for determining the magnitude of the health effects was initiated in 2025. It involves using a triangulation approach to develop outcome-specific decision thresholds (DTs) for judging the magnitude of the effects for the following health outcomes: death, sustained treatment success, treatment failure or recurrence, LTFU, AEs and amplification of drug resistance. GDG members deemed these outcomes to be critical or important for decision-making based on a prioritization survey using the GRADE approach. The survey included health outcome descriptors that had previously been developed for each of the health outcomes, to facilitate the GDG's understanding of the outcomes during the decision-making process.

The GDG first reviewed judgements about the magnitude of health effects made by other GDGs for prior WHO MDR-TB guidelines *(3, 14)* to determine approximate ranges of effect sizes that the group considered to be trivial, small, moderate or large. Members then identified a systematic review to inform suggested health utility values for the health state of having DR-TB disease and treatment

success (reported as about 0.5 and 0.9, respectively) *(36)*. For the other outcomes (treatment failure, LTFU, amplification of drug resistance and AEs), a health utility value of 0.5 was used, considering that these would be similar health states to having DR-TB disease, and to align with previous judgements made in other TB guidelines.

The group then used the empirical evidence from the GRADE-THRESHOLD trial *(37)* to calculate suggested utility-adjusted absolute effect thresholds for the health outcomes. The calculated thresholds were as follows *(38)*:

- death (health utility: 0):
  - trivial or no effect: up to 12 fewer or more deaths per 1000 people;
  - small effect: 13–33 fewer or more deaths per 1000 people;
  - moderate effect: 34–66 fewer or more deaths per 1000 people; and
  - large effect: ≥67 fewer or more deaths per 1000 people;
- sustained treatment success (health utility: 0.9):
  - trivial or no effect: up to 17 fewer or more treatment successes per 1000 people;
  - small effect: 18–48 fewer or more treatment successes per 1000 people;
  - moderate effect: 49–93 fewer or more treatment successes per 1000 people; and
  - large effect: ≥94 fewer or more treatment successes per 1000 people;
- treatment failure or recurrence, LTFU, AEs and amplification (acquisition) of drug resistance (all with health utility 0.5):
  - trivial or no effect: up to 41 fewer or more failures or recurrences per 1000 people;
  - small effect: 42–106 fewer or more failures or recurrences per 1000 people;
  - moderate effect: 107–201 fewer or more failures or recurrences per 1000 people; and
  - large effect: ≥202 fewer or more failures or recurrences per 1000 people.

These suggested thresholds (assumed to occur over the duration of follow-up in the trials) were generally consistent with judgements that were made in the previous WHO MDR-TB guidelines *(3)*.

Finally, in preparation for the GDG meeting at which recommendations would be formulated, an online survey was administered to the group to obtain their feedback on the suggested DTs. The survey asked members to agree with the suggested thresholds, or to disagree with them and suggest alternative thresholds based on their expert experience. The agreed-upon thresholds were again reviewed at the start of the GDG meeting, and the group decided to use them to inform their judgements on the magnitude of health effects in the GRADE EtD frameworks. Figures were created to visually depict absolute effects and 95% CIs from the research evidence of the relevant trial in relation to the DTs for each health outcome, to facilitate the GDG's discussion and judgements about whether the health effects were trivial, small, moderate or large, and to judge the level of imprecision of estimates. The same thresholds were used to inform the group's judgements about imprecision, in line with GRADE guidance for decision-making *(39)*.

Summary of evidence on desirable and undesirable effects and certainty of evidence

The evidence on the novel regimens to inform PICO questions was derived from two trials. It included information on 419 of 423 participants who were enrolled in four arms of the TB-PRACTECAL trial and on 172 of 181 participants who were enrolled in four arms of the ZeNix trial.[26]

Data from patients in relevant arms of these trials were used in each of the comparisons that led to the conclusions and final recommendation on the use of the BPaL/M/C regimens. Even though the TB-PRACTECAL trial was not designed to compare the investigational regimens against each other and not designed to compare arms dropped at stage 1 (BPaL and BPaLC) with the SoC, the comparisons

[26] Several participants were excluded in each dataset owing to unconfirmed rifampicin resistance.

of the different arms of the trial to the BPaLM arm (sub-PICOs 6.4–2022 to 6.6–2022 and PICOs 2–, 3– and 6–2025) were performed to aid the panel in making final decisions.

Sub-PICO 3.2–2022: Should BPaL regimens with lower linezolid exposure (BPaL 1200 mg – 9 weeks) be used instead of the original BPaL regimen (BPaL 1200 mg – 26 weeks) in patients who are eligible for the BPaL regimen?

The BPaL 1200–9 arm of the ZeNix trial (where linezolid 1200 mg daily was used for 9 weeks) was compared with the BPaL 1200–26 arm (where linezolid 1200 mg daily was used for 26 weeks) in the same population of patients with MDR/RR-TB, with or without fluoroquinolone resistance. Primary analysis was undertaken at 12 months post-treatment initiation.

Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving BPaL with linezolid 1200–9 (n=43) compared with participants with the same resistance patterns receiving BPaL with linezolid 1200–26 (n=44) experienced:

- lower levels of treatment success (93% vs 98%); that is, a 5% relative reduction (RR=0.95, 95% CI: 0.87 to 1.05);
- higher levels of failure and recurrence (4.7% vs 2.3%); that is, a twofold relative increase (RR=2.1, 95% CI: 0.19 to 22);
- higher levels of deaths (2.3% vs 0%); that is, a 2% absolute increase (RD=0.02, 95% CI: –0.06 to 0.12);
- the same levels of LTFU (0% vs 0%); that is, a 0% absolute difference (RD=0.00, 95% CI: –0.08 to 0.08);
- lower levels of AEs (16% vs 18%); that is, a 10% relative reduction (RR=0.90, 95% CI: 0.36 to 2.3); and
- the same levels of amplification of drug resistance (0% vs 0%); that is, a 0% absolute difference (RD=0.00, 95% CI: –0.08 to 0.08).

The GDG judged the benefits of BPaL with linezolid 1200–9 to be small and the undesirable effects to be moderate compared with BPaL with linezolid 1200–26. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaL with linezolid 1200–26.

Conclusion

The use of the 26 weeks of 1200 mg linezolid is suggested over 9 weeks of 1200 mg linezolid as part of the BPaL regimen in adults with MDR/RR-TB or pre-XDR-TB.

Sub-PICO 3.3–2022: Should BPaL regimens with lower linezolid exposure (BPaL 600 mg – 26 weeks) be used instead of the original BPaL regimen (BPaL 1200 mg – 26 weeks) in patients who are eligible for the BPaL regimen?

The BPaL 600–26 arm of the ZeNix trial (where linezolid 600 mg daily was used for 26 weeks) was compared with the BPaL 1200–26 arm (where linezolid 1200 mg daily was used for 26 weeks) in the same population of patients with MDR/RR-TB, with or without fluoroquinolone resistance. Primary analysis was undertaken at 12 months post-treatment initiation.

Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving BPaL with linezolid 600–26 (n=43), compared with participants with the same resistance patterns receiving BPaL with linezolid 1200–26 (n=44), experienced:

- higher levels of treatment success (100% vs 98%); that is, a 2% relative increase (RR=1.02, 95% CI: 0.98 to 1.07);
- lower levels of failure and recurrence (0% vs 2.3%); that is, a 2% absolute reduction (RD= –0.02, 95% CI: –0.12 to 0.06);
- lower levels of Grade 3–5 AEs (14% vs 18.6%); that is, a 23% relative reduction (RR=0.77, 95% CI: 0.29 to 2.03); and
- the same levels of deaths (0% vs 0%), LTFU (0% vs 0%) or amplified resistance (0% vs 0%).

The GDG judged the benefits of BPaL with linezolid 600–26 to be moderate and the undesirable effects to be trivial compared with BPaL with linezolid 1200–26. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaL with linezolid 600–26.

Conclusion

The use of the 26 weeks of 600 mg linezolid over 26 weeks of 1 200 mg linezolid is suggested as part of the BPaL regimen in adults with MDR/RR-TB or pre-XDR-TB.

Sub-PICO 3.4–2022: Should BPaL regimens with lower linezolid exposure (BPaL 600 mg – 9 weeks) be used instead of the original BPaL regimen (BPaL 1200 mg – 26 weeks) in patients who are eligible for BPaL regimen?

The BPaL 600–9 arm of the ZeNix trial (where linezolid 600 mg daily was used for 9 weeks) was compared with the BPaL 1200–26 arm (where linezolid 1 200 mg daily was used for 26 weeks) in the same population of patients with MDR/RR-TB, with or without fluoroquinolone resistance. Primary analysis was undertaken at 12 months post-treatment initiation.

Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving BPaL with linezolid 600–9 (*n*=42) compared with participants with the same resistance patterns receiving BPaL with linezolid 1200–26 (*n*=44) experienced:

- lower levels of treatment success (93% vs 98%); that is, a 5% relative reduction (RR=0.95, 95% CI: 0.86 to 1.05);
- higher levels of failure and recurrence (4.8% vs 2.3%); that is, a twofold increase (RR=2.10, 95% CI: 0.20 to 22.26);
- higher levels of LTFU (2.4% vs 0%); that is, a 2% absolute increase (RD=0.02, 95% CI: –0.06 to 0.12);
- lower levels of Grade 3–5 AEs (14.3% vs 18.2%); that is, a 21% relative reduction (RR=0.79, 95% CI: 0.30 to 2.07); and
- the same levels of deaths (0% vs 0%) or amplified resistance (0% vs 0%).

The GDG judged the benefits of BPaL with linezolid 600–9 to be small and the undesirable effects to be moderate compared with the BPaL with linezolid 1200–26. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaL with linezolid 1200–26.

Conclusion

The use of the 26 weeks of 1 200 mg over 9 weeks of 600 mg linezolid is suggested as part of the BPaL regimen in adults with MDR/RR-TB or pre-XDR-TB.

PICO 3–2022 – Intermediate summary conclusion

The assessment of PICO 3 allowed for the decision on the optimal dosing and duration of linezolid within the BPaLM/BPaL regimen, and narrowed down the subsequent comparisons to the intervention regimen with this particular dose and duration of linezolid – BPaL (600 mg – 26 weeks).

Sub-PICO 4.1–2022: Should a 6-month regimen using bedaquiline, pretomanid and linezolid be used in patients with pulmonary pre-XDR-TB (MDR/RR-TB with fluoroquinolone resistance)?

The BPaL 600–26 arm of the ZeNix trial (where linezolid 600 mg daily was used for 26 weeks and the population included patients with MDR/RR-TB with fluoroquinolone resistance) was compared with a cohort of MDR/RR-TB patients with fluoroquinolone resistance from the 2021 IPD who were receiving longer regimens for treatment of MDR/RR-TB, designed in line with 2020 WHO guidelines. Primary analysis was undertaken at 18 months post-treatment initiation.

Participants with pulmonary pre-XDR-TB (MDR/RR-TB with fluoroquinolone resistance) receiving BPaL 600–26 (*n*=33) compared with participants receiving longer regimens for MDR/RR-TB (*n*=839) experienced:

- higher levels of treatment success (100% vs 75%); that is, a 34% relative increase (RR=1.34, 95% CI: 1.20 to 1.40);
- lower levels of failure and recurrence (0% vs 6.6%); that is, a 7% absolute reduction (RD= –0.07, 95% CI: –0.08 to –0.04);
- lower levels of deaths (0% vs 9.9%); that is, a 10% absolute reduction (RD= –0.10, 95% CI: –0.12 to –0.01);
- lower levels of LTFU (0% vs 9.1%); that is, a 9% absolute reduction (RD= –0.09, 95% CI: –0.11 to –0.01);
- higher levels of AEs (15% vs 4.4%); that is, a 3.4-fold increase (RR=3.44, 95% CI: 1.44 to 8.17); and
- lower levels of amplification of drug resistance (0% vs 7.4%); that is, a 7% absolute reduction (RD= –0.07, 95% CI: –0.09 to –0.03).

The GDG judged the benefits of BPaL with linezolid 600–26 to be large and the undesirable effects to be moderate compared with longer regimens recommended by WHO. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaL with linezolid 600–26.

Conclusion

The use of the 6-month treatment regimen composed of bedaquiline, pretomanid and linezolid (BPaL) rather than a longer (18-month) regimen is suggested in patients with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR-TB), who have either had no previous exposure to bedaquiline and linezolid, or have been exposed for less than 1 month.

PICO 4–2022 – Intermediate conclusion

The assessment of PICO 4 resulted in the conditional recommendation for use of the BPaL (600 mg – 26 weeks) regimen over the currently recommended longer regimens in patients with MDR/RR-TB and additional fluoroquinolone resistance (pre-XDR-TB).

Sub-PICO 5.1–2022: Should a 6-month regimen using bedaquiline, pretomanid and linezolid be used in patients with pulmonary MDR/RR-TB and without fluoroquinolone resistance? (Comparator: 9-month regimen with ethionamide.)

The BPaL 600–26 arm of the ZeNix trial (where linezolid 600 mg daily was used for 26 weeks and the population included patients with MDR/RR-TB with or without fluoroquinolone resistance) was compared with a cohort of MDR/RR-TB patients without fluoroquinolone resistance treated in South Africa with the WHO-recommended 9-month regimen with ethionamide for 4 months. Primary analysis was undertaken at 12 months post-treatment initiation.

Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving the BPaL 600–26 regimen (*n*=43) compared with participants with MDR/RR-TB (without fluoroquinolone resistance) receiving the 9-month regimen with ethionamide (*n*=785) experienced:

- higher levels of treatment success (100% vs 69%); that is, a 45% relative increase (RR=1.45, 95% CI: 1.32 to 1.53);
- lower levels of failure and recurrence (0% vs 1.3%); that is, a 1% absolute reduction (RD= –0.01, 95% CI: –0.02 to 0.07);
- lower levels of deaths (0% vs 19%); that is, a 19% absolute reduction (RD= –0.19, 95% CI: –0.22 to –0.1);
- lower levels of LTFU (0% vs 11%); that is, an 11% absolute reduction (RD= –0.11, 95% CI: –0.14 to –0.03); and

- the same levels of amplified resistance (0% vs 0%); that is, a 0% absolute difference (RD= 0.00, 95% CI: –0.01 to 0.08).

Grade 3–5 AEs were noted in 14% of participants receiving the BPaL 600–26 regimen; however, no comparison could be undertaken because no data were available for participants receiving the 9-month regimen with ethionamide.

The GDG judged the benefits of BPaL with linezolid 600–26 to be large and the undesirable effects to be moderate compared with the WHO-recommended 9-month regimen with ethionamide. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaL with linezolid 600–26.

Conclusion

The use of the 6-month treatment regimen composed of bedaquiline, pretomanid and linezolid (BPaL) rather than the 9-month regimen (with ethionamide) is suggested in patients with MDR/RR-TB without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid, or have been exposed for less than 1 month.

Sub-PICO 5.2–2022: Should a 6-month regimen using bedaquiline, pretomanid and linezolid be used in patients with pulmonary MDR/RR-TB and without fluoroquinolone resistance? (Comparator: longer regimens.)

The BPaL 600–26 arm of the ZeNix trial (where linezolid 600 mg daily was used for 26 weeks and the population included patients with MDR/RR-TB, with or without fluoroquinolone resistance) was compared with a cohort of MDR/RR-TB patients without fluoroquinolone resistance from the 2021 IPD, treated with longer regimens for MDR/RR-TB, designed in line with the 2020 WHO guidelines. Primary analysis was undertaken at 18 months post-treatment initiation.

Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving the BPaL 600–26 regimen (*n*=43) compared with participants with MDR/RR-TB (without fluoroquinolone resistance) receiving longer regimens recommended by WHO (*n*=850) experienced:

- higher levels of treatment success (98% vs 74%); that is, a 32% relative increase (RR=1.32, 95% CI: 1.19 to 1.39);
- lower levels of failure and recurrence (2.3% vs 3.3%); that is, a 29% relative reduction (RR=0.71, 95% CI: 0.12 to 3.8);
- lower levels of deaths (0% vs 11%); that is, an 11% absolute reduction (RD= –0.11, 95% CI: –0.13 to –0.03);
- lower levels of LTFU (0% vs 12%); that is, a 12% absolute reduction (RD= –0.12, 95% CI: –0.14 to –0.04);
- higher levels of Grade 3–5 AEs (14% vs 5%); that is, a fourfold relative increase (aRR=3.99, 95% CI: 1.67 to 9.57); and
- lower levels of amplified resistance (0% vs 2.4%); that is, a 2% absolute decrease (RD= –0.02, 95% CI: –0.04 to 0.06).

The GDG judged the benefits of BPaL with linezolid 600–26 to be large and the undesirable effects to be moderate compared with longer regimens recommended by WHO. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaL with linezolid 600–26.

Conclusion

The use of the 6-month treatment regimen composed of bedaquiline, pretomanid and linezolid (BPaL) rather than longer (18-month) regimens is suggested in patients with MDR/RR-TB and without

resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid, or have been exposed for less than 1 month.

Sub-PICO 5.3–2022: Should a 6-month regimen using bedaquiline, pretomanid and linezolid be used in patients with pulmonary MDR/RR-TB and without fluoroquinolone resistance? (Comparator: 9-month regimen with linezolid.)

The BPaL 600–26 arm of the ZeNix trial (where linezolid 600 mg daily was used for 26 weeks and the population included patients with MDR/RR-TB with or without fluoroquinolone resistance) was compared with a cohort of MDR/RR-TB patients without fluoroquinolone resistance treated in South Africa with a 9-month regimen with linezolid for 2 months. Primary analysis was undertaken at 12 months post-treatment initiation.

Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving BPaL with linezolid 600–26 (*n*=43) compared with participants with MDR/RR-TB (without fluoroquinolone resistance) receiving a 9-month regimen with linezolid (*n*=4216) experienced:

- higher levels of treatment success (100% vs 66%); that is, a 52% relative increase (RR=1.52, 95% CI: 1.38 to 1.55);
- lower levels of failure and recurrence (0% vs 1.2%); that is, a 1% absolute reduction (RD= –0.01, 95% CI: –0.02 to 0.07);
- lower levels of deaths (0% vs 18%); that is, an 18% absolute reduction (RD= –0.18, 95% CI: –0.19 to –0.1);
- lower levels of LTFU (0% vs 15%); that is, a 15% absolute reduction (RD= –0.15, 95% CI: –0.16 to –0.07);
- higher levels of Grade 3–5 AEs (14% vs 4.9%); that is, a threefold increase (aRR=2.92, 95% CI: 1.38 to 6.18); and
- lower levels of amplified resistance (0% vs 0.6%); that is, a 1% absolute reduction (RD= –0.01, 95% CI: –0.01 to 0.08).

The GDG judged the benefits of BPaL with linezolid 600–26 to be large and the undesirable effects to be moderate compared with receiving a 9-month regimen with linezolid. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaL with linezolid 600–26.

Conclusion

The use of the 6-month treatment regimen composed of bedaquiline, pretomanid and linezolid (BPaL) rather than the 9-month regimen (with linezolid) is suggested in patients with MDR/RR-TB without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid, or have been exposed for less than 1 month.

PICO 5–2022 – Intermediate summary conclusion

The three assessments performed under PICO 5 resulted in the conditional recommendations for the BPaL (600 mg – 26 weeks) regimen over the currently recommended 9-month regimen with ethionamide (sub-PICO 5.1), over longer (18-month) regimens (sub-PICO 5.2) and over the new 9-month regimen where ethionamide is replaced with 2 months of linezolid (sub-PICO 5.3) in patients with pulmonary MDR/RR-TB without fluoroquinolone resistance.

Sub-PICO 6.1–2022: Should a 6-month regimen using bedaquiline, pretomanid and linezolid with or without addition of moxifloxacin (BPaLM) or clofazimine be used in patients with pulmonary MDR/RR-TB (with or without fluoroquinolone resistance)? (BPaLM vs.TB-PRACTECAL comparator)

The BPaLM regimen arm of the TB-PRACTECAL trial with a population including patients with MDR/RR-TB, with or without fluoroquinolone resistance (MDR/RR-TB or pre-XDR-TB), was compared

with the comparator arm of the TB-PRACTECAL trial, which comprised MDR/RR-TB or pre-XDR-TB patients treated with multiple local SoC regimens recommended by WHO at the time the trial was conducted (including a 9–12-month injectable-containing regimen, an 18–24-month WHO-recommended regimen [pre-2019], a 9–12-month all-oral regimen and an 18–20-month all-oral regimen). Primary analysis was undertaken at 72 weeks post-treatment initiation.

Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving the BPaLM regimen (*n*=62) compared with participants receiving WHO-recommended SoC regimens used in the TB-PRACTECAL trial (*n*=66) experienced:

- higher levels of treatment success (89% vs 52%); that is, a 73% relative increase (aRR=1.73, 95% CI: 1.31 to 2.27);
- lower levels of failure and recurrence (8% vs 26%); that is, a 74% relative reduction (aRR=0.26, 95% CI: 0.10 to 0.71);
- lower levels of deaths (0% vs 3.0%); that is, a 3% absolute reduction (RD= –0.03, 95% CI: –0.10 to 0.03);
- lower levels of LTFU (3.2% vs 20%); that is, an 84% relative reduction (RR=0.16, 95% CI: 0.04 to 0.61);
- lower levels of Grade 3–5 AEs (21% vs 51%); that is, a 59% relative reduction (aRR=0.41, 95% CI: 0.26 to 0.63); and
- lower levels of amplified resistance (0% vs 1.9%); that is, a 2% absolute reduction (RD= –0.02, 95% CI: –0.07 to 0.02).

The GDG judged the benefits of BPaLM to be large and the undesirable effects to be trivial compared with WHO-recommended SoC regimens. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours the BPaLM regimen.

Conclusion

The use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) rather than a 9-month or longer (18-month) regimen is suggested in MDR/RR-TB patients with or without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid, or have been exposed for less than 1 month.

Sub-PICO 6.2–2022: Should a 6-month regimen using bedaquiline, pretomanid and linezolid with or without addition of moxifloxacin (BPaLM) or clofazimine (BPaLC) be used in patients with pulmonary MDR/RR-TB (with or without fluoroquinolone resistance)? (BPaLM vs. BPaL comparator)

The BPaLM regimen arm of the TB-PRACTECAL trial with a population including patients with MDR/RR-TB, with or without fluoroquinolone resistance (MDR/RR-TB or pre-XDR-TB), was compared with the BPaL arm of the TB-PRACTECAL trial, which comprised MDR/RR-TB or pre-XDR-TB patients. Primary analysis was undertaken at 72 weeks post-treatment initiation.

Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving the BPaLM regimen (*n*=62) compared with participants receiving BPaL in the TB-PRACTECAL trial (*n*=60) experienced:

- higher levels of treatment success (89% vs 77%); that is, a 15% relative increase (aRR=1.15, 95% CI: 0.95 to 1.38);
- lower levels of failure and recurrence (8.1% vs 13%); that is, a 47% relative reduction (aRR=0.53, 95% CI: 0.17 to 1.63);
- lower levels of LTFU (3.2% vs 10%); that is, a 68% relative reduction (aRR=0.32, 95% CI: 0.08 to 1.34);
- no difference in deaths (0% vs 0%); that is, a 0% absolute difference (RD=0, 95% CI: –0.06 to 0.06);
- higher levels of Grade 3–5 AEs (21% vs 20%); that is, a 7% relative increase (aRR=1.07, 95% CI: 0.62 to 1.88); and
- lower levels of amplified resistance (0% vs 2.9%); that is, a 3% absolute reduction (RD= –0.03, 95% CI: –0.08 to 0.01).

The GDG judged the benefits of BPaLM to be moderate and the undesirable effects to be small compared with BPaL. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaLM.

Conclusion

The use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) rather than BPaL is suggested in MDR/RR-TB patients with or without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid, or have been exposed for less than 1 month.

Sub-PICO 6.3–2022: Should a 6-month regimen using bedaquiline, pretomanid and linezolid with or without addition of moxifloxacin (BPaLM) or clofazimine (BPaLC) be used in patients with pulmonary MDR/RR-TB (with or without fluoroquinolone resistance)? (BPaLM vs. BPaLC comparator)

The BPaLM regimen arm of the TB-PRACTECAL trial with a population including patients with MDR/RR-TB, with or without fluoroquinolone resistance (MDR/RR-TB or pre-XDR-TB), was compared with the BPaLC arm of the TB-PRACTECAL trial that comprised MDR/RR-TB or pre-XDR-TB patients. Primary analysis was undertaken at 72 weeks post-treatment initiation.

Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving the BPaLM regimen (*n*=62) compared with participants receiving the BPaLC regimen (*n*=64) in the TB-PRACTECAL trial experienced:

- higher levels of treatment success (89% vs 81%); that is, an 11% relative increase (aRR=1.11, 95% CI: 0.94 to 1.31);
- lower levels of failure and recurrence (8.1% vs 9.4%); that is, a 30% relative reduction (aRR=0.70, 95% CI: 0.2 to 2.29);
- lower levels of deaths (0% vs 1.6%); that is, a 2% absolute reduction (RD= –0.02, 95% CI: –0.08 to 0.04);
- lower levels of LTFU (3.2% vs 7.8%); that is, a 59% relative reduction (RR=0.41, 95% CI: 0.09 to 1.77);
- lower levels of Grade 3–5 AEs (21% vs 34%); that is, a 39% relative reduction (aRR=0.61, 95% CI: 0.37 to 1.00); and
- lower levels of amplified resistance (0% vs 1.9%); that is, a 2% absolute reduction (RD= –0.02, 95% CI: –0.07 to 0.02).

The GDG judged the benefits of BPaLM to be moderate and the undesirable effects to be trivial compared with BPaLC. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaLM.

Conclusion

The use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) rather than BPaLC is suggested in patients with MDR/RR-TB with or without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid, or have been exposed for less than 1 month.

Sub-PICO 6.4–2022: Should a 6-month regimen using bedaquiline, pretomanid and linezolid with or without addition of moxifloxacin (BPaLM) or clofazimine (BPaLC) be used in patients with pulmonary MDR/RR-TB (with or without fluoroquinolone resistance)? (BPaLC vs TB-PRACTECAL comparator)

The BPaLC regimen arm of the TB-PRACTECAL trial with a population including patients with MDR/RR-TB, with or without fluoroquinolone resistance (MDR/RR-TB or pre-XDR-TB), was compared with the comparator arm of the TB-PRACTECAL trial, which comprised MDR/RR-TB or pre-XDR-TB patients treated with multiple local SoC regimens recommended by WHO at the time of trial conduct

(including a 9–12-month injectable-containing regimen, 18–24-month WHO-recommended regimen [pre-2019], 9–12-month all-oral regimen and 18–20-month all-oral regimen). Primary analysis was undertaken at 72 weeks post-treatment initiation.

Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving BPaLC (*n*=64) compared with participants receiving WHO-recommended SoC regimens used in the TB-PRACTECAL trial (*n*=66) experienced:

- higher treatment success (81% vs 52%); that is, a 55% relative increase (aRR=1.55, 95% CI: 1.15 to 2.11);
- lower levels of failure and recurrence (9.4% vs 26%); that is, a 66% relative reduction (aRR=0.34, 95% CI: 0.14 to 0.87);
- lower levels of deaths (1.6% vs 3.0%); that is, a 48% relative reduction (RR=0.52, 95% CI: 0.07 to 3.85);
- lower levels of LTFU (7.8% vs 20%); that is, a 57% relative reduction (aRR=0.43, 95% CI: 0.15 to 1.23);
- lower levels of Grade 3–5 AEs (34% vs 51%); that is, a 33% relative reduction (aRR=0.67, 95% CI: 0.46 to 0.97); and
- higher levels of amplified resistance (1.9% vs 1.9%); that is, a 4% relative increase (RR=1.04, 95% CI: 0.19 to 5.80).

The GDG judged the benefits of BPaLC to be large and the undesirable effects to be trivial compared to WHO-recommended SoC regimens. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaLC.

Conclusion

The use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid and clofazimine (BPaLC) rather than a 9-month or longer (18-month) regimen is suggested in MDR/RR-TB patients with or without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid, or have been exposed for less than 1 month (overruled by conclusions of sub-PICO 6.5 and sub-PICO 6.6).

Sub-PICO 6.5–2022: Should a 6-month regimen using bedaquiline, pretomanid and linezolid with or without addition of moxifloxacin (BPaLM) or clofazimine (BPaLC) be used in patients with pulmonary MDR/RR-TB (with or without fluoroquinolone resistance)? (BPaLC vs BPaL comparator)

The BPaLC regimen arm of the TB-PRACTECAL trial with a population including patients with MDR/RR-TB, with or without fluoroquinolone resistance (MDR/RR-TB or pre-XDR-TB), was compared with the BPaL arm of the TB-PRACTECAL trial, which comprised MDR/RR-TB or pre-XDR-TB patients. Primary analysis was undertaken at 72 weeks post-treatment initiation.

Participants with pulmonary MDR/RR-TB or pre-XDR-TB receiving BPaLC (*n*=64) compared with participants receiving BPaL 600–300 (*n*=60) experienced:

- higher levels of treatment success (81% vs 77%); that is, a 4% relative increase (aRR=1.04, 95% CI: 0.84 to 1.30);
- lower levels of failure and recurrence (9.4% vs 13%); that is, a 14% relative reduction (aRR=0.86, 95% CI: 0.28 to 2.69);
- higher levels of deaths (1.6% vs 0%); that is, a 2% absolute increase (RD=0.02, 95% CI: –0.05 to 0.08);
- lower levels of LTFU (7.8% vs 10%); that is, a 28% relative reduction (aRR=0.72, 95% CI: 0.21 to 2.47);
- higher levels of AEs (34% vs 20%); that is, a 64% relative increase (aRR=1.64, 95% CI: 0.97 to 2.79); and
- lower levels of amplification of drug resistance (1.9% vs 2.9%); that is, a 35% relative reduction (RR=0.65, 95% CI: 0.13 to 3.21).

The GDG judged both the desirable and the undesirable effects of BPaLC to be small compared with BPaL. The certainty of evidence was judged to be very low. The balance of health effects did not favour either the intervention or the comparator; however, the panel judged against the intervention after taking into consideration the higher cost of the regimen, increased pill burden, reduced acceptability owing to skin discolouration and other potential AEs related to clofazimine without noticeable net benefit in terms of health effects.

Conclusion

The use of the 6-month treatment regimen composed of bedaquiline, pretomanid and linezolid (BPaL) rather than BPaLC is suggested in MDR/RR-TB patients with or without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid, or have been exposed for less than 1 month.

Sub-PICO 6.6–2022: Should a 6-month regimen using bedaquiline, pretomanid and linezolid with or without addition of moxifloxacin (BPaLM) or clofazimine (BPaLC) be used in patients with pulmonary MDR/RR-TB (with or without fluoroquinolone resistance)? (BPaL vs TB-PRACTECAL comparator)

The BPaL arm of the TB-PRACTECAL trial with a population including patients with MDR/RR-TB, with or without fluoroquinolone resistance (MDR/RR-TB or pre-XDR-TB), was compared with the comparator arm of the TB-PRACTECAL trial, which comprised MDR/RR-TB or pre-XDR-TB patients treated with multiple local SoC regimens (including a 9–12-month injectable-containing regimen, an 18–24-month WHO-recommended regimen [pre-2019], a 9–12-month all-oral regimen and an 18–20-month all-oral regimen). Primary analysis was undertaken at 72 weeks post-treatment initiation.

Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving BPaL (*n*=60) compared with participants receiving WHO-recommended SoC regimens used in the TB-PRACTECAL trial (*n*=66) experienced:

- higher levels of treatment success (77% vs 52%); that is, a 47% relative increase (aRR=1.47, 95% CI: 1.09 to 1.99);
- lower levels of failure and recurrence (13% vs 26%); that is, a 48% relative reduction (aRR=0.52, 95% CI: 0.22 to 1.18);
- lower levels of deaths (0% vs 3%); that is, a 3% absolute reduction (RD= –0.03, 95% CI: –0.10 to 0.03);
- lower levels of LTFU (10% vs 20%); that is, a 40% relative reduction (aRR=0.60, 95% CI: 0.24 to 1.56);
- lower levels of AEs (20% vs 51%); that is, a 62% relative reduction (RR=0.38, 95% CI: 0.24 to 0.60); and
- higher levels of amplification of drug resistance (2.9% vs 1.9%); that is, a 59% relative increase (RR=1.59, 95% CI: 0.32 to 7.84).

The GDG judged the benefits of BPaL to be large and the undesirable effects to be trivial compared with WHO-recommended SoC regimens. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours the BPaL regimen.

Conclusion

The use of the 6-month treatment regimen composed of bedaquiline, pretomanid and linezolid (BPaL) rather than a 9-month or longer (18-month) regimen is suggested in patients with MDR/RR-TB with or without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid, or have been exposed for less than 1 month.

PICO 6–2022 – Intermediate summary conclusion

The main assessment that defined the overall decision was that of sub-PICO 6.1, which resulted in the conditional recommendation for use of the BPaLM regimen over the internal mix of SoC regimens conforming to the WHO recommendations on 9-month or longer regimens. The assessments of the investigational regimens against each other and with the SoC in sub-PICOs 6.2–6.6 helped the panel in making final decisions.

PICO 2–2025: Should a BPaL regimen be used in patients with pulmonary pre-XDR-TB over the TB-PRACTECAL comparator regimens? (NEW)

The BPaL regimen arm of the TB-PRACTECAL trial, with a population including patients with MDR/RR-TB, with or without fluoroquinolone resistance (MDR/RR-TB or pre-XDR-TB), was compared with the comparator arm comprising MDR/RR-TB or pre-XDR-TB patients treated with multiple local SoC regimens recommended by WHO at the time the trials were conducted (including a 9–12-month injectable-containing regimen, 18–24-month WHO-recommended regimen [pre-2019], 9–12-month all-oral regimen and 18–20-month all-oral regimen). Although the research question focused explicitly on pre-XDR-TB patients, the analysis included both MDR/RR and pre-XDR-TB patients in both groups, to increase the sample size and improve statistical precision, because excluding fluoroquinolone-susceptible cases would have resulted in insufficiently small cohorts.

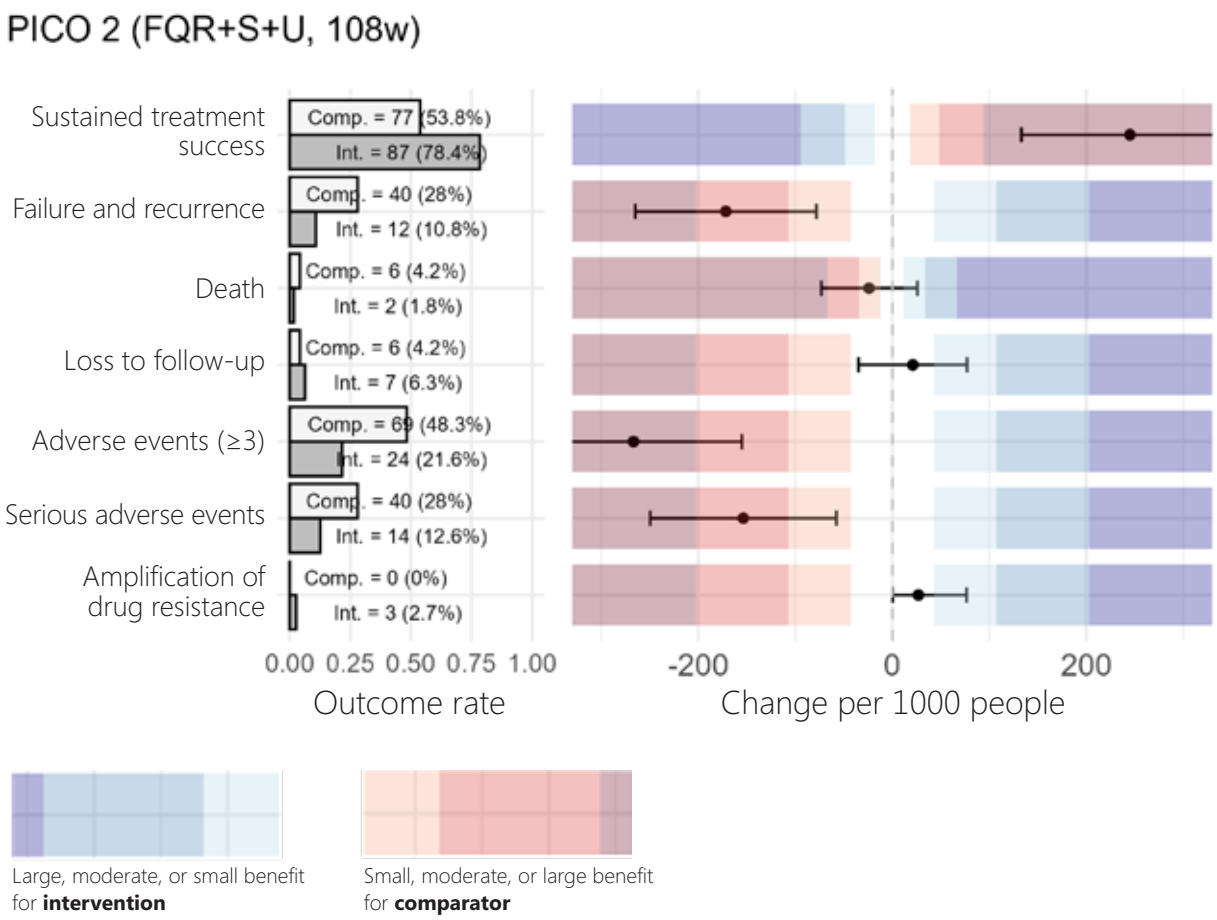
In the intervention group, use of the BPaL regimen, which does not include a fluoroquinolone, meant that fluoroquinolone susceptibility had no effect on treatment benefit; in contrast, in the comparator group, inclusion of fluoroquinolone-susceptible patients allowed regimens that could potentially perform better, thereby biasing the comparison against the intervention rather than favouring it, which was acceptable given the objective to demonstrate the added benefit of the BPaL regimen. Primary analysis was undertaken at 108 weeks post-treatment initiation.

Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving BPaL (n=111) compared with participants receiving WHO-recommended SoC regimens used in the TB-PRACTECAL trial (n=143) experienced:

- lower levels of failure and recurrence (10.8% vs 28%); RD=172 fewer per 1000, 95% CI: 265 fewer to 78 fewer per 1000);
- lower levels of deaths (1.8% vs 4.2%); RD=24 fewer per 1000, 95% CI: 73 fewer to 26 more per 1000);
- higher levels of LTFU (6.3% vs 4.2%); RD=21 more per 1000, 95% CI: 35 fewer to 77 more per 1000);
- lower levels of AEs (21.6% vs 48.3%); RD=267 fewer per 1000, 95% CI: 378 fewer to 155 fewer per 1000); and
- higher levels of amplification of drug resistance (2.7% vs 0%); RD=27 more per 1000, 95% CI: 0 fewer to 77 more per 1000).

Fig. 2.1 visually depicts absolute effects and 95% CIs from the evidence in relation to the DTs for each health outcome, to facilitate the GDG's discussion and judgements about whether the health effects were trivial, small, moderate or large, and to judge the level of imprecision of estimates.

Fig. 2.1. Visual depiction of absolute effects in relation to the DTs used by the 2025 GDG (PICO 2–2025)



Comp.: comparator; DT: decision threshold; FQR: fluoroquinolone resistance; GDG: Guideline Development Group; Int.: intervention; PICO: population, intervention, comparator and outcome; S: susceptible; U: unfavourable; w: weeks.

The GDG also reviewed the data from a small cohort of patients (*n*=16) treated with the BPaL regimen under programmatic conditions at a single site in Italy. The cohort included a limited number of patients with MDR-TB in the WHO IPD dataset, none of whom had pre-XDR-TB. Treatment outcomes were broadly consistent with those observed in the BPaL arm of the TB-PRACTECAL trial. These findings support the feasibility of implementing the BPaL regimen in routine care settings.

The GDG judged the benefits of BPaL to be large and the undesirable effects to be small compared with the WHO-recommended SoC regimens used in the TB-PRACTECAL trial. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours the BPaL regimen.

Conclusion

The use of the 6-month treatment regimen composed of bedaquiline, pretomanid and linezolid (BPaL) rather than a longer (18-month) regimen is suggested in patients with pre-XDR-TB, who have either had no previous exposure to bedaquiline and linezolid, or have been exposed for less than 1 month.

PICO 3–2025: Should a BPaLC regimen be used in patients with pulmonary pre-XDR-TB over the TB-PRACTECAL comparator regimens? (NEW)

The BPaLC regimen arm of the TB-PRACTECAL trial, with a population including patients with MDR/RR-TB, with or without fluoroquinolone resistance (MDR/RR-TB or pre-XDR-TB), was compared with the comparator arm, which comprised MDR/RR-TB or pre-XDR-TB patients treated with multiple local SoC regimens recommended by WHO at the time of trial conduct, including a 9–12-month injectable-containing regimen, 18–24-month WHO-recommended regimen (pre-2019), 9–12-month all-oral regimen and 18–20-month all-oral regimen. Although the research question focused explicitly on pre-XDR-TB patients, the analysis included both MDR/RR and pre-XDR-TB patients in both groups to increase the sample size and improve statistical precision, because excluding fluoroquinolone-susceptible cases would have resulted in insufficiently small cohorts.

In the intervention group, use of the BPaLC regimen, which does not include a fluoroquinolone, meant that fluoroquinolone susceptibility had no effect on treatment benefit; in contrast, in the comparator group, inclusion of fluoroquinolone-susceptible patients allowed regimens that could potentially perform better, thereby biasing the comparison against the intervention rather than favouring it, which was acceptable given that the objective was to demonstrate the added benefit of the BPaLC regimen.

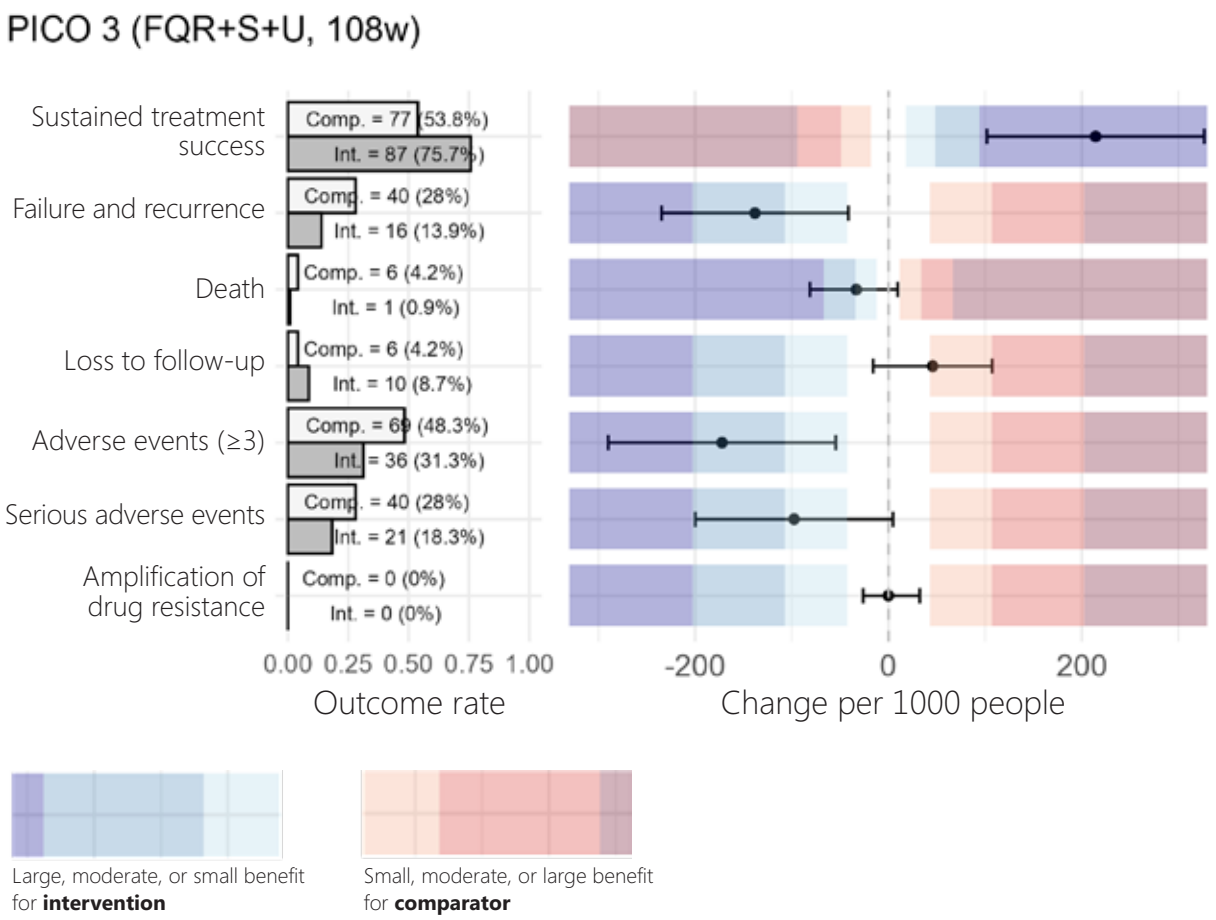
Primary analysis was undertaken at 108 weeks post-treatment initiation.

Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving BPaLC (*n*=115) compared with participants receiving WHO-recommended SoC regimens used in the TB-PRACTECAL trial (*n*=143) experienced:

- lower levels of failure and recurrence (13.9% vs 28%); RD=138 fewer per 1000, 95% CI: 234 fewer to 41 fewer per 1000);
- lower levels of deaths (0.9% vs 4.2%); RD=33 fewer per 1000, 95% CI: 81 fewer to 10 more per 1000);
- higher levels of LTFU (8.7% vs 4.2%); RD=46 more per 1000, 95% CI: 16 fewer to 107 more per 1000);
- lower levels of grade 3 to 5 AEs (31.3% vs 48.3%); RD=172 fewer per 1000, 95% CI: 290 fewer to 55 fewer per 1000); and
- and similar levels of amplified resistance (0% vs 0%); RD=0 fewer per 1000, 95% CI: 26 fewer to 32 more per 1000).

Fig. 2.2 visually depicts absolute effects and 95% CIs from the evidence in relation to the DTs for each health outcome, to facilitate the GDG's discussion and judgements about whether the health effects were trivial, small, moderate or large, and to judge the level of imprecision of estimates.

Fig. 2.2. Visual depiction of absolute effects in relation to the DTs used by the 2025 GDG (PICO 3–2025)



Comp.: comparator; DT: decision threshold; FQR: fluoroquinolone resistance; GDG: Guideline Development Group; Int.: intervention; PICO: population, intervention, comparator and outcome; S: susceptible; U: unfavourable; w: weeks.

The GDG also reviewed data from programmatic sites in Belarus (*n*=261) and Uzbekistan (*n*=42). Most patients had pre-XDR-TB and were treated with the BPaLC regimen. Treatment was delivered under routine programmatic conditions. Outcomes were broadly consistent with those observed in clinical trial settings, supporting the feasibility of BPaLC implementation in routine care.

The GDG judged the benefits of BPaLC to be large and the undesirable effects to be small compared with the WHO-recommended SoC regimens used in the TB-PRACTECAL trial. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaLC.

Conclusion

The use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid and clofazimine (BPaLC) rather than a longer (18-month) regimen is suggested in pre-XDR-TB patients who have either had no previous exposure to bedaquiline and linezolid, or have been exposed for less than 1 month.

PICO 6a–2025: Should a BPaLC regimen be used in patients with non-severe pulmonary pre-XDR-TB over the BPaL regimen? (NEW)

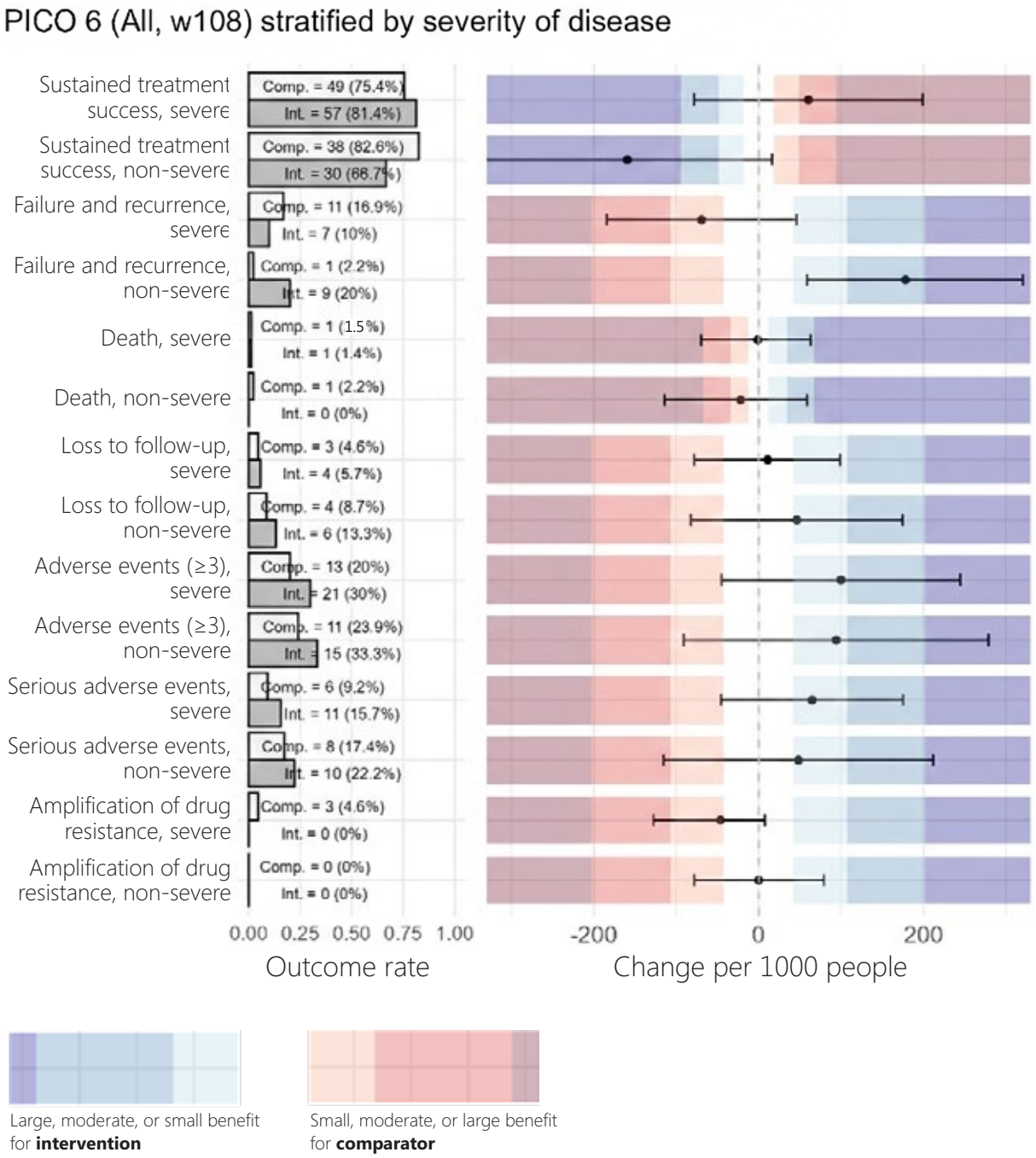
The BPaLC regimen arm of the TB-PRACTECAL trial, with a population including patients with MDR/RR-TB or pre-XDR-TB, was compared with the BPaL arm of the TB-PRACTECAL trial, which comprised MDR/RR-TB or pre-XDR-TB patients. Primary analysis was undertaken at 108 weeks post-treatment initiation. Each arm was stratified into those with non-severe and severe pre-XDR-TB.

Participants with non-severe pulmonary MDR/RR-TB or pre-XDR-TB receiving BPaLC (*n*=45) compared with participants receiving BPaL (*n*=46) experienced:

- higher levels of failure and recurrence (20% vs 2.2%); RD=178 more per 1000, 95% CI: 59 more to 321 more per 1000);
- lower levels of deaths (0% vs 2.2%); RD=22 fewer per 1000, 95% CI: 114 fewer to 59 more per 1000);
- higher levels of LTFU (13.3% vs 8.7%); RD=46 more per 1000, 95% CI: 82 fewer to 175 more per 1000);
- higher levels of AEs (33.3% vs 23.9%); RD=94 more per 1000, 95% CI: 91 fewer to 279 more per 1000); and
- similar levels of amplification of drug resistance (0% vs 0%); RD=0 per 1000, 95% CI: 78 fewer to 80 more per 1000).

Fig. 2.3 visually depicts absolute effects and 95% CIs from the evidence in relation to the DTs for each health outcome, to facilitate the GDG's discussion and judgements about whether the health effects were trivial, small, moderate or large, and to judge the level of imprecision of estimates.

Fig. 2.3. Visual depiction of absolute effects in relation to the DTs used by the 2025 GDG (PICO 6a–b–2025)



Comp.: comparator; DT: decision threshold; GDG: Guideline Development Group; Int.: intervention; PICO: population, intervention, comparator and outcome; w: weeks.

The GDG judged the desirable effects to be trivial and the undesirable effects of BPaLC to be moderate compared with BPaL. The certainty of evidence was judged to be very low. The balance of health effects was judged to be in favour of BPaL, with a small net benefit in people with non-severe disease (or small net harm for BPaLC in this population), favouring the comparison (BPaL), although there was very low certainty evidence owing to indirectness and severe imprecision, in particular for the subgroup with non-severe disease. In addition, there was probably no important uncertainty or variability in values.

Conclusion

The use of the 6-month treatment regimen composed of bedaquiline, pretomanid and linezolid (BPaL) rather than BPaLC is suggested in patients with non-severe pre-XDR-TB, who have either had no previous exposure to bedaquiline and linezolid, or have been exposed for less than 1 month.

PICO 6b–2025: Should a BPaLC regimen be used in patients with severe pulmonary pre-XDR-TB over the BPaL regimen? (NEW)

The BPaLC regimen arm of the TB-PRACTECAL trial, including patients with MDR/RR-TB or pre-XDR-TB, was compared with the BPaL arm of the TB-PRACTECAL trial, which comprised MDR/RR-TB or pre-XDR-TB patients. Primary analysis was undertaken at 108 weeks post-treatment initiation. The patient cohort was stratified into those with non-severe and severe pre-XDR-TB.

Participants with severe pulmonary MDR/RR-TB or pre-XDR-TB receiving BPaLC (*n*=70) compared with participants receiving BPaL (*n*=65) experienced:

- lower levels of failure and recurrence (10% vs 16.9%); RD=69 fewer per 1000, 95% CI: 416 fewer to 211 fewer per 1000);
- lower levels of deaths (1.4% vs 1.5%); RD=1 fewer per 1000, 95% CI: 222 fewer to 267 more per 1000);
- higher levels of LTFU (5.7% vs 4.6%); RD=11 more per 1000, 95% CI: 144 fewer to 384 more per 1000);
- higher levels of AEs (30% vs 20%); RD=100 more per 1000, 95% CI: 198 fewer to 463 more per 1000); and
- lower levels of amplification of drug resistance (0% vs 4.6%); RD=46 fewer per 1000, 95% CI: 321 fewer to 205 more per 1000).

The GDG judged the desirable effects to be moderate and the undesirable effects of BPaLC to be small compared with BPaL. The certainty of evidence was judged to be very low. The balance was judged to be in favour of BPaLC, with a small net benefit in people with severe disease, favouring the intervention (BPaLC), although the evidence was very low in certainty owing to indirectness and severe imprecision, particularly for the subgroup with non-severe disease. In addition, there was probably no important uncertainty or variability in values.

Conclusion

The use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid and clofazimine (BPaLC) rather than BPaL is suggested in patients with severe pre-XDR-TB, who have either had no previous exposure to bedaquiline and linezolid, or have been exposed for less than 1 month.

Summary of other evidence

Additional data reviewed by the 2022 GDG relevant to these PICO questions were a cost–effectiveness analysis, a study on the acceptability and likelihood of implementation of the BPaL regimen, modelled pharmacokinetic (PK) data based on the development of a PK toxicodynamic model, and a summary of data on potential reproductive toxicity of pretomanid. No additional research data were available during review of sub-PICO questions 3.2–3.5–2022.

At the time of the 2025 GDG review, a substudy evaluating quality of life (QoL) and patient reported outcomes studies had been published, reporting that patients receiving short, all-oral BPaL-based regimens show improvements across all measured QoL domains, a positive impact on personal relationships, and a return to productive life *(40)*, and the prices of medicines available through the Global Drug Facility (GDF) have decreased, bringing the price of the BPaLM regimen below US$ 300.

Pharmacokinetic data

Early data from the PK study embedded in the TB-PRACTECAL were presented to the GDG panel convened in 2022, in one of the preparatory webinars. The final results of this substudy were not available at the time of the assessment and could not be fully considered.

The PK of linezolid are highly variable, with efficacy and toxicity dependent on factors such as pathogen susceptibility, drug exposure and the combination of companion drugs. The toxicity of linezolid, especially when used at higher doses and longer durations, is a known phenomenon and various strategies have been suggested to reduce it. However, except for the data available from the ZeNix and TB-PRACTECAL trials, no other strategies have been tested in a trial environment.[27]

Data on reproductive toxicity of pretomanid

New data on the safety of pretomanid based on hormone evaluations in four clinical trials and a paternity survey were assessed; these data have largely alleviated previous concerns about reproductive toxicities observed in animal studies,[28] suggesting that AEs on human male fertility are unlikely. A study assessing semen in men undergoing treatment that includes pretomanid is in progress and will address any remaining concerns. Below is a summary of preclinical and clinical data relevant to testicular toxicity of pretomanid:

- rodent toxicology studies – evidence of direct testicular toxicity;
- monkey toxicology studies – no evidence of direct testicular toxicity; abnormal sperm findings considered to be secondary to declining physical condition;
- hormone data from clinical studies – no changes in follicle stimulating hormone (FSH), luteinizing hormone (LH) and inhibin B, consistent with testicular toxicity;
- paternity survey – 44 children were fathered by 38 men (12%) who participated in pretomanid studies of 4–6 months treatment duration; and
- semen study – ongoing study evaluating semen in men undergoing pretomanid treatment *(41)*.

Resources required and cost–effectiveness

Estimated regimen costs (in adults) at GDF prices[29] are about US$ 278 for BPaL, US$ 304 for BPaLM, US$ 365 for BPaLC, an average of US$ 475 for a longer regimen (depending on length and composition) and US$ 205–1748 for a 9-month regimen. Data from three studies were available on more detailed analyses of resources required and cost–effectiveness. Two of these studies compared the BPaL regimen with longer (18-month) regimens *(43, 44)*; the other study compared the BPaL, BPaLM and BPaLC regimens with longer (18-month) regimens and with the 9-month regimen with ethionamide *(45)*. The applicability of the results from these studies varied by PICO and sub-PICO question, and the panel noted associated caveats when discussing these results (details available in the GRADE EtD tables in **Annex 5**). Overall, based on these three publications, estimates for comparative total cost (drugs and delivery) within country appear to be between 1.4-fold and 6-fold higher (longer regimens) or 1–18% higher (9-month regimens) than for BPaLM/BPaL. Thus, the panel judged that implementation of BPaL/M/C would probably lead to large savings when replacing the longer (18-month) regimens, and moderate savings when replacing the 9-month regimens.

The cost–effectiveness study *(45)* found that, in most settings, BPaL/M/C is cost saving, mainly because of reduced time in care and therefore reductions in numbers of outpatient visits, inpatient bed-days and laboratory tests. The panel judged that cost–effectiveness probably favours BPaL/M/C.

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[27] As presented in the expert review (by Dr J-W. Alffenaar, University of Sydney) to the GDG panel in one of the preparatory webinars.

[28] Pretomanid has been shown to cause testicular atrophy and impaired fertility in male rats.

[29] Estimated regimen prices were calculated using the average weighted price for each medicine (average weighted price accounts for the different prices for each supplier of that medicine weighted by the market share allocation received from each GDF tender), the duration indicated (in months) and assuming 30 days of treatment per month. Actual final costs may differ based on the products delivered *(42)*.

Equity, acceptability and feasibility

The panel considered the treatment duration and the ability to decentralize treatment (to enable access for remote, underserved settings and disadvantaged populations) to affect equity. Despite not being able to identify relevant research evidence, the panel used their collective experience to judge that there would probably be advantages associated with the use of the BPaL/M/C regimen owing to its reduced complexity and shorter duration. Therefore, the panel judged that use of the BPaL/M/C regimen would probably increase equity.

A study on the acceptability and feasibility of the BPaL regimen from the provider perspective *(46)* was considered to be relevant evidence for the assessment of BPaL and indirectly for the assessment of BPaLM. This was a mixed-methods study among a cross section of health care workers, and programmatic and laboratory stakeholders that was carried out between May 2018 and May 2019 in Indonesia, Kyrgyzstan and Nigeria. The results from this study suggested that acceptability and feasibility overall were high. BPaL was rated as acceptable by more than 80% of participants across domains and stakeholders, and 88% of interviewed stakeholders stated that they would probably implement BPaL once it became available. Stakeholders appreciated that BPaL would reduce the workload and financial burden on the health care system; expressed concerns about BPaL safety (monitoring), long-term efficacy and national regulatory requirements; and stressed the importance of addressing current health systems constraints, especially in treatment and safety monitoring systems. Results from a second qualitative study *(47)* with a focus on the patient perspective were presented to the panel; this study suggested that patients would welcome the positive impact of shorter treatment on employment status.[30]

The panel noted these study results and, as part of their deliberations, they considered patients and health care providers as key stakeholders. The panel considered the following aspects to be critical with regard to the acceptability of BPaLM/BPaL: regimen duration and the need for drug-safety monitoring (relating both to necessary travel, loss of income and general disruption of life for patients, and to workload for the health care system), and the need for DST. The panel judged that the BPaLM/BPaL regimen would probably be acceptable. Regarding feasibility, the panel noted the limited availability of pure substances of drugs in the BPaLM/BPaL regimen for use in DST as a potential barrier to implementation; they also noted that data on the critical concentration of pretomanid for use in DST are limited. However, given the reduced duration, complexity and associated workload of BPaLM/BPaL, the panel judged that implementation of BPaLM/BPaL is probably feasible.

Evidence to recommendations: considerations

Based on the decisions taken during the review and the combination of assessments described above, the recommendation is to use the BPaLM regimen as the first choice in the defined patient group with MDR/RR-TB, with the regimen to be used under routine programmatic conditions. Patients with MDR/RR-TB who cannot use the BPaLM regimen (because of either ineligibility or unavailability of its components) can instead be treated with 6-month BDLLfx/C (see Recommendation B1.2) or one of the 9-month regimens (see Section 2). The use of the longer regimens is reserved (see Recommendation B4) for individuals with MDR/RR-TB and fluoroquinolone resistance, with further resistance or intolerance to bedaquiline, linezolid (XDR-TB) or pretomanid, and those with complicated extrapulmonary TB; such patients would receive a longer regimen designed with remaining effective medicines from Groups A, B and C, according to their drug susceptibility profile and other parameters.

The conclusions reached in 2022 and 2025 GDGs suggest the following:

- When fluoroquinolone susceptibility is unknown at treatment initiation, the regimen should begin as BPaLM and be adjusted once DST results are available.
- If the strain is susceptible to fluoroquinolones, treatment can continue as BPaLM.

[30] Personal communication, Beverley Stringer, Manson unit, Médecins Sans Frontières.

- In people with severe pulmonary pre-XDR-TB, moxifloxacin should be replaced by clofazimine, and the regimen should be started or continued as BPaLC.
- In people with non-severe pulmonary pre-XDR-TB, treatment can be started or continued as BPaL.

Table 2.5 lists the comparisons and decisions on each of the sub-PICO questions that were eventually used by the GDGs (2022 and 2025) to conclude with this summary recommendation. Throughout the discussion, the GDG panels focused on direct (within-trial) comparisons among the TB-PRACTECAL trial arms, to ensure consistency and because it was felt that results based on random allocation to interventions were far more reliable than indirect, nonrandomized comparisons. Whereas the certainty of evidence of these (TB-PRACTECAL-internal) comparisons was still judged to be very low, the panel deemed the certainty to be higher than that of other (indirect, between-trial or cohort) comparisons.

Although assessments of PICO questions 3, 4, 5 and 6 (2022) have all contributed to the summary recommendation, the main assessment that defined the overall decision was that of sub-PICO 6.1–2022 on the comparison of the BPaLM regimen of stage 2 (which corresponds to Phase 3) in the TB-PRACTECAL trial with the mix of SoC regimens (conforming to the WHO-recommended 9-month or longer regimens). Although the TB-PRACTECAL trial was not designed to compare the investigational regimens against each other and with the SoC, the comparisons of the different arms of the trial with the BPaLM arm (sub-PICOs 6.2–6.6) were performed to aid the panel in making final decisions.

The assessment of PICO 3–2022 allowed for the decision on the optimal dosing and duration of linezolid within the BPaLM/BPaL regimen and narrowed down the subsequent comparisons to the intervention regimen with this particular dose and duration of linezolid – BPaL (600 mg – 26 weeks). The justification for how the other assessments have contributed to the overall recommendation can be summarized as follows:

a. The assessment of PICO 4–2022 resulted in the conditional recommendation for use of the BPaL (600 mg – 26 weeks) regimen over the currently recommended longer regimens in patients with MDR/RR-TB and additional fluoroquinolone resistance.

b. The three assessments performed under PICO 5–2022 resulted in the conditional recommendations for the BPaL (600 mg – 26 weeks) regimen over the currently recommended 9-month regimen with ethionamide (sub-PICO 5.1), over longer regimens (sub-PICO 5.2) and over the new 9-month regimen where ethionamide is replaced with 2 months of linezolid (sub-PICO 5.3) in patients with pulmonary MDR/RR-TB without fluoroquinolone resistance.

c. The assessment of sub-PICO 6.1–2022 resulted in the conditional recommendation for use of the BPaLM regimen of the TB-PRACTECAL trial over the comparator, with the mix of SoC regimens under this trial conforming to the WHO recommendations on 9-month or longer regimens, depending on the trial site.

d. The assessments of sub-PICOs 6.4–2022 and 6.6–2022 resulted in the conditional recommendations for BPaLC and BPaL over the SoC in the TB-PRACTECAL trial; thus, all three 6-month BPaL-based regimens were assessed to be preferred over the mix of SoC regimens under this trial.

e. The assessments of sub-PICOs 6.3–2022 and 6.5–2022 resulted in the conditional recommendations for BPaLM and BPaL over BPaLC; based on these assessments, the 2022 GDG concluded that BPaLC should *not* be recommended as a regimen in the population considered. The BPaLC part of the recommendation has changed following 2025 review and is presented below (under points h. and i.).

f. The assessment of sub-PICO 6.2–2022 resulted in the conditional recommendations for BPaLM over BPaL; thus, it highlighted the use of the BPaLM regimen as the preferred regimen under the conditions specified in the recommendation and remarks. Compared with BPaL, BPaLM led to more treatment success, fewer failures or recurrences, and less emerging drug resistance, while showing little difference in AEs.

g. The assessment of PICO 2–2025 reconfirmed the review of PICO 6.6–2022 supporting the use of BPaL over the SoC regimens used in TB-PRACTECAL.

h. The assessment of PICO 3–2025 reconfirmed the review of PICO 6.4–2022 supporting the use of BPaLC over the SoC regimens used in TB-PRACTECAL.

i. The assessment of PICO 6–2025 (a, b) added a nuance to the previous review of PICO 6.5–2022, suggesting the use of BPaL in patients with non-severe pre-XDR-TB and BPaLC in patients with severe forms of pre-XDR-TB (overruling the outcomes of the review of PICO 6.5–2022 for patients with severe pre-XDR-TB).

Table 2.5. PICO questions and decisions of the GDG panels (2022 and 2025)

No.	PICO	Population	Intervention	Comparator [data source]	Sub-PICO	Recommendation direction
3–2022	Should BPaL regimens with lower linezolid exposure (dose or duration) be used instead of the original BPaL regimen in patients who are eligible for BPaL regimen?	MDR/RR-TB or pre-XDR-TB	BPaL (1 200 mg – 9 weeks)	BPaL 1200–26 [ZeNix][a]	3.2	Conditional against the intervention
			BPaL (600 mg – 26 weeks)		3.3	Conditional for the intervention
			BPaL (600 mg – 9 weeks)		3.4	Conditional against the intervention
			BPaL (600 mg then 300 mg)		3.5	No recommendation because the panel felt that comparison of data from different trials was less reliable and indirect
4–2022	Should a 6-month regimen using bedaquiline, pretomanid and linezolid be used in patients with pulmonary pre-XDR-TB (MDR/RR-TB with fluoroquinolone resistance)?	Pre-XDR-TB	BPaL (600 mg – 26 weeks) (data from FQ-res only)	Longer regimens [IPD][b]	4.1	Conditional for the intervention
5–2022	Should a 6-month regimen using bedaquiline, pretomanid and linezolid be used in patients with pulmonary MDR/RR-TB and without fluoroquinolone resistance?	MDR/RR-TB	BPaL (600 mg – 26 weeks) (data from FQ-res and FQ-susc)	9-month (Eto)	5.1	Conditional for the intervention
				Longer regimens [IPD][b]	5.2	Conditional for the intervention
				9-month (Lzd)	5.3	Conditional for the intervention

No.	PICO	Population	Intervention	Comparator [data source]	Sub-PICO	Recommendation direction
6–2022	Should a 6-month regimen using bedaquiline, pretomanid and linezolid with or without addition of moxifloxacin (BPaLM) or clofazimine (BPaLC) be used in patients with pulmonary MDR/RR-TB (with or without fluoroquinolone resistance)?	MDR/RR-TB or pre-XDR-TB	BPaLM	Mix of 9-month and longer regimens [TB-PRACTECAL][c]	6.1	Conditional for the intervention
			BPaLM	BPaL (600 mg then 300 mg) [TB-PRACTECAL][c]	6.2	Conditional for the intervention
			BPaLM	BPaLC [TB-PRACTECAL][c]	6.3	Conditional for the intervention
			BPaLC	Mix of 9-month and longer regimens [TB-PRACTECAL][c]	6.4	Conditional for the intervention
			BPaLC	BPaL (600 mg then 300 mg) [TB-PRACTECAL][c]	6.5	Conditional against the intervention
			BPaL (600 mg then 300 mg)	Mix of 9-month and longer regimens [TB-PRACTECAL][c]	6.6	Conditional for the intervention
2–2025	Should a BPaL regimen be used in patients with pulmonary pre-XDR-TB over the TB-PRACTECAL comparator regimens?	MDR/RR-TB or pre-XDR-TB in the intervention and pre-XDR-TB in the comparator	BPaL	Mix of 9-month and longer regimens [TB-PRACTECAL][c]		Conditional for the intervention

No.	PICO	Population	Intervention	Comparator [data source]	Sub-PICO	Recommendation direction
3–2025	Should a BPaLC regimen be used in patients with pulmonary pre-XDR-TB over the TB-PRACTECAL comparator regimens?	MDR/RR-TB or pre-XDR-TB in the intervention and pre-XDR-TB in the comparator	BPaLC	Mix of 9-month and longer regimens [TB-PRACTECAL][c]		Conditional for the intervention
6a–2025	Should a BPaLC regimen be used in patients with non-severe pulmonary pre-XDR-TB over the BPaL regimen?	MDR/RR-TB or pre-XDR-TB	BPaL	BPaLC		Conditional for the intervention in patients with non-severe pre-XDR-TB disease[d]
6b–2025	Should a BPaLC regimen be used in patients with severe pulmonary pre-XDR-TB over the BPaL regimen?	MDR/RR-TB or pre-XDR-TB	BPaL	BPaLC		Conditional against the intervention in patients with severe pre-XDR-TB disease[d]

BPaL: bedaquiline, pretomanid and linezolid; BPaLC: bedaquiline, pretomanid, linezolid and clofazimine; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; Eto: ethionamide; FQ-res: fluoroquinolone resistant; FQ-susc: fluoroquinolone susceptible; GDG: Guideline Development Group; IPD: individual patient data; Lzd: linezolid; MDR/RR-TB: multidrug- or rifampicin-resistant TB; PICO: population, intervention, comparator and outcome; pre-XDR-TB: pre-extensively drug-resistant TB; TB: tuberculosis.

[a] ZeNix trial.

[b] 2021 IPD.

[c] TB-PRACTECAL trial.

[d] See definition of pre-XDR-TB disease severity.

The GDG panels (2022 and 2025) discussed the subgroups and implementation considerations, and the monitoring and evaluation and research priorities as they pertain to the summary recommendation rather than for each individual sub-PICO question.

Subgroup considerations

Children and adolescents

Children were excluded from the ZeNix trial (aged 0–13 years) and the TB-PRACTECAL trial (aged 0–14 years); therefore, no analysis specific to this subgroup of patients could be performed. All medicines in the BPaLM regimen except for pretomanid have been used in children. New data on bedaquiline has recently been reviewed and its use has been expanded to all ages (see recommendation B 2.4, B3.4 and in the *WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents (27)*). The lack of safety data on pretomanid in children aged below 14 years was the main barrier for potential extrapolation of the BPaL/M/C recommendation to the threshold of being aged below 14 years. Thus, the recommendation of the BPaL/M/C regimen applies to adults and adolescents aged 14 years and older.

People living with HIV

HIV was diagnosed in 34 of 172 (19.8%) people enrolled in the ZeNix trial. Owing to the small sample size, it was impossible to perform any stratified analyses for people living with HIV for comparisons in sub-PICO 3.2–3.5. People living with HIV were eligible for enrolment in the ZeNix trial if they had a CD4 count of more than 100 cells/mm^3 and if they were using antiretroviral medications.[31] No aspects specific to HIV status or CD4 count were given in the list of TB-PRACTECAL exclusion criteria, and people living with HIV represented 27% of those enrolled. The median CD4 count among people living with HIV was 322 (interquartile range [IQR] 217–622) across the four arms.

It is important to take drug–drug interactions into account when administering TB and HIV medications in combination; such interactions are discussed below under implementation considerations. Although some therapies are to be avoided, there are alternative antiretroviral agents that can be considered when pretomanid is used. Thus, the recommendation of the BPaL/M/C regimen applies to all people aged 14 and older regardless of HIV status, although some caution should be used when enrolling patients with CD4 counts lower than 100 cells/mm^3.

Pregnant and breastfeeding women

Pregnant and breastfeeding women were excluded from the ZeNix and TB-PRACTECAL trials owing to unknown effects of the new medicine, pretomanid, on fetal development; therefore, no analysis specific to this subgroup of patients could be performed. The use of bedaquiline in pregnancy has been associated with infants born with a lower mean birth weight than infants whose mothers did not take bedaquiline; however, when infants were followed up over time, no evidence of late adverse impacts was found (see Section 3). Breastfeeding is not recommended for women taking pretomanid *(48)*. Thus, the recommendation of the BPaL/M/C regimen does not apply to pregnant and breastfeeding women. Although the safety of pretomanid during pregnancy and breastfeeding is unclear, other treatment options need to be used.

[31] In the ZeNix trial, permitted antiretroviral treatments were nevirapine in combination with any nucleoside reverse transcriptase inhibitors (NRTIs); lopinavir/ritonavir in combination with any NRTIs; tenofovir/lamivudine/abacavir (if normal renal function); triple NRTI therapy consisting of zidovudine, lamivudine and abacavir (noting the increased risk of peripheral nerve toxicity with zidovudine and linezolid); and raltegravir in combination with NRTIs.

Extrapulmonary TB

Patients with extrapulmonary TB were excluded from the ZeNix and TB-PRACTECAL trials; therefore, no analysis specific to this subgroup of patients could be performed. The available data on the CNS penetration of bedaquiline or pretomanid are limited. Although all forms of extrapulmonary TB were excluded from the clinical trials, the 2022 GDG felt that extrapolation to extrapulmonary TB and other forms of TB was warranted except in cases involving severe forms of TB that may require special treatment arrangements and decisions, particularly TB involving the CNS, and osteoarticular and disseminated forms of TB with multiorgan involvement. Thus, the recommendation of the BPaL/M/C regimen applies to people with pulmonary TB and all forms of extrapulmonary TB, except for TB involving the CNS, and osteoarticular and disseminated forms of TB with multiorgan involvement.

Implementation considerations

High treatment success rates shown for the BPaLM and BPaL regimens in the Nix-TB study and in the ZeNix and TB-PRACTECAL trials, and favourable comparison with the current SoC regimens, led to thorough discussions during the 2022 GDG meeting of an overall recommendation for implementation under routine programmatic conditions and of the implementation considerations for this regimen. Given that this recommendation is conditional, the results of additional or ongoing operational research will help to add further knowledge that can be used to adjust and improve implementation guidance for the regimen.

In 2025, following the review of the additional evidence on BPaL and BPaLC, the 2025 GDG concluded by recommending the BPaLC regimen in patients with severe pulmonary pre-XDR-TB, and the use of BPaL in patients with non-severe pre-XDR-TB disease.

Patient selection

Overall, to reproduce the treatment success rates observed in the ZeNix and TB-PRACTECAL trials, it is important to carefully select eligible patients. Once those patients are enrolled, it is also important to provide effective patient support to enable adherence to treatment. It is also important to maintain close monitoring for AEs, response to treatment and emerging drug resistance, and to properly manage adverse drug reactions and prevent complications from drug–drug interactions.

The selection of patients is best aligned with the eligibility criteria of two trials (also reflected in the subgroup consideration above). The patients that can be enrolled on the BPaL/M/C regimen should have bacteriologically confirmed MDR/RR-TB, with or without resistance to fluoroquinolones.

Drug susceptibility testing

It is important to pay attention to the previous use and susceptibility status of the medicines comprising this regimen. Patients with a known history of more than 1 month use of bedaquiline, pretomanid (or delamanid, given some degree of cross-resistance) and linezolid should not be enrolled on this regimen, unless the results of recent DST of these medicines has confirmed susceptibility. In cases where there is no prior use of these medicines or confirmed susceptibility, fluoroquinolone-susceptibility testing should also be done before the start of treatment. However, fluoroquinolone-susceptibility testing should not delay treatment initiation (e.g. in cases where this DST is not available or results are delayed). When DST results confirm fluoroquinolone susceptibility, treatment can be continued without any modifications.

In cases of fluoroquinolone resistance and severe pulmonary disease, moxifloxacin may be replaced by clofazimine and the regimen continued as the BPaLC combination. Severity in pulmonary pre-XDR-TB for this regimen selection is defined by either the presence of cavitary lesions on chest radiography and high bacillary load – shown by sputum smear results of 1+ or higher

positivity, or smear results of 2+ or higher (or an equivalent result on WHO-recommended molecular tests) – even when cavities are not present or in the absence of chest radiography results.

In cases of fluoroquinolone resistance and non-severe pulmonary disease, moxifloxacin should be ceased and the regimen continued as the BPaL combination only. This modification may seem counterintuitive, because patients with TB that is resistant to an increased number of drugs will receive fewer TB medicines. However, moxifloxacin is unlikely to provide a benefit in the presence of fluoroquinolone resistance, and the BPaL regimen has been shown to have high efficacy without moxifloxacin. In the context of fluoroquinolone resistance, omitting moxifloxacin will help to avoid potential toxicity related to this medicine. Conversely, in the absence of fluoroquinolone resistance, the use of moxifloxacin further increases the efficacy of the regimen and may provide protection against acquired bedaquiline resistance, and thus is recommended. If fluoroquinolone DST results are unavailable, the 2025 GDG) judged the likely benefits of retaining moxifloxacin as part of the regimen as outweighing the potential harms; therefore, WHO suggests using the BPaLM regimen in this situation.

The establishment and strengthening of DST services is a vital consideration for implementation of all treatment regimens for MDR/RR-TB. In patients with bacteriologically confirmed MDR/RR-TB, the Xpert® MTB/XDR (Cepheid) or GenoType® MTBDR*sl* (Hain Lifescience) assays may be used as the initial test, in place of culture and phenotypic DST, to detect resistance to fluoroquinolones *(49, 50)*. WHO has recently endorsed the use of targeted next-generation sequencing (NGS) for the detection of drug resistance, as outlined in the third edition of *WHO consolidated guidelines on tuberculosis. Module 3: Diagnosis – rapid diagnostics for tuberculosis detection (51)*. Targeted NGS involves amplifying specific genes and then using sequencing technology to identify resistance markers to multiple drugs in one test. This method can scrutinize entire genes for mutations linked to resistance, potentially offering greater accuracy than other molecular tests recommended by WHO. It is particularly useful for detecting resistance to three drugs in the BPaLM regimen: bedaquiline, linezolid and moxifloxacin. For pretomanid, the fourth drug in this regimen, new DST criteria have been set. Countries implementing programmes to manage DR-TB should develop laboratory infrastructure to perform culture-based phenotypic DST for drugs used in the treatment of MDR/RR-TB, where reliable methods exist (e.g. bedaquiline, linezolid, pretomanid, cycloserine, clofazimine and delamanid). Additionally, the latest guidelines include a new molecular test for pyrazinamide, which should simplify its testing process *(51)*.

Currently, there is limited capacity globally for DST for bedaquiline and linezolid. As these medicines and the regimens containing these medicines become more widely used, laboratory capacity in this area must be strengthened. National and reference laboratories will need to have the necessary facilities and reagents to make DST available; also, they will need data on the minimum inhibitory concentration (MIC) distribution of all *M. tuberculosis* lineages that are circulating globally. Establishing or expanding capacity for *M. tuberculosis* sequencing can provide a strong, future-proof platform for DST. If resistance to any of the component medicines in the BPaL regimen is detected, treatment with an alternative recommended regimen should be initiated. The WHO TB Supranational Reference Laboratory Network (SRLN) is available to support national TB reference laboratories in performing quality-assured DST. A WHO technical consultation established critical concentrations for DST for the fluoroquinolones, bedaquiline, delamanid, clofazimine, pretomanid and linezolid *(51, 52)*. When methods for DST are available, countries will need to add surveillance of resistance to new medicines to their routine efforts or surveys. These data can guide the adoption and use of new regimens, and protect against the amplification of resistance profiles.

Drug–drug interactions

It is important to take drug–drug interactions into account when administering TB and HIV medications in combination, including the documented interactions between bedaquiline and efavirenz *(53)*. The non-NRTI efavirenz is contraindicated with bedaquiline. Efavirenz reduces pretomanid exposures

significantly; therefore, an alternative antiretroviral agent should be considered for use together with the BPaL/M/C regimen *(48)*. The NRTI zidovudine should be avoided because of the overlapping toxicity of myelosuppression. The preferred ART regimens for co-administration with BPaL/M/C are dolutegravir-based regimens in combination with two nucleoside reverse transcriptase inhibitors (NRTIs).

Other considerations

Several other groups of patients were excluded from the two trials; for example, patients with liver enzyme measurements three or more times over the upper limit of normal; people with a corrected QT interval by Fredericia (QTcF) of more than 500 ms, or a history of cardiac disease, syncopal episodes, significant arrythmias, congenital QT prolongation, torsade de pointes or cardiomyopathy; those with a current peripheral neuropathy of Grade 3–4; and moribund patients with very low BMI (<17). These groups of patients may only receive the regimen if the treating physician judges that it is the best option, despite these contraindications, and where adequate monitoring is available.

Regimen composition, dosing of component medicines and frequency

The BPaL/M/C regimen comprises bedaquiline, pretomanid and linezolid, with or without moxifloxacin or clofazimine, throughout the regimen duration. Pretomanid is administered at 200 mg once daily for the duration of the regimen. When moxifloxacin is part of the regimen, it is dosed at 400 mg once daily throughout the treatment course. When clofazimine is part of the regimen, it is dosed at 100 mg once daily throughout the treatment course. The fluoroquinolone of choice used in the TB-PRACTECAL trial was moxifloxacin; given that no evidence on using other fluoroquinolones was available at the time of the GDG (2022 and 2025) assessments, the replacement of moxifloxacin with levofloxacin or any other fluoroquinolone cannot be recommended at this stage. New evidence on the use of levofloxacin instead of moxifloxacin may emerge from the countrywide programmatic implementation of BPaLLfx in South Africa. The frequency of dosing should be 7 days a week with treatment support or video-supported therapy; that is, as it was administered in both the trials.

Bedaquiline dosing schemes

The TB-PRACTECAL and ZeNix trials used slightly different dosing schemes for bedaquiline, although the overall drug exposure was comparable *(33)*. The dosing schedule used in the TB-PRACTECAL trial was consistent with the product label, whereas the dosing schedule used in the ZeNix trial presented the advantage of daily dosing throughout the regimen and may be used as one of the options for administration. Either of the bedaquiline dosing schemes may be used for programmatic implementation:

- daily throughout treatment: 200 mg once daily for 8 weeks followed by 100 mg once daily; or
- daily for loading dose and three times per week thereafter: 400 mg once daily for 2 weeks followed by 200 mg three times per week.

Dosing of linezolid

The ZeNix trial used several different dosing and duration schemes of linezolid, with the aim of determining the optimal administration schedule for this medicine. Linezolid is known to cause several potentially serious adverse effects; among those of most concern are peripheral neuropathy, optic neuritis and myelosuppression *(54)*. The 2022 GDG) review of the ZeNix trial data identified the optimal dosing for linezolid to be 600 mg once a day for 26 weeks, and this arm of the ZeNix trial was used for the main comparisons. Study participants in this arm of the trial received 600 mg of linezolid once daily for 26 weeks, with a reduction to 300 mg daily allowed in the event of linezolid-specific toxicities. In the TB-PRACTECAL trial, dosing of linezolid was slightly different – participants

were given 600 mg daily for 16 weeks and then 300 mg daily for the remaining 8 weeks (the duration of BPaLM in this trial was 24 weeks).

The 2022 GDG panel considered that it would be preferable to use linezolid 600 mg daily throughout the regimen, but the dose can be reduced to 300 mg daily if necessary to mitigate toxicity.

Regimen duration, changes and extensions

The BPaLM, BPaLC and BPaL regimens have been studied as the standardized courses of treatment. Therefore, modification of the regimen through early discontinuation or replacement of any of the component medicines may result in different (and possibly worse) treatment outcomes. In the TB-PRACTECAL trial, patients received 24 weeks of BPaLM and BPaLC. In the ZeNix trial, treatment was extended to a total of 9 months in patients on the BPaL regimen who remained sputum culture positive or who reverted to being sputum culture positive between months 4 and 6, or whose clinical condition suggested they may have progressive TB. In cases where treatment was interrupted and treatment duration was extended to make up for missed doses, it was necessary for patients to complete 6 months of the regimen (i.e. 26 weeks of prescribed doses) within 8 months; also, for patients in whom treatment was extended, it was necessary to complete 9 months of treatment (i.e. 39 weeks of prescribed doses) within 12 months.

Eligible patients with susceptibility to fluoroquinolones can be started on the BPaLM regimen for 6 months, with dosing of individual medicines as described above. This combination of medicines can be continued throughout the regimen without any prolongation (unless there is a need to make up the missed doses). In cases of resistance to fluoroquinolones, the selection of the regimens between BPaL and BPaLC will depend on the disease severity based on the definition presented earlier.

When the regimen is BPaL from the start or is changed to BPaL, it can be extended to a total of 39 weeks (counting from the start of the therapy with BPaLM/BPaL). This extension is justified in cases of failure to convert culture or reverted to culture positive between months 4 and 6 while on treatment; alternatively, it can be based on the clinical judgement of the treating physician. Up to 1 month can be added to the overall treatment duration if there is a need to make up the missed doses.

The 2022 GDG panel acknowledged these slight differences in the treatment duration of the BPaLM and BPaL regimens as studied in these two trials, and suggested standardizing the treatment duration of BPaLM to 6 months (26 weeks) during programmatic implementation; for BPaL they suggested the possibility of extension to a total of 9 months (39 weeks) if sputum cultures are positive between months 4 and 6. All medicines in the regimen are to be used throughout treatment duration, including a potential extension from 26 to 39 weeks (when BPaL is used). Where possible, missing doses of all three or four drugs in the regimen should be avoided; however, if doses are missed, any interruption of longer than 7 days should be made up by extending the treatment duration (for the number of missed doses); therefore, in such cases, 26 or 39 weeks of prescribed doses should be completed within an overall period of 7 or 10 months, respectively.

Missing doses and tolerances for treatment interruptions

The TB-PRACTECAL and ZeNix trials used different tolerances for treatment interruption and missing doses, and the ZeNix trial protocol provided specific rules for linezolid administration.

The 2022 GDG panel suggested standardizing the allowable missing doses and the approach to linezolid administration. The following pragmatic approach is suggested to guide clinical judgement and potential minor deviations in individual cases:

- all possible efforts should be made to support the patient and manage the AEs to ensure uninterrupted treatment and intake of all medicines in the regimen; however, when medicine cannot be tolerated it should be stopped (with potential implications for the whole regimen);

- consecutive treatment interruption (of all medicines in the regimen) of up to 2 weeks should be made up and added to the treatment duration;
- non-consecutive missed doses of all medicines in the regimen up to a cumulative total of 4 weeks should be made up and added to the treatment duration; and
- after consecutive administration of linezolid at recommended doses (600 mg daily) for at least 9 weeks, in case of intolerability the dose can either be adjusted down (to linezolid 300 mg daily) or omitted (while other medicines in the regimen are continued) for a maximum total of 8 weeks throughout the treatment course.

In case any single one of these tolerances is exceeded, a thorough assessment of the patient's status will be required to decide whether to continue the treatment strategy or modify it.

Recommendation B1.2 The 6-month bedaquiline, delamanid, linezolid, levofloxacin and clofazimine (BDLLfx/C) regimen

No.	Recommendation
B1.2	WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, delamanid, linezolid, levofloxacin and clofazimine (BDLLfx/C) in MDR/RR-TB patients with or without fluoroquinolone resistance (**UPDATED**). *(Conditional recommendation, very low certainty of evidence)*
B1.2a	WHO suggests the use of a 6-month BDLC regimen in patients with non-severe pulmonary pre-XDR-TB (see remarks) over the currently recommended longer (18 months or longer) regimens (**NEW**). *(Conditional recommendation, very low certainty of evidence)*
B1.2b	WHO suggests against using the 6-month BDLC regimen in patients with severe pulmonary pre-XDR-TB (see remarks) compared to the currently recommended longer regimens (18 months or longer) (**NEW**). *(Conditional recommendation, very low certainty of evidence)*

Remarks

- Drug susceptibility testing (DST) for fluoroquinolones is strongly encouraged in people with MDR/RR-TB. Although DST should not delay the initiation of the BDLLfx/C regimen, the test results should guide the decision on whether levofloxacin or clofazimine should be retained.
- This recommendation applies to the following:
  - people with MDR/RR-TB or people with non-severe forms of pre-XDR-TB (i.e. MDR/RR-TB and resistance to fluoroquinolones);
  - patients with less than 1 month of previous exposure to bedaquiline, linezolid, delamanid or clofazimine. When exposure is greater than 1 month, these patients may still receive the regimen if resistance to the specific medicines involved in such exposure has been ruled out;
  - people with diagnosed pulmonary TB of all ages, including children, adolescents, people living with HIV, and pregnant and breastfeeding women;
  - people with all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular TB or disseminated forms of TB with multiorgan involvement; and
  - children and adolescents who do not have bacteriological confirmation of TB or drug resistance patterns but who do have a high likelihood of MDR/RR-TB (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB).
- When resistance to fluoroquinolones is unknown, the regimen should be started as BDLLfxC and then adjusted based on the DST results. In cases of quinolone susceptibility, clofazimine should be dropped and the regimen started or continued as bedaquiline, delamanid, linezolid and levofloxacin

(BDLLfx). In people with non-severe pulmonary pre-XDR-TB, levofloxacin should be ceased and the regimen started or continued as bedaquiline, delamanid, linezolid and clofazimine (BDLC). In people with severe forms of pulmonary pre-XDR-TB, the BDLC regimen may not be used and other regimen options may need to be considered based on individual clinical and programmatic factors.

- Severity in pulmonary pre-XDR-TB for this regimen selection in adolescents and adults is defined by either the presence of cavitary lesions on chest radiography and high bacillary load shown by sputum smear results of 1+ or higher positivity, or smear results of 2+ or higher (or an equivalent result on WHO-recommended molecular tests) even when cavities are not present. In children aged below 10 years, severe pulmonary pre-XDR-TB can manifest differently and may include extensive intrathoracic lymph node disease with airway obstruction, cavitary disease, or signs of extensive pulmonary involvement on imaging and severe respiratory compromise even without cavitation. Non-severe, in this context, refers to all situations not covered by the above definition of severe pulmonary pre-XDR-TB.

Rationale

The rationale for this recommendation is based on the evidence and considerations described in detail in the two subsections below. Data from an RCT (BEAT Tuberculosis trial: NCT04062201) showed that the efficacy and safety of the BDLLfx/C regimen was similar to that of the control arm regimen (9-month or longer regimens), and offers advantages based on its shorter duration and lower pill burden than the comparators. It was judged that implementing this regimen was probably feasible and acceptable, with equity probably improved, and that implementing this regimen was probably suitable for most population groups, including pregnant and breastfeeding women, children and people living with HIV.

New evidence from the endTB-Q trial enabled meta-analysis of the two trials. The review of the meta-analysis results suggested that in people manifesting severe forms of pulmonary pre-XDR-TB, the efficacy of the BDLC regimen may be suboptimal with increased risk of amplification of drug resistance to core medicines in this regimen. Therefore, the use of BPaLC or longer (18 months) WHO-recommended regimens (depending on age-based eligibility) was suggested instead for this subgroup of patients with severe forms of pulmonary pre-XDR-TB.

Summary of evidence

This section provides the PICO questions, and the data and studies considered to answer the questions; the methods used for analysis and data synthesis; a summary of evidence on desirable and undesirable effects, and the certainty of that evidence; and a summary of other evidence considered during the recommendation's development. Additional details on the evidence are available in **Annex 5** containing the GRADE evidence summary tables and GRADE EtD tables.

PICO questions

The recommendations in this section are the result of assessments of the PICO questions below:

> ***PICO question 1–2024 (MDR/RR-TB, 2024):*** *Should a 6-month regimen using bedaquiline, delamanid and linezolid – with or without the addition of levofloxacin or clofazimine or both (BDLLfx/C) – be used in patients with pulmonary RR-TB (with or without fluoroquinolone resistance) over the currently recommended 9-month regimen (for patients without fluoroquinolone resistance) or an individualized long regimen (for patients with fluoroquinolone resistance)?*
>
> ***PICO question 1 (a; b)–2025 (MDR/RR-TB, 2025):*** *Should a BDLC regimen be used in patients with pulmonary pre-XDR-TB over the longer 18-month regimens?*

Data and studies considered

The review of PICO question 1–2024 during the GDG meeting convened by WHO in June 2024 was based on the new evidence from the BEAT Tuberculosis trial in South Africa. That trial was an RCT led by the University of the Witwatersrand designed to compare the safety and efficacy of a novel regimen, BDLLfx/C, for the treatment of MDR/RR-TB or pre-XDR-TB with either a 9-month oral regimen (linezolid-containing) or a longer individualized regimen. Patient populations included in this trial were recruited based on the criteria shown in Table 2.6.

The data from the endTB-Q trial, provided to WHO in 2025, enabled a meta-analysis of evidence from both trials (BEAT Tuberculosis and endTB-Q) in response to PICO question 1–2025, which was reviewed at the GDG meeting in November 2025.

Table 2.6. High-level summary of main inclusion and exclusion criteria: BEAT Tuberculosis and endTB-Q trials

	BEAT Tuberculosis	endTB-Q
Inclusion	• Male or female, aged 6 years or older, including breastfeeding and pregnant women • Weigh more than or equal to 16 kg • Participants above the age of 12 years must have confirmed pulmonary TB with initial laboratory result of resistance to at least rifampicin as confirmed by genotypic or phenotypic susceptibility testing in the past 3 months • Participants between the ages of 6 and 12 years must have either confirmed pulmonary RR-TB or probable pulmonary RR-TB, and the referring clinician or investigator has decided to treat the child for RR-TB • Participants who are pregnant should have an ultrasound done to confirm a viable intrauterine pregnancy before enrolment • People willing to have an HIV test and, if positive, willing to be treated with appropriate ART	• Male or female, aged 15 years or older • Weigh more than or equal to 16 kg • Diagnosed with pulmonary TB. Documented or probable resistance to rifampicin and fluoroquinolones (pre-XDR-TB) by WHO-endorsed rapid molecular tests. Inconclusive rapid molecular fluoroquinolone results were sufficient for enrolment in specific high-prevalence areas (India and Pakistan). • Inclusion was irrespective of HIV serostatus or CD4 lymphocyte count

	BEAT Tuberculosis	endTB-Q
Exclusion	• Had taken more than 28 days, but less than 24 weeks, of second-line TB drugs including bedaquiline, linezolid, clofazimine, FQs or delamanid • Has complicated or severe extrapulmonary manifestations of TB, including osteoarticular, pericardial and CNS infection, as per the investigator's opinion • Has a QTcF interval of >480 ms. Has clinically significant ECG abnormality in the opinion of the site investigator within 60 days before entry, including but not limited to second or third-degree atrioventricular block or clinically important arrhythmia. • Participants with the following laboratory abnormality at screening (please note: these investigations may be repeated if abnormal, provided the results are available within the screening period): – haemoglobin level of <8.0 g/dL – platelet count <75 000/mm^3 – absolute neutrophil count <1000/mm^3 – an estimated creatinine clearance <30 mL/min as calculated by the National Health Laboratory Service equation – alanine aminotransferase ≥3 × ULN – total bilirubin Grade 3 or greater (>2.0 × ULN, or >1.50 × ULN when accompanied by any increase in other liver function test) – serum potassium <3.2 mmol/L	• Pregnancy or breastfeeding • Previous exposure (≥30 days) to any drug in the study regimen (bedaquiline, delamanid, linezolid or clofazimine) • Resistance to any drug in the study regimen • Treatment for 15 days or longer with any second-line antituberculosis drug during the current episode • QTcF interval ≥450 ms (Grade 1 or higher) or other cardiac risk factors for arrhythmia • Participants with the following laboratory abnormalities at screening: – low haemoglobin (Grade 3 or higher) – elevated liver enzymes (Grade 2 or higher) or bilirubin (Grade 3 or higher) – uncorrectable electrolyte disorders (hypocalcaemia, hypomagnesaemia, hypokalaemia or hyperkalaemia) – serum creatinine (Grade 3 or higher)

ART: antiretroviral therapy; CNS: central nervous system; ECG: electrocardiogram; FQ: fluoroquinolone; HIV: human immunodeficiency virus; pre-XDR-TB: pre-extensively drug-resistant TB; RR-TB: rifampicin-resistant TB; QTcF: corrected QT interval by Fredericia; TB: tuberculosis; ULN: upper limit of normal; WHO: World Health Organization.

BEAT Tuberculosis trial

The BEAT Tuberculosis trial was an open-label, Phase 3, non-inferiority RCT designed to establish the efficacy and safety of a regimen comprising 6 months (24 weeks) of bedaquiline (B), delamanid (D) and linezolid (L), with levofloxacin (Lfx) and clofazimine (C), compared with the current South African SoC for the treatment of MDR/RR-TB or pre-XDR-TB.

The objectives of the trial were to compare the proportion of participants with a successful outcome at the end of treatment and the end of follow-up at 76 weeks after randomization on the study regimen with the proportion of participants having a successful outcome on the control regimen, and to compare the proportion of participants who experienced Grade 3 or more significant AEs during treatment.

Eligible participants aged between 6 and 12 years diagnosed with confirmed or probable pulmonary RR-TB and aged above 12 years with confirmed RR-TB were randomized to receive either the experimental or SoC regimen. All participants were followed up for 76 weeks from randomization.

The trial used a treatment strategy in which either levofloxacin or clofazimine was dropped from the regimen depending on fluoroquinolone DST results: BDLLfxC was initiated without delay in the case of unknown fluoroquinolone resistance at the time of RR-TB diagnosis (and continued with both levofloxacin and clofazimine if fluoroquinolone DST results could not be obtained); or BDLLfx was continued for fluoroquinolone-susceptible TB; or BDLC for fluoroquinolone-resistant TB. Within the trial, outcomes with this treatment strategy were compared with outcomes with the recommended all-oral, bedaquiline-containing 9-month or longer regimens (most of the control group received a 9-month linezolid-containing regimen). The dataset included patients with severe TB disease, people living with HIV, children aged 8 years and older, adolescents, and a small group of pregnant and breastfeeding women. The regimen could be given for 6 months or extended to 9 months if there was no clinical or bacteriological improvement.

The control group included participants on the WHO-recommended 9-month regimen with 2 months of linezolid (the SoC in South Africa at the time), and fewer patients on the longer individualized regimens designed for patients with pre-XDR-TB.

endTB-Q trial

This was an open-label, Phase 3, non-inferiority RCT designed to evaluate the efficacy and safety of an all-oral, stratified, shortened regimen of bedaquiline, delamanid, linezolid and clofazimine compared with the WHO-recommended longer SoC for patients with pre-XDR-TB.

The primary objective of the trial was to compare the proportion of participants with a favourable outcome – defined as negative cultures or favourable bacteriological, radiological and clinical evolution – at week 73 after randomization in the modified intention-to-treat (mITT) and per-protocol populations. Safety outcomes assessed at weeks 73 and 104 included the proportion of participants experiencing Grade 3 or higher AEs, serious AEs, death or discontinuation of study drugs because of toxicity.

Eligible participants were male and female patients aged 15 years and older with pulmonary TB and documented or probable resistance to rifampicin and fluoroquinolones. Participants were randomly assigned (2:1) to either the experimental BDLC group or the control group receiving an individualized WHO-recommended longer SoC. All participants were followed up until the final participant reached week 73 after randomization, with a maximum follow-up of 104 weeks.

The trial used a stratified medicine approach where the duration of the BDLC regimen was assigned based on baseline disease extent and microbiological response: participants with limited disease received a 6-month (24-week) regimen, while those with extensive disease or delayed culture conversion (positive at 8 weeks or later) received a 9-month (39-week) regimen. Outcomes in the BDLC group were compared against the SoC, which consisted of individualized regimens administered for 18 months in accordance with WHO guidelines for pre-XDR-TB. The dataset included patients with various comorbidities, including those living with HIV, diabetes, and hepatitis B or C, as well as adolescents aged 15–18 years.

The control group received individualized regimens that initially included four to six drugs; most participants (91%) received a core regimen of BDLC plus one or more other drugs, with a median treatment duration of 78 weeks. Individualized control regimens commonly included bedaquiline, clofazimine, linezolid, cycloserine and delamanid.

Methods used for analysis and data synthesis

Descriptive analyses of the baseline characteristics of participants in the study were performed. Characteristics included demographics, pregnancy status, laboratory parameters (e.g. HIV status and CD4 count, if applicable), drug susceptibility tests and diagnostic test results, TB treatment received before randomization, AEs and treatment regimens, and end-of-treatment and end-of-follow-up outcomes.

Statistical analyses were based on the WHO treatment outcome definitions listed in Annex 2, slightly modified for use in a clinical trial that included post-treatment follow-up to 76 weeks after randomization (see Table 2.7). The study team performed the analyses and presented them to the WHO panel. For the end-of-follow-up outcome measured at 76 weeks after initiation of treatment, a successful outcome was defined as follows:

- Cured – culture negative at the end of follow-up or culture negative when last seen, if the participant was lost before the end of follow-up and provided that the person had a successful treatment outcome at the last study visit attended.

For the end-of-follow-up outcome measured at 76 weeks after initiation of treatment, an unsuccessful outcome was defined as one of the following:

- Recurrence – two consecutive positive cultures separated by at least 14 days, or one positive culture after confirmed culture conversion with clinical signs and symptoms of TB, or no improvement or worsening of radiological changes since baseline. An isolated positive smear or culture without clinical or radiographic deterioration after treatment completion provides insufficient evidence to define recurrent TB.
- Death (from any cause) during follow-up.
- LTFU with clinical signs or symptoms of TB (or both) when last seen, or sputum culture positive when last seen, or not sputum culture negative and with clinical signs and symptoms of TB when last seen.

For the primary analysis, a successful outcome was required at the end of treatment and at the end of follow-up.

If treatment was modified or extended for participants allocated to either strategy, those people may still have been on treatment at the final follow-up visit 76 weeks after randomization. In this situation, for the primary efficacy outcome classification, the end-of-treatment outcome was defined at this time point (or the last participant visit while on treatment) and the end-of-follow-up outcome was considered to be the same as the end-of-treatment outcome.

The primary safety endpoint was the incidence of all treatment-emergent AEs of Grade 3 or higher, using the Division of AIDS (DAIDS) table for grading the severity of adult and paediatric AEs by treatment arm and up to 30 days following the end of treatment. Serious AEs were collected until the end of the follow-up.

Table 2.7. Cross-tabulation of outcomes from the BEAT Tuberculosis and endTB-Q trials and WHO outcomes

BEAT Tuberculosis trial outcomes	WHO Week 76 outcomes					
	Sustained treatment success	Not sustained treatment success				
		Failure or recurrence	Death[b]	LTFU	Withdrawn consent	Total
Favourable[a]	346					346
Unfavourable		31	17	6	2	56
On treatment			11			
Death						
LTFU on treatment				6		
Treatment failure (no culture conversion or reversion)		17				
Post-treatment						
Death			6			
Recurrence		14				
Withdrawn consent during treatment					2	
Withdrawn consent before treatment					1	
Total started treatment	346	31	17	6	2	402
Total	346	31	17	6	3	403

endTB-Q trial outcomes	WHO Week 76 outcomes					
	Sustained treatment success	Not sustained treatment success				
		Failure or recurrence	Death[b]	LTFU	Withdrawn consent	Total
Favourable[a]	216					216
Unfavourable		19	6	1	5	31
On treatment Death			5			5
LTFU on treatment				1		1
Treatment failure (no culture conversion or reversion)		12				12
Post-treatment						
Death			1			1
Recurrence		7				7
Withdrawn consent					5	5
Total	216	19	6	1	5	247

LTFU: loss to follow-up; TB: tuberculosis; WHO: World Health Organization.

[a] Culture negative at week 76 or cured at the end of treatment, culture negative when last seen with no symptoms of TB.

[b] A total of 20 deaths occurred during the study period, including 14 during treatment and six after completion of treatment. In the BEAT Tuberculosis trial primary outcome analysis, outcomes were classified according to the predefined efficacy outcome framework, which prioritizes the event that occurred first where a participant experiences more than one event leading to an unsuccessful outcome. Consequently, two participants who died after experiencing treatment failure were classified under treatment failure rather than death, and one participant who died after completing study follow-up was classified as having a successful efficacy outcome, having met all microbiological criteria. These three participants are included in the overall count of deaths but are not classified under death categories in the primary outcome table.

Meta-analysis using data from the BEAT Tuberculosis and endTB-Q trials was conducted for PICO question 1 (a; b)–2025 (MDR/RR-TB, 2025): "Should a BDLC regimen be used in patients with pulmonary pre-XDR-TB over the longer 18-month regimens?"

Given that only two trials were included, estimates of between-trial variability from a random-effects model were considered unreliable. Therefore, a fixed effect term for trial was included to account for differences in baseline risk of the outcome across trials. The primary approach to adjusting for baseline severity involved the direct inclusion of smear status and chest radiography findings (including cavitation or the extent of disease when available) as covariates. In addition, a classification model developed from the endTB-Q trial, which stratified patients by severity, was used to predict severity across both trials. Predicted severity was included as a covariate in exploratory analyses where appropriate.

Estimation of risk measures. Adjusted RRs were estimated using modified Poisson regression. Robust standard errors were calculated using the sandwich estimator. Adjusted RDs were estimated using a

generalized linear model with a binomial distribution and identity link, or via marginal standardization following logistic regression, depending on model convergence. Unadjusted RRs and RDs were calculated to assess the impact of covariate adjustment. CIs for unadjusted estimates were calculated using the score method.

Improving precision. To enhance the precision of effect estimates, analyses were adjusted for strong baseline predictors and stratification factors. Candidate variables for adjustment included HIV status and ART information, including drug interactions, smear status, chest radiography findings (e.g. presence of cavities or extent of disease where available), age, BMI, diabetes status, smoking status, sex and history of past treatment. Final inclusion of covariates was guided by data completeness, sample size and collinearity assessment. Non-linearity in continuous confounders (e.g. age) was evaluated and, where appropriate, modelled using simple non-linear terms, including lower-order fractional polynomials or restricted cubic splines with few knots to minimize the risk of overfitting.

Multiple imputation was employed to address missing data in explanatory variables, using predictive mean matching for continuous covariates and logistic regression for binary covariates. When "missingness" across all covariates was less than 20%, primary outcomes were reported using imputed data. When missingness exceeded 20% for any covariate, or when concerns arose about the missing-at-random assumption, three approaches were compared: multiple imputation for missing values, complete case analysis for covariates of concern, and exclusion of the covariate from the adjustment set.

When these methods produced qualitatively similar effect sizes, CIs and *P*-values, results from multiple imputation were presented for the primary outcomes. When results differed qualitatively, the method used for reporting the primary outcome was selected on a case-by-case basis, with a rationale provided. Results from alternative methods were included in the annexes.

Decision thresholds

A more structured method for determining the magnitude of the health effects was initiated in 2025. It involves using a triangulation approach to develop outcome-specific DTs for judging the magnitude of the effects for the following health outcomes: death, sustained treatment success, treatment failure or recurrence, LTFU, AEs and amplification of drug resistance. GDG members deemed these outcomes to be critical or important for decision-making based on a prioritization survey using the GRADE approach. The survey included health outcome descriptors that had previously been developed for each of the health outcomes, to facilitate the GDG's understanding of the outcomes during the decision-making process.

The GDG first reviewed judgements about the magnitude of health effects made by other GDGs for prior WHO MDR-TB guidelines *(3, 14)*, to determine approximate ranges of effect sizes that the group considered to be trivial, small, moderate or large. Members then identified a systematic review to help inform suggested health utility values for the health state of having DR-TB disease and treatment success (reported as about 0.5 and 0.9, respectively) *(36)*. For the other outcomes (treatment failure, LTFU, amplification of drug resistance and AEs), a health utility value of 0.5 was used, considering that these would be similar health states to having DR-TB disease, and to align with previous judgements made in other TB guidelines.

The group then used the empirical evidence from the GRADE-THRESHOLD trial *(37)* to calculate suggested utility-adjusted absolute effect thresholds for the health outcomes. The calculated thresholds were as follows *(38)*:

- death (health utility: 0):
  - trivial or no effect: up to 12 fewer or more deaths per 1000 people;
  - small effect: >12–34 fewer or more deaths per 1000 people;
  - moderate effect: >34–67 fewer or more deaths per 1000 people; and

  - large effect: >67 fewer or more deaths per 1000 people;
- sustained treatment success (health utility: 0.9):
  - trivial or no effect: up to 17 fewer or more treatment successes per 1000 people;
  - small effect: >17–49 fewer or more treatment successes per 1000 people;
  - moderate effect: >49–94 fewer or more treatment successes per 1000 people; and
  - large effect: ≥>4 fewer or more treatment successes per 1000 people;
- treatment failure or recurrence, LTFU, AEs and amplification (acquisition) of drug resistance (all with health utility 0.5):
  - trivial or no effect: up to 41 fewer or more failures or recurrences per 1000 people;
  - small effect: >41–107 fewer or more failures or recurrences per 1000 people;
  - moderate effect: >107–202 fewer or more failures or recurrences per 1000 people; and
  - large effect: >202 fewer or more failures or recurrences per 1000 people.

These suggested thresholds (assumed to occur over the duration of follow-up in the trials) were generally consistent with judgements that were made in the previous WHO MDR-TB guidelines *(3)*.

Finally, in preparation for the GDG meeting at which recommendations would be formulated, an online survey was administered to the group to obtain their feedback on the suggested DTs. The survey asked members to agree with the suggested thresholds, or to disagree and suggest alternative thresholds based on their expert experience. The agreed-upon thresholds were again reviewed at the start of the GDG meeting, and the group decided to use them to inform their judgements on the magnitude of health effects in the GRADE EtD frameworks. Figures were created to visually depict absolute effects and 95% CIs from the research evidence of the relevant trial in relation to the DTs for each health outcome, to facilitate the GDG's discussion and judgements about whether the health effects were trivial, small, moderate or large, and to judge the level of imprecision of estimates. The same thresholds were used to inform the group's judgements about imprecision, in line with GRADE guidance for decision-making *(39)*.

Summary of evidence on desirable and undesirable effects and certainty of evidence

The review of PICO question 1–2024 during the GDG meeting convened by WHO in June 2024 was based on the new evidence from the BEAT Tuberculosis trial in South Africa. That trial was an RCT led by the University of the Witwatersrand designed to compare the safety and efficacy of a novel regimen, BDLLfxC, for the treatment of MDR/RR-TB or pre-XDR-TB with either a 9-month oral regimen (linezolid-containing) or a longer individualized regimen.

The data from the endTB-Q trial, provided to WHO in 2025, enabled a meta-analysis of evidence from both trials (BEAT Tuberculosis and endTB-Q) in response to PICO question 1–2025, which was reviewed at the GDG meeting in November 2025.

PICO 1–2024: Should a 6-month regimen using bedaquiline, delamanid and linezolid – with or without the addition of levofloxacin or clofazimine or both (BDLLfx/C) – be used in patients with pulmonary RR-TB (with or without fluoroquinolone resistance) over the currently recommended 9-month regimen (for patients without fluoroquinolone resistance) or an individualized long regimen (for patients with fluoroquinolone resistance)?

Outcomes among patients with MDR/RR-TB with or without quinolone resistance (MDR/RR-TB or pre-XDR-TB) receiving the BDLLfx/C regimen were compared to those receiving the SoC (9–12-month) all-oral regimens with linezolid for patients with MDR/RR-TB and (18–20-month) all-oral regimens for patients with pre-XDR-TB.

Participants with MDR/RR-TB (with or without quinolone resistance) receiving the BDLLfxC regimen (*n*=202) compared to participants receiving WHO-recommended SoC regimens used in the BEAT Tuberculosis trial (*n*=200) experienced:

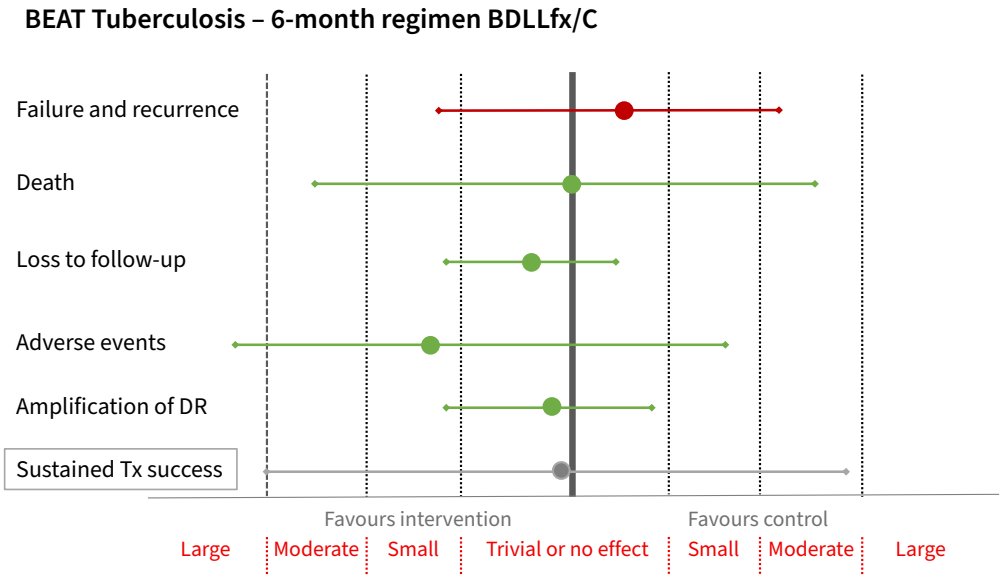
- higher levels of failure or recurrence (8.4% vs 7.0%); RD=14 more per 1000, 95% CI: 38 fewer to 66 more per 1000)
- lower levels of death: 5.0% vs 5.0%; RD= 0.5 fewer per 1000 (95% CI: from 43 fewer to 42 more per 1000);
- lower levels of LTFU: 1.0% vs 2.0%; RD= 10 fewer per 1000 (95% CI: from 34 fewer to 14 more per 1000);
- lower levels of grade 3–5 AEs: 34% vs 38%; RD=38 fewer per 1000 (95% CI: 132 fewer to 55 more per 1000); and
- lower levels of amplified resistance: 2.5% vs 3.0%; RD=5 fewer per 1000 (95% CI: 37 fewer to 27 more per 1000).

The GDG also considered the duration and pill burden of the intervention and comparator regimens. The intervention regimen is 24 weeks (5.5 months), so the treatment duration is reduced by 3–18 months compared with the control arm. The exact magnitude of reduction in time on treatment depends on the specific comparator regimen, which includes shorter (9–12 months) and longer (18–24 months) regimens. The pill burden of the intervention regimen is lower than that for the comparator regimens. The exact magnitude of reduction in pill burden depends on the specific comparator regimen.

The GDG judged the benefits of BDLLfxC to be small and the undesirable effects to be trivial compared with WHO-recommended SoC regimens. The overall certainty of evidence was very low, primarily due to imprecision in the effect estimates. Based on this, the panel determined that the balance of health effects probably favours the BDLLfxC regimen.

Fig. 2.4 visually depicts absolute effects and 95% CIs from the evidence in relation to the DTs for each health outcome, to facilitate the GDG's discussion and judgements about whether the health effects were trivial, small, moderate or large, and to judge the level of imprecision of estimates.

Fig. 2.4. Visual depiction of absolute effects in relation to the DTs used by the 2024 GDG (PICO 1–2024)



BDLLfxC: bedaquiline, delamanid, linezolid, levofloxacin and clofazimine; CI: confidence interval; DR: drug resistance; DT: decision threshold; GRADE: Grading of Recommendations Assessment, Development and Evaluation. Note: The positioning of point estimates and CIs is indicative and for illustration purposes only; exact figures are available in the GRADE evidence profiles. As indicated above in the sections on desirable and undesirable effects, DTs vary for some of the outcomes and therefore only the descriptive labels (trivial, small, moderate or large) are used for the x-axis rather than numerical values.

Conclusion

The BDLLfxC regimen is suggested over currently recommended 9-month (containing 7 drugs) or longer regimens in patients with MDR/RR-TB.

PICO 1a–2025: Should a BDLC regimen be used in patients with pulmonary pre-XDR-TB over the longer 18-month regimens (in patients with non-severe pre-XDR-TB)? (NEW)

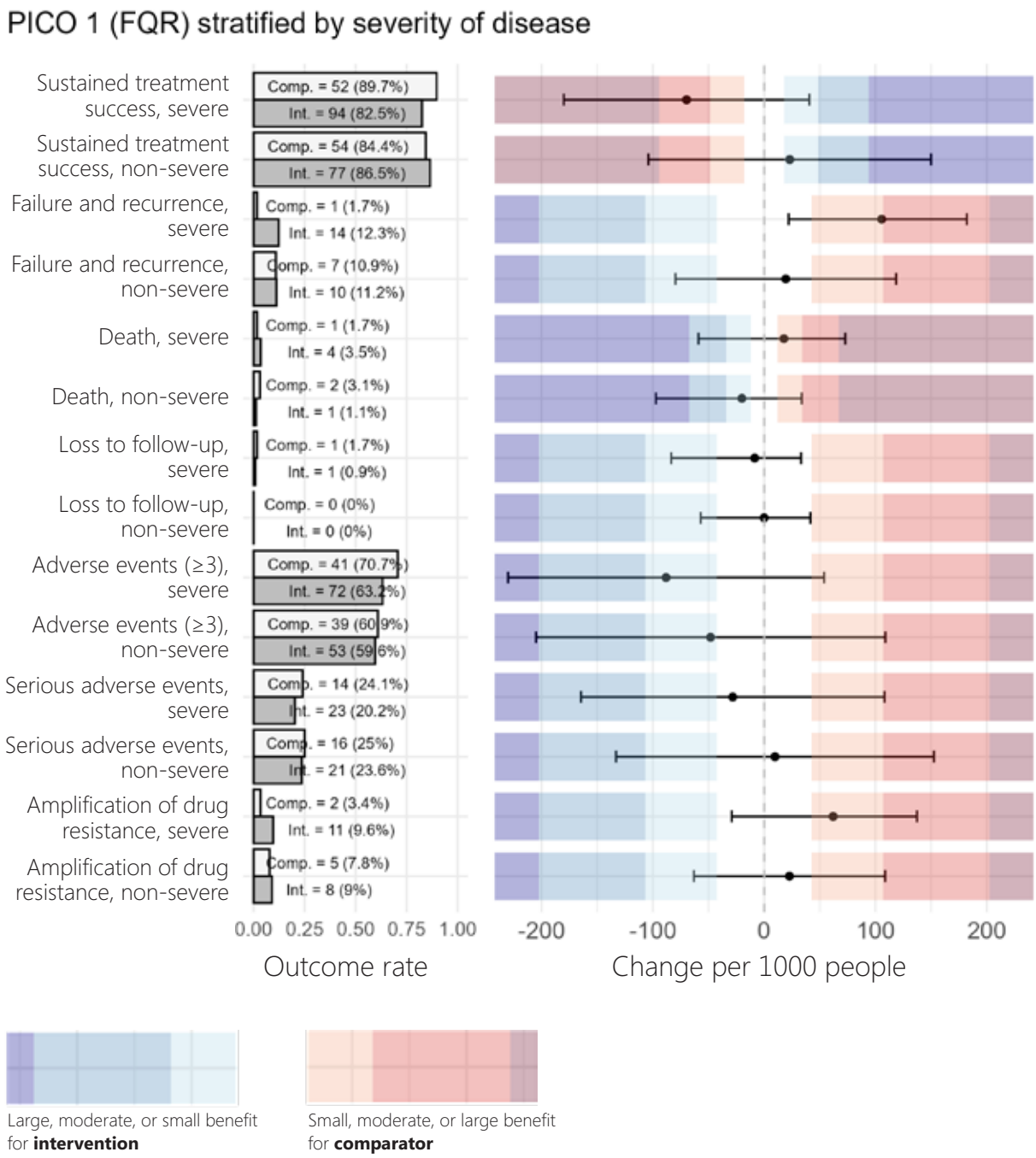
Outcomes among patients with pre-XDR-TB receiving the BDLC regimen were compared with those receiving the SoC 18–20-month all-oral regimens for patients with pre-XDR-TB used in the BEAT Tuberculosis and endTB-Q trials. Primary analysis was undertaken at 76 weeks post-treatment initiation. The patient cohort was stratified into those with non-severe and severe pre-XDR-TB.

Participants with non-severe pre-XDR-TB receiving the BDLC regimen (*n*=87) compared with participants receiving WHO-recommended SoC regimens used in the BEAT Tuberculosis and endTB-Q trials (*n*=61) experienced:

- higher levels of failure or recurrence (11.2% vs 10.9%); RD=20 more per 1000, 95% CI: 80 fewer to 119 more per 1000)
- lower levels of death: 1.1% vs 3.1%; RD= 20 fewer per 1000 (95% CI: from 97 fewer to 34 more per 1000);
- similar levels of LTFU: 0.0% vs 0.0%; RD= 0 fewer per 1000 (95% CI: from 57 fewer to 42 more per 1000);
- lower levels of Grade 3–5 AEs: 59.6% vs 60.9%; RD=48 fewer per 1000 (95% CI: 205 fewer to 109 more per 1000); and
- higher levels of amplified resistance: 9.0% vs 7.8%; RD=23 more per 1000 (95% CI: 63 fewer to 109 more per 1000).

Fig. 2.5 visually depicts absolute effects and 95% CIs from the evidence in relation to the DTs for each health outcome, to facilitate the GDG's discussion and judgements about whether the health effects were trivial, small, moderate or large, and to judge the level of imprecision of estimates.

Fig. 2.5. Visual depiction of absolute effects in relation to the DTs used by the 2025 GDG (PICO 1a–2025)



Comp.: comparator; DT: decision threshold; FQR: fluoroquinolone resistance; GDG: Guideline Development Group; Int.: intervention; PICO: population, intervention, comparator and outcomes.

In patients with non-severe pre-XDR-TB, the GDG judged the desirable effects to be small and the undesirable effects of BDLC to be trivial compared with the WHO-recommended SoC regimens used in the BEAT Tuberculosis and endTB-Q trials. The certainty of evidence was judged to be very low. The balance of health effects was judged to be in favour of BDLC, with a small net benefit in people with non-severe disease (or small net harm for longer regimens in this population), favouring the intervention (BDLC), although there was very low certainty evidence owing to indirectness and severe imprecision, in particular for the subgroup with non-severe disease.

Conclusion

The use of the 6-month treatment regimen composed of bedaquiline, delamanid, linezolid and clofazimine (BDLC) rather than the WHO-recommended SoC regimens used in the BEAT Tuberculosis and endTB-Q trials is suggested in patients with non-severe pre-XDR-TB, who have either had no previous exposure to the medicines in this regimen or have been exposed for less than 1 month.

PICO 1b–2025: Should a BDLC regimen be used in patients with pulmonary pre-XDR-TB over the longer 18-month regimens (in patients with severe pre-XDR-TB)? (NEW)

Outcomes among patients with MDR/RR-TB with quinolone resistance (pre-XDR-TB) receiving the BDLC regimen were compared to those receiving the SoC 18–20-month all-oral regimens for patients with pre-XDR-TB. Primary analysis was undertaken at 76 weeks post-treatment initiation. The patient cohort was stratified into those with non-severe and severe pre-XDR-TB.

Participants with severe pre-XDR-TB receiving the BDLC regimen (*n*=114) compared with participants receiving WHO-recommended SoC regimens used in the BEAT Tuberculosis and endTB-Q trials (*n*=58) experienced:

- higher levels of failure or recurrence (12.3% vs 1.7%); RD=106 more per 1000, 95% CI: 22 more to 182 more per 1000)
- higher levels of death: 3.5% vs 1.7%; RD= 18 more per 1000 (95% CI: from 59 fewer to 73 more per 1000);
- lower levels of LTFU: 0.9% vs 1.7%; RD= 9 fewer per 1000 (95% CI: from 84 fewer to 33 more per 1000);
- lower levels of Grade 3–5 AEs (63.2% vs 70.7%); RD=88 fewer per 1000 (95% CI: 230 fewer to 54 more per 1000); and
- higher levels of amplified resistance: 9.6% vs 3.4%; RD=62 more per 1000 (95% CI: 29 fewer to 137 more per 1000).

In patients with severe pre-XDR-TB, the GDG judged both the desirable and undesirable effects of BDLC to be small when compared with those of the WHO-recommended SoC regimens used in the BEAT Tuberculosis and endTB-Q trials. The certainty of evidence was judged to be very low. The balance of health effects was judged to favour longer regimens, supporting the comparison, although the evidence certainty was very low owing to indirectness and severe imprecision, particularly for the subgroup with non-severe disease.

Conclusion

The use of the WHO-recommended SoC regimens used in the BEAT Tuberculosis and endTB-Q trials rather than the 6-month treatment regimen composed of bedaquiline, delamanid, linezolid, and clofazimine (BDLC) is suggested in patients with severe pre-XDR-TB, who have either had no previous exposure to the medicines in this regimen or have been exposed for less than 1 month.

Summary of other evidence

Resources required and cost–effectiveness

Additional data reviewed by the GDG relevant to these PICO questions were the estimates of the regimen price provided by the Stop TB Partnership's GDF, based on the drug pricing included in the GDF online catalogue *(55)* on 20 June 2024 and 2 July 2026 (Table 2.8).

Table 2.8. Regimen cost estimates

	Regimen	Estimated regimen price (US$) 2024	Estimated regimen price (US$) 2026
BEAT Tuberculosis and endTB-Q trial regimens	6 BDLLfx (FQ-S)	1374	1078
	6 BDLC (FQ-R)	1460	1140
	6 BDLLfxC (FQ – unknown)	1479	1158
WHO-recommended regimens	6 BPaLM		305
	6 BPaL		279
	6 BPaLC		365
	9-month regimen (with Eto)	418	319
	9-month regimen (with Lzd)	396	296
	9 BLMZ		205
	9 BLLfxCZ		324
	9 BLLfxZ		1748
	Longer regimen ($18B_6$LLfxC)	632	475

BDLC: bedaquiline, delamanid, linezolid and clofazimine; BDLLfx: bedaquiline, delamanid, linezolid and levofloxacin; BDLLfxC: bedaquiline, delamanid, linezolid, levofloxacin and clofazimine; FQ: fluoroquinolones; FQ-R: FQ resistant; FQ-S: FQ susceptible; Lzd: linezolid; WHO: World Health Organization.

The GDG also considered the following example of country-specific costs (both patient-borne and health system costs) over a 3-month span (excluding drug costs), based on modelling analysis in Ryckman et al. (2024) *(56)*. Costs may vary depending on the composition of the regimen being used (Table 2.9).

Table 2.9. Patient-borne and health system costs for RR-TB

	Costs over 3 months (US$)		
Country	**Patient**	**Health system**	**Total**
India	384	87	471
Philippines	774	234	1008
South Africa	342	642	984

RR-TB: rifampicin-resistant TB; TB: tuberculosis.

The GDG noted that affordability will vary depending on country (and resources available), health system differences and the population the regimen would be used for; accordingly, they judged that costs would vary between moderate and large.

The price of delamanid is one of the major cost drivers in BDLLfxC. The drug is off-patent; hence, prices have decreased as generics have been developed (e.g. generic delamanid that became available in 2025 is priced at US$ 800 for a 6-month course). The GDG highlighted that there are costs to a longer duration of treatment (especially for patients and families, but also for the health system) – some estimates were available and discussed by the group. Considering these costs together with the drug prices may attenuate some of the increased costs for the health system and lead to cost savings from the patient perspective. However, countries looking to implement a specific treatment regimen typically focus on the drug cost. No evidence on cost–effectiveness was available.

Equity, acceptability and feasibility

When considering the impact on health equity, the panel considered the treatment duration and the ability to decentralize treatment (to enable access for remote, underserved settings and disadvantaged populations).

The GDG highlighted that health equity would probably increase in parts of the population that would have access to the shorter regimen and the medications included (e.g. pregnant women and children, and possibly other groups as well). Conversely, certain populations might not be able to afford the regimen, and there could be differences in impact on health equity among countries because of differences in availability of medications.

Despite not being able to identify relevant research evidence, the panel used their collective experience to judge that there would probably be advantages associated with the use of the BDLLfxC regimen, owing to its reduced complexity and shorter duration. The panel judged that use of the BDLLfxC regimen would probably increase equity.

When considering the acceptability of the intervention, the panel considered patients and health care providers to be key stakeholders. The GDG considered the following aspects as critical with regards to acceptability: regimen duration and drug-safety monitoring needs (relating to necessary travel, loss of income and general disruption of the life of patients; and workload for the health care system), and needs for DST. The GDG highlighted that delamanid requires taking medicines twice per day in this regimen, which may affect acceptability. The panel judged that the BDLLfxC regimen would probably be acceptable.

The GDG considered the following aspects to affect feasibility (i.e. to be potential barriers to implementation): regulatory approval of drugs in the regimen, requirements for drug-safety monitoring and requirements for DST.

BEAT Tuberculosis was a pragmatic trial. Similar intervention regimens have been given in other studies across a range of countries, increasing the likelihood that the implementation of BDLLfxC is feasible in settings beyond the trial setting in South Africa.

Approval by regulators influences the access and feasibility of implementing the regimen; also, alternative regimens are not always available. Access to some of the medications is hampered by licensing differences. For example, in USA there is no Food and Drug Administration (FDA) approval for delamanid – it is only available under compassionate use restrictions.

A few patients with low haemoglobin levels in the BEAT Tuberculosis trial received a blood transfusion before initiation of treatment; the need for this may be a limiting factor in some settings for patients with low haemoglobin levels.

Overall, given the reduced duration, complexity and associated workload, the panel judged that implementation is probably feasible.

Evidence to recommendations: considerations

Based on the decisions taken during the review and the combination of assessments described above, the new recommendation is to use the BDLLfx/C regimen rather than the 9-month or longer (18-month) regimens in MDR/RR-TB patients. The BDLLfx/C regimen is intended for use under routine programmatic conditions, which include pregnant and breastfeeding women and children aged below 14 years. However, the cost of the regimen (driven by the price of delamanid) remains a barrier to widespread adoption.

The review of the meta-analysis performed in 2025 provided an additional nuance for the group of patients with pre-XDR-TB. This evidence suggested that in patients with confirmed pre-XDR-TB and severe pulmonary TB disease, as specified in the remarks to the recommendation (see above), the use of longer, 18-month regimens or BPaLC is preferred over BDLC. In patients with non-severe pulmonary pre-XDR-TB, BDLC can be used.

Subgroup considerations

Based on research evidence and expert experience, the panel identified subpopulations who might be affected differently by this recommendation. These subpopulations were people living with HIV, children, pregnant and breastfeeding women, patients with extrapulmonary TB and patients with severe pulmonary TB disease and resistance to fluoroquinolones. The panel noted specific considerations for the subpopulations listed below.

Children and adolescents

Thirty participants aged 8–17 years with confirmed RR-TB were enrolled in the BEAT Tuberculosis trial, with 17 in the control group and 13 in the intervention group. Among them, seven (24%) had FQ resistance. One participant aged 17 years was found to have resistance to bedaquiline and clofazimine at baseline, and was switched to an individualized rescue regimen. There were three Grade 3 or 4 AEs related to linezolid (one case each of anaemia, peripheral neuropathy and optic neuritis). Delamanid was discontinued in one participant on the control arm owing to neuropsychiatric side-effects.

In addition to the trial data, all medicines in the BDLLfx/C regimen have been used in children and adolescents, have well-documented safety and efficacy profiles, and have sufficient PK and pharmacodynamic (PD) data. The recent new recommendation for the use of bedaquiline in children with MDR/RR-TB aged below 6 years was considered *(27)*. Thus, the recommendation of the BDLLfx/C regimen applies to adults, adolescents and children of any age.

In children younger than 10 years, severe pulmonary pre-XDR-TB can manifest differently and may include extensive intrathoracic lymph node disease with airway obstruction, cavitary disease, or signs of extensive pulmonary involvement on imaging and severe respiratory compromise even without cavitation. Non-severe, in this context, refers to all situations not covered by the definition of severe pulmonary pre-XDR-TB in adults.

People living with HIV

All participants of the BEAT Tuberculosis trial were required to undergo an HIV test, but their eligibility for the trial was not affected by the test result or their CD4+ count, or whether they were receiving ART at the time of randomization. The management of HIV infection followed the guidelines of the National Department of Health of South Africa. ART included either dolutegravir or a protease inhibitor to prevent drug–drug interactions, and non-NRTIs were prohibited. In BEAT Tuberculosis, 202 people living with HIV were enrolled, with 105 randomized to the study arm. The median CD4+ in this group was 168 (95% CI: 85.0, 299). No major effect of HIV status on the efficacy of the intervention regimen versus the control was observed (RD=2.1%, 95% CI: –7.9% to +12.2%). In the endTB-Q trial, the inclusion was irrespective of HIV serostatus or CD4 lymphocyte count. Thus, the recommendation for

the BDLLfx/C regimen applies to all people, regardless of HIV status or degree of immunosuppression, and it appeared preferable to the comparator.

Pregnant and breastfeeding women

The components of BDLLfx/C have been used in pregnancy in women with MDR/RR-TB. Pregnant women could be enrolled in the BEAT Tuberculosis trial in any trimester of pregnancy. Also, women who became pregnant during the trial could continue their treatment without any changes. Of the 10 pregnant women enrolled (4 to the trial regimen), all pregnancies resulted in singleton live births, with one premature delivery. One woman in the study strategy experienced a relapse. There were two severe AEs in this group, but neither were drug related.

Based on existing experience using the BDLLfx/C regimen's component drugs, the trial data and other currently recommended alternatives, the regimen is recommended for use in pregnant and breastfeeding women.

Extrapulmonary TB

Patients with complicated extrapulmonary TB involving the CNS, and osteoarticular and pericardial forms of TB were not included in the BEAT Tuberculosis or endTB-Q trials. Therefore, no specific analysis could be performed for this patient subgroup. Patients with uncomplicated extrapulmonary TB were included if they also had pulmonary TB. Thus, the recommendation for the BDLLfx/C regimen applies to people with pulmonary TB and all forms of extrapulmonary TB except for TB involving the CNS, and osteoarticular or disseminated forms of TB with multiorgan involvement.

Severe pulmonary TB disease and resistance to fluoroquinolones

Patients with DR-TB who have severe pulmonary disease face greater challenges in treatment across all regimens, and are at a higher risk of unfavourable outcomes and amplification of drug resistance. This risk is further elevated in those infected with pathogens that have advanced resistance profiles, particularly with additional resistance to fluoroquinolones. These patients may experience slightly worse outcomes compared with those without pre-XDR-TB and may develop resistance to regimen components. In the BEAT Tuberculosis trial among patients with pre-XDR-TB, the outcomes also appeared worse than among those who were fluoroquinolone susceptible. This reduction in the proportion with successful treatment outcomes was numerically greater in the BDLLfx/C arm than in the control arm (14.3% vs 3.3%); however, this difference was within the range of statistical uncertainty and the 2024 GDG judged that this should not affect the recommendation or remarks. The rate of acquisition of resistance to bedaquiline was similar between the two groups (11% in BDLLfx/C and 9.1% in control). The evidence from the BEAT Tuberculosis trial was insufficient to draw definitive conclusions owing to the small sample when stratified by fluoroquinolone resistance and related imprecision.

The review of the meta-analysis, including the data from BEAT Tuberculosis and endTB-Q trials, suggested that the use of the BDLC regimen in patients with severe pulmonary pre-XDR-TB, as defined using the endTB-Q trial definition, may not only lead to less favourable outcomes, but may also amplify resistance to bedaquiline in patients with a failure outcome. Accordingly, in patients with severe pulmonary pre-XDR-TB, alternative regimens should be considered – either longer regimens individualized to the resistance profile or the BPaLC regimen – rather than the BDLC regimen.

Implementation considerations

The high treatment success rates shown for the BDLLfx/C regimen in the BEAT Tuberculosis trial and favourable comparison with the current SoC regimens led to an overall recommendation for implementation under routine programmatic conditions. Given that this recommendation is conditional,

ongoing operational research will be needed, to add further knowledge that can be used to adjust and improve implementation guidance for the regimen *(8)*.

Patient selection

Eligibility for the BDLLfx/C regimen should generally align with the criteria outlined in the BEAT Tuberculosis trial. Patients with confirmed pre-XDR-TB and severe disease may be prescribed the BPaLC regimen or the individually designed, longer, 18-month regimen. Once patients are started on treatment, providing effective support is crucial to ensure treatment adherence. Close monitoring (for AEs, responses to treatment and developing drug resistance) is essential, as are proper management of side-effects and prevention of complications from drug–drug interactions.

Drug susceptibility testing

It is important to take a comprehensive history of prior exposure to the regimen's components and the outcomes of previous episodes of TB. Prior loss to the programme while on a bedaquiline-containing regimen, particularly if the culture is still positive when this occurs, increases the risk of developing bedaquiline resistance *(57)*.

DST for fluoroquinolones is strongly advised, although it should not delay the initiation of the BDLLfx/C. When DST results confirm fluoroquinolone susceptibility, clofazimine should be stopped, then BDLLfx can continue. When DST results confirm fluoroquinolone resistance, levofloxacin should be stopped, then BDLC can continue. If DST is not undertaken or is unavailable, then all five drugs should be given. In patients with severe pre-XDR-TB disease, the preferred regimen is either BPaLC or the longer, 18-month individually designed regimen following WHO recommendations.

There is an opportunity to improve global capacity for DST for bedaquiline, delamanid and linezolid, given that current resources are limited and no rapid molecular tests are available for these medications. Prompt treatment initiation is vital, especially for patients with no prior exposure; this is particularly relevant in countries where bedaquiline usage is low, minimizing the risk of resistance transmission. Individuals with a history of receiving bedaquiline, delamanid (or pretomanid), linezolid and clofazimine for more than a month should have recent DST results confirming susceptibility before being enrolled on the BDLLfx/C regimen. In settings where DST for bedaquiline, delamanid and linezolid can be done and resistance to any of these medicines is confirmed, the regimen should not be used.

Drug–drug interactions

It is essential to consider drug–drug interactions when administering TB and HIV medications in combination. The preferred ART regimens for co-administration with BDLLfx/C are dolutegravir-based in combination with two NRTIs. The NRTI zidovudine should be avoided because of the overlapping toxicity of myelosuppression. The non-NRTI efavirenz is contraindicated with bedaquiline. For newer agents, package inserts should be consulted.

Other considerations

There were no exclusions based on BMI. Eighty-five (42%) patients randomized to BDLLfx/C had a BMI below 18.5 g/m^2. No major effect of a low BMI was noted on the efficacy of the BDLLfx/C versus the control (RD= –4.1%, 95% CI: –16.5%, 8.3%), but the evidence is too uncertain to draw specific conclusions.

In the BEAT Tuberculosis trial patients with severe anaemia (haemoglobin <8 g/dL) could receive a transfusion before starting treatment in either group. If the person's haemoglobin levels recovered to above 8 g/dL, they could then be enrolled in the trial. In programmatic settings, if transfusion is unavailable or considered too risky, the treating physician must consider the benefit–risk profile of

starting treatment with the linezolid-containing BDLLfx/C regimen versus the 9-month treatment regimen that does not include linezolid, or a longer individualized regimen that is linezolid sparing.

Some groups of patients were excluded from the BEAT Tuberculosis trial, such as those with liver enzyme measurements three or more times over the upper limit of normal, people with a corrected QT interval by Fredericia (QTcF) of more than 480 ms, or with a current peripheral neuropathy of Grade 3–4. These groups of patients may still receive the regimen if the treating physician judges it to be the best option despite these contraindications and where adequate monitoring is available.

Regimen composition, dosing of component medicines and frequency

The dosing frequency should be 7 days a week. The BDLLfx/C regimen comprises bedaquiline, delamanid and linezolid with levofloxacin or clofazimine (or both) throughout the duration of the regimen, depending on quinolone susceptibility.

Bedaquiline dosing schemes

The dosing strategy used in the BEAT Tuberculosis and endTB-Q trials was daily as a loading dose of 400 mg for 2 weeks, then 200 mg three times weekly for the remainder of treatment duration. As an alternative, it is possible to use the daily dosing strategy (i.e. loading dose daily of 200 mg) for the first 2 months and then continue daily 100 mg for the next 4 months.

Dosing of linezolid

For adults, the prescribed dose of linezolid was 600 mg for the entire duration of therapy in the BEAT Tuberculosis trial, without any planned dose reductions. In the endTB-Q trial, the initial dose of linezolid was 600 mg once daily for 16 weeks. After 16 weeks, the dose was reduced to either 300 mg once daily or 600 mg three times per week. This dose reduction could occur earlier than 16 weeks if a participant experienced linezolid-related toxicity.

Regimen duration, changes and extensions

Treatment may be extended to 9 months if culture conversion is not sustained by week 16. In the BEAT Tuberculosis trial, the regimen was prolonged for three patients because of late culture conversion. All possible efforts should be made to support the patient and manage AEs to ensure uninterrupted treatment and the intake of all medicines in the regimen; however, when medicine cannot be tolerated, it should be stopped.

Linezolid is the leading cause of most AEs. If the clinician determines that the patient has responded well to treatment and that continuing therapy with linezolid would not be in the patient's best interest, permanent discontinuation of linezolid may occur.

Of the patients studied, 159 (78.7%) completed the entire 6-month course of BDLLfx/C without interruptions. Eighteen patients had their linezolid treatment permanently discontinued owing to AEs: three patients experienced anaemia, six developed optic neuritis and nine had peripheral neuropathy. The earliest time of linezolid discontinuation was at 6 weeks and the latest at 22 weeks. The BDLLfx/C regimen has been studied as a standardized course of treatment. Therefore, modifying the regimen through early discontinuation or replacement of any component medicines, except in the case of linezolid-related AEs, is not advised because it may result in different (and possibly worse) treatment outcomes.

Missing doses and tolerances for treatment interruptions

Linezolid could be temporarily or permanently interrupted but the other medicines are to be used throughout the treatment duration. Ideally, missing doses of drugs because of AEs or non-adherence

in the regimen should be avoided. If doses of all medicines are missed, any consecutive interruption of 7 days or more but less than 1 month should be made up for by extending the treatment duration (for the number of missed doses).

B2. Treatment of drug-resistant TB using 9-month regimens

Recommendation B2.1 The 9-month all-oral regimen for MDR/RR-TB

No.	Recommendation
B2.1	**WHO suggests the use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded.** *(Conditional recommendation, very low certainty of evidence)*

Remarks

- The 9-month all-oral regimen consists of bedaquiline (used for 6 months), in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high-dose), pyrazinamide and clofazimine (for 4 months, with the possibility of extending to 6 months if the patient remains sputum smear-positive at the end of 4 months), followed by treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide (for 5 months). Ethionamide can be replaced by 2 months of linezolid (600 mg daily).
- A 9-month regimen with linezolid instead of ethionamide may be used in pregnant women, unlike the regimen with ethionamide.
- This recommendation applies to:
  - people with MDR/RR-TB and without resistance to fluoroquinolones;
  - patients without extensive pulmonary TB disease[32] and without severe extrapulmonary TB;[33]
  - patients with less than 1 month exposure to bedaquiline, fluoroquinolones, ethionamide, linezolid and clofazimine; when exposure is greater than 1 month, these patients may still receive this regimen if resistance to the specific medicines with such exposure has been ruled out;
  - all people regardless of HIV status; and
  - children (and patients in other age groups) who do not have bacteriological confirmation of TB or drug resistance patterns but who do have a high likelihood of MDR/RR-TB (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB).

Rationale

The rationale for this recommendation is based on the evidence and considerations described in detail in the two subsections below. The 9-month regimens can be used in patients not eligible for the shorter, 6-month regimens; also, they represent a preferred treatment option over the longer regimens. The intention to determine a relatively shorter duration of treatment for patients with forms

[32] Extensive (or advanced) pulmonary TB disease is defined as the presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged below 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest radiography.

[33] Severe extrapulmonary TB is defined as presence of miliary TB, TB meningitis, or osteoarticular or pericardial TB. In children aged below 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are considered to be severe.

of DR-TB or other eligibility criteria not compatible with the 6-month regimen drove the assessments presented in this section.

Briefly, two assessments were performed that compared:

- first, the outcomes of the 9-month regimen including linezolid for 2 months and the identical regimen that included ethionamide for 4 months; and
- second, the outcomes of the 9-month regimen including linezolid with the longer regimens that were designed individually but included both bedaquiline and linezolid along with other medicines as recommended by WHO.

Most of the data on the 9-month regimens were obtained from a programmatic setting in South Africa.

The first assessment showed similar levels of treatment success (64% vs 66%), failure or recurrence (1.1% vs 1.4%), deaths (20% vs 21%), LTFU (15% vs 12%) and amplification of drug resistance (0.6% vs 0%) between the 9-month regimen including linezolid for 2 months and the identical regimen that included ethionamide for 4 months. AEs were noted in 5% of participants receiving the 9-month regimen with linezolid; however, no comparisons could be made because no data were available for participants receiving the 9-month regimen with ethionamide. The second assessment of the 9-month regimen including linezolid compared with longer regimens also showed lower levels of treatment success (64% vs 74%), failure or recurrence (1% vs 3%) and amplification of drug resistance (1% vs 2%); and higher levels of deaths (20% vs 11%) and LTFU (15% vs 12%). AEs were noted in 5% of participants receiving the 9-month regimen with linezolid and in participants receiving longer regimens.

Based on a combined review of these two assessments, it was considered that the 9-month regimen with linezolid can be recommended as an alternative to the 9-month regimen with ethionamide, and that both regimens can be used in preference to the longer (18-month) regimens in eligible patients. These assessments were performed against the background of the previous assessment during the GDG meeting in 2019 that led to the conditional recommendation for use of the 9-month all-oral bedaquiline-containing regimen *(31)*. The datasets of both 9-month regimens systematically excluded patients with extensive TB disease and severe forms of extrapulmonary TB; therefore, this recommendation is not extended to these groups of patients.

Summary of evidence

This section provides the PICO questions posed, and the data and studies considered to answer the questions; the methods used for analysis and data synthesis; a summary of evidence on desirable and undesirable effects, and certainty of evidence; and a summary of other evidence considered during development of the recommendation. Additional detail on the evidence is available in the annexes containing the GRADE evidence summary tables and GRADE EtD tables (**Annex 5**).

PICO questions

The following PICO question was used for the evidence assessment in 2019 that led to the conditional recommendation for use of the all-oral bedaquiline-containing 9-month regimen:

PICO question 2–2019 (MDR/RR-TB, 2019): *In MDR/RR-TB patients, does an all-oral treatment regimen lasting 9–12 months and including bedaquiline safely improve outcomes when compared with other regimens conforming to WHO guidelines?*

The following PICO question (split into two sub-PICO questions because of different comparators) guided the analyses and the assessment, and eventually led to a summary recommendation:

PICO question 1–2022 (MDR/RR-TB, 2022): *Should a shorter all-oral regimen (less than 12 months) containing at least three Group A medicines*[34] *be used in patients with MDR/RR-TB and with fluoroquinolone resistance excluded?*

[34] The three medicines included in Group A used for classification of second-line medicines are bedaquiline, fluoroquinolones and linezolid.

Data and studies considered

In 2019, for the WHO guideline update, the South African Department of Health provided WHO with access to programmatic data on injectable-free regimens that had been used in South Africa since 2017, when most eligible patients were enrolled on a shorter regimen, with bedaquiline replacing the injectable *(58)*. In August 2019, WHO issued a public call for IPD on the use of all-oral shorter regimens of 9–12 months *(59)*, but this call yielded no additional evidence on the implementation of such regimens. Consequently, the evidence review on injectable-free regimens in 2019 was based primarily on programmatic data from South Africa, recorded in the Electronic Drug-Resistant Tuberculosis Register (EDRWeb). Secondary comparative analyses were carried out using the IPD, to balance the assumptions and adequacy of the data, and adding to the generalizability of findings – in particular, the applicability to a global population. The IPD used at that time was a global dataset of the records of individual patients who have been treated for MDR/RR-TB; as of November 2019, it contained 13 273 records from 55 studies or centres in 38 countries. The evidence reviews focused on the performance of a standardized shorter regimen in which the injectable agent was replaced by bedaquiline, in combination with levofloxacin (or moxifloxacin), clofazimine, and high-dose isoniazid, ethambutol, pyrazinamide and ethionamide (or prothionamide). Patients on this regimen did not receive any injectable agents, nor were they administered cycloserine, terizidone, *p*-aminosalicylic acid, delamanid or linezolid. According to the clinical guidance issued by the South African Department of Health, at the time of regimen roll-out patients were not enrolled on the all-oral shorter regimen if they had extensive disease, severe extrapulmonary TB, fluoroquinolone resistance, previous exposure to second-line treatment for more than 1 month or genotypic DST showing mutations in both *inh*A and *kat*G genes.

In June 2021, WHO issued a public call *(60)* for IPD on the treatment of DR-TB. The call for individual patients' data on bacteriologically confirmed MDR/RR-TB patients (including MDR/RR-TB, MDR/RR-TB with additional resistance to second-line TB drugs, and patients with pre-XDR-TB or XDR-TB) included the following specifics:

- use of the modified shorter (<12 months) all-oral regimens using at least bedaquiline and linezolid;
- use of the WHO-recommended shorter all-oral bedaquiline-containing regimen (9–11 months) in the following combination: 4 or 6 months of bedaquiline (used for at least 6 months), levofloxacin (or moxifloxacin), clofazimine, pyrazinamide, ethionamide, ethambutol and high-dose isoniazid, followed by 5 months of levofloxacin (or moxifloxacin), clofazimine, pyrazinamide and ethambutol; and
- use of the WHO-recommended longer all-oral treatment regimen containing at least bedaquiline and linezolid.

The South African Department of Health provided WHO with the programmatic data from 2018 to 2019 on the use of a 9-month regimen in which ethionamide was replaced by linezolid. Several country programmes that provided WHO with IPD on the use of longer regimens according to WHO recommendations are listed in the Introduction (See *Scope of the 2022 update and available evidence*).

Once again, in 2021, the evidence review was based on programmatic data from South Africa on treatment outcomes of patients treated with the 9-month regimen (with either ethionamide or linezolid), recorded in the EDRWeb. Both datasets from South Africa (2017 and 2018–2019) with the 9-month regimens systematically excluded patients with extensive TB disease (extensive bilateral pulmonary cavitations), severe forms of extrapulmonary TB (meningoencephalitis, osteoarticular TB, pericardial effusion), fluoroquinolone resistance, previous exposure to second-line treatment for more than 1 month or with genotypic DST showing mutations in both *inh*A and *kat*G genes. In addition, comparative analyses were carried out using the 2021 IPD, which was compiled for the review and analyses in preparation for the GDG 2022; this IPD was of individual patients who had been treated for MDR/RR-TB. The evidence review focused on the performance of a standardized shorter regimen in which the injectable agent was replaced by bedaquiline (used for 6 months), in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high-dose), pyrazinamide and clofazimine for 4 months (with the possibility of extending to 6 months if the patient remained

sputum smear-positive at the end of 4 months), followed by 5 months of treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide. The comparators used included a nearly identical regimen where ethionamide was replaced by 2 months of linezolid (600 mg once daily) and the set of longer regimens designed based on the 2020 WHO recommendations.

Methods used for analysis and data synthesis

For comparisons between dataset or cohorts, outcomes were presented as unadjusted RRs and aRRs; the latter were calculated using a log-binomial generalized linear regression (binomial error distribution with log link function). Confounders were adjusted for using inverse probability propensity score weighting. No convergence issues with the log-binomial model arose. When outcome rates were close to the boundary (<5 positive or negative cases) aRRs were not calculated and unadjusted RRs alone were presented. For outcomes where the number of outcome events was zero, an unadjusted RD was calculated. For unadjusted RDs or RRs, the score method was used for calculating CIs. These approaches applied where one arm of a randomized trial was being compared with an external population, and in randomized trials in which subgroup analyses were performed (including by fluoroquinolone resistance status). Covariate selection for calculation of propensity scores was based on data availability and clinical knowledge. The covariates considered for inclusion in the propensity scores analysis included age, gender, baseline smear result, HIV status (including antiretroviral therapy status), prior treatment history (including whether previous infection was drug resistant), body mass index, smoking status, diabetes diagnosis, cavitation at baseline, disease site and presence of bilateral disease. For the calculation of aRRs, multiple imputation by chain equations using the "within" propensity score approach was used to account for missing data in potential confounders when the proportion of missing values for a confounder was less than 45%.

Summary of evidence on desirable and undesirable effects and certainty of evidence

PICO question 2–2019 (MDR/RR-TB, 2019): In MDR/RR-TB patients, does an all-oral treatment regimen lasting 9–12 months and including bedaquiline safely improve outcomes when compared with other regimens conforming to WHO guidelines?

A total of 10 152 records of patients with MDR/RR-TB initiating TB treatment anytime between January and June 2017 were considered, of which the following were included for primary analyses: 891 patients who received a shorter all-oral bedaquiline-containing regimen (intervention), 987 patients treated with a shorter regimen that included an injectable agent, 1437 patients treated with longer (2016) regimens, and 474 treated with longer regimens that included at least bedaquiline.

The primary analysis performed in 2019 using programmatic data from South Africa indicated that the use of a shorter all-oral bedaquiline-containing regimen in patients with MDR/RR-TB was associated with:

- higher treatment success rates (73% all-oral versus 60% standardized shorter regimen success rates, adjusted odds ratio [aOR] for success versus failure or recurrence: 2.1, 95% CI: 1.1–4.0; aOR success versus death: 1.6, 95% CI: 1.2–2.1; aOR success versus failure, recurrence or death: 1.7, 95% CI: 1.3–2.2; and aOR success versus all unfavourable outcomes: 1.9, 95% CI: 1.6–2.4); and
- lower loss to follow-up than a standardized shorter regimen in which an injectable agent was used (aOR loss to follow-up versus all other outcomes: 0.5, 95% CI: 0.4–0.7).

A similar effect for subgroups of patients with acid-fast bacilli (AFB) smear-positive sputum and people living with HIV and HIV-negative patients was observed with the use of the shorter all-oral bedaquiline-containing regimen.

The analysis also indicated that when the shorter all-oral bedaquiline-containing regimen was compared with an injectable-free longer regimen containing bedaquiline, there seemed to be no marked differences in the outcomes observed. However, relatively modest beneficial effects were noted in the direction of the intervention; in particular, success versus failure or recurrence (aOR: 3.9, 95% CI: 1.7–9.1), success versus all unfavourable outcomes (aOR: 1.6, 95% CI: 1.2–2.2) and loss to follow-up (aOR: 0.5, 95% CI: 0.4–0.8), all favouring the use of the all-oral shorter regimen. Further subgroup analysis suggested consistent differences in treatment outcomes, as observed in primary analyses among subgroups, in particular among AFB smear-positive patients and in people living with HIV on ART; however, differences in treatment outcomes in all-oral shorter and longer regimens were no longer significant when looking at outcomes for HIV-negative individuals, with the exception of loss to follow-up, which favoured the intervention. The additional comparison also illustrated the effect of a shorter all-oral bedaquiline-containing regimen in comparison with longer regimens without any new drugs. The all-oral shorter regimen performed significantly better across all outcomes and all subgroups in this comparison.

Conclusion

A shorter all-oral bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded. (conditional recommendation, very low certainty of evidence).

PICO 1–2022 (MDR/RR-TB, 2022): Should a shorter all-oral regimen (less than 12 months) containing at least three Group A medicines be used in patients with MDR/RR-TB and with fluoroquinolone resistance excluded?

For the assessment performed in preparation for the 2022 GDG, 8653 records of patients with MDR/RR-TB initiating TB treatment at any time between January and December 2017 were considered, of which the following were included for analyses: 4244 patients treated with a shorter regimen that included linezolid (used in South Africa in 2019) (intervention), 880 patients who received a shorter all-oral bedaquiline-containing 9-month regimen with ethionamide (used in South Africa in 2017) (comparator), and 850 patients treated with longer regimens that included at least bedaquiline and linezolid.

Sub-PICO 1.1–2022 (MDR/RR-TB, 2022): Should a shorter all-oral regimen (less than 12 months) containing at least three Group A medicines be used in patients with MDR/RR-TB and with fluoroquinolone resistance excluded? (comparison with 9-month ethionamide regimen)

In sub-PICO 1.1, two observational studies were compared – the 9-month regimen with linezolid (used in South Africa in 2019) (intervention) and the 9-month regimen with ethionamide (used in South Africa in 2017) (comparator). Both datasets were obtained from a programmatic setting in South Africa.

Participants with MDR/RR-TB with fluoroquinolone susceptibility receiving the 9-month regimen with linezolid (*n*=4244) compared with participants receiving the 9-month regimen with ethionamide (*n*=880) experienced:

- lower levels of treatment success (64% vs 66%); that is, a 4% relative reduction (aRR=0.96, 95% CI: 0.91 to 1.01);
- lower levels of failure and recurrence (1.1% vs 1.4%); that is, a 20% relative reduction (aRR=0.80, 95% CI: 0.42 to 1.53);
- higher levels of deaths (20% vs 21%); that is, a 3% relative increase (aRR=1.03, 95% CI: 0.89 to 1.20);[35]

[35] Note that while unadjusted effect estimates suggest a small reduction in levels of death, the adjusted effect estimates suggest a small increase in levels of death.

- higher levels of loss to follow-up (15% vs 12%); that is, a 19% relative increase (aRR=1.19, 95% CI: 0.98 to 1.45); and
- higher levels of amplification of drug resistance (0.6% vs 0%); that is, a 1% absolute increase (RD=0.01, 95% CI: 0.00 to 0.01).

AEs were noted in 5% of participants receiving the 9-month regimen with linezolid but no comparisons could be made because no data were available for participants receiving the 9-month regimen with ethionamide.

The GDG judged the benefits of the 9-month regimen with linezolid to be small and the undesirable effects to be moderate compared with the 9-month regimen with ethionamide. The certainty of evidence was judged to be very low. Based on this, the GDG judged that the balance of health effects does not favour either the 9-month regimen with linezolid or the 9-month regimen with ethionamide.

Conclusion

The use of either the 9-month regimen with linezolid or the 9-month regimen with ethionamide is suggested in people with pulmonary MDR/RR-TB without fluoroquinolone resistance (conditional recommendation, very low certainty of evidence).

Sub-PICO 1.2–2022 (MDR/RR-TB, 2022): Should a shorter all-oral regimen (less than 12 months) containing at least three Group A medicines be used in patients with MDR/RR-TB and with fluoroquinolone resistance excluded? (comparison with longer regimens)

In sub-PICO 1.2, two observational datasets were compared – the 9-month regimen with linezolid (used in South Africa in 2019) (intervention) and the all-oral longer regimens containing bedaquiline from the 2021 IPD dataset.

Participants with MDR/RR-TB with fluoroquinolone susceptibility receiving the 9-month regimen with linezolid (*n*=4244) compared with participants receiving longer regimens for MDR/RR-TB (*n*=850) experienced:

- lower levels of treatment success (64% vs 74%); that is, a 10% relative reduction (aRR=0.90, 95% CI: 0.83 to 0.98);
- lower levels of failure and recurrence (1.1% vs 3.4%); that is, a 71% relative reduction (aRR=0.29, 95% CI: 0.14 to 0.58);
- higher levels of deaths (20% vs 11%); that is, a 38% relative increase (aRR=1.38, 95% CI: 1.00 to 1.91);
- higher levels of loss to follow-up (15% vs 12%); that is, a 33% relative increase (aRR=1.33, 95% CI: 0.97 to 1.81);
- similar levels of AEs (5.0% vs 4.7%), (aRR=1.00, 95% CI: 0.59 to 1.69); and
- lower levels of amplification of drug resistance (0.6% vs 1.4%); that is, a 73% relative reduction (aRR=0.27, 95% CI: 0.12 to 0.61).

The GDG judged both the benefits of the 9-month regimen with linezolid and the undesirable effects to be moderate compared with the longer regimens. The certainty of evidence was judged to be very low. Based on this, the GDG judged that the balance of health effects did not favour either the 9-month regimen with linezolid or the longer regimens. The panel judged that although the balance of effects did not favour either the intervention or the comparator, several other criteria in the GRADE evidence-to-decision tables (e.g. resources, acceptability, equity and feasibility) favoured the 9-month regimen.

Conclusion

The use of either the 9-month regimen with linezolid or the longer (18-month) regimens is suggested in people with pulmonary MDR/RR-TB without fluoroquinolone resistance (conditional recommendation, very low certainty of evidence).

Summary of other evidence

During assessment of sub-PICO 1.1, the panel noted that the cost of component medicines is likely to be similar because both regimens are of the same duration and use the same component medicines except for one – linezolid instead of ethionamide. The duration of linezolid use is 2 months compared with 4 months for ethionamide. Based on GDF prices *(55)* the cost difference was negligible (2 months of linezolid at 600 mg/day US$ 21, and 4 months of ethionamide at 450 mg/day US$ 32).

The health care costs are also likely to be similar because the two regimens are of the same duration and have the same component medicines, except for one – linezolid instead of ethionamide.

The panel also assumed no difference in DST needs. Both regimens are indicated for patients with MDR/RR-TB and without fluoroquinolone resistance. These patients are usually tested for rifampicin and fluoroquinolone resistance – rapid DSTs for both of these medicines are available. It might also be useful to perform genotypic DST because mutations in the *inh*A gene also confer resistance to ethionamide.

Evidence to recommendations: considerations

PICO question 2–2019 (MDR/RR-TB, 2019): In MDR/RR-TB patients, does an all-oral treatment regimen lasting 9–12 months and including bedaquiline safely improve outcomes when compared with other regimens conforming to WHO guidelines?

The primary analysis performed in 2019 using programmatic data from South Africa indicated that a shorter all-oral bedaquiline-containing regimen in patients with MDR/RR-TB was associated with higher treatment success rates and lower loss to follow-up than a standardized shorter regimen that included an injectable agent. A similar effect for subgroups of patients with acid-fast bacilli (AFB) smear-positive sputum and people living with HIV and HIV-negative patients was observed with the use of the shorter all-oral bedaquiline-containing regimen.

The GDG acknowledged that, during the analysis, the intervention and comparator groups were made as comparable as possible. However, the GDG considered possible unmeasured confounding due to a lack of systematic collection of information on comorbidities and radiological findings through the EDRWeb system, as well as methodological challenges, such as a potential selection bias. However, apart from the selection criteria listed, the risk of major selection bias was considered low, given that this intervention represented a complete and comprehensive switch in the countrywide programmatic approach.

In 2022, new evidence from programmatic implementation in South Africa was made available to WHO where the regimen was modified to include 2 months of linezolid (600 mg) instead of 4 months of ethionamide.

Based on an assessment of the certainty of the evidence, carried out using predefined criteria and documented in the GRADEpro software, the certainty of the evidence was rated as very low for both comparisons.

Table 2.10 lists the comparisons and decisions on each of the sub-PICO questions that were assessed by the GDGs (2019 and 2022) to conclude with the summary recommendation (Recommendation 2.1). The main assessment that defined the overall decision was based on sub-PICO 1.1. The background for this decision was provided by the previous review and recommendation for the use of the 9-month regimen with ethionamide agreed during the GDG meeting in November 2019 and reflected in the recommendations published in the 2020 DR-TB treatment guidelines update *(31)*.

Table 2.10. PICO questions and decisions of the GDG panel in 2019

#	PICO	Population	Intervention	Comparator [data source]	Comparison #	Decision
2–2019	In MDR/RR-TB patients, does an all-oral treatment regimen lasting 9–12 months and including bedaquiline safely improve outcomes when compared with other regimens conforming to WHO guidelines?	MDR/RR-TB	9-month regimen with ethionamide	9-month regimen with injectables; or longer regimens	1	Conditional for intervention
1–2022	Should a shorter all-oral regimen (less than 12 months) containing at least three Group A medicines be used in patients with MDR/RR-TB and fluoroquinolone resistance excluded?	MDR/RR-TB	9-month regimen with linezolid	9-month regimen with ethionamide	1.1	Conditional for either intervention or comparator
				Longer regimens	1.2	Conditional for either intervention or comparator

GDG: Guideline Development Group; MDR/RR-TB: multidrug- or rifampicin-resistant TB; PICO: population, intervention, comparator and outcome; TB: tuberculosis; WHO: World Health Organization.

Sub-PICO 1.1–2022 (MDR/RR-TB, 2022): Should a shorter all-oral regimen (less than 12 months) containing at least three Group A medicines be used in patients with MDR/RR-TB and with fluoroquinolone resistance excluded? (comparison with 9-month ethionamide regimen)

The GDG (2022) acknowledged that, during the analysis, the intervention and comparator groups were made as comparable as possible. However, the GDG considered possible unmeasured confounding due to a lack of systematic collection of information on comorbidities and radiological findings through the EDRWeb system, as well as methodological challenges (e.g. a potential selection bias). Apart from the selection criteria listed, the risk of major selection bias was considered to be low, given that this intervention represented a complete and comprehensive switch in the countrywide programmatic approach.

Regarding generalizability, the GDG deliberated whether the genetic diversity of *M. tuberculosis* strains in South Africa was comparable to strains present in other settings; the group concluded that strains found in other settings were adequately represented in the country. The group also considered potential interactions in relation to HIV status and the effect of ART, but this was not considered a major factor given that treatment outcomes were similar in people living with HIV and HIV-negative people. The GDG agreed that results of the STREAM Stage 2 trial – a large-scale, multicountry Phase 3 trial examining a shorter all-oral bedaquiline-containing regimen – will provide additional important insight into the efficacy and safety of this regimen, and may increase the certainty of the evidence.

A clear limitation emphasized by the GDG was the lack of data on AEs in the EDRWeb. No direct comparative evidence was available on AEs because the data on such events were not systematically collected for the 9-month regimen with ethionamide. The rate of Grade 3–5 AEs was 5% for the 9-month regimen with linezolid. The panel nevertheless considered the potential AEs of both ethionamide and linezolid in balancing the benefits and harms (Table 2.11).

Table 2.11. Summary of AEs associated with linezolid and ethionamide

Linezolid AEs	Ethionamide AEs
• Myelosuppression (anaemia, decreased level of white blood cells or decreased level of platelets) • Peripheral or optic neuropathy – these conditions may be irreversible, and linezolid should be stopped if they develop • Lactic acidosis – patients who develop recurrent nausea or vomiting, unexplained acidosis or a low bicarbonate level while receiving linezolid should receive immediate medical evaluation, including a lactic acid blood test • Diarrhoea and nausea	• Gastrointestinal upset and anorexia (sometimes intolerable) – symptoms are moderated by food or by taking at bedtime • Hepatotoxicity • Endocrine effects (e.g. gynaecomastia, hair loss, acne, impotence, menstrual irregularity and reversible hypothyroidism) • Neurotoxicity – patients taking ethionamide should take high doses of vitamin B6

AE: adverse event.

The panel also considered the duration and pill burden with the intervention and comparator regimens. Both regimens have the same duration, so neither offers an advantage of shorter treatment, although the duration of the linezolid regimen is shorter than that of ethionamide. The pill burden is likely to be slightly lower with the intervention because linezolid is prescribed for 2 months in the 9-month regimen with linezolid and ethionamide for 4 months in the 9-month regimen with ethionamide.

Considering this evidence, the panel judged that the 9-month regimen with linezolid may have small desirable effects and noted the very low certainty of the evidence. Certainty of the evidence was rated "very low" for all outcomes on account of potential misclassification bias and confounding bias (downgraded 1 level), and serious indirectness (downgraded 1 level). The overall certainty is generally based on the lowest certainty for the agreed critical outcomes; thus, it was judged to be very low. The panel noted that the evidence on both the intervention and on the comparator regimen was obtained from programmatic data from South Africa such that, overall, the population and health care context were comparable. However, the panel stressed that important differences exist between the two cohorts or datasets that were compared, making it difficult to draw conclusions with full confidence.

The panel judged that there was probably no important uncertainty or variability in how much people value the main outcomes. The panel used available data on cost of component medicines combined with professional judgement to estimate the cost of the 9-month regimen with linezolid compared with the 9-month regimen with ethionamide among patients with MDR/RR-TB, susceptible to fluoroquinolones. The panel suggested that the cost would be expected to be very similar; that is, for there to be negligible costs or savings. The panel also noted that no data were available on the cost of managing potential long-term consequences of neurotoxicity that can be caused by the use of linezolid, and that the risk is greater if linezolid is used for longer periods. The panel has also noted that health care and patient costs are likely to be similar for regimens when used in a similar group of patients and for the same duration.

The GDG attempted to discuss cost–effectiveness of the two regimens; however, no evidence was available, the two regimens are identical in duration and they only differ in one component drug, which would not change the overall cost of the regimen in any significant way. The similarity of the two regimens also prevented a substantial discussion on the equity. The panel considered patients and health care providers as key stakeholders. The panel considered the following aspects as critical with regard to acceptability: regimen duration, drug-safety monitoring needs (relating both to the necessary travel, loss of income and general disruption of the life of patients, and to workload for the health care system) and DST needs. The panel judged that there were probably no differences in acceptability between the 9-month regimen with linezolid and the 9-month regimen with ethionamide, given the overall similarity of the regimens, and that the 9-month regimen with linezolid would probably be acceptable. The panel considered the following aspects to affect feasibility (i.e. to be potential barriers to implementation): requirements for drug-safety monitoring and for DST. The 9-month regimen with linezolid would require monitoring of toxicity (e.g. anaemia) and DST.

The panel judged that the balance of desirable and undesirable consequences favours neither the 9-month regimen with linezolid nor the 9-month regimen with ethionamide in this population. Specifically, the panel felt that there is a fine balance between the two options in terms of benefits and harms that is uncertain given the overall very low certainty in the evidence (due to potential misclassification bias, confounding bias and serious indirectness). The panel judged that for most other evidence-to-decision criteria (e.g. resources, acceptability and feasibility) there was unlikely to be a large difference between the 9-month regimen with linezolid and the 9-month regimen with ethionamide because the only difference between the two regimens is the replacement of ethionamide with linezolid. Overall, the panel judged that either regimen could be used and that the flexibility of using either linezolid or ethionamide was helpful to optimize patient care. These considerations also guided the agreement of the panel on the strength of the recommendation being conditional.

Sub-PICO 1.2–2022 (MDR/RR-TB, 2022): Should a shorter all-oral regimen (less than 12 months) containing at least three Group A medicines be used in patients with MDR/RR-TB and with fluoroquinolone resistance excluded? (comparison with longer regimens)

The GDG (2022) acknowledged that, during the analysis, the intervention and comparator groups were made as comparable as possible. The panel noted that the evidence on the 9-month regimen

was obtained from programmatic data from South Africa, whereas the evidence on the longer regimen represented only subsets of patients from the countries and researchers that submitted data. The panel also noted substantial inconsistency between cohorts in the comparator group (on the longer regimens). Overall, there was concern that the selective nature of the data on the longer regimens may have biased the comparison in favour of the longer regimen. As a result, there were serious concerns about the comparability of the data, making it difficult to draw conclusions with confidence. The panel also considered the duration and overall pill burden with the intervention and comparator regimens, which are both lower in the 9-month regimen and thus represent a benefit of the intervention. Considering this evidence and the totality of observed effects of the 9-month regimen with linezolid on the outcomes, the panel judged that the 9-month regimen with linezolid may have moderate desirable effects and that it may also have moderate undesirable effects.

Certainty in the estimates was rated "very low" for all outcomes owing to very serious risk of bias (potential misclassification bias and confounding bias), inconsistency (inconsistency in the effect estimates among 14 comparator cohorts) and indirectness (with data for the intervention regimen being from a single country). The overall certainty is generally based on the lowest certainty for the agreed critical outcomes and thus was judged to be very low.

The panel noted that the costs for people with MDR/RR-TB receiving the 9-month regimen with linezolid are expected to be lower than those for longer regimens (18 months or longer) because costs for drugs, care and monitoring are expected to be lower.

The panel considered the ability to decentralize treatment (to enable access for remote, underserviced settings and disadvantaged populations) as affecting equity. Despite not being able to identify relevant research evidence, the panel used their collective experience to judge that there would probably be advantages associated with the use of the 9-month regimen owing to its reduced complexity and shorter duration. The panel judged that use of the 9-month regimen with linezolid would probably increase equity.

The panel considered patients and health care providers as key stakeholders and the following aspects as critical with regard to acceptability: regimen duration and drug-safety, monitoring needs (relating both to the necessary travel, loss of income and general disruption of the life of patients, and to workload for the health care system) and needs for DST. The panel judged that the 9-month regimen with linezolid would probably be acceptable to key stakeholders.

The balance of desirable and undesirable consequences was judged to not favour either the use of the 9-month regimen or the longer, 18-month regimens in this population. Specifically, the panel felt that there is a fine balance between the two options in terms of benefits and harms that is uncertain given the overall very low certainty in the evidence. The panel judged that although the balance of effects did not favour either the intervention or the comparator, several other evidence-to-decision table criteria (e.g. resources, acceptability, equity and feasibility) favoured the 9-month regimen.

Overall, the panel judged that either regimen could be used in the eligible patient group presented in the analysis; they noted the more limited eligibility for the 9-month regimen and acknowledged that the applicability of the longer, individualized regimens is more flexible and significantly broader, including many patient groups that are not eligible for the shorter regimen. These considerations have also guided the agreement of the panel on the conditionality of this recommendation.

Subgroup considerations

Based on research evidence and expert experience, the panel identified subpopulations of people who might be affected differently than most by this recommendation; these subpopulations were people living with HIV, children, pregnant women, breastfeeding women, patients with extrapulmonary TB and patients with extensive TB disease. The recent new recommendation for use of bedaquiline in children

with MDR/RR-TB aged below 6 years was considered *(27)*. The panel noted specific considerations for the subpopulations listed below.

People living with HIV

The data evaluated corresponded to a setting with a high prevalence of HIV; of particular significance was that most people living with HIV (>90%) who started the 9-month regimens were receiving ART. In view of the treatment outcomes described in the analysis, there were no grounds to believe that the regimen would perform any differently in people living with HIV. It is necessary to consider significant clinical interactions that may increase bedaquiline exposure or that of other agents with potential for cardiotoxicity when these are co-administered with antiretroviral drugs. However, because the data evaluated did not include information on changes to the regimen as a result of management of adverse drug reactions, or complications from drug–drug interactions, the GDG reiterated that it is worth paying attention to any potential drug–drug interactions or overlapping drug toxicities that may not have been captured. For example, bedaquiline concentrations can be reduced by efavirenz (these drugs should not be co-administered) or increased by boosted protease inhibitors (resulting in a need for greater vigilance in monitoring for drug-related QT effects) *(61–63)*. Neuropathy, liver enzyme elevations and CNS side-effects can be attributed to HIV or TB drugs or their interactions *(64)*.

Children and adolescents

The datasets included only small numbers of people aged below 15 years (*n*=69), and thus did not allow for reliable comparisons in both datasets from South Africa (*n*=69 and *n*=7) and in the 2021 IPD (*n*=7). However, analysis in the subgroup aged below 15 years showed a relative increase in treatment success of 42% (aRR=1.42, 95% CI: 0.7 to 2.89) in sub-PICO 1.1 and a 5% relative reduction (RR=0.95, 95% CI: 0.78 to 1.15) in sub-PICO 1.2. Although a small number of participants were aged between 10 and 15 years (19/50, 38% in the intervention group, and 75/162, 46% in the comparator group), extrapolation of the findings to children was deemed reasonable for efficacy because components of the regimen had been used safely in children based on other available data regarding linezolid use in children. This extrapolation was considered applicable to children of all ages, taking into account the recommendation for use of bedaquiline in children aged below 6 years, as described in recommendation 2.4 *(27)*.

Pregnant and breastfeeding women

In the research studies analysed, pregnant women were not identified, and subgroup data were unavailable. Ethionamide is usually contraindicated in pregnancy (because animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans), and this is the main reason that the 9-month regimen has not been recommended for this subgroup in the past. There is experience in using linezolid during pregnancy *(65, 66)*. For pregnant and breastfeeding women, it is therefore recommended to use the regimen with linezolid instead of ethionamide.

Extrapulmonary TB

A subgroup of people with extrapulmonary TB were included in the research studies (81 in the regimen containing linezolid and 23 in the regimen with ethionamide). In view of the unavailability of evidence on surrogates for severity or extent of disease, the use of this regimen in patients with severe forms of extrapulmonary TB is not recommended.

Implementation considerations

Drug susceptibility testing

DST for bedaquiline and linezolid is an important implementation consideration that will need to be enhanced in many countries, given the increasing use of these medicines in all regimens for MDR/RR-TB and the possible further inclusion of new medicines in MDR-TB treatment regimens. The implementation of these recommendations must be accompanied by continued efforts to increase access to DST for all medicines for which reliable methods are currently available, and for the development and roll-out of DST methods for newer medicines.

Access to WHO-recommended rapid DST is essential, especially for detecting resistance to rifampicin and fluoroquinolones, before starting the 9-month regimens. Baseline DST will confirm eligibility for different regimen options; therefore, the establishment and strengthening of DST services is a vital consideration for implementation. The DST methods for identifying resistance to bedaquiline and linezolid have been developed on available phenotypic platforms and need to be implemented in all settings where these medicines are being used. Resistance to other anti-TB drugs should be monitored in accordance with WHO recommendations.

One of the exclusion criteria for all shorter regimens in the datasets from South Africa was mutations in both *inh*A promoter and *kat*G regions, confirmed using a line probe assay (LPA). This means that patients with only *inh*A or only *kat*G mutations were included. A first-line LPA (MTBDRplus) and Xpert MTB/XDR cartridge can determine mutations in the *inh*A promoter or *kat*G regions; both mutations confer resistance to isoniazid, with the resistance being low level when *inh*A mutations alone are present, or high level with *kat*G gene mutations alone or *inh*A promoter and *kat*G gene mutations combined. Mutations at the *inh*A promoter are also associated with resistance to ethionamide and prothionamide. The presence of mutations in both the *inh*A promoter and *kat*G suggests that isoniazid at high dose and thioamides are not effective, and that the 9-month regimen may not therefore be used. In the absence of information on mutation patterns for an individual patient, the decision can be informed by knowledge of the frequency of the concurrent occurrence of both mutations, obtained from drug-resistance surveillance *(50)*. Phenotypic DST for some medicines included in the regimen (e.g. ethambutol and ethionamide) is not considered reliable and reproducible; therefore, this testing should be employed with caution to inform the use of this regimen.[36]

Currently, there is limited capacity globally to carry out DST for bedaquiline; however, laboratory capacity should be strengthened in this area as new medicines and regimens begin to be used more widely. National and reference laboratories will need to have the relevant reagents available to enable DST to be carried out and will need data on the MIC distribution of all *M. tuberculosis* lineages that are circulating globally. The WHO TB SRL Network is available to support national TB reference laboratories in performing quality-assured DST. A WHO technical consultation in 2017 established critical concentrations for susceptibility testing for the fluoroquinolones, bedaquiline, delamanid, clofazimine and linezolid *(52)*.

Selection of fluoroquinolones

Selection of fluoroquinolones may take into account the evidence from South Africa available for the review – 83% of patients analysed using the 2017 dataset received levofloxacin and the rest received moxifloxacin at standard dose (400 mg daily). Both levofloxacin and moxifloxacin have shown similar efficacy for treating DR-TB. The choice between levofloxacin and moxifloxacin was guided by the potential risk of cumulative cardiotoxicity. Levofloxacin is often preferred because of moxifloxacin's slightly higher potential for cardiotoxicity. Therefore, irrespective of the choice of fluoroquinolone,

[36] See the list of high-confidence resistance-conferring mutations in the WHO guide on the use of next-generation sequencing technologies, WHO (2018) *(67)*.

NTPs need to implement active TB drug-safety monitoring and management in all patients enrolled on treatment of DR-TB *(68, 69)*.

Assessment of TB disease

To determine regimen options, it is important to know the extent of pulmonary TB disease, in addition to the DST results and other considerations mentioned above. Extensive pulmonary TB disease is defined in this document as the presence of bilateral cavitary disease or extensive parenchymal damage on CXR. In children aged below 15 years, advanced pulmonary disease is usually defined by the presence of cavities or bilateral disease on CXR. This highlights the importance of CXR as part of the diagnostic and clinical management work-up for patients.

Regimen duration

The regimen comprises an intensive phase of 4 months that may be extended to 6 months when no bacteriological conversion is seen at the end of the fourth month of treatment, and a continuation phase of 5 months; hence, if extended, the regimens may last 11 months. In the dataset reviewed, the duration of bedaquiline and linezolid was restricted to 6 and 2 months, respectively.

Patient-centred approach

Efforts are required to provide patient support to enable full adherence to treatment.

Recommendations B2.2 and B2.3 The modified 9-month all-oral regimens for MDR/RR-TB

No.	Recommendation
B2.2	**WHO suggests using the 9-month all-oral regimens (BLMZ, BLLfxCZ and BDLLfxZ) over currently recommended longer (>18 months) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. Among these regimens, using BLMZ is suggested over using BLLfxCZ, and BLLfxCZ is suggested over BDLLfxZ.** *(Conditional recommendation, very low certainty of evidence)*
B2.3	**WHO suggests against using 9-month DCLLfxZ or DCMZ regimen compared with currently recommended longer (>18 months) regimens in patients with fluoroquinolone-susceptible MDR/RR-TB.** *(Conditional recommendation, very low certainty of evidence)*

Remarks

- The recommended modified 9-month all-oral regimens comprise bedaquiline, linezolid and pyrazinamide in different combinations with levofloxacin/moxifloxacin, clofazimine and delamanid.
- This recommendation applies to the following:
  - People with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded.
  - People with diagnosed pulmonary TB, including children, adolescents, people living with HIV, and pregnant and breastfeeding women.
  - People with extensive pulmonary TB disease and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular TB or disseminated forms of TB with multiorgan involvement.
  - People with MDR/RR-TB and less than 1 month of previous exposure to any of the component medicines of the regimen (apart from pyrazinamide and fluoroquinolones). When exposure is greater than 1 month, these patients may still receive one of the regimens if resistance to the specific medicines with such exposure has been ruled out.

– Children and adolescents who do not have bacteriological confirmation of TB or resistance patterns but do have a high likelihood of MDR/RR-TB (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB).

Rationale

The rationale for these recommendations is based on the evidence and considerations detailed in the subsections below. These 9-month regimens (BLMZ, BLLfxCZ and BDLLfxZ) can be used in patients with MDR/RR-TB (in whom resistance to FQ has been excluded) who cannot be offered one of the 6-month regimens. These regimens are the preferred option over the longer (>18-month) regimens, and the GDG panel (2024) has advised a relative ranking of preference among the three modified 9-month regimens based on the review of multiple criteria.

The evidence from the endTB trial (NCT02754765) *(70)* of all five regimens was assessed. The outcomes of participants in five trial arms receiving modified 9-month regimens were compared with the trial's comparator arm, in which most participants received longer regimens. All five experimental regimens were of 9 months duration. Three of these regimens included bedaquiline (for the whole duration of the regimen), a quinolone (either moxifloxacin or levofloxacin), linezolid, pyrazinamide, and either delamanid or clofazimine, or no fifth drug. The two remaining regimens were without bedaquiline but included delamanid, a quinolone (moxifloxacin or levofloxacin), clofazimine and pyrazinamide, with or without linezolid as a fifth medicine (see Table 2.13). The assessment of three bedaquiline-containing regimens showed higher levels of treatment success (89%, 88.7% and 85.2% vs 77%), slightly higher or lower failure or recurrence (3.4%, 6.1% and 1.6% vs 2.5%), lower levels of deaths (1.7%, 0.9% and 2.5% vs 3.4%), lower levels of LTFU (5.9%, 4.3% and 10.7% vs 16.8%) and similar levels of amplification of drug resistance (0.0%, 1.6% and 0.0% vs 0%) than the comparator. The two regimens without bedaquiline showed variable levels of treatment success (76.3% and 84.6% vs 77%), failure or recurrence (11% and 8.7% vs 2.5%), deaths (2.5% and 2.9% vs 3.4%) and LTFU (10.2% and 3.8% vs 16.8%), and higher amplification of drug resistance (4.0% and 6.7% vs 0%).

Based on a review of these five assessments, it was considered that three bedaquiline-containing regimens (BLMZ, BLLfxCZ and BDLLfxZ) can be suggested for use in preference to currently recommended longer (>18 months) regimens in patients with MDR/RR-TB and in whom resistance to FQ has been excluded. Additional assessment of multiple factors (including resource requirements, health equity, acceptability and access to delamanid) led to the conclusion that BLMZ is preferred over BLLfxCZ, and that BLLfxCZ is preferred over BDLLfxZ, because the net health effects appeared to be most favourable for BLMZ, followed by BLLfxCZ. The endTB trial enrolled patients with important comorbidities and patients with extensive TB disease (see Table 2.15); therefore, in contrast to the recommendation for the 9-month all-oral regimen, this recommendation can be extended to these groups of patients.

Summary of evidence

This section provides the PICO questions posed, the data and studies considered to answer the questions, the methods used for analysis and data synthesis, and summaries of evidence on desirable and undesirable effects, certainty of evidence and other evidence considered during the recommendation's development. Additional detail on the evidence is available in the annexes containing the GRADE evidence summary tables and GRADE evidence-to-decision tables (Annex 5).

PICO questions

The recommendations in this section result from assessments of the PICO questions listed below.

PICO question 2–2024 (MDR/RR-TB, 2024): *Should any 9-month endTB trial regimens be used in patients with pulmonary RR-TB (without FQ resistance) over the currently recommended longer regimens?*

Because of the different interventions tested, PICO 2 has been split into several sub-PICO questions, as shown in Table 2.12.

Sub-PICO question 2.1–2024 (MDR/RR-TB, 2024): Should a 9-month regimen using bedaquiline, linezolid, moxifloxacin, and pyrazinamide ***(9BLMZ)*** *vs. currently recommended longer WHO regimens be used in patients with pulmonary RR-TB (without fluoroquinolone resistance)?*

Sub-PICO question 2.2–2024 (MDR/RR-TB, 2024): Should a 9-month regimen using bedaquiline, clofazimine, linezolid, levofloxacin, and pyrazinamide ***(9BLLfxCZ)*** *vs. currently recommended longer WHO regimens be used in patients with pulmonary RR-TB (without fluoroquinolone resistance)?*

Sub-PICO question 2.3–2024 (MDR/RR-TB, 2024): Should a 9-month regimen using bedaquiline, delamanid, linezolid, levofloxacin, and pyrazinamide ***(9BDLLfxZ)*** *vs. currently recommended longer WHO regimens be used in patients with pulmonary RR-TB (without fluoroquinolone resistance)?*

Sub-PICO question 2.4–2024 (MDR/RR-TB, 2024) Should a 9-month regimen using delamanid, clofazimine, linezolid, levofloxacin, and pyrazinamide ***(9DCLLfxZ)*** *vs. currently recommended longer WHO regimens be used in patients with pulmonary RR-TB (without fluoroquinolone resistance)?*

Sub-PICO question 2.5–2024 (MDR/RR-TB, 2024) Should a 9-month regimen using delamanid, clofazimine, moxifloxacin, and pyrazinamide ***(9DCMZ)*** *vs. currently recommended longer WHO regimens be used in patients with pulmonary RR-TB (without fluoroquinolone resistance)?*

Table 2.12. Sub-PICO questions to PICO 2

Sub-PICO	PICO	Population	Intervention	Comparator	Recommendation direction
2.1	Should a 9-month regimen using bedaquiline, linezolid, moxifloxacin and pyrazinamide (9BLMZ) versus currently recommended longer WHO regimens be used in patients with pulmonary RR-TB (without FQ resistance)?	MDR/RR-TB	9BLMZ	Currently WHO-recommended longer regimens	Conditional for the intervention
2.2	Should a 9-month regimen using bedaquiline, clofazimine, linezolid, levofloxacin and pyrazinamide (9BLLfxCZ) versus currently recommended longer WHO regimens be used in patients with pulmonary RR-TB (without FQ resistance)?	MDR/RR-TB	9BLLfxCZ	Currently WHO-recommended longer regimens	Conditional for the intervention
2.3	Should a 9-month regimen using bedaquiline, delamanid, linezolid, levofloxacin and pyrazinamide (9BDLLfxZ) versus currently recommended longer WHO regimens be used in patients with pulmonary RR-TB (without FQ resistance)?	MDR/RR-TB	9BDLLfxZ	Currently WHO-recommended longer regimens	Conditional for the intervention
2.4	Should a 9-month regimen using delamanid, clofazimine, linezolid, levofloxacin and pyrazinamide (9DCLLfxZ) versus currently recommended longer WHO regimens be used in patients with pulmonary RR-TB (without FQ resistance)?	MDR/RR-TB	9DCLLfxZ	Currently WHO-recommended longer regimens	Conditional against the intervention
2.5	Should a 9-month regimen using delamanid, clofazimine, moxifloxacin and pyrazinamide (9DCMZ) versus currently recommended longer WHO regimens be used in patients with pulmonary RR-TB (without FQ resistance)?	MDR/RR-TB	9DCMZ	Currently WHO-recommended longer regimens	Conditional against the intervention

FQ: fluoroquinolones; MDR/RR-TB: multidrug- or rifampicin-resistant TB; PICO: population, intervention, comparator and outcome; RR-TB: rifampicin-resistant TB; TB: tuberculosis; WHO: World Health Organization.

Data and studies considered

This group of PICO questions was reviewed during the GDG meeting convened by WHO in June 2024, using the evidence from the endTB trial *(70)*. The endTB trial was an RCT that was led by Partners In Health (PIH), Médecins Sans Frontières (MSF), and Interactive Research and Development (IRD); the aim was to improve the efficacy and safety of treatment for patients with FQ-susceptible MDR/RR-TB.

endTB trial

The endTB trial was a Bayesian response-adaptive randomized Phase 3, multicountry, controlled, parallel, open-label clinical trial. Participants were randomly assigned to either the control arm, which follows the SoC longer (18-month) regimens for MDR/RR-TB, or to one of five 39-week multidrug regimens that incorporate newly approved and repurposed drugs. The duration of follow-up for all arms ranged from a minimum of 73 weeks to a maximum of 104 weeks post-randomization.

The primary objective of the endTB trial was to assess whether the efficacy of each experimental regimen is non-inferior to that of the control. The endTB clinical trial started in 2017 and randomized and followed 754 participants over 7 years and across 12 sites in seven countries: Georgia, India, Kazakhstan, Lesotho, Pakistan, Peru and South Africa.

Eligible participants were aged at least 15 years and had pulmonary TB suspected or confirmed to be resistant to rifampicin and susceptible to FQ. Participants living with HIV (regardless of CD4 count), diabetes (regardless of A1c), substance use disorders and various degrees of TB disease severity were enrolled in the trial. All study arms were similar in size (ranging from 107 to 122) with 699 participants in the modified intention-to-treat (mITT) population for the analysis (see Table 2.14).

All five experimental regimens were of 9 months (i.e. 39 weeks) duration. Three of these regimens included bedaquiline for the whole duration of the regimen (400 mg once daily for the first 2 weeks of treatment, followed by 200 mg 3 times per week), a quinolone (either moxifloxacin or levofloxacin), linezolid, pyrazinamide, and either delamanid (100 mg BID) or clofazimine or no fifth drug. The remaining two regimens were without bedaquiline but included delamanid, a quinolone (moxifloxacin or levofloxacin), clofazimine and pyrazinamide, with or without linezolid as a fifth medicine (see Table 2.13). All patients who received linezolid started at 600 mg daily but were later randomized to a reduced dose (300 mg daily or 600 mg 3 times a week) at 16 weeks or earlier in case of dose-limiting toxicity.

Table 2.13. endTB trial regimens

Regimens	Bedaquiline	Delamanid	Linezolid	Quinolone	Clofazimine	Pyrazinamide
endTB 1	**B**		**L**	**M**		**Z**
endTB 2	**B**		**L**	**Lfx**	**C**	**Z**
endTB 3	**B**	**D**	**L**	**Lfx**		**Z**
endTB 4		**D**	**L**	**Lfx**	**C**	**Z**
endTB 5		**D**		**M**	**C**	**Z**
Control	The longer (18-month) standard of care control composed according to WHO guidelines.					

Lfx: levofloxacin; M: moxifloxacin; WHO: World Health Organization.

Methods used for analysis and data synthesis

Descriptive analyses

Descriptive analyses of the baseline characteristics of participants in the study were performed. Characteristics included demographics, pregnancy status and laboratory parameters such as HIV status, CD4 count (if applicable), drug susceptibility tests and diagnostic test results, TB treatment received before randomization, AEs and treatment regimens, and end-of-treatment and end-of-follow-up outcomes.

Statistical analyses

Statistical analyses were based on the WHO outcome definitions listed in Annex 2.

The endTB trial specified follow-up for at least 73 weeks, but most participants were followed up until the end of the control regimen and 104 weeks post-randomization. The outcome was assigned for endpoints at 73 and 104 weeks. For the WHO review, the efficacy analyses used the week 104 endpoint (see Table 2.14). The study team performed the analyses and presented them to the WHO panel.

The endTB outcome definitions were similar to the WHO outcome definitions, except for the LTFU. Patients who were originally classified as being LTFU based on the endTB protocol and statistical analysis plans (and thus assigned an unfavourable outcome) were reclassified as "sustained treatment success" if all of the following conditions were met:

- the participant had completed treatment;
- the participant had been assigned an unfavourable outcome at week 104 based on the endTB protocol solely because of missed visits, LTFU, or withdrawal of consent; and
- the participant had at least one negative culture and no positive cultures after treatment completion.

Table 2.14. Cross-tabulation of endTB and WHO outcomes at week 104 – mITT population

endTB W104 outcomes	WHO W104 outcomes				
	Sustained treatment success	Not sustained treatment success			
		Failure or recurrence	Death	LTFU	Total
Favourable	574	0	0	0	574
Unfavourable	7	41	16	61	125
Death	0	0	16	0	16
Positive culture	0	25	0	0	25
Poor evolution	0	0	0	0	0
Recurrence	0	4	0	0	4
AEs[a]	0	12	0	0	12
Poor adherence[a]	0	0	0	17	17
Consent withdrawal	0	0	0	17	17
LTFU	4	0	0	17	21
Other[b]	3	0	0	10	13
Total	581	41	16	61	699

AE: adverse event; LTFU: loss to follow-up; mITT: modified intention-to-treat; W104: week 104; WHO: World Health Organization.

[a] Treatment discontinued for specified reasons

[b] Not assessable after completing treatment (6), Investigator's judgement (4), Pregnancy or breastfeeding (2), Use of prohibited concomitant medication (1)

The evidence on the novel regimens to inform PICO questions was derived from one trial. Data from patients in relevant arms of this trial were used in each of the endTB trial comparisons that led to the conclusions and final recommendation on the use of the BLMZ, BLLfxCZ and BDLLfxZ.

Table 2.15. High-level summary of main inclusion and exclusion criteria: endTB trial

	endTB
Inclusion	• Has documented pulmonary TB due to strains of *M. tuberculosis* resistant to rifampin (RIF) and susceptible to FQ, diagnosed by validated rapid molecular test. • Is ≥15 years of age. • Is willing to use contraception: premenopausal women or women whose last menstrual period was within the preceding year, who have not been sterilized, must agree to use contraception unless their partner has had a vasectomy; men who have not had a vasectomy must agree to use condoms.

Exclusion	• Is known to be pregnant or is unwilling or unable to stop breastfeeding an infant. • Has had exposure (intake of the drug for 30 days or more) in the past 5 years to bedaquiline, delamanid, linezolid or clofazimine, or has proven or likely resistance. • Has received second-line drugs for 15 days or more prior to screening visit date in the current MDR/RR-TB treatment episode. • Has one or more of the following: – haemoglobin ≤7.9 g/dL; – uncorrectable electrolytes disorders; – total calcium <7.0 mg/dL (1.75 mmol/L); – potassium <3.0 mEq/L (3.0 mmol/L) or ≥6.0 mEq/L (6.0 mmol/L); – magnesium <0.9 mEq/L (0.45 mmol/L); – serum creatinine >3 × upper limit of normal (ULN); – aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3 × ULN; or – total bilirubin ≥3 × ULN. • Unless otherwise specified, Grade 4 result as defined by the MSF severity scale on any of the screening laboratory tests. • Has cardiac risk factors defined QTcF intervals of ≥450 ms.

FQ: fluoroquinolones; *M. tuberculosis*: *Mycobacterium tuberculosis*; MDR/RR-TB: multidrug- or rifampicin-resistant TB; MSF: Médecins sans Frontières; QTcF: corrected QT interval by Fredericia; TB: tuberculosis.

Decision thresholds

In contrast to previous recommendations, a new method of determining the magnitude of the health effects was used. A triangulation approach was used to develop outcome-specific decision thresholds (DTs) for judging the magnitude of the effects for the following health outcomes: death, sustained treatment success, treatment failure or recurrence, LTFU, AEs and amplification of drug resistance. These outcomes were deemed critical or important for decision-making based on a prioritization survey of the GDG members using the GRADE approach. The survey included health outcome descriptors that had previously been developed for each of the health outcomes to facilitate understanding of the outcomes by the GDG during their decision-making process.

The GDG first reviewed judgements about the magnitude of health effects made by other GDGs for previous WHO MDR-TB guidelines *(3, 14)* to determine approximate ranges of effect sizes that the group considered to be trivial, small, moderate or large. Members then identified a systematic review to help inform suggested health utility values for the health state of having DR-TB disease and treatment success (about 0.5) and treatment success (about 0.9) *(36)*. For the other outcomes (treatment failure, LTFU, amplification of drug resistance and AEs), a health utility value of 0.5 was used, considering that these would be similar health states to having DR-TB disease, and to align with previous judgements made in other TB guidelines.

Second, the group used the empirical evidence from the GRADE THRESHOLD trial *(37)* to calculate suggested utility-adjusted absolute effect thresholds for the health outcomes. The calculated thresholds were as follows *(38)*:

- death (health utility: 0):
  - trivial or no effect: ≤14 fewer or more deaths per 1000 people;
  - small effect: 15–32 fewer or more deaths per 1000 people;
  - moderate effect: 33–63 fewer or more deaths per 1000 people;
  - large effect: ≥64 fewer or more deaths per 1000 people;

- sustained treatment success (health utility: 0.9):
  - trivial or no effect: ≤15 fewer or more treatment successes per 1000 people;
  - small effect: 16–35 fewer or more treatment successes per 1000 people;
  - moderate effect: 36–68 fewer or more treatment successes per 1000 people;
  - large effect: ≥69 fewer or more treatment successes per 1000 people;
- treatment failure or recurrence, LTFU, AEs and amplification (acquisition) of drug resistance (all with health utility 0.5):
  - trivial or no effect: ≤30 fewer or more failures or recurrences per 1000 people;
  - small effect: 31–59 fewer or more failures or recurrences per 1000 people;
  - moderate effect: 60–119 fewer or more failures or recurrences per 1000 people; and
  - large effect: ≥120 fewer or more failures or recurrences per 1000 people.

These suggested thresholds (assumed to occur over the duration of follow-up in the trials) were generally consistent with judgements that were made in the previous WHO MDR-TB guidelines *(3)*.

Third, in preparation for the GDG meeting at which recommendations would be formulated, an online survey was administered to the group to obtain their feedback on the suggested DTs. The survey asked members to agree with the suggested thresholds, or to disagree and suggest alternative thresholds based on their expert experience. The agreed-upon thresholds were again reviewed at the start of the GDG meeting, and the group decided to use those thresholds to inform their judgements about the magnitude of health effects in the GRADE EtD frameworks. Figures were created to visually depict absolute effects and 95% CIs from the research evidence of the relevant trial in relation to the DTs for each health outcome, to facilitate the GDG's discussion and judgements about whether the health effects were trivial, small, moderate or large, and to judge the level of imprecision of estimates (Figs. 2.1–2.5). The same thresholds were used to inform the group's judgements about imprecision, in line with GRADE guidance for decision-making *(39)*.

Summary of evidence on desirable and undesirable effects and certainty of evidence

Sub-PICO 2.1–2024 (MDR/RR-TB, 2024): Should a 9-month regimen using bedaquiline, linezolid, moxifloxacin, and pyrazinamide (9BLMZ) vs. currently recommended longer WHO regimens be used in patients with pulmonary RR-TB (without fluoroquinolone resistance)?

Patients with MDR/RR-TB receiving the BLMZ regimen (*n*=118 for death, failure and recurrence and LTFU; *n*=126 for AEs and *n*=127 for amplification of drug resistance) compared with those receiving the currently recommended longer WHO regimens (*n*=119 for death, failure and recurrence and LTFU; *n*=126 for AEs and *n*=130 for amplification of drug resistance) experienced:

- lower levels of death: 1.7% versus 3.4%; RD=17 fewer per 1000 (95% CI: from 57 fewer to 23 more per 1000);
- lower levels of LTFU: 5.9% versus 16.8%; RD=109 fewer per 1000 (95% CI: from 188 fewer to 29 fewer per 1000);
- lower levels of people with at least one grade 3 to 5 AEs: 55.6% versus 65.1%; RD=95 fewer per 1000 (95% CI: from 216 fewer to 25 more per 1000);
- lower levels of people with at least one serious AE: 15.9% versus 19.0%; RD=32 fewer per 1000 (95% CI: from 125 fewer to 62 more per 1000);
- similar levels of amplified resistance: 0.0% versus 0.0%; RD=0 fewer per 1000 (95% CI: from 29 fewer to 29 more per 1000); and
- higher levels of failure or recurrence: 3.4% versus 2.5%; RD=9 more per 1000 (95% CI: from 34 fewer to 52 more per 1000).

The GDG judged the benefits of BLMZ to be moderate and the undesirable effects to be trivial compared with WHO-recommended longer regimens. The certainty of evidence was judged to be overall very low, with probably no important uncertainty in the values that people place on the

outcomes. Hence, the GDG determined that the balance of health effects probably favours the BLMZ regimen.

Conclusion

The BLMZ regimen (composed of bedaquiline, linezolid, moxifloxacin and pyrazinamide) is suggested over currently recommended longer regimens in patients with FQ-susceptible RR-TB.

Sub-PICO 2.2–2024 (MDR/RR-TB, 2024): Should a 9-month regimen using bedaquiline, clofazimine, linezolid, levofloxacin, and pyrazinamide (9BLLfxCZ) vs. currently recommended longer WHO regimens be used in patients with pulmonary RR-TB (without fluoroquinolone resistance)?

Patients with MDR/RR-TB receiving the BLLfxCZ regimen (*n*=115 for death, failure and recurrence and LTFU and *n*=122 for AEs; and *n*=124 for amplification of drug resistance) compared with those receiving the currently recommended longer WHO regimens (*n*=119 for death, failure and recurrence and LTFU and *n*=126 for AEs; and *n*=130 for amplification of drug resistance) experienced:

- lower levels of death: 0.9% versus 3.4%; RD=25 fewer per 1000 (95% CI: from 62 fewer to 12 more per 1000);
- lower levels of LTFU: 4.3% versus 16.8%; RD=125 fewer per 1000 (95% CI: from 201 fewer to 48 fewer per 1000);
- lower levels of people with at least one Grade 3 to 5 AEs: 59.0% versus 65.1%; RD=61 fewer per 1000 (95% CI: from 181 fewer to 60 more per 1000);
- lower levels of people with at least one serious AE: 14.8% versus 19.0%; RD=43 fewer per 1000 (95% CI: from 136 fewer to 50 more per 1000);
- higher levels of failure or recurrence: 6.1% versus 2.5%; RD=36 more per 1000 (95% CI: from 16 fewer to 123 more per 1000); and
- higher levels of amplified resistance: 1.6% versus 0%; RD=16 more per 1000 (95% CI: from 13 fewer to 56 more per 1000).

The GDG judged the benefits of BLLfxCZ to be moderate and the undesirable effects to be small compared with WHO-recommended longer regimens. The certainty of evidence was judged to be very low overall, with probably no important uncertainty in the values that people place on the outcomes. Hence, the GDG determined that the balance of health effects probably favours the BLLfxCZ regimen.

Conclusion

The BLLfxCZ regimen composed of bedaquiline, linezolid, levofloxacin, clofazimine and pyrazinamide is suggested over currently recommended longer regimens in patients with FQ-susceptible RR-TB.

Sub-PICO 2.3–2024 (MDR/RR-TB, 2024): Should a 9-month regimen using bedaquiline, delamanid, linezolid, levofloxacin, and pyrazinamide (9BDLLfxZ) vs. currently recommended longer WHO regimens be used in patients with pulmonary RR-TB (without fluoroquinolone resistance)?

Patients with MDR/RR-TB receiving the BDLLfxZ regimen (*n*=122 for failure and recurrence, death, and LTFU; *n*=127 for AEs and *n*=128 for amplification of drug resistance) compared with those receiving the currently recommended longer WHO regimens (*n*=119 for failure and recurrence, death and LTFU; *n*=126 for AEs and *n*=130 for amplification of drug resistance) experienced:

- lower levels of failure or recurrence: 1.6% versus 2.5%; RD=9 fewer per 1000 (95% CI: from 45 fewer to 27 more per 1000);
- lower levels of death: 2.5% versus 3.4%; RD=9 fewer per 1000 (95% CI: from 52 fewer to 33 more per 1000);

- lower levels of LTFU: 10.7% versus 16.8%; RD=62 fewer per 1000 (95% CI: from 148 fewer to 25 more per 1000);
- lower levels of people with at least one Grade 3 to 5 AEs: 63.0% versus 65.1%; RD=21 fewer per 1000 (95% CI: from 139 fewer to 97 more per 1000);
- lower levels of people with at least one serious AE: 15.7% versus 19.0%; RD=33 fewer per 1000 (95% CI: from 126 fewer to 60 more per 1000); and
- similar levels of amplified resistance: 0.0% versus 0.0%; RD=0 fewer per 1000 (95% CI: from 29 fewer to 29 more per 1000).

The GDG judged the benefits of BDLLfxZ to be small and the undesirable effects to be trivial compared with WHO-recommended longer regimens. The certainty of evidence was judged to be very low overall, with probably no important uncertainty in the values that people place on the outcomes. Hence, the GDG determined that the balance of health effects probably favours the BDLLfxZ regimen.

Conclusion

The BDLLfxZ regimen composed of bedaquiline, delamanid, linezolid, levofloxacin and pyrazinamide is suggested over currently recommended longer regimens in patients with FQ-susceptible RR-TB.

Sub-PICO 2.4–2024 (MDR/RR-TB, 2024) Should a 9-month regimen using delamanid, clofazimine, linezolid, levofloxacin, and pyrazinamide (9DCLLfxZ) vs. currently recommended longer WHO regimens be used in patients with pulmonary RR-TB (without fluoroquinolone resistance)?

Patients with MDR/RR-TB receiving the DCLLfxZ regimen (*n*=118 for death, failure and recurrence and LTFU; *n*=124 for AEs and n=125 for amplification of drug-resistance) compared with those receiving the currently recommended longer WHO regimens (*n*=119 for death, failure and recurrence and LTFU and *n*=126 for AEs; and *n*=130 for amplification of drug resistance) experienced:

- lower levels of death: 2.5% versus 3.4%; RD=8 fewer per 1000 (95% CI: from 51 fewer to 35 more per 1000);
- lower levels of LTFU: 10.2% versus 16.8%; RD=66 fewer per 1000 (95% CI: from 153 fewer to 20 more per 1000);
- lower levels of Grade 3 to 5 AEs: 62.9% versus 65.1%; RD=22 fewer per 1000 (95% CI: from 141 fewer to 97 more per 1000);
- lower levels of people with at least one serious AE: 15.3% versus 19.0%; RD=37 fewer per 1000 (95% CI: from 131 fewer to 56 more per 1000);
- higher levels of failure or recurrence: 11.0% versus 2.5%; RD=85 more per 1000 (95% CI: from 22 more to 148 more per 1000); and
- higher levels of amplified resistance: 4.0% versus 0%; RD=40 more per 1000 (95% CI: from 9 more to 87 more per 1000).

The GDG judged the benefits of DCLLfxZ to be small and the undesirable effects to be moderate compared with WHO-recommended longer regimens. The certainty of evidence was judged to be very low overall, with probably no important uncertainty in the values that people place on the outcomes. Hence, the GDG determined that the balance of health effects probably favours the WHO-recommended longer regimens.

Conclusion

The GDG suggested against the use of the DCLLfxZ regimen in patients with FQ-susceptible RR-TB.

Sub-PICO 2.5–2024 (MDR/RR-TB, 2024) Should a 9-month regimen using delamanid, clofazimine, moxifloxacin, and pyrazinamide (9DCMZ) vs. currently recommended longer WHO regimens be used in patients with pulmonary RR-TB (without fluoroquinolone resistance)?

Patients with MDR/RR-TB receiving the DCMZ regimen (*n*=107 for death, failure and recurrence and LTFU; *n*=120 for AEs and for amplification of drug resistance) compared with those receiving the currently recommended longer WHO regimens (*n*=119 for death, failure and recurrence and LTFU and *n*=126 for AEs; and *n*=130 for amplification of drug resistance) experienced:

- lower levels of death: 2.8% versus 3.4%; RD=5 fewer per 1000 (95% CI: from 50 fewer to 41 more per 1000);
- lower levels of LTFU: 3.7% versus 16.8%; RD=131 fewer per 1000 (95% CI: from 207 fewer to 54 fewer per 1000);
- lower levels of people with at least one Grade 3 to 5 AEs: 60.0% versus 65.1%; RD=51 fewer per 1000 (95% CI: from 172 fewer to 70 more per 1000);
- lower levels of people with at least one serious AE: 17.5% versus 19.0%; RD=15 fewer per 1000 (95% CI: from 112 fewer to 81 more per 1000);
- higher levels of failure or recurrence: 11.2%% versus 2.5%; RD=87 more per 1000 (95% CI: from 21 more to 153 more per 1000); and
- higher levels of amplified resistance: 6.7% versus 0%; RD=67 more per 1000 (95% CI: from 32 more to 119 more per 1000).

The GDG judged the benefits of DCMZ to be moderate and the undesirable effects to be moderate compared with WHO-recommended longer regimens. The certainty of evidence was judged to be very low overall, with probably no important uncertainty in the values that people place on the outcomes. Within the category of moderate effects, the undesirable effects were considered of greater weight and had higher certainty associated with them – in particular for the amplification of drug resistance. The trial data suggest that drug resistance includes losing FQ in almost all patients who failed treatment. Hence, the GDG determined that the balance of health effects probably favours the WHO-recommended longer regimens.

Conclusion

The GDG suggested against the use of the DCMZ regimen in patients with FQ-susceptible RR-TB.

Summary of other evidence

Additional data reviewed by the GDG relevant to these PICO questions.

Resources required and cost–effectiveness

Additional data reviewed by the GDG relevant to these PICO questions were the estimates of the regimen prices provided by the GDF based on the most recent drug pricing included in the GDF online catalogue *(55)*, as shown in Table 2.16.

Table 2.16. Regimen cost estimates[a]

	Regimen	Estimated regimen price (US$)
endTB trial regimens	BLMZ	205
	BLLfxCZ	324
	BDLLfxZ	1748
WHO-recommended regimens	Longer regimen ($18B_6$LfxLC)	475

BDLLfxZ: bedaquiline, delamanid, linezolid, levofloxacin and pyrazinamide; BLLfxCZ: bedaquiline, linezolid, levofloxacin, clofazimine and pyrazinamide; BLMZ: bedaquiline, linezolid, moxifloxacin and pyrazinamide; GDF: Global Drug Facility; WHO: World Health Organization.

[a] Prices are based on the GDF online catalogue on 13 February 2026 *(55)*.

As shown in Table 2.17, the GDG also considered the following example of country-specific patient-borne and health system costs over a 9-month span (excluding drug costs) (based on modelling analysis in Ryckman et al. 2024 *(56)*. Costs may vary, depending on the composition of the regimen being used.

Table 2.17. Patient-borne and health system costs

	Costs over 9 months (US$)		
Country	**Patient**	**Health system**	**Total**
India	1152	261	**1413**
Philippines	2322	702	**3024**
South Africa	1026	1926	**2952**

For all three recommended regimens, the drug prices were elicited from the Stop TB Partnership's GDF; health system and patient costs in the three settings were estimated based on data from an economic modelling analysis *(56)*, and extrapolated to the 9-month time period to account for the difference in the treatment durations. The estimated costs from the economic modelling analysis do not account for possible imprecision in the cost estimates; however, they do provide indirect data for other settings where the treatment regimen would be used. Therefore, the panel judged the certainty of evidence of required resources to be low.

The GDG noted that the drug prices for BLMZ and BLLfxCZ, are lower than the typical costs of the longer (18 month) regimens. In addition, shortening the treatment duration from 18 to 9 months would result in savings to both patients and the health system. Therefore, the GDG considered that – when compared with the currently recommended longer WHO regimens – the BLMZ and BLLfxCZ regimens would result in large savings. Although no research evidence on cost–effectiveness was available, the GDG discussed that, given the moderate net benefit and large cost savings with BLMZ and BLLfxCZ, a judgement of cost–effectiveness favouring the intervention is appropriate. This judgement is based on logical arguments that a cheaper regimen with better health outcomes will be cost-effective, although the exact savings are not known without such analyses.

For BDLLfxZ, the GDG noted that affordability will vary, depending on country (and resources available), health system differences and the population the regimen would be used for; accordingly, the GDG judged that costs would vary between moderate and large.

Delamanid is one of the major cost drivers in BDLLfxZ. With the drug being off-patent, prices may change with generic development. It was highlighted that a longer duration of treatment bears costs (especially for patients and families but also the health system) and some estimates were available and discussed by the group. Considering these costs together with the drug costs may attenuate some of the increased costs for the health system and lead to cost savings from the patient perspective. However, countries seeking to implement a specific treatment regimen typically focus on the drug cost. No evidence on cost–effectiveness was available for BDLLfxZ.

Equity, acceptability and feasibility

The panel considered the treatment duration and the ability to decentralize treatment (to enable access for remote, underserved settings and disadvantaged populations) to affect equity. Despite not being able to identify relevant research evidence, the panel used their collective experience to judge that there would probably be advantages associated with the use of BLMZ, BLLfxCZ and BDLLfxZ regimens, owing to their reduced complexity and shorter duration. In the case of BLMZ and BLLfxCZ, the panel also highlighted the possible positive effect of the overall lower cost. Therefore, the panel judged that use of the BLMZ, BLLfxCZ and BDLLfxZ regimens would probably increase equity.

In judging the acceptability of the regimens, the GDG considered patients and health care providers as key stakeholders. The GDG considered the regimen duration as critical with regards to acceptability, and therefore judged that the BLMZ, BLLfxCZ and BDLLfxZ regimens would probably be acceptable when compared with the longer 18-month regimens. Regarding BLLfxCZ, the GDG additionally noted that clofazimine may be less acceptable (e.g. because of skin discolouration), and noted 4% discontinuation due to clofazimine in the intervention arm in the trial. For the regimens BLLfxCZ and BDLLfxZ, there is also one additional drug (giving a total of 5 drugs) compared with the BLMZ regimen. Regarding BDLLfxZ, the GDG highlighted that delamanid requires taking medicines twice per day in this regimen, which may affect acceptability. Despite this, the GDG judged that BLLfxCZ and BDLLfxZ would probably be acceptable.

In judging the feasibility, the panel highlighted that the cost of BDLLfxZ (driven by delamanid) may affect feasibility for programme managers in particular.

Evidence to recommendations: considerations

Based on the decisions taken during the review and the combination of assessments described in Annex 5, WHO suggests using the 9-month all-oral regimens (BLMZ, BLLfxCZ and BDLLfxZ) over currently recommended longer (>18 months) regimens in patients with MDR/RR-TB and in whom resistance to FQ has been excluded. Also, WHO suggests against using 9-month DCLLfxZ or DCMZ regimens compared with currently recommended longer (>18 months) regimens in patients with FQ-susceptible MDR/RR-TB.

Among the newly recommended regimens, using BLMZ is suggested over using BLLfxCZ, and BLLfxCZ is suggested over BDLLfxZ. This ranking is based on an evaluation of all evidence and judgements made for individual sub-PICOs 2.1, 2.2 and 2.3, and deliberation by the panel. The panel was first asked to make judgements for each decision criterion about a comparative ranking the regimens (Table 2.18).

Table 2.18. Multiple comparisons of three recommended endTB trial regimens[a]

	BLMZ	BLLfxCZ	BDLLfxZ
Balance of effects	★★★★	★★★	★★★
Resources required	★★★★★	★★★★★	★★
Cost–effectiveness	★★★★	★★★	★★
Equity	★★★★	★★★★	★★★
Acceptability	★★★★	★★★	★★
Feasibility	★★★★★	★★★★★	★★★★

BDLLfxZ: bedaquiline, delamanid, linezolid, levofloxacin and pyrazinamide; BLLfxCZ: bedaquiline, linezolid, levofloxacin, clofazimine and pyrazinamide; BLMZ: bedaquiline, linezolid, moxifloxacin and pyrazinamide.

[a] The number of stars is used as a measure of ranking with a maximum of 5.

Following this, the panel was asked to deliberate about the ranking of the three regimens considering their previous judgements and all available evidence. The rationale for the ranking can be summarized as follows:

- **BLMZ was preferred over BLLfxCZ and BDLLfxZ:**
  - BLMZ appeared preferable in terms of the balance of health effects compared with both BLLfxCZ and BDLLfxZ.
  - BLMZ also has the lowest cost and pill burden, and appeared either preferable or equivalent for all other decision criteria.
  - Therefore, BLMZ was deemed to be the preferred regimen between the three.
- **BLLfxCZ was preferred over BDLLfxZ:**
  - BLLfxCZ, compared with BDLLfxZ, was deemed to have a similar but slightly preferable balance of health effects.
  - BLLfxCZ also has a significantly lower cost and a lower pill burden than BDLLfxZ.
  - The much greater cost of BDLLfxZ was judged to be likely to have negative effects on equity, acceptability and feasibility.
  - Therefore, BLLfxCZ was deemed to be the preferrable over BDLLfxZ.

Subgroup considerations

Children and adolescents

Children and adolescents (aged 0–14 years) were excluded from the endTB trial; therefore, no analysis specific to this subgroup could be performed. Ten participants aged between 15 and 18 years were enrolled in the experimental arms (2 to BLMZ, 3 to BLLfxCZ, and 5 to BDLLfxZ). However, all medicines in the regimens have been used in children and have well-documented safety and efficacy profiles and sufficient PK/PD data. The GDG judged that it was appropriate to extrapolate from the efficacy data in adults from the endTB trial to children and adolescents.

As with adults, the BLMZ regimen is the preferred modified 9-month regimen for children, where its low pill burden and the availability of child-friendly formulations offers additional advantages. When these formulations are unavailable, practical guidance on adjusting adult formulations for children is provided in the operational handbook, to ensure that the lack of paediatric-specific formulations does not hinder treatment.

People living with HIV

The study included people living with HIV regardless of their immunological status. HIV was diagnosed in 98 (14.1%) people enrolled in the endTB trial, with 15 enrolled to BLMZ, 14 to BLLfxCZ, 17 to BDLLfxZ and 19 in the control arm. Provided that suppressive antiretroviral therapy is given, similar efficacy should be expected (stratified analyses largely supported this).

Pregnant and breastfeeding women

There were no data from the endTB trial on using the recommended regimens in pregnant and breastfeeding women. Other studies support that MDR/RR-TB can be managed during pregnancy with caution regarding the drugs used in BLMZ, BLLfxCZ, and BDLLfxZ *(71, 72)*. Close monitoring and systematic collection of data from pregnant, breastfeeding and postpartum patients will offer valuable insights into treatment outcomes, thereby contributing to safer, evidence-based care for pregnant women with MDR/RR-TB.

Extrapulmonary TB

The endTB trial enrolled participants with extrapulmonary TB if they also had pulmonary TB; no specific analysis could be performed for participants with extrapulmonary TB. However, the GDG felt that extrapolation to extrapulmonary TB and other forms of TB was warranted except in cases involving severe forms of TB that may require special treatment arrangements and decisions, particularly TB involving the CNS, osteoarticular and disseminated forms of TB. Thus, the recommendation of the BLMZ, BLLfxCZ and BDLLfxZ regimens applies to people with pulmonary TB and all forms of extrapulmonary TB except for TB involving the CNS, and osteoarticular and disseminated forms of TB.

Other considerations

Several other patient groups were evaluated in the endTB trial. Excluded from enrolment were people with anaemia, uncorrectable electrolyte disorders, renal dysfunction, liver dysfunction AST, ALT or total bilirubin at least three times the upper limit of normal, with cardiac risk factors, a QTcF above 450 ms and other Grade 4 results. These groups of patients may still receive the regimens if the treating physician considers it the best option despite these possible contraindications.

Participants with diabetes, regardless of their HbA1c levels, could be enrolled. The panel found no evidence suggesting different conclusions for this group compared with the overall recommendations.

Implementation considerations

Patient selection

Eligibility for the three modified 9-month regimens is outlined under remarks on Recommendation 2.2. The regimens are considered for the treatment of patients with MDR/RR-TB in whom resistance to FQ has been excluded, and who cannot be offered any of the two recommended 6-month regimens (see consolidated operational handbook *(73)*).

The regimens are suitable for patients with pulmonary or all forms of extrapulmonary TB disease, except for TB involving the CNS, osteoarticular, or disseminated forms of TB with multiorgan involvement.

Participants of all ages, including children and adolescents or people living with HIV (regardless of CD4 count), diabetes (regardless of A1c), substance use disorders and mental illness could be enrolled.

Individuals with MDR/RR-TB who have had less than 1 month of previous exposure to any of the component medicines of the regimen (apart from PZA, where prior exposure is permitted; and quinolones, where resistance should be excluded), are eligible for treatment with these regimens.

Additionally, the treatment programme may enrol children and adolescents who do not have bacteriological confirmation of TB or defined resistance patterns but are deemed to have a high likelihood of MDR/RR-TB, based on clinical signs and symptoms of TB and a history of contact with a confirmed MDR/RR-TB patient.

Drug susceptibility testing

A WHO-recommended rapid molecular test to confirm FQ susceptibility should be conducted before starting the treatment with the modified 9-month regimens. In settings where DST for other drugs in the regimen can be done and resistance to any of the component medicines of the regimen (apart from PZA, discussed separately below) is confirmed, the regimens should not be used.

The endTB trial data suggested reduced efficacy among patients with PZA resistance. However, the best estimates suggested higher success rates than with the longer regimen, even in cases of PZA resistance. Therefore, the GDG suggested that PZA can be dropped from the modified 9-month regimens if resistance to PZA is reliably confirmed or if there are PZA-associated AEs. However, if PZA is discontinued, the rest of the regimen should continue as prescribed. In settings where PZA testing is not widely available, PZA should be maintained unless there are PZA-related AEs.

Adverse events and drug–drug interactions

For patients on treatment with modified 9-month regimens, it is essential to undertake active TB drug-safety monitoring and management for close monitoring and adequately managing AEs and preventing complications from drug–drug interactions.

An important AE in patients using the modified 9-month regimens is hepatoxicity in relation to PZA. In the endTB trial, screening for elevation of liver enzymes was performed monthly throughout treatment, regardless of symptoms. Elevation in liver enzymes, with or without accompanying symptoms, occurred frequently during treatment. Grade 3 hepatotoxicity was defined in the trial as ALT (SGPT) or AST (SGOT) levels greater than five times but less than or equal to 10 times the upper limit of normal. Specifically, transient Grade 3 or higher hepatotoxicity occurred in 18% of patients in BLMZ, 16% in BLLfxCZ and 8.7% in BDLLfxZ in the safety population of the endTB trial. Imprecision in these estimates meant that it was not possible to draw any firm conclusions about differences between regimens. During the trial, suspension of PZA was recommended when liver enzyme levels exceeded five times the upper limit of the upper limit normal (5×ULN). PZA was permanently discontinued in an average of 17% of patients, with no significant differences among the three regimens. Most patients receiving the modified 9-month regimens received 39 weeks of PZA, and patients who permanently discontinued PZA received the drug for between 85 and 112 days, again with minimal variation between the regimens.

Regimen composition, dosing of component medicines and frequency

The short names of the regimens with one-letter abbreviations for the drugs, the three-letter abbreviations and compositions of the modified 9-month regimens are given in Table 2.19. All of the modified 9-month regimens have bedaquiline, linezolid, pyrazinamide and a fluoroquinolone as core, with one or two other additional drugs.

Table 2.19. The composition of the three modified 9-month regimens

Regimen name	Three-letter drug abbreviations	Composition with full drug names
BLMZ	9Bdq-Lzd-Mfx-Z	Bedaquiline-linezolid-moxifloxacin-pyrazinamide
BLLfxCZ	9Bdq-Lzd-Lfx-Cfz-Z	Bedaquiline-linezolid-levofloxacin-clofazimine-pyrazinamide
BDLLfxZ	9Bdq-Dlm-Lzd-Lfx-Z	Bedaquiline-delamanid-linezolid-levofloxacin-pyrazinamide

The dosing for linezolid and bedaquiline in these regimens deviates slightly from the standard dosing used in other treatment regimens:

- in the trial participants received linezolid at 600 mg once daily for 16 weeks then randomized to either reduced dose of 300 mg once daily or 600 mg three times a week until the end of treatment, outcomes appeared to be similar for both options;
- bedaquiline was dosed at 400 mg daily for the first 2 weeks, followed by 200 mg three times a week for the full 9-month period.

Both options for linezolid dosing strategy can be used. The alternative daily dosing of bedaquiline was not used in the modified 9-month regimens; however, it is considered an equivalent option that may simplify treatment for the patient by requiring the same number of pills every day, streamlining the dosing schedule. Dosing of the other drugs in the modified 9-month regimen follows the standardized weight-based dosing of medicines used in MDR/RR-TB regimens, for adults and children

Regimen duration, extension and discontinuation

In general, the individual drugs in the modified 9-month regimens are all used for the full 9-month duration. All three endTB trial regimens were stopped at month 9 without an option for extending the duration. Discontinuation of either pyrazinamide or linezolid due to AEs may be considered, and the regimen may continue with the remaining drugs. However, if more than a single drug needs to be discontinued, the regimen should be stopped and an alternative treatment started.

Where there is a lack of clinical or bacteriological response (e.g. culture remains positive or reverts positive at month 4 or beyond), there should be an investigation for a possible undiagnosed or acquired drug resistance.

Missing doses and treatment interruptions

Making up for missed doses follows routine TB practice when accumulative interruption of all medicines in the regimen exceeds 7 days but is less than a month.

Care and support

Treatment administration coupled with patient support can boost adherence and ensure optimal drug effectiveness and safety of patients on treatment. Measures to support patient adherence (e.g. by facilitating patient visits to health care facilities or home visits by health care staff, or by using digital technologies for daily communication) may be important to retain patients on treatment, even when a regimen is comparatively short. WHO recommendations on care and support are discussed in Chapter 3.

Recommendation B2.4 The use of bedaquiline in children with MDR/RR-TB aged below 6 years

No.	Recommendation
B2.4	In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used *(Conditional recommendation, very low certainty of the evidence)*.

Remarks

This recommendation applies to and complements current WHO recommendations on shorter and longer regimens that contain bedaquiline:

- A shorter all-oral bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded.
  (Conditional recommendation, very low certainty of evidence)
- Bedaquiline should be included in longer multidrug-resistant TB (MDR-TB) regimens for patients aged 18 years or more.
  (Strong recommendation, moderate certainty of evidence)
- Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years.
  (Conditional recommendation, very low certainty of evidence)

Justification and evidence

> ***PICO question**: In MDR/RR-TB patients aged below 6 years, should an all-oral treatment regimen containing bedaquiline versus other regimens conforming to WHO guidelines without bedaquiline be used?*

Historical context: In 2012, for the first time in over 40 years, a new TB drug with a novel mechanism of action – namely bedaquiline – was granted accelerated approval by the United States Food and Drug Administration (FDA) for the treatment of MDR-TB among adults (≥18 years of age) for whom an effective treatment regimen was not otherwise available *(74)*. In 2013, following an expert group meeting which reviewed available Phase IIb trial data on the efficacy and safety of bedaquiline, the WHO issued an interim policy guidance comprising a conditional recommendation and based on very low confidence in the estimates of effect, indicating that bedaquiline may be added to a WHO-recommended regimen in adults with MDR-TB (≥18 years of age) under specific conditions *(14)*.

In 2016, after the introduction and roll-out of bedaquiline in an increasing number of countries and with more data available on its use, WHO convened a GDG meeting to re-evaluate the added benefit of bedaquiline in conjunction with a WHO-recommended longer regimen for the treatment of MDR-TB. At this time, the GDG (2016) agreed that there was not enough evidence to prompt a change in the 2013 recommendation *(14)*.

In 2019, after a GDG meeting where new evidence was reviewed from the adult IPD and two ongoing paediatric studies (TMC207-C211 and IMPAACT P1108), WHO issued the consolidated guidelines on DR-TB treatment *(2)*, where bedaquiline was recommended for inclusion in longer MDR-TB regimens for persons aged 18 years or more (strong recommendation, moderate certainty of evidence) and in longer MDR-TB regimens for children and adolescents aged 6–17 years (conditional recommendation, very low certainty of evidence). Also in 2019, following the review of available data on the programmatic implementation of a shorter, all-oral treatment regimen including bedaquiline in South Africa, WHO recommended a shorter, all-oral bedaquiline-containing regimen of 9–11 months for eligible persons

with confirmed MDR/RR-TB who were not exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones was excluded (conditional recommendation, very low certainty in the evidence) *(31)*. This recommendation for the shorter all-oral bedaquiline-containing regimen replaced earlier recommendations for shorter regimens that included an injectable agent. In a new IPD meta-analysis used as evidence for the 2020 WHO guidelines, bedaquiline use resulted in significantly fewer episodes of treatment failure, relapse and death *(75)*. At the time, there was limited experience in the use of bedaquiline in children aged below 6 years, but experience of its use in adolescents, patients with EPTB disease and people living with HIV was growing. Earlier recommendations on the composition of longer regimens indicated that bedaquiline could also be included in such regimens for patients aged 6–17 years; hence, the all-oral bedaquiline-containing regimen was also conditionally recommended for use in eligible children and adolescents aged 6 years and above.

Gap: The recommendations that apply to children were based on extrapolation of efficacy data from adults, combined with PK and safety data from phase II trials in children aged 6–17 years. However, a recommendation on the use of bedaquiline in children aged less than 6 years was not possible in the past, due to a lack of evidence, particularly on PK, safety and tolerability. The medicines that compose the shorter all-oral bedaquiline-containing regimen have been part of MDR-TB regimens for many years, in similar combinations, for both adults and children. The associated adverse drug reactions have been widely described and the drug dosages established. This however did not apply to bedaquiline at the time of the 2019 GDG on DR-TB, and the use of bedaquiline for young children in both shorter and longer regimens was therefore identified as a gap to be addressed as part of the 2021 update of the child and adolescent TB guidelines.

Evidence: To answer the PICO question on the use of bedaquiline in children under the age of 6 years, data from two phase II trials (TMC207-C211 and IMPAACT P1108) were reviewed by the GDG 2021. TMC207-C211 is a phase II, open-label, single-arm study to evaluate the PK, safety, tolerability and anti-mycobacterial activity of bedaquiline in combination with a background regimen of MDR-TB medications for the treatment of children and adolescents 0–17 years of age who have bacteriologically confirmed or clinically diagnosed pulmonary and selected forms of extrapulmonary MDR-TB.[37] IMPAACT P1108 is a phase I/II dose-finding modified age de-escalation study to evaluate the PK, safety, and tolerability of bedaquiline in combination with optimized individualized MDR-TB regimens in HIV-infected and HIV-uninfected children with clinically diagnosed or confirmed pulmonary (intrathoracic) and selected forms of extrapulmonary MDR-TB.[38]

As data reviewed from TMC207-C211 corresponded to children aged 5–18 years and that from IMPAACT P1108 included children aged 0–6 years, the review of PK and safety data focused mainly on data from IMPAACT P1108. Although the sample size of the available interim data for review was small (n=12), the GDG 2021 concluded that in children 0–6 years of age, cardiac safety signals were not distinct from those reported in adults. Population PK models from both studies suggest that drug exposures observed in adults can be reached in most children receiving bedaquiline, although some dose modification may be necessary depending on the age and weight of the child.

In addition, data from a paediatric MDR/RR-TB IPD were analysed descriptively (24 231 records from all six WHO regions, the majority from India and South Africa). The search was conducted in April 2020. Just under 20 000 of these records were used for a matched analysis of treatment outcomes in children being treated for DR-TB. The analysis included 40 children aged below 6 years and 68 children aged 6–12 years who received bedaquiline. In the matched analysis, bedaquiline was significantly associated with shorter treatment duration and a lower adjusted odds ratio of injectable TB drug use.

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[37] Pharmacokinetic study to evaluate anti-mycobacterial activity of TMC207 in combination with background regimen (BR) of multidrug-resistant tuberculosis (MDR-TB) medications for treatment of children/adolescents pulmonary MDR-TB (https://clinicaltrials.gov/ct2/show/NCT02354014, accessed 21 January 2022).

[38] P1108. A Phase I/II, open-label, single-arm study to evaluate the pharmacokinetics, safety and tolerability of bedaquiline (Bdq) in combination with optimized individualized multidrug-resistant tuberculosis (MDR-TB) therapy in HIV-infected and HIV-uninfected infants, children and adolescents with MDR-TB disease (https://www.impaactnetwork.org/studies/p1108, accessed 21 January 2022).

There was no statistically significant difference in successful treatment outcomes between children aged less than 6 years receiving an all-oral bedaquiline-based regimen versus those not receiving bedaquiline (89% versus 97%, p=0.9). Residual confounding (including confounding by indication) was thought to be likely.

A child-friendly formulation of bedaquiline (20 mg scored uncoated tablet) is being used in the Janssen C211 study to dose children aged below 5 years was not used in IMPAACT study P1108 (this study used the 100 mg formulation to date in all age groups). Indirect bioequivalence testing showed that both tablets have the same bioavailability and can be used interchangeably at the same total dose. Findings from the bedaquiline crush study (*85*) also showed that bioavailability of bedaquiline tablets suspended in water was the same as for tablets swallowed whole.

GDG considerations: The GDG discussed the desirable effects that were previously reported and noted that including bedaquiline in all-oral regimens for children will allow the construction of regimens that are more child- and family-friendly, with shorter durations (as shown by the IPD analysis, where bedaquiline-containing regimens were usually shorter than those not including bedaquiline). The GDG rated the desirable effects as moderate. The main concern noted by the panel was the lack of data on long-term safety and AEs. However, the GDG noted that clinical experience with using bedaquiline in young children showed that the drug is tolerated well and often better than in the adult population. Therefore, the GDG agreed that the undesirable effects were small. Overall, the GDG determined that the balance between desirable and undesirable effects probably favours the use of bedaquiline in children aged below 6 years. The GDG highlighted that the benefits may vary depending on specific contexts and population characteristics, such as by nutritional status. The GDG also noted that the potential higher cost of bedaquiline in an MDR/RR-TB treatment regimen should be considered in the context of the benefits of shorter injectable-free regimens (i.e. less travel, reduced time spent in clinics, and fewer AEs). In addition, they judged that equity might increase when bedaquiline becomes available to younger children, as its use would be acceptable to the majority of stakeholders, and that one of the main feasibility aspects would be related to the need for safety monitoring (i.e. access to ECG monitoring, as well as staff capacity for monitoring). However, the panel judged that the use of bedaquiline in young children was probably feasible.

Subgroup considerations

Children living with HIV: While trial TMC207-C211 has not yet enrolled children living with HIV, the IMPAACT study P1108 study enrolled HIV-infected and HIV-uninfected infants, children and adolescents with MDR-TB disease (of the nine children aged below 6 years enrolled and with PK data at the time of the GDG report, one was HIV-infected). In the paediatric IPD, 12 of the 40 children (30%) aged below 6 years treated with a bedaquiline-containing regimen were HIV-positive, as compared to 364 out of 1992 (20%) treated with DR-TB regimens not including bedaquiline.

The composition of treatment regimens for MDR/RR-TB does not usually differ substantially for people living with HIV; bedaquiline may be used in all children, irrespective of HIV status. Known drug–drug interactions, such as between bedaquiline and efavirenz, need to be avoided.

Extrapulmonary TB: The shorter, all-oral bedaquiline-containing regimen is contraindicated in children with extrapulmonary forms of TB other than TB lymphadenopathy (see implementation considerations for the full eligibility criteria). Children with these forms of EPTB should be treated with longer regimens, composed of medicines from groups A, B and C *(31)*. Data on the penetration of bedaquiline across the blood–brain barrier are sparse.

Implementation considerations

Eligibility for the shorter, all-oral, bedaquiline-containing regimen: The removal of the age restriction for the use of bedaquiline means that children of all ages with confirmed MDR/RR-TB and without fluoroquinolone resistance may be offered the shorter, all-oral regimen with bedaquiline,

if they meet the eligibility criteria. This regimen is composed of bedaquiline (used for 6 months), in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high-dose), pyrazinamide and clofazimine for four months (with the possibility of extending to 6 months if the patient remains sputum smear-positive at the end of four months); followed by 5 months of treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide. The eligibility criteria are:

- No extensive TB disease
- No severe EPTB (any form other than TB lymphadenopathy)
- No resistance or suspected ineffectiveness of a medicine in the shorter regimen (except isoniazid resistance)
- No exposure to previous treatment with second-line medicines in the regimen for more than one month (unless susceptibility to these medicines is confirmed).
- children (and patients in other age groups) who do not have bacteriological confirmation of TB or resistance patterns but who do have a high likelihood of MDR/RR-TB (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB).

Extensive (or advanced) TB disease refers to the presence of bilateral cavitary disease or extensive parenchymal damage on CXR in adults. In children aged below 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on CXR. Severe EPTB refers to the presence of miliary TB or meningitis or osteoarticular TB *(76)*. In children aged below 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are considered as severe *(77)*. The shorter regimen should not be used in the presence of mutations in both the inhA promoter and katG on first-line LPA (MTBDRplus) in the child as this suggests that both isoniazid at high dose and thioamides are not effective *(78)*.

Promoting the use of bedaquiline in all-oral regimens for children will allow the construction of regimens that are more child- and family-friendly and shorter, which may reduce the use of second-line drugs with potentially more severe AEs compared to bedaquiline (including, but not limited to injectables). Implementation of shorter, all-oral regimens may also facilitate the implementation of DR-TB treatment at peripheral levels of the health care system. NTPs and clinicians are therefore discouraged from using injectable agents as part of treatment regimens for MDR/RR-TB in children of all ages.

Administration of bedaquiline: Dosing guidance for the use of bedaquiline in children below 6 years of age is provided in the operational handbook, based on an expert consultation on dosing that was conducted as a follow-up to the GDG meeting. The guidance takes into account the child- friendly formulation of bedaquiline that was approved by the FDA in May 2020 and has been available from the Stop TB Partnership GDF since June 2020, namely a 20 mg scored tablet which can be taken whole or dispersed in water for patients who have difficulty swallowing intact tablets. This formulation of bedaquiline has been included in the 8th WHO Essential Medicine List for Children (EMLc), released in October 2021 *(79)*. To aid with administration, the dispersed mixture in water can be further mixed with a beverage or soft food or crushed and mixed with soft food immediately prior to its use and administered (see below for more details). It should also be noted that the findings from the bedaquiline crush study showed that bioavailability of bedaquiline 100 mg tablets suspended in water was the same as for tablets swallowed whole *(80)*. Therefore, if the 20 mg formulation of bedaquiline is not available, the crushed 100 mg formulation dissolved in water can be used to dose younger children without compromising bioavailability.

Concomitant food intake is an important factor to consider when evaluating bioavailability. Bedaquiline bioavailability was optimized in the trials when co-administered with a high-fat meal. In practice, feeding frequency needs to be considered. In infants, feeding frequency is higher and favours the administration with high-fat meals, but it should also be considered that buffering capacity increases with increased feeding frequency. The paediatric bedaquiline formulation can be prepared and administered with a variety of foodstuffs (including water, milk products, apple juice, orange juice, cranberry juice, carbonated beverages, yoghurt, apple sauce, mashed banana and porridge) to

improve palatability. The formulation is also stable for eight hours if the preparation is stored in a syringe. It should ideally be taken with a high-fat meal, and administration on an empty stomach should be avoided as bedaquiline drug exposures are reduced.

B3. Treatment of drug-resistant TB using longer regimens

Recommendations B3.1–B3.17 Longer regimens

No.	Recommendation
B3.1	In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of the treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. *(Conditional recommendation, very low certainty of evidence)*
B3.2	**Kanamycin and capreomycin** are not to be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
B3.3	**Levofloxacin or moxifloxacin** should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)*
B3.4	**Bedaquiline** should be included in longer multidrug-resistant TB (MDR-TB) regimens for patients aged 18 years or more. *(Strong recommendation, moderate certainty of evidence)* **Bedaquiline** may also be included in longer MDR-TB regimens for patients aged 6–17 years. *(Conditional recommendation, very low certainty of evidence)* In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing **bedaquiline** may be used. *(Conditional recommendation, very low certainty of evidence)*
B3.5	**Linezolid** should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)*
B3.6	**Clofazimine and cycloserine or terizidone** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
B3.7	**Ethambutol** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*

B3.8	**Delamanid** may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens. *(Conditional recommendation, moderate certainty of evidence)* In children with MDR/RR-TB aged below 3 years **delamanid** may be used as part of longer regimens. *(Conditional recommendation, very low certainty of evidence)*
B3.9	**Pyrazinamide** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
B3.10	**Imipenem–cilastatin or meropenem** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*[39]
B3.11	**Amikacin** may be included in the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions. *(Conditional recommendation, very low certainty of evidence)*
B3.12	**Ethionamide or prothionamide** may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. *(Conditional recommendation, very low certainty of evidence)*
B3.13	***P*-aminosalicylic acid** may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. *(Conditional recommendation, very low certainty of evidence)*
B3.14	**Clavulanic acid** should not be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, low certainty of evidence)*[39]
B3.15	In MDR/RR-TB patients on longer regimens, a **total treatment duration of 18–20 months** is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)*
B3.16	In MDR/RR-TB patients on longer regimens, a **treatment duration of 15–17 months after culture conversion** is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)*
B3.17	In MDR/RR-TB patients on longer regimens containing amikacin or streptomycin, **an intensive phase of 6–7 months** is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)*

Table 2.20 gives details of the grouping of medicines recommended for use in longer MDR-TB regimens; the groups are summarized here for clarity:

- Group A = levofloxacin or moxifloxacin, bedaquiline and linezolid;
- Group B = clofazimine, and cycloserine or terizidone; and

[39] Imipenem–cilastatin and meropenem are administered with clavulanic acid, which is available only in formulations combined with amoxicillin. Amoxicillin–clavulanic acid is not counted as an additional effective TB agent, and should not be used without imipenem–cilastatin or meropenem.

- Group C = ethambutol, delamanid, pyrazinamide, imipenem–cilastatin or meropenem, amikacin (or streptomycin), ethionamide or prothionamide, and *p*-aminosalicylic acid.

Justification and evidence

This section refers to recommendations on MDR/RR-TB treatment regimens that are of longer duration than the regimens described in the previous sections.

PICO questions

The recommendations in this section address PICO questions formulated in 2018 and 2019. The questions formulated in 2018 were as follows:

> ***PICO question 3–2018*** *(MDR/RR-TB, 2018): In patients with MDR/RR-TB, which individual agents are more likely to improve outcomes when forming part of a longer regimen conforming to WHO guidelines?40*
>
> ***PICO question 4–2018*** *(MDR/RR-TB, 2018): In patients with MDR/RR-TB on longer regimens composed in accordance with WHO guidelines, are outcomes safely improved with fewer or more than five effective medicines in the intensive phase?*
>
> ***PICO question 5–2018*** *(MDR/RR-TB, 2018): In patients with MDR/RR-TB on longer regimens composed in accordance with WHO guidelines, are outcomes safely improved with an intensive phase shorter or longer than 8 months?*
>
> ***PICO question 6–2018*** *(MDR/RR-TB, 2018): In patients with MDR/RR-TB on longer regimens composed in accordance with WHO guidelines, are outcomes safely improved with a total duration shorter or longer than 20 months?*
>
> ***PICO question 7–2018*** *(MDR/RR-TB, 2018): In patients with MDR/RR-TB on longer regimens composed in accordance with WHO guidelines, what is the minimum duration of treatment after culture conversion that is most likely to improve outcomes?*

The two relevant PICO questions considered by the GDG for the 2020 update were as follows:

> ***PICO question 8–2019*** *(MDR/RR-TB, 2019): In MDR/RR-TB patients, does a treatment regimen containing bedaquiline for more than 6 months safely improve outcomes when compared with bedaquiline for up to 6 months as part of longer regimens otherwise conforming to WHO guidelines?*
>
> ***PICO question 9–2019*** *(MDR/RR-TB, 2019): In MDR/RR-TB patients, does concurrent use of bedaquiline and delamanid safely improve outcomes when compared with other treatment regimen options otherwise conforming to WHO guidelines?*

Two additional PICO questions were reviewed in 2021 as part of the GDG formed to update childhood TB guidelines *(27)*:

PICO question 1–2021 *(Childhood TB, 2021):* In MDR/RR-TB patients aged below 6 years, should an all-oral treatment regimen containing bedaquiline versus other regimens conforming to WHO guidelines without bedaquiline be used?

PICO question 2–2021 *(Childhood TB, 2021):* In MDR/RR-TB patients aged below 3 years, should an all-oral treatment regimen containing delamanid versus other regimens conforming to WHO guidelines without delamanid be used?

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[40] Given that few trials or other studies have made head-to-head comparisons of MDR-TB medicines at different dosage regimens, it is not expected that guidance on dosage adjustment will be affected by the findings of the systematic review.

Recommendations for the design of longer MDR-TB regimens have been issued by WHO for several years and have been implemented in many countries worldwide *(2, 6, 13, 16)*. The recommendations in this section cover all forms of MDR/RR-TB; they include treatment of patients with strains resistant to rifampicin and susceptible to isoniazid (i.e. RR-TB), or with additional resistance to isoniazid (i.e. MDR-TB), or with resistance to other medicines (i.e. pre-XDR or XDR-TB). All patients with TB – children or adults – diagnosed with strains shown to be resistant to rifampicin can be placed on an MDR/RR-TB treatment regimen *(2)*.

The likelihood of treatment success in MDR/RR-TB patients on longer regimens depends on factors related to the patient and strain of TB (e.g. location or severity of disease, resistance patterns and comorbidities), and access to health care (e.g. regimens with sufficient effective agents, medications of good quality, management of AEs and patient support). Longer regimens with sufficient effective agents are known to increase the likelihood of cure and lower the risk of death in adults and children *(81–84)*. The composition of longer regimens is governed by the selection of individual medicines considered to be effective, and by a need to combine sufficient medicines to maximize the likelihood of relapse-free cure without increasing toxicity. Regimens may be of standardized (fixed) composition or may be individualized to the patient's needs. Longer regimens usually last 18–20 months or more; this document provides recommendations on the duration of such regimens, updated since publication of the 2011 WHO guidelines *(13)*. In summary, in 2018, a total treatment duration of 18–20 months and a treatment duration of 15–17 months after culture conversion were suggested for most patients, with the duration being modified according to the patient's response to therapy.

Evidence base and analyses

Ahead of the GDG discussion in 2018, WHO made a public call for individual MDR/RR-TB patient data, complete with results of treatment *(85)*{, 2018 #35;, 2018 #35}. IPD meta-analysis in adults and children treated with longer MDR/RR-TB regimens allows the study of useful correlates of outcome, including the regimen composition *(81–83)*. The evidence base for the effectiveness of many of the medicines used in MDR/RR-TB regimens relies on the 2018 IPD meta-analysis. In turn, this IPD meta-analysis relies heavily on observational studies, only a few of which have employed randomized controlled designs *(21)*; hence, the overall certainty of evidence is often graded as low or very low. The sources of data used by the GDGs to address the PICO questions in this section are summarized below.

PICO question 3–2018 (MDR/RR-TB, 2018) (choice of individual medicines)

First, to analyse treatment success, treatment failure, relapse and death for the individual medicines in longer regimens, the 2018 IPD meta-analysis was used, with 13 104 records from 53 studies in 40 countries. The 2018 IPD contained datasets from preceding years and from several countries, including a large dataset from South Africa with many patients treated with bedaquiline-containing regimens. Second, to analyse AEs resulting in permanent discontinuation of individual medicines in longer regimens, a subset of 5450 records from 17 studies in the 2018 IPD was used, supplemented with additional information from 10 other studies that only reported AEs for either bedaquiline (n=130), linezolid (n=508) or carbapenems (n=139).

In addition to these data, the GDG 2018 assessed unpublished results from the Phase 3 Trial 213 of delamanid *(86, 87)* and safety and pharmacological exposure data from unpublished paediatric studies of bedaquiline (Phase 2 TMC207-C211 and Phase 1–2 IMPAACT P1108) and delamanid (Phase 1 242–12–245, Phase 1 242–12–232, Phase 2 242–07–204 and Phase 2 242–12–233). The GDG 2018 also searched the literature for studies reporting outcomes of patients treated with agents other than those included in the 2016 guidelines (e.g. perchlozone, interferon gamma and sutezolid).

PICO question 4–2018 (MDR/RR-TB, 2018) (number of agents likely to be effective)

To analyse treatment success, treatment failure, relapse and death for the optimal number of medicines to be included in longer regimens, the data were derived from a subset of 8957 patients in 47 studies

included in the IPD used for PICO question 2–2018 (MDR/RR-TB, 2018) above. Of these, 3570 patients in 16 studies had information on the start and end dates for individual medicines in which DST was reported, and 5387 patients in 31 studies had information on individual medicines used in both the intensive and continuation phases of treatment, as well as DST results. This question focused on the number of agents in the intensive phase; hence, patients who did not receive an injectable agent or in whom an initial intensive phase was not defined were excluded (*n*=476). Patients who were designated "cured" or "treatment completed" but received less than 18 months of treatment – the minimum duration for longer regimens recommended by WHO in the past – were also excluded (*n*=346). In cases where DST results were available, a medicine was considered effective if results showed susceptibility, and was considered not effective if results showed resistance. Where DST results were missing, two situations existed. First, if the prevalence of resistance to that medicine was less than 10% in the same population (i.e. from the same country or study site if within one country, or overall at all sites if local data were not available), then the medicine was counted as effective. This situation applied to the following agents: cycloserine or terizidone, linezolid, clofazimine, bedaquiline, the carbapenems and delamanid. Second, if the prevalence of resistance to that medicine was more than or equal to 10% in the same population (from the same country or study site if within one country, or overall, at all sites if local data were not available), then imputed DST results were used to determine effectiveness if DST was missing. If the imputed DST result showed susceptibility, then the medicine was counted as effective; if the imputed DST result showed resistance, then the medicine was not counted as effective. This situation applied to the following agents: pyrazinamide, ethambutol, second-line injectable agents, fluoroquinolones, *p*-aminosalicylic acid, ethionamide and prothionamide. The following agents were not included when counting the number of medicines likely to be effective (regardless of any DST result that may have been available): isoniazid (including high-dose isoniazid), rifampicin, rifabutin, thioacetazone, amoxicillin–clavulanate and macrolide antibiotics.

Subsets of the main 2018 IPD meta-analysis with 13 104 patients overall from 53 studies in 40 countries were analysed for the risk of treatment failure and relapse versus success associated with different durations in these three recommendations on the duration of treatment (see Annex 5 for the GRADE tables). Patients were followed up for relapse but numbers of patients reported with relapse were relatively small. The three IPD subsets for PICO questions 5, 6 and 7–2018 are discussed below.

PICO question 5–2018 (MDR/RR-TB, 2018) (different durations of the intensive phase)

The primary analysis used a subset of records from 3750 patients from 42 observational studies; of these patients, 2720 were treated with an individualized MDR-TB regimen and 1030 were treated with standardized MDR-TB regimens. Of the 13 104 records in the main IPD, 9354 records were excluded for the following reasons: lost to follow-up (*n*=2261), died (*n*=2043), did not receive an injectable (*n*=1094), no information on duration of injectable (*n*=2341), number of medicines likely to be effective less than five or less than four plus pyrazinamide (*n*=1450) and duration of injectable longer than 20 months (*n*=165).

PICO question 6–2018 (MDR/RR-TB, 2018) (on regimen duration)

The evidence to inform PICO question 6–2018 (MDR/RR-TB, 2018) was derived from a subset of 6356 patients from 51 observational studies for the primary analysis. Of the 6356 patients, 5352 were treated with an individualized MDR-TB regimen and 1004 were treated with a standardized MDR-TB regimen. Of the 13 104 records in the main IPD, 6748 records were excluded for the following reasons: lost to follow-up (*n*=2261), died (*n*=2043), treatment duration not available (*n*=230), number of effective drugs less than five or less than four plus pyrazinamide (*n*=2072), treatment duration less than 6 months (*n*=52) and treatment duration more than or equal to 36 months (*n*=90).

PICO question 7–2018 (MDR/RR-TB, 2018) (on treatment duration after culture conversion)

The analysis to address PICO question 7–2018 (MDR/RR-TB, 2018) was derived from a subset of 4175 patients from 39 observational studies. All but three of the 4175 patients were on individualized

regimens. The reasons for exclusion of 8929 records from the main dataset were as follows: lost to follow-up (*n*=2261), died (*n*=2043), treatment duration not reported (*n*=230), culture information not reported (*n*=1945), baseline culture negative (*n*=754), patient never culture converted (*n*=426), number of effective drugs less than five or less than four plus pyrazinamide (*n*=1215), treatment duration less than 6 months (*n*=4), treatment duration more than or equal to 36 months (*n*=49) and culture converted post-treatment (*n*=2).

PICO question 1–2019 (MDR/RR-TB, 2019) (use of bedaquiline longer than 6 months)

To analyse treatment success, failure, relapse and death for the use of bedaquiline longer than 6 months, the data were derived from the endTB observational study, with the overall dataset comprising a total of 1094 patients from 13 countries *(88)*.[41] The data analysed to answer this question were patients from the endTB observational study cohort who received bedaquiline for at least 6 months, had started bedaquiline within the first month of the treatment episode and did not receive delamanid concomitantly with bedaquiline during treatment; among patients with treatment success, data were from those who received at least 17.5 months of treatment overall. A total of 515 patients met these criteria. The intervention group comprised 242 patients who received bedaquiline for more than 203 days[42] overall, and they were compared to 273 patients who received bedaquiline for a total of 168–203 days. Additional data sources considered by the GDG 2019 included a cohort of 112 patients from Belarus treated with bedaquiline (of whom two had inadequate treatment information and were excluded), and a cohort of 123 patients from an MSF-managed clinic in Uzbekistan treated with bedaquiline (with one patient excluded due to inadequate treatment information). Of these 232 eligible patients, 65 received bedaquiline for more than 203 days and 72 received bedaquiline for 168–203 days. The primary analyses featured the endTB observational study data only.

PICO question 2–2019 (MDR/RR-TB, 2019) (use of bedaquiline and delamanid together)

To analyse treatment success, failure, relapse and death for the concurrent use of bedaquiline and delamanid, the data were derived from the same cohort of patients from the endTB observational study that informed PICO question 1–2019. However, in this dataset, only 92 patients received both medicines together for any period of time, and even fewer started bedaquiline and delamanid at the same time and within the first month of treatment (*n*=35). Another three patients were receiving concomitant bedaquiline and delamanid by the end of the first month of treatment, bringing the total number to 38. The remaining 57 patients started the two medicines more than 30 days apart and were therefore not included. Additional data sources comprised a cohort of 100 patients treated with bedaquiline in Mumbai, India (from an MSF-supported project), of whom 86 received some form of concomitant treatment with bedaquiline and delamanid during therapy; 62 of these 86 initiated the two medicines within 30 days of each other, and 46 of these 62 began both medicines during the first month of their treatment episode. The total intervention population therefore comprised 84 patients: 38 from the endTB observational study cohort and 46 from the Mumbai dataset. Because the data available were limited, the sources of data for the comparator populations were derived from the endTB observational study, and the datasets from Belarus, Mumbai and Uzbekistan. There were inadequate numbers of patients available in the IPD for any meaningful analyses (*n*=4 patients who received bedaquiline and delamanid together). The primary comparison group included 401 patients (*n*=302 from the endTB observational study, *n*=82 from the Belarus dataset, *n*=17 from the Uzbekistan dataset and *n*=0 from the Mumbai dataset). These patients initiated bedaquiline within the first month of treatment and did not receive bedaquiline beyond 6 months duration. The secondary comparison group was derived from the endTB observational study and comprised 102 patients who received delamanid within the first month of treatment and who did not receive an extended duration of delamanid. No patients in the datasets from Belarus, Mumbai or Uzbekistan received delamanid

[41] These countries are Armenia, Bangladesh, Belarus, the Democratic People's Republic of Korea, Ethiopia, Georgia, Indonesia, Kazakhstan, Kenya, Lesotho, Myanmar, Pakistan and Peru.

[42] 203 days was chosen as a cut-off as the intermodal trough of bedaquiline use for all patients in the endTB observational study was 203 days; the cut-off was not 6 months exactly, but 203 days.

for this duration. The median duration of concurrent use of bedaquiline and delamanid among the 84 patients in the intervention group was 18.5 months (IQR: 9 months, 21 months).

Additional data presented included safety data from the DELamanId Bedaquiline for ResistAnt TubErculosis (DELIBERATE) trial (AIDS Clinical Trials Group A5343). The DELIBERATE trial is a randomized, open-label, three-arm pharmacokinetic and safety trial conducted at study sites in Peru and South Africa. Eligible patients were aged 18 years and older, with pulmonary MDR-TB (or rifampicin monoresistance) receiving treatment for MDR-TB, but without clofazimine, and with moxifloxacin replaced by levofloxacin and a baseline QTcF of less than 450 ms. In addition to the MDR-TB treatment regimen with the conditions described above, the regimens used in the three study arms comprised the addition of bedaquiline 400 mg once daily for 2 weeks, then 200 mg thrice weekly for 22 weeks; the addition of delamanid 100 mg twice daily for 24 weeks; and the addition of both bedaquiline and delamanid. The primary objective of the trial was to compare the mean change from baseline in QTcF (averaged over weeks 8–24) when bedaquiline and delamanid were co-administered with the mean change observed when each drug was administered alone.

In addition to the data reviewed for PICO questions 1–2019 and 2–2019, the GDG 2019 was provided with and reviewed data from a study in South Africa on the use of bedaquiline during pregnancy. This observational cohort study included information from 108 pregnant women with RR-TB who were recruited from one MDR/RR-TB referral hospital in South Africa between January 2013 and December 2017. As part of their MDR/RR-TB regimen, 58 women received bedaquiline; they were compared with 50 women who had no bedaquiline in their regimen. The women in this study gave birth to 109 live infants, of whom 49 had bedaquiline exposure in utero and 60 had no bedaquiline exposure in utero. Clinical assessments were carried out at 2, 6 and 12 months after birth to document infant outcomes. The main objective of the study was to document treatment, pregnancy and infant outcomes among women treated for RR-TB with second-line TB drugs during pregnancy.

When reviewing evidence and formulating the recommendations, the GDG 2019 considered the need for the guidelines to also cater to key subgroups that were not well represented in the 2018 IPD meta-analysis – notably, children. Where data on children were unavailable, evidence from adults was extrapolated to children. The best available evidence was used to construct recommendations for a regimen that has high relapse-free cure rates, and that reduces the likelihood of death and the emergence of additional resistance while minimizing harms. The GDG 2019 was aware of the paediatric MDR-TB IPD meta-analysis on 975 clinically diagnosed or bacteriologically confirmed pulmonary or extrapulmonary TB cases that was used for the 2016 treatment recommendations *(82)*. Children with XDR-TB (pre-2021 definition) were excluded from that analysis (*n*=36) because their treatment regimens were not considered to be comparable with those of other MDR-TB patients, and their numbers were too low to be analysed independently. No RCTs were included (or known to exist) at the time this dataset was compiled, and the overall certainty in the estimates of effect based on this evidence was judged to be very low. However, in July 2019, preliminary data from the DELIBERATE trial were made available to the GDG 2019 to partly address PICO question 9; the overall certainty in the estimates of effect for this study was judged to be low.

PICO question 1–2021 (Childhood TB, 2021) (use of bedaquiline in MDR/RR-TB patients aged below 6 years)

To answer the PICO question on the use of bedaquiline in children aged below 6 years, data from two Phase 2 trials (TMC207-C211 and IMPAACT P1108) were reviewed by the GDG 2021. The resulting recommendation is consolidated into this edition of the guidelines and appears under Recommendation 2.4 The use of bedaquiline in children with MDR/RR-TB aged below 6 years.

PICO question 2–2021 (Childhood TB, 2021) (use of delamanid in MDR/RR-TB patients aged below 3 years)

To answer the PICO question on the use of delamanid in children aged below 3 years, data were reviewed by the GDG 2021 from a Phase 1, open-label, age de-escalation trial designed to assess the pharmacokinetics, safety and tolerability of delamanid administered twice daily for 10 days in children with MDR/RR-TB on treatment with an optimized background regimen (protocol 242–12–232)[43] and from the corresponding open-label extension study (protocol 242–12–233).[44] Data from cohorts 1 (age 12–17 years), 2 (age 6–11 years), 3 (age 3–5 years) and 4 (age 0–2 years) for both protocols were reviewed. Exposures in the 0–2-year age group were lower than those of children aged 3 years and older, necessitating a modelling or simulation approach to dosing. No cardiac safety signals distinct from those reported in adults were observed in children aged 0–2 years. However, consideration of these findings should take into account that children had lower drug exposures than adults. Pharmacodynamic simulations suggested that clinically meaningful changes in QT (i.e. prolongation) would be unlikely in children aged below 3 years, even if higher doses were used to reach drug exposures comparable to those achieved in adults.

CNS effects (paraesthesia, tremors, anxiety, depression and insomnia) were included in the delamanid label for both adults and children as important potential safety concerns for the drug. In March 2021, the study sponsor released a statement of intent to modify the labelling to include hallucinations as an adverse reaction. This new safety signal has been more prevalent among children than adults, with 15 reports in 14 children aged 2–16 years in India, the Philippines, South Africa, Tajikistan and Ukraine. Children experiencing this safety signal included some with extensively resistant forms of TB (MDR/XDR-TB) treated with delamanid under programmatic conditions (12 reports) and children enrolled in a clinical trial studying delamanid for TB prevention (3 reports). Seven of the 15 reports were for children also receiving cycloserine (under programmatic conditions). The GDG noted the importance of side-effects involving the CNS in young children, considering their dynamic brain development.

In addition to data from the trials, data from a paediatric DR-TB IPD were analysed descriptively (24 231 records from all six WHO regions, the majority from India and South Africa). The search was conducted in April 2020. Just under 20 000 of these records were used for a matched analysis of treatment outcomes in children being treated for DR-TB. The paediatric DR-TB IPD included only seven children aged below 3 years treated with delamanid, 14 children aged 3–6 years and 69 children aged 6–12 years. All 21 children aged below 6 years were successfully treated. The number of children was insufficient for a matched analysis.

Remarks

The GDG 2018 assessed the individual contribution to patient outcomes of medicines used in longer MDR-TB regimens, using primarily the estimates of effect from the 2018 IPD meta-analysis and Trial 213 (delamanid) for PICO question 3–2018 (MDR/RR-TB, 2018) (see **Annex 5** for the respective GRADE summaries of evidence for each medicine, and the evidence-to-decision framework). Following a thorough assessment of the relative benefits and harms, recommendations were made for each medicine and they were classified into three groups (see Table 2.20, Table 2.21 and Table 2.22 below).

- **Group A**: fluoroquinolones (levofloxacin and moxifloxacin), bedaquiline and linezolid were considered highly effective and strongly recommended for inclusion in all regimens unless contraindicated.
- **Group B**: clofazimine and cycloserine or terizidone were conditionally recommended as agents of second choice.

[43] Pharmacokinetic and safety trial to determine the appropriate dose for pediatric patients with multidrug-resistant tuberculosis (https://clinicaltrials.gov/ct2/show/NCT01856634, accessed 21 January 2022).

[44] A 6-month safety, efficacy, and pharmacokinetic (PK) trial of delamanid in pediatric participants with multidrug-resistant tuberculosis (MDR-TB) (https://clinicaltrials.gov/ct2/show/NCT01859923, accessed 21 January 2022).

- **Group C**: included all other medicines that can be used when a regimen cannot be composed with Group A or Group B agents. The medicines in Group C are ranked by the relative balance of benefit to harm usually expected of each.

Other medicines that are not included in Groups A–C are as follows:

- **Kanamycin and capreomycin** – these medicines were associated with poorer outcomes when used; therefore, they are no longer recommended for use in MDR-TB regimens.
- **Gatifloxacin and high-dose isoniazid, and thioacetazone** – gatifloxacin and high-dose isoniazid were used in only a few patients, and thioacetazone was not used at all. Currently, quality-assured preparations of gatifloxacin are not available, following its withdrawal from the market due to concerns about dysglycaemias. Thioacetazone is unlikely to have a role in contemporary longer regimens and is not currently available in a quality-assured formulation. High-dose isoniazid may have a role in patients with confirmed susceptibility to isoniazid (see Subgroup considerations).
- **Clavulanic acid** – this medicine should be included in MDR/RR-TB regimens only as a companion agent to the carbapenems (imipenem–cilastatin and meropenem). When used in this way, it should be given with every dose of carbapenem, and should not be counted as an additional effective TB agent.

No recommendation on perchlozone, interferon gamma or sutezolid was possible owing to the absence of final patient treatment outcome data from appropriate patient studies.

Regarding the use of bedaquiline in patients aged below 18 years, and considering that exposure–response (efficacy) profiles can be extrapolated from adults to children, the GDG concluded that the doses evaluated in children and adolescents in two trials (Phase 2 trial TMC207-C211 and Phase 1–2 IMPAACT P1108) do not appear to result in exposures that would put patients aged 6–17 years at increased risk for treatment failure. The safety risk in children aged 6 years and older enrolled in the trials – all of whom were HIV-negative and had limited exposure to other QT interval-prolonging medications – did not appear to exceed that of adults. The variability present in the limited sample size precluded a comment on exposure–response (safety). The GDG 2018 also concluded that the risk–benefit considerations for the use of bedaquiline in patients aged 6–17 years are similar to those considered for adults; however, the GDG stressed the need for more data before considering upgrading this recommendation to "strong".

The GDG review in 2021 determined that the balance between desirable and undesirable effects probably favours the use of bedaquiline in children aged below 6 years. The GDG 2021 highlighted that the benefits may vary depending on specific contexts and population characteristics, such as by nutritional status. The GDG also noted that the potential higher cost of bedaquiline in an MDR/RR-TB treatment regimen should be considered in the context of the benefits of shorter injectable-free regimens (i.e. less travel, reduced time spent in clinics and fewer AEs). In addition, they judged that equity might increase when bedaquiline becomes available to younger children, because its use would be acceptable to most stakeholders, and that one of the main feasibility aspects would be related to the need for safety monitoring (i.e. access to ECG monitoring, as well as staff capacity for monitoring). However, the panel judged that implementing the use of bedaquiline in young children was probably feasible.

With respect to the use of delamanid in children aged below 6 years, the GDG review in 2018 decided that – based on findings in adults, and on the pharmacological and safety data reviewed – extrapolations on efficacy and safety should be restricted to children aged 3–5 years, but not to children aged below 3 years (see Annex 5). Exposure profiles in children aged 3–5 years were comparable to adults, and were no higher than in children aged 6 years and older, for whom past GDGs convened by WHO had already recommended the use of delamanid *(15, 28)*. Based on the laboratory and cardiac data provided, no safety signals distinct from those reported in adults were observed in children aged 3–5 years. The GDG nonetheless had concerns about the feasibility of administering the correct dose to children aged 3–5 years, given that the special formulation used

in the trial (25 mg) would not be available in the foreseeable future, and that only the adult tablet (50 mg) is available, which is not bioequivalent and presents challenges to manipulating its contents without compromising its effectiveness.

The GDG review in 2021 concluded that the balance between desirable and undesirable effects probably favours the use of delamanid in children aged below 3 years. The GDG 2021 further stated that when the 25 mg dispersible tablet became available in the future, the resource implications could vary. It was thought that delamanid containing longer treatment regimens could potentially increase equity and be acceptable to stakeholders. In addition, the GDG 2021 judged that it would probably be feasible to use delamanid in children of all ages, especially as the child-friendly formulation of delamanid was expected to become available later in 2021 (this formulation is now available). This judgement also considered that adult tablets cannot be split, crushed or dissolved to ease administration in children without potentially altering bioavailability.

As a result of these multiple reviews as new data have gradually become available, the use of bedaquiline and delamanid are no longer restricted by the age of the patient.

Table 2.20. Grouping of medicines recommended for use in longer MDR-TB regimens[a]

Groups and steps	Medicine	Abbreviation
Group A: **Include all three medicines**	Levofloxacin *or* moxifloxacin	Lfx Mfx
	Bedaquiline[b,c]	Bdq
	Linezolid[d]	Lzd
Group B: **Add one or both medicines**	Clofazimine	Cfz
	Cycloserine *or* terizidone	Cs Trd
	Ethambutol	E
	Delamanid[e]	Dlm
	Pyrazinamide[f]	Z
Group C: **Add to complete the regimen and when medicines from Groups A and B cannot be used**	Imipenem–cilastatin *or* meropenem[g]	Ipm–Cln Mpm
	Amikacin (*or* streptomycin)[h]	Am (S)
	Ethionamide *or* prothionamide[i]	Eto Pto
	P-aminosalicylic acid[i]	PAS

DST: drug susceptibility testing; ECG: electrocardiogram; GDG: Guideline Development Group; IPD: individual patient data; LPA: line probe assay; MDR-TB: multidrug-resistant TB; TB: tuberculosis.

[a] This table is intended to guide the design of individualized, longer MDR-TB regimens (the composition of the recommended shorter MDR-TB regimen is largely standardized; see Treatment of drug-resistant TB using 9-month regimens). Medicines in Group C are ranked by decreasing order of usual preference for use, subject to other considerations. The 2018 IPD meta-analysis for longer regimens included no patients on thioacetazone and too few patients on gatifloxacin and high-dose isoniazid for a meaningful analysis. No recommendation on perchlozone, interferon gamma or sutezolid was possible owing to the absence of final patient treatment outcome data from appropriate studies.

[b] Bedaquiline is usually administered at 400 mg orally once daily for the first 2 weeks, followed by 200 mg orally three times per week for 22 weeks (total duration of 24 weeks). As a result of multiple reviews as new data have gradually become available, the use of bedaquiline is no longer restricted by the age of the patient. Evidence on the safety and effectiveness of bedaquiline use beyond 6 months was insufficient for review in 2018. Therefore, the use of bedaquiline beyond 6 months was implemented following best practices in "off-label" use *(89)*. New evidence on the safety profile of bedaquiline use beyond 6 months was available to the GDG 2019, but the GDG was not able to assess the impact of prolonged bedaquiline use on efficacy, owing to the limited evidence and potential residual confounding in the data. However, the evidence supports the safe use of bedaquiline beyond 6 months in patients who receive appropriate schedules of baseline and follow-up monitoring. The use of bedaquiline beyond 6 months remains as off-label use and, in this regard, best practices in off-label use still apply.

[c] Evidence on the concurrent use of bedaquiline and delamanid was insufficient for review in 2018. In 2019, new evidence on the concurrent use of bedaquiline and delamanid was made available to the GDG. Regarding safety, the GDG concluded that the data suggest no additional safety concerns regarding concurrent use of bedaquiline and delamanid. Both medicines may be used concurrently in patients who have limited other treatment options available to them, provided that sufficient monitoring (including baseline and follow-up ECG and electrolyte monitoring) is in place. The data on the effectiveness of concurrent use of bedaquiline and delamanid were reviewed by the GDG; however, owing to the limited evidence and potential residual confounding in the data, the GDG was unable to proceed with a recommendation on effectiveness.

[d] Use of linezolid for at least 6 months was shown to increase effectiveness, although toxicity may limit use. The analysis suggested that using linezolid for the entire duration of treatment would optimize its effect (about 70% of patients on linezolid with data received it for >6 months and 30% for 18 months or the entire duration). No patient predictors for early cessation of linezolid could be inferred from the IPD subanalysis.

[e] Evidence on the safety and effectiveness of delamanid beyond 6 months was insufficient for review. The use of delamanid beyond these limits should follow best practices in "off-label" use *(89)*. As a result of multiple reviews as new data have gradually become available, the use of delamanid is no longer restricted by the age of the patient.

[f] Pyrazinamide is counted as an effective agent only when DST results confirm susceptibility.

[g] Every dose of imipenem–cilastatin and meropenem is administered with clavulanic acid, which is available only in formulations combined with amoxicillin. Amoxicillin–clavulanic acid is not counted as an additional effective TB agent and should not be used without imipenem–cilastatin or meropenem.

[h] Amikacin and streptomycin are to be considered only if DST results confirm susceptibility, and if high-quality audiometry monitoring for hearing loss can be ensured. Streptomycin is to be considered only if amikacin cannot be used (i.e. if it is unavailable or there is documented resistance) and if DST results confirm susceptibility (i.e. resistance to streptomycin is not detectable with second-line molecular LPAs and phenotypic DST is required). Kanamycin and capreomycin are no longer recommended for use in MDR-TB regimens.

[i] These agents showed effectiveness only in regimens without bedaquiline, linezolid, clofazimine or delamanid, and are thus proposed only when other options to compose a regimen are not possible.

Table 2.21. Relative risk for treatment failure or relapse, and death (versus treatment success), 2018 IPD meta-analysis for longer MDR-TB regimens and delamanid Trial 213 (intent-to-treat population)[a]

	Medicine	Treatment failure or relapse versus treatment success		Death versus treatment success	
		Number treated	Adjusted odds ratio (95% CL)	Number treated	Adjusted odds ratio (95% CL)
A	Levofloxacin *or* moxifloxacin	3143	0.3 (0.1–0.5)	3551	0.2 (0.1–0.3)
	Bedaquiline	1391	0.3 (0.2–0.4)	1480	0.2 (0.2–0.3)
	Linezolid	1216	0.3 (0.2–0.5)	1286	0.3 (0.2–0.3)
B	Clofazimine	991	0.3 (0.2–0.5)	1096	0.4 (0.3–0.6)
	Cycloserine *or* terizidone	5483	0.6 (0.4–0.9)	6160	0.6 (0.5–0.8)
C	Ethambutol	1163	0.4 (0.1–1.0)	1245	0.5 (0.1–1.7)
	Delamanid	289	1.1 (0.4–2.8)[b]	290	1.2 (0.5–3.0)[b]
	Pyrazinamide	1248	2.7 (0.7–10.9)	1272	1.2 (0.1–15.7)
	Imipenem–cilastatin *or* meropenem	206	0.4 (0.2–0.7)	204	0.2 (0.1–0.5)
	Amikacin	635	0.3 (0.1–0.8)	727	0.7 (0.4–1.2)
	Streptomycin	226	0.5 (0.1–2.1)	238	0.1 (0.0–0.4)
	Ethionamide *or* prothionamide	2582	1.6 (0.5–5.5)	2750	2.0 (0.8–5.3)
	P-aminosalicylic acid	1564	3.1 (1.1–8.9)	1609	1.0 (0.6–1.6)
Other medicines	Kanamycin	2946	1.9 (1.0–3.4)	3269	1.1 (0.5–2.1)
	Capreomycin	777	2.0 (1.1–3.5)	826	1.4 (0.7–2.8)
	Amoxicillin–clavulanic acid	492	1.7 (1.0–3.0)	534	2.2 (1.3–3.6)

CL: confidence limits; GDG: Guideline Development Group; IPD: individual patient data; MDR-TB: multidrug-resistant tuberculosis.

[a] See also text, Table 2.21 and Annex 5 for more detail on how the estimates were derived and the additional factors considered by the GDG when reclassifying medicines for use in longer MDR-TB regimens, as shown in Table 2.20.

[b] The values are the unadjusted risk ratios, as defined by the study investigators of Trial 213 by month 24.

PICO question 4–2018 (MDR/RR-TB, 2018) (number of agents likely to be effective)

Regarding PICO question 4–2018 (MDR/RR-TB, 2018), the analysis showed that in longer MDR-TB treatment regimens, the risk of treatment failure, relapse and death was comparable when the treatment started with four, five or six medicines that were likely to be effective. It also showed that patients who took three agents in the continuation phase – the situation expected when starting with four agents and stopping the injectable agent at the end of the intensive phase – fared no worse than those who took four agents in the continuation phase.

Given that drug–drug interactions, pill burden and likelihood of AEs all increase with the number of agents in a regimen, it would be desirable to give patients the minimum number of medicines necessary to obtain comparable levels of relapse-free cure. When deciding on the minimum number of agents to recommend, the GDG 2018 considered analyses that included injectable agents in the regimens, while fully cognizant that future longer regimens are expected to be increasingly injectable free. Moreover, it was important to provide for situations in which more than one medicine is stopped at some point during treatment, either because of its indication for use – bedaquiline and delamanid on-label use is 6 months – or because of tolerability (particularly linezolid; Table 2.22) *(90)*; hence, for most of its duration, the regimen would contain two key agents fewer than at the start. Although bedaquiline use beyond 6 months is referred to as off-label use, new evidence on the safety profile of bedaquiline use beyond 6 months was available to the GDG 2019. This evidence supports the safe use of bedaquiline beyond 6 months in patients who receive appropriate schedules of baseline and follow-up monitoring. The use of bedaquiline beyond 6 months continues to be off-label use; thus, best practices in off-label use still apply.

The 2018 IPD included experience from more than 300 patients who were treated with linezolid for at least 1 month, mostly at a dose of 600 mg/day, with information on duration of use. About 30% only received linezolid for 1–6 months, but more than 30% received it for more than 18 months, and these patients had the lowest frequency of treatment failure, LTFU and death. A plot of linezolid duration and treatment failure suggests that the optimal duration of use would be about 20 months, corresponding to the usual total duration of a longer MDR-TB regimen. However, such an analysis does not account for survivorship bias, meaning that those who complete the full length of treatment are more likely to have a successful outcome, given that deaths and losses to follow-up occur earlier. No clear pattern could be discerned for type of AE and duration of use, although a few cases were reported with optic neuropathy, known to be associated with long-term use of linezolid *(91)*, whereas haematological toxicity was reported regardless of duration of use.

Table 2.22. Serious AEs in patients on longer MDR-TB regimens[a]

Medicine	Absolute risk of serious AE	
	Median (%)	95% credible interval
Bedaquiline	2.4	[0.7, 7.6]
Moxifloxacin	2.9	[1.4, 5.6]
Amoxicillin–clavulanic acid	3.0	[1.5, 5.8]
Clofazimine	3.6	[1.3, 8.6]
Ethambutol	4.0	[2.4, 6.8]
Levofloxacin	4.1	[1.9, 8.8]
Streptomycin	4.5	[2.3, 8.8]
Cycloserine or terizidone	7.8	[5.8, 10.9]
Capreomycin	8.4	[5.7, 12.2]
Pyrazinamide	8.8	[5.6, 13.2]
Ethionamide or prothionamide	9.5	[6.5, 14.5]
Amikacin	10.3	[6.6, 17.0]
Kanamycin	10.8	[7.2, 16.1]
P-aminosalicylic acid	14.3	[10.1, 20.7]
Thioacetazone	14.6	[4.9, 37.6]
Linezolid	17.2	[10.1, 27.0]

AE: adverse event; GDG: Guideline Development Group; IPD: individual patient data; MDR-TB: multidrug-resistant TB; TB: tuberculosis.

[a] From an "arm-based network" meta-analysis of a patient subset from the 2016 IPD for which AEs resulting in permanent discontinuation of a TB medicine (27 studies) or classified as Grade 3–5 (three studies) were reported. There are slight differences between the final estimates cited in the resultant publication *(90)* and the values derived at the time of the GDG and shown in this table, because an expanded dataset was used in the publication; however, the slight differences have no impact on the conclusions drawn on the use of these medicines. There were insufficient records on delamanid, imipenem–cilastatin and meropenem to estimate risks. Agents that are not in Groups A, B or C are italicized.

In 2018, the GDG recommended that, where possible, regimens be composed of all three Group A agents and at least one Group B agent, so that treatment starts with at least four medicines likely to be effective, and that at least three agents are continued for the remaining duration of treatment if bedaquiline is stopped after 6 months. New evidence on the safety profile of bedaquiline use beyond 6 months was available to the GDG 2019. This evidence supports the safety of using bedaquiline beyond 6 months in patients who receive appropriate schedules of baseline and follow-up monitoring. If only one or two Group A agents can be used, both Group B agents are included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. **For patients in whom two agents from Group A are more likely to be stopped before the end of treatment (e.g. pre-existing comorbidities require that both bedaquiline and linezolid be stopped early because of health risks), then starting with five effective agents rather than four may be advisable.** These provisions are expected to apply to most MDR/RR-TB patients, including those with additional resistance to fluoroquinolones or other medicines.

PICO question 8–2019 (MDR/RR-TB, 2019) (use of bedaquiline longer than 6 months)

Regarding PICO question 8–2019 (MDR/RR-TB, 2019), the analysis yielded aORs of 1.5 (95% CI: 0.7–2.7) for treatment success versus failure, 0.8 (95% CI: 0.2–0.4) for treatment success versus death, 1.0 (95% CI: 0.5–1.7) for treatment success versus failure or death, and 0.8 (95% CI: 0.5–1.2) for treatment success versus all unfavourable outcomes. The evidence reviewers had planned to use two analytical approaches designed to minimize bias; that is, marginal structural models to account for time-varying confounders, and for exact and propensity score matching of patient characteristics. However, sample size meant that there were limitations in how the first approach could be applied; also, owing to limitations with the dataset, biostatisticians advised that it was not possible to adjust for confounders according to the original data analysis plan. The GDG 2019 noted that the population included in the studies that were assessed was highly selected, with the potential for confounding by indication (i.e. the people who received bedaquiline for >6 months were likely to have done so because of clinical factors that indicated prolonged treatment with bedaquiline). The GDG concluded that there was a high likelihood of residual confounding in the data, and that the patient population addressed in the study did not permit extrapolation to routine use in all MDR/RR-TB patients. This precluded a formal recommendation on the efficacy or effectiveness of bedaquiline use beyond 6 months duration; however, the GDG 2019 concluded that a statement on safety could be made. This information is included in Implementation considerations and in a table note for Table 2.22.

Regarding **AEs**, among the 750 patients receiving bedaquiline without concomitant delamanid in the endTB observational study (total exposure of 6316 person-months), 26 patients experienced a drug-related AE (rate: 0.44 per 100 person-months of exposure), with 16 patients having this event classified as a serious AE (rate: 0.25 per 100 person-months of exposure). In the first 203 days of exposure to bedaquiline (total exposure of 4304 person-months), 20 of the 26 drug-related AEs and 15 of the 16 serious AEs occurred; the remaining six of the 26 drug-related AEs and one of the 16 serious AEs occurred subsequently. All patients who received bedaquiline for more than 203 days did not experience a drug-related AE (of any grade) in the first 203 days of treatment. Also, rates of treatment drug-related AEs appeared to be lower after the first 203 days – at 0.51 in the first 203 days versus 0.30 in the subsequent days per 100 person-months. Similarly, rates of drug-related serious AEs appeared to be lower after the first 203 days – at 0.35 in the first 203 days versus 0.05 in the subsequent days per 100 person-months.

QTcF values among people receiving bedaquiline increased by an average of 22 ms (from 397 ms to 419 ms) from those taken before or at the time of first receipt of bedaquiline to the end of the first month. In subsequent months of exposure, the mean QTcF values were all lower than at the end of the first month (range: 404–419 ms). Increases in QTcF of more than 60 ms from baseline occurred in about 12% of patients. QTcF prolongation of more than 500 ms was rare, occurring in 0.4–1.5% of patients during each of the first 9 months, but not thereafter. The greatest number of occurrences of QTcF of more than 500 ms happened among people receiving bedaquiline and clofazimine; however, this was also the most common combination of medicines received.

Drug-related cardiac AEs occurred in 22 people; of these, 15 were among people receiving bedaquiline with clofazimine, but no moxifloxacin or delamanid (rate: 0.3 per 100 person-months), five were among people receiving bedaquiline with clofazimine and moxifloxacin, but no delamanid (rate: 0.3 per 100 person-months), and two were among people receiving bedaquiline and delamanid, regardless of clofazimine and moxifloxacin use (rate: 0.2 per 100 person-months). No events occurred among people receiving bedaquiline without clofazimine, moxifloxacin and delamanid.

Regarding **bedaquiline exposure during pregnancy**, the findings of the cohort study demonstrated no statistically significant differences in birth or pregnancy outcomes when comparing infants who had intrauterine bedaquiline exposure with those who did not have this exposure (P=0.741 for birth outcomes and P=0.312 for pregnancy outcomes) *(66)*. There were 45 live births (92% of total) in the bedaquiline exposed group compared with 54 live births (90% of total) in the unexposed group. In addition, there were four fetal and neonatal deaths in the infants exposed to bedaquiline (8% of the

total bedaquiline exposed group, with three stillbirths and one termination of pregnancy) and six fetal and neonatal deaths in the bedaquiline unexposed group (10% of the total unexposed group, comprising three stillbirths and three miscarriages) *(66)*. The results of the study also demonstrated that treatment outcomes were favourable for pregnant women exposed to bedaquiline compared with those not exposed (71% vs 62%, respectively, *P*=0.349) *(66)*. Pregnancy outcomes included live births and unfavourable pregnancy outcomes (fetal and neonatal deaths, preterm births <37 weeks and low birth weight <2500 g); infant outcomes included weight gain and developmental milestones and the diagnosis of TB *(66)*. Of all pregnancy and infant outcomes assessed, only low birth weight was associated with bedaquiline exposure in utero (45% vs 26%, *P*=0.034). The average weight in bedaquiline exposed infants was 2690 g versus 2900 g in infants not exposed to bedaquiline. However, it was not possible to conclusively ascribe this effect to bedaquiline, and more investigation is needed to explore this relationship *(66)*. There were no significant differences in infant growth after birth: in a subanalysis of 86 babies followed up prospectively – 41 exposed to bedaquiline in utero and 45 not exposed – 88% of babies exposed to bedaquiline in utero had normal weight gain at 1 year of age versus 82% of babies not exposed (*P*=0.914) *(66)*.

PICO question 9–2019 (MDR/RR-TB, 2019) (use of bedaquiline and delamanid together)

Regarding PICO question 9 (MDR/RR-TB, 2019), the analyses yielded aORs of 1.6 (95% CI: 0.5–5.4) for treatment success versus treatment failure, 0.8 (95% CI: 0.3–2.1) for treatment success versus death, 1.2 (95% CI: 0.6–2.5) for treatment success versus failure or death, and 0.6 (95% CI: 0.3–1.1) for treatment success versus all unfavourable outcomes. Regarding AEs, among the 92 patients receiving bedaquiline with concomitant delamanid during treatment in the endTB observational study (total exposure of 1095 person-months), two bedaquiline-related AEs and delamanid-related AEs occurred (combined rate: 0.46 per 100 person-months of exposure). This rate was comparable to the rates among people receiving bedaquiline alone (0.41 per 100 person-months of exposure) and delamanid alone (0.68 per 100 person-months of exposure). Two drug-related serious AEs occurred among the 92 patients receiving concomitant bedaquiline and delamanid, one attributed to each drug (combined rate: 0.09 per 100 person-months of exposure). The rate of these events was lower than the rates of drug-related serious AEs among patients receiving either of these drugs alone (bedaquiline, 0.28; delamanid, 0.39). No fatal drug-related events occurred among patients receiving bedaquiline and delamanid concurrently.

QTcF values among people receiving bedaquiline and delamanid increased by an average of 15 ms (from 398 ms to 413 ms) from those taken before or at the time of first receipt of concurrent bedaquiline and delamanid use, to the end of the first month. In subsequent months of exposure, the mean QTcF values were similar to those at the end of the first month (range: 404–420 ms). QTcF prolongation of more than 500 ms was rare, occurring in only one patient in month 7 of concomitant exposure. Drug-related cardiac AEs were infrequent, occurring in only two of 92 people exposed to concomitant bedaquiline and delamanid (rate: 0.2 per 100 person-months). Only one drug-related cardiac serious AE occurred (rate: 0.1 per 100 person-months). No fatal drug-related cardiac events occurred among the 92 people exposed to bedaquiline and delamanid concurrently.

In the endTB observational study overall (*n*=1094), there were two fatal drug-related cardiac events (sudden deaths attributable to QT prolongation), and one other patient experienced a cardiac arrhythmia. The two deaths occurred among patients receiving bedaquiline, clofazimine, capreomycin and *p*-aminosalicylic acid (but not moxifloxacin or delamanid); in both patients, hypokalaemia was present. These patients were not included in the analysis related to this PICO question because they did not meet the criteria for inclusion according to the predefined statistical analysis plan. However, recognizing that these estimates of serious AEs were absolute and not relative, the panel felt that this additional evidence was important for close monitoring when the final data of the endTB observational study become available.

The GDG agreed that there was insufficient evidence to assess the efficacy or effectiveness of the concomitant use of bedaquiline and delamanid, given that there were only 84 patients in the intervention group and the data did not lend themselves to a meaningful analysis for the secondary comparator (extended use of delamanid alone) because the populations were too different to allow for the matching that is usually carried out. This precluded a formal recommendation on the efficacy or effectiveness of the concomitant use of bedaquiline and delamanid; however, the GDG concluded that a statement on safety could be made. This information is included in Implementation considerations and in a table note for Table 2.22.

Additional data presented from the DELIBERATE trial highlighted that – among the patients randomized to bedaquiline (*n*=28), delamanid (*n*=27) or both medicines (*n*=27) – the on-treatment change in QTcF from baseline was 11.9 ms, 8.6 ms and 20.7 ms, respectively.[45] Of the 27 patients who received both medicines, 10 (37.0%) experienced a Grade 1[46] QT prolongation AE, and two (7.4%) experienced a Grade 2 QT AE. In the bedaquiline arm, 32.0% and 3.6% of patients experienced Grade 1 and 2 QT AEs; in the delamanid arm, these figures were 41.0% for a Grade 1 QT AE and 7.4% for a Grade 2 QT AE. No patients experienced Grade 3 or 4 QT AEs. The study investigators concluded that the QTcF prolongation effects of concurrent delamanid and bedaquiline use were not greater than their additive effects. The GDG noted that the QT AEs in the DELIBERATE trial were surrogate markers of sudden cardiac death. They also noted that levofloxacin was the fluoroquinolone of choice in regimens given to patients in the DELIBERATE trial and that serum potassium was closely monitored.

PICO question 1–2021 (Childhood TB 2021) (use of bedaquiline in MDR/RR-TB patients aged below 6 years) and PICO question 2–2021 (Childhood TB 2021) (use of delamanid in MDR/RR-TB patients aged below 3 years)

Regarding PICO question 1–2021 (Childhood TB 2021) and PICO question 2–2021 (Childhood TB 2021), the details of the evidence review and GDG deliberations can be found in Module 5. Management of tuberculosis in children and adolescents. The recommendation on the use of bedaquiline in children also applies to the 9–11 month regimens, it also appears under recommendation B2.4 in section 2.

Subgroup considerations

MDR/RR-TB alone or with additional resistance

A longer regimen is used where a shorter regimen cannot be used; it is more likely to be effective if its composition is guided by reliable information on drug susceptibility. The design of longer regimens for MDR/RR-TB patients with additional resistance follows a similar logic to that used for other MDR/RR-TB patients. All MDR/RR-TB patients should be tested for resistance to fluoroquinolones as a minimum before starting MDR-TB treatment. If the use of amikacin is being considered in the regimen, then rapid testing for second-line injectable agents should be performed. Other tests that may help to inform regimen choice and composition are those for resistance to agents such as bedaquiline, delamanid, linezolid and pyrazinamide, and for mutation patterns commonly associated with resistance to isoniazid and ethionamide or prothionamide. In many settings, DST for other medicines commonly used for MDR-TB treatment is not usually reliable enough to guide regimen composition. Because of this, other elements may be necessary to determine the likelihood of effectiveness (see Implementation considerations). NTPs should possess or rapidly build the capacity to undertake DST, and all efforts should be made to ensure access to approved rapid molecular tests. Until the capacity for second-line

[45] Personal communication, K Dooley, Johns Hopkins Medicine, November 2019 – for this statement and the rest of this paragraph.

[46] In the DELIBERATE trial, a Grade 1 QT adverse event was classified as an absolute QTcF in the following situations: >480 ms and ≤500 ms and QTcF change from baseline from >0 ms to ≤30 ms *OR* an absolute QTcF ≤480 ms and QTcF change from baseline from >30 ms to ≤60 ms. A Grade 2 QT adverse event was classified as an absolute QTcF in the following situations: >480 ms and ≤500 ms and QTcF change from baseline from >30 ms to ≤60 ms *OR* an absolute QTcF ≤480 ms and QTcF change from baseline >60 ms. A Grade 3 QT adverse event was classified as an absolute QTcF in the following situation: >500 ms *OR* an absolute QTcF >480 ms and QTcF change from baseline >60 ms. A Grade 4 QT adverse event was a life-threatening consequence; for example, torsade des pointes or other associated serious ventricular dysrhythmia (personal communication, K Dooley, Johns Hopkins Medicine, November 2019).

DST – including for bedaquiline, linezolid and clofazimine – becomes available, treatment decisions may need to rely on the likelihood of resistance to medicines, based on an individual patient's clinical history and surveillance data from the country or region.

The analysis for the three PICO questions on the duration of treatment did not show any differences overall in treatment failure or relapse when comparing patients with MDR-TB with or without additional second-line drug resistance, including those with additional resistance to fluoroquinolones and injectable agents. In patients with resistance to amikacin and streptomycin, Recommendation 3.17 does not apply. The duration of treatment may need to be longer than 20 months overall in MDR/RR-TB cases with extended resistance patterns, subject to the clinical response to treatment.

Rifampicin-resistant TB

A patient (child or adult) in whom isoniazid resistance is absent needs to be treated with a recommended MDR-TB regimen – either a longer MDR-TB regimen to which isoniazid is added, or a shorter MDR-TB regimen in eligible patients (see also Treatment of drug-resistant TB using 6-month regimens). Although high-dose isoniazid is not included in Groups A–C, given the rarity of its use in contemporary longer regimens for adults with MDR/RR-TB, it may still be used in patients with confirmed susceptibility or in the presence of mutations that do not usually confer complete resistance to isoniazid *(92)*. High-dose isoniazid was shown to be an important component in paediatric regimens in a 2016 evidence review of the WHO guidelines; based on this finding its use in adults was extrapolated *(82)*. In this analysis, high-dose isoniazid was associated with treatment success among children with confirmed MDR-TB (aOR: 5.9, 95% confidence limits [CL]: 1.7–20.5, P=0.007).

Children and adolescents

The 2018 IPD of longer regimens comprised mainly data from adult patients, with only 181 of the 13 104 (1.4%) cases being in children and adolescents aged below 15 years. Nonetheless, WHO recommendations on longer MDR-TB regimens apply to children as well as adults. Most medicines that are used in longer regimens have been part of MDR-TB regimens for many years, in similar combinations, for both adults and children. The GDG 2021 recommended the use of bedaquiline and delamanid in children of all ages *(27)*. Reproducing the delamanid exposure achieved with the special 25 mg tablet tested in the trial in children aged 3–5 years is expected to be challenging, given that this formulation is not bioequivalent with the 50 mg delamanid adult tablet – the only preparation available at that time *(2)*. There are also concerns that the adult tablet may shatter if attempts are made to split it, and that its contents are exceedingly bitter and unpalatable. Further, bioavailability may be altered when the 50 mg tablet is split, crushed or dissolved. Delamanid is susceptible to oxidation and heat; therefore, retaining pill fragments for use at a time other than the time of initial administration is likely to result in the delivery of lower-than-expected active compound and unspecified oxidation by-products.

The avoidance of an injectable-containing regimen is particularly desirable in children, especially those who are very young and those with mild disease (as determined by the absence of malnutrition), serious forms of extrapulmonary disease, cavitation on chest radiography or HIV infection. Hearing loss can have a permanent effect on the acquisition of language and the ability to learn at school; therefore, if amikacin or streptomycin use is resorted to in children, regular audiometry is required.

The recommendations on treatment duration apply also to children. Given that many patients in the paediatric age group may only be clinically diagnosed or have extrapulmonary disease, it is expected that treatment duration will largely be guided by Recommendation 3.15, subject to response to treatment. Shortening the total treatment duration to less than 18 months may be considered in the case of children without extensive disease (see **Definitions**).

Extrapulmonary TB and TB meningitis

The WHO recommendations on longer MDR-TB regimens apply also to patients with extrapulmonary disease. Adjustments may be required, depending on the specific location of the disease. Treatment of MDR/RR-TB meningitis is best guided by DST of the infecting strain and by knowledge of the properties of TB medicines that cross the blood–brain barrier. Levofloxacin and moxifloxacin penetrate the CNS well *(93)*, as do ethionamide or prothionamide, cycloserine or terizidone, linezolid and imipenem–cilastatin *(94, 95)*. Seizures may be more common in children with meningitis treated with imipenem–cilastatin; thus, meropenem is preferred for meningitis cases and in children. High-dose isoniazid and pyrazinamide can also reach therapeutic levels in the cerebrospinal fluid, and they may be useful if the strains are susceptible. *P*-aminosalicylic acid and ethambutol do not penetrate the CNS well, and they should not be counted on as effective agents for MDR/RR-TB meningitis. Amikacin and streptomycin penetrate the CNS only in the presence of meningeal inflammation. There are few data on the CNS penetration of clofazimine, bedaquiline or delamanid *(96–98)*. In addition, cerebrospinal fluid concentrations may not mirror concentrations in the meninges or brain.

Pregnancy

Amikacin, streptomycin, prothionamide and ethionamide are usually contraindicated during pregnancy. Because of the potential for teratogenic effects from these medications, including the injectable agents, Recommendation 3.17 is of limited relevance in this subgroup. Following the changes made in the 2018 guidelines update, these agents are expected to be used less frequently in longer regimens. Knowledge about the safety of bedaquiline and delamanid in pregnancy and breastfeeding was sparse during that period. However, new evidence from an observational study in South Africa was presented to the GDG 2019; it included information on 58 mothers who received bedaquiline during pregnancy *(66)*. The results of this study indicated that fetal exposure to bedaquiline in utero was associated with low birth weight[47] (45% of babies exposed to bedaquiline had a low birth weight compared with 26% of babies not exposed, *P*=0.034) *(66)*. However, there were no other significant differences in infant outcomes, pregnancy outcomes or maternal treatment outcomes, including weight gain in the infants until 1 year of age *(66)*. The outcomes of treatment and pregnancy, including data from postpartum surveillance for congenital anomalies, should be documented to help inform future recommendations for MDR-TB treatment during pregnancy.

HIV infection

The composition of the treatment regimen for MDR-TB does not usually differ substantially for people living with HIV. With careful attention, it is possible to avoid certain drug–drug interactions (e.g. bedaquiline and efavirenz; see also the HIV drug interactions website of the University of Liverpool *(53)*).

Patients with extensive pulmonary TB disease

The duration of treatment post culture conversion may be modified according to the patient's response to therapy[48] (e.g. culture conversion before 2 months of treatment) and other risk factors for treatment failure or relapse. This should be considered in patients with extensive TB disease.

[47] Low birth weight was defined as less than 2500 g.

[48] "Bacteriological response" refers to bacteriological conversion with no reversion; "bacteriological conversion" describes a situation in a patient with bacteriologically confirmed TB where at least two consecutive cultures (for DR-TB and drug-susceptible TB) or smears (for drug-susceptible TB only), taken on different occasions at least 7 days apart, are negative; and "bacteriological reversion" describes a situation where at least two consecutive cultures (for DR-TB and drug-susceptible TB) or smears (for drug-susceptible TB only), taken on different occasions at least 7 days apart, are positive either after the bacteriological conversion or in patients without bacteriological confirmation of TB. *(99)*

Patients on regimens without amikacin or streptomycin

In patients on regimens that do not contain injectable agents in the intensive phase, Recommendation 3.17 does not apply, and the length of treatment is determined by recommendations on total duration and on time after culture conversion (i.e. Recommendations 3.15 and 3.16). In the future, this situation is expected to apply to an increasing proportion of patients who are treated with oral-only regimens. If bedaquiline or other agents (e.g. linezolid or delamanid) are given only for the initial part of a regimen, this period does not equate to an "intensive phase" unless an injectable agent is used concurrently, as premised by the meta-analysis that informed Recommendation 3.17.

Implementation considerations

The implementation of MDR/RR-TB treatment on a large scale is feasible under programmatic conditions, as has been shown by the global expansion in the use of standardized and individualized MDR-TB regimens in low-, middle- and high-income countries worldwide, particularly in the past decade *(6)*. The 2018 revision of the guidelines brought important changes to the grouping of medicines, the composition of longer MDR-TB regimens and the duration of medicine use, but it is expected that implementation of these changes will be feasible. The rapidity with which the new recommendations are applied in (or to) programmes may be influenced by a range of factors, but these should not stand in the way of increased access to life-saving treatment for patients who need it.

All of the agents recommended for use are available via the GDF, and most are also available in quality-assured, affordable generic formulations from other sources. Bedaquiline was available via a donation programme until March 2019; it is now available via the GDF, and a decrease in price has been negotiated with the manufacturer for low-resource settings. The evidence assessed during the GDG meeting in November 2019 did not allow the group to make any judgements about the efficacy or effectiveness of bedaquiline when used for longer than 6 months; however, it did allow the GDG to determine that the safety profile of bedaquiline use for longer than 6 months is becoming clearer. The group concluded that bedaquiline can be safely used in patients beyond 6 months, if decided by the programme or treating clinician, and if appropriate schedules of baseline testing and monitoring are in place. In addition, the treating clinician should be aware of the use of other potentially QT-prolonging medications in any MDR/RR-TB regimen, and the comparatively long half-life of bedaquiline, which means that bedaquiline will remain in human tissue beyond the duration of its use. The half-life of bedaquiline is about 6 months, and the half-life of the *N*-monodesmethyl metabolite (M2) is about 5.5 months *(74)*.[49]

Concurrent bedaquiline and delamanid use

The GDG 2019 felt that there was insufficient evidence to assess the efficacy or effectiveness of the concurrent use of bedaquiline and delamanid. However, the group concluded that the safety data assessed in 2019 suggest there are no additional safety concerns regarding the concurrent use of bedaquiline and delamanid. Therefore, bedaquiline and delamanid may be used in patients who have limited options for other treatment; that is, for patients with a small number of other effective drugs included in their regimen, probably due to an extensive drug-resistance profile or intolerance to other second-line TB medications. Appropriate schedules of safety monitoring (at baseline and throughout treatment) should be in place for these patients, including ECG and electrolyte monitoring, and clinicians should be cognizant of other medicines in the regimen that can either prolong the QT interval or cause other potential AEs.

The 2021 WHO model list of essential medicines *(100)* includes all agents required for longer regimens.

[49] This is the mean terminal half-life of bedaquiline and the M2 metabolite; this longer terminal elimination phase probably reflects the slow release of bedaquiline and M2 from peripheral tissues *(74)*.

Drug susceptibility testing

These guidelines stress past advice that a patient's MDR/RR-TB strain should be tested for susceptibility to medicines planned for inclusion in the regimen, so that effectiveness can be maximized. Access to rapid diagnostic testing would help clinicians to decide whether the patient is eligible for a specific MDR/RR-TB regimen, and what agents to include in a longer MDR-TB regimen. The recommendations on regimen design need to be accompanied by continued efforts to increase access to DST for medicines for which there are reliable methods, and by the development and roll-out of DST for the newer medicines. However, potentially life-saving treatment should not be withheld until all DST results become available, and empirical treatment with a regimen that is likely to be effective may need to be started, then adjusted once DST results become available.

An important observation in the 2018 IPD meta-analysis for longer regimens is that when a DST result indicates resistance to an agent, it is better to replace that agent. This also applies to medicines for which DST or the DST method used is known to be unreliable for clinical decision-making. Although DST is important for guiding effective treatment, DST results present uncertainties for several regimen components (e.g. cycloserine, streptomycin and ethambutol). "Likelihood of effectiveness" is generally assessed in the programmatic setting on the basis of one or more of the following: confirmed susceptibility in the individual patient, confirmed susceptibility in the presumed source case, no known resistance to another drug that has cross-resistance to the medicine, rare use of the medicine in an area (possibly supported by low drug-resistance levels from surveillance activities), and no previous use of the medicine in a regimen that failed to cure that same patient. When there is uncertainty about the effectiveness of a certain agent, that agent may still be included in the regimen, but it should not be considered as one of the target number of medicines needed; clinical judgement should be used to decide whether the benefit from its inclusion outweighs any added toxicity, pill burden or other disadvantages. The design of the regimen must consider the relative benefits and harms to the individual patient, including drug–drug interactions.

Dosage and duration

The guidelines update in 2018 revised the weight-based dosage schedules for medicines used in MDR-TB regimens for both children and adults (see the *WHO consolidated operational handbook on tuberculosis. Module 4: Treatment and care (8)*). The update to the dosages benefited from the expertise of the GDG members, and from a consultation with other specialists in different fields. It was based on the latest knowledge available about the optimal use of the medicines involved *(101)*. Adherence to the schedules is advised as far as possible. Manipulation of tablets (e.g. splitting, crushing or dissolving in water) outside their indications is to be avoided because this may interfere with the bioavailability of the drugs.[50]

It is important to prevent treatment interruption, to increase the likelihood of treatment success. One measure that can help to increase retention is supporting patient adherence, either by facilitating patient visits to health care facilities or home visits by health care staff, or by using digital technologies for daily communication *(102)*.

[50] This is particularly problematic with the delamanid tablet, the contents of which are most unpalatable.

B4. Treatment of rifampicin-susceptible and isoniazid-resistant TB (Hr-TB)

Recommendations B4.1–B4.2 Treatment of Hr-TB

No.	Recommendation
B4.1	In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months. *(Conditional recommendation, very low certainty of evidence)*
B4.2	In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen. *(Conditional recommendation, very low certainty of evidence)*

Justification and evidence

The recommendations in this section address one PICO question:

> ***PICO question*** *(Hr-TB, 2018): In patients with isoniazid-resistant TB (other than MDR-TB), which treatment regimen composition and duration, when compared with 6 months or more of rifampicin–pyrazinamide–ethambutol, leads to a higher likelihood of success with least possible risk of harm?*

Treatment with rifampicin, ethambutol and pyrazinamide – with or without isoniazid – has been used for the treatment of patients with rifampicin-susceptible, isoniazid-resistant TB (Hr-TB) *(103–105)*. The evidence reviewed for this guideline compared treatment regimens with isoniazid, rifampicin, ethambutol, pyrazinamide ((H)REZ)[51] of different durations (e.g. 6-month regimens versus longer duration ones). Additionally, the review of evidence focused on determining whether treatment outcomes in Hr-TB patients receiving (H)REZ treatment regimens of variable duration could be improved with the addition of a fluoroquinolone or streptomycin.

The evidence used to determine the composition and duration of regimens relied primarily on an analysis of IPD that comprised 33 databases with an analysable population of 5418 Hr-TB patients. All data used to develop these recommendations were derived from observational studies conducted in various settings (33% in Europe, 31% in the Americas, 26% in Asia and 6% in Africa) *(106)*.[52] In the IPD analysed, patient treatment regimens contained rifampicin, ethambutol, pyrazinamide, streptomycin, isoniazid and fluoroquinolones; thus, recommendations could be made only for regimens containing these anti-TB agents. Based on an assessment of the certainty of the evidence, carried out using predefined criteria, the certainty of the evidence was rated as very low.

Duration of (H)REZ

The analysis comparing (H)REZ treatment regimens for 6 months (6(H)REZ) and more than 6 months (>6(H)REZ) demonstrated that a 6(H)REZ regimen had a higher likelihood of treatment success than a >6(H)REZ regimen. Further analyses determined that there was no statistically significant difference in the treatment outcomes of patients receiving regimens of 6-month REZ (6REZ) and those receiving more than 6 months REZ (>6REZ). Data on intermittent dosing of the 6(H)REZ and >6(H)REZ regimens were not included; hence, no inferences could be drawn about the use of alternating

[51] "(H)" indicates that isoniazid is optional.

[52] The number of patients highlighted in this section refers to the sample size of each study. However, the analysable sample size was later modified, depending on the availability of IPD for each analysable outcome (success and mortality).

versus daily regimens. The effect of length of pyrazinamide use in the (H)REZ regimen was assessed, to investigate whether the use of this medicine could be minimized to the shortest possible duration. The reduction in treatment with pyrazinamide to less than 3 months was associated with a worse treatment outcome, even with the addition of streptomycin (aOR: 0.4, 95% CL: 0.2–0.7). In 118 patients on fluoroquinolone-containing regimens who received pyrazinamide for less than 4 months, the odds of treatment success were higher than in those who received a 6(H)REZ regimen, although the difference was not statistically significant.

Duration of levofloxacin use

In a subsample of 241 patients on an (H)REZ plus fluoroquinolone regimen, the median duration of fluoroquinolone use was 6.1 months (IQR: 3.5, 8.4), and for REZ it was 9 months (IQR: 7, 11). Hence, in the observational studies that informed the IPD, it seems that treatment length was based on the completion of 6 months of treatment with fluoroquinolone.

Acquisition of drug resistance

The analysis suggested that amplification of resistance to rifampicin was lower in patients receiving the 6(H)REZ regimen (0.6%) than in those receiving >6(H)REZ (4.3%). This observation could be due to the selection and allocation of patients into specific regimens; for instance, the number of patients with extensive disease was slightly larger in those receiving >6(H)REZ. However, overall, the number of observations for each comparison was small and the effect was not statistically significant (aOR, 0.2, 95% CL: 0.02–1.70).

Adverse events

Data on AEs were not evaluated owing to a lack of standardization (dissimilar reporting). The GDG also considered two reports containing data from patients from the USA in whom a detailed assessment of AEs suggested a risk of excess hepatotoxicity with the 6(H)REZ combination *(107)*. Drug-induced hepatotoxicity is not uncommon with anti-TB drugs. It has also been reported in individuals receiving rifampicin and pyrazinamide for 2 months for the treatment of TB infection – in such individuals, a much higher occurrence of hepatotoxicity has been observed than in those receiving only isoniazid preventive therapy *(108)*. It is not known whether the risk of hepatotoxicity differs between 6REZ and 6HREZ.

Addition of a fluoroquinolone

In patients with Hr-TB, treatment success rates were higher when fluoroquinolones were added to (H)REZ regimens than when patients were treated with 6(H)REZ or >6(H)REZ, without the addition of fluoroquinolones (aOR: 2.8, 95% CL: 1.1–7.3). With the addition of fluoroquinolones in patients receiving (H)REZ, the number of deaths was reduced (aOR: 0.4, 95% CL: 0.2–1.1). Acquisition of additional resistance with progression to MDR-TB was also reduced when fluoroquinolones were added to a ≥6(H)REZ regimen (aOR: 0.10, 95% CL: 0.01–1.2), albeit with small absolute numbers; 0.5% (1/221) of patients on ≥6(H)REZ plus fluoroquinolones acquired resistance to rifampicin compared with 3.8% (44/1160) of patients who did not receive fluoroquinolones. Residual confounding could have increased this observed effect. The directness of the evidence was therefore downgraded because it was unclear whether fluoroquinolones were used at the beginning of treatment or only once DST results were available (in the second month or later).

Addition of streptomycin

The analysis showed that the addition of streptomycin (up to 3 months) to an (H)REZ regimen with less than 4 months of pyrazinamide decreased the likelihood of treatment success (aOR: 0.4, 95% CL: 0.2–0.7), an effect that may in part be due to confounding. The addition of streptomycin did not

significantly reduce mortality. There were no data on the use of other injectable agents (i.e. kanamycin, amikacin and capreomycin) for the treatment of Hr-TB.

Treatment outcomes

When analysing the overall treatment outcomes for each one of the regimens assessed for this review, other limitations related to the characteristics of patients included in these studies were evident and could not be controlled for. Those limitations were patient selection, and allocation to treatment with specific regimens and their relationship with disease severity. Outcomes appeared to be worse in patients with cavitary disease, persistence of sputum smear positivity and previous history of TB treatment, who received a 6(H)REZ or >6(H)REZ regimen with an additional 3 months of pyrazinamide and 1–3 months of streptomycin (see Hr-TB, 2018 in Annex 5). However, the limited number of observations made it difficult to draw definitive conclusions based on the severity of TB disease or the effect of other comorbidities on this regimen.

In formulating the recommendations, the GDG assessed the overall balance between benefits and harms of an (H)REZ–levofloxacin regimen; they also considered values and preferences (paying special attention to considerations of equity, acceptability and feasibility), in addition to clinical outcomes and the potential risks of increasing toxicities (see Annex 5 for details). The conclusions of the GDG were that a regimen composed of 6 months of REZ plus fluoroquinolones was associated with higher treatment success rates (with or without the addition of isoniazid). The difference between the 6(H)REZ and >6(H)REZ regimens was modest, slightly favouring the 6-month regimen (not statistically significant). The GDG acknowledged that it was not possible to control for all possible confounding by indication when comparing the 6(H)REZ and >6(H)REZ regimens. As an example, although data on the extent of disease were not systematically captured for all patients, it is possible that a larger number of cases with extensive disease received >6(H)REZ regimens, resulting in poor outcomes for this group of patients (given the extent of disease) and possibly favouring the 6(H)REZ regimen.

The GDG acknowledged the safety implications of (H)REZ–levofloxacin, particularly the hepatotoxicity associated with prolonged use of pyrazinamide-containing multidrug regimens. However, reducing the duration of the treatment with pyrazinamide to 3 months or less was associated with worse treatment outcomes, at least in Hr-TB regimens without a fluoroquinolone. Furthermore, the use of streptomycin in these regimens was associated with no significant added benefit. The use of streptomycin and other injectable agents has also been associated with increased serious AEs *(109–111)*. On this basis, the GDG agreed that current data supported the use of the (H)REZ–levofloxacin regimen without streptomycin or any other injectable agent in Hr-TB cases, unless there is a compelling reason to use these agents (e.g. certain forms of polydrug resistance).

The GDG also noted that patients were likely to place a high value on a 6-month regimen, the likelihood of a relapse-free successful outcome and, especially, the implementation of a regimen without the use of injectable agents. GDG members agreed that the use of the 6(H)REZ regimen would probably increase health equity, given that the cost of the components is relatively low (compared with the recommended regimens for MDR/RR-TB) and the increased probability of cure in a substantial number of patients. In addition, the exclusion of streptomycin and other injectable agents reduces potential barriers to regimen administration.

Although patient costs were not factored into the analysis, the GDG agreed that improving diagnostic capacity to detect isoniazid resistance would be beneficial. A modelling analysis performed for the 2011 update of the WHO *Guidelines for the programmatic management of drug-resistant tuberculosis (13)* estimated that the best strategy for averting deaths and preventing acquired MDR-TB was to undertake DST in all patients before treatment, using a rapid test that detects resistance to isoniazid and rifampicin *(112)*. The modelling work also showed that rapid testing for resistance to both isoniazid and rifampicin at the time of diagnosis was the most cost-effective testing strategy for any patient group or setting, even at very low levels of resistance among TB patients (MDR-TB in >1% and isoniazid resistance [other than MDR-TB] in >2%).

In general, the GDG considered that the use of the 6(H)REZ–levofloxacin regimen would be feasible in most DR-TB treatment settings, and that the use of a regimen based on medicines that are administered orally may increase feasibility. Altogether, based on present evidence, when discussing the balance between benefits and harms, preferences and values for patients and other end-users, the GDG reached overall agreement on the beneficial effect that the Hr-TB regimen may have, if used in conformity with these policy recommendations. Although there was no clear evidence to suggest that the addition of isoniazid to this regimen would be beneficial, the four-drug (H)REZ fixed-dose combination (FDC) may be more convenient for the patient and the health service because it removes the need to use single drugs.

Consistent with the overall framework for the management and care of patients diagnosed with DR-TB, careful selection of patients is a fundamental principle. Ahead of starting the (H)REZ–levofloxacin regimen, it is essential that resistance to rifampicin be excluded, using WHO-recommended genotypic or phenotypic methods *(50, 113)*. Ideally, resistance to fluoroquinolones (and, if possible, to pyrazinamide) should be similarly excluded before treatment, to help avert the acquisition of additional drug resistance (see Implementation considerations).

Empirical treatment of Hr-TB is generally not advised. In cases where a diagnosis of Hr-TB is strongly presumed (e.g. close contacts of Hr-TB cases with active TB but without laboratory confirmation of Hr-TB), (H)REZ–levofloxacin may be introduced pending laboratory confirmation of isoniazid resistance, provided that rifampicin resistance has been reliably excluded. Should DST results eventually indicate susceptibility to isoniazid, levofloxacin is stopped, and the patient completes a 2HREZ/4HR regimen (i.e. 2 months of HREZ followed by 4 months of HR). For patients in whom Hr-TB is detected after the start of treatment with the 2HREZ/4HR regimen, the (H)REZ component drugs are continued (or pyrazinamide and ethambutol are reintroduced) and levofloxacin added, once rifampicin resistance has been excluded.

The duration of an (H)REZ–levofloxacin regimen is usually determined by the need to complete 6 months of a levofloxacin-containing regimen. Thus, in cases where the diagnosis of Hr-TB is made after first-line TB treatment has already been initiated, the patient may receive more than 6 months of (H)REZ by the end of treatment. When the confirmation of isoniazid resistance arrives late into treatment with a 2HREZ/4HR regimen (e.g. 5 months after start during the continuation phase), the clinician would need to decide, based on an assessment of the patient's condition, whether a 6-month course of (H)REZ–levofloxacin needs to be started at that point or not.

The addition of levofloxacin to (H)REZ is recommended in all patients with Hr-TB, with the exception of the following situations: resistance to rifampicin cannot be excluded; known or suspected resistance to levofloxacin; known intolerance to fluoroquinolones; known or suspected risk for prolonged QT interval; and pregnancy or during breastfeeding (not an absolute contraindication). In a patient with Hr-TB in whom a fluoroquinolone cannot be used, the patient may still be treated with 6(H)REZ.

When additional resistance (especially to pyrazinamide) is suspected or confirmed, appropriate treatment regimens will have to be designed individually. The data reviewed for this guideline could not provide separate evidence-based recommendations for such cases.

Where possible, isoniazid resistance testing should also include information on the specific mutations associated with resistance to isoniazid (*kat*G or *inh*A). In addition, knowledge about overall host acetylator[53] status at country or regional level will be useful, given that these may have implications for regimen design *(114)*.

Automated, cartridge-based and high-throughput diagnostic platforms are available (as an alternative to LPA) and countries have the capacity to use them. These platforms can, simultaneously or in separate tests, detect TB, and resistance to rifampicin, fluoroquinolones and isoniazid.

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[53] Decreased efficacy and toxicity of isoniazid have been related to its increased metabolism (acetylation) in certain individuals, as determined by mutations in the *N*-acetyltransferase type 2 (NAT2) gene.

Subgroup considerations

Children

In the IPD review, only 2% of Hr-TB patients were children; thus, a separate estimate of effect for paediatric patients was not possible. However, there is no reason why the results and recommendations cannot be extrapolated from adults to children, considering that the regimen components have been standard paediatric TB medicines for many years.

Patients with extensive disease

Although the IPD analysis did not provide evidence for duration of treatment extension, the prolongation of the 6(H)REZ–levofloxacin regimen to more than 6 months could be considered on an individual basis for patients with extensive disease *(115)*. Prolongation of treatment may increase the risk of AEs in some cases (see Implementation considerations).

People living with HIV

The effect of longer duration TB treatment among people living with HIV with and without ART has been studied among patients with drug-susceptible TB (DS-TB) *(116)*. In these cases, relapse has been reported to be 2.4 times higher in people living with HIV who were not on ART and who received 6 months of treatment than in patients in whom treatment was prolonged (up to 9 months). In patients with DS-TB initiated on ART, no significant benefit from prolonging rifampicin-containing regimens for over 6 months has been observed *(102)*. In the current analysis, only a limited number of patients received ART; nonetheless, in TB patients with HIV coinfection, the first priority is to ensure that they are started on ART within 8 weeks of TB treatment initiation (regardless of CD4 count), in accordance with WHO guidelines *(117)*. The 6(H)REZ–levofloxacin regimen is therefore recommended in people living with HIV.

Extrapulmonary disease

No data were available for patients with exclusive extrapulmonary Hr-TB. The regimen composition proposed is likely to be effective even in these patients. However, the treatment of patients with extrapulmonary TB should be designed in close consultation with appropriate specialists (e.g. infectious disease physicians and neurologists), to decide upon individual variations in treatment duration and supportive care, as needed.

Implementation considerations

Case scenarios

Implementing these recommendations requires the (H)REZ–levofloxacin regimen to be administered only in patients in whom resistance to isoniazid has been confirmed and resistance to rifampicin has been excluded. Preferably, testing for resistance to fluoroquinolones (and, if possible, to pyrazinamide) is also done before starting treatment. It is envisaged that the treatment regimen for Hr-TB will apply in the following situations:

- *Hr-TB and rifampicin susceptibility are confirmed before TB treatment is started.* Treatment with (H)REZ–levofloxacin is started immediately. If the diagnosis is strongly presumed (e.g. close contacts of a confirmed Hr-TB source case) but results of DST are still pending, the regimen may be introduced. If the DST results taken at the start eventually show susceptibility to isoniazid, then levofloxacin is stopped, and the patient continues treatment to complete a 2HREZ/4HR regimen.
- *Hr-TB is confirmed after the start of treatment with the 2HREZ/4HR regimen.* This includes patients who had undiagnosed isoniazid resistance initially or who developed isoniazid resistance later while

on treatment with a first-line regimen. In such cases, rapid molecular testing for rifampicin resistance must be done (or repeated). Once rifampicin resistance has been excluded, a full 6-month course of (H)REZ–levofloxacin is given. The duration is driven by the need to give levofloxacin for 6 months, which usually implies that the companion first-line medicines are taken for longer than this.

If rifampicin resistance is detected, the patient needs to be started on a recommended MDR-TB treatment regimen, as described in other sections of these guidelines.

Diagnostic capabilities

The overall aim of TB treatment is to achieve cure without relapse in all patients, interrupting *M. tuberculosis* transmission and preventing the acquisition (or amplification) of additional drug resistance. Globally, Hr-TB is more prevalent than MDR-TB. Thus, all countries need to move towards universal testing of both isoniazid and rifampicin resistance at the start of TB treatment, and to ensuring careful selection of patients eligible for the (H)REZ–levofloxacin regimen.[54] The minimum diagnostic capacity to appropriately implement these recommendations is rapid molecular testing for rifampicin resistance before the start of treatment with the Hr-TB regimen and, preferably, the ruling out of fluoroquinolone resistance using WHO-recommended tests.

Rapid molecular tests such as Xpert MTB/RIF, Xpert MTB/XDR and LPAs are preferred, to guide patient selection for the (H)REZ–levofloxacin regimen *(50, 118)*.

Surveillance of DR-TB indicates that fluoroquinolone resistance among patients with rifampicin-susceptible TB is generally low worldwide *(119)*. However, national data on the prevalence of fluoroquinolone resistance – including targeted or whole-genome sequencing to detect specific mutations associated with resistance to fluoroquinolones *(50)* – could help to guide testing policies when countries implement the Hr-TB treatment recommendations.

When additional resistance (e.g. to both fluoroquinolones and pyrazinamide) is suspected or confirmed, treatment regimens that include other second-line TB medicines may have to be designed individually. The current review could not provide further evidence on effective regimens in patients with polyresistant disease.

Support and close monitoring of patients are needed to maximize treatment adherence and enable early detection of patients who are not responding to treatment (e.g. those with persistent sputum culture or smear positivity). In the presence of non-response to treatment, DST for rifampicin and the fluoroquinolones should be repeated, preferably with Xpert MTB/XDR or LPA. Documented acquisition of resistance to rifampicin or a fluoroquinolone while on the Hr-TB treatment regimen should alert the clinician to the need to review the entire clinical and microbiological status of the patient, and change the regimen where necessary.

Levofloxacin is proposed as the fluoroquinolone of first choice in the Hr-TB treatment regimen for several reasons. First, the safety profile of this medicine is better characterized than that of other fluoroquinolones, and levofloxacin was the fluoroquinolone most frequently used in the studies reviewed for this guidance. Second, in comparison to moxifloxacin, levofloxacin has fewer known drug interactions with other medications. For example, although both plasma peak concentration and exposure to moxifloxacin decrease significantly when the drug is combined with rifampicin *(120)*, the same effect has not been reported for levofloxacin, possibly because levofloxacin undergoes limited metabolism in humans and is excreted unchanged in the urine *(121)*. Third, although levofloxacin may interfere with lamivudine clearance, in contrast to moxifloxacin, there are no contraindications for its use with other antiretroviral agents *(53)*.

[54] The association between previous TB treatment history and Hr-TB is less strong than the association in MDR-TB. As a result, previous TB treatment is less reliable as a proxy for Hr-TB and a laboratory diagnosis is therefore important.

The addition of levofloxacin to (H)REZ is recommended in patients with Hr-TB, with the exception of the following situations:

- resistance to rifampicin cannot be excluded (i.e. unknown susceptibility to rifampicin, or indeterminate or error results on Xpert MTB/XDR);
- known or suspected resistance to levofloxacin;
- known intolerance to fluoroquinolones;
- known or suspected risk for prolonged QT interval; and[55]
- if possible, in pregnancy or during breastfeeding (not an absolute contraindication).

Sometimes, the confirmation of isoniazid resistance arrives late (e.g. 5 months into a 2HREZ/4HR regimen). In such cases, a decision to start 6 months of (H)REZ–levofloxacin depends on the patient's clinical condition and microbiological status.

If levofloxacin cannot be used because of toxicity or resistance, the patient may be given 6(H)REZ as an alternative. Based on the results of the evidence review for these guidelines, replacement of levofloxacin with an injectable agent is NOT advised. The evidence review could not inform on the effect of other second-line TB medicines on treatment effectiveness.

Addition of isoniazid

There was no clear evidence that the addition of isoniazid affects patients (i.e. adding benefit or harm). For patient convenience and ease of administration, the four-drug HREZ FDCs[56] may be used to deliver the Hr-TB treatment regimen alongside levofloxacin.

The use of high-dose isoniazid (10–15 mg/kg per day in adults) was not evaluated in this review owing to insufficient data. However, the GDG discussed the effect of increasing isoniazid dosing beyond that provided in weight-banded FDCs, depending on the type of molecular mutations identified. In vitro evidence suggests that when specific *inh*A mutations are detected (and when *kat*G mutations are absent), increasing the dose of isoniazid is likely to be effective; thus, additional isoniazid up to a maximum dose of 15 mg/kg per day could be considered. In the case of *kat*G mutations, which usually confer a higher level resistance, the use of isoniazid even at a higher dose is less likely to be effective *(122)*.[57]

Dosage

Although the IPD analysis did not provide evidence to address the frequency of dosing, it is best to avoid intermittent or divided dosing of the 6(H)REZ–levofloxacin regimen *(29, 102, 123)*. In the absence of full information about optimal drug doses, a weight-band dosing scheme for levofloxacin is recommended.[58]

Drug–drug interactions

Levofloxacin may interfere with lamivudine clearance (increasing the levels of lamivudine) but it is not contraindicated with other antiretroviral agents, and no drug dosing adjustments are needed *(53)*. Co-administration of levofloxacin with oral divalent cation-containing compounds (e.g. antacids) may

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[55] Baseline-corrected QT. Prolongation of the QT interval and isolated cases of *torsades de pointes* have been reported. Avoid use in patients with known prolongation, those with hypokalaemia, and with other drugs that prolong the QT interval.

[56] Although most countries currently procure the four-drug FDC via the Stop TB Partnership's GDF, in settings where only the three-drug combination FDC (i.e. HRZ) is available, ethambutol has to be administered separately.

[57] An isolated *kat*G or *inh*A mutation can correspond to variable MIC levels. This implies that *inh*A mutations do not always indicate low-level isoniazid resistance, and that *kat*G mutations are not necessarily correlated with high-level isoniazid resistance. However, the presence of both mutations is usually an indication of high-level resistance *(122)*.

[58] Studies included in this IPD analysis involved the use of regimens containing levofloxacin (usually at a dose of 750–1 000 mg/day), moxifloxacin (400 mg/day) or gatifloxacin (400 mg/day), as well as early-generation fluoroquinolones (ciprofloxacin and ofloxacin), which are no longer recommended for the treatment of DR-TB. Gatifloxacin is currently unavailable in quality-assured formulations, and ciprofloxacin and ofloxacin are no longer recommended for use in DR-TB care.

impair its absorption and should be avoided *(15)*. Restriction of concomitant use of milk products is not necessary.

Treatment prolongation beyond 6 months

Prolonging of treatment beyond 6 months may be considered for patients with extensive disease or in those slow to convert to smear or culture negative. In the latter, acquisition of additional resistance to rifampicin must be ruled out, as must resistance to fluoroquinolones and pyrazinamide, if possible. Such patients require careful monitoring and follow-up.

Cost

A cost–effectiveness analysis was not performed for this review. Table 2.23 presents approximate prices for a full course of medicines with the different regimens in adults, based on the cost of products available from the GDF *(55)*. Use of FDCs, even for part of the regimen, reduces costs. Medicines needed for a 6HREZ–levofloxacin regimen cost about three times as much as a 2HREZ/4HR regimen when using the HREZ FDC. The treatment of Hr-TB according to these guidelines is not expected to significantly increase operational costs.

Table 2.23. Illustrative costs of regimens used to treat Hr-TB compared with the 6-month first-line TB regimen

Regimen	Average weighted prices, US$[a]
2HREZ/4HR	36
6HREZ	55
6REZ–Lfx	99
6HREZ–Lfx	76
9HREZ–Lfx	113

FDC: fixed-dose combination; HR: isoniazid and rifampicin; HREZ: isoniazid, rifampicin, ethambutol and pyrazinamide; Hr-TB: rifampicin-susceptible, isoniazid-resistant TB; Lfx: levofloxacin; REZ: rifampicin, ethambutol and pyrazinamide; TB: tuberculosis.

[a] Prices are as of 15 March 2020 for a 60 kg adult, and they reflect the use of FDCs whenever possible. Average weighted prices are based on prospective market share allocation and are indicative only. For budgeting purposes, it is recommended to use the budgeting prices from the Stop TB Partnership *(55)*.

Source: Stop TB Partnership (2020) *(55)*.

Adherence

The IPD analysis contained limited data on the treatment adherence strategies used, such as directly observed treatment and self-administered therapy (SAT). Improved treatment success rates appeared to be associated with increased patient support, including medication adherence support (e.g. by means of digital technologies) or other means, as recommended by WHO *(102)*. In contrast to regimens for DS-TB and MDR-TB, the recommended Hr-TB treatment regimen does not have an intensive phase and a continuation phase, simplifying the delivery and monitoring of treatment.

B5. Monitoring and management strategies for MDR/RR-TB treatment

People receiving MDR/RR-TB regimens should be monitored through an integrated system that covers clinical and bacteriological response, safety, drug resistance surveillance and programme performance.

Clinical monitoring should include regular history taking, physical examination, weight measurement and chest radiography, both at baseline and at the end of treatment. In children, monitoring of response relies on clinical improvement, weight gain and, where relevant, neurodevelopmental progress. In children with bacteriologically confirmed disease, all reasonable efforts should be made to document bacteriological conversion. In children without confirmed disease, repeated respiratory sampling is not required if there is clear clinical improvement. Weight and height should be measured regularly in all children, and drug doses adjusted promptly to reflect weight gain. The risk of emergence of bedaquiline resistance should be a key consideration when the drug is being used. Owing to difficulties in obtaining suitable specimens from children aged below 6 years, performing DST may be challenging. However, if there are concerns about acquired drug resistance, every effort should be made to obtain a suitable sample, such as gastric aspirate, sputum induction or nasopharyngeal aspirate (stool is not a suitable sample for conducting DST).

Bacteriological monitoring should include monthly smear microscopy and culture, where feasible. Most patients are expected to achieve culture conversion within the first months of treatment. Failure to convert by month 4, persistence of culture positivity beyond the expected time frame, or recurrence should trigger prompt regimen review and repeat DST. Where reliable methods are available, DST for rifampicin, fluoroquinolones and other key medicines in the regimen, including bedaquiline and linezolid, is essential to investigate a lack of response. Adding a single medicine to a failing regimen should be avoided to prevent the amplification of resistance.

Access to baseline and follow-up DST, particularly for fluoroquinolones, is required for appropriate patient selection into standardized shorter regimens and to monitor acquisition of resistance. Surveillance systems, including the use of sequencing where feasible, should accompany programme scale-up of new regimens.

Active drug-safety monitoring and management should be implemented for all MDR or RR-TB regimens. Laboratory and clinical monitoring should be tailored to the medicines used. Liver function tests, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), are required for all regimens; these tests should be performed more frequently when hepatotoxic agents such as prolonged pyrazinamide are used or in patients at increased risk of liver disease. Electrocardiography is indicated when regimens include QT-prolonging agents, and electrolyte abnormalities should be corrected when corrected QT interval (QTc) prolongation is detected. Audiometry, visual acuity assessment and peripheral neurological examination should be conducted when relevant medicines are used. In children receiving ethambutol, monitoring for optic toxicity, including colour vision testing in older children, should be ensured.

Systematic monitoring of AEs should be complemented by structured documentation of regimen modifications. Changes in dosing and duration of linezolid, in particular, should be prospectively recorded to inform the evidence base on tolerability and optimal use in 6-month and 9-month regimens.

NTPs should ensure complete case registration and routine cohort analysis. Prospective, case-based electronic recording and reporting systems are strongly recommended to capture diagnosis, DST results, regimen composition, dosing adjustments, AEs, bacteriological response and final outcomes. High-quality electronic data systems strengthen individual patient care and support the refinement of national and global policies.

Structured adherence-support mechanisms should accompany treatment delivery to improve retention and reduce the risk of treatment interruption.

Treatment administration coupled with patient support can boost adherence; it can also ensure optimal drug effectiveness and safety of patients on treatment. Measures to support patient adherence (e.g. facilitating patient visits to health care facilities or home visits by health care staff, or using digital technologies for daily communication) may be important to retain patients on treatment, even when a regimen is comparatively short. WHO recommendations on care and support are given in Chapter 3.

A chest X-ray at baseline and the end of treatment can help in judging the treatment response, which should be monitored by monthly sputum smear microscopy and culture (ideally at the same frequency). Failure to convert sputum culture at or after the fourth month of treatment or recurrence is a potential predictor of a failing treatment regimen. Persistence of culture positivity beyond that point should trigger DST and a potential review of the regimen. Follow-up after treatment completion, ideally for at least 12 months and including bacteriological assessment where feasible, should be considered to detect relapse and assess long-term programme performance.

In the 2018 update of the guidelines, a separate recommendation was made on the use of culture and microscopy to monitor bacteriological response during treatment. A suggested monitoring schedule is provided in the *WHO consolidated operational handbook on tuberculosis. Module 4: treatment and care (73)*.

Recommendation B5.1 Monitoring patient response

No.	Recommendation
B5.1	In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, the performance of sputum culture in addition to sputum smear microscopy is recommended to monitor treatment response. *(Strong recommendation, moderate certainty in the estimates of test accuracy)* It is desirable for sputum culture to be repeated at monthly intervals.

Justification and evidence

The recommendation in this section addresses the following PICO question:

> ***PICO question (MDR/RR-TB, 2018)**. In patients with MDR/RR-TB treated with longer or shorter regimens composed in accordance with WHO guidelines, is monitoring using monthly cultures, in addition to smear microscopy, more likely to detect non-response to treatment?*

Previous studies have indicated that monthly culture is the optimum strategy to detect non-response as early as possible; hence, monthly culture was conditionally recommended by WHO in 2011 as the preferred approach *(13, 124, 125)*. The findings of the evidence review and analysis performed for this question are expected to influence the continued validity, in its present form, of the 2011 WHO recommendation *(13)*. Since then, significant changes in MDR-TB treatment practices have taken place on a large scale globally, such as the wider use of later-generation fluoroquinolones, bedaquiline and linezolid; a tendency towards an intensive phase of longer duration; and the widespread use of the shorter regimen, which could influence the speed and durability of culture conversion during the continuation phase, when this PICO question is of greatest relevance.

Achieving sustained bacteriological conversion from positive to negative is widely used to assess the response to treatment in both DS-TB and DR-TB. Culture is a more sensitive test for bacteriological confirmation of TB than direct microscopy of sputum and other biological specimens. Culture also facilitates phenotypic testing for DST, a critical consideration in TB diagnostics. However, performing

culture requires considerable logistical organization and a well-equipped laboratory to limit cross-contamination, ensure proper bacterial growth and match other quality standards. Apart from the resource requirements, culture results become available after a significant delay of weeks or months, contrasting markedly with the relative immediacy of the result of direct microscopy (although microscopy cannot confirm mycobacterial viability). Although molecular techniques can now provide a rapid and reliable diagnosis, they cannot replace culture or microscopy for the monitoring of bacteriological status during treatment.

The evidence used to explore the added value of culture over sputum smear microscopy alone, and the optimal frequency of monitoring, was obtained from a subset of the IPD reported to WHO by South Africa for the 2018 update. The observational data from South Africa comprised 26 522 patients overall. Of these, 22 760 records were excluded from the dataset for the following reasons: 11 236 had a treatment outcome of death or LTFU; 698 had a successful treatment outcome but had received less than 17.5 months of treatment; 1357 had fewer than six culture samples recorded; 1632 had no baseline culture recorded; 2502 were baseline culture negative; 2920 were smear negative at baseline or had a missing smear at baseline; and 2415 had insufficient smear data to match the culture data. This left 3762 MDR/RR-TB patients (with 1.8% being children; i.e. aged <15 years) treated with longer MDR-TB regimens between 2010 and 2015, who had both monthly smear and culture data throughout treatment. About 60% of these patients were people living with HIV. The analysis focused on whether monthly culture versus monthly smear microscopy or culture every 2 months is needed to avoid missing treatment failure in MDR/RR-TB patients on treatment. The odds of treatment failure in patients who do not convert at 6 months or later were also discussed (see Implementation considerations and Table 2.24). The data could not address the outcome on acquisition (amplification) of additional drug resistance, nor could it directly assess whether the frequency of culture or smear microscopy had an identical effect on failure in patients on the 9–12-month shorter MDR-TB regimen, as envisaged in the original PICO question. Based on an assessment of the certainty of the evidence, carried out using predefined criteria and documented in GRADEpro, the test accuracy certainty of the evidence was rated as moderate.

The IPD meta-analysis compared the performance of the two methods in terms of sensitivity and specificity, and culture testing once a month compared with once every 2 months (to assess the minimum frequency of testing needed to not unnecessarily delay any revision of the treatment). The focus of the analysis was to compare how the two tests performed in terms of predicting treatment failure or relapse.

The main findings of the analysis were that monthly culture had a higher sensitivity than monthly smear microscopy (0.93 vs 0.51) but slightly lower specificity (0.97 vs 0.99). Likewise, the sensitivity of culture done every month was much higher than once every 2 months (0.93 vs 0.73) but had a slightly lower specificity (0.97 vs 0.98). Monthly culture increased the number of patients detected with a true positive bacteriological result by 13 per 1000 patients and reduced false negative results by 13 per 1000 patients when compared with sputum smear microscopy alone. In contrast, monthly culture was estimated to lead to 17 per 1000 fewer true negative results and 17 per 1000 more false positive results for treatment failure, implying that treatment may be prolonged in the case of false positivity or where true negativity is missed. This added inconvenience to the patient and programme is considered relatively small, given that taking sputum and many other biological specimens is usually a non-invasive and routine practice in many programmes. In a setting where testing is repeated at monthly intervals, a single false positive test result is unlikely to prove harmful to the patient because treatment decisions usually rely on at least two consecutive positive results (to denote prolonged positivity or reversion) and the effect of one spurious result would last only until the test repeated 1 month later is reported.

The crude odds of treatment failure increased steadily with each additional month without bacteriological conversion, from 3.6 at the end of the first month to 44.5 at the eighth month when using culture (Table 2.24). However, no discrete cut-off point (to serve as a reliable marker of a failing

regimen) could be discerned at which the odds of failure increased sharply when monitoring with either sputum smear microscopy or culture. The threshold for when to change treatment thus depends on the clinician's desire to minimize the risk of failure and, in particular, to limit the risk of prolonging a failing regimen.

Table 2.24. Crude odds ratios (95% CIs) of treatment failure in MDR/RR-TB patients without sputum conversion by the end of successive months of treatment compared with patients who converted, by testing method used; IPD meta-analysis (South Africa, n=3762)

Crude odds ratios according to	Month							
	1	2	3	4	5	6	7	8
Culture	**3.6**	**4.1**	**5.2**	**7.4**	**10.3**	**16.4**	**24.7**	**44.5**
	(2.11, 5.97)	(2.76, 6.09)	(3.55, 7.55)	(5.00, 10.80)	(6.88, 15.38)	(10.72, 25.00)	(15.53, 39.20)	(26.53, 74.46)
Smear microscopy	**1.9**	**2.7**	**3.2**	**4.2**	**6.8**	**10.4**	**16.5**	**28.9**
	(1.27, 2.73)	(1.82, 3.88)	(2.11, 4.73)	(2.69, 6.48)	(4.19, 10.97)	(6.00, 17.92)	(9.15, 29.77)	(14.87, 56.14)

CL: confidence limit; IPD: individual patient data; MDR/RR-TB: multidrug- or rifampicin-resistant tuberculosis; PICO: population, intervention, comparator and outcome; TB: tuberculosis.

There was moderate certainty in the estimates of test accuracy, and the GDG considered that, under normal conditions, culture would always be a more sensitive test of positive bacterial status than sputum smear microscopy. However, the overall quality of the evidence was judged to be low. The effects observed may vary in patients or populations with a profile markedly different from the one included in the analysis; for example, in low HIV prevalence settings, children, patients with extrapulmonary forms of disease or those treated with the shorter MDR-TB regimen. The 3762 patients included in the analysis had similar clinical characteristics to the 22 760 individuals excluded, although they were slightly less likely to be coinfected with HIV, have a history of previous treatment or have second-line drug resistance. Conversely, the rate of failure in those included in the analysis was only 3% compared with 12.7% of those excluded from the analysis.

Subgroup considerations

The recommendation would apply to any longer regimen, regardless of the number of Group A, B or C agents used and whether an injectable (intensive) phase was used or not. The GDG considered that the findings may apply to other key patient subgroups.

Patients aged below 15 years with MDR/RR-TB

Patients aged below 15 years with MDR/RR-TB comprised less than 2% of the IPD meta-analysis. Younger children usually cannot produce sufficient sputum spontaneously to allow a bacteriological diagnosis (many are typically sputum smear microscopy negative). In these patients, culture may be a more sensitive way to detect viable TB bacilli even if very few organisms are present in the sputum or other samples that are below the detection threshold of direct microscopy. In children who are unable to expectorate, gastric aspirates or induced sputa may be possible, but the repetition of such tests at monthly frequency may not be acceptable.

Extrapulmonary disease

Extrapulmonary disease is commonly paucibacillary; therefore, biological specimens may contain few or no bacilli. In such situations, detection of persistent disease is more likely with culture, although collection of samples often poses problems. Direct microscopy should still be attempted because it may determine positivity much faster than culture.

HIV-negative individuals

HIV-negative individuals with TB typically have higher bacterial counts in the sputum and a greater likelihood of detection with smear microscopy. In such a situation, it might be expected that the difference in test sensitivity between smear and culture would be less extreme, because fewer patients would have subthreshold bacterial counts. However, past studies on datasets from multiple sites in which HIV positivity was low reported findings that led to the WHO recommendation, even in 2011, for the use of both microscopy and culture, preferably every month.

Patients on the shorter MDR-TB regimen

Patients on the shorter MDR-TB regimen have a much shorter duration of intensive phase and total treatment. They receive seven drugs in the initial phase and, if fully compliant with the inclusion and exclusion criteria, usually have a more favourable prognostic outlook than other MDR-TB patients. Programmes may thus consider that patients on a shorter MDR-TB regimen may need less frequent or no culture to monitor treatment. Although the current analysis did not include patients treated with shorter regimens, the GDG proposes that programmes that implement this regimen should aim for more frequent culture testing, especially after the intensive phase, to confirm bacteriological cure in patients who complete treatment without signs of failure. Any sign of recurrence after termination of treatment should also be investigated using sputum smear microscopy, culture and DST.

Implementation considerations

Good-quality sputum specimens are necessary to ensure that laboratories can diagnose TB properly. In addition, laboratories should have sufficient space to ensure the quality, safety and efficiency of the services provided to clients whose samples are tested, and to ensure the safety of laboratory personnel, patients and visitors *(126)*. Some countries experience difficulties with the implementation and quality assurance of sputum culture, which affects this recommendation because it is dependent on access to quality-assured laboratories that can offer TB culture. Sputum smear and culture examinations are also dependent on the quality of the sputum produced, so care should be taken to obtain adequate specimens and transport them to the laboratory according to standard procedures, to maintain the viability of the bacilli and thus obtain a valid culture result.

In programmatic settings, the practitioner treating MDR-TB patients is typically guided not only by bacteriological tests but also by markers of response to treatment or of disease progression, such as the patient's general condition, weight gain over time, resolution of disease manifestations, blood indices and results of imaging (e.g. chest radiography). The potential use of Xpert MTB/RIF assay in monitoring treatment response has yet to be determined *(127, 128)*.

The implementation of more frequent microbiological testing would require appropriate resources to be made available, both for the laboratories undertaking the tests and for the patient, who may have to spend more time visiting the facilities and, in some cases, pay for the testing. Patient values and preferences need to be considered to ensure a more acceptable service and patient-centred delivery of care. Increased monitoring should not be done at the expense of overburdening the laboratory services or upsetting health equity by displacing resources from other essential components of the programme.

Monitoring and evaluation

Culture and microscopy results for tests performed in patients on MDR-TB treatment should be captured in the second-line TB treatment register as well as the respective laboratory registers *(129)*. Sometimes these registers may exist as part of an electronic laboratory or patient information system, which makes it much easier for multiple users to access the data in real time and can also help to limit errors. It is important for the programme manager to assess the records in the second-line TB treatment register for completeness of testing using both culture and sputum smear microscopy, or any discordance between the two modalities, and whether decisions on regimen changes or assignment of outcome are coherent (e.g. does a case have sufficient negative culture test results available to be classified as "cured"?). Performance indicators help to improve the quality of care; such indicators include contamination rates, turnaround times and proportion of culture tests done without results being recorded in the patient information system. In the case of repeated positive cultures, repeat testing for drug susceptibility or resistance is important.

B6. Starting antiretroviral therapy in patients on MDR/RR-TB regimens

Recommendation B6.1 Starting ART

No.	Recommendation
B6.1	Antiretroviral therapy is recommended for all patients with HIV and drug-resistant tuberculosis requiring second-line antituberculosis drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of antituberculosis treatment. *(Strong recommendation, very low certainty of evidence)*

Justification and evidence

The recommendation in this section addresses one PICO question:

> ***PICO question*** *(DR-TB, 2011): In patients with HIV infection and drug-resistant TB receiving antiretroviral therapy, is the use of drugs with overlapping and potentially additive toxicities, compared with their avoidance, more or less likely to lead to cure or other outcomes?*[59]

Evidence was reviewed from 10 studies *(130–139)*, to assess patient treatment outcomes when ART and second-line antituberculosis drugs were used together. None of the data were from RCTs. IPD were available for 217 patients with DR-TB, of whom 127 received ART. The level of evidence in individual observational studies varied from low to very low quality.

[59] The outcomes considered for this question comprised: 1. Cure (treatment failure), 2. Prompt initiation of appropriate treatment, 3. Avoiding the acquisition or amplification of drug resistance, 4. Survival (death from TB), 5. Staying disease-free after treatment; sustaining a cure (relapse), 6. Case-holding so the TB patient remains adherent to treatment (default or treatment interruption due to non-adherence), 7. Population coverage or access to appropriate treatment of DR-TB, 8. Smear or culture conversion during treatment, 9. Accelerated detection of drug resistance, 10. Avoidance of unnecessary MDR-TB treatment, 11. Population coverage or access to diagnosis of DR-TB, 12. Prevention or interruption of transmission of DR-TB to other people, including other patients and health care workers, 13. Shortest possible duration of treatment, 14. Avoiding toxicity and adverse reactions from antituberculosis drugs, 15. Cost to the patient, including direct medical costs and other costs such as transportation and lost wages due to disability, 16. Resolution of TB signs and symptoms; ability to resume usual life activities, 17. Interaction of antituberculosis drugs with non-TB medications, and 18. Cost to the TB control programme.

Summary of findings

The pooled IPD from longitudinal cohort studies showed a lower risk of death and a higher likelihood of cure, and resolution of TB signs and symptoms in patients using ART, compared with those not using ART (low certainty evidence). There is very low certainty evidence for other outcomes that were considered critical or important for decision-making (e.g. severe adverse effects from second-line drugs for DR-TB, occurrence of sputum smear or culture conversion, interactions of ART with antituberculosis drugs and default from treatment). Available data did not allow assessment for several other outcomes of interest; namely, avoiding the acquisition of additional drug resistance, preventing TB transmission, sustaining relapse-free cure, establishing the optimal duration of MDR-TB treatment, avoiding unnecessary MDR-TB treatment, reducing costs and improving population access to appropriate care.

Benefits

The strong recommendation for the use of ART is based in part on indirect evidence from its use in any patient with active TB, which shows large beneficial effects and a very high mortality when ART is not employed *(140)* particularly in highly immunocompromised patients (CD4 cell count <50 cells/mm^3) *(141, 142)*. In the absence of other data specific to patients with DR-TB receiving second-line antituberculosis medication, the decision on when to start ART should be no different from the approach to a patient living with HIV with drug-susceptible TB. ART should thus be initiated regardless of CD4 cell count and as soon as antituberculosis treatment is tolerated, ideally as early as 2 weeks and no later than 8 weeks after initiation of antituberculosis treatment *(140, 143)*. However, for TB patients living with HIV with profound immunosuppression (e.g. CD4 counts <50 cells/mm^3), they should receive ART within the first 2 weeks of initiating TB treatment *(117)*.

Risks

The successful implementation of this recommendation will depend on the availability of more providers trained specifically in the care of HIV and DR-TB, and drug–drug interactions. A substantial increase in the availability of and patient's access to treatment, and additional support for ensuring adherence would probably be needed. The need for increased integration of HIV and TB care for effective patient management, prompt evaluation of AEs and case-holding throughout treatment will necessitate more resources. Updated information on drug–drug interactions between antiretroviral and antituberculosis medicines is now available online *(53)*.

Values and preferences

A high value was placed on outcomes such as prevention of early death and TB transmission, and a lower value was placed on the resources required to make ART available to all MDR-TB patients infected with HIV.

B7. Surgery for patients on MDR/RR-TB treatment

Recommendation B7.1 Surgery for MDR/RR-TB patients

No.	Recommendation
B7.1	In patients with rifampicin-resistant tuberculosis (RR-TB) or multidrug-resistant TB (MDR-TB), elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen. *(Conditional recommendation, very low certainty of evidence)*

Justification and evidence

The recommendation in this section addresses one PICO question:

> ***PICO question*** *(DR-TB, 2016): Among patients on MDR-TB treatment, are the following two interventions (delay in start of treatment and elective surgery) likely to lead to cure and other outcomes?*[60]

Surgery has been employed in treating TB patients since before the advent of chemotherapy. In many countries, it remains one of the treatment options for TB. With the challenging prospect in many settings of inadequate regimens to treat DR-TB, and the risk of serious sequelae, the role of pulmonary surgery is being re-evaluated as a way to reduce the amount of lung tissue with intractable pathology and reduce bacterial load, and thus improve prognosis. The review for this question was based on both an IPD meta-analysis to evaluate the effectiveness of different forms of elective surgery as an adjunct to combination medical therapy for MDR-TB *(144)*, and a systematic review and study-level meta-analysis *(145)*. Demographic, clinical, bacteriological, surgical and outcome data of MDR-TB patients on treatment were obtained from the authors of 26 cohort studies that supplied data for the adult IPD (aIPD) *(81)*. The analyses summarized in the GRADE tables consist of three strata comparing treatment success (e.g. cure and completion) with different combinations of treatment failure, relapse, death and LTFU. Two sets of such tables were prepared, one for partial pulmonary resection and one for pneumonectomy. Based on an assessment of the certainty of the evidence, carried out using predefined criteria and documented in GRADEpro, the certainty of the evidence was rated as very low to low, depending on the outcome being assessed and type of study.

In the study-level meta-analysis that examined all forms of surgery together, there was a statistically significant improvement in cure and successful treatment outcomes among patients who received surgery. However, when the aIPD meta-analysis examined patients who underwent partial lung resection and those who had a more radical pneumonectomy compared with patients who did not undergo surgery, those who underwent partial lung resection had statistically significantly higher rates of treatment success. Patients who underwent pneumonectomy did not have better outcomes than those who did not undergo surgery. Prognosis appeared to be better when partial lung resection was performed after culture conversion. This effect was not observed in patients who underwent pneumonectomy. There are several important caveats to these data. Substantial bias is likely to be present, because only patients judged to be fit for surgery would have been operated on. No patient with HIV coinfection in the aIPD underwent lung resection surgery. Therefore, the effects of surgery among people living with HIV with MDR-TB could not be evaluated. Rates of death did not differ significantly between those who underwent surgery and those who received medical treatment only. However, the outcomes could be biased because the risk of death could have been much higher among patients in whom surgery was prescribed had they not been operated on.

Subgroup considerations

The relative benefits of surgery are expected to depend substantially on the population subgroups that are targeted. The analysis could not provide a refined differentiation of the type of patient who would be best suited to benefit from the intervention or the type of intervention that would have the most benefit. The effect is expected to be moderate in the average patient considered appropriate for surgery. The odds of success for patients with XDR-TB (pre-2021 definition) were statistically significantly lower when they underwent surgery compared with other patients (aOR: 0.4, 95% CL: 0.2–0.9). This effect is likely to be biased, given that patients who underwent surgery would have had other factors predisposing to poor outcomes that could not be adjusted for.

[60] The outcomes comprise 1. Cured/completed by end of treatment, 2. Culture conversion by 6 months, 3. Failure, 4. Relapse, 5. Survival (or death), 6. Adverse reactions (severity, type, organ class), and 7. Adherence to treatment (or treatment interruption due to non-adherence).

Implementation considerations

Partial lung resection for patients with MDR-TB is to be considered only under conditions of good surgical facilities and trained and experienced surgeons, and with careful selection of candidates.

B8. Hepatitis C virus (HCV) and MDR/RR-TB treatment co-administration

Recommendation B8.1 HCV and MDR/RR-TB treatment

No.	Recommendation
B8.1	In patients with MDR/RR-TB and HCV coinfection, WHO suggests the co-administration of HCV and TB treatment over delaying HCV treatment until after treatment of MDR/RR-TB is completed. *(Conditional recommendation, very low certainty of evidence)*

Remarks

1. This recommendation applies to people with confirmed MDR/RR-TB and HCV.
2. Treatment initiation should take into account potential DDI and other comorbidities.

Rationale

The rationale for this recommendation is based on the expert evidence and considerations detailed in the next subsections.

Globally, an estimated 400 000 people (95% UI: 360 000–440 000) developed MDR/RR-TB in 2023. There have been steady improvements in the treatment success rate for people diagnosed with MDR/RR-TB, but the rate remains alarmingly low. Globally in 2021, the treatment success rate was 68%, up from 60% in 2019 and 50% in 2012. MDR/RR-TB treatment poses many challenges, which are further exacerbated for those with pre-existing liver disease due to the potential hepatotoxicity of some anti-TB medicines, which may increase the risk of drug-induced liver injury *(5)*.

There is a substantial overlap in the epidemiology of chronic hepatitis C and TB owing to common risk factors (e.g. injection drug use, homelessness or incarceration). Chronic viral hepatitis C or B may negatively impact TB treatment by increasing the risk of hepatotoxicity related to TB drugs, and thus affecting drug choices; in turn, this may reduce the rate of TB treatment success. The global HCV antibody seroprevalence in TB patients has been estimated to be 10.4%, surpassing the general population's average of 1.4%. Moreover, studies among TB patients who inject illicit drugs show an HCV prevalence of 92.5% (95% CI: 80.8–99.0) *(146)*.

Curative short-course (12–24 weeks) oral direct-acting antivirals (DAAs) have transformed the landscape of HCV treatment, with high rates of cure – more than 90% of patients attain a sustained virologic response (SVR), indicating virus clearance – alongside an excellent safety profile and high tolerability. Known DDIs with rifamycins preclude co-administration of DAAs in the context of drug-susceptible TB (few or no interactions are anticipated to occur with drugs for MDR/RR-TB treatment) *(147)*. However, relatively little is known about how to manage chronic HCV infection among MDR-TB patients, and national policies and practices vary, highlighting the need for global guidance. There is limited clinical research evidence on the safety and efficacy of TB treatment in patients with signs of liver toxicity; most pivotal trials exclude participants with liver enzymes more than three times the upper limit of normal values. Despite the limited direct evidence, concomitant therapy for HCV and

MDR/RR-TB seems feasible and potentially beneficial for patients with coinfection. To address this need, WHO commissioned a systematic review of the literature on the co-administration of treatment for DR-TB and hepatitis C. The results of this systematic review highlighted that published evidence on this subject is minimal *(148)*.

Expert evidence has been defined as the observations or experience obtained from a person who is knowledgeable about or skilful in a particular area *(149)*. This approach can be considered under certain circumstances if there is little or no published direct evidence. To address this knowledge gap, "expert evidence" can be considered in the same way as case reports or case series are used within the GRADE framework, as if systematic and transparent methods are used for its collection, and the description of the evidence minimizes interpretation of the extent to which it supports a conclusion.

Despite the lack of general data and potential DDI, concomitant treatment for HCV and MDR/RR-TB seems feasible, halting the viral replication. This reasoning suggests that the overall benefits will probably outweigh the potential harms.

Summary of evidence

This section provides the PICO questions, data and studies considered to answer the questions; the methods used for analysis and data synthesis; a summary of evidence on desirable and undesirable effects and certainty of evidence; and a summary of other evidence considered during the recommendation's development.

PICO question

The recommendation in this section results from assessments of the PICO question listed below.

> ***PICO question*** *(DR-TB, 2022): Should HCV treatment be co-administered with MDR-TB treatment in patients coinfected by MDR/RR-TB and HCV?*

Data and studies considered

In 2022, a systematic review identified a total of 106 studies reporting on the prevalence of HCV among TB patients. The review reported that the global pooled prevalence of HCVAb positivity across studies was 10.4% (95% CI: 8.5–12.5). Pooled prevalence of HCVAb positivity by WHO region was highest in the European Region at 17.5% (95% CI: 12.2–23.5), followed by the South-East Asia Region at 7.9% (95% CI: 3.5–13.9), the Region of the Americas at 7.5% (95% CI: 5.2–10.1), the Western Pacific Region at 6.2% (95% CI: 3.6–9.5), the Eastern Mediterranean Region at 5.7% (95% CI: 3.1–8.9) and the African Region at 3.5% (95% CI: 0–16.1) *(149, 150)*.

As a follow-up to this review, an online survey was designed to gather expert evidence on treatment strategies for patients coinfected with HCV and MDR/RR-TB.

The above-mentioned PICO question was originally put forward, and a systematic review was conducted to gather relevant data from published research studies. This systematic review identified only one small study fulfilling the eligibility criteria. Two additional small studies described concomitant treatment and suggested that co-administration of treatment may be well tolerated and associated with SVR for HCV infection. None of the studies compared the outcomes of patients receiving co-administered treatment with those of patients receiving MDR/RR-TB treatment alone. Given the current state of evidence, no conclusion could be drawn with regards to co-administration of MDR/RR-TB and HCV treatment and MDR/RR-TB outcomes based on available research studies.

Collection of expert evidence was identified as a solution for addressing a guideline question where published research evidence is lacking for completion of a GRADE EtD framework. It follows previously developed concepts and established steps used with GDGs *(149, 150)*. After identifying an external group of experts to survey for the collection of data about co-administration of treatment for patients

with MDR-TB and HCV coinfection, WHO contacted its regional offices to identify experts with relevant experience in this area. In addition to providing patient outcome data to inform the PICO question, experts were asked for input on other criteria for decision-making including costs, feasibility, and acceptability of co-administration of MDR-TB and HCV treatments. The expert evidence was collected using an online survey, and a quality check of data submitted was completed (e.g. checking that the sum of health outcomes added up correctly across patients), with contact and email follow-up of individual respondents if any clarifications were required.

Methods used for analysis and data synthesis

Data collected from respondents who treated at least one patient with MDR/RR-TB and HCV treatment co-administration (i.e. the intervention arm) and at least one patient with MDR/RR-TB treatment with delay of HCV treatment (i.e. the comparator arm) were included in a comparative analysis. The analysis calculated the risk ratio (RR) to assess treatment effects for the outcomes of interest (i.e. TB treatment success, TB treatment failure, death, LTFU, AEs, hepatic AEs and HCV treatment success).

Forest plots were constructed to calculate pooled effect estimates, with 95% CIs, using random-effects meta-analysis. RRs were pooled using the Mantel-Haenszel method, which is robust in the case of sparse data *(151)*. The estimate of heterogeneity was calculated using the restricted maximum-likelihood method *(152)* and the standard error of the pooled effect estimate was derived from the Hartung-Knapp-Sidik-Jonkman method *(153)*. Simulations have shown that these methods are less biased than the alternatives, and more robust to changes in the heterogeneity variance estimate *(154)*. In instances of zero events in one arm, an adaptive continuity correction inversely proportional to the relative group size was applied, improving upon a constant correction. The method considers sparse data and imbalanced groups *(155)*. Between-study heterogeneity was assessed using Cochran's Q test *(156)*, with a 0.10 significance threshold and the I-squared metric *(157)* (>50% indicating significant heterogeneity). For descriptive analysis, the pooled proportions of the seven outcomes of interest were calculated in the groups of patients receiving MDR-TB and HCV treatment co-administration and, separately, in the groups receiving MDR-TB treatment with delay of HCV treatment. The single-arm proportions were pooled by fitting binomial generalized linear mixed models with a logit link. Although the analysis of comparative data was used for decision-making, the pooled proportions (which included additional data, albeit from a mix of comparative and non-comparative cohorts) were also considered, to support the GDG's discussions (e.g. when considering the direction of effects).

Summary of evidence on desirable and undesirable effects and certainty of evidence

Sixteen respondents (expert clinicians) from nine countries provided patient outcome data in the expert evidence survey, with outcomes reported for a total of 135 patients who received co-administration of treatment for MDR-TB and HCV, and 439 patients who received treatment for MDR-TB only, with delay of HCV treatment. Among these responses, eight respondents contributed data from both cohorts (i.e. intervention and comparator) for the comparative analysis, and the other eight contributed data only for the intervention or comparator cohorts for the descriptive analysis. The overall certainty of the evidence was very low, with the calculated estimates of effects based on outcome data from recall or records obtained from the expert evidence survey; hence, there was a very serious risk of bias due to potential confounding, selection bias, and recall (i.e. outcome assessment) bias, as well as imprecision in the effect estimates for most outcomes.

Desirable effects

Co-administration of MDR-TB and HCV treatments as compared to MDR-TB treatment only with delay of HCV treatment may result in an increase in MDR-TB treatment success, but the evidence is very uncertain (RR: 1.25; 95% CI: 1.07 to 1.46; very low certainty in the evidence of effects); this corresponds to 163 more MDR-TB treatment successes per 1000 patients (95% CI: 46 more to 300 more). Use of MDR-TB and HCV treatment co-administration may also result in fewer cases of

MDR-TB treatment failure, but again the evidence is very uncertain (RR: 0.30; 95% CI: 0.12 to 0.74; very low certainty in the evidence of effects); this corresponds to 27 fewer failed MDR-TB treatments per 1000 patients (95% CI: 34 fewer to 10 fewer). Co-administration of treatments may also result in fewer losses to follow-up, but the evidence is very uncertain (RR: 0.42; 95% CI: 0.24 to 0.73; very low certainty in the evidence of effects); this corresponds to 103 fewer losses to follow-up per 1000 patients (95% CI: 135 fewer to 48 fewer).

Use of MDR-TB and HCV treatment co-administration may also result in a small decrease in deaths, although the evidence is again very uncertain (RR: 0.98; 95% CI: 0.22 to 4.33; very low certainty in the evidence of effects); this corresponds to two fewer deaths per 1000 patients (95% CI: 92 fewer to 391 more). For HCV treatment success, very few events were reported based on only seven patients in one of the comparative cohorts, and no conclusions could be drawn regarding this health outcome. The GDG noted the knowledge gap about HCV treatment outcomes due to insufficient data. In nine cohorts with a total of 124 patients receiving co-administration of MDR-TB and HCV treatments, the pooled estimate for HCV treatment success was 95.1% (95% CI: 84.3% to 98.6%). With respect to additional considerations, the GDG also noted the potential benefit of additional adherence support for HCV treatment while also receiving MDR-TB treatment. The GRADE evidence profile provides a complete description of the estimates of effects, as well as the descriptive analysis of pooled proportions of events from all cohorts for each of the health outcomes.

Undesirable effects

With respect to the potential harms of co-administration of MDR-TB and HCV treatments, experts were asked to report on AEs and, as a subset of these events, hepatic AEs. Co-administration of treatments may result in a decrease in overall AEs, but the evidence is very uncertain (RR: 0.72; 95% CI: 0.49 to 1.07; very low certainty in the evidence of effects); this corresponds to 223 fewer AEs per 1000 patients (95% CI: 405 fewer to 56 more). Among these AEs there may be an increase in hepatic AEs with co-administration of MDR-TB and HCV treatments, but the evidence is very uncertain (RR: 1.19; 95% CI: 0.23 to 6.16; very low certainty in the evidence of effects); this corresponds to 59 more hepatic AEs per 1000 patients (95% CI: 240 fewer to 1000 more).

Evidence to recommendations: considerations

The GDG judged that the balance of effects probably favours co-administration of MDR-TB and HCV treatments for MDR/RR-TB patients coinfected with HCV, despite the very low certainty in the evidence for the critical outcomes, considering risk of bias in the available expert evidence as well as imprecision in the calculated effect estimates. The GDG was of the view that there is probably no important variability or uncertainty in how MDR/RR-TB patients coinfected with HCV would value the outcomes related to MDR-TB and HCV treatments, and judged that the option of co-administration of treatments would be acceptable and feasible. The GDG also noted that the option of co-administration of treatments would have presumed cost–effectiveness when both treatments were initiated together, without delay of HCV treatment. Given these considerations, the GDG issued the conditional recommendation suggesting co-administration of both MDR-TB and HCV treatments, in preference to delaying HCV treatment until after treatment of MDR/RR-TB is completed.

Costs and cost–effectiveness

A cost–effectiveness analysis was not performed for this review, but the experts' survey responses revealed varying perspectives on the cost implications of co-administering MDR-TB and HCV treatments. A notable 39% (*n*=7) of respondents indicated additional costs incurred, 11% (*n*=2) noted no cost implications and 28% (*n*=5) were uncertain about specific cost factors. However, the GDG considered that co-administration of MDR-TB and HCV treatments may have favourable cost–effectiveness, in particular considering that this option may result in fewer losses to follow-up. Even though MDR-TB treatment is typically free of charge to patients, whereas HCV treatment may lack

coverage, the overall cost remains constant whether HCV treatment is co-administered or provided with a delay. In settings where HCV treatment is not covered by national health insurance, considering generic drugs is suggested as a way to alleviate the financial burden on patients.

Subgroup considerations

Despite acknowledging the data limitations and very low certainty of the evidence, the GDG believed that extrapolating to broader patient groups, including children, is warranted, especially regarding the potential benefits of co-administration of both treatments. However, the absence of data for specific subgroups (e.g. pregnant women, people living with HIV, younger children and patients with liver cirrhosis) necessitates caution in extrapolating the findings to all patients. The GDG discussed whether the specific findings could be applied to people living with HIV, with reservations stemming from the absence of specific data on subgroups such as older individuals and people with comorbidities, and other factors that could not be obtained through the expert evidence survey. The GDG underscored the lack of comprehensive data for these subgroups and emphasized the necessity of cautiously approaching such extrapolations.

Implementation considerations

The GDG noted that clinicians should initiate co-administration of MDR-TB and HCV treatments in line with knowledge and consideration about DDIs and patients' comorbidities. The group highlighted that, when implementing the recommendation, the type of evidence and very low certainty on which the recommendation is based should be made transparent and clearly communicated to patients during the decision-making process. Finally, when considering the implementation of the recommendation, it was highlighted that the unavailability of HCV treatment should not delay MDR/RR-TB treatment.

Drug–drug interaction

Although data on DDIs between newer HCV treatments (DAAs) and MDR-TB medications are limited, current evidence suggests minimal interactions. However, caution is still advised.

Bedaquiline, a key component of most MDR-TB regimens, may increase the risk of liver toxicity, particularly when co-administered with some HCV treatments. Additionally, some MDR-TB drugs (e.g. ethionamide/prothionamide and clofazimine) might interact with specific DAAs (daclatasvir) by affecting how the body processes them, although this has not been proven *(158)*.

Owing to these potential interactions, consulting with a specialist is essential. The specialist can assess individual patient factors and recommend the optimal treatment plan that minimizes DDIs and maximizes treatment success for both HCV and MDR-TB *(147)*.

Patient-centred approach

Efforts are required to provide patient support to enable full adherence to treatment. Supporting patient adherence may be important to retain patients on treatment even when a regimen is relatively short. WHO recommendations on care and support and a related handbook are available through the previously published *WHO consolidated guidelines on tuberculosis. Module 4: Treatment – tuberculosis care and support (159)* and in the chapter 3 of this consolidated document.

Patients undergoing treatment for both HCV and MDR/RR-TB require close monitoring throughout the treatment course. The GDG emphasized the importance of regular clinical assessments and laboratory testing. The specific schedule of testing will be determined by the health care provider, but may include:

- **HCV monitoring** – this typically involves HCV RNA testing to track viral load and measure treatment response. An SVR at 12 weeks after the end of treatment indicates a cure. Other tests, including

liver function, are also critical to monitor for potential liver damage and have to be observed during the course of treatment *(160)*.

- **MDR-TB monitoring** – the treatment response should be monitored by using monthly sputum and smear microscopy and culture (ideally at the same frequency). The schedule should be similar to that for bacteriological monitoring recommended for shorter all-oral MDR-TB regimens *(8)*.

Based on guidance in current literature and clinical experience, the panel advised the following with regard to monitoring and evaluation of the safety and effectiveness of the co-administration of HCV and MDR-TB treatment regimens:

- implementation of both regimens requires access to both treatments; however, the unavailability of HCV treatment should not delay the initiation of MDR treatment;
- programmes need to have access to reliable DST for MDR-TB medicines, bacteriological tests (sputum smear microscopy and culture), and monitoring of the virological response for HCV; and
- although the data assessed did not unearth any major signals of risk, active TB drug-safety monitoring and management systems must be functional to conduct rigorous active monitoring of AEs and promptly detect, manage and report suspected or confirmed drug toxicities.

Research gaps

In addition to summarizing the available evidence, the reviews undertaken for these consolidated guidelines revealed several gaps in current knowledge about critical areas in DR-TB treatment and care. The estimates of effect for patient studies were commonly assigned a low or very low certainty rating, which explains why most of the recommendations in these guidelines are conditional. Some gaps identified in previous TB treatment guidelines persist *(2, 16)*. When completing the GRADE EtD tables, studies were lacking on 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 AEs). Areas that would be relevant to many priority questions in the programmatic management of DR-TB include implementation research; studies of resource use; incremental cost, acceptability, feasibility and equity; values and preferences of patients and health care workers; and the inclusion of indicators of quality of life.

The research gaps that were identified by successive GDGs are grouped by the respective sections of these guidelines, although some are interlinked.

The 6-month BPaL/M/C regimen for treatment of MDR/RR-TB or pre-XDR-TB

Further research is needed in the following areas:

- the efficacy, safety and tolerability of the BPaL/M regimen for subpopulations for whom current data are limited or missing; that is, children aged below 14 years, patients with extrapulmonary TB, people living with HIV with CD4 counts below 100, and pregnant and breastfeeding women;
- data from other regions and countries (beyond countries with sites included in recent studies);
- description of the mechanism and molecular markers of pretomanid resistance, allowing development of the DST, clinical implications of the lineage 1 effect on efficacy of pretomanid,[61] cross-resistance with delamanid and surveillance for the development of resistance, with adequate consideration paid to the impact of selected mutations;
- documenting the full AE profile of pretomanid and the frequency of relevant AEs, with a focus on hepatotoxicity and reproductive toxicity in humans;
- evidence on the safety and dosing of pretomanid (Pa) in those younger than 14 years;
- exploring the relative efficacy (and added value in multidrug regimens) of pretomanid and delamanid;
- studies capturing outcomes for which currently evidence is scarce (e.g. acquisition of drug resistance and quality of life);
- larger trials and programmatic data for BPaL and BPaLC regimens to further refine recommendations;
- research on geographical differences in the frequency and severity of linezolid-related AEs and the underlying cause (north–south differences were observed in post-hoc analyses of large and unexplained differences in linezolid-related AEs between sites);
- exploring the possibility of replacing moxifloxacin with levofloxacin;
- exploring the extent of cross-resistance between bedaquiline and clofazimine;
- monitoring of resistance to new and repurposed medicines;

[61] A lineage effect is observed for lineage 1 strains that are shown to exhibit higher MICs than other lineages in vitro. The in vivo clinical significance of such an effect is unknown *(161)*.

- exploring methods to ensure treatment adherence;
- exploring regimen composition when the new generation of component medicines are available; and
- exploring the efficacy of other 6-month regimens.

The 6-month bedaquiline, delamanid, linezolid, levofloxacin and clofazimine (BDLLfx/C) regimen

Further research is needed in the following areas:

- research on choice of quinolones for 6-month regimens and treatment outcomes (e.g. moxifloxacin/levofloxacin); and
- cost–effectiveness studies.

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

Further research is needed in the following areas:

- 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 or less;
- comparison of the effectiveness of these variants of the shorter regimen in:
  - patient subgroups that have often been systematically excluded from studies or country programme cohorts (e.g. children, patients with additional resistance, those with extrapulmonary TB, and pregnant or breastfeeding women);
  - settings where background resistance to drugs other than FQ and second-line injectable agents is high (e.g. PZA or high-level isoniazid resistance);
- additional RCTs and odds ratios on all-oral shorter MDR-TB treatment regimens, also allowing comparison of all-oral shorter regimens with all-oral longer regimens;
- programmatic data from countries other than South Africa;
- data from children, pregnant women, older people, patients with diabetes and other special populations;
- data on patients presenting with extensive TB disease;
- information on the frequency and mechanisms of bedaquiline resistance acquisition, and the genetic markers that indicate probable resistance; and
- identification of optimal companion drugs that protect bedaquiline and limit the acquisition of bedaquiline resistance, including consideration of the need to protect the long "tail" of potential single drug exposure (given its exceptionally long half-life) if bedaquiline is stopped at the same time as companion drugs.

The modified 9-month all-oral regimens for MDR/RR-TB

Further research is needed in the following areas:

- the role of PZA resistance and the requirement for its use in the regimens;
- information on bedaquiline resistance in countries through surveillance research;
- the effect of the regimens in other patient groups, e.g. in children or those with diabetes;
- research on the acceptability of the regimens; and
- for the 9BDLLFxZ regimen, research about patient support and adherence to delamanid.

Longer regimens for MDR/RR-TB

Further research is needed in the following areas:

- the optimal combination of medicines and the approach to regimen design for adults and children with MDR/RR-TB, with or without additional resistance to key agents;
- RCTs, which are lacking, especially those involving new drugs and regimens – the release of results from the first Phase 3 trials for MDR-TB has led to debate about the clinical relevance of the design and endpoints chosen for these studies, requiring at times additional, off-protocol analysis of data to explore the potential added value of the experimental interventions;
- inclusion and separate reporting of outcomes for key subgroups in RCTs, especially children, pregnant and breastfeeding women and people living with HIV on treatment;
- studies of pharmacokinetics and safety to determine optimal drug dosing (especially in pregnancy), and the effect of extemporaneous manipulation of existing dosing forms;
- complete recording of AEs and standardized data on organ class, seriousness, severity and certainty of association, to allow meaningful comparison of the association between AEs and exposure to different medicines between studies, patient subgroups and different regimens;
- determination of the minimum number of drugs and treatment duration (especially in patients previously treated for MDR-TB);
- improved diagnostics and DST methods (e.g. which test to use for resistance to PZA) especially for medicines for which no rapid molecular methods are currently available in the field;
- 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 on this *(162)*;
  - *bedaquiline:* 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 patient predictors for adverse reactions;
  - *clofazimine:* optimization of the dose (especially in children), any added value in using a loading dose and availability of DST methods;
  - *cycloserine and terizidone:* differences in efficacy between the two medicines, approaches to test for susceptibility to them, 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 in both adults and children;
  - *PZA:* molecular testing for resistance (pursuing either LPA or other approaches);
  - *carbapenems:* given their effectiveness in the evidence reviews, further research on their role in MDR-TB regimens is important, including the potential role and cost–effectiveness of ertapenem (which can be given intramuscularly) as a substitute for meropenem and imipenem–cilastatin;
  - *amikacin:* the safety and effectiveness of thrice-weekly administration at a higher dose (about 25 mg/kg per day) *(101)*;
- identification of factors that determine the optimal duration of treatment (e.g. previous treatment history, baseline resistance patterns, site of disease and age); and
- exploration of strategies to optimize the balance of benefits versus harms of regimen duration through risk-stratification approaches.

Regimens for rifampicin-susceptible, isoniazid-resistant TB (Hr-TB)

The development of the current recommendations was made possible by the availability of a global Hr-TB 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 *(83)*. 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 the recommendations were conditional and were based on very low certainty of evidence; thus, further research is needed to inform the refinement of policies to optimize the treatment of Hr-TB. The GDG identified various research priorities, including the following:

- the need for RCTs evaluating the efficacy, safety and tolerability of regimens for Hr-TB, and for cases with additional resistance to other medicines such as ethambutol or PZA (e.g. polydrug resistance);
- research to clarify the potential benefits and risks of treatment with high-dose isoniazid;
- high-quality studies on optimizing the composition and duration of regimens in children and adults, particularly of high-dose isoniazid, FQ and other second-line medicines, and of reducing the duration of PZA;
- modelling studies to estimate the number-needed-to-treat for empirical use of an Hr-TB regimen, balancing risks and benefits;
- high-quality studies on treatment prolongation among people living with HIV;
- high-quality studies evaluating regimens for extrapulmonary or disseminated TB;
- feasibility of developing FDCs for REZ alone (with or without integrating levofloxacin);
- monitoring patient response by isoniazid resistance genotype (e.g. *katG* vs *inhA* mutations), either in an individual patient or in a population;
- cost–effectiveness of different approaches to DST, including rapid testing of all TB patients for both isoniazid and rifampicin resistance before the start of treatment;
- participatory action research within communities and with other stakeholders (e.g. field practitioners and community workers) to explore sociocultural factors that can facilitate treatment adherence and influence outcomes; and
- effect of underlying FQ and isoniazid polydrug resistance on treatment outcomes.

Monitoring and management strategies for MDR/RR-TB treatment

Further research is needed in the following areas:

- analysis of the predictors and biomarkers of treatment failure (related to strain, regimen and host), and of the bacteriological response, in the following important subgroups, which would help to identify more resource-saving options and reduce the time needed to make decisions:
  - patients aged below 15 years;
  - patients with extrapulmonary disease (different forms);
  - patients on shorter MDR-TB regimens (standardized or all-oral variants);
- continuing to assess the potential role of future-generation rapid molecular testing beyond diagnostic testing, to also monitor the treatment response; and
- evaluation of the engineering challenges to implementing more affordable liquid culture systems.

Starting antiretroviral therapy in patients on MDR/RR-TB regimens

No research gaps were identified.

Surgery for patients on MDR/RR-TB treatment

Further research is needed in the following areas:

- the role of surgery – that is, decisions about when to operate and the type of surgical intervention to use, and drug-resistance patterns; and

- improved collection, reporting and standardization of data on surgery, including long-term survival post-surgery.

HCV and MDR/RR-TB treatment co-administration

The co-administration of treatments for HCV and MDR-TB presents a complex challenge. Prioritizing research is essential to address critical knowledge gaps and enhance treatment outcomes. The GDG outlined several research priorities:

- conducting high-quality observational studies to evaluate the efficacy and safety of combined HCV and MDR-TB treatments, with a focus on patient adherence and final treatment outcomes;
- establishing a global and more comprehensive dataset to assess the effectiveness of modern HCV treatment regimens in young children;
- developing tailored approaches for co-administering HCV and MDR-TB treatments for high-risk populations, including injecting drug users, children, pregnant women and people living with HIV;
- collecting comprehensive DDI data to better understand the potential interactions between HCV medicines and bedaquiline, a crucial component of the MDR/RR-TB treatment regimen; and
- defining the optimal treatment approach that permits the concurrent administration of MDR-TB and HCV treatments, refining combinations, dosages and treatment duration to ensure both effectiveness and safety.

Cross-cutting research priorities

Cross-cutting research priorities are as follows:

- dose reduction strategies of linezolid within 6-month regimens and treatment outcomes;
- early and practical markers of linezolid toxicity;
- research to refine definitions of disease severity and the risk assessment model (RAM) to define severe and non-severe patients;
- programmatic and real-world data, including outcomes in key subpopulations such as individuals with malnutrition;
- predictors of disease recurrence;
- patient cost studies capturing both direct and indirect costs to better understand the financial burden of treatment, alongside the evaluation of equitable access to newer TB regimens across different populations; key feasibility concerns include barriers related to procurement and supply chains, implementation, and regulatory approvals
- bedaquiline concentrations in breast milk and its effects on neonates;
- component drug interactions with a view on drugs used for other frequent comorbidities;
- values people place on outcomes;
- quality of life outcomes in TB treatment trials;
- operational research including strategies on testing;
- the efficacy of the regimens in patients with disseminated forms of TB;
- clinically significant effects of QT-prolonging drugs in elderly patients; and
- cost–effectiveness research, including comparisons of cost per QALY.

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Chapter 3
Tuberculosis care and support

Introduction

The World Health Organization (WHO) aims to use the best available evidence on interventions to ensure adequate patient care and support for those with tuberculosis (TB), and to inform policy decisions made by managers of national TB programmes (NTPs), national policy-makers and medical practitioners in a variety of geographical, economic and social settings.

This chapter of the *WHO consolidated guidelines on tuberculosis. Module 4: treatment and care* summarizes existing WHO recommendations on care and support during TB treatment.

The recommendations included in this chapter were developed by four Guidelines Development Groups (GDGs) convened by the WHO in 2011, 2016, 2021 and 2025 *(1–3)* to review the evidence available on key aspects of TB care and support. The GDGs were composed of multidisciplinary groups of TB experts external to WHO (see Annex 2).

The recommendations were formulated by the GDGs using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, then reviewed by external review groups composed of experts and end-users from all WHO regions.

Structure of the chapter

The chapter has four main sections on elements of TB care and support. The elements covered are:

1. Care and support interventions for all people with TB.
2. Models of care for people with drug-resistant TB (DR-TB).
3. Models of care for children and adolescents exposed to TB or with TB disease.
4. Palliative care interventions for multidrug- or rifampicin-resistant TB (MDR/RR-TB) patients.

Each section starts with the current WHO recommendations for that element. It then gives information on the evidence used to inform the recommendations; summarizes the analyses that were carried out on the basis of the evidence; and describes considerations for specific subgroups, for monitoring and evaluation and for implementation. Research gaps that were identified for each of the sections are presented at the end of the document; annexes provide more details on the methods, GDGs, reports of systematic reviews and data analyses, evidence profiles, unpublished data and statistical analysis plans. Each section reflects discussions held at GDG meetings. Additional information on implementation of patient care interventions is presented in the relevant chapter of the *WHO consolidated operational handbook on tuberculosis. Module 4: treatment and care (4)* – a separate document that is designed to aid implementation efforts.

Summary of WHO recommendations on TB care and support

The recommendations for TB care and support presented in this document are derived from earlier WHO guideline documents and a recent WHO GDG meeting held in November 2025. The recommendations are presented in Table 3.1 below and labelled as either new or updated, based on a review of new evidence. Recommendations without these labels are reprinted from existing guidelines (where no new evidence was available or searched for in the review).

Table 3.1. List of recommendations on TB care and support, where NEW or UPDATED recommendations based on review of the new evidence are highlighted in red

C1. Care and support interventions for all people with TB	
C1.1	Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment. *(Strong recommendation, moderate certainty of evidence)*
C1.2	A package of treatment adherence intervention[62] may be offered for patients on TB treatment in conjunction with the selection of a suitable treatment administration option[63]. *(Conditional recommendation, low certainty of evidence)*
C1.3	One or more of the following treatment adherence interventions (complementary and not mutually exclusive) may be offered to patients on TB treatment or to health care providers: a. tracers[64] or digital medication monitor[65] *(conditional recommendation, very low certainty of evidence);* b. material support to patient[66] *(conditional recommendation, moderate certainty of evidence)*; c. psychological support[67] to patient *(conditional recommendation, low certainty of evidence)*; d. staff education[68] *(conditional recommendation, low certainty of evidence)*.
C1.4	The following treatment administration options may be offered to patients on TB treatment: a. Community- or home-based treatment support is recommended over health facility-based treatment support or unsupervised treatment. *(Conditional recommendation, moderate certainty of evidence).* b. Treatment support administered by trained lay providers or health care workers is recommended over treatment support administered by family members or unsupported treatment. *(Conditional recommendation, very low certainty of evidence)* c. Video-supported treatment (VST) can replace in-person treatment support when the video communication technology is available and can be appropriately organized and operated by health care providers and patients. *(conditional recommendation, very low certainty of evidence)*

[62] Treatment adherence interventions include social support such as: patient education and counselling; material support (e.g. food, financial incentive and transport fees); psychological support; tracers such as home visits or digital health communications (e.g. SMS, telephone calls); medication monitor; and staff education. The interventions should be selected on the basis of the assessment of the individual patient's needs, provider's resources and conditions for implementation.

[63] Suitable treatment administration options include various forms of treatment support, such as video-supported treatment and regular community or home-based treatment support.

[64] Tracers refer to communication with the patient including via SMS, telephone (voice) calls, or home visit.

[65] A digital medication monitor is a device that can measure the time between openings of the pill box. The medication monitor may have audio reminders or send an SMS to remind patient to take medications, along with recording when the pill box is opened.

[66] Material support can be food or financial support such as: meals, food baskets, food supplements, food vouchers, transport subsidies, living allowance, housing incentives, or financial bonus. This support addresses indirect costs incurred by patients or their attendants in order to access health services and, possibly, tries to mitigate consequences of income loss related to the disease.

[67] Psychological support can be counselling sessions or peer-group support.

[68] Staff education can be adherence education, chart or visual reminder, educational tools and desktop aids for decision-making and reminder.

C2. Models of care for people with drug-resistant TB	
C2.1	Patients with multidrug-resistant TB (MDR-TB) should be treated using mainly ambulatory care rather than models of care based principally on hospitalization. *(Conditional recommendation, very low certainty of evidence)*
C2.2	A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment. *(Conditional recommendation, very low certainty of evidence)*
C3. Models of care for children and adolescents exposed to TB or with TB disease	
C3.1	In TB high burden settings, decentralized models of care may be used to deliver TB services to children and adolescents with signs and symptoms of TB and/or those exposed to TB. *(Conditional recommendation, very low certainty of evidence)*
C3.2	Family-centred, integrated models of care to deliver TB services may be used in children and adolescents with signs and symptoms of TB and/or those exposed to TB, in addition to standard models of care. *(Conditional recommendation, very low certainty of evidence)*
C4. Palliative care interventions for MDR/RR-TB patients (NEW)	
C4.1	In patients with pulmonary MDR/RR-TB, in addition to effective treatment, WHO recommends integrating palliative care assessment and interventions by trained providers, as described in WHO palliative care guidance documents (**NEW**). *(Conditional recommendation, moderate certainty of evidence).*

MDR/RR-TB: multidrug- or rifampicin-resistant TB; SMS: short message service or text message; TB: tuberculosis; WHO: World Health Organization.

Recommendations

C1. Care and support interventions for all people with TB

Recommendations C1.1-C1.4

No.	Recommendation
C1.1	Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment. *(Strong recommendation, moderate certainty of evidence)*
C1.2	A package of treatment adherence interventions[69] may be offered to patients on TB treatment in conjunction with the selection of a suitable treatment administration option.[70] *(Conditional recommendation, low certainty of evidence)*
C1.3	One or more of the following treatment adherence interventions (complementary and not mutually exclusive) may be offered to patients on TB treatment or to health care providers: a. tracers[71] and/or digital medication monitor[72] *(Conditional recommendation, very low certainty of evidence);* b. material support[73] to patient *(Conditional recommendation, moderate certainty of evidence);* c. psychological support[74] to patient *(Conditional recommendation, low certainty of evidence);* d. staff education[75] *(Conditional recommendation, low certainty of evidence).*

[69] Treatment adherence interventions include social support such as: patient education and counselling; material support (e.g. food, financial incentives, transport fees); psychological support; tracers such as home visits or digital health communications (e.g. SMS, telephone calls); medication monitor; and staff education. The interventions should be selected based on the assessment of the individual patient's needs, provider's resources and conditions for implementation.

[70] Suitable treatment administration options include various forms of treatment support, such as video-supported treatment and regular community or home-based treatment support.

[71] Tracers refer to the communication with the patient – including via SMS, telephone (voice) calls or home visits.

[72] A digital medication monitor is a device that can measure the time between openings of the pill box. The medication monitor may have audio reminders or may send an SMS to remind the patient to take the medications, along with recording when the pill box is opened.

[73] Material support can be food or financial support: meals, food baskets, food supplements, food vouchers, transport subsidies, living allowance, housing incentives or financial bonus. This support addresses indirect costs incurred by patients or their attendants in accessing health services and, possibly, tries to mitigate the consequences of income loss related to the disease.

[74] Psychological support can be counselling sessions or peer-group support.

[75] Staff education can be adherence education, charts or visual reminders, educational tools and desktop aids for decision-making and reminder.

No.	Recommendation
C1.4	The following treatment administration options may be offered to patients on TB treatment: a. Community- or home-based treatment support is recommended over health facility-based treatment support or unsupported treatment *(Conditional recommendation, moderate certainty of evidence).* b. Treatment support by trained lay providers or health care workers is recommended over treatment support by family members or unsupported treatment *(Conditional recommendation, very low certainty of evidence).* c. Video-supported treatment (VST) may replace in-person treatment support when the video communication technology is available and it can be appropriately organized and operated by health care providers and patients *(Conditional recommendation, very low certainty of evidence).*

Justification

Treatment support

Treatment support terminology in this document is used to describe an approach to supporting patients who are taking prescribed doses of TB medicines to help ensure adherence to treatment and maximize its efficacy. Treatment support needs to be provided in the context of person-centred care and should be based on the individual patient's needs, acceptability and preferences. It includes aspects of support, motivation and understanding of patients without coercion. Historically, this group of interventions were labelled as "directly observed treatment" or DOT. However, with a need to emphasize the need to support people in adhering to treatment, as recommended by the WHO TB ethics guidance of 2010 and 2017 *(5, 6)*, this legacy terminology has been replaced by "treatment support" throughout this document in order to align the language with the essence of the recommendation of the WHO TB ethics guidance.

In the systematic review that led to the recommendations on treatment adherence, "treatment support" was defined as any person observing the patient taking medications in real time. The treatment supporter does not need to be a health care worker, but could be a friend, a relative or a lay person who works as a treatment supporter.

Treatment support may also be achieved with real-time video feed and video recording which is referred to as video-supported treatment (VST). VST was analysed separately in this review.

Adherence definitions varied across the studies. In general, however, adherence was defined as taking more than 90% of medications under conditions of observation by another person.

The systematic review conducted in support of this guideline was based on synthesis of data from randomized controlled trials (RCTs) *(7–14)* and from observational studies *(15–28)*, with preference given to the results of RCTs. Outcomes from treatment support with observation were compared with outcomes from self-administered treatment (SAT) given under standard TB practice and without any additional support. Treatment support could be given by a health care worker, a family member or a community member and could be done at home, in the patient's community or at a clinic. Treatment support was generally performed daily. The GDG (2016) focused preferentially on RCT data from the systematic review. When the data from RCTs were limited or not available, observational data were examined and their results were presented. Interpretation of the associations, however, requires caution due to limitations of the observational data when the associations are confounded by different factors. In uncontrolled observational studies, for instance, patients with more severe disease or higher risk of non-adherence are likely to be assigned treatment support and the less sick

or, less likely, incompliant patients are assigned SAT. The same may apply to the selection of treatment support location, treatment support provider or other interventions in cohort studies.

When treatment support alone was compared with SAT, patients who were on treatment support had better rates of treatment success, adherence and 2-month sputum conversion, and also had slightly lower rates of loss to follow-up and acquired drug resistance. However, patients on treatment support had a slightly higher relapse rate. The GDG considered that, overall, the evidence was inconsistent in showing clear advantages of treatment support alone over SAT or vice versa. However, the evidence showed that some subgroups of patients (e.g. TB patients living with HIV) with factors affecting treatment adherence are likely to benefit from treatment support more than other patients do, and that specific types of treatment support delivery (e.g. locations of treatment support or support providers) are likely to work better than others. The evidence also showed that, when patients received treatment adherence interventions (e.g. different combinations of patient education, staff education, material support, psychological support, tracers and use of medication monitor) in conjunction with treatment support or SAT, the treatment outcomes were significantly improved compared to treatment support with observation or SAT alone (see below).

Only cohort studies were available to examine treatment support and SAT in HIV-positive TB patients *(29–45)*, and many of these studies were conducted in the pre-ART era prior to antiretroviral therapy (ART) or shortly after the introduction of this treatment for HIV-positive TB patients *(29, 30, 35, 38)*. As above, treatment support could have been administered by a variety of people in a variety of settings, including homes and clinics; occasionally, during initial intensive-phase treatment, the treatment support was hospital-based. A few studies provided incentives and enablers or provided treatment support only for persons considered to be at higher risk of loss to follow-up. HIV-positive TB patients on SAT had lower rates of treatment success, treatment completion and cure; they also had higher rates of mortality, treatment failure and loss to follow-up. The evidence showed that HIV-positive TB patients, as a subgroup, benefit more from treatment support than TB patients in general do and that SAT alone is not advisable in HIV-positive TB patients. Reasons such as increased rates of drug–drug interactions and more severe disease in this cohort may cause treatment support to offer a significant advantage over SAT.

Treatment support and SAT in MDR-TB patients were also examined in the systematic review. However, very limited data were available from a cohort study *(32)*. There were higher rates of mortality and non-adherence and lower rates of treatment completion in MDR-TB patients on SAT compared with those on treatment support, although the differences were not significant.

Treatment support provider

RCTs *(9, 11–13)* and observational studies *(16, 17, 20, 22, 27, 31, 33–35, 41, 45)* were available for examination of the effect of treatment support providers versus SAT. Providers were classed as health care workers, lay providers or family members. The health care worker group was varied and included personnel working at different levels of health care systems and who had received health training. Health care workers could be nurses, physicians or trained community health workers. Lay providers were also varied and could include teachers, community volunteers or traditional healers. Treatment support by lay providers had higher rates of treatment success and cure, and a slightly lower rate of loss to follow-up compared with SAT. However, in one cohort study there was a higher rate of treatment completion with SAT compared to treatment support with lay providers. Patients receiving treatment support from a family member had higher rates of treatment success and lower rates of loss to follow-up compared with patients using SAT. When treatment support provided by a health care worker was compared to SAT, there were higher rates of cure and adherence and lower rates of relapse and acquisition of drug resistance with the treatment support provided by a health care worker. However, there was a higher rate of treatment completion with SAT compared to treatment support provided by health care workers in cohort studies.

The effect that different types of treatment support provider had on outcomes was also examined. Treatment support provided by health care workers and treatment support provided by lay persons were compared. Only observational studies were available in the literature *(17, 20, 31, 46–50)*. There were no significant differences although slightly higher rates of success – and lower rates of mortality, failure and loss to follow-up – were observed among patients who had received treatment support administered by a lay provider as opposed to a health care worker.

When provision of treatment support by a family member was compared to health care worker provision of treatment support, there were higher rates of mortality, loss to follow-up and failure, and lower rates of successful treatment, cure and treatment adherence among patients who had treatment support administered by a family member. Therefore, although treatment support by a health care worker, trained lay provider and family member showed advantages compared to SAT, provision by trained lay providers and health care workers are the preferred options for treatment support, with the least preferred treatment support provider being a family member.

Treatment support location

RCTs *(9, 11, 13, 27, 51–54)* and observational studies *(15, 22, 31, 33, 35, 41, 55–88)* examined how the location of treatment support affected the treatment outcome. Locations were grouped by community- or home-based treatment support and health facility-based treatment support. Community- or home-based treatment support was defined as treatment support delivered in the community that is close to the patient's home or workplace. In general, community- or home-based treatment support was provided close to the patients. Health facility-based treatment support was defined as treatment support delivered at a health centre, clinic or hospital, although there were some instances of community- or home-based treatment support being provided by health care workers. When comparing treatment support locations, community- or home-based treatment support had higher rates of treatment success, cure, treatment completion and 2-month sputum conversion. Community- or home-based treatment support also had lower rates of mortality and lower rates of unfavourable outcomes compared with health facility-based treatment support.

When comparing community/home-based treatment support or health facility-based treatment support with SAT, there were no significant differences across the outcomes in RCTs. However, cohort studies showed higher rates of treatment success and adherence, and a lower rate of loss to follow-up, with community/home-based treatment support compared with SAT.

Observational data from cohort studies also showed lower rates of treatment completion and slightly higher rates of failure and loss to follow-up in health-facility treatment support compared to SAT.

Consequently, community- or home-based treatment support is the preferred option rather than health facility-based treatment support and SAT.

Combining the evidence on treatment support provider and treatment support location, treatment support should preferably be delivered at home or in the community by a health care worker or trained lay provider. Treatment support that is delivered at a health facility or provided by a family member, and treatment that is unsupported are not preferable options.

Video-supported treatment (VST)

For VST there were only two cohort studies from high-income countries and no data from low- and middle-income countries *(89, 90)*. These studies compared in-person treatment support with VST done in real time. Patients given VST had no statistically significant difference in treatment completion and mortality compared to patients who had in-person treatment support.

Although there is some concern as to the indirectness of evidence for VST, given that the studies were conducted in high-income countries and there is uncertainty of evidence regarding the use of VST, the

results from the two cohort studies showed that in-person treatment support was not better than VST. Treatment support has been the standard of care that many programmes aim for, even if in practice they have to resort to SAT for many patients because of lack of resources. The advantages of using VST are its potential to observe adherence to treatment from a distance – even when people travel and cannot visit or be visited by a treatment support provider. VST is also more flexible with regard to people's schedules as it offers virtual observation at different times of the day. VST could help achieve better levels of patient interaction at a much lower cost and less inconvenience when compared with in-person treatment support. VST can be used in addition to, or may be interchangeable with, in-person treatment support or other treatment administration options. For instance, it is not expected that a patient receives VST as the sole option of supervision during the whole duration of treatment.

Furthermore, the technology required for VST (broadband Internet and smartphone availability) is becoming increasingly available in resource-constrained settings. Moreover, VST delivery options are evolving (e.g. enhanced possibility for real-time communication in addition to recorded video), and therefore evidence and best practices are likely to develop further in the coming years, especially from the ongoing RCTs. The benefits of VST may become more apparent as programmes are able to choose forms of VST that best meet their needs. In fact, VST may be particularly useful for easing the burden on the health care system in low- and middle-income countries.

Package of combined treatment adherence interventions

Both RCTs *(90–95)* and observational studies *(55–61, 96)* examined the effects of combined treatment adherence interventions. When patients receiving combined treatment adherence interventions along with treatment support or SAT were compared to those receiving treatment support or SAT alone, the patients who received the combined treatment adherence interventions had higher rates of treatment success, treatment completion, cure and adherence, and lower rates of mortality and loss to follow-up. The mixture of types of adherence intervention was varied (Table 3.2). These included different combinations of patient education, staff education, material support (e.g. food, financial incentives, transport fees, bonuses for reaching treatment goals), psychological support and counselling. The treatment adherence interventions also included tracers such as home visits, use of digital health communication (e.g. SMS, telephone calls) or a medication monitor. Interventions should be selected on the basis of an assessment of individual patients' needs, providers' resources and conditions for implementation.

Table 3.2. Treatment adherence interventions

Treatment adherence intervention	Description
Patient education	Health education and counselling.
Staff education	Education, chart or visual reminder, educational tool and desktop aid for decision-making and reminder.
Material support	Food or financial support such as meals, food baskets, food supplements, food vouchers, transport subsidies, living allowance, housing incentives or financial bonus. This support addresses indirect costs incurred by patients or their attendants in accessing health services and, possibly, tries to mitigate the consequences of income loss related to the disease.
Psychological support	Counselling sessions or peer-group support.
Tracer	Communication with the patient, including home visit or via mobile telephone communication such as SMS or telephone (voice) call.
Digital medication monitor	A digital medication monitor is a device that can measure the time between openings of the pill box. The medication monitor can give audio reminders or send an SMS to remind the patient to take medications, along with recording when the pill box is opened.

SMS: short message service or text message.

Tracers and digital health interventions rather than VST

Varied tracers were included in RCTs *(97–104)* and observational studies *(89, 90, 105–109)*. These interventions included, for instance, SMS, telephone calls or automated telephone reminders. Patients who missed appointments or failed to collect their medication received reminder letters or home visits by health care workers. Medication monitors or computer systems in the clinic were also used to aid health care workers in tracing patients. Medication monitors can measure the time between openings of the pill box, give audio reminders, record when the pill box is opened or send SMS reminders to take medications.

There were higher rates of treatment success, treatment adherence and 2-month sputum conversion, and lower rates of mortality, loss to follow-up and drug resistance acquisition with tracers, either through home visits or mobile telephone communication (SMS or telephone call).

When mobile telephone interventions were examined separately, there were higher rates of treatment success, cure and 2-month sputum conversion and lower rates of treatment failure, loss to follow-up, poor adherence and unfavourable outcomes with mobile telephone reminders as opposed to no intervention.

Medication monitors had better rates of adherence and favourable outcomes, and combined interventions of SMS and medication monitors also showed better adherence compared to no intervention.

It should be noted, however, that only a small number of studies were available for all digital health interventions. There was only one small RCT *(98)* on which these data are based. With all the digital interventions and tracers, including VST, it is important to preserve patient support and the ability of patients to interact with health care workers. In fact, these digital interventions should be considered

as tools to enable better communication with the health care provider rather than as replacements for other adherence interventions. In practice, it is expected that SMS, telephone calls and VST may replace in-person treatment support for certain periods of time rather than for the entire duration of treatment and that they promote patient-centred approaches to care.

Mobile telephone interventions, tracers and VST may also increase health equity if the need to travel to a health clinic or to a patient's home is reduced. However, the ability of patients to participate in these programmes depends on the patient living in an area with a good telecommunications infrastructure.

Material support for patients

The effects of material support were examined both with RCTs *(68–71)* and observational studies *(77, 110–117)*. The interventions included giving meals with treatment support with observation, monthly food vouchers, food baskets, food supplements and vitamins. Food support for patients and family members is an important incentive for TB patients and also helps protect patients from the catastrophic costs associated with TB. Food may be an incentive but it may also improve the outcome biologically by reducing malnutrition and consequently improving immune function. Other material support could be in the form of financial incentives, transport subsidies, living allowance, housing incentives, or financial bonuses after reaching treatment targets.

There were higher rates of treatment success, completion and sputum conversion in patients who received material support, and lower rates of treatment failure and loss to follow-up compared with patients who did not receive material support. It is of note that all these studies were in low- and middle-income countries, so presumably these incentives were of significant value to the patients in these settings. However, the material support would also be of significant value to TB patients even in higher-income countries, especially in countries that do not have a good social welfare system, since TB is a disease of poverty.

The studies in this review found that material support was usually given to the most vulnerable groups, and therefore health equity was presumably improved by this intervention. However, if these incentives are not applied equitably, health disparities may be increased. The distribution of material support is likely to depend on the country context and may have different effects both within and between countries.

Patient education or educational counselling

Analysis of the benefit of patient education included RCTs *(63–66)* and observational studies *(74)*. Patients who received education or educational counselling had better rates of treatment success, treatment completion, cure and treatment adherence, and had lower rates of loss to follow-up. It should be noted in this case that "counselling" refers to educational counselling and not psychological counselling. Patient education could include oral or written education via health care workers or pharmacists. The education could be a one-time session at discharge from the intensive phase of therapy or at each presentation for follow-up care. The educational session might include only the health care worker and patient, or it could involve the patients' social network and family members. It is important to make sure that education and counselling are done in a culturally appropriate manner. Additionally, specific marginalized populations may require special educational efforts.

Staff education

Staff education may include peer training, visual aids to help initiate conversations with patients, other tools to aid in decision-making and as reminders, as well as the education of laboratory staff. This intervention was examined in both RCTs *(67, 68, 117)* and observational studies *(118)*. Staff education led to higher rates of treatment success and slightly lower rates of mortality and loss to follow-up. With better staff education, treatment for patients is likely to improve. Any stigma that health care

workers may hold towards patients would decrease as the health care workers better understand TB disease and TB treatment.

Psychological support

Psychological support was varied and could include self-help groups, alcohol cessation counselling and TB clubs *(55, 73, 119)*. Patients who had access to psychological support had higher rates of treatment completion and cure, as well as lower rates of treatment failure and loss to follow-up. However, the GDG expressed concerns about confounding in these studies due to the severity of illness in the groups receiving support. Additionally, allocation of patients to the support groups was not always randomized.

When considering these data, it should also be noted that types of psychological support are very broad and may not be adequately represented in this review. To maximize health equity, psychological support should be targeted at the most marginalized populations.

Subgroup considerations

The evidence that was reviewed did not allow for conclusions about the advantages of treatment support over SAT or vice versa for TB patients; however, in a subgroup analysis of TB patients living with HIV, treatment support showed clear benefit with significantly improved treatment outcomes. It is probable that treatment support may not be beneficial for all patients but that it is likely to have more benefit in certain subgroups of TB patients. Apart from HIV-positive TB patients, other factors or groups of patients that were more or less likely to result in treatment adherence (and therefore require treatment support) were not examined in the scope of the systematic review.

Implementation considerations

Treatment adherence interventions

As treatment support alone is not likely to be sufficient to ensure good TB treatment outcomes, additional interventions for treatment adherence need to be provided. Patient education should be provided to all patients on TB treatment. A package of the other treatment adherence interventions also needs to be offered to patients on the basis of an assessment of individual patients' needs, providers' resources and conditions for implementation.

With regard to telephone or video-assisted interventions, there may be reluctance to use new technology, making implementation more difficult. There may be privacy concerns regarding the security of telephone data, so encryption and other measures to safeguard privacy will need to be considered. The feasibility of implementing these types of interventions depends on telecommunications infrastructure, telephone availability and connection costs. Multiple organizations have initiated programmes such as these, so TB programmes may find it helpful to collaborate and communicate with other medical service delivery programmes that have already set up such infrastructure.

There may be reluctance on the part of implementers (e.g. national or local governments, health partners) to pay for incentives. Implementers may be more willing to pay for material support for smaller subgroups at particularly high risk (e.g. patients with MDR-TB). However, one of the components of the End TB Strategy *(120)* is to provide "social protection and poverty alleviation" for patients with TB. The strategy specifically calls for measures to "alleviate the burden of income loss and nonmedical costs of seeking and staying in care". Included in the suggested measures are social welfare payments, vouchers and food packages. The benefit of material support found in this review supports these components of the End TB Strategy *(120)*.

In order to distribute the material support, a government or nongovernmental organization (NGO) infrastructure would need to be in place, including anti-fraud mechanisms (e.g. reliable unique

personal identifiers) and appropriate accounting to ensure that incentives are distributed equitably and to the people who need them most. Countries should choose incentives that are the most appropriate for their situation.

Treatment administration

Community-based or home-based treatment support has more advantages than health facility-based treatment support, although family members should not be the first or only option for administering treatment support. Treatment support is better provided at home or in the community by trained lay providers or health care workers. However, there may be challenges in providing community- or home-based treatment support by health care workers because of the increased number of health care workers required and the increased costs for staff time and daily travel to the community or to a patient's home. Treatment support provided in the community or at home by trained local lay persons is more feasible. A combination of lay provider and health care worker for provision of community- or home-based treatment support is also an option. Community-based or home-based treatment support is more likely to be acceptable and accessible to patients than other forms of treatment support. Nevertheless, stigma may continue to be a concern with community- or home-based treatment support. Having a health care worker coming regularly to a patient's house may be stigmatizing, and the feeling of being "watched over" may be disempowering to patients. Other forms of treatment support (e.g. administered by an emotionally supportive relative or close friend) may be more acceptable but may still be stigmatizing.

Given complex family social dynamics, family members may not always be the best people to supervise treatment, so the suitability of such treatment adherence supervisors needs to be carefully analysed in each national or local context. If family members are already providing treatment support, careful identification and training of those persons is required. Additional supervision of local supporters or health care workers is still needed, as family members cannot be depended on as the only option for care. Patients will continue to need social support, even if family members are providing treatment support.

Assessment of potential risk factors for poor adherence must be taken into account by health care workers at the start of a patient's treatment in order to decide which treatment administration option should be selected for that patient. Some groups of patients who are less likely to adhere to treatment may gain more benefit from treatment support than others do. Another factor to consider when selecting options for treatment administration is that some patients with inflexible work or family responsibilities may not be able to provide treatment support. Any treatment administration option offered to a patient must also be provided in conjunction with proper medical care, including regular pick-up of TB drugs, consultations with a physician or other health care workers when necessary, TB treatment that is free of charge, and provision to the patient of essential information on TB treatment.

Monitoring and evaluation

Programmes should attempt to measure whether the provision of incentives improves programme performance.

C2. Models of care for people with drug-resistant TB

Recommendations C2.1–2.2

No.	Recommendation
C2.1	Patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalization. *(Conditional recommendation, very low certainty of evidence)*
C2.2	A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment. *(Conditional recommendation, very low certainty of evidence)*

Justification

Ambulatory care: Outcomes from models of MDR-TB care based mainly on clinic-based ambulatory treatment were compared with those using mainly hospital-based inpatient treatment. The data used came from cost–effectiveness studies in four countries, namely: Estonia and the Russian Federation [Tomsk oblast] *(121)*, Peru *(122)* and the Philippines *(123)*.The design of these observational studies did not allow direct comparison of effects between models of care. Because none of the studies were RCTs, the evidence was considered to be of very low quality. Cost–effectiveness was modelled for all possible WHO Member States in a probabilistic analysis of the data from the four countries *(124)*.

Decentralized care: As the use of Xpert® MTB/RIF expands, more patients will be diagnosed and enrolled on MDR-TB treatment. Having treatment and care provided in decentralized health care facilities is a practical approach for scaling up treatment and care for patients who are eligible for MDR-TB treatment. Therefore, a systematic review of the treatment and care of bacteriologically confirmed or clinically diagnosed MDR-TB patients in decentralized versus centralized systems was conducted to gather evidence on whether the quality of treatment and care is likely to be compromised with a decentralized approach. Data from both RCTs and observational studies were analysed, with the majority being from low- and middle-income countries *(59, 119, 120, 125–131)*. The review provided additional value to the recommendation in the previous guidelines on ambulatory over hospitalized models of care for MDR-TB patients for which the evidence was examined only for treatment and care of patients outside or inside hospitals *(132)*.

In the review, decentralized care was defined as care that is provided in the local community where the patient lives at non-specialized or peripheral health centres, by community health workers or nurses, non-specialized doctors, community volunteers or treatment supporters. Care could also occur at local venues or at the patient's home or workplace. Treatment and care included treatment and patient support plus injections during the intensive phase. In this group, a brief phase of hospitalization of less than one month was accepted for patients who were in need during the initial phase of treatment or when they had any treatment complications.

Centralized care was defined as inpatient treatment and care provided solely by centres or teams specialized in drug-resistant TB for the duration of the intensive phase of therapy or until culture or smear conversion. Afterwards, patients could have received decentralized care. Centralized care was usually delivered by specialist doctors or nurses and could include centralized outpatient clinics (i.e. outpatient facilities located at or near the site of the centralized hospital).

Analysis of the data showed that treatment success and loss to follow-up improved with decentralized care versus centralized care. However, the risk of death and treatment failure showed minimal difference between patients undergoing decentralized care and those receiving centralized care. There were limited data on adverse reactions, adherence, acquired drug resistance and cost.

Both HIV-negative and HIV-positive persons were included in the reviewed studies although the studies did not stratify patients on the basis of HIV status.

There was some discussion regarding the quality of the data. The GDG (2016) expressed concerns that health care workers may have selected for the centralized care groups those patients who they thought might have a worse prognosis. None of the studies controlled for this risk of bias.

Subgroup considerations

Decentralized care may not be appropriate for patients with severe TB disease, extremely infectious forms of the disease, serious comorbidities or patients for whom treatment adherence is a concern.

Measures to protect the safety of patients on MDR-TB regimens – especially those containing new or novel medicines – need to be maintained in outpatient settings.

These recommendations for decentralized care should not preclude hospitalization if appropriate. This review did not include patients requiring surgical care.

Implementation considerations

Ambulatory care: The cost varied widely across the modelled settings. The cost per disability-adjusted life year (DALY) averted by an ambulatory model in one setting was sometimes higher than the cost per DALY averted by a hospitalization model in another setting. However, cost per DALY averted was lower under outpatient-based care than under inpatient-based care in the vast majority (at least 90%) of settings for which cost–effectiveness was modelled. The variation in cost–effectiveness among settings correlated most strongly with the variation in the cost of general health care services and other non-drug costs. Despite the limitations in the data available, there was no evidence that conflicted with the recommendation or which indicated that treatment in a hospital-based model of care leads to a more favourable treatment outcome.

The overall cost–effectiveness of care for a patient receiving treatment for MDR-TB can be improved with an ambulatory model. The benefits include reduced use of resources, and at least as many deaths avoided among primary and secondary cases as with hospitalization models. This result is based on clinic-based ambulatory treatment (i.e. patients attended a health care facility); in some settings, home-based ambulatory treatment (provided by a health worker in the community) might improve cost– effectiveness even further. The benefit of reduced transmission can be expected only if proper infection control measures are in place in both the home and the clinic. Potential exposure to people who are infectious can be minimized by reducing or avoiding hospitalization where possible, reducing the number of outpatient visits, avoiding overcrowding in wards and waiting areas, and prioritizing community-care approaches for TB management *(133)*. The regimen used in one of the studies on ambulatory care derived from a period when the combinations of medicines were not yet optimized, so the outcomes achieved were probably inferior to those that can be obtained with the regimens in use today. Admission to hospital for patients who do not warrant it may also have important social and psychological consequences that need to be taken into account.

There may be some important barriers to accessing clinic-based ambulatory care, including distance of travel and other costs to individual patients. Shifting costs from the service provider to the patient must be avoided, and implementation may need to be accompanied by appropriate enablers. While placing patients on adequate therapy would be expected to decrease the bacterial load and transmission of DR-TB, infection control measures for home-based and clinic-based measures will need to be part of an ambulatory model of care in order to decrease the risk of transmission in households, the community and clinics. TB control programmes will have to consider whether they are capable of reallocating resources from hospital care to ambulatory care support in order to undertake the necessary changes in patient management. The choice between these options will affect the feasibility of implementing the recommendation in a particular programme.

A high value was placed on conserving resources and on patient outcomes such as preventing death and transmission of MDR-TB as a result of delayed diagnosis and inpatient treatment. There should always be provision for a back-up facility to manage patients who need inpatient treatment. This may be necessary in certain groups of patients at particular risk, such as children during the intensive phase, among whom close monitoring may be required for a certain period of time.

Decentralized care: National TB programmes should have standardized guidelines regarding which patients are eligible for decentralized care. Patient preference should be given a high value when choosing between centralized or decentralized care.

Decentralized care for MDR-TB patients requires appropriate treatment supervision, patient education and social support, staff training, infection control practices and quality assurance. The optimal treatment supervision options and treatment adherence interventions recommended in section 2.1 should be considered for MDR-TB patients on decentralized care.

Several of the studies in the review addressed treatment costs. However, cost estimates were found to vary widely and no concrete recommendations could be made on that basis. Resource requirements are likely to vary because TB treatment programmes are highly variable and costs vary across different countries. The GDG raised several issues for TB programmes to consider. Although hospitalization is generally thought to be more expensive than outpatient care, the costs of good outpatient programmes can also be significant. Additionally, outpatient costs may vary significantly according to the services provided. One cost-saving measure to consider in decentralized care is that patients may be able to receive treatment faster. The financial benefits of decentralized care would include finding patients before they become very ill and require more medical care, while treating people before TB can be transmitted to contacts would be a public health benefit.

If a patient is living with a person from a high-risk group (i.e. HIV-positive or a young child), there may be complications in sending the patient home for treatment. However, the risk posed to high-risk groups varies significantly, depending on whether the TB programme gives preventive treatment to high-risk persons. Studies involving preventive therapy for MDR-TB are ongoing.

An additional implementation concern is that in some places it may be illegal to treat MDR-TB patients in a decentralized setting, especially when the treatment involves injections. Such legal concerns need to be addressed.

C3. Models of care for children and adolescents exposed to TB or with TB disease

Recommendations C3.1–3.2

No.	Recommendation
C3.1	In TB high burden settings, decentralized models of care may be used to deliver TB services to children and adolescents with signs and symptoms of TB and/or those exposed to TB. *(Conditional recommendation, very low certainty of evidence)*
C3.2	Family-centred, integrated models of care to deliver TB services may be used in children and adolescents with signs and symptoms of TB and/or those exposed to TB, in addition to standard models of care. *(Conditional recommendation, very low certainty of evidence)*

Remarks

- These recommendations relate to TB services along the full range of care with a focus on case detection and provision of TB preventive treatment (TPT).
- The recommendations apply to children and adolescents with signs and symptoms of TB in terms of the impact on case detection. They also concern children and adolescents who are exposed to TB (i.e. TB contacts), and who are eligible for TPT, in terms of the impact on provision of TPT. Children and adolescents with signs and symptoms who need evaluation for TB disease may also have a history of exposure to TB (i.e. TB contacts). Children and adolescents who are TB contacts and who do not have signs and symptoms should be evaluated for TPT eligibility.
- The recommendation on decentralized services refers to enhancing child and adolescent TB services at peripheral levels of the health system where they are closer to the community, and not to replacing specialized paediatric TB services at higher levels of the health system.
- Decentralization should be prioritized for settings and populations with poor access to existing services and/or in high TB-prevalence areas.
- Family-centred, integrated approaches are recommended as an additional option to standard TB services (e.g. alongside specialized services that may have a limited level of integration with other programmes or links to general health services).
- Family-centred care is a cross-cutting principle of childcare at all levels of the health system.

This section contains two recommendations on the implementation of decentralized models of care and integrated family-centred models of care to improve both case detection and the provision of TPT.

Capacity for paediatric TB is often highly centralized at secondary/tertiary levels, where children may present as seriously ill, after delays in accessing care. At higher levels of care services are often managed in a vertical, non-integrated way *(134, 135)*. Health care workers at the primary health care (PHC) level may have limited capacity for and confidence in managing paediatric TB, although this is the level at which most children with TB or at risk of TB seek care *(135)*. In addition, TB screening is often not systematically part of clinical algorithms for child health – such as integrated management of childhood illness (IMCI) or integrated community case management (iCCM). Private-sector providers play an increasing role as the first point of care in many countries *(136)*. Nevertheless, there are many missed opportunities for contact-tracing, as well as for TB prevention, detection and care, because of weak integration of child and adolescent TB services with other programmes and services.

Decentralization and provision of family-centred, integrated care are highlighted as one of 10 key actions in the 2018 *Roadmap towards ending TB in children and adolescents (135)*. The Roadmap highlights that consistently and systematically addressing gaps and bottlenecks along children's and adolescents' pathway through TB exposure, infection and disease can lead to reduced transmission of TB, expanded prevention of TB infection and earlier TB diagnosis with better outcomes. Achieving this continuum of care requires collaboration across service areas, practice disciplines and sectors, and community engagement, as well as decentralization and integration of service delivery at the PHC level *(135)*.

The Roadmap suggests actions to integrate child and adolescent TB into family- and community-centred care, including by:

- strengthening country-level collaboration and coordination across all health-related programmes engaged in woman, adolescent and child health – especially reproductive health, maternal, neonatal, child and adolescent health (MNCAH), nutrition, HIV, primary and community health – with clearly defined roles, responsibilities and joint accountability;
- decentralizing and integrating successful models of care for TB screening, prevention and diagnosis with other existing service delivery platforms for maternal and child health – such as antenatal care, iCCM and IMCI – as well as other related services (e.g. HIV, nutrition, immunization);
- ensuring that children and adolescents with other common comorbidities (such as meningitis, malnutrition, pneumonia, chronic lung disease and HIV infection) are routinely evaluated for TB;

- ensuring that community health strategies integrate child and adolescent TB education, screening, prevention and case-finding into training and service delivery activities; and
- increasing awareness of and demand for child and adolescent TB services in communities and among health workers *(135)*.

The set of PICO (population, intervention, comparator and outcomes) questions examined the impact of decentralization[76] and of family-centred, integrated approaches[77] of child and adolescent TB services on case detection in children and adolescents who present with signs and symptoms of TB. The questions also examined the impact of these approaches on coverage of TPT among children and adolescents.

Justification and evidence

PICO questions:

a. In children and adolescents with signs and symptoms of TB, should the decentralization of child and adolescent TB services versus centralized child and adolescent TB services (at referral or tertiary hospital level) be used?

b. In children and adolescents exposed to TB, should the decentralization of child and adolescent TB prevention and care services versus centralized prevention and care services (at referral or tertiary hospital level) be used to increase coverage of TPT in eligible children and adolescents?

c. In children and adolescents with signs and symptoms of TB, should family-centred, integrated services versus standard, non-family-centred, non-integrated services be used?

d. In children and adolescents exposed to TB, should family-centred, integrated services versus standard, non-family-centred, non-integrated services be used to increase TPT coverage in eligible children and adolescents?

Evidence:

A systematic review of studies assessing the impact of decentralized, integrated or family-centred care models on TB diagnosis, treatment or prevention outcomes in children and adolescents with TB between 0 and 19 years of age, comprising both children (0–9 years of age) and adolescents (10–19 years of age), was conducted to answer this group of PICO questions. The PubMed, Embase, Web of Science, Global Index Medicus, Global Health and Cochrane Central databases were searched in February 2021, as were the references of 17 related reviews. A total of 3265 abstracts from databases and 129 additional references from related reviews were identified and assessed. Of these, 516 full-text articles were assessed for eligibility, from which 25 comparative studies (7 randomized, 18 observational) were identified; one unpublished observational study was added, making a total of 26 studies. Four studies (1 randomized, 3 observational) were excluded after review because the care model described was community-based treatment support, for which a WHO recommendation already exists *(137)*. Of the remaining studies that were included, 16 had elements of decentralization,

[76] ***Decentralization:*** Depending on the standard in the research settings used for the comparator, decentralization includes the provision of, access to or capacity for child and adolescent TB services at a lower level of the health system than the lowest level at which this is currently routinely provided. In most settings, decentralization would apply to the district hospital (first referral level hospital) and/or the primary health care level and/or community level. Interventions for decentralization can include capacity-building of various cadres of health care workers, expanding access to diagnostic services.

[77] ***Family-centred, integrated care:*** Family-centred models of care refer to interventions selected on the basis of the needs, values and preferences of the child or adolescent and his or her family or caregiver. This can include health education, communication and material or psychological support. Integrated services refer to approaches to strengthen collaboration, coordination, integration and harmonization of child and adolescent TB services with other child health-related programmes and services. This can include integration of models of care for TB screening, prevention, diagnosis and treatment with other existing service delivery platforms for maternal and child health (such as antenatal care, integrated community case management, integrated management of childhood illnesses) and other related services (e.g. HIV, nutrition, immunization). Other examples include the evaluation of children and adolescents with common comorbidities (e.g. meningitis, malnutrition, pneumonia, chronic lung disease, diabetes, HIV infection) for TB, as well as community health strategies to integrate child and adolescent TB awareness, education, screening, prevention and case-finding into training and service delivery activities.

five had elements of integration, and three had elements of family-centred care. Four studies had elements of more than one care model of interest but were included only on the basis of their main model – such as either decentralization or family-centred, integrated care. Most studies focused on the 0–14-year age group.

Studies in which the primary intervention was decentralization chiefly assessed diagnosis or case notification outcomes (*n*=16) *(138–153)*, with fewer assessing TPT outcomes (*n*=3) *(58, 144, 154)*. In general, interventions that included both strengthening of diagnostic capacity in primary care settings and strengthening links between communities and facilities consistently showed an increase in case notifications and TPT initiations, while interventions that involved only community-based activities did not.

Two studies of service integration were identified *(155, 156)* as showing limited impact on case notifications of screening in IMCI clinics or co-location of TB and ART services. The two studies of family-centred care *(157, 158)* showed that the provision of socioeconomic support packages to families affected by TB was associated with increased TPT initiation and completion.

The reviewers noted that, while substantial wider literature on integration and family-centred care is available, evidence for the specific impact on child and adolescent TB outcomes is limited. Some overlap was noted between the integration of TB services into non-specialized settings such as general outpatient or primary care services or decentralization. This was a slightly artificial separation for the evidence review since in practice decentralization and integration into PHC may occur together.

GDG considerations:

With regard to the evidence reviewed on the impact of decentralization on TB case detection, the GDG (2021) observed that two trials *(147, 149)* and one observational study of home-based screening (without facility-based strengthening) *(152)* had fewer diagnoses or notifications among children aged below 15 years in the intervention group compared to the control group, but that none of these differences were statistically significant. The GDG considered that, while there may be a reduction in case notifications at higher levels of care, TB detection may improve if children are seen by a competent clinician at the first point of access (such as at PHC level). The evidence overall was recognized as uncertain. The benefit of increased case-finding and an increased number of children with TB who are initiated on TB treatment was considered to outweigh the concern for overtreatment. Therefore, the undesirable effects of case detection were considered trivial. The GDG discussed the potential risks of provision and management of TPT at the peripheral level, including undetected drug-related adverse events such as hepatotoxicity and insufficient capacity to manage these events. In addition, there may be a risk of TB disease being treated with a course of TPT rather than with a complete treatment regimen. All these undesirable events can potentially happen but were considered rare and not of major concern. Therefore, the undesirable effects for TPT provision were also considered trivial. Overall, the GDG agreed that the balance of desirable and undesirable effects probably favours decentralized TB services for case detection and provision of TPT to children and adolescents. The panel noted that differences in the setting and the availability of adequate resources are important considerations.

The GDG also discussed the fact that family-centred, integrated care includes interventions at the household level to identify members of the household who require evaluation for TB disease, TPT, treatment support etc. Some overlap between the integration of TB services into non-specialized settings – such as general outpatient or primary care services and decentralization – was noted. However, this was considered to be a somewhat artificial separation since in practice decentralization and integration into PHC may occur at the same time. Overall, despite a lack of evidence on undesirable effects and low quality of the data, the panel agreed that there is evidence of positive effects of family-centred integrated care. It was suggested that family-centred, integrated care could be an addition to both the standard of care and specialized services which do not have an integration component.

Family-centred care (in the sense of family involvement) was highlighted as a core principle of child health care.

The GDG noted that setting-specific factors related to the TB burden or the organization of health services may have an impact on feasibility, acceptability and equity. GDG members also pointed out that the initial health system costs for establishing decentralized and family-centred, integrated services may be relatively high (e.g. for infrastructure, human resources, training, equipment, community engagement), but that costs are likely to decrease over time – assuming that people with TB are effectively managed and that TPT is provided at the peripheral level, leading to a reduction in TB incidence. Decentralized and family-centred, integrated services may result in important savings for affected families. Equity was considered an important cross-cutting issue that also has an impact on cost. The GDG highlighted that TPT implementation can be very challenging with high levels of loss to follow-up in programmes implemented at higher levels of the health system, considering that children who are eligible for TPT are not sick. The panel agreed that the decentralization and integration of services can potentially increase equity and enhance the success of the programme and judged that cost–effectiveness probably favours decentralized and family-centred, integrated approaches to both case-finding and the provision of TPT.

While the GDG stressed the importance of taking into consideration the potential impact of stigma when decentralizing TB services for children and adolescents to lower levels, the panel judged that decentralized approaches are probably acceptable to key stakeholders. Overall, decentralized and family-centred, integrated approaches were judged to be feasible to implement, although feasibility may vary depending on factors such as infrastructure, availability of funding and the structure of the national TB programme. However, adequate investment is critical to enable the acceptability, equity and feasibility of decentralized approaches.

Subgroup considerations

Adolescents have a disease presentation that is similar to that of adults and therefore may need different interventions than those for young children. Additional subgroup considerations for adolescents are included in the WHO operational handbook, taking into account their specific health-seeking behaviour and the need for adolescent-friendly services.

TB contacts: Provision of TPT has for many years focused mainly on children under five years of age. In 2018, target groups for the provision of TPT were expanded to include contacts of all ages *(159)*. Available data from the global TB database *(160)* show that coverage of TPT in household contacts is poor – especially in contacts over five years of age.

In children with common illnesses with overlapping signs and symptoms of TB, approaches that integrate TB services in their care can improve case detection and provision of TPT.

These subgroups include:

- children with SAM;
- children with severe pneumonia;
- children living with HIV; and
- children with other chronic diseases.

Implementation considerations

Health system requirements: Training of health care workers at peripheral levels of the health system is a critical requirement for ensuring that decentralized approaches are implemented adequately. Similarly, resources are needed at the peripheral level – especially initially to establish services. It is expected that, as services are established and effectively implemented, the long-term impact will result in a decrease in TB incidence with an associated reduction in resource requirements. A

phased approach may be applied if this is most appropriate in the country or area, depending on the local burden of TB, the availability of domestic or donor funding and the amount of technical and programmatic support.

Factors to consider in decentralizing child and adolescent TB services include: the existing infrastructure (such as baseline health infrastructure, needs for expansion or upgrading); an applicable regulatory framework; financing; the choice between an operational research setting or programmatic implementation; human resource issues (including staffing requirements and human resources development, such as capacity-building/training and consultation skills); monitoring and evaluation; qualitative research into community needs; perceptions (including views on stigma); and suggestions. Decentralization of services to the PHC level requires that child and adolescent TB services are integrated within general PHC services, resulting in possible significant overlap between decentralization and family-centred, integrated approaches.

Contact investigation: Active contact investigation at community and household level is a critical intervention for enhancing both case-finding and the provision of TPT to children and adolescents.

Task-shifting: Decentralization not only concerns the levels of the health system but should ideally also take place within the same structure, by training all health care providers of all child and adolescent care services in the recognition and management of TB. This so-called task-shifting was mentioned by the GDG as an important implementation factor.

Family-centred and integrated care: Although in child health, care evolves around the family, the concept of family-centred care has not been well defined. Family-centred care is related to the more common concept of patient-centred care. The End TB Strategy *(120)* states: "Patient-centred care involves systematically assessing and addressing the needs and expectations of patients. The objective is to provide high-quality TB diagnosis and treatment to all patients – men, women and children – without their having to incur catastrophic costs. Depending on patients' needs, educational, emotional and economic support should be provided to enable them to complete the diagnostic process and the full course of prescribed treatment". Multiple descriptions exist that include components of support and education based on individual needs, building a patient–provider partnership and participatory decision-making. Family-centred care also includes interventions at household level to identify members of the household requiring evaluation for TB disease, TPT, treatment support and so on. As the concept of family-centred, integrated care may be specific to the setting, one of the first steps in implementation includes clarifying which definition applies to the setting in which the care is to be implemented. Similarly, the implementation strategy varies by setting and needs to be country- or region-specific and informed by social, cultural and societal values.

The package of TB services to be provided should be defined and developed by the national TB programme in close coordination with other relevant programmes, such as through an existing child and adolescent TB technical working group. This package should seek to identify and address capacity needs for national programmes interested in the uptake of proposed interventions, and should ideally be based on family and community perceptions of the ideal family-centred model of care. The package could include community-based models for active contact investigation, identifying children with TB signs and symptoms or exposure as part of routine growth-monitoring services, or an integrated model for IMCI integration, starting with the sick child and identifying signs and symptoms pointing to a high likelihood of TB.

Integration can start within the family by equipping family members with the knowledge to recognize signs and symptoms in order to understand the importance of a history of contact, to know when to seek help at the health care facility and how to minimize stigma related to TB. High-yield entry points provide a good place to start within the health system. For instance, child and adolescent TB services can be integrated with malnutrition clinics, ANC, the Expanded Programme on Immunization, inpatient sites, adult TB and chest clinics, HIV and general paediatric clinics. TB care should ideally be integrated into general health services rather than being limited to enhanced coordination between

two programmes. However, defining an optimal patient flow between services and creating strong links between child health entry points and TB clinics remains essential, especially in facilities where services are physically separated. This is critical for enhancing the quality of services, including the follow-up of persons with TB during the diagnostic evaluation, and also for ensuring the accuracy of recording and reporting. In the early phase, pilot programmes could be considered, and should be evaluated and adjusted as needed and then scaled up.

Factors to consider in designing an integrated approach to child and adolescent TB care include: the existing infrastructure (e.g. baseline health infrastructure, need for expansion or upgrading); the applicable regulatory framework; financing; the choice between an operational research setting or programmatic implementation; human resource issues (including staffing requirements and human resources development such as capacity-building/training and consultation skills); monitoring and evaluation; qualitative research into community needs; perceptions (including views on stigma; and suggestions.

Differentiated service delivery (DSD): DSD is a person-centred approach developed in the HIV programme that simplifies and adapts HIV services across the range of care in ways that both serve the needs of people living with and vulnerable to HIV and optimize the available resources in health systems. The principles of DSD can be applied to prevention, testing, linkage to care, ART initiation and follow-up, as well as to the integration of HIV care, coinfections and comorbidities *(161)*. This approach is based on the principle that when families are given the choice to interact with the health system, this provides a possible mechanism for integration of child and adolescent TB services within PHC or other programmes. Examples of implementing DSD for children and adolescents with or at risk of TB are provided in WHO's operational handbook.

Monitoring and evaluation

The move to decentralized, family-centred, integrated services requires careful planning and regular monitoring of implementation against the plan. The capacity needs of national TB programmes for implementing the proposed interventions need to be identified and addressed.

Enhanced data collection on child and adolescent TB potentially takes a substantial amount of additional time, and detailed data collection may be feasible only in specific operational research settings. Programmes generally have registers in place for contact investigation, treatment registration and outcomes, as well as TPT registers. The use of these (preferably electronic) tools is important for ensuring comprehensive management and treatment as programmes move to a more decentralized and family-centred, integrated approach. The use of the tools should be evaluated and enhanced, including through operational research.

It will be important to monitor the number of children diagnosed at different levels of the health system – including the proportion of children who have bacteriological confirmation, the proportion who were clinically diagnosed and the number of children initiated on and completing TPT. Disaggregation of data by sex will be important to evaluate the impact on gender equity. Evaluating the quality of services (covering the quality of all steps in the patient pathway, from screening to diagnosis and treatment) as well as client satisfaction are also important components.

C4. Palliative care interventions for MDR/RR-TB patients

Recommendation C4.1

No.	Recommendation
C4.1	In patients with pulmonary MDR/RR-TB, in addition to effective treatment, WHO recommends integrating palliative care assessment and interventions by trained providers, as described in WHO palliative care guidance documents (NEW). *(Conditional recommendation, moderate certainty of evidence)*

Remarks

- The underlying evidence stems from an RCT in Uganda involving nurses with advanced palliative care training delivering the intervention in addition to effective MDR/RR-TB treatment; however, the findings suggest that other appropriately trained providers could also deliver this care.
- The interventions may be applicable to selected people with drug-susceptible TB (DS-TB) who need palliative care interventions following needs assessment based on the WHO palliative care guidance documents *(162, 163)*.

Rationale

Palliative care is an important component of comprehensive, person-centred TB care; it should be considered for people with TB who have severe disease, significant symptom burden or complex physical, psychological, social or spiritual needs. Palliative care focuses on the prevention and relief of suffering through early identification of pain and other distressing symptoms, and careful assessment and management of those symptoms, while supporting quality of life for people with TB and their families. Palliative care should be provided in addition to effective TB treatment, not as a substitute for such treatment, based on individual needs and preferences.

The evidence informing this recommendation is derived mainly from an RCT conducted in Uganda that found palliative care interventions delivered by trained nurses to patients with MDR/RR-TB improved palliation or health-related quality of life outcomes and TB treatment adherence. Although the certainty of evidence is moderate, the 2025 GDG considered the overall balance of effects to be favourable to the palliative care interventions.

Summary of evidence

This section provides the PICO questions, and the data and studies considered to answer the questions; the methods used for analysis and data synthesis; a summary of evidence on desirable and undesirable effects, and the certainty of that evidence; and a summary of other evidence considered during the development of the recommendation. Additional details on the evidence are available in Annex 5, which contains the GRADE evidence summary tables and GRADE evidence-to-decision (EtD) tables.

PICO question

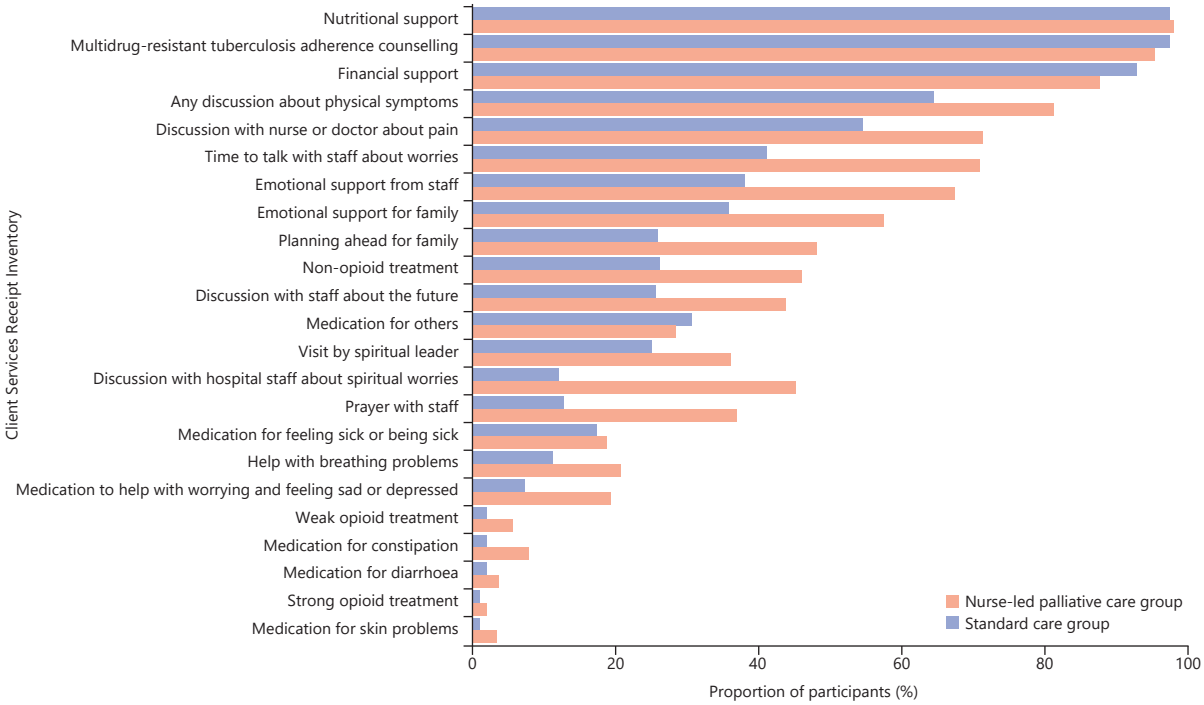
PICO 7–2025*: Should nurse-led palliative care interventions, in addition to effective treatment versus effective treatment without such interventions, be used for patients with pulmonary MDR/RR-TB?*

Data and study

The RCT was conducted in Uganda to test whether nurse-led palliative care interventions improve patient-reported outcomes for patients with MDR/RR-TB, compared with usual care. A total of 154 participants were recruited and randomly assigned to the intervention group (76 individuals) or the control group (78 individuals). Intervention group participants received nurse-led, person-centred holistic assessment in line with WHO's palliative care guidance; care planning; and palliative care support delivered on inpatient wards or at home. Selection and provision of palliative care interventions were based on the individual patient needs that were identified from the assessment. A package of palliative care interventions provided in the trial included components such as social support (e.g. material, educational, psychological and spiritual), nutritional support and medications for relief of symptoms (Fig. 3.1) *(164)*.

The research team made the trial data available to WHO and presented it to the GDG for review at the meeting in November 2025.

Fig. 3.1. Palliative care interventions provided in the trial and percentage of participants receiving components of care by study group *(164)*



Methods used for analysis and data synthesis

The primary outcome of the study was multidimensional palliative care-related symptoms and concerns, measured using the African Palliative Care Association Integrated Palliative Outcome Scale *(165)*, and those were measured monthly from baseline to the primary 4-month endpoint. Key secondary outcomes included quality of life, measured by WHOQOL-BREF indicators *(166)*, psychological morbidity measured using the General Health Questionnaire (GHQ-12) *(167)*, drug adherence (whether the participant had missed any doses of their TB treatment in the previous month) *(168)* and alcohol consumption (whether the participant used alcohol in the previous month).

Given that the outcomes of the trial were measured as continuous outcomes, decision thresholds were established based on the standardized mean difference (SMD) *(169)*, and were used for assessment

and decision-making. Decision thresholds of continuous outcomes on palliation, quality of life and psychological well-being were as follows:

- trivial or no important effect: <0.2 standardized mean difference (SMD);
- small effect: 0.2–0.49 SMD;
- moderate effect: 0.5–0.79 SMD; and
- large effect: >0.8 SMD.

Decision thresholds used for assessment of continuous outcome on TB drug adherence were:

- trivial or no important effect: up to 58 fewer or more events per 1000 people;
- small effect: >58–143 fewer or more events per 1000 people;
- moderate effect: >144–269 fewer or more events per 1000 people; and
- large effect: >270 fewer or more events per 1000 people.

Summary of desirable and undesirable effects and certainty of evidence

Participants with MDR/RR-TB receiving palliative care interventions in addition to effective TB treatment (*n*=76), compared with participants with the same resistance patterns receiving effective TB treatment without palliative care interventions (*n*=78), experienced:

- higher level of palliation of their symptoms and concerns assessed with the Integrated Palliative Outcome Scale – month 4 follow-up: the mean palliation in the intervention group was 0.61 standard deviations (SD) higher (0.35 higher to 0.86 higher) (moderate effect was defined based on the decision thresholds);
- higher level of (better) total quality of life assessed with WHOQOL-BREF – month 4 follow-up: the mean total quality of life in the intervention group was 0.79 SD higher (0.44 higher to 1.14 higher) (moderate effect was defined based on the decision thresholds);
- lower level of psychological distress assessed with GHQ-12 – month 4 follow-up: the mean psychological well-being (lower scores indicate less psychological distress) in the intervention group was 0.49 SD lower (0.68 lower to 0.3 lower) (small effect was defined based on the decision thresholds); and
- higher level of TB drug adherence assessed with number of patients with no missed doses in the past 30 days – month 4 follow-up: (932 vs 559 per 1000); that is, 373 more per 1000 (276 more to 419 more), relative effect (odds ratio [OR]): 10.77 (3.99 to 35.10) (large effect was defined based on the decision thresholds).

Based on the thresholds for the prioritized outcomes, quality of life and TB treatment adherence, the 2025 GDG judged the desirable effects to be moderate. Based on the available evidence, no undesirable health effects were identified.

There was low overall certainty for moderate benefit and, thus, low certainty in the overall effect owing to very severe imprecision (multiple thresholds crossed). If the target for the certainty rating of the desirable effects is a small effect, then there is moderate overall certainty for a small benefit and the resulting small net benefit because of severe imprecision (i.e. no thresholds have been crossed for main outcomes, but the review information size has not been met).

Summary of other evidence

Alcohol consumption was assessed as a categorical outcome, at baseline and follow-up at month 4 of treatment, with proportion of patients who had consumed alcohol in the past month. The intervention group showed less alcohol consumption at the month 4 follow-up (15% vs 40%), relative risk (OR): 0.21 (95% confidence interval [CI]: 0.08–0.51). Two other alcohol-related outcomes – alcohol without food and being invited by others for alcohol in the past month – also showed less alcohol consumption at month 4 in the intervention group receiving palliative care interventions. In addition,

the trial also assessed as an outcome the Client Service Receipt Inventory *(170)* components of care received by patients in the previous month. However, the GDG identified alcohol consumption and Client Service Receipt Inventory as lower priority outcomes for the specific review and assessment of the PICO question.

Evidence to recommendations: considerations

In developing this recommendation, the GDG considered the anticipated benefits, potential harms, certainty of the evidence, feasibility, acceptability, equity implications and resource considerations. The GDG judged that integrating palliative care into TB services is feasible in most settings, including those with limited resources, because many palliative care interventions can be delivered by trained TB health care providers. The approach supports continuity of care and may be particularly relevant in settings with a high burden of DR-TB and TB-related morbidity.

Resources required and cost–effectiveness

The cost of palliative care varies by setting, delivery model and scope of services. Despite this variability, several studies show that palliative care can be cost-effective. One study reported the cost of universal access to the WHO essential package of palliative care in a low-income country (Rwanda) as US$ 219, in a lower-middle-income country (Viet Nam) as US$ 119, and in an upper-middle-income country (Mexico) as US$ 796 *(171)*.

A systematic review identified 10 eligible studies across a range of diseases that reported both palliative care outcomes and economic data in low- and middle-income countries (LMIC) settings. Among those studies, four provided a "true cost–effectiveness analysis", meaning that they compared palliative care with alternative or usual care (no palliative care), and assessed costs relative to outcomes. In those analyses, palliative care was associated with cost savings, favourable palliative outcomes (comfort, satisfaction, symptom relief and quality of life), and positive feedback from patients and families *(172)*.

Direct evidence on cost–effectiveness was not evaluated and reported by the RCT. However, some studies provided indirect evidence on the cost–effectiveness of palliative care. The evidence from five studies conducted in the USA, the United Kingdom of Great Britain and Northern Ireland, Australia and Italy suggests that palliative care can be a cost-effective model compared with usual care *(173)*, given methodological limitations (small sample sizes) that limit generalization of the conclusion. More robust data are needed, ideally from large, well-designed studies that capture a full range of costs and patient-centred outcomes.

Equity, acceptability and feasibility

The recommendation in favour of palliative care interventions is likely to increase access to palliative care for TB patients, including patients with MDR/RR-TB or DS-TB.

Given the lack of research evidence on acceptability, the panel judged nurse-led palliative care as probably acceptable. Palliative care improves symptom management and patient satisfaction, and this intervention supports patient-centred care for those with TB. For trained providers or health care workers, providing palliative care expands the scope of work for nurses or other health care workers who likely require extra training, workload management and compensation.

Despite the lack of research evidence on feasibility, nurse-led palliative care was judged by the panel as probably feasible. The trial also provided information on the feasibility of palliative care interventions being provided in the Ugandan setting, where Hospice Africa Uganda delivered the interventions alongside a strong network of programmatic and clinical care services that allow proper needs assessment and referral of patients to palliative care.

Conclusion

Although there was only one trial in a single country, the balance of the effects generally favoured the intervention based on low and moderate certainty evidence, depending on the target of the certainty rating for the benefits. There is little uncertainty about the values, but there is a moderate cost and concerns about implementability, which led to a conditional recommendation.

Subgroup considerations

There are no restrictions on the use of this intervention across population subgroups, including adults, children and adolescents. Although the recommendation is for patients with MDR/RR-TB, the GDG suggested that individuals with DS-TB be considered eligible if they need palliative care interventions based on needs assessment using the WHO palliative care definition. Considerations related to rights, dignity and access are particularly relevant for people with severe TB disease and complex needs. People with TB may experience substantial physical and psychosocial suffering, stigma and social vulnerability, especially in advanced stages of disease. Integrating palliative care into TB services can help to ensure respectful, compassionate care that responds to individual needs and preferences. Programme implementation should consider equitable access to palliative care interventions, including availability of essential medicines for symptom control, appropriate training of health care providers, and linkage with existing palliative care and social support services. Special attention should be given to vulnerable populations, including children, people with disabilities, and those facing social or economic barriers to care.

Implementation considerations

Capacity-building is essential to ensure high-quality palliative care delivery. This includes the provision of basic palliative care training for relevant health workers, aligned with the WHO model of palliative care.

Implementation of the recommendation requires a proper assessment of each patient's palliative care needs before initiation of TB treatment or during treatment. The package of palliative care interventions, as described in the trial, includes a broad range of social support (e.g. material, educational, psychological or emotional, and spiritual), nutritional support, relief of symptoms such as pain, dyspnoea, diarrhoea and depression using medications (e.g. non-opioid, opioid and oxygen) *(164)*. Selection and provision of palliative care interventions are based on the individual needs identified in the assessment.

Implementation of this recommendation requires careful attention to confidentiality and patient privacy. Individuals should be supported to choose their preferred place of care, whether at a health facility or at home, in line with their needs and circumstances. The GDG noted that there was a risk of stigma when palliative interventions were delivered at home. There may also be cultural differences in delivering and receiving palliative care.

Clinical decision-making regarding the choice and dosing of medicines should consider individual patient factors, including organ function and drug–drug interactions. Health system support and regulatory frameworks play a key role in implementation. Clear regulations are needed to define who is authorized to prescribe palliative care medications and under what conditions. Broader regulatory considerations should also address access to essential medicines. A reliable medicine supply is critical, particularly the consistent availability of pain-relief and symptom-control medications, including controlled medicines such us morphine. Health systems should ensure uninterrupted access to these essential medicines. Additional considerations include strengthening linkages with existing palliative care services and integrating palliative care with social support services where available.

Research gaps

The GDGs (2017, 2022, 2025) discussed research priorities and highlighted several gaps.

The effectiveness of different forms of interventions to improve treatment adherence

- The interventions for patient support and treatment supervision that are best suited to particular populations.
- The interventions for patient support 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 VST in low- and middle-income countries, because the current available data are from high-income countries.
- The types of psychological support that are most appropriate.

Models of care for all people with TB

- Evaluation of the risk of TB transmission in different settings; that is, does treatment centred 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 at least systematically collect – their data.

Models of TB care for children and adolescents

Decentralization of TB services for children and adolescents with signs and symptoms of TB and for children and adolescents exposed to TB

- The cost–effectiveness of decentralization and integration for case detection and provision of TPT.
- The impact of decentralization of services on health equity.
- The acceptability and feasibility of decentralized approaches to child and adolescent TB care for case detection and for TPT provision.

Family-centred, integrated services for children and adolescents with signs and symptoms of TB and for children and adolescents exposed to TB

- A detailed description of currently operating family-centred and integrated services, with associated costs and cost–effectiveness.
- Implementation research on the components of the interventions, and assessment of real-world implementation of the programmes.
- The acceptability and feasibility and of family-centred, integrated and/or decentralized approaches to child and adolescent TB care for case detection and TPT provision in different settings, from the perspectives of the persons with TB, the caregivers and trained providers.
- Costs and catastrophic costs.

- Cost–effectiveness evaluations of family-centred, integrated and/or decentralized approaches, considering currently available resources (note: some models assume that these interventions are built on existing structures that may not be available).
- Outcomes of interest: initiation of TPT; number of additional children and adolescents diagnosed; delay, retention in care, treatment completion, clinical outcomes (such as treatment success); qualitative research related to stigma, mental health outcome, school interruption, equity.
- Evaluation of outcomes of interest using randomized/nonrandomized designs and qualitative designs.
- A baseline needs assessment in the community, community perceptions of TB care and prevention for children and adolescents.
- Research on the quality of TB diagnosis in children – addressing both under-diagnosis and over-diagnosis.

Palliative care for TB patients

- Further research is needed with similar studies but larger sample size to increase certainty of the evidence and to address the current imprecision of the estimate of effect.
- Priority areas include evaluating the impact of palliative care on tuberculosis treatment outcomes, such as cure rates, sputum conversion, and mortality.
- Economic evaluations are also required to assess the cost–effectiveness of integrating palliative care into tuberculosis services.
- Implementation research should examine acceptability and feasibility of palliative care interventions for patients, caregivers, and health workers.
- Research should explore different models of palliative care service delivery, including the involvement of additional provider cadres, and models' performance across diverse geographical settings and contexts with varying tuberculosis burden.
- Further studies are needed to better understand which components of palliative care interventions are critical to achieving meaningful patient and health system outcomes.
- Research should assess the potential risk of transmission of drug-resistant *Mycobacterium tuberculosis* strains within palliative care settings, with particular attention to the safety of caregivers and health workers.

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Annex 1. Summary of recommendations

This annex contains three tables that summarize the recommendations given in these World Health Organization (WHO) consolidated guidelines on the treatment and care of people with tuberculosis (TB):

- Table A1.1 summarizes changes to WHO treatment recommendations for drug-susceptible TB (DS-TB) between 2010 and the 2026 update and consolidation;
- Table A1.2 summarizes changes to WHO treatment recommendations for multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB) between 2019 and the 2026 update and consolidation; and
- Table A1.3 summarizes changes to WHO treatment recommendations for TB care and support between 2011 and the 2025 update and consolidation.

This document – the *WHO consolidated guidelines on tuberculosis. Module 4: treatment and care, second edition* – includes new recommendations developed in 2024–26 and all valid, relevant recommendations that had been previously published. It groups the recommendations as follows:

- recommendations on treatment of DS-TB treatment are grouped in Chapter 1;
- recommendations on treatment of DR-TB treatment are grouped in Chapter 2; and
- recommendations on TB care and support are grouped in Chapter 3.

Table A1.1. Summary of changes to WHO treatment recommendations for DS-TB between 2010 and the update and consolidation in 2026

Treatment of DS-TB using 6-month regimen				
Treatment of tuberculosis: guidelines. Fourth edition, 2010	**Guidelines for treatment of drug-susceptible tuberculosis and patient care. 2017 update**	**WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-susceptible tuberculosis treatment. 2022**	**WHO consolidated guidelines on tuberculosis. Module 4: treatment and care. 2025**	**WHO consolidated guidelines on tuberculosis. Module 4: treatment and care. Second edition, 2026**
Recommendation 1.1 New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR *(Strong recommendation, high certainty of evidence)*	Recommendation 1 (2017) / 1.1 (2025) New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR *(Strong recommendation, high certainty of evidence)*			Recommendation A1.1 New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR. *(Strong recommendation, high certainty of evidence)* ***(Unchanged)***
Recommendation 1.2 The 2HRZE/6HE treatment regimen should be phased out *(Strong recommendation, high certainty of evidence)*	Remained valid	Redundant. The 2HRZE/6HE regimen has not been recommended since 2010 and has been phased out		

Treatment of DS-TB using 6-month regimen			
Recommendation 2.1 Wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy *(Strong recommendation, high certainty of evidence)*	Recommendation 2 (2017) / 2.1 (2025) Wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy *(Strong recommendation, high certainty of evidence)*		Recommendation A1.2 Wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy. *(Strong recommendation, high certainty of evidence)* ***(Unchanged)***
Recommendation 2.1A New patients with pulmonary TB may receive a daily intensive phase followed by a three-times-weekly continuation phase [2HRZE/4$(HR)_3$], provided that each dose is directly observed *(Conditional recommendation, high or moderate certainty of evidence)*	Recommendation 1.3 In all patients with drug-susceptible pulmonary TB, the use of thrice-weekly dosing is not recommended in both the intensive and continuation phases of therapy, and daily dosing remains the recommended dosing frequency *(Conditional recommendation, very low certainty of evidence)*	Recommendation 3 (2022) / 1.3 (2025) In all patients with drug-susceptible pulmonary TB, the use of thrice-weekly dosing is not recommended in both the intensive and continuation phases of therapy, and daily dosing remains the recommended dosing frequency *(Conditional recommendation, very low certainty of evidence)*	Recommendation A1.3 In all patients with drug-susceptible pulmonary TB, the use of thrice-weekly dosing is not recommended in both the intensive and continuation phases of therapy, and daily dosing remains the recommended dosing frequency. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***
Recommendation 2.1B Three-times-weekly dosing throughout therapy [2$(HRZE)_3$/4$(HR)_3$] may be used as another alternative to daily dosing, provided that every dose is directly observed, and the patient is NOT living with HIV or living in an HIV-prevalent setting *(Conditional recommendation, high or moderate certainty of evidence)*			

Treatment of DS-TB using 6-month regimen			
Not included	(Recommendation 1.2) The use of FDC tablets is recommended over separate drug formulations in the treatment of patients with drug-susceptible TB *(Conditional recommendation, low certainty of evidence)*	Recommendation 4 (2022) / 1.4 (2025) The use of fixed-dose combination tablets is recommended over separate drug formulations in treatment of patients with drug-susceptible TB *(Conditional recommendation, low certainty of evidence)*	Recommendation A1.4 The use of fixed-dose combination tablets is recommended over separate drug formulations in treatment of patients with drug-susceptible TB. *(Conditional recommendation, low certainty of evidence)* ***(Unchanged)***
Recommendation 2.2 New patients with TB should not receive twice-weekly dosing for the full course of treatment unless this is done in the context of formal research *(Strong recommendation, high certainty of evidence)*	Remained valid	Redundant All treatment of DS-TB is daily as stated in recommendations 2 and 3.	
Recommendation 3 In populations with known or suspected high levels of isoniazid resistance, new TB patients may receive HRE as therapy in the continuation phase as an acceptable alternative to HR *(Conditional recommendation, insufficient evidence, expert opinion based)*	Remained valid	Redundant New policy on treatment of isoniazid-resistant TB in consolidated guidelines on DR-TB treatment 2020. *(3)*	

Treatment of DS-TB using 6-month regimen		
Recommendation 5.1 For smear-positive pulmonary TB patients treated with first-line drugs, sputum smear microscopy may be performed at completion of the intensive phase of treatment *(Conditional recommendation, high or moderate certainty of evidence)*	Remained valid	Redundant Recommendation was based on evidence derived from studies using 6-month regimens. Bacteriological monitoring of DS-TB treatment is included in the WHO operational handbook.
Recommendation 5.2 In new patients, if the specimen obtained at the end of the intensive phase (month 2) is smear-positive, sputum smear microscopy should optimally be obtained at the end of the month 3 *(Strong recommendation, high certainty of evidence)*	Remained valid	Redundant Recommendation was based on evidence derived from studies using 6-month regimens. Bacteriological monitoring of DS-TB treatment is included in the WHO operational handbook.
Recommendation 5.3 In new patients, if the specimen obtained at the end of month 3 is smear-positive, sputum culture and drug susceptibility testing (DST) should be performed *(Strong recommendation, high certainty of evidence)*	Remained valid	Redundant Rapid molecular tests are recommended for use as initial tests for TB and for rifampicin-resistance in people with symptoms of TB, without or with prior history of TB. Bacteriological monitoring of DS-TB treatment is included in the WHO operational handbook.

Treatment of DS-TB using 6-month regimen			
Recommendation 5.4 In previously treated patients, if the specimen obtained at the end of the intensive phase (month 3) is smear-positive, sputum culture and drug susceptibility testing (DST) should be performed *(Strong recommendation, high certainty of evidence)*	Remained valid	Redundant Rapid molecular tests are recommended for use as initial tests for TB and for rifampicin-resistance in people with symptoms of TB, without or with prior history of TB. Bacteriological monitoring of DS-TB treatment is included in the WHO operational handbook.	
Recommendation 6 In new pulmonary TB patients treated with the regimen containing rifampicin throughout treatment, if a positive sputum smear is found at completion of the intensive phase, the extension of the intensive phase is not recommended *(Strong recommendation, high certainty of evidence)*	Recommendation remains valid for 6-month regimens due to evidence used for review. Extension of the 4-month regimens is not part of pertinent recommendations Recommendation 5 (2017) / 1.5 (2025) In new pulmonary TB patients treated with the regimen containing rifampicin throughout treatment, if a positive sputum smear is found at completion of the intensive phase, the extension of the intensive phase is not recommended *(Strong recommendation, high certainty of evidence)*		Recommendation A1.5 In new pulmonary TB patients treated with the regimen containing rifampicin throughout treatment, if a positive sputum smear is found at completion of the intensive phase, the extension of the intensive phase is not recommended. *(Strong recommendation, high certainty of evidence)* ***(Unchanged)***

Treatment of DS-TB using 6-month regimen		
Recommendation 7.1 Specimens for culture and drug-susceptibility testing should be obtained from all previously treated TB patients at or before the start of treatment. Drug-susceptibility testing should be performed for at least isoniazid and rifampicin *(Based on expert opinion)*	Remained valid	Expert opinion has been changing over time influenced by new evidence, experience and changing policies. Therefore, if not redundant and still relevant these statements are featured in the WHO operational handbook.
Recommendation 7.2 In settings where rapid molecular-based drug susceptibility testing is available, the results should guide the choice of regimen *(Based on expert opinion)*	Remained valid	Expert opinion has been changing over time influenced by new evidence, experience and changing policies. Therefore, if not redundant and still relevant these statements are featured in the WHO operational handbook.
Recommendation 7.3.1 In settings where rapid molecular-based drug susceptibility testing results are not routinely available to guide the management of individual patients, TB patients whose treatment has failed or other patient groups with high likelihood of MDR-TB should be started on an empirical MDR regimen *(Based on expert opinion)*	Remained valid	Expert opinion has been changing over time influenced by new evidence, experience and changing policies. Therefore, if not redundant and still relevant these statements are featured in the WHO operational handbook.

Treatment of DS-TB using 6-month regimen		
Recommendation 7.3.2 In settings where rapid molecular-based drug susceptibility testing results are not routinely available to guide the management of individual patients, TB patients returning after defaulting or relapsing from their first treatment course may receive the retreatment regimen containing first-line drugs 2HRZES/1HRZE/5HRE if country-specific data show low or medium levels of MDR in these patients or if such data are unavailable *(Expert opinion based)*	Recommendation 1.7 In patients who require TB retreatment, the Category II regimen should no longer be prescribed, and drug-susceptibility testing should be conducted to inform the choice of treatment regimen *(Good practice statement)*	2017 good practice statement included in the operational handbook
Recommendation 7.4 In settings where drug-susceptibility testing results are not yet routinely available to guide the management of individual patients, the empirical regimens will continue throughout the course of treatment *(Based on expert opinion)*	Remained valid	Expert opinion has been changing over time influenced by new evidence, experience and changing policies. Therefore, if not redundant and still relevant these statements are featured in the WHO operational handbook.
Recommendation 7.5 National TB control programmes should obtain and use their country-specific drug resistance data on failure, relapse and loss to follow-up of patient groups to determine the levels of MDR-TB *(Based on expert opinion)*	Remained valid	Expert opinion has been changing over time influenced by new evidence, experience and changing policies. Therefore, if not redundant and still relevant these statements are featured in the WHO operational handbook.

Treatment of DS-TB using 6-month regimen				
	Rapid advice: treatment of tuberculosis in children. 2010	**Guidance for national tuberculosis programmes on the management of tuberculosis in children. Second edition, 2014**	**WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents. 2022**	
	Recommendation 3 Children with suspected or confirmed pulmonary tuberculosis or tuberculous peripheral lymphadenitis who live in settings with low HIV prevalence or low resistance to isoniazid and children who are HIV-negative can be treated with a three-drug regimen (HRZ) for 2 months followed by a two-drug (HR) regimen for 4 months at the following dosages: isoniazid (H) – 10 mg/kg (range 10–15 mg/kg); maximum dose 300 mg/day rifampicin (R) – 15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/day pyrazinamide (Z) – 35 mg/kg (30–40 mg/kg) *(Strong recommendation, moderate-quality evidence)*	Recommendation 9 Children with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis who live in settings with low HIV prevalence and/or low prevalence of isoniazid resistance1 and children who are HIV-negative, can be treated with a three-drug regimen (HRZ) for 2 months followed by a two-drug (HR) regimen for 4 months at the dosages specified in Recommendation 8 *(Strong recommendation, moderate certainty of evidence)*	Children with pulmonary TB or tuberculous peripheral lymphadenitis who live in settings with low HIV prevalence and/or low prevalence of isoniazid resistance and children who are HIV- negative, can be treated with a three-drug regimen (HRZ) for 2 months followed by a two-drug (HR) regimen for 4 months at standard dosages. *(Strong recommendation, moderate certainty of evidence)*	Recommendation A1.6a Children with pulmonary TB or tuberculous peripheral lymphadenitis who live in settings with low HIV prevalence and/or low prevalence of isoniazid resistance and children who are HIV-negative, can be treated with a three-drug regimen (HRZ) for 2 months followed by a two-drug (HR) regimen for 4 months at standard dosages. *(Strong recommendation, moderate certainty of evidence)* ***(Unchanged)***

Treatment of DS-TB using 6-month regimen				
	Recommendation 2 Children living in settings where the prevalence of the HIV is high or where resistance to isoniazid is high, or both, with suspected or confirmed pulmonary tuberculosis or peripheral lymphadenitis; or children with extensive pulmonary disease living in settings of low HIV prevalence or low isoniazid resistance, should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 4 months at the following dosages: isoniazid (H) – 10 mg/kg (range 10–15 mg/kg); maximum dose 300 mg/day rifampicin (R) – 15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/day pyrazinamide (Z) – 35 mg/kg (30–40 mg/kg) ethambutol (E) – 20 mg/kg (15–25 mg/kg) *(Strong recommendation, moderate-quality evidence)*	Recommendation 10 Children with suspected or confirmed pulmonary TB or tuberculosis peripheral lymphadenitis and/or children with extensive pulmonary disease, living in settings where the prevalence of HIV is high and/or the prevalence of isoniazid resistance is high2 should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 4 months at the dosages specified in Recommendation 8 *(Strong recommendation, moderate certainty of evidence)*	Children and adolescents with severe pulmonary disease should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 4 months at standard dosages. *(Strong recommendation, moderate certainty of evidence)*	Recommendation A1.6b Children and adolescents with severe pulmonary disease should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 4 months at standard dosages. *(Strong recommendation, moderate certainty of evidence)* ***(Unchanged)***

Treatment of DS-TB using 6-month regimen				
	Recommendation 6 Infants (aged 0–3 months) with suspected or confirmed pulmonary tuberculosis or tuberculous peripheral lymphadenitis should be promptly treated with the standard treatment regimens, as described above. *(Strong recommendation, low certainty evidence)* Remarks Treatment may require adjustment of dosages to reconcile the effect of age and possible toxicity in young infants. The decision to adjust dosages should be taken by a clinician experienced in managing paediatric tuberculosis.	Recommendation 11 Infants aged 0–3 months with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis should be promptly treated with the standard treatment regimens, as described in recommendation 9 or 10. Treatment may require dose adjustment to reconcile the effect of age and possible toxicity in young infants. The decision to adjust doses should be taken by a clinician experienced in managing paediatric TB *(Strong recommendation, low certainty of evidence)*	Infants aged 0–3 months with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis should be promptly treated with the 6-month treatment regimen (2HRZ(E)/4HR). Treatment may require dose adjustment to reconcile the effect of age and possible toxicity in young infants. The decision to adjust doses should be taken by a clinician experienced in managing paediatric TB. *(Strong recommendation, low certainty of evidence)*	Recommendation A1.6c Infants aged 0–3 months with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis should be promptly treated with the 6-month treatment regimen (2HRZ(E)/4HR). Treatment may require dose adjustment to reconcile the effect of age and possible toxicity in young infants. The decision to adjust doses should be taken by a clinician experienced in managing paediatric TB. *(Strong recommendation, low certainty of evidence)* ***(Unchanged)***
	Recommendation 7 (2010)/13 (2014) Streptomycin should not be used as part of first-line treatment regimens for children with pulmonary tuberculosis or tuberculous peripheral lymphadenitis. *(Strong recommendation, moderate-quality evidence)*			Redundant No injectable medicines are used in the treatment of DS-TB

Treatment of DS-TB using 4-month regimens			
Not included	Recommendation 1.1 In patients with drug-susceptible pulmonary TB, 4-month fluoroquinolone-containing regimens should not be used and the 6-month rifampicin-based regimen 2HRZE/4HR remains the recommended regimen *(Strong recommendation, moderate certainty of evidence)*	Recommendation 6 (2022) / 2.1 (2025) People aged 12 years or older with drug-susceptible pulmonary TB, may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide *(Conditional recommendation, moderate certainty of evidence)*	Recommendation A2.1 People aged 12 years or older with drug-susceptible pulmonary TB, may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide. *(Conditional recommendation, moderate certainty of evidence)* ***(Unchanged)***
Not included	Not included	Recommendation 7 (2022) / 2.2 (2025) In children and adolescents between 3 months and 16 years of age with non-severe TB (without suspicion or evidence of MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used *(Strong recommendation, moderate certainty of evidence)*	Recommendation A2.2 In children and adolescents between 3 months and 16 years of age with non-severe TB (without suspicion or evidence of MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used. *(Strong recommendation, moderate certainty of evidence)* ***(Unchanged)***

DS-TB treatment and ART in people living with HIV		
Recommendation 4.1 TB patients with known positive HIV status and all TB patients living in HIV-prevalent settings should receive daily TB treatment at least during the intensive phase *(Strong recommendation, high certainty of evidence)* (recommendation 4.2) For the continuation phase, the optimal dosing frequency is also daily for these patients *(Strong recommendation, high certainty of evidence)* (recommendation 4.3) If a daily continuation phase is not possible for these patients, three times weekly dosing during the continuation phase is an acceptable alternative *(Conditional recommendation, high or moderate certainty of evidence)*	Redundant	Redundant Dosing frequency is daily in all TB treatment regimens.
WHO's policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders. **2012 *(4)***		

DS-TB treatment and ART in people living with HIV		
Recommendation B1.3 TB patients with known positive HIV status and TB patients living in HIV-prevalent settings should receive at least 6 months of rifampicin-containing treatment regimen *(Strong recommendation, high certainty of evidence)* The optimal dosing frequency is daily during the intensive and continuation phases *(Strong recommendation, high certainty of evidence)*	Remained valid	Redundant 4-month regimens for DS-TB treatment are non-inferior to 6-month regimen in TB patients living with HIV. Dosing frequency is daily in all TB treatment regimens.
Recommendation 4.4 It is recommended that TB patients who are living with HIV should receive at least the same duration of TB treatment as HIV-negative TB patients *(Strong recommendation, high certainty of evidence)*	Recommendation 8 (2017) / 3.1 (2025) It is recommended that TB patients who are living with HIV should receive at least the same duration of daily TB treatment as HIV-negative TB patients *(Strong recommendation, high certainty of evidence)*	Recommendation A3.1 It is recommended that TB patients who are living with HIV should receive at least the same duration of daily TB treatment as HIV-negative TB patients. *(Strong recommendation, high certainty of evidence)* ***(Unchanged)***

DS-TB treatment and ART in people living with HIV		
Not included	Recommendation 1.5 In patients with drug-susceptible pulmonary TB who are living with HIV and receiving antiretroviral therapy during TB treatment, a 6-months standard treatment regimen is recommended over an extended treatment for 8 months or longer *(Conditional recommendation, very low certainty of evidence)*	Redundant No recommended treatment regimens for DS-TB treatment exceed 6 months duration. 4-month regimens for DS-TB treatment are non-inferior to 6-month regimen in TB patients living with HIV.
Consolidated guidelines on the use of antiretroviral drugs 2016 *(5)*		

DS-TB treatment and ART in people living with HIV			
HIV antiretroviral medications should be started in all TB patients living with HIV regardless of their CD4 cell count *(Strong recommendation, high certainty of evidence)*	Recommendation 1.4.1 ART should be started in all TB patients living with HIV regardless of their CD4 cell count *(Strong recommendation, high certainty of evidence)*	Recommendation 9 (2022) / 3.2 (2025) ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV. Adults and adolescents *(Strong recommendation, low to moderate certainty of evidence);* Children and infants *(Strong recommendation, very low certainty of evidence)*	Recommendation A3.2 ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV. Adults and adolescents *(Strong recommendation, low to moderate certainty of evidence)*; Children and infants *(Strong recommendation, very low certainty of evidence)* ***(Unchanged)***
TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment *(Strong recommendation, high certainty of evidence)*	Recommendation 1.4.2 TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment *(Strong recommendation, high certainty of evidence)*		
HIV-positive TB patients with profound immunosuppression (e.g. CD4 cell counts less than 50 cells/mm^3) should receive ART within the first 2 weeks of initiating TB treatment *(Based on expert opinion)*	HIV-positive patients with profound immunosuppression (e.g. CD4 cell counts less than 50 cells/mm^3) should receive ART within the first 2 weeks of initiating TB treatment.		

The use of adjuvant steroids in the treatment of TB meningitis and pericarditis		
Not included	Recommendation 1.6.1 (2017) / 10 (2022) / 4.1 (2025) In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks should be used *(Strong recommendation, moderate certainty of evidence)*	Recommendation A4.1 In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks should be used. *(Strong recommendation, moderate certainty of evidence)* ***(Unchanged)***
Not included	Recommendation 1.6.2 (2017) / 11 (2022) / 4.2 (2025) In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used *(Conditional recommendation, very low certainty of evidence)*	Recommendation A4.2 In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***
Treatment regimens for extrapulmonary TB in children and adolescents		
	Rapid advice: treatment of tuberculosis in children. 2010	**Guidance for national tuberculosis programmes on the management of tuberculosis in children.** **Second edition, 2014**

Treatment regimens for extrapulmonary TB in children and adolescents				
	Recommendation 8 Children with suspected or confirmed tuberculous meningitis should be treated with a four-drug regimen (HRZE) for 2 months, followed by a two-drug regimen (HR) for 10 months; the total duration of treatment being 12 months. The dosages recommended for the treatment of tuberculous meningitis are the same as those described for pulmonary tuberculosis. *(Strong recommendation, low certainty evidence)*	Recommendation 14 Children with suspected or confirmed tuberculous meningitis and children with suspected or confirmed osteoarticular TB should be treated with a four-drug regimen (HRZE) for 2 months, followed by a two-drug regimen (HR) for 10 months, the total duration of treatment being 12 months. The doses recommended for the treatment of tuberculous meningitis are the same as those described for pulmonary TB *(Strong recommendation, low certainty of evidence)*	Children with suspected or confirmed tuberculous meningitis should be treated with a four-drug regimen (HRZE) for 2 months, followed by a two-drug regimen (HR) for 10 months. The total duration of treatment should be 12 months. *(Strong recommendation, low certainty of evidence)*	Recommendation A5.1 Children with suspected or confirmed tuberculous meningitis or osteoarticular tuberculosis should be treated with a four-drug regimen (HRZE) for 2 months, followed by a two-drug regimen (HR) for 10 months. The total duration of treatment should be 12 months. *(Strong recommendation, low certainty of evidence)* ***(Unchanged)***
	Recommendation 9 Children with suspected or confirmed osteoarticular tuberculosis should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 10 months; the total duration of treatment being 12 months. The doses recommended for the treatment of osteoarticular tuberculosis are the same as those described for pulmonary tuberculosis. *(Strong recommendation, low certainty of evidence)*		Children with suspected or confirmed osteoarticular TB should be treated with a four-drug regimen (HRZE) for 2 months, followed by a two-drug regimen (HR) for 10 months, the total duration of treatment being 12 months. *(Strong recommendation, low certainty of evidence)*	

Treatment regimens for extrapulmonary TB in children and adolescents			
		Recommendation 5.2 In children and adolescents with bacteriologically confirmed or clinically diagnosed TB meningitis (without suspicion or evidence of MDR/RR-TB), a 6-month intensive regimen (6HRZEto) may be used as an alternative option to the 12-month regimen (2HRZE/10HR) *(Conditional recommendation, very low certainty of evidence)*	Recommendation A5.2 In children and adolescents with bacteriologically confirmed or clinically diagnosed TB meningitis (without suspicion or evidence of MDR/RR-TB), a 6-month intensive regimen (6HRZEto) may be used as an alternative option to the 12-month regimen (2HRZE/10HR). *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***

ART: antiretroviral therapy; DR-TB: drug-resistant TB; DS-TB: drug-susceptible TB; DST: drug-susceptibility testing; E: ethambutol; FDC: fixed-dose combination; H: isoniazid; HIV: human immunodeficiency virus; M: moxifloxacin; MDR-TB: multidrug-resistant TB; MDR/RR-TB: multidrug- or rifampicin-resistant TB; P: rifapentine; R: rifampicin; RR-TB: rifampicin-resistant TB; TB: tuberculosis; WHO: World Health Organization; Z: pyrazinamide.

Table A1.2. Summary of changes to the WHO treatment recommendations for MDR/RR-TB between 2019 and the 2026 update and consolidation

WHO consolidated guidelines on drug-resistant tuberculosis treatment 2019	WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment. 2020	WHO consolidated guidelines on tuberculosis. Module 4: treatment–drug-resistant tuberculosis treatment. 2022	WHO consolidated guidelines on tuberculosis. Module 4: treatment and care. 2025	WHO consolidated guidelines on tuberculosis. Module 4: treatment and care. Second edition, 2026
The 6-month BPaL/M/C regimen				
Not included	Recommendation 4.1 A treatment regimen lasting 6–9 months, composed of bedaquiline, pretomanid and linezolid (BPaL), may be used under operational research conditions in multidrug-resistant tuberculosis (MDR-TB) patients with TB that is resistant to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for no more than 2 weeks. *(Conditional recommendation, very low certainty of evidence)*	Recommendation 1.1 WHO suggests the use of the 6-month treatment regimen, composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM), rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients. *(Conditional recommendation, very low certainty of evidence)*		Recommendation B1.1 WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) rather than the 9-month or longer (18-month) regimens in MDR/RR-TB patients. *(Conditional recommendation, very low certainty of evidence)* ***(UPDATED)***

The 6-month BPaL/M/C regimen	
	Recommendation B1.1a WHO suggests the use of a 6-month regimen composed of bedaquiline, pretomanid and linezolid (BPaL) in patients with non-severe* pulmonary pre-XDR-TB rather than the BPaLC regimen. *(Conditional recommendation, very low certainty of evidence)* ***(NEW)***
	Recommendation B1.1b WHO suggests the use of a 6-month regimen composed of bedaquiline, pretomanid, linezolid, and clofazimine (BPaLC) in patients with severe* pulmonary pre-XDR-TB rather than the BPaL regimen. *(Conditional recommendation, very low certainty of evidence)* ***(NEW)***

The 6-month bedaquiline, delamanid, linezolid, levofloxacin and clofazimine (BDLLfx/C) regimen				
Not included	Not included	Not included	Recommendation 1.2 WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, delamanid, linezolid (600 mg), levofloxacin, and clofazimine (BDLLfxC) in MDR/RR-TB patients with or without fluoroquinolone resistance. *(Conditional recommendation, very low certainty of evidence)*	Recommendation B1.2 WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, delamanid, linezolid, levofloxacin, and clofazimine (BDLLfx/C) in MDR/RR-TB patients with or without fluoroquinolone resistance. *(Conditional recommendation, very low certainty of evidence)* ***(UPDATED)***
				Recommendation B1.2a WHO suggests the use of a 6-month BDLC regimen in patients with non-severe pulmonary pre-XDR-TB over the currently recommended longer (18 months or longer) regimens. *(Conditional recommendation, very low certainty of evidence)* ***(NEW)***

The 6-month bedaquiline, delamanid, linezolid, levofloxacin and clofazimine (BDLLfx/C) regimen	
	Recommendation B1.2b WHO suggests against using the 6-month BDLC regimen in patients with severe pulmonary pre-XDR-TB compared to the currently recommended longer regimens (18 months or longer). *(Conditional recommendation, very low certainty of evidence)* ***(NEW)***

The 9-month all-oral regimen for MDR/RR-TB			
In MDR/RR-TB patients who have not been previously treated for more than 1 month with second-line medicines used in the shorter MDR-TB regimen or in whom resistance to fluoroquinolones and second-line injectable agents has been excluded, a shorter MDR-TB regimen of 9–12 months may be used instead of the longer regimens. *(Conditional recommendation, low certainty of evidence)*	Recommendation 2.1 A shorter all-oral bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded. *(Conditional recommendation, very low certainty of evidence)*	WHO suggests the use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded *(Conditional recommendation, very low certainty of evidence)*	Recommendation B2.1 WHO suggests the use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***

The modified 9-month all-oral regimens for MDR/RR-TB				
Not included	Not included	Not included	Recommendation 2.2 WHO suggests using the 9-month all-oral regimens (BLMZ, BLLfxCZ and BDLLfxZ) over currently recommended longer (>18 months) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. Amongst these regimens, using BLMZ is suggested over using BLLfxCZ, and BLLfxCZ is suggested over BDLLfxZ. *(Conditional recommendation, very low certainty of evidence)*	Recommendation B2.2 WHO suggests using the 9-month all-oral regimens (BLMZ, BLLfxCZ and BDLLfxZ) over currently recommended longer (>18 months) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. Amongst these regimens, using BLMZ is suggested over using BLLfxCZ, and BLLfxCZ is suggested over BDLLfxZ. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***

The modified 9-month all-oral regimens for MDR/RR-TB			
		Recommendation 2.3 WHO suggests against using 9-month DCLLfxZ or DCMZ regimen compared with currently recommended longer (>18 months) regimens in patients with fluoroquinolone-susceptible MDR/RR-TB *(Conditional recommendation, very low certainty of evidence)*	Recommendation B2.3 WHO suggests against using 9-month DCLLfxZ or DCMZ regimen compared with currently recommended longer (>18 months) regimens in patients with fluoroquinolone-susceptible MDR/RR-TB. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***
		WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents. 2022	
		Recommendation 5.3.1 In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used *(Conditional recommendation, very low certainty of evidence)*	Recommendation B2.4 In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***

Treatment of drug-resistant TB using longer regimens		
In MDR/RR-TB patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of the treatment after bedaquiline is stopped.[78] If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. *(Conditional recommendation, very low certainty of evidence)*	In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. *(Conditional recommendation, very low certainty of evidence)* (Editing of the word "after" to "if" with reference to stopping bedaquiline)	Recommendation B3.1 In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of the treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***

[78] Group A = levofloxacin/moxifloxacin, bedaquiline, linezolid; Group B = clofazimine, cycloserine/terizidone; Group C = ethambutol, delamanid, pyrazinamide, imipenem–cilastatin, meropenem, amikacin (streptomycin), ethionamide/prothionamide, *p*-aminosalicylic acid (see also Table 3.1).

Treatment of drug-resistant TB using longer regimens		
Kanamycin and capreomycin are not to be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*	Kanamycin and capreomycin are not to be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*	Recommendation B3.2 Kanamycin and capreomycin are not to be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***
Levofloxacin or moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)*	Levofloxacin or moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)*	Recommendation B3.3 Levofloxacin or moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)* ***(Unchanged)***

Treatment of drug-resistant TB using longer regimens			
Bedaquiline should be included in longer MDR-TB regimens for patients aged 18 years or more. *(Strong recommendation, moderate certainty of evidence)* Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years. *(Conditional recommendation, very low certainty of evidence)*	Recommendation 3.4 Bedaquiline should be included in longer multidrug-resistant TB (MDR-TB) regimens for patients aged 18 years or more. *(Strong recommendation, moderate certainty certainty of evidence)* Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years. *(Conditional recommendation, very low certainty of evidence)*	Bedaquiline should be included in longer multidrug-resistant TB (MDR-TB) regimens for patients aged 18 years or more. *(Strong recommendation, moderate certainty of evidence)* Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years. *(Conditional recommendation, very low certainty of evidence)* In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used. *(Conditional recommendation, very low certainty of evidence)*	Recommendation B3.4 Bedaquiline should be included in longer multidrug-resistant TB (MDR-TB) regimens for patients aged 18 years or more. *(Strong recommendation, moderate certainty of evidence)* ***(Unchanged)*** Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)*** In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***

Treatment of drug-resistant TB using longer regimens		
Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)*	Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)*	Recommendation B3.5 Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)* ***(Unchanged)***
Clofazimine and cycloserine or terizidone may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*	Clofazimine and cycloserine or terizidone may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*	Recommendation B3.6 Clofazimine and cycloserine or terizidone may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***
Ethambutol may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low of evidence)*	Ethambutol may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*	Recommendation B3.7 Ethambutol may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***

Treatment of drug-resistant TB using longer regimens			
Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens. *(Conditional recommendation, moderate certainty of evidence)*	Recommendation 3.8 Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens. *(Conditional recommendation, moderate certainty of evidence)*	Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens. *(Conditional recommendation, moderate certainty of evidence)* In children with MDR/RR-TB aged below 3 years delamanid may be used as part of longer regimens. *(Conditional recommendation, very low certainty of evidence)*	Recommendation B3.8 Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens. *(Conditional recommendation, moderate certainty of evidence)* ***(Unchanged)*** In children with MDR/RR-TB aged below 3 years delamanid may be used as part of longer regimens. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***
Pyrazinamide may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*	Pyrazinamide may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*		Recommendation B3.9 Pyrazinamide may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***

Treatment of drug-resistant TB using longer regimens		
Imipenem–cilastatin or meropenem may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*	Imipenem–cilastatin or meropenem may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*[79]	Recommendation B3.10 Imipenem–cilastatin or meropenem may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*[1] ***(Unchanged)***
Amikacin may be included in the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions. *(Conditional recommendation, very low certainty of evidence)*	Amikacin may be included in the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions. *(Conditional recommendation, very low certainty of evidence)*	Recommendation B3.11 Amikacin may be included in the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***

Treatment of drug-resistant TB using longer regimens		
Ethionamide or prothionamide may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. *(Conditional recommendation, very low certainty of evidence)*	Ethionamide or prothionamide may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. *(Conditional recommendation, very low certainty of evidence)*	Recommendation B3.12 Ethionamide or prothionamide may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***
P-aminosalicylic acid may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used or if better options to compose a regimen are not possible. *(Conditional recommendation, very low certainty of evidence)*	*P*-aminosalicylic acid may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. *(Conditional recommendation, very low certainty of evidence)*	Recommendation B3.13 *P*-aminosalicylic acid may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***

Treatment of drug-resistant TB using longer regimens		
Clavulanic acid should not be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, low certainty of evidence)*[79]	Clavulanic acid should not be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, low certainty of evidence)*[79]	Recommendation B3.14 Clavulanic acid should not be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, low certainty of evidence)*[1] ***(Unchanged)***
In MDR/RR-TB patients on longer regimens, a total treatment duration of 18–20 months is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)*	In MDR/RR-TB patients on longer regimens, a total treatment duration of 18–20 months is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)* *(No change to wording but combined with section above called: Section 3: Recommendations on the use of longer regimens for multidrug-/ rifampicin-resistant tuberculosis)*	Recommendation B3.15 In MDR/RR-TB patients on longer regimens, a total treatment duration of 18–20 months is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***

[79] Imipenem–cilastatin and meropenem are administered with clavulanic acid, which is available only in formulations combined with amoxicillin (amoxicillin–clavulanic acid). When included, clavulanic acid is not counted as an additional effective TB agent and should not be used without imipenem–cilastatin or meropenem.

Treatment of drug-resistant TB using longer regimens		
In MDR/RR-TB patients on longer regimens, a treatment duration of 15–17 months after culture conversion is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)*	In MDR/RR-TB patients on longer regimens, a treatment duration of 15–17 months after culture conversion is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)* *(No change to wording but combined with section above called: Section 3: Recommendations on the use of longer regimens for multidrug-/ rifampicin-resistant tuberculosis)*	Recommendation B3.16 In MDR/RR-TB patients on longer regimens, a treatment duration of 15–17 months after culture conversion is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***
In MDR/RR-TB patients on longer regimens that contain amikacin or streptomycin, an intensive phase of 6–7 months is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)*	In MDR/RR-TB patients on longer regimens containing amikacin or streptomycin, an intensive phase of 6–7 months is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)* *(No substantive change to wording but combined with section above called: Section 2.2: Recommendations on the use of longer regimens for multidrug-/ rifampicin-resistant tuberculosis)*	Recommendation B3.17 In MDR/RR-TB patients on longer regimens containing amikacin or streptomycin, an intensive phase of 6–7 months is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***

Treatment of rifampicin-susceptible and isoniazid-resistant tuberculosis		
In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months. *(Conditional recommendation, very low certainty of evidence)*	In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis (Hr-TB), treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months. *(Conditional recommendation, very low certainty of evidence)*	Recommendation B4.1 In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis (Hr-TB), treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***
In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen. *(Conditional recommendation, very low certainty of evidence)*	In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen. *(Conditional recommendation, very low certainty of evidence)*	Recommendation B4.2 In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***

Monitoring and management strategies for MDR/RR-TB treatment		
In MDR/RR-TB patients on longer regimens, the performance of sputum culture in addition to sputum smear microscopy is recommended to monitor treatment response. It is desirable for sputum culture to be repeated at monthly intervals. *(Strong recommendation, moderate certainty in the estimates of test accuracy)*	In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, the performance of sputum culture in addition to sputum smear microscopy is recommended to monitor treatment response. *(Strong recommendation, moderate certainty in the estimates of test accuracy)* It is desirable for sputum culture to be repeated at monthly intervals.	Recommendation B5.1 In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, the performance of sputum culture in addition to sputum smear microscopy is recommended to monitor treatment response. *(Strong recommendation, moderate certainty in the estimates of test accuracy)* It is desirable for sputum culture to be repeated at monthly intervals. ***(Unchanged)***

Starting antiretroviral therapy in patients on MDR/RR-TB regimens		
Antiretroviral therapy is recommended for all patients with HIV and DR-TB requiring second-line antituberculosis drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of antituberculosis treatment. *(Strong recommendation, very low-certainty of evidence)*	Antiretroviral therapy is recommended for all patients with HIV and drug-resistant tuberculosis requiring second-line antituberculosis drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of antituberculosis treatment. *(Strong recommendation, very low certainty of evidence)*	Recommendation B6.1 Antiretroviral therapy is recommended for all patients with HIV and drug-resistant tuberculosis requiring second-line antituberculosis drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of antituberculosis treatment. *(Strong recommendation, very low certainty of evidence)* ***(Unchanged)***
Surgery for patients on MDR/RR-TB treatment		
In patients with RR-TB or MDR-TB, elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen. *(Conditional recommendation, very low certainty of evidence)*	In patients with rifampicin-resistant tuberculosis (RR-TB) or multidrug-resistant TB (MDR-TB), elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen. *(Conditional recommendation, very low certainty of evidence)*	Recommendation B7.1 In patients with rifampicin-resistant tuberculosis (RR-TB) or multidrug-resistant TB (MDR-TB), elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***

(HCV) and MDR/RR-TB treatment co-administration				
Not included	*Not included*	*Not included*	Recommendation 8.1 In patients with MDR/RR-TB and HCV co-infection, the WHO suggests the co-administration of HCV and TB treatment over delaying HCV treatment until after treatment of MDR/RR-TB is completed. *(Conditional recommendation, very low certainty of evidence)*	Recommendation B8.1 In patients with MDR/RR-TB and HCV co-infection, WHO suggests the co-administration of HCV and TB treatment over delaying HCV treatment until after treatment of MDR/RR-TB is completed. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***

B: bedaquiline; C: clofazimine; D: delamanid; DR-TB: drug-resistant TB; HCV: hepatitis C virus; HIV: human immunodeficiency virus; Hr-TB: rifampicin-susceptible, isoniazid-resistant TB; L: linezolid; Lfx: levofloxacin; M: moxifloxacin; MDR-TB: multidrug-resistant TB; Pa: pretomanid; pre-XDR-TB: pre-extensively drug-resistant TB; RR-TB: rifampicin-resistant TB; TB: tuberculosis; WHO: World Health Organization; Z: pyrazinamide.

Table A1.3. Summary of changes to the WHO treatment recommendations for TB care and support between 2011 and the update and consolidation in 2025

Guidelines for the programmatic management of drug-resistant tuberculosis. 2011	Guidelines for treatment of drug-susceptible tuberculosis and patient care. 2017 update	WHO consolidated guidelines on tuberculosis. Module 4: treatment – tuberculosis care and support. 2022	WHO consolidated guidelines on tuberculosis. Module 4: treatment and care. 2025	WHO consolidated guidelines on tuberculosis. Module 4: treatment and care. Second edition, 2026
Care and support interventions for all people with TB				
Not included	Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment *(Strong recommendation, moderate certainty of evidence)*			Recommendation C1.1 Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment. *(Strong recommendation, moderate certainty of evidence)* ***(Unchanged)***
	A package of treatment adherence interventions may be offered to patients on TB treatment in conjunction with the selection of a suitable treatment administration option *(Conditional recommendation, low certainty of evidence)*			Recommendation C1.2 A package of treatment adherence interventions may be offered to patients on TB treatment in conjunction with the selection of a suitable treatment administration option. *(Conditional recommendation, low certainty of evidence)* ***(Unchanged)***

Care and support interventions for all people with TB		
	One or more of the following treatment adherence interventions (complementary and not mutually exclusive) may be offered to patients on TB treatment or to health-care providers: a. tracers or digital medication monitor *(Conditional recommendation, very low certainty of evidence)* b. material support to patient *(Conditional recommendation, moderate certainty of evidence);* c. psychological support to patient *(Conditional recommendation, low certainty of evidence);* d. staff education *(Conditional recommendation, low certainty of evidence)*	Recommendation C1.3 One or more of the following treatment adherence interventions (complementary and not mutually exclusive) may be offered to patients on TB treatment or to health care providers: tracers or digital medication monitor *(Conditional recommendation, very low certainty of evidence);* material support to patient *(Conditional recommendation, moderate certainty of evidence);* psychological support to patient *(Conditional recommendation, low certainty of evidence);* staff education *(Conditional recommendation, low certainty of evidence)* ***(Unchanged)***

Care and support interventions for all people with TB

Recommendation 1.4

The following treatment administration options may be offered to patients on TB treatment:

a. Community- or home-based treatment support is recommended over health facility-based treatment support or unsupervised treatment *(Conditional recommendation, moderate certainty of evidence)*

b. Treatment support administered by trained lay providers or health-care workers is recommended over treatment support administered by family members or unsupported treatment *(Conditional recommendation, very low certainty of evidence)*

c. Video-supported treatment (VST) can replace in-person treatment support when the video communication technology is available and can be appropriately organized and operated by health-care providers and patients *(Conditional recommendation, very low certainty of evidence)*

Recommendation C1.4

The following treatment administration options may be offered to patients on TB treatment:

a. Community- or home-based treatment support is recommended over health facility-based treatment support or unsupervised treatment *(Conditional recommendation, moderate certainty of evidence)*

b. Treatment support administered by trained lay providers or health care workers is recommended over treatment support administered by family members or unsupported treatment *(Conditional recommendation, very low certainty of evidence)*

c. Video-supported treatment (VST) can replace in-person treatment support when the video communication technology is available and can be appropriately organized and operated by health care providers and patients *(Conditional recommendation, very low certainty of evidence).* ***(Unchanged)***

Models of care for people with drug-resistant TB		
Patients with MDR-TB should be treated using mainly ambulatory care rather than with models of care based principally on hospitalization *(Conditional recommendation, very low certainty of evidence)*		Recommendation C2.1 Patients with MDR-TB should be treated using mainly ambulatory care rather than with models of care based principally on hospitalization. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***
Not included	A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment *(Conditional recommendation, very low certainty of evidence)*	Recommendation C2.2 A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***

Models of care for children and adolescents exposed to TB or with TB disease		
	Recommendation 3.2 1 In TB high-burden settings, decentralized models of care may be used to deliver TB services to children and adolescents with signs and symptoms of TB and/or those exposed to TB *(Conditional recommendation, very low certainty of evidence)*	Recommendation C3.1 In TB high-burden settings, decentralized models of care may be used to deliver TB services to children and adolescents with signs and symptoms of TB and/or those exposed to TB. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***
	Recommendation 3.2 Family-centred, integrated models of care to deliver TB services may be used in children and adolescents with signs and symptoms of TB and/or those exposed to TB, in addition to standard models of care *(Conditional recommendation; very low certainty of evidence)*	Recommendation C3.2 Family-centred, integrated models of care to deliver TB services may be used in children and adolescents with signs and symptoms of TB and/or those exposed to TB, in addition to standard models of care. *(Conditional recommendation, very low certainty of evidence)* ***(Unchanged)***

Palliative care interventions for MDR/RR-TB patients	
	Recommendation C4.1 In patients with pulmonary MDR/RR-TB, in addition to effective treatment, WHO recommends integrating palliative care assessment and interventions by trained providers, as described in WHO palliative care guidance documents. *(Conditional recommendation, moderate certainty of evidence)* ***(NEW)***

MDR-TB: multidrug-resistant TB; RR-TB: rifampicin-resistant TB; TB: tuberculosis; VST: video-supported treatment; WHO: World Health Organization.

Annex 2. Expert panels

Drug-susceptible TB treatment

Experts participating in the Guideline Development group meeting on drug-susceptible TB in 2009

Solange Cavalcante

TB Control Program Coordinator, Rio de Janeiro municipality, Rio de Janeiro, RJ, Brazil

Jeremiah Muhwa Chakaya (Chairperson)

Technical Expert, National Leprosy and TB Programme, Kenya Medical Research Institute, Nairobi, Kenya

Saidi M. Egwaga

Programme Manager, National TB and Leprosy Programme, Ministry of Health and Social Welfare, Dar es Salaam, United Republic of Tanzania

Robert Gie

Professor of Medicine, Department of Paediatrics & Child Health, University of Stellenbosch, Faculty of Medicine, Tygerberg, South Africa

Peter Gondrie

Executive Director, KNCV Tuberculosis Foundation, The Hague, Netherlands (Kingdom of the)

Anthony D. Harries

Senior Consultant, International Union Against Tuberculosis and Lung Disease, Winchester, Hants, United Kingdom

Phillip Hopewell

Professor of Medicine, Division of Pulmonary & Critical Care, San Francisco General Hospital, University of California San Francisco (UCSF), San Francisco, USA

Blessina Kumar

Global Coalition of TB advocates, New Delhi, India

Kitty Lambregts-van Weezenbeck

Senior Consultant, KNCV Tuberculosis Foundation, The Hague, Netherlands (Kingdom of the)

Sundari Mase

Division of TB Elimination National Centre for HIV, STD and TB, Centers for Disease Control and Prevention, Atlanta, USA

Richard Menzies

Director, Respiratory Division, MUHC and McGill University, Montreal, Canada

Anna Nakanwagi Mukwaya

Chief of Party, TBCAP Program, International Union Against Tuberculosis and Lung Disease, Wandegeya, Uganda

Mahshid Nasehi

National TB Programme Manager, Centre for Disease Control & Prevention, Ministry of Health and Medical Education, Tehran, Islamic Republic of Iran

Andrew Nunn

Professor of Epidemiology, Associate Director, MRC Clinical Trials Unit, London, United Kingdom

Madhukar Pai

Assistant Professor, Department of Epidemiology, Biostatistics & Occupational Health, McGill University, Montreal, Canada

Holger Schünemann

Methodologist, Chair, McMaster University Medical Centre, Clinical Epidemiology and Biostatistics, Health Sciences Centre Hamilton, Canada

Zarir F. Udwadia

Private Practitioner and Consultant Physician, Hinduja Hospital and Research Centre, Mumbai, India

Andrew Vernon

Division of TB Elimination, National Centre for HIV, STD and TB, Centers for Disease Control and Prevention, Atlanta, USA

Rozalind G. Vianzon

National TB Programme Manager, National Center for Disease Control and Prevention, Department of Health, Manila, Philippines

Virginia Williams

TB Project Direct or, International Council of Nurses, Suffolk, United Kingdom

External Review Group

Olayide Akanni, Nigeria

Margareth Pretti Dalcolmo, Brazil

Francis Drobniewski, United Kingdom

Paula Fujiwara, USA

Salmaan Keshavjee, USA

G.R. Khatri, India

Michail Perelman, Russian Federation

Charles Sandy, Zimbabwe

Pedro Guillermo Suarez, Peru

Marieke van der Werf, Netherlands (Kingdom of the)

Wang Lixia, China

Nadia Wiweko, Indonesia

Mohamed Abdel Aziz, The Global Fund to Fight AIDS, Tuberculosis and Malaria

Daniel Kibuga, WHO Regional Office for Africa

Giampaolo Mezzabotta, WHO Viet Nam

Jamhoih Tonsing, Family Health International Cambodia

Richard Zaleskis, WHO Regional Office for Europe

Experts participating in the Guideline Development group meeting on treatment of tuberculosis in children

Professor Robert GIE – Chair of the Guidelines Group

Department Head, Department of Paediatrics & Child Health, University of Stellenbosch, Faculty of Medicine. P.O. Box 19063, 7505 Tygerberg, South Africa

Professor Cleotilde HIDALGO HOW

Professor, Department of Pharmacology & Toxicology, University of Philippines (UP) College of Medicine, 547 Pedro Gil Street, Ermita 1000, Manila, Philippines

Dr Kalle HOPPU

Director. Poison Information Centre, Helsinki University Central Hospital. P.O. Box 790 (Tukholmankatu 17). 00029 HUS (Helsinki), Finland

Dr Gregory KEARNS

Director, Pediatric Pharmacology Research Unit. Children's Mercy Hospitals and Clinics. 2401 Gillham Road. Kansas City, MO 64108, USA

Dr Nicola MAGRINI

NHS CeVEAS, Centre for the Evaluation of Effectiveness of Health Care. WHO Collaborating Centre for Evidence-based Research Synthesis. and Guideline Development in Reproductive Health. Modena Local Health Authority, Modena, Italy

Dr Charles MWANSAMBO

Head, Department of Paediatrics. Lilongwe Central Hospital. P.O. Box 149, Lilongwe, Malawi

Dr Iveta OZERE

State Agency for Tuberculosis and Lung Diseases. p/o Cekule, Upeslejas, LV 2118 – Riga District, Latvia

Dr Mary REICHLER

Division of Tuberculosis Elimination, United States Centers for Disease Control and Prevention (CDC), 1600 Clifton Road, NE, MS E-10, Corporate Square Building, Bldg 10. Atlanta, GA 30333, USA

Experts participating in the Guideline Development Group meeting on DS-TB treatment and patient care in 2016

Si Thu Aung

Deputy Director (TB) and National TB Programme Manager

Department of Public Health, Ministry of Health Nay Pyi Taw, Myanmar

(Unable to attend the meeting)

Frank Bonsu

National TB Programme Manager Ministry of Health

Accra, Ghana

Jeremiah Muhwa Chakaya

Clinician

National TB Programme Manager Kemri, Nairobi, Kenya

Lucy Chesire

Nairobi, Kenya

Daniela Cirillo

Head of Emerging Bacterial Pathogens Unit

WHO Collaborating Centre and TB Supranational Reference Laboratory

San Raffaele Scientific Institute Milano, Italy

Poonam Dhavan

Migration Health Programme Coordinator

International Organization for Migration Geneva, Switzerland

(Unable to attend the meeting)

Kelly Dooley

Associate Professor of Medicine, Pharmacology & Molecular Sciences Divisions of Clinical Pharmacology & Infectious Diseases

Center for Tuberculosis Research Faculty Leader, Janeway Firm of the Osler Residency Program

Johns Hopkins University School of Medicine, Baltimore, MD

USA

Kathy Fiekert

Senior TB Consultant

KNCV Tuberculosis Foundation The Hague

Netherlands (Kingdom of the)

Paula Fujiwara

Scientific Director International Union Against Tuberculosis and Lung Disease (The Union)

Paris, France

Mike Frick

TB/HIV Project Treatement Action Group New York, NY

USA

Andrei Mariandyshev

Head of Phthisiopulmonary Department Arkhangelsk

Russian Federation

Nguyen Viet Nhung

Director of National Lung Hospital Manager of Viet Nam of National TB Programme

Hanoi, Viet Nam

Ejaz Qadeer

Ministry of Health

Islamabad, Pakistan

Abdul Hamid Salim

Advisor to of National TB Programme Bangladesh on Global Fund and MDR-TB TB Gate, Leprosy Hospital Compound, Mohakhali Dhaka, Bangladesh

Simon Schaaf

Paediatrician

Paediatrics and Child Health Faculty of Medicine and Health Sciences, University of Stellenbosch, South Africa

Holger Schünemann (Chair)

Methodologist

McMaster University, Canada

Pedro Guillermo Suarez

Management Sciences for Health Arlington

USA (Unable to attend the meeting)

Carrie Tudor

TB Project Director International Council of Nurses Durban,

South Africa

Justin Wong Yun Yaw

Head, Disease Control Division Ministry of Health

Jalan Menteri Besar, Brunei Darussalam

External Review Group

Mohammed Aziz

WHO Regional Office for the Eastern Mediterranean

Masoud Dara

WHO Regional Office for Europe

Riitta Dlodlo

International Union Against Tuberculosis and Lung Disease

France

Celine Garfin

Ministry of Health Philippines National programme

Philippines

Mirtha del Granado

WHO Regional Office for the Americas

Khurshid Alam Hyder

WHO Regional Office for South-East Asia

Vaira Leimane

Riga East University Hospital

Centre of Tuberculosis and Lung Diseases, Latvia

Nobuyuki Nishikiori

WHO Regional Office for the Western Pacific

Lee Reichman

Rutgers New Jersey Medical School, USA

Rohit Sarin

National Institute of TB & Respiratory Diseases Ministry of Health, India

Dalene von Delft

TB Proof South Africa

Fraser Wares

Royal Dutch Tuberculosis Foundation (KNCV), Netherlands (Kingdom of the)

Evidence reviewers

Narges Alipanah

Physician

Santa Clara Valley Medical Center San Jose,

USA

Lelia Chaisson

Epidemiologist

Infectious Disease Epidemiology Department of Epidemiology Johns Hopkins Bloomberg School of Public Health

Baltimore, USA

James Johnston

Evaluation Lead, TB Services British Columbia Centre for Disease Control

Vancouver, British Columbia, Canada

Jennifer Ho

Woolcock Institute of Medical Research

University of Sydney, Australia

Dick Menzies

RECRU/ Montreal Chest Institute Montreal, Quebec, Canada

Payam Nahid

Professor

University of California San Francisco

San Francisco, USA

Observers and external partners

Amy Bloom

Senior Technical Advisor, Bureau of Global Health

Agency for International Development (USAID), USA

Janet Ginnard

UNITAID, Geneva, Switzerland

Experts participating in the Guideline Development Group meeting on DS-TB treatment in 2021

Charles Daley (Co-Chair)
National Jewish Health, Denver (clinician), USA

Tamara Kredo (Co-Chair)
South Africa Medical Research Council (methodologist, academia), South Africa

Susan Abdel Rahman
Children's Mercy Kansas City (clinician), USA

Kunle Victor Babawale
Government of Nigeria (National TB programme, end user), Nigeria

Grania Brigden
The International Union Against TB and Lung Disease (clinician, technical NGO), France

Xu Caihong
Government of China (National TB programme, end user), People's Republic of China

Daniela Cirillo
TB Supranational Reference Laboratory Milan (TB diagnostics specialist), Italy

Gerry Davies
The University of Liverpool (clinician, academia), United Kingdom

Fernanda Dockhorn
Government of Brazil (National TB programme, end user), Brazil

Allan Fabella
Government of Philippines (National TB programme, end user), Philippines

Anneke Hesseling
Stellenbosch University (clinician, academia), South Africa

Cathy Hewison
Médecins sans Frontières (clinician, technical NGO), France

Muhammad Amir Khan
Association for Social Development (civil society representative), Pakistan

Khum Kim Eam
Government of Cambodia (National TB programme, end user), Cambodia

Ravinder Kumar
Government of India (National TB programme, end user), India

Endang Lukitosari
Government of Indonesia (National TB programme, end user), Indonesia

Aung Kya Jai Maug
The Damien Foundation (clinician, technical NGO), Bangladesh

Graeme Meintjes
The University of Cape Town (clinician, academia), South Africa

Jeremiah Muhwa Chakaya
The Respiratory Society of Kenya (clinician, professional association), Kenya

Andrew Owuor
Government of Kenya (National TB programme, end user), Kenya

Laia Ruiz Mingote
Independent consultant (civil society representative), Spain

Anastasia Samoilova
Government of the Russian Federation (National TB programme, end user), Russian Federation

Hadi Syed Hussain
Government of Pakistan (National TB programme, end user), Pakistan

Carrie Tudor
International Council of Nurses (nurse, technical NGO), South Africa

Fraser Wares
KNCV Tuberculosis Foundation (public health specialist, technical NGO), Netherlands (Kingdom of the)

External Review Group

Rafael Laniado Laborin
National TB Programme / Regional Green Light Committee, Mexico

Andrei Maryandyshev
Northern State Medical University Arkhangelsk, Russian Federation

Greg Fox
The University of Sydney, Australia

Harald Hoffmann
Supranational Reference Laboratory (Institute of Microbiology and Laboratory Medicine), Germany

Moorine Sekadde
National TB and Leprosy Programme, Uganda

Lisa Chen
Curry International Tuberculosis Center, USA

Ken Castro
Emory University, USA

Sangeeta Sharma
National Institute of Tuberculosis and Respiratory Diseases, India

Mahshid Nasehi
National TB and Leprosy Control Programmes, Iran (Islamic Republic of)

Giovanni Battista Migliori
Maugeri Institute, Italy

Evidence contributors and reviewers

Wendy Carr
Centers for Disease Control and Prevention, USA

Susan Dorman
Medical University of South Carolina, USA

Nora Engel
University of Maastricht, Netherlands (Kingdom of the)

Katya Kurbatova
Centers for Disease Control and Prevention, USA

Muthoni Mwaura
University of Maastricht, Kenya

Payam Nahid
University of California, San Francisco, USA

Patrick Phillips
University of California, San Francisco, USA

Andrew Vernon
Centers for Disease Control and Prevention, USA

Observers and external partners

Draurio Barreira
UNITAID, Switzerland

Padmapriyadarsini Chandrasekaran
Indian Council of Medical Research, India

Mike Frick
Treatment Action Group, USA

Brian Kaiser
Stop TB Partnership, Global Drug Facility, Switzerland

Ya Diul Mukadi
United States Agency for International Development, USA

Samuel Schumacher
FIND, Switzerland

Jamie Tonsing
Global Fund to Fight AIDS, Tuberculosis and Malaria, Switzerland

Brenda Waning
Stop TB Partnership, Global Drug Facility, Switzerland

WHO Guideline Steering Committee

The following staff served as the WHO Steering Committee for the development of the current policy guideline: Fuad Mirzayev (lead), Dennis Falzon, Medea Gegia, Kerri Viney, Matteo Zignol, Linh Nguyen, Annemieke Brands, Farai Mavhunga, Nazir Ismail (Global Tuberculosis Programme, WHO Headquarters), Lorenzo Moja (Essential Medicines, WHO Headquarters), Vineet Bhatia (WHO Regional Office for South-East Asia), Askar Yedilbayev (WHO Regional Office for Europe).

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Drug-resistant TB treatment

Experts participating in the Guideline Development Group meeting on isoniazid-resistant tuberculosis in 2018

Refer to Annex 1: GRADE evidence summary tables in the WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment. Online annexes. (https://iris.who.int/handle/10665/332678, accessed 10 October 2022).

Experts participating in the Guideline Development Group meeting on rifampicin- and multidrug-resistant tuberculosis in 2018

Refer to Annex 1: GRADE evidence summary tables in the WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment. Online annexes. (https://iris.who.int/handle/10665/332678, accessed 10 October 2022).

Experts participating in the Guideline Development Group meeting on drug-resistant TB treatment in 2019

Refer to Annex 1: A2 Expert panels in the WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment. Online annexes. (https://iris.who.int/handle/10665/332678, accessed 13 September 2022).

Experts participating in the Guideline Development Group meeting on drug-resistant TB treatment in 2022

Guideline Development Group

The chairs of the GDG were Holger J. Schünemann (Chair, Grading of Recommendations Assessment, Development and Evaluation [GRADE] methodologist: Cochrane Canada & McMaster University, Canada) and Jeremiah Muhwa Chakaya (Technical expert, National TB Programme, Kenya).

The following experts served as members of the GDG: Denise Arakaki (national TB programme, end-user, clinician: Ministry of Health MDR-TB referral centre, Brazil); Padmapriyadarsini Chandrasekaran (researcher, end user: National Institute for Research in Tuberculosis, India); Daniela Maria Cirillo (laboratory specialist: San Raffaele Scientific Institute, Supranational TB Reference Laboratory, Italy); Charles Daley (pulmonologist, MDR-TB expert: National Jewish Health Hospital, USA); Gerry Davies

(trials expert, pharmacologist: University of Liverpool, United Kingdom); Amita Gupta (scientist, maternal health medicine: Johns Hopkins University, USA); Elmira Gurbanova (rGLC member, clinician, end-user: Lung Clinic, University of Tartu, Estonia); Anneke Hesseling (paediatrician, end-user: Stellenbosch University, South Africa); Christoph Lange (researcher: Research Center Borstel, Germany); Christian Lienhardt (researcher, end user: French Institute for Research on Sustainable Development, France); Leslie Christine Magsayo-Salon (national TB programme, clinician (TB/HIV), end user: National TB Programme, Northern Mindanao Medical Center, Philippines); Guy Marks (clinician, researcher: International Union Against Tuberculosis and Lung Disease); Graeme Meintjes (researcher, end user: University of Cape Town, South Africa); Asif Mujtaba (clinician, end-user: Asgar Ali Hospital, Bangladesh); Mahshid Nasehi (national TB programme, end user: National Tuberculosis Programme, Iran (Islamic Republic of)); Nguyen Viet Nhung (national TB programme, end-user: National TB Control Programme, Ministry of Health, Viet Nam); Andrew Nunn (researcher, end user: University College London, United Kingdom); Ingrid Schoeman (former MDR-TB patient: TB PROOF, South Africa); Sabira Tahseen (laboratory, national TB programme, end-user: National TB Control Programme, Pakistan); Ye Tun (clinician, end-user: Thingankyun General Hospital, University of Medicine, Myanmar); Debrah Vambe (national TB programme, end-user: National TB Control Program, Eswatini); Andrew Vernon (trials expert, technical agency, end-user: United States Centers for Disease Control and Prevention, USA); Paran Winarni (civil society representative: TB Civil Society Task Force, Indonesia Youth Movement Against TB, Indonesia); Yanlin Zhao (national TB programme, end-user: National Tuberculosis Control and Prevention Center, Chinese Center for Disease Control, China).

External Review Group

Giovanni Battista Migliori (WHO Collaborating Centre for TB and Lung Diseases, Fondazione S. Maugeri, Tradate, Italy); Anuj K. Bhatnagar (clinician; researcher: Rajan Babu Institute for Pulmonary Medicine and Tuberculosis, India); Lisa Chen (clinician, academic: UCSF Curry International Tuberculosis Center, USA); Edwin H. Herrera-Flores (clinician, end-user: Hospital Nacional MDR-TB Referral Centre, Arzobispo Loayza, Peru); Ivan Solovic (national TB programme, clinician, end-user: National Institute for TB, Lung Diseases and Thoracic Surgery, Slovakia); Rafael Laniado (clinician, end-user: National TB Programme, Mexico); Anna Cristina C. Carvalho (clinician, researcher: Fiocruz Institute, Brazil); Philipp du Cros (clinician, researcher: Burnet Institute, Australia).

Evidence reviewers

Greg Fox, Tasnim Hasan, Timothy Schlubb, Hannah Morgan and Ellie Medcalf from The University of Sydney; Claudia Denkinger and Ioana Olaru from Heidelberg University

Observers and external partners

Draurio Barreira Cravo Neto (technical manager, TB: Unitaid, Switzerland); Michael Campbell (Senior director, Tuberculosis: Clinton Health Access Initiative, Inc.); Abdul Ghafoor (Advisor MDR-TB: Ministry of National Health Services Regulations & Coordination, Pakistan); Mustapha Gidado (executive director: KNCV TB Foundation, Netherlands (Kingdom of the)); Brian Kaiser (technical officer: Stop TB Partnership's Global Drug Facility, Switzerland); YaDiul Mukadi (technical advisor: United States Agency for International Development [USAID], USA); Payam Nahid (Director: UCSF center for Tuberculosis, University of California San Francisco); Fraser Wares (Senior consultant: KNCV TB Foundation); Wojtek Wiercioch (GRADE methodologist: McMaster University, Canada); and Mohammed Yassin (senior disease advisor, TB: The Global Fund to Fight AIDS, Tuberculosis and Malaria, Switzerland).

WHO Guideline Steering Committee

Fuad Mirzayev (lead), Dennis Falzon, Medea Gegia, Annabel Baddeley, Nazir Ismail, Linh Nguyen, Samuel Schumacher, Sabine Verkuijl, Kerri Viney, Matteo Zignol from the Global TB Programme, WHO headquarters; Askar Yedilbayev from WHO Regional Office for Europe; Corinne Simone

Collette Merle from the Special Programme for Research and Training in Tropical Diseases, WHO headquarters; Lorenzo Moja from the Medicines Selection, Intellectual Property and Affordability / Essential Medicines, WHO headquarters; Andreas Alois Reis from Health Ethics and Governance, WHO headquarters; and Olufunmilayo Lesi and Marco Vittoria from the Global HIV, Hepatitis and STIs Programmes / Treatment, Care and Service Delivery, WHO headquarters.

Experts participating in the Guideline Development Group meeting on drug-resistant TB treatment in 2024

Guideline Development Group

The chair of the GDG was Jeremiah Muhwa Chakaya (London School of Hygiene and Tropical Medicine, United Kingdom). Professor Holger J. Schünemann and Wojtek Wiercioch (GRADE methodologist: McMaster University, Canada) served as the methodologist for developing this guideline update.

The following experts served as members of the GDG: Ashna Ashesh (WHO Civil Society Task Force – TB; Survivors Against TB (SATB), India), Erlina Burhan (Persahabatan Hospital Jakarta; Faculty of Medicine – Universitas Indonesia), Raymond Byaruhanga (National TB and Leprosy Programme, Ministry of Health, Uganda), Daniela Cirillo (San Raffaele Supranational TB Reference Laboratory, Italy), Charles Daley (National Jewish Health Hospital, USA), Geraint Gerry Rhys Davies (University of Liverpool, United Kingdom), Fernanda Dockhorn Costa Johansen (National TB programme, Ministry of Health, Brazil), Razia Fatima (National TB programme, Pakistan), Elmira Gurbanova (Lung Clinic, University of Tartu, Estonia), Anneke Hesseling (Stellenbosch University, South Africa), Christoph Lange (Research Center Borstel, Germany), Graeme Meintjes (University of Cape Town, South Africa), Gopalan Narendran (Indian Council of Medical Research –National Institute for Research in Tuberculosis, Chetpet, Chennai, India), Mahshid Nasehi (National Tuberculosis Programme of the Islamic Republic of Iran), Kim Cuong Nguyen (National Lung Hospital, Viet Nam), Andrew Vernon (Centers for Disease Control and Prevention, USA), Wenhong Zhang (National Medical Center for Infectious Diseases, China).

External Review Group

Andrew Nunn (Emeritus Professor of Epidemiology. MRC Clinical Trials Unit at UCL, United Kingdom), Giovanni Battista Migliori (WHO Collaborating Centre for TB and Lung Diseases, Fondazione S. Maugeri, Tradate, Italy); Anuj K. Bhatnagar (clinician; researcher: Rajan Babu Institute for Pulmonary Medicine and Tuberculosis, India); Lisa Chen (clinician, academic: UCSF Curry International Tuberculosis Center, USA); Rafael Laniado (clinician, end-user: National TB Programme, Mexico); Philipp du Cros (clinician, researcher: Burnet Institute, Australia), Ingrid Shoeman (Civil Society, former TB patient, South Africa), Patrick Lungu (East, Central and Southern Africa Health Community (ECSA), Zambia), Tasnim Hassan (University of Sydney, Australia), Mamel Quelapio (National TB Programme, Philippines), Sobia Faisal (NTP team, Pakistan).

Observers and external partners

Cherise Scott (senior programme manager Unitaid, Switzerland); Mukadi YaDiul (technical advisor: United States Agency for International Development [USAID], USA); Brian Kaiser (technical officer: Stop TB Partnership's Global Drug Facility, Switzerland); Michael Campbell (Senior director, Tuberculosis: Clinton Health Access Initiative, Inc.); Lele Rangaka University College London, United Kingdom), Agnes Gebhard (Senior consultant: KNCV TB Foundation); Maria Regina Christian (National Professional officer, Indonesia) Parmar Malik (Medical officer, WHO country office, India), Brenda Waning (Chief, Global Drug Facility, Switzerland), Kobto Ghislain Koura (Tuberculosis Departmental Director, The UNION, France), Anna Scradigli (TB advisor, The Global Fund, Switzerland), Christina Ho (Center for Disease control and prevention, USA).

WHO Guideline Steering Committee

Fuad Mirzayev (lead), Dennis Falzon, Medea Gegia, Annabel Baddeley, Linh Nguyen, Samuel Schumacher, Kerri Viney, Sabine Verkuijl, Matteo Zignol from the Global TB Programme, WHO headquarters; Askar Yedilbayev from WHO Regional Office for Europe; and Elena Vovc from the Global HIV, Hepatitis and STIs Programmes / Treatment, Care and Service Delivery, WHO headquarters.

TB treatment and care

Experts participating in the Guideline Development Group meeting on programmatic management of drug-resistant TB in 2011

Guideline Development Group

Jaime Bayona, Socios En Salud Sucursal, Peru (programme management, public health)

José A. Caminero, University General Hospital of Gran Canaria, Spain and the UNION, Paris, France (clinical practice)

Charles L. Daley, National Jewish Health, USA (clinical practice)

Agnes Gebhard, Royal Dutch Tuberculosis Foundation (KNCV), Netherlands (Kingdom of the) (programme management)

Myriam Henkens, Médecins Sans Frontières, France (programme management)

Timothy H. Holtz, HIV/STD Research Program, United States Centers for Disease Control and Prevention (CDC), Asia Regional Office, Thailand (epidemiology, surveillance, programme evaluation)

Joël Keravec, Management Sciences for Health, Brazil (drug management)

Salmaan Keshavjee, Harvard Medical School, USA (programme management, public health)

Aamir J. Khan, Indus Hospital TB Program, Pakistan (epidemiology, programme management)

Vaira Leimane, State Infectology Center, Clinic of Tuberculosis and Lung Diseases, Latvia (programme management, clinical practice)

Andrey Mariandyshev, Northern State Medical University, Archangelsk, Russian Federation (clinical practice)

Carole D. Mitnick, Harvard Medical School, USA (epidemiology, programme support)

Gloria Nwagboniwe, Alliance for Hope, Nigeria (civil society)

Domingo Palmero, Pulmonology Division, Hospital Muñiz, Argentina (clinical practice)

Ma. Imelda Quelapio, Tropical Disease Foundation, Philippines (programme management)

Michael L. Rich, Partners In Health, USA (clinical practice)

Sarah Royce, PATH, USA (surveillance, public health)

Sabine Rüsch-Gerdes, National Reference Centre for Mycobacteria, Germany (laboratory specialist)

Archil Salakaia, Management Sciences for Health, USA (programme management)

Rohit Sarin, LRS Institute of TB and Allied Diseases, India (clinical practice)

Holger Schünemann, McMaster University, Canada (Chairman of the Guideline Development Group; epidemiology, guideline methodology)

Elena Skachkova, Federal Centre of TB Monitoring, Russian Federation (surveillance)

Francis Varaine, Médecins Sans Frontières, France (clinical and programme management)

WHO headquarters, Geneva, Switzerland

Global TB Programme: Léopold Blanc, Dennis Falzona, Christopher Fitzpatrick, Katherine Floyd, Haileyesus Getahun, Malgorzata Grzemska, Christian Gunneberg, Ernesto Jaramillo, Christian Lienhardt, Fuad Mirzayev, Paul Nunn, Mario C. Raviglione, Delphine Sculiera, Fraser Wares, Karin Weyer, Matteo Zignol.

HIV Department: Chris Duncombe, Marco Antonio de Avila Vitoria.

External Review Group

Samiha Baghdadi, WHO Regional Office for the Eastern Mediterranean, Egypt

Mercedes Becerra, Harvard Medical School, USA (academia)

Vineet Bhatia, WHO Regional Office for South-East Asia, India

Masoud Dara, WHO Regional Office for Europe, Denmark

Mirtha del Granado, WHO Regional Office for the Americas, USA

Reuben Granich, WHO HIV Department, Switzerland

Lindiwe Mvusi, Department of Health, South Africa (programme management)

Nani Nair, WHO Regional Office for South-East Asia, India

Norbert Ndjeka, Department of Health, South Africa (programme management, clinical practice)

Wilfred A.C Nkhoma, WHO Regional Office for Africa, Zimbabwe

Katsunori Osuga, WHO Regional Office for the Western Pacific, Philippines

Hendrik Simon Schaaf, Department of Paediatrics and Child Health, Stellenbosch University and Tygerberg Children's Hospital, South Africa (clinical practice, paediatric MDR-TB, surveillance)

Catharina van Weezenbeek, WHO Regional Office for the Western Pacific, Philippines

Irina Vasilyeva, Central TB Research Institute of RAMS, Russian Federation (research, clinical practice)

Wang Xie Xiu, Tianjin Centers for Disease Control and Prevention, China (surveillance)

Richard Zaleskis, WHO Regional Office for Europe, Denmark

Evidence review teams

Chunling Lu, Carole D. Mitnick, Harvard Medical School, Boston MA, and Richard A. White, Harvard School of Public Health, Boston MA, USA.

Gail Kennedy, George Rutherford, Karen Steingart, University of California (San Francisco), California, USA.

Matthew Arentz, David Horne, Patricia Pavlinac, Judd L. Walson, University of Washington, Seattle, Washington WA, USA.

Melissa Bauer, Richard (Dick) Menzies, Olivia Oxlade, McGill University, Montreal, Quebec, Canada.

Consultant: Patricia Whyte, Griffith University, Queensland, Australia (guideline development).

Experts participating in the Guideline Development Group meeting on DS-TB treatment and patient care in 2016

Guideline Development Group (GDG) members

Si Thu Aung, Deputy Director (TB) and National TB Programme Manager, Ministry of Health, Nay Pyi Taw, Myanmar (Unable to attend the meeting)

Frank Bonsu, National TB Programme Manager, Ministry of Health, Accra, Ghana

Jeremiah Muhwa Chakaya, Clinician, National TB Programme Manager, Nairobi, Kenya

Lucy Chesire, Nairobi, Kenya

Daniela Cirillo, Head of Emerging Bacterial Pathogens Unit, WHO Collaborating Centre and TB Supranational Reference Laboratory, San Raffaele Scientific Institute, Milan, Italy

Poonam Dhavan, Migration Health Programme Coordinator, International Organization for Migration, Geneva, Switzerland (Unable to attend the meeting)

Kelly Dooley, Associate Professor of Medicine, Pharmacology & Molecular Sciences, Divisions of Clinical Pharmacology & Infectious Diseases, Center for Tuberculosis Research, Faculty Leader, Janeway Firm of the Osler Residency Program, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Kathy Fiekert, Senior TB Consultant, Royal Dutch Tuberculosis Foundation (KNCV), The Hague, Netherlands (Kingdom of the)

Paula Fujiwara, Scientific Director, International Union Against Tuberculosis and Lung Disease, Paris, France

Mike Frick, TB/HIV Project, Treatment Action Group, New York, NY, USA

Andrei Mariandyshev, Head of Phthisiopulmonary Department, Arkhangelsk, Russian Federation

Nguyen Viet Nhung, Director of National Lung Hospital, Manager of National TB Programme, Hanoi, Viet Nam

Ejaz Qadeer, Ministry of Health, Islamabad, Pakistan

Abdul Hamid Salim, Advisor to National TB Programme Bangladesh on Global Fund and MDR-TB, Mohakhali, Dhaka, Bangladesh

Simon Schaaf, Paediatrician, Paediatrics and Child Health, Faculty of Medicine and Health Sciences, University of Stellenbosch, South Africa

Holger Schünemann (Chair), Methodologist, McMaster University, Hamilton, Canada

Pedro Guillermo Suarez, Management Sciences for Health, Arlington, VA, USA (Unable to attend the meeting)

Carrie Tudor, TB Project Director, International Council of Nurses, Durban, South Africa

Justin Wong Yun Yaw, Head, Disease Control Division, Ministry of Health, Jalan Menteri Besar, Brunei Darussalam

Evidence reviewers

Narges Alipanah, Santa Clara Valley Medical Center, San Jose, CA, USA

Lelia Chaisson, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Jennifer Ho, Woolcock Institute of Medical Research, University of Sydney, Australia

James Johnston, TB Services, British Columbia Centre for Disease Control, Vancouver, Canada

Dick Menzies, RECRU/Montreal Chest Institute, Montreal, Canada

Payam Nahid, Professor, University of California, San Francisco, CA, USA.

Observers

Amy Bloom, Agency for International Development (USAID), Washington, DC, USA

Janet Ginnard, UNITAID, Geneva, Switzerland.

WHO headquarters Secretariat

Global TB Programme: Annabel Baddeley, Dennis Falzon, Giuliano Gargioni, Nebiat Gebresselassie, Haileyesus Getahun, Licé Gonzalez-Angulo, Malgorzata Grzemska, Elizabeth Harausz, Ernesto Jaramillo, Avinash Kanchar, Soleil Labelle, Christian Lienhardt, Knut Lönnroth, Fuad Mirzayev, Linh Nguyen, Marco Vitoria, Diana Weil, Karin Weyer, Matteo Zignol.

Members of the External Review Group

Mohammed Aziz, WHO Regional Office for the Eastern Mediterranean

Masoud Dara, WHO Regional Office for Europe

Riitta Dlodlo, International Union Against Tuberculosis and Lung Disease, France (technical agency/ programme implementation)

Celine Garfin, Ministry of Health, Philippines (national programme/end-user)

Mirtha del Granado, WHO Regional Office for the Americas

Daniel Kibuga, WHO Regional Office for Africa

Md Khurshid Alam Hyder, WHO Regional Office for South-East Asia

Vaira Leimane, Riga East University Hospital, Centre of Tuberculosis and Lung Diseases, Latvia (clinician/end-user)

Nobuyuki Nishikiori, WHO Regional Office for the Western Pacific

Lee Reichman Rutgers, New Jersey Medical School, Newark, NJ, USA (clinician/end-user)

Rohit Sarin, National Institute of TB & Respiratory Diseases, Ministry of Health, India (national programme/end-user)

Dalene von Delft, TB Proof, South Africa (patient representative)

Fraser Wares, Royal Dutch Tuberculosis Foundation (KNCV), The Hague, Netherlands (Kingdom of the) (technical agency/programme implementation).

Experts participating in the Guideline Development Group meeting on management of tuberculosis in children and adolescents in 2021

Guideline Development Group (GDG) members

Susan Abdel-Rahman (Children's Mercy Research Institute, USA)

Deepak Agrawal (Aarogyam Paediatrics Hospital, India)

Shakil Ahmed (Dhaka Medical College, Bangladesh)

Elie Akl (American University of Beirut and Center for Systematic Reviews of Health Policy and Systems Research, Lebanon)

Valentina Aksenova (Research Institute of Phthisiopulmonology of the First M.I. Sechenov Moscow State Medical University, Russian Federation)

Farhana Amanullah (Indus Hospital, Pakistan)

Grace Bolie (National TB Programme, Democratic Republic of the Congo)

Chishala Chabala (University Teaching Hospital, Zambia)

Gunta Dravniece (PATH, Ukraine)

Connie Erkens (KNCV Tuberculosis Foundation, Netherlands (Kingdom of the))

Betina Mendez Alcântara Gabardo (Clinical Hospital Federal University of Paraná, Brazil)

Stephen Graham (University of Melbourne, Australia)

Patrik Hummel (Friederich-Alexander University, Germany)

Amir M. Khan (Association for Social Development, Pakistan)

Margaret Nasil Kal (National TB Programme, Papua New Guinea)

Tamara Kredo (South African Cochrane Centre, South African Medical Research Council, South Africa)

Susan Maloney (Centers for Disease Control and Prevention, USA)

Anna Mandalakas (Baylor College of Medicine, Texas Children's Hospital, USA)

Sushant Mane (Grant Government Medical College and Sir J.J. Group of Hospitals, India)

Lindsay McKenna (Treatment Action Group, USA)

Imran Pambudi (National TB Programme, Indonesia)

Phan Huu Phuc (National Paediatric Hospital, Viet Nam)

Moorine Sekadde (National TB and Leprosy Programme, Uganda)

Kathryn Snow (University of Melbourne, Australia)

Sabira Tahseen (National TB Reference Laboratory, Pakistan)

Elie Akl, Farhana Amanullah, Stephen Graham and Tamara Kredo co-chaired the GDG meeting.

Technical resource persons and observers

Pete Dodd (Sheffield University, United Kingdom), Anneke Hesseling (Stellenbosch University, South Africa), Oliver Marcy (University of Bordeaux, France), Nicole Salazar-Austin (Johns Hopkins University, USA) and James Seddon (Imperial College London, United Kingdom) served as technical resource persons during the GDG meeting.

The following persons participated as observers during the GDG meeting: Draurio Barreira Cravo Neto (Unitaid, Switzerland); Charlotte Colvin (USAID, USA); Anne Detjen (UNICEF, USA); Thomas Gradel (Unitaid, Switzerland); Brian Kaiser (Stop TB Partnership Global Drug Facility, Switzerland); Michael McCaul (Stellenbosch University, South Africa); Lawrence Mbuagbaw (St Joseph's Healthcare, Canada); Celeste Naude (Stellenbosch University, South Africa); Oxana Rucsineanu (TB Community Advisory Board); Anna Scardigli (Global Fund to Fight AIDS, Tuberculosis and Malaria, Switzerland); Cherise Scott (Unitaid, Switzerland).

External Review Group

Martina Casenghi (Elizabeth Glaser Pediatric AIDS Foundation, Switzerland)

Anthony Enimil (Komfo Anokye Teaching Hospital, Ghana)

Malgorzata Grzemska (former WHO staff member, Poland)

Catherine Hewison (Médecins Sans Frontières, France)

Devan Jaganath (University of California San Francisco, USA)

Kobto Ghislain Koura (The International Union Against Tuberculosis and Lung Disease, France)

Celia Martínez de Cuellar (Hospital de Clínicas, Universidad Nacional de Asunción, Paraguay)

Ya Diul Mukadi (United States Agency for International Development [USAID], USA)

Rahab Mwaniki (Kenya Aids NGOs Consortium [KANCO], Kenya)

Marc Nicol (University of Western Australia, Australia)

Elizabeth Maleche Obimbo (University of Nairobi, Kenya)

Peter Owiti (Wote Youth Development Project, Kenya)

Nyan Win Phyo (Civil Society Taskforce; World Vision, Thailand)

Ramatoulaye Sall (Independent Consultant, Senegal)

Rina Triasih (Universitas Gadyah Mada, Indonesia)

Eric Wobudeya (Mulago National Referral Hospital, Uganda; Makerere University – Johns Hopkins University [MU-JHU] Research Collaboration, Uganda).

Evidence reviewers

Yael Hirsch-Moverman (Columbia University, USA), Hamidah Hussain (Interactive Research and Development [IRD] Global, Singapore), Daria Szkwarko (Brown University, USA) and Courtney Yuen

(Harvard Medical School, USA) conducted the evidence review for PICO Question 6: Models of care for TB case detection and TB prevention in high TB burden settings.

WHO Steering Group

The WHO guidelines Steering Group comprised: Annabel Baddeley, Lice Gonzalez Angulo, Ernesto Jaramillo, Avinash Kanchar, Charalambos Sismanidis (Global Tuberculosis Programme, WHO headquarters); Martina Penazzato (Global HIV, Hepatitis and Sexually Transmitted Infections Programme, WHO headquarters); Bernadette Cappello, Lorenzo Moja (Department of Health Products, Policy and Standards, WHO headquarters); Marie Valentin (Department of Regulation and Prequalification); Corinne Simone Collette Merle (Special Programme for Research and Training in Tropical Diseases, WHO headquarters); Valentina Baltag, Wilson Milton Were (Department of Maternal, Newborn, Child & Adolescent Health & Ageing, WHO headquarters); Lina Mahy (Department of Nutrition and Food Safety, WHO headquarters); Chiara Servili (Department of Mental Health and Substance Use, WHO headquarters); Sarah Rylance (Department of Noncommunicable Diseases Management), WHO headquarters; Ogtay Gozalov (WHO Regional Office for Europe); Mukta Sharma (WHO Regional Office for South-East Asia); Kyung Hyun Oh (WHO Regional Office for the Western Pacific); Pedro Avedillo (WHO Regional Office for the Americas); Kenza Bennani, Martin van den Boom (WHO Regional Office for the Eastern Mediterranean); André Ndongosieme (WHO Regional Office for Africa).

Experts participating in the Guideline Development Group meeting on TB treatment and care in 2025

Guideline Development Group

The chair of the GDG was Jeremiah Muhwa Chakaya (London School of Hygiene and Tropical Medicine, United Kingdom). Professor Holger J. Schünemann and Mercy Mulaku (Humanitas University, Milan, Italy) served as the methodologists for developing this guideline update.

The following experts served as members of the GDG: Ashna Ashesh (WHO Civil Society Task Force – TB; Survivors Against TB, India), Erlina Burhan (Persahabatan Hospital Jakarta; Faculty of Medicine – Universitas Indonesia), Jeremiah Muhwa Chakaya (National Tuberculosis Programme of Kenya), Gerry Davies (University of Liverpool, United Kingdom), Fernanda Dockhorn Costa Johansen (Ministry of Health MDR-TB referral centre, Brazil), Kelly Dooley (Vanderbilt University Medical Center, USA), Sobia Faisal (Greenstar Social Marketing, Pakistan), Elmira Gurbanova (Lung Clinic, University of Tartu, Estonia), Eric Krakauer (Harvard Medical School, USA), Christoph Lange (Research Center Borstel, Germany), Yuhong Liu (Beijing Chest Hospital, China), Andrey Maryandyshev (Phthisiopulmonology Department of the Northern State Medical University, Arkhangelsk, Russian Federation), Graeme Meintjes (University of Cape Town, South Africa), Mahshid Nasehi (National Tuberculosis Programme of the Islamic Republic of Iran), Mamel Quelapio (Independent consultant, Philippines), Moorine Sekkade (National Tuberculosis Programme of Uganda), Wei Sha (Shanghai Pulmonary Hospital, China), Urvashi Singh (National TB Programme, Ministry of Health, India), Shaheed Vally Omar (South Africa Supranational TB Reference Laboratory), Luan Vo (Friends for International Tuberculosis Relief (FIT), Viet Nam).

External Review Group

Anuj K. Bhatnagar (Rajan Babu Institute for Pulmonary Medicine and Tuberculosis, India), Lisa Chen (UCSF Curry International Tuberculosis Center, USA), Philipp du Cros (Burnet Institute, Australia), Anthony Garcia Prats (University of Wisconsin School of Medicine and Public Health, USA), Jennifer Hughes (Desmond Tutu Centre, Stellenbosch University, South Africa), Ernesto Jaramillo (Independent consultant, Colombia), Patrick Lungu (East, Central and Southern Africa Health Community (ECSA),

Zambia), Ignacio Monedero (International Union Against TB and Lung Disease, Spain), Mary Rosary Santiago (Independent consultant, Philippines), Sabera Tahseen (National TB Reference Laboratory, Pakistan).

Evidence reviewers

Justin Denholm, Greg Fox, Tasnim Hasan and Timothy Schlub from The University of Sydney (Australia); Richard Harding, Emeka Chukwusa, Matthew Maddocks, Buyinza Nasur, Kennedy Nkhoma and Toby Prevost from King's College London (United Kingdom).

Data contributors

Carole Mitnick (Partners in Health, USA), Maelenn Gouillou (Epicentre, France), Lorenzo Guglielmetti and Francis Varaine (MSF, France), Nathalie Lachenal (MSF, Switzerland), Bern-Thomas Nyang'wa (MSF, United Kingdom), Francesca Conradie (France), Patrick Phillips (UCSF, USA).

Observers and external partners

Cherise Scott (senior programme manager Unitaid, Switzerland); Brian Kaiser (technical officer: Stop TB Partnership's Global Drug Facility, Switzerland), Michael Campbell (Senior director, Tuberculosis: Clinton Health Access Initiative, Inc., USA); Agnes Gebhard (Senior consultant: KNCV TB Foundation, Netherlands (Kingdom of the)); Ruth Goodall (Institute of Global Health, University College London (UCL), United Kingdom); Kobto Ghislain Koura (Tuberculosis Department Director, The Union, France); Ilaria Motta (Principal Clinical Research Fellow, Institute of Clinical Trials & Methodology, MRC Clinical Trials Unit at UCL, United Kingdom); Lele Rangaka (University College London, United Kingdom); Anna Scradigli (TB advisor, The Global Fund, Switzerland).

WHO Guideline Steering Committee

Fuad Mirzayev (lead), Annabel Baddeley, Dennis Falzon, Medea Gegia, Patricia Hall-Eidson, Linh Nguyen, Samuel Schumacher, Sabine Verkuijl, Kerri Viney, Elena Vovc, Matteo Zignol from the Department for HIV, TB, Hepatitis and STIs; Megan Doherty from the Department of Integrated Health Services at WHO headquarters; Askar Yedilbayev from WHO Regional Office for Europe.

Annex 3. Declarations of interest

3.1 Drug-susceptible tuberculosis treatment

2009 Guideline Development Group

All members of the group completed a Declaration for the Conflict of Interest; there were no conflicts declared.

2016 Guideline Development Group

The following members declared no interests: Si Thu Aung; Frank Bonsu; Jeremiah Chakaya; Lucy Chesire; Daniela Cirillo; Poonam Dhavan; Kathy Fiekert; Andrei Mariandyshev; Nguyen Viet Nhung; Ejaz Qadeer; Abdul Hamid Salim; Holger Schünemann; Pedro Suarez; Justin Wong Yun Yaw.

The following GDG members declared interests that were judged not to be in conflict with the policy of WHO, or the objectives of the meeting:

Kelly Dooley declared that she did not receive any salary support from drug companies for her work in the following roles and activities: Co-chair of the AIDS Clinical Trials Group (ACTG) study assessing bedaquiline and delamanid for MDR-TB; principal investigator, assessing pretomanid for tuberculosis trial, assessing pretomanid (PA-824, investigational drug) for treatment of drug-sensitive TB; investigator on trials assessing rifapentine for pregnant women with latent TB infection, rifapentine for treatment shortening in patients with pulmonary TB, high-dose rifampicin and levofloxacin for pediatric TB meningitis, high-dose isoniazid for MDR-TB, and delamanid for MDR-TB in children with and without HIV.

Mike Frick declared that his organization received noncommercial support 1) to track investment made in TB research and development; 2) to host a symposium at the Union meeting; 3) to advocate for increased funding for TB research and development, research and access to evidence-based interventions; and 4) for the management of the community research advisors' group. Simon Schaaf declared receiving grants for pharmacokinetic drug studies in children of second-line drugs and for studying preventive therapy in MDR-TB. Carrie Tudor declared that her organization receives funding from Eli Lilly Foundation for activities related to TB and MDR-TB projects.

2021 Guideline Development Group

Twenty-five individuals from various areas of expertise were invited to attend. All the experts completed and submitted their Declaration of Interest (DOI) and Confidentiality Undertaking forms between March – April 2021. On review of the completed DOIs, the following 8 experts declared interests that required further consideration and discussion with WHO Office of Compliance, Risk Management and Ethics (CRE): Susan ABDEL RAHMAN; Grania BRIGDEN; Daniela CIRILLO; Charles DALEY; Geraint DAVIES; Anneke HESSELING; Laia RUIZ MINGOTE; Carrie TUDOR.

Following thorough assessment and review in collaboration with the CRE no competing interests were identified with the scope of the work being undertaken by the GDG. The note for the record with details of the assessment was filed.

3.2 Drug-resistant tuberculosis treatment

WHO guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update

Funding for the meetings and reviews involved in the updating of the guidelines came entirely from the United States Agency for International Development (USAID). The experts on the Guideline Development Group (GDG) and the institutions where they work contributed time for the various discussions and other activities involved in the update process.

The Declaration of interest forms were completed by all non-WHO members of the GDG and the External Review Group, as well as the members of the academic centres who were involved in the reviews. Four members of the GDG declared interests that were judged to represent a potential conflict and were excused from the sessions of the meeting on 25–27 October 2010 during which recommendations relating to the drug regimens were discussed. Jaime BAYONA was a consultant for the development of clinical trial design for studies of an anti-tuberculosis drug manufactured by Otsuka Pharmaceutical Co. Ltd (OPC-67683). Charles L. DALEY was chairperson of drug-safety monitoring for two trials conducted by Otsuka Pharmaceutical Co. Ltd. Carole D. MITNICK served as a member of the Scientific Advisory Board of Otsuka Pharmaceutical Co. Ltd and had an advisory role on drug OPC-67683. Ma. Imelda QUELAPIO received support (monetary and non-monetary) for research from Otsuka Pharmaceutical Co. Ltd.

The following members of the academic centres, who performed the reviews of evidence from which the recommendations contained in these guidelines are derived, presented their findings at the meeting: Matthew ARENTZ, Melissa BAUER, Richard MENZIES, Carole D. MITNICK, Olivia OXLADE, Patricia PAVLINAC and Judd L. WALSON. They did not participate in the formulation of recommendations related to the respective reviews of evidence that they performed.

This information is included in the Funding and declarations of interest section in the Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update, page 2, available at: https://iris.who.int/handle/10665/44597.

WHO treatment guidelines for drug-resistant tuberculosis, 2016 update

Guideline Development Group

The scope of the guidelines update, and the composition of the GDG, including their biographies, were made public for comment ahead of the meeting in line with WHO's conflict of interest policy. All GDG members completed the WHO Declaration of Interest forms. The WHO Guideline Steering Committee, in preparation for the update of the guidelines and the GDG meeting, reviewed the completed forms. The following GDG members declared no conflicting interests: Luis Gustavo do Valle BASTOS, José A CAMINERO, Tsira CHAKHAIA, Michel GASANA, Armen HAYRAPETYAN, Antonia KWIECIEN, Sundari MASE, Nguyen Viet NHUNG, Maria RODRIGUEZ, Holger SCHÜNEMANN, James SEDDON and Alena SKRAHINA.

The following GDG members declared interests that were judged not to be in conflict with the objectives of the meeting:

Farhana AMANULLAH declared having received funding for consultancies (US$ 500/ day) and travel from WHO; and grants from the Global Fund and TB-REACH to cover her salary (10% full-time equivalent).

Daniela CIRILLO declared having received funding from FIND to conduct evaluation of drugsusceptibility testing (DST) for new drugs (US$ 16 000), and from Otsuka to evaluate DST for delamanid (US$ 25 000). She also declared being the head of a supranational TB reference laboratory in Italy involved in country capacity-building in DST technologies for second-line drugs and new diagnostics for drug-resistant TB; and being a member of the Italian national committee for the use of bedaquiline.

Charles L. DALEY declared having received funding from Otsuka to serve as chair of the data monitoring committee for trials of delamanid (US$ 47 000 over 7 years–current).

Kelly DOOLEY declared having received funding to provide expert advice on a trial design for TB/ HI (US$ 2000/ year paid to the university/ employer); she also declared the following activities and roles: co-chair AIDS Clinical Trials Group (ACTG) study assessing bedaquiline and delamanid; principal investigator for adjuvant paclitaxel and trastuzumab (APT) trial assessing pretomanid (PA-824); and investigator in trials assessing high-dose isoniazid for MDR-TB, rifapentine for pregnant women and children with latent TB infection (LTBI), high- dose rifampicin and levofloxacin for paediatric TB meningitis, as well as bedaquiline and delamanid for children with MDR-TB and HIV infection.

Agnes GEBHARD declared that she works for the KNCV TB Foundation, which has two projects funded by the Eli Lilly and Company Foundation: (i) engaging the private sector in diagnosis and treatment of TB and MDR-TB with quality-assured second-line TB drugs, and (ii) the roll-out of QuanTB (a drug forecasting tool) in countries not supported by the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) implemented by Management Sciences for Health. In addition, she declared that the KNCV TB Foundation has a collaborative project with Cepheid in two countries (Nigeria, Viet Nam), with KCNV providing services for the installation and initial training on the use of GeneXpert machines.

Carlos TORRES-DUQUE declared having received honoraria from Janssen Pharmaceuticals for presentations on TB prevention and WHO policy on bedaquiline at a Latin American Meeting on MDR-TB held in 2014 (US$ 2000). Tom SHINNICK declared being an employee of the United States Centers for Disease Control and Prevention (CDC). CDC supports his travel and research related to his work on laboratory services needed for TB control. He declared having often represented CDC's position on laboratory services needed for TB diagnosis, treatment and control. As part of his official duties for CDC, he served on the Data and Safety Monitoring Board (DSMB) organized by Otsuka for the clinical trial of delamanid. He did not receive any remuneration for serving on the DSMB nor for travel expenses (CDC paid for all travel expenses related to serving on the DSMB). The DSMB has completed its work for the trial.

The following GDG members declared interests that were judged to be in conflict with some of the objectives of the meeting and were thus recused from some of the discussions: Lindsay MCKENNA declared non-commercial support to Treatment Action Group (TAG), her employer, from Stop TB Partnership; Bill & Melinda Gates Foundation; the Department of Veteran Affairs (on behalf of CDC); Janssen Therapeutics for Hepatitis C and HIV projects and the Global Alliance for TB Drug Development (a public–private entity developing new drugs and regimens for TB treatment). She was thus recused from participating in the 9 November 2015 meeting session on Patients, Intervention, Comparator and Outcomes (PICO) question 1 on MDR-TB regimen composition for adults and children. José A CAMINERO stated in his biosketch that he is a staff consultant of the International Union Against Tuberculosis and Lung Disease (UNION), an agency directly involved in the implementation and evaluation of programmes using shorter MDR-TB regimens. He was therefore recused from the 10 November 2015 meeting session on PICO question 3 on shorter regimens for MDR-TB.

External Review Group

The following ERG members declared no interest related to the objectives of this meeting: Chen-Yuan CHIANG, Celine GARFIN, Michael KIMERLING, Vaira LEIMANE, Gao MENGQIU, Norbert NDJEKA, Ejaz QADEER, Lee REICHMAN, Rohit SARIN and Irina VASILYEVA.

The following two ERG members declared interests which were judged not to be in conflict with the objectives of the guidelines. Guy MARKS declared research support from AERAS (US$ 450 000) related to the evaluation of latent TB infection and the rate of recurrence of TB after initial treatment in Viet Nam. He also declared being the Vice-President (and a board member) of the UNION and Editor-in-Chief of the International Journal of Tuberculosis and Lung Disease (for which he receives an honorarium). Dalene VON DELFT declared having received support from TAG, USAID, UNITAID, Janssen Pharmaceuticals, Critical Path to TB Drug Regimens (CPTR) and AERAS to cover travel costs and accommodation to give presentations/speeches on drug-resistant TB. She declared that in 2011 she received bedaquiline as part of her MDR-TB treatment through a compassionate use access programme.

Evidence Reviewers

The following reviewers declared interests that were judged not to be in conflict with the objectives of the meeting:

Gregory J FOX declared having received research and non-monetary support from the UNION (sponsored by Otsuka) valued at about US$ 5000 to attend the 2015 International UNION Conference and to receive the Young Innovator Award (he declares no work for Otsuka or any relationship of this award with any commercial or research activities with Otsuka).

Katherine FIELDING declared that her employer (LSHTM) was a recipient of an award from Médecins Sans Frontières (MSF) (£26 890) for the period February–December 2015 to provide statistical support for the TB-PRACTECAL study on which she is a co-investigator. The study is a Phase II–III randomized controlled trial (RCT) to evaluate the efficacy and safety of shorter MDR-TB regimens for adults.

Rebecca HARRIS declared she is consulting for a clinical research organization (Cromsource) working for Glaxo SmithKline (GSK) vaccines (~£90 000 in 2013); and on GSK vaccines not related to TB (~£10 000 since 2013) for Manpower Solutions.

David MOORE declared receiving research support from the Wellcome Trust Research Training Fellowship Programme to supervise a PhD student to study MDR-TB in Peru (£207 056 in 2014).

Anneke HESSELING declared that her employer (Stellenbosch University) is a recipient of an award from Otsuka Pharmaceutical (~US$ 70 000 to date) for her work on the Phase III delamanid clinical trials in children.

This information is included in the Declaration of interest section in the WHO treatment guidelines for drug-resistant tuberculosis, 2016 update, pages 2–5, available at: https://iris.who.int/handle/10665/250125.

WHO guidelines for the treatment of drug-susceptible tuberculosis and patient care, 2017 update

The scope for the update of the Guidelines for treatment of drug-susceptible tuberculosis and patient care and the composition of the Guideline Development Group (GDG), as well as the External Review Group, were established in line with WHO's policy on conflict of interest. All contributors completed a WHO Declaration of Interest form. All stated declarations of interest were evaluated by three members of the steering group for the existence of any possible financial or intellectual conflict of interest. In some cases there was possible conflict of interest justifying the exclusion from membership of the GDG,

and the Director of the WHO Global TB Programme, the WHO Guideline Review Committee and the WHO Legal Office were consulted on this and a decision was made. Diversity and broad representation in the GDG were sought in an effort to address and overcome any potential intellectual conflicts of interest. The GDG was composed of representatives of technical partners and academia, a GRADE methodologist, national TB programme managers from different WHO regions, representatives of civil society organizations, experts from WHO collaborating centres, professional organizations and a representative from the International Organization for Migration (see **Annex 2**). The biographies of the GDG members were made public ahead of the meeting, and the WHO Guidelines Steering Committee, which was formed in preparation for the update of the guidelines, reviewed the completed forms at the beginning of the meeting with everyone present.

Guideline Development Group

The following members declared no interests: Si Thu AUNG; Frank BONSU; Jeremiah CHAKAYA; Lucy CHESIRE; Daniela CIRILLO; Poonam DHAVAN; Kathy FIEKERT; Andrei MARYANDYSHEV; Nguyen Viet NHUNG; Ejaz QADEER; Abdul Hamid SALIM; Holger SCHÜNEMANN; Pedro SUAREZ; Justin Wong Yun YAW.

The following GDG members declared interests that were judged not to be in conflict with the policy of WHO, or the objectives of the meeting:

Kelly DOOLEY declared that she did not receive any salary support from drug companies for her work in the following roles and activities: Co-chair of the AIDS Clinical Trials Group (ACTG) study assessing bedaquiline and delamanid for MDR-TB; principal investigator, assessing pretomanid for tuberculosis trial, assessing pretomanid (PA-824, investigational drug) for treatment of drug-sensitive TB; investigator on trials assessing rifapentine for pregnant women with latent TB infection, rifapentine for treatment shortening in patients with pulmonary TB, high-dose rifampicin and levofloxacin for paediatric TB meningitis, high-dose isoniazid for MDR-TB, and delamanid for MDR-TB in children with and without HIV.

Mike FRICK declared that his organization received non-commercial support (1) to track investment made in TB research and development; (2) to host a symposium at the UNION meeting; (3) advocate for increased funding for TB research and development, research and access to evidence-based interventions; and (4) management of community research advisors group.

Simon SCHAAF declared receiving grants for pharmacokinetic drug studies in children of second-line drugs and for studying preventive therapy in MDR-TB.

Carrie TUDOR declared that her organization receives funding from Eli Lilly Foundation for activities related to TB and MDR-TB projects.

External Review Group

The following External Review Group members declared no interest related to the objectives of this meeting: Riitta DLODLO, Celine GARFIN, Lee REICHMAN, Vaira LEIMANE, Rohit SARIN, Dalene VON DELFT and Fraser WARES. The following WHO staff from the regional offices reviewed the final draft of the guideline document: Masoud DARA (Europe), Mirtha DEL GRANADO (Americas), Daniel KIBUGA (Africa), Hyder KHURSHID (South-East Asia), Mohamed AZIZ (Eastern Mediterranean), and Nobuyuki NISHIKIORI (Western Pacific).

Evidence Reviewers

The researchers who undertook the systematic reviews of evidence for this revision were the following: Narges ALIPANAH, Cecily MILLER, Payam NAHID (team leader for PICO 1, 2 & 7–10), University of California, San Francisco, USA; and Lelia CHAISSON, Johns Hopkins Bloomberg School of Public

Health, Baltimore, USA. Richard MENZIES, McGill University, Montreal, Canada (team leader for PICO 3, 4 & 6); and James JOHNSTON, University of British Columbia, Vancouver, Canada. Gregory FOX (team leader for PICO 11) and Jennifer HO, University of Sydney, Sydney, Australia. The evidence reviewers did not participate in the formulation of the policy recommendations.

The following reviewers declared no interest related to the objectives of and their attendance at the meeting: Narges ALIPANAH, Jennifer HO and James JOHNSTON. The following reviewer declared interests that were judged not to be in conflict with the policy of WHO, or the objectives of the meeting: Payam NAHID declared that his research unit received support from the United States Centers for Disease Control and Prevention through a federal contract to support clinical trial units in San Francisco, USA, and in Hanoi, Viet Nam.

This information is included in the Declaration and management of conflict of interest section in the Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update, pages 6–7, available at: https://iris.who.int/handle/10665/255052.

WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018

Guideline Development Group:

The scope of the guidelines update and the composition of the Guidelines Development Group (GDG), including the biographies of the members, were made public for comment ahead of the meeting, in line with WHO requirements. All GDG members completed the WHO Declaration of interest (DoI) form and agreed to the confidentiality undertaking. The WHO Guideline Steering Committee reviewed the completed forms.

The following GDG members declared no interests conflicting with the objectives of the guidelines: Eden ABADIANO MARIANO, Sarabjit S CHADHA, Fernanda DOCKHORN COSTA JOHANSEN, Edwin HERRERA-FLORES, Ayuko HIRAI, Alexander KAY, Rafael LANIADO-LABORIN, Lawrence MBUAGBAW, Austin Arinze OBIEFUNA, Cristina POPA, Wipa REECHAIPICHITKUL, Maria RODRIGUEZ, Holger SCHÜNEMANN, Adman Skirry SHABANGU and Sabira TAHSEEN.

The following GDG members declared interests that were judged not to be in conflict with the objectives of the guidelines:

Susan ABDEL-RAHMAN declared that a research grant (US$ 196 356) was received by her institution from the Thrasher Foundation in September 2017 for her role as Principal Investigator to study whether second-line TB medicines can be accurately quantified from dried blood spots (funding ongoing). Daniela CIRILLO declared that a grant (US$ 26 000) was provided to her research unit by the Foundation for Innovative New Diagnostics (FIND) to evaluate new TB diagnostics (funding ongoing). In 2014, she received funding from Janssen (US$ 10 000) and Otsuka (US$ 25 000) for work on drug-susceptibility testing (DST) of new drugs. In 2014, Janssen Italy funded her participation in an expert working group on the use of bedaquiline in Italy (US$ 1000). Geraint (Gerry) Rhys DAVIES declared that he was until November 2017 the academic coordinator of the PreDiCT-TB consortium, a public–private partnership funded by the European Union Innovative Medicines Initiative and the European Federation of Pharmaceutical Industries and Associations (EFPIA). Although this role involved engagement with industrial partners (GSK, Sanofi, Janssen) in pre-competitive areas of research into TB drug development, these activities were fully supported by public funding from the European Union (EU) and neither he nor his research institution have received any funding from EFPIA or from the individual industrial partners. He has been asked and intends to provide advice to the STREAM study team on possible PK studies, which may be carried out in future using existing or further prospectively collected samples (no payment or research support has been offered for this activity). In 2017, he was paid fees by WHO for expert consultancies (US$ 5000). He is a member

of a steering group convened by Critical Path to TB Regimens to advise on development of the lipoarabinomannan (LAM) biomarker developed by Otsuka in the context of adaptive clinical trials (receives no payment for this activity). Bernard FOURIE declares receiving US$ 16 000 per year (ongoing) to act as a non-executive director and member of the Board of the National Bioproducts Institute in South Africa, which is exclusively involved in the production and marketing of blood- and plasma-derived products. Payam NAHID declares an ongoing Federal Centers for Disease Control and Prevention (CDC) contract to the University of California San Francisco to support clinical trial units in San Francisco and Viet Nam (total amount not specified). Carrie TUDOR declares that her employer receives funding from the Eli Lilly Foundation (~US$ 1000 000 for 2013–2017; ongoing at US$ 243 000 in 2018) to run the International Council of Nurses' TB/MDR-TB project. The project focuses on building the capacity of nurses and allied professionals on TB and DR-TB care through training and currently operates in China, Eswatini, Ethiopia, Lesotho, Malawi, the Russian Federation, Uganda and Zambia. She also received US$ 20 000 from the KwaZulu Natal Research Institute for TB & HIV (South Africa) and Fogarty/NIH (USA) for her dissertation and postdoctoral research on TB until 2014. Zarir UDWADIA declares that he has supported about 40 patients to access bedaquiline and three patients to access delamanid through the compassionate use programmes of Janssen and Otsuka, respectively. He declares that he did not charge fees to the patients involved and there were no financial transactions with the manufacturers. Andrew VERNON declares that he heads a clinical research group at CDC (Tuberculosis Trials Consortium [TBTC]) doing TB trials. TBTC often collaborates with pharmaceutical companies, which may provide modest support, e.g. drug supplies, funding for PK sub-studies. Sanofi Aventis awarded ~US$ 2.8 million in six unrestricted grants to CDC Foundation in 2007–2015 to facilitate or support TBTC work on rifapentine (e.g. PK studies, staff contracts, travel for invited speakers, preparation of data to support regulatory filings). These funds have not otherwise benefited the research group. TBTC has studies under way with rifapentine (TBTC Study 31) and levofloxacin (Opti-Q, TBTC Study 32). He declares that his branch has supported studies of drug-susceptible TB that have included moxifloxacin (TBTC Study 27, Study 28 and Study 31). His branch has also supported enrolment at two of the three sites involved in the Opti-Q Study. This study evaluates different doses of levofloxacin in the treatment of DR-TB and has no comparator arm. There is no involvement with drug procurement. The principal investigator and management of the study, including data handling, analysis and drug procurement, are at Boston University. The Opti-Q outcomes are not yet known and the final analysis has yet to start. The majority of the study was funded by the NIH (National Institutes of Allergy and Infectious Diseases [NIAID]). The following GDG member declared an interest that was judged to conflict with the objectives of the guidelines (funding for new medicines for use in MDR-TB regimens). He therefore withdrew from the GDG panel and participated as a technical resource. Gary MAARTENS declared that his laboratory will receive US$ 2 184 608 from the NIH (NIAID) to undertake drug assays for a trial on the safety, tolerability and PK of bedaquiline and delamanid, alone and in combination, among patients on MDR-TB treatment (AIDS Clinical Trials Group study A5343). He will receive no salary support.

External Review Group (ERG)

The following ERG members declared no interest conflicting with the objectives of the guidelines: Essam ELMOGHAZI, Mildred FERNANDO-PANCHO, Anna Marie Celina GARFIN, Barend (Ben) MARAIS, Andrei MARYANDYSHEV, Alberto MATTEELLI, Giovanni Battista MIGLIORI, Nguyen Viet NHUNG, Rohit SARIN, Welile SIKHONDZE, Ivan SOLOVIC, Pedro SUAREZ and Carlos TORRES.

The following ERG member declared interests that were judged not to be in conflict with the objectives of the guidelines:

Thato MOSIDI declares that she represents people affected by and living with TB on the Global Fund Country Coordinating Mechanism in South Africa. She is also an active member of TB Proof, a notfor-profit organization that advocates for patient access to TB medicines.

The following evidence reviewers were from McGill University, Montréal, Canada – Syed ABIDI, Jonathon CAMPBELL, Zhiyi LAN and Dick MENZIES. They declared no interest conflicting with the objectives of the guidelines.

The following evidence reviewer declared interests that were judged not to be in conflict with the objectives of the guidelines: Faiz Ahmad KHAN declared payment by WHO to collect data and carry out a meta-analysis on the shorter MDR-TB regimens for the 2016 guidelines (CAD$ 4080) and travel fees to present these findings at a GDG meeting in 2015. He also declares undertaking an update of the same analysis in 2016–2018 for the ATS guidelines for which he receives no remuneration.

WHO treatment guidelines for isoniazid resistant tuberculosis, 2018

In conformity with the WHO guidelines for declarations of interest1 for WHO experts issued by the WHO Compliance, Risk Management and Ethics Office, members of the Guideline Development Group (GDG), Evidence Review Group (ERG) and evidence reviewers were requested to submit completed WHO Declaration of Interest forms (DoIs) and declare in writing any competing interest (whether academic, financial or other) that could be deemed as conflicting with their role in the development of this guideline. In order to ensure the neutrality and independence of experts, an assessment of the DoI forms, curricula vitae, research interests and activities was conducted by the WHO Guideline Steering Committee. For cases in which potential conflicts were identified, the WHO Compliance, Risk Management and Ethics Office was consulted for further clarification and advice as to how to manage competing interests. If any declared interests were judged significant, individuals were not included in the GDG.

ERG members were also requested to declare interests and these were also assessed for potential conflict. As per WHO rules, the objectives of the guideline development process and the composition of the GDG, including member biographies, were made public 4 weeks ahead of the meeting.

This public notice was conducted to allow the public to provide comments pertinent to any competing interests that may have gone unnoticed or not reported during earlier assessments.

Guideline Development Group

The following GDG members declared no interests: Daniela CIRILLO, Kelly DOOLEY (Co-Chair), Gustavo DO VALLE BASTOS, Raquel DUARTE, Christopher KUABAN, Rafael LANIADO-LABORIN, Gary MAARTENS, Andrei MARYANDYSHEV, Ignacio MONEDERO-RECUERO, Maria Imelda Josefa QUELAPIO, Wipa REECHAIPICHITKUL, Nancy SANTESSO (Co-Chair), Welile SIKHONDZE and Armand VAN DEUN.

Five GDG members declared interests that were judged non-significant and not affecting the neutrality of the guideline development process. Therefore, no restrictions to their participation applied:

Farhana AMANULLAH: (1b) paediatric expert for WHO TB monitoring mission in Indonesia (value US$ 600/day, 14–27 January 2017); (2a) paediatric TB expert for Harvard Medical School Global Health Delivery grant (20% full-time equivalent [FTE]; June 2016–June 2018); (2b) paediatric TB expert for Global Fund grant (20% FTE; June 2016–December 2017).

Tsira CHAKHAIA: (1b) Research coordinator for TB Alliance NC-006 clinical trial (2016); community engagement project coordinator for TB Alliance (current); research coordinator for NiX-TB (from May 2017).

Philipp DU CROS: (2a) Member of the protocol writing committee and steering committee of the TB-PRACTECAL Clinical Trial, which has received a grant of €6.8 million from the Dutch Postcode Lottery to Médecins Sans Frontières, Operational Centre Amsterdam (currently active).

Michael RICH: (1a) employed by Partners in Health to work on clinical care guidelines and in the programmatic management of DR-TB; (1a) WHO consultancies on treatment of drug-resistant TB to national TB programmes; (2a) conduct research and develop regimens for drug-resistant tuberculosis (DR-TB) as a recipient of the UNITAID's Expand new drug markets for TB [EndTB] grant (all active during the development of the present recommendations).

Rada SAVIC: (1b) Member of the panel of the WHO Meeting on Target Regimen Profiles (value US$ 2500); grant reviewer for European and Developing Countries Clinical Trials Partnership (value US$ 1000); (2a) principal investigator or co-principal investigator of research grants by United States National Institutes of Health (NIH) and Gates Foundation on improving TB treatment options (all currently active).

External Review Group

The following ERG members declared no interests related to the objectives of this meeting: Essam ELMOGHAZI, James JOHNSTON, Enos MASINI, Rohit SARIN, Kitty VAN WEEZENBEEK, Irina VASILYEVA and Piret VIIKLEPP.

The below-mentioned ERG members declared interests that were judged not to be significant to the topic of the guideline. Some of the ERG members were involved in clinical trials not related to the treatment of Hr-TB and therefore no restrictions applied to their participation as expert reviewers.

Charles L. DALEY: (1b) Chair and member of data monitoring committees for delamanid studies (US$ 45 000 provided by Otsuka Pharmaceutical over 8 years; ongoing); Chair of data monitoring committee for clofazimine studies (US$ 2500 provided by Novartis; finished in 2016).

Ingrid OXLEY: (5b) at the Union Conference 2015 in Cape Town, TB Proof campaigns advocated for treatment of latent TB infection (LTBI) among health care workers. She is a health care worker and has had two episodes of TB. Many members of TB Proof who are health care workers may have benefited Annex 2: Declarations of interest 39 from the WHO guidelines for the treatment of LTBI or received funding for LTBI treatment. This was not the focus of the current guideline.

Simon SCHAAF: (2a) research support to employer for pharmacokinetics work on second-line TB medicines in children from the NIH and Otsuka Pharmaceutical (approximately ZAR 5 million/year). NIH grant ceased in 2015; Otsuka Pharmaceutical grant is still active.

Helen STAGG: (1b) grant to employer for consultancy work on MDR-TB clinical pathways in eastern Europe (Otsuka Pharmaceutical: £59 925; 2013–2015); (2a) grant to employer for Hepatitis and Latent TB Infection (HALT) study (Department of Health of the United Kingdom; National Institute for Health Research, United Kingdom; £86 000 for HALT study (2014); £315 265 for fellowship, salary, research costs; 2015–2017); (2b) non-monetary support for HALT study (Sanofi provides free rifapentine to the research study participants; 2014–2017); (6d) received International Trainee Scholarship Award (US$ 1000 value) at the American Thoracic Society (ATS) conference 2016 where she presented the results of a review she conducted (1).

Carlos A. TORRES-DUQUE: (5a) & (5b) as member of the National Advisory Committee for Tuberculosis (Ministry of Health of Colombia) participates in the updates of national TB treatment guidelines. His expert opinion is based upon evidence and local/international experience and does not generate any profits for him.

Evidence reviewers

The independent experts who undertook the systematic reviews of evidence for this revision declared no interests related to the topic of the policy guideline objectives.

This information is included in the Declaration of interest section in the WHO treatment guidelines for isoniazid-resistant tuberculosis, pages ix–xi, available at: https://iris.who.int/handle/10665/260494.

WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2020

In conformity with WHO guidelines for declaration of interests for WHO experts issued by the WHO Office for Compliance and Risk Management and Ethics, members of the Guideline Development Group, External Review Group and evidence reviewers were requested to submit completed WHO Declaration of Interest forms (DOIs) and declare in writing any competing interest (whether academic, financial or other) which could be deemed as conflicting with their role in the development of this guideline. In order to ensure the neutrality and independence of experts, an assessment of the DOI forms, curricula vitae, research interests and activities was conducted by the WHO Guideline Steering Committee. For cases in which potential conflicts were identified, the WHO Office for Compliance and Risk Management and Ethics was consulted for further clarification and advice as to how to manage competing interests. If any declared interests were judged significant, individuals were not included as members of the Guideline Development Group.

As per WHO rules, the objectives of the guideline development process and the composition of the GDG, including member biographies, were made public ahead of the meeting (https://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/drug-resistant-tb-gdg/en/). This public notice was conducted to allow the public to provide comments pertinent to any competing interests that may have gone unnoticed or not reported during earlier assessments.

Guideline Development Group

The following Guideline Development Group members declared no conflicts of interest: Holger Schünemann (Chair); Rafael Laniado-Laborin (Co-Chair); Erlina Burhan; Fernanda Dockhorn Costa Johansen; Bernard Fourie; Elmira Gurbanova; Muhammad Amir Khan; Marian Loveday; Mahshid Nasehi; Ben Marais; Beatrice Mutayoba; Maria Rodríguez; Debrah Vambe; and Nguyen Viet Nhung. One member of the Guideline Development Group submitted additional information, which required no further action as this did not result in any conflict.

Ingrid Schoeman: As an XDR-TB survivor, she went through the side-effects of being on treatment for 2 years. She works at TB Proof, and advocacy organization which is often invited to attend key stakeholder meetings where they share the experiences of DR-TB survivors and advocated for high-quality TB care. She has been employed by TB Proof since 2017. She is certain that better evidence-based guidelines for treating DR-TB would benefit her colleagues, friends and local communities.

Six members of the Guideline Development Group declared interests that were judged non-significant and were believed not to affect the independence and impartiality of the experts during the guideline development process. Therefore, no restrictions to their participation applied:

Charles Daley: Participation in the Data Monitoring Committee (DMC) for delamanid. A total of 5000 USD by Otsuka Pharmaceutical for services rendered in 2016 as the Chairman of the Committee. Participation in the DMC for pediatric trials of delamanid (Role Member). A total of 4000 USD by Otsuka Pharmaceutical for current services as a member of the Committee.

Gerry Davies: Participation in the PreDiCT-TB consortium, a public-private partnership funded by the European Union Innovative Medicines Initiative and the European Federation of Pharmaceutical Industries and Associations (EFPIA). Role as academic coordinator (2012–2017) led to engagement with industrial partners in pre-competitive areas of research into TB drug development. All of these activities were fully supported by public funding from the European Union. No financial support was

received from EFPIA. Current collaborator on pharmacokinetic sub-studies deriving from the STREAM Stage 1 trial. Funding support will be provided through research institution [University of Liverpool] to support analysis of pharmacokinetic samples and data later in late 2019/early 2020. This works focuses on evaluating clofazimine and fluoroquinolones. Academic co-supervisor of PhD candidate who is currently involved in the TB-PRACTECAL trial (chief investigator) at the London School of Hygiene and Tropical Medicine. Funding support will be provided through research institution [University of Liverpool] from Médecins Sans Frontières to support analysis of pharmacokinetic samples in early 2020. This work will involve bedaquiline, pretomanid, clofazimine, linezolid and moxifloxacin.

Yuhong Liu: China's New Drug Introduction and Protection Program (NDIP) was supported by the Bill & Melinda Gates Foundation (BMGF) and Janssen Pharmaceutica. Bedaquiline was provided by Janssen Pharmaceutica through the global donation project (4000 patients). BMGF and Janssen Pharmaceutica also project support to doctors' training, project activity implementation, quality control, etc. A total of 500 000 USD was provided for project implementation by BMGF including training, data collection, project supervision, between 2016–2020. Financial interests (resulting from funding source) that could directly affect, or could appear to affect, the professional judgment of the expert was not identified.

Iqbal Master: Non-monetary support provided by Janssen Pharmaceutica to attend the 2016 International Lung conference in Liverpool. Only flights and accommodation were sponsored. No direct or indirect payments were made. As a manger in the MDR unit, I provide a link for the implementation of research studies, including STREAM 1 and the Nix-TB trial from 2013 onwards. I received no monetary support or remuneration for involvement in these studies. My involvement was purely from an altruistic wish to facilitate research in order to improve treatment regimens and outcomes in MDR patients in general. As a government official, working in at a public health hospital, participation in the roll-out of bedaquiline and delamanid through a Clinical access programme, launched by the National TB programme. Member of the Provincial and National MDR-TB Advisory Committee of South Africa which makes recommendations and advises Government sites on clinical management.

Payam Nahid: Federal CDC contract to support clinical trial units in San Francisco and Hanoi, Viet Nam United States Centers for Disease Control and Prevention University of California, San Francisco Federal contract to support clinical trial units in San Francisco and Hanoi, Viet Nam. Participation as a member of the DSMB for an MDR-TB clinical trial, TB-PRACTECAL. All DSMB related materials are obviously kept confidential. Discussions are underway with Médecins Sans Frontières (MSF) for future potential participation of Viet Nam clinical trial units in Hanoi and Ho Chi Minh city in EndTB MDR-TB clinical trials. No contracts or agreements have been offered, signed or formalized. If agreements are formalized, enrolments into the EndTB trials would be anticipated to begin in 2020.

Carrie Tudor: Grant from Eli Lilly Foundation – Lilly MDR-TB Partnership for TB Project managed by the International Council of Nurses. Award of approximately USD 1 000 000 from 2013–2019.

The below-mentioned members of the Guideline Development Group declared interests which were judged to be significant, and which required further discussion and assessment by the WHO Office for Compliance and Risk Management and Ethics to outline a management plan:

Susan Abdel-Rahman: (Significant) Research Support from the Thrasher Foundation for an amount of 197 000 USD. Funding ended on 30 October 2017. The Thrasher Research Fund provides grants for paediatric medical research. The Fund is currently supporting over 150 projects, including but not limited to research on childhood blindness, nutritional deficiencies, brain injuries, diabetes, asthma, cancer, genetic diseases and a number of infections including HIV, malaria, TB, schistosomiasis, cytomegalovirus and otitis media. Employment & Consultancies: WHO Agreement for performance of work to conduct a summary review of preclinical and EBA data on pretomanid use. Financial interests (resulting from research support) that could directly affect, or could appear to affect, the professional judgment of the expert were not identified. Financial interest resulting from WHO Agreement for performance of work may be perceived to compromise the expert's objectivity or independent

professional judgment in the discharge of GDG duties and responsibilities led to partial exclusion from decision-making and voting limited to BPaL regimen.

Daniela Cirillo: Research grant to measure minimum inhibitory concentrations (MIC) for bedaquiline. Work sponsored through the Ospedale San Raffaele by Janssen Therapeutics. The amount granted was 50 000 USD in 2018. Research grant to study MIC distributions for new TB drugs. Work sponsored through the Ospedale San Raffaele by the TB Alliance. The amount granted was 30 000 USD in 2018. Payment for MIC work for new TB drugs was done through Ospedale San Raffaele and not direct to the individual. Although these interests are tangentially related to the subject of the current guideline development meeting (i.e. diagnostics), a significant conflict of interest was identified for participation in the decision-making process and voting related to funding from the TB Alliance, leading to partial exclusion from decision-making and voting limited to BPaL regimen.

Kelly Dooley: Participation as PI of the "Assessing Pretomanid for TB (APT)" trial, assessing pretomanid for treatment of drug-sensitive TB. Support and funding is from the FDA. Drug donation from TB Alliance (pretomanid) and Pfizer (rifabutin). No salary support. Participation as investigator on trials sponsored by the NIH, FDA, the CDC or UNITAID, assessing: Use of rifapentine for TB infection in pregnant women, young children, patients with HIV co-infection; use of rifapentine for treatment shortening in patients with pulmonary TB (rifapentine donated by Sanofi); use of high-dose rifampin and levofloxacin for pediatric TB meningitis (NIH funded); use of high-dose isoniazid for MDR-TB (NIH funded, ACTG A5312); delamanid for MDR-TB in children with HIV infection (NIH funded, IMPAACT 2005; drug donation by Otsuka); bedaquiline for children with MDR-TB and HIV infection (NIH Funded, IMPAACT 1108); meropenem/amox/clav for drugsensitive- and MDR-TB (FDA funded). No salary support. Protocol Co-Chair ACTG study A5343 assessing use of delamanid and bedaquiline among patients with MDR-TB. Drug donation by Otsuka, Janssen and ViiV Healthcare. Support and funding for this trial are provided by the NIH, Division of AIDS (DAIDS); no salary support. Involvement in the DELamanId BEdaquiline for ResistAnt TubErculosis study (A53439) led to partial exclusion limited to discussions and voting processes related to the combined use of bedaquiline and delamanid.

Agnes Gebhard: Research grant provided to KNCV by the TB Alliance to conduct a situational analysis in 3 countries (Indonesia, Kyrgyzstan, Nigeria) to understand the current infrastructure, resources, and practices for management of all forms of TB, and potential hurdles for integrating regimens (BPaL, BPaMZ, separately and together as a comprehensive solution to TB treatment). Research grant provided by the TB Alliance (305 000 USD – Between 2018 and 2019) to develop a country roadmap for introduction of new regimens. Four countries were chosen as examples (Kazakhstan, Kyrgyzstan, Uzbekistan and Indonesia). These roadmaps are flexible for use with any new (DR) TB regimen. Public support for the approval of Pretomanid in combination with bedaquiline and linezolid submitted to the FDA Antimicrobial Drugs Advisory Committee in response to a request for comments. The letter is in the public domain (https://www.regulations.gov/docketBrowser?rpp=25&so=DESC&sb=commentDueDate&po=0&dct=PS&D=FDA-2019-N-1317). Financial interest (Institutional) resulting from research grants provided by the TB Alliance led to partial exclusion from decision-making and voting limited to BPaL regimen.

Alberto Piubello: Involvement in the Union-sponsored study "Treatment Regimen of Antituberculosis Drugs for Patients With Multi-Drug-Resistant TB (STREAM), Stage 2" led to partial exclusion from decision-making and voting limited to the all-oral bedaquiline-containing shorter regimen.

Alena Skrahina: Principal Investigator in the Pragmatic Clinical Trial for a More Effective Concise and Less Toxic MDR-TB Treatment Regimen(s) (TB-PRACTECAL) led to partial led to partial exclusion from decision-making and voting limited to BPaL regimen.

Andrew Vernon: Work in the Division of TB Elimination at CDC which involved collaboration with NIH and Sanofi on the conduct of a multinational phase 3 trial of TB treatment using daily rifapentine. Sanofi provided medications for the trial, and has supported costs of PK testing. Total contribution to CDC Foundation was ~$3million (from 2007–17). No payment was received through these funds.

Moreover, these funds were only a small proportion of overall trial costs, the vast majority of which were borne by CDC as the trial sponsor. In his capacity as a TB researcher and clinician at CDC, Andrew participated in meetings, both internal and external, concerned with the development of guidelines for the treatment of active TB and of LTBI in the United States. Role of the CDC as temporary voting members within the FDA's Antimicrobial Drugs Advisory Committee Meeting. The latter interest led to partial exclusion from decision-making and voting limited to BPaL regimen.

External Review Group

The following External Review Group members declared no conflicts of interest: Heather ALEXANDER, Sarabjit Singh CHADHA, Lisa CHEN, Edwin H HERRERA-FLORES, Anna Marie Celina GARFIN, Mathilde JACHYM, Giovanni Battista MIGLIORI, Thato MOSIDI, Welile SIKHONDZE, Bhabana SHRESTHA, Ivan SOLOVIC, Carlos TORRES, Zarir UDWADIA.

The following ERG member declared interests that were judged not to be in conflict with the objectives of the guidelines:

Amanullah FARHANA: Declared that she has been employed and undertaken consultancy work for WHO and that she has had research activities funded by WHO and the Global Fund.

Guy MARKS: Is the President of The Union (IUATLD), which undertakes projects and work in the field of MDR-TB. He is an investigator on the VQUIN trial, an investigated-initiated, publicly funded study on preventive therapy for contacts of patients with MDR-TB.

Andrei MARYANDYSHEV: Declared research undertaken on MDR/RR-TB. The new TB drugs were investigated in the clinical trials in the hospital where Dr Maryandyshev works, i.e. Arkhangelsk clinical antituberculosis dispensary, Russian Federation where he was a main investigator. He participated in the clinical trials of new TB drugs: TMC207-TiDP13-C209 and TMC207TBC3001 phase II-III from 1.02.2012 to 3.10.2016; "An international, multicenter, prospective, randomized, double-blind, controlled study evaluating the efficacy and tolerability of a chemotherapy regimen including SQ 109 in pulmonary tuberculosis patients with multiple drug-resistant M. tuberculosis (phase IIc-III) from 19.08.2014 to 13.07.2016; PBTZ169-A15-C2b-1 "An international multicenter, doubleblind, placebo-controlled, randomized trial to evaluate the efficacy, safety, and pharmacokinetics of PBTZ169 when used in combination therapy for patients with respiratory tuberculosis with bacterial excretion and drug resistance, phase IIb-III" from 13.12.2016 to 29.05.2017; Compassionate use of Delamanid (OPC-6768) for patients MDR TB, 6.12.2016 his hospital has received Delamanid for 5 patients from Otsuka company.

Lawrence MBUAGBAW: Undertook a biostatistical consultation to support FDA reporting requirements for the use of bedaquiline, for Janssen Pharmaceuticals for which he received payment.

Anuj K BHATNAGAR: Is the Co-Principal investigator for the STREAM 2 trial (Medical Research Council Clinical Trials Unit, London), for the Rajan Babu Institute of Pulmonary Medicine and Tuberculosis (RBIPMT) site, Delhi in India. The trial was initiated in this site in March 2019. The monetary aspects of the trial are being looked after by Vital Strategies as an affiliate of IUATLD for refurbishment of the ward, equipment, hiring of staff, upgrading laboratory facilities, access to all laboratory tests and patient support including monetary compensation. No money has been transferred to the institute for this trial. In addition, the National Institute for Research in Tuberculosis, Chennai (NIRT), an organization of the Indian Council of Medical Research (ICMR), Ministry of Health and Family Welfare, Government of India has initiated a Phase 3 trial – called BEAT-TB, to study the efficacy and tolerability of a combination of newer drugs for shortening the treatment for pre-XDR and XDR-TB in 5 sites of India. At the RBIPMT site, of which Dr Bhatnagar is the Principal Investigator for this trial, they have just completed a site initiation visit and recruitment of personnel.

The first instalment of the grant for the initiation of this trial by NIRT Chennai has been given for recruitment of staff, equipment, laboratory reagents and patient and DOT provider support.

Evidence reviewers:

The following experts who conducted the evidence for to inform the revision of the recommendations declared the below interests, which require no action beyond reporting for transparency purposes.

Amrita Daftary: Columbia University Consultancy (2016–2021) – This is an ongoing consultancy to provide qualitative expertise to the design and evaluation of an adherence intervention in people with XDRTB-HIV in KwaZulu Natal, South Africa. Commissioned qualitative research for current GDG meeting. IC-IMPACTS funded grant (2015 – 2018) – study has been completed at McGill University; this was an intervention to engage pharmacy providers in Patna, India, to screen and refer TB symptomatic persons for a chest x-ray and doctor for timely TB detection. BMGF funded grant (2017–2020) – This study is held at McGill University where she was based until June 2019; this is an observational study using standardized patients to assess quality of clinical care for TB diagnosis in Cape Town and Durban, South Africa. NIH funded grant (2018 – 2020) – study is based at CAPRISA and Columbia University; this is an intervention to reduce XDRTB-HIV stigma in coinfected patients in KwaZulu Natal, South Africa.

David Dowdy: Research grant Bill and Melinda Gates Foundation Grant to Institution (not owned by me) approx $300,000 current year interest, approximately $50,000. Travel to meetings Bill and Melinda Gates Foundation Travel paid for me to attend, approx. $10,000.

Gabriela Gomez: Consultant providing modelling results for an investment case on a universal drug regimen for TB. Direct funding granted through BMGF for an amount of USD 40000. Funding concluded in 2018. Managed research grant to LSHTM for an economic evaluation of TB-PRACTECAL. Funding provided through MSF to research unit. Approximately £ 150 000. Her involvement stopped August 2019, although the project continues. In addition, a second grant from TB Alliance was granted to conduct an economic evaluation of the BPaL regimen. Approximately £ 60 000. Since 12 August 2019, she has been employed by Sanofi Pasteur. She is the lead for Europe in Vaccine Epidemiology and Modelling. There is no TB vaccine in the commercial pipeline of Sanofi Pasteur to her knowledge currently. She was not representing Sanofi Pasteur at this meeting, but only presenting work done as part of her previous position as Associate Professor at LSHTM.

Richard Menzies: Commissioned WHO evidence reviews (2016-current) to identify, assess and synthesize the evidence for the development of guidelines for treatment of MDR-TB.

Rada Savic: She received research funding from NIH, UNITAID and BMGF. Research funding to her institution (UCSF) where she is a principal investigator. She serves on Scientific Advisory Committee for TB Alliance, but receives no income for that role. She is a member of Core Science Group for NIH clinical trial network (ACTG) and for CDC clinical trial consortia (TBTC).

WHO guidelines on the management of TB in children and adolescents, 2022

Declarations of interest and management of conflicts of interest

The members of the GDG and ERG completed a WHO declaration of interests form. All declarations were evaluated by the WHO Guideline Steering Group for any financial or other conflict of interest that might warrant exclusion from membership or from certain discussions of the GDG. The completed forms were summarized and presented to all GDG members at the first meeting, at which point the members were requested to update their declarations. Intellectual conflict of interest was not considered a motive for exclusion from the GDG as expertise on the topic was considered an important criterion for selection, and the diversity and representation in the Group was large enough to balance any individual member's intellectual interest. The lead evidence reviewers also completed a WHO

declarations of interest form. A summary of the declarations and any management actions taken is provided below, by group and individual concerned.

As per WHO rules, the objectives of the guideline development process and the composition of the GDG, including member biographies, were made public ahead of the meeting (https://www.who.int/publications/m/item/public-notice-guideline-development-group-meeting-on-who-consolidated-guidelines-on-the-management-of-tuberculosis-in-children-and-adolescents-2021). This public notice was conducted to allow the public to provide comments pertinent to any competing interests that may have gone unnoticed or not reported during earlier assessments.

Guideline Development Group

The following GDG members declared no conflicts of interest: Deepak Agarwal, Elie Akl (GRADE methodologist/Chair), Grace Bolie, Gunta Dravniece, Amir Khan, Betina Mendez Alcantara Gabardo Margaret Nasil Kal, Susan Maloney, Sushant Mane, Imran Pambudi, Phan Huu Phuc, Sabira Tahseen.

Five members of the GDG declared interests that were judged non-significant and were believed not to affect the independence and impartiality of the experts during the guideline development process.

Therefore, no restrictions to their participation applied:

Connie Erkens: was provided with non-monetary support by the company Qiagen in 2018, namely QuantiFERON-TB Gold plus kits (worth €24 000) supplied free of charge in the context of three pilot studies included in the TB Endpoint project that focused on the optimization of screening for TB infection and provision of TPT among high-risk migrant populations. Qiagen read the final manuscript of the publication on the pilot studies but did not have any role in the study design, implementation and analysis, and reporting of results, nor in the decision to publish the results.

Patrik Hummel: received remuneration of US$ 24 800 between November 2020 and March 2021 for a consultancy to support the WHO Working Group on Ethics and COVID-19, and the ACT-A Ethics & Governance Working group. Dr Hummel was contracted by the WHO Health Ethics & Governance Unit for this work.

Lindsay McKenna: was the TB co-director of Treatment Action Group (TAG), which was a subcontractor under the Unitaid-funded Elizabeth Glaser Pediatric AIDS Foundation (EGPAF) Catalyzing Pediatric TB Innovations (CaP TB) project in 2018–2019. Some of the funding received supported part of Ms McKenna's salary at TAG. TAG's involvement in the CaP-TB project was limited to community engagement and advocacy, mostly at the global level in year 1 of the project in the lead up to the United Nations General Assembly (UNGA) High-Level Meeting (HLM) on TB and focused on training civil society organizations on paediatric TB in year 2 of the project. Under the project, TAG primarily developed global advocacy materials (paediatric TB pipeline reports, paediatric section of annual TB R&D resource tracking reports, research priorities for paediatric TB) and strengthened capacity of civil society and community organizations networks to advocate for the needs of children and families affected by TB. There was no direct involvement in any of the research or other activities that EGPAF conducted at the site or community level. Even though the Cap-TB project is contributing data to PICO 6a and 6b, TAG's involvement in CaP-TB was very limited with a focus on community engagement and training on paediatric TB, and not linked to research and other activities conducted by EGPAF within the scope of the project. Therefore, the disclosure was deemed not to be in conflict with the scope of the work being undertaken by the GDG.

Moorine Sekkade: as the national coordinator for the Uganda child and adolescent TB response, represented the Uganda National TB and Leprosy Programme in the Decentralise TB services and Engage Communities to Transform lives of Children with TB (DETECT child TB) project that was conducted in Uganda. No remuneration was received for this work other than per diem for accommodation and incidentals for in-country travel. Even though data from the DETECT child TB project has informed PICO question 6a, Dr Sekkade's involvement in this project was limited and was

carried as part of her role in the NTLP as it mainly involved training. Thus, the disclosure was deemed not to be in conflict with the scope of the work being undertaken by the GDG.

Kathryn Snow: is currently consulting with the Department of Health, Victorian Public Service (A$ 67 000 per year). In 2016–2019 (contract ceased), she received remuneration for a consultancy with the WHO Global Tuberculosis Programme (A$ 40 000) on TB epidemiology in adolescents and on TB surveillance. In 2019 (contract ceased), she received remuneration for TB research related to adolescents (epidemiology and quality of care) from the University of Melbourne and Murdoch Children's Research Institute (A$ 60 000).

The below-mentioned members of the GDG declared interests that were judged to be significant and required further discussion and assessment by the WHO Office for Compliance and Risk Management and Ethics to outline a management plan:

Susan Abdel-Rahman: served as technical advisor to WHO (US$ 11 000) on the management of drug resistant TB in 2019. She also served as technical advisor for WHO Global Tuberculosis Programme to review paediatric pharmacokinetic and tolerability data on bedaquiline and delamanid made available to the WHO by Janssen Pharmaceutica, Otsuka and independent investigators ahead of the GDG meeting in June 2021, which will inform discussions and decisions around PICO 4a and 4b. The contract period was from April until end of June 2021 (US$ 5000). A significant competing interest was identified, which led to her exclusion from the discussion, decision-making and voting for PICO 4a and 4b. However, she was allowed to respond to specific questions about her analysis when asked during the GDG meeting.

Shakil Ahmed: contributed to a research project to assess the diagnostic performance of Xpert Ultra on stool to diagnose pulmonary TB in children. The study recruited children and young adolescents aged below 15 years with presumptive pulmonary TB, admitted in four tertiary care hospitals in Dhaka, Bangladesh between January 2018 and April 2019. Results of this project were published in a peer-reviewed journal with Dr Ahmed as the co-author of this publication (Kabir S, Rahman SMM, Ahmed S, et al. Xpert Ultra assay on stool to diagnose pulmonary tuberculosis in children. Clin Infect Dis. 2020 May 18:ciaa583). A significant competing interest was identified, given that the above-mentioned study is one of the nine studies included in the systematic review to inform PICO 2b, which led to his exclusion from discussions, decision-making and voting for PICO 2b.

Valentina Aksenova: participated as a Principal Investigator of the Janssen trial TMC207-C211, an open multicentre, non-comparative phase 2 study to evaluate the pharmacokinetics, safety, tolerability and antimycobacterial activity of the drug TMC207 (bedaquiline) when used in combination with a background regimen of drugs for the treatment of MDR-TB in children and adolescents aged ≥5 and <18 years. For this work, Dr Aksenova received 161 450 (corresponding to €1797.30 at the current exchange rate) during 2016–2017 and 441,924.5 (corresponding to WHO treatment guidelines for drug-resistant TB treatment, 2022 update interest was identified, given that data from the Janssen study C211 informed discussions and decisions around PICO 4a, which led to exclusion from discussion, decision-making and voting for PICO 4a.

Farhana Amanullah (content chair): was employed at the Indus Hospital Karachi, Pakistan until 2020 (10% of FTE), to support the zero TB cities initiative as a paediatric TB clinical expert. Dr Amanullah's salary was supported by a Global Fund TB grant. In 2019, Dr Amanullah served as a technical expert for WHO to participate in a Programme Review, and received US$ 50/day for a two-week mission. In 2019, WHO and Stop TB Partnership supported Dr Amanullah with air travel and per diem to participate in the Stop TB Partnership board meeting. Data from the Indus Hospital were included in the pooled cohort of individual patient data (IPD) to inform decisions on PICO 2a on treatment decision algorithms. Data from the Indus Hospital were also included in the systematic review to inform decisions on PICO 6a on decentralized TB care. These studies were carried out under her direct supervision. One study ceased in 2012 and the other in 2017. The study in 2017 was remunerated in the form of a 15% FTE from a TBREACH 4 grant. Dr Amanullah's team also contributed data to IPD

relevant to PICO 4, however these data are not being used to answer PICO questions 4a and 4b. A significant competing interest was identified, as Dr Amanullah's group contributed data for PICO 2a and PICO 6a, which led to her exclusion from discussions, decision-making and voting for these two PICO questions. Dr Amanullah is the content chair for the GDG meeting. However, given the significant competing interests identified for PICO 2a and 6a, Professor Graham (content chair) and Dr Kredo (GRADE methodologist) chaired the sessions on PICO 2a and 6a, respectively.

Chishala Chabala: participated as a country Principal Investigator for the SHINE Trial [ISRCTN63579542], a randomized controlled trial which evaluated treatment shortening in children with minimal TB. He implemented the study in the Zambian site and is currently participating in the publications, policy briefs and dissemination of the study findings. Funds received from the Medical Research Council Clinical Trials Unit (University College London) for the implementation of the SHINE trial in Zambia correspond to £576 000. This project has been completed (https://www.isrctn.com/ISRCTN63579542). Dr Chabala also indicated participation as one of the principal investigators in the Unitaid-funded TB Speed research project [https://www.tb-speed.com/], implementing the study in Zambia. This study aims to evaluate the systematic use of Xpert Ultra as a diagnostic tool for TB using stool and nasopharyngeal aspirate in children with severe pneumonia, severe acute malnutrition and HIV infection. Funds received from Unitaid for the implementation of the TB SPEED project in Zambia (currently ongoing) correspond to US$ 750 000. The TB SPEED project is implemented in six African countries and one Asian country. The University of Bordeaux coordinated data sharing to inform PICO 2b. Dr Chabala is also involved in the SURE trial (Short intensive treatment for children with tuberculous meningitis, https://www.isrctn.com/ISRCTN40829906). Funds received for the implementation of the SURE trial in Zambia (currently ongoing) correspond to £250 000. Dr Chabala is also involved in the EMPIRICAL trial (Empirical Treatment Against Cytomegalovirus and Tuberculosis in HIV-infected Infants with Severe Pneumonia; https://clinicaltrials.gov/ct2/show/NCT03915366), with funding from the European & Developing Countries Clinical Trials Partnership of US$ 1 200 200. This project is ongoing. Of the four research grants declared, two are relevant to PICO questions discussed in the context of this GDG meeting. Dr Chabala is the country Principal Investigator for the SHINE Trial, which is the trial reviewed for PICO 3. He also presented data on pharmacokinetics from the SHINE trial for PICO 3 during the GDG meeting. Also, the pooled cohort for the systematic review for PICO 2b includes data from the TB Speed project, where Dr Chabala is one of the Principal Investigators. Thus, significant competing interests were identified, which led to his exclusion from discussions, decision-making and voting for PICO 2b and 3.

Steve Graham (content chair): declared research support and involvement in several studies including: collaboration on the SHINE trial (with MRC/Wellcome Trust), that ceased in 2020; collaboration on the RaPaed study (with EDCTP); collaboration on EGPAF TB CONTACT study and Chair of the Scientific Advisory Board of TB Speed (both funded by Unitaid); co-investigator of the VQUIN study (with NHMRC, Australia); chair of the Trial Steering Committee of the TB CHAMP study (Medical Research Council, the United Kingdom); lead author of a paper on clinical case definitions for the classification of intrathoracic TB (NIH, USA) in 2015; co-Principal Investigator of the DETECT TB project, published in the IJTLD in 2018 (Union, Uganda) (activity ceased in 2017). No remuneration was received for any of these involvements, as per a follow-up clarification with Professor Graham. Professor Graham is also a former chair and core member of the WHO Child and Adolescent Working Group. Significant competing interests were identified, as Professor Graham is a collaborator on the SHINE trial and a co-Principal Investigator for the DETECT TB study, which contributed data to PICO 3 and 6a, respectively. Thus, he was excluded from discussions, decision-making and voting on PICO 3 and 6a. He is also Chair of the Scientific Advisory Board for the TB Speed project, which contributed data to PICO 2b. However, he was not personally involved in any of the data contributions, as the data were transferred from the central investigation team, so this did not lead to his exclusion from discussions and decisions on PICO 2b.

Tamara Kredo (GRADE methodologist): collaborates on the Unitaid-funded research project 'Better Evidence and Formulations for Improved MDR-TB Treatment for Children – Benefit Kids',

contributing to systematic reviews on MDR-TB in children (clinical and pharmacokinetic reviews). This is a three-year project (2019–2022) supported by Unitaid (R321 000, approximately US$ 20 000 for costs for employing research assistants). Funding is provided from Unitaid to Stellenbosch University, with a subcontract to Cochrane South Africa, South African Medical Research Council. Dr Kredo is employed by the Research Unit of the Cochrane South Africa, South African Medical Research Council. Stellenbosch University and Cochrane South Africa have previously collaborated on a systematic review on MDR-TB treatment in children (Harausz EP, Garcia-Prats AJ, Law S, Schaaf HS, Kredo T, Seddon JA, et al. Treatment and outcomes in children with multidrug-resistant tuberculosis: A systematic review and individual patient data meta-analysis. PLoS Med. 2018;15(7):e1002591). In 2019, the Stellenbosch team was planning an update of this review and conduct a review of pharmacokinetic data in the same population. Through a new funding mechanism with Unitaid, Cochrane South Africa has come on board as a collaborator to support with research assistants (where needed) to complete the review. The Unitaid project led by Professor Hesseling and Dr Garcia-Prats is for the period of October 1, 2019 – September 30, 2022. Significant competing interests were identified, as the analysis of the IPD data conducted by the Unitaid-funded Benefit Kids project team informed decisions on PICO 4b and 4a. Thus, Dr Kredo did not participate in discussions, decision-making and voting for PICO 4a and 4b. Dr Kredo also did not chair the GDG session on PICO 4. Professor Akl, who did not have competing interests for this PICO, chaired this session.

Anna Mandalakas: received US$ 2000 from WebMD (an American corporation known primarily as an online publisher of news and information pertaining to human health and well-being) to support the development of a Medscape CME opportunity regarding paediatric TB infection (contract ceased in 2020). Dr Mandalakas received US$ 5000 from Oxford Immunotec in 2020 to provide a lecture in conjunction with the 2020 ID Week meeting in a satellite symposium regarding paediatric TB infection. The symposium was sponsored by Oxford Immunotec. The company did not have any input into the content of the lecture. Dr Mandalakas is serving on the data safety and monitoring board of the Janssen Pharmaceutical N.V. sponsored study TMC207-C211, which evaluates the use of bedaquiline in children (four-year contract, ongoing, worth US$ 5750). A significant competing interest was identified, given that data from the TMC207–211 Janssen-supported trial were shared with the WHO to inform discussions and decisions on PICO 4a. Professor Mandalakas was therefore not involved in discussions, decision-making and voting for PICO 4a.

External Review Group

The following ERG members declared no conflicts of interest: Anthony Enimil, Catherine Hewison, Kobto Ghislain Koura, Celia Martinez, Ya Diul Mukadi, Rahab Mwaniki, Elisabeth Obimbo, Peter Owiti, Ramatoulaye Sall, Rina Triasih, Nyan Win Phyo, Eric Wobudeya.

The following ERG members declared interests that were judged not to be in conflict with the objectives of the guidelines:

Martina Casenghi: is the Technical Director of the Unitaid-funded CaP TB Project. Her salary is supported through a Unitaid grant awarded to EGPAF.

Malgorzata Grzemska: was employed by the WHO Global Tuberculosis Programme until 30 March 2020 as Unit Head, with a salary according to the WHO salary scale. She was directly involved in policy development, including the policies for the management of TB in children and adolescents.

Devan Jaganath: is the assistant professor of paediatrics at the University of California, San Francisco (USA) and received research grants from the NIH (USA) worth US$ 195 000. Additional information was gathered by email exchange, where Dr Jaganath shared more details on his work on biomarkers in children (https://reporter.nih.gov/search/9Qe_V38A5kCSrV_v_zY8Ew/projectdetails/10248492) and declared a grant worth US$ 201 000 on host proteomic biosignatures for a urine-based diagnosis of pulmonary TB in children, which will complete in August 2022.

Marc Nicol: works at the University of Cape Town, which received funding from the Wellcome Trust, EDCTP, NIH, Bill and Melinda Gates Foundation. This funding supports Dr Nicol's work to conduct studies on a range of novel diagnostics for TB in children (including Xpert, LAM, RNAseq and others). The total funding is approximately US$ 5 million over 15 years. The only active research grant is from the NIH. Other grants ceased within the past five years.

Evidence reviewers

The following experts who conducted the evidence review to inform the revision of the recommendations declared no conflict of interest: Andrea Benedetti, Delia Boccia, Maryline Bonnet, Silvia Chiang, Vivian Cox, Angela Crook, Manuela De Allegri, Mary Gaeddert, Maria Garcia-Cremades Mira, Ken Gunasekera, Yael Hirsch-Moverman, Graeme Hoddinott, Hamidah Hussain, Manon Lounnas, Nyashadzaishe Mafirakureva, Nancy Medley, Patricia Moscibrodzki, Pamela Nabeta, Tara Ness, How Thi Nguyen, Sandy Oliver, Kendra Radtke, Paul Revill, Morten Ruhwald, Nicole Salazar-Austin, James Seddon, Giorgia Sulis, Yemisi Takwoingi, Gamuchirai Tavaziva, Anna Turkova, Susan van Wyk, Bryan Vonasek.

The following experts who conducted evidence reviews informing the revision of the recommendations did declare potential conflicts of interest listed below, which did not require any action beyond reporting for transparency purposes.

Susan Abdel-Rahman *see above.*

Salla Atkins: Dr Atkins received grants for studying the socioeconomic impact of TB from Vetenskapsrådet, Sweden, as Principal Investigator (approximately €500 000 for four years, current employment)

Martina Casenghi: *see above.*

Chishala Chabala: *see above.*

Claudia Denkinger: was employed at FIND between February 2014 and 2019 and also declared an active collaboration agreement with FIND to support policy-relevant analysis, economic evaluation and modelling FIND, with no project-specific funding.

Pete Dodd: works at the University of Sheffield, and his department received research funding from Unitaid to carry out modelling work for the CaP TB and TB Speed projects (subcontracted as technical partner). The total fund corresponds to £390 000 and provides salary support for researchers involved during the period 1/2018 to 9/2022.

Anthony Garcia-Prats: received grant funding from Otsuka Pharmaceuticals (through University of Stellenbosch) for implementation of the paediatric delamanid trials for which Dr Garcia-Prats was the site Principal Investigator. (Fair market value. The contract ceased in 2020). Dr Garcia-Prats also received grant funding from Novartis (through the University of Stellenbosch) for implementation of a paediatric clofazimine trial; Dr Garcia-Prats is a Protocol Co-Chair for this trial, but he is not receiving any financial support for his participation in this trial (ongoing). Stellenbosch University and University of Wisconsin, where Dr Garcia-Prats works, receive research funding from NIH for work on paediatric clinical trials of bedaquiline, delamanid and other second-line TB drugs. (Fair market value. Ongoing). Stellenbosch University and University of Wisconsin also receive grant funding from Unitaid for implementation of paediatric clinical trials including delamanid and other second-line TB drugs. (Fair market value. Ongoing). The evidence synthesis that Dr Garcia-Prats presented at the GDG meeting is funded by Unitaid through a grant to Stellenbosch University via the BENEFIT Kids project (October 2019 to September 2022).

Diana Gibb: received a donation of trial drugs from ViiV Healthcare, Janssen, Mylan, Cipla Pharmaceuticals (ongoing, until the trials are completed). Dr Gibb also received research grants

from ViiV Healthcare UK Limited via PENTA Foundation, Janssen, European and Developing Countries Clinical Trials Partnership, (DFID), the Wellcome Trust, Medical Research Council, the United Kingdom, National Institute for Health Research. Total amount received: £50.2 million (ongoing, until trials completed).

Anneke Hesseling: works at the University of Stellenbosch, which receives US$ 2 million per annum for several investigator-initiated research studies including with the NIH IMPAACT network, TBTC, Unitaid, BMRC/Wellcome Trust and South African MRC, for therapeutic trials and diagnostics in childhood TB.

Hayley Jones: is receiving funding of £17 203.95 (paid at the University of Bristol, received from UCL).

Alexander Kay: receives research supplies (cartridges) from Cepheid (to Baylor Children's Foundation-Eswatini), at a discounted price (valued at approximately US$ 2000 in test cartridges) as an ongoing collaborative agreement.

Faiz Ahmad Khan: and team were contracted by the WHO through an APW (amount: CAD$ 30 818) to review evidence for PICO 5 (treatment of paediatric TB meningitis) in the context of the GDG meeting on child and adolescent TB.

Olivier Marcy: works at the University of Bordeaux that receives research support for paediatric TB from a Unitaid grant (US$ 14.6 million for 2017–2022). The University of Bordeaux and consortium partners also receive research support for paediatric TB from the French 5% Initiative Grant (€1.5 million) for the period 2017–2021. The University of Bordeaux and partners also receive research support for the paediatric TB ANRS study (€160 000), a two-year project to be implemented during 2021–2023.

Rada Savic: receives research funding from NIH, Unitaid and BMGF through UCSF, where she works as Principal Investigator of several research projects. She serves on Scientific Advisory Committee for TB Alliance and receives no income for that role. She is also a member of Core Science Group for NIH clinical trial network (ACTG) and co-chair on the CDC clinical trial consortia (TBTC) Study 35 and receives no income for that role.

Karen Steingart: declared several ongoing or ceased consultancy contracts, including: (i) a consultancy with WHO (current) to carry out systematic reviews on the use of Xpert MTB/RIF Ultra assay in specific paediatric specimens for the diagnosis of active pulmonary TB and rifampicin resistance in children under 10 years of age and screening approaches for TB in children under the age of 10 years. Amount received: US$ 17 500 (of which US$ 14 000 were distributed to other members of the review team); (ii) a consultancy (current) with Research, Evidence and Development Initiative (READ-It), Cochrane Infectious Diseases Group (Liverpool School Tropical Medicine). Role: mentoring and technical support for Cochrane Reviews. Received US$ 11 200 for the period 2019–2020; will receive US$ 9600 in 2021; (iii) a consultancy with WHO (2020, ceased) to carry out systematic reviews for a GDG meeting on nucleic acid amplification tests to detect TB and drug-resistant TB: NAATs of low complexity for detection of resistance to INH, FQ, ETO, AMK and user perspectives of NAATs of low complexity. Amount received: US$ 24 500 (of which US$ 13 000 were distributed to other members of the review team); (iv) a consultancy with WHO (2020, ceased) to carry out a systematic review on screening tests for active pulmonary TB and rifampicin resistance in children. Amount received: US$ 8250; (v) a consultancy with WHO (2019, ceased) to carry out a systematic review on lateral flow urine lipoarabinomannan assay for detecting active TB in people living with HIV. Amount received: US$ 20 000 (of which US$ 10 000 was distributed to other team members of the review team); (vi) a consultancy with WHO (2019, ceased) to prepare GRADE tables, Xpert (WHO role) in the context of a GDG meeting. Amount received: US$ 6400; (vii) a consultancy with the foundation for Innovative New Diagnostics (FIND) (2019, ceased): Preparation of GRADE tables, Truenat. Amount received: US$ 3200; (viii) a consultancy with McGill University (2019, ceased) to carry out a systematic review Xpert MTB/RIF and Xpert MTB/RIF Ultra for pulmonary TB and rifampicin resistance in adults. Amount received:

US$ 16 970; (viii) a consultancy (2019, ceased) to carry out a systematic review of symptom screening for active TB in pregnant women living with HIV. Amount received: US$ 1000; (ix) a consultancy with the foundation for Innovative New Diagnostics (FIND) (2018, ceased) to carry out a systematic review of commercial products for preserving clinical specimens. Amount received: US$ 3200. Dr Steingart also declared that she was a co-author in a three-year grant study from Canadian Institutes of Health Research (CIHR) through the McGill University, Montreal entitled "Evaluating diagnostic accuracy of tests and decision rules in the absence of a perfect reference standard" in the period 2018–2020. In 2018, she received support from the McGill University to attend two conferences: Methods for Evaluating Medical Tests & Biomarkers, 2–3 July 2018 in Utrecht, the Kingdom of the Netherlands and the 49th Union World Conference on Lung Health, 24–27 October 2018 in The Hague, the Kingdom of the Netherlands. In 2019 and 2020, she received support to attend the 50th and 51st Union World Conference on Lung Health (total of US$ 10 000 for attending two conferences). In 2020, she received support to purchase a laptop and software (US$ 2400).

Daria Szkwarko: received research support from the Thrasher Foundation (US$ 25 000) during 2018–2020.

Courtney Yuen: received or is currently receiving research support from several entities, including: Research support from Janssen Global Public Health to Harvard Medical School, as co-investigator (2019); research support from Patient-Centered Outcomes Research Institute to Brigham and Women's Hospital (Dr Yuen's employer), as Principal Investigator (2018); research support from the Bill and Melinda Gates Foundation Grant to Brigham and Women's Hospital (Dr Yuen's employer), as Principal Investigator (2019); research support from National Institutes of Health Grant to Brigham and Women's Hospital (Dr Yuen's employer), as Principal Investigator (current).

WHO treatment guidelines for drug-resistant TB treatment, 2022 update

In conformity with WHO guidelines for declaration of interests for WHO experts issued by the WHO Office for Compliance and Risk Management and Ethics, members of the Guideline Development Group, External Review Group and evidence reviewers were requested to submit completed WHO Declaration of Interest forms (DOIs) and declare in writing any competing interest (whether academic, financial or other) which could be deemed as conflicting with their role in the development of this guideline. In order to ensure the neutrality and independence of experts, an assessment of the DOI forms, curricula vitae, research interests and activities was conducted by the WHO secretariat. For cases in which potential conflicts were identified, there was some further consideration as to how to manage competing interests. If any declared interests were judged significant, individuals were either not included as members of the Guideline Development Group or asked to refrain from contributing to the decision-making process under specific PICO questions. As per WHO rules, the objectives of the guideline development process and the composition of the GDG, including member biographies, were made public ahead of the meeting (https://www.who.int/publications/m/item/public-notice-guideline-development-group-for-the-update-of-the-who-consolidated-guidelines-on-the-treatment-of-drug-resistant-tuberculosis_2022). This public notice was conducted to allow the public to provide comments pertinent to any competing interests that may have gone unnoticed or not reported during earlier assessments.

Guideline Development Group

The following Guideline Development Group members declared no conflicts of interest: Muhwa Chakaya, Geraint Gerry Rhys Davies, Denise Arakaki, Elmira Gurbanova, Yanlin Zhao, Leslie Christine Magsayo-Salon, Asif Mujtaba, Mahshid Nasehi, Nguyen Viet Nhung, Sabira Tahseen, Ye Tun, Debrah Vambe, Paran Winarni, Christian Lienhardt, Graeme Meintjes, Christoph Lange.

On review of the completed DOIs, the following 12 experts declared interests that required further consideration: Charles Daley, Geraint Davies, Daniela Cirillo, Holger Schünemann, Guy Marks, Amita Gupta, Anneke Hesseling, Andrew Nunn, Ingrid Shoeman, Andrew Vernon, Christoph Lange, Padma Chandrakesaran.

Nine members of the Guideline Development Group declared interests that were judged nonsignificant and were believed not to affect the independence and impartiality of the experts during the guideline development process. Therefore, no restrictions to their participation applied.

Charles Daley: Participation in the Data Monitoring Committee (DMC) for delamanid. A total of US$ 4000 by Otsuka Pharmaceutical for services as a member of the Committee. The work ended in 2019.

Gerry Davies: Participation in the PreDiCT-TB consortium, a public-private partnership funded by the European Union Innovative Medicines Initiative and the European Federation of Pharmaceutical Industries and Associations (EFPIA). Role as academic coordinator (2012–2017) led to engagement with industrial partners in pre-competitive areas of research into TB drug development. All of these activities were fully supported by public funding from the European Union. No financial support was received from EFPIA. Since 2017 G. Davies has been an academic partner to the PanACEA clinical trials consortium, funded by the European and Developing Countries Clinical Trials Partnership. Though the consortium has involved contact and collaboration with pharmaceutical partners, his role at the University of Liverpool is as a partner without budget supporting the clinical trials site at the College of Medicine in Blantyre, Malawi. Neither himself, the University of Liverpool nor the University of Malawi College of Medicine receive any funding from pharmaceutical collaborators as part of these activities. G. Davies attended expert advisory meetings relating to TB drug development convened by GSK and Janssen for which I received no payment or benefit (honorarium, expenses, hospitality). In 2017, G. Davies received travel and accommodation expenses from Medecins Sans Frontieres to attend and speak at the 6th Regional TB Symposium (Eastern Europe and Central Asia) in Minsk, Belarus. Academic co-supervisor of PhD candidate who is currently involved in the TB-PRACTECAL trial (chief investigator) at the London School of Hygiene and Tropical Medicine. Funding support will be provided through research institution [University of Liverpool] from Médecins Sans Frontières to support analysis of pharmacokinetic samples in early 2020. This work involves the BPaLM regimen comprising of bedaquiline, pretomanid, clofazimine, linezolid and moxifloxacin. University of Liverpool received a service contract for bioanalytical work related to a pharmacokinetic sub-study of the PRACTECAL trial (£98 741) but G. Davies personally received no direct financial/salary benefit for this work.

Daniela Cirillo: Research grant of €440 000 via Universita Vita Saluute, which is partner in the IMI UNITE4TB consortium (EU funded). This partnership is ongoing. Research grant through the Ospedale San Raffaele by the TB Alliance of US$ 38 000 in 2020 to study MIC distributions for new TB medicine (pretomanid). The microbiological laboratory of Ospedale San Raffaele participates in the EUCAST (European Committee on Antimicrobial Susceptibility Testing). EUCAST coordinated work on standard protocol for different TB medicines involving reference labs.

Holger SCHÜNEMANN: Research on disseminating and presenting WHO tuberculosis recommendations, via employer, McMaster University. $700 000 grant from WHO, ended in 11/2021. The work commissioned by WHO GTB to the McMaster University was to develop better formats for presentation of WHO current policy recommendations in TB, not influencing content or direction of any recommendations.

Amita GUPTA: A significant number of research projects led by the John Hopkins University (JHU) or Amita Gupta as collaborator, principal investigator or protocol chair or co-chair with substantial amounts of funding from multiple institutional donors. However, the focus of the listed research activities does not directly overlap with the scope of the GDG meeting.

Anneke HESSELING: Stellenbosch University, where A. Hesseling is an academician, receives $2 million per annum for several investigator-initiated research studies including with the NIH IMPAACT network, TBTC UNITAID, BMRC/Wellcome Trust and South African MRC, for therapeutic trials and diagnostics in childhood TB. The largest single support is from UNITAID for BENEFIT-KIDS project (led by Stellenbosch University), which includes evidence synthesis, formulation development and also investigator-related clinical trials. This grant and other grants are to the institution, Stellenbosch University. Support to activities directly led by A. Hesseling is an estimated US$ 600 000 per annum at present, including for the TB-CHAMP trial, where A. Hesseling serves as Principal Investigator. Other support to activities directly led by A. Hesseling are: approximately $250 000 per annum, provided by the CDC, through the TBTC network, for TBTC Study 35 and approximately $150 000 per annum for IMPAACT P1108 from the NIH. The research looks at therapeutic trials and diagnostics in childhood TB. These matters are not the subject of the GDG.

Ingrid SHOEMAN: The employer, TB Proof – a TB advocacy organization based in South Africa, is funded by Bill and Melinda Gates Foundation 2021- 2024, and Stop TB Partnership 2020–2022, Global Fund 2021–2024, Treatment Action Group 2021–2022. As a current board member of The International Union Against Tuberculosis and Lung Disease (The Union) Ingrid Shoeman have received allowances for travel, per diem and accommodation to attend board meetings and conferences. Grant for short-term contract work to TB Proof received from Capital for Good USA in the amount of $217 198 in July 2016 to December 2017. Multiple conflicts indicated by Ingrid Shoeman were considered not representing a conflict interest as her work and work of the current employer (TB Proof) are matching a role of the patient advocate.

Andrew VERNON: Andrew Vernon works in the Division of TB Elimination at CDC, where he directs a branch that conducts clinical trials in tuberculosis treatment and prevention. This group has worked with various commercial collaborators for over 2 decades. Most recently, group has collaborated with NIH and Sanofi on the conduct of a multinational phase 3 trial of TB treatment using daily rifapentine. Sanofi provided medications for the trial and has supported costs of pharmacokinetic testing. The group has conducted trials in treatment of latent TB infection and is beginning a new LTBI trial in summer 2022. Sanofi is providing medication for this trial but is not involved in the design or conduct of the trial. Total contribution to CDC Foundation over 10 years was ~$3 million. Sanofi provides drug for a current prevention trial also. CDC is a National Health Institution involved in multiple kinds of research and development of national level recommendations by its purpose.

Christoph LANGE: Christoph Lange received in the past an honorarium from Janssen pharmaceuticals for a lecture in the amount of $1000.

The below mentioned members of the Guideline Development Group declared interests which were judged to be significant, and which required further assessment to outline a management plan:

Guy MARKS: Guy Marks received public research grants through National Health and Medical Research Council of Australia (NHMRC Australia) for research on TB control and he is currently President of the International Union Against Tuberculosis and Lung Disease. International Union Against Tuberculosis and Lung Disease (The Union) is a membership-based technical and scientific organization established in 1920. The Union members are organizations and individuals from all parts of the world. Although the Union has been supporting clinical trials on treatment of DR-TB (STREAM phase 1 and phase 2) results of these trials are not in the scope of this GDG meeting. The STREAM Stage 2 trial is on-going and the regimen evaluated in the stage 2 trial is almost identical to the regimens that will be discussed in comparisons under several PICOs looking at RR/MDR-TB and FQ-sensitive patient groups (PICO 1, 2, 5, 8, 10). The results of the completed STREAM stage 1 trial have been published and the regimen evaluated is not anymore recommended by WHO. The STREAM Stage 2 trial is ongoing and is expected to complete in 2022. Guy Marks is not directly involved in the STREAM trial management, however his leadership role at the Union and the fact that the regimen evaluated in the stage 2 trial is almost identical to the regimens that will be discussed in comparisons under several PICOs looking at RR/MDR-TB and FQ-sensitive patient groups (PICO 1, 2, 5, 8, 10) led

to a conclusion that to avoid any potential intellectual conflicts of interest. Guy Marks was asked to refrain from contributing to the decision-making process under these PICO questions. No significant competing interests identified for the discussion and decision-making under PICO questions 3, 4, 6, 7 and 9 in this GDG as the disclosure is not in conflict with the scope of these questions.

Andrew NUNN: The STREAM trial on which Andrew Nunn is co-chief investigator is partly funded by Janssen Pharmaceuticals and part by USAID and covers part of his salary. STREAM Stage 1 compared a 9–11-month injectable-containing MDR-TB regimen (with fluoroquinolone and injectables and no bedaquiline) and contributed important evidence to support the introduction of shorter MDR-TB regimens. STREAM Stage 2 is evaluating the efficacy, safety, and cost of an all oral, bedaquiline containing regimen that is potentially as effective as, and more tolerable than, injectable-containing regimens like the 9–11-month regimen evaluated in STREAM Stage 1. The results of the completed STREAM stage 1 trial have been published and the regimen evaluated is not anymore recommended by WHO. The STREAM Stage 2 trial is ongoing and is expected to complete in 2022. The regimen evaluated in the stage 2 trial is almost identical to the regimens that will be discussed in comparisons under several PICOs looking at RR/MDR-TB and FQ-sensitive patient groups (PICO 1, 2, 5, 8, 10) therefore, to avoid any potential conflict of interest, Andrew Nunn was asked to refrain from contributing to the decision-making process under these PICO questions. No significant competing interests identified for the discussion and decision-making under PICO questions 3, 4, 6, 7 and 9 in this GDG meeting as the disclosure is not in conflict with the scope of these questions.

Padma CHANDRASEKARAN: Padma Chandrasekaran is a Director of the ICMR -National Institute for Research in Tuberculosis that conducts multiple clinical studies for new drugs in MDR-TB, PreXDR and XDR-TB patients. The disclosed conflict is broadly related to all research work on treatment of TB and DR-TB and is not specific to the specific questions posed to the panel during this GDG. The following studies coordinated by the ICMR are in the scope of the review: 1) BEAT-TB Study: an all-oral, short course regimen with bedaquiline, delamanid, linezolid and clofazimine for PreXDR & XDR-TB. Funded by USAID for 3 years (2018–2021), grant Amount: $1 122 921; 2) mBPaL study: regimen with bedaquiline, pretomanid with different doses of Linezolid for Pulmonary MDR with FQ-resistant patients. Funded by The UNION (2021), grant Amount: $1 019 372. Involvement in the mBPaL study may lead to a potential intellectual conflict of interest during review of PICO questions on BPaL regimens. Potential intellectual conflict of interest is considered in relation to the scope of the PICO questions on BPaL or BPaL-like regimens. Padma Chandrasekaran was asked to refrain from contributing to the decision-making process under PICO questions 3–10. No competing interests identified with PICOs 1–2 as the disclosure is not considered to be in conflict with the scope of these questions.

Evidence reviewers:

The following experts who conducted the evidence analysis to inform the revision of the recommendations declared non-monetary support for the research or previous employment, which required no action beyond reporting for transparency purposes: Greg Fox, Tasnim Hasan.

WHO treatment guidelines for drug-resistant TB treatment, 2025 update

On review of the completed DOIs, the following 9 experts out of 18 declared interests that required further consideration:

Charles DALEY: Professor Daley disclosed receiving a one-time honorarium of USD 4,000 from Otsuka for serving as a member of a data monitoring committee for pediatric clinical trials of delamanid, with the activity ending in 2019. His role was limited to independent data monitoring, and the financial value was modest. This interest was assessed as unlikely to influence his judgment and was not considered a competing interest for the GDG's work.

Gerry DAVIES: In 2011–2017 G. Davies was the academic coordinator of the PreDiCT-TB consortium and continues to be a partner in the UNITE4TB consortium (EU funded), both public-private partnerships funded by the European Union Innovative Medicines Initiative and the European Federation of Pharmaceutical Industries and Associations. However, though these roles involve engagement with industrial partners (GSK, Sanofi, Janssen) in pre-competitive areas of research into TB drug development, these activities were fully supported by public funding from the EU and neither G. Davies nor his research institution received any funding from EFPIA or from the individual industrial partners.

Since 2017 G. Davies has been an academic partner to the PanACEA clinical trials consortium, funded by the European and Developing Countries Clinical Trials Partnership. Since 2020, G.Davies an academic partner to the UNITE4TB consortium. However, though this role he received no funding from EFPIA or from individual industrial partners. G. Davies attended expert advisory meetings relating to TB drug development convened by GSK and Janssen, for which he received no payment or benefit (honorarium, expenses, hospitality). In 2017, G. Davies received travel and accommodation expenses from Medecins Sans Frontieres to attend and speak at the 6th Regional TB Symposium (Eastern Europe and Central Asia) in Minsk, Belarus. In 2021, the University of Liverpool received a service contract for bioanalytical work related to a pharmacokinetic sub-study of the PRACTECAL trial (£98,741) but G. Davies personally received no direct financial/salary benefit for this work.G. Davies is a coinvestigator on a drug interaction study of dolutegravir and high-dose rifampicin (DoRIS) funded by ViiV Healthcare (£374,574) but receives no direct salary or other financial benefits from the grant.

Participation in publicly funded (EU) research consortiums is not considered a conflict of interest. DMC is a group of clinicians and biostatisticians appointed by study sponsors who provide independent assessment of the safety, scientific validity and integrity of clinical trials, therefore, being a member or a chair of the DMC does not represent an intellectual conflict of interest since the DMC has no influence on the design, focus, objectives and analysis of the trial outcomes. Terms of engagement for UNITE4TB are exactly the same as for PreDICT-TB (they are both IMI projects). University of Liverpool (UoL) is a partner to UNITE4TB in the WPs for Clinical Trial Design and Pharmacology and only receives funding from the EU. All funding for academic partners in the consortium comes from EU and none from the industry partners (EFPIA partners). G. Davies is not involved in trials management under these consortia and will be providing some pharmacokinetics and pharmacogenetics work for the trials that may start in the near future (no trials are ongoing at this point in time). Involvement in the UNITE4TB consortium dates back to 2020 and may continue for the duration of this project (7 years). G. Davies is an independent chair of the TRUNCATE-TB steering committee (last 5 years and will end in one year), and RIFASHORT DMC has an independent and advisory role, not influencing the trial setup, main decisions, and changes. One additional in-person meeting of the TRUNCATE-TB steering committee is expected to take place next year. Funding for the TRUNCATE-TB is from the government of Singapore and the Medical Research Council, the United Kingdom, both public funding streams with no industry funding input. **No competing interests identified,** as the disclosure is not in conflict with the scope of the work being undertaken by the GDG.

Daniela CIRILLO via Universita Vita Saluute is partner in the IMI UNITE4TB consortium (EU funded coordinating microbiology WP for clinical trials, monitoring of trial sites and re-testing. This partnership via Universita Vita Saluute received a grant. The funds were for implementation of microbiology procedures on the sites, sequencing mic determination for new drugs No funds are allocated to UNISR for biomarkers. Dr Cirillo via microbiological laboratory of Ospedale San Raffaele participates in the EUCAST (European Committee on Antimicrobial Susceptibility Testing). EUCAST coordinated work on standard protocol for different TB medicines involving reference labs. Unite4TB under IMI (Innovative Medicines Initiative of EU).

The aim of UNITE4TB is to accelerate and improve clinical trials of combinations of existing and new drugs, with the goal of developing new and highly active treatment regimens for TB, including drug-resistant TB. Participation in publicly funded (EU) research consortiums is not considered a conflict of

interest. In addition, the institution where D. Cirillo works is involved in laboratory work to support the development of the new trial platforms, not influencing the direction or results of the trials. All funding for academic partners in the consortium comes from the EU and none from the industry partners. **TB Alliance** financed MIC study on pretomanid (new anti-TB medicine) to assess the distribution of MIC to the drug in different lineages. Development of new diagnostic tests for susceptibility of Mycobacteria TB to various TB medicines is an overall positive development as it allows precision medicine, i.e. more effective treatment regimens, be it with first-line or second-line medicines.

EUCAST is a standing committee jointly organized by ESCMID, ECDC and European national breakpoint committees. EUCAST deals with breakpoints and technical aspects of phenotypic in vitro antimicrobial susceptibility testing and functions as the breakpoint committee of EMA and ECDC. EUCAST does not deal with antibiotic policies, surveillance or containment of resistance or infection control.

No competing interests are identified, as the disclosure is not in conflict with the scope of the work being undertaken by the GDG.

Muhwa CHAKAYA: In 2023, he gave two talks at health care worker educational events sponsored by Cepheid and received honoraria from Cepheid. The interest was related to TB research in general and was a one-time event. Although it included small financial support, it could not affect the expert's professional judgment. **No competing interests** identified as the disclosure is not in conflict with the scope of the work being undertaken by the GDG.

Anneke HESSELING Stellenbosch University receives $2 million per annum for several investigator-initiated research studies, including with the NIH IMPAACT network, TBTC UNITAID, BMRC/Wellcome Trust and South African MRC, for therapeutic trials and diagnostics in childhood TB.

Hesseling is an academic at Stellenbosch University, a leading teaching and academic institution in South Africa. The university receives annual grants for several investigator-initiated research studies, including from the NIH IMPAACT network, TBTC, UNITAID, BMRC/Wellcome Trust, and the South African MRC. These studies focus on therapeutic trials and diagnostics in childhood TB, and although these subgroups will be discussed under each PICO question, this is not a key focus of this GDG. **No significant competing interests** identified as the disclosure is not in conflict with the scope of the work being undertaken by the GDG.

Graeme MEINTJES: He gave a talk at a Gilead internal meeting. Besides, he currently serves as a member of an independent DSMB for Otsuka for one trial and one trial for which the Gates MRI is the Sponsor.

G. Mentjes served as an independent member of the Trial Steering Committee for the BEAT-TB trial (no remuneration) and the Independent Scientific Advisory Committee of the endTB trial (no remuneration).

Dr Mentjes's participation in the advisory committees of two trials, the evidence of which will be reviewed during the GDG, required additional due diligence and a thorough review of the terms of reference of the TSC of the Beat-Tuberculosis trial and the SAC of the end-TB trial. The review of the TSC ToR showed clearly that the committee had a potential influence on both the trial protocol and changes to it. The terms of reference of the SAC of the endTB trial clearly excluded the members of that committee from any critical to the trial protocol or trial management decisions and reserved the deliberations of the SAC to general or specific scientific advice, without any direct influence on the design or conduct of the trial.

The review judged that Dr Mentjes may have a potential intellectual conflict of interest stemming from participation in the TSC of the BEAT-TB trial. Although a potential conflict of interest was also declared due to the membership in the SAC of the endTB trial, the review considered it non-significant. Due to a potential intellectual conflict of interest stemming from the membership in the TSC for the

BEAT-TB trial, Dr Mentjes will be asked to abstain from the discussion and decision-making based on the evidence from the BEAT-TB trial during the GDG in June 2024.

Christoph LANGE: He gave a lecture on tuberculosis at symposia sponsored by Gilead, Astra Zeneca, GSK. The lecture topic and content were not influenced by the company. The interest was one-time, and the topic was related to TB research in general. The sponsors did not directly influence the content. Although it included small financial support, it could not affect the expert's professional judgment. **No competing interests** identified as the disclosure is not in conflict with the scope of the work being undertaken by the GDG.

Gopalan NARENDRAN was a local PI for the STREAM trial, stage 1, which was completed in September 2022. He received approximately 122 USD for this activity. The STREAM clinical trial is a large, multi-country study to evaluate shortened regimens for MDR-TB. The trial was concluded, the trial regimens are not within the scope of this GDG. **No competing interests** identified as the disclosure is not in conflict with the scope of the work being undertaken by the GDG.

Andrew VERNON worked from 1995–2021 in the Division of TB Elimination at CDC, where from 2004–2021 he directed a branch that conducts clinical trials in tuberculosis treatment and prevention. This group has worked with various commercial collaborators for over two decades. Most recently, the group has collaborated with NIH and Sanofi on the conduct of a multinational phase 3 trial of TB treatment using daily rifapentine. Sanofi provided medications for the trial and supported the costs of pharmacokinetic testing. The group has conducted trials in the treatment of latent TB infection and has begun a new rifapentine-based LTBI trial.

CDC is a National Health Institution involved in multiple kinds of research and development of national-level recommendations by its purpose. The support from pharma, as mentioned, and the research disclosed are related to the treatment of drug-susceptible TB. It is not relevant and cannot directly influence judgments on the review questions in scope for this GDG development. Therefore, the disclosed conflict is considered non-significant. **No competing interests** identified as the disclosure is not in conflict with the scope of the work being undertaken by the GDG.

WHO treatment guidelines for drug-resistant TB treatment, 2026 update

Upon review of the completed DOIs, 7 of 18 experts declared interests that required further consideration.

Chishala Chabala

Dr Chabala disclosed consultancy work for the WHO Global TB Programme in 2023 related to the development of a child TB e-course, with modest remuneration. He also reported multiple research grants awarded to his institution from public and philanthropic funders to support child TB diagnostics, pharmacokinetic studies, treatment decision algorithms, and treatment shortening research, some ongoing and some completed. These interests are institutional, non-commercial, and not directly related to the shorter treatment regimens under review, and were assessed as unlikely to influence his judgment in the work of the GDG.

Geraint Rhys Davies

Dr Davies disclosed participation as a co-investigator and academic partner in several tuberculosis research consortia funded through public or mixed public-private mechanisms, including EDCTP, IMI, and a ViiV Healthcare-funded pharmacokinetic study. He receives no personal financial benefit from these activities, which are academic and collaborative in nature, and has not been involved in product promotion or policy formulation. These interests were assessed as not constituting a competing interest for the GDG's work.

Graeme Meintjes

Professor Meintjes disclosed serving in independent Data and Safety Monitoring Boards for clinical trials sponsored by Otsuka and Gates MRI, with total remuneration below USD 5,000. His role was limited to independent review of blinded safety data and provision of scientific recommendations, without involvement in trial design, analysis, or product promotion. These activities were considered unlikely to influence his judgment and were not deemed a competing interest for the GDG.

Luan NQ Vo

Dr Vo disclosed current employment with an international NGO, prior technical advisory work on a USAID-funded TB project, and limited non-monetary support from industry for conference presentations and academic publications. These activities relate to programmatic implementation, health systems, and community engagement rather than guideline content under review. They were assessed as not constituting a competing interest for the GDG.

Maria Imelda Josefa Quelapio

Dr Quelapio disclosed consultancy and advisory roles related to operational research on BPaL regimens, conducted under institutional arrangements with KNCV and funded by TB Alliance and KOICA. Her contributions focused on implementation support, training, and research coordination rather than regimen development or policy decision-making. These interests were assessed as not conflicting with her role in the GDG.

Shaheed Vally Omar

Dr Omar disclosed institutional research funding from the TB Alliance to support laboratory-based surveillance of pretomanid resistance. The work is technical and limited to MIC testing and data reporting, without involvement in clinical decision making or guideline development. This was assessed as not constituting a competing interest for the GDG.

Wei Sha

Dr Sha disclosed multiple sources of institutional research funding and collaborations received by her hospital department, primarily from public and academic bodies, with some industry-supported research collaborations. The funding was provided to the institution, not to her personally, and she had no role in product promotion or endorsement. These interests were assessed as not constituting a competing interest for the GDG's work.

Annex 4. PICO questions

4.1. Drug-susceptible TB

Research questions in a Population, Intervention, Comparator, Outcomes (PICO) format are listed below as they related to the recommendations retained in this policy consolidation.

4.1.1. Guideline update 2010

PICO question (Recommendation A1.1.)

Should new pulmonary TB patients be treated with the 6-month or the 2-month rifampicin regimen?

PICO question (Recommendation A1.2.)

When a country selects 2HRZE/4HR, should patients be treated daily or three times weekly during the intensive phase?

PICO question (Recommendation A1.5.)

In new pulmonary TB patients, how effective is extension of treatment for preventing failure or relapse?

PICO question (Recommendation A.3.1.)

Should intermittent regimens be used for persons living with HIV? What should be the duration of TB treatment in people living with HIV?

4.1.2. Guideline update 2017

PICO questions (Recommendation A.1.3.)

Does intermittent dosing in the intensive phase have outcomes similar to daily dosing in the intensive phase for treatment of drug-susceptible pulmonary tuberculosis?

Population	Intervention	Comparator	Outcomes
Pulmonary tuberculosis patients on intensive phase of treatment for drug-susceptible TB	3-times-weekly dosing of drugs throughout duration of treatment	Daily dosing of drugs throughout duration of treatment	• Cure or treatment completion • Treatment failure • Disease relapse • Death • Acquired drug resistance among patients who failed or relapsed

Does intermittent dosing in the continuation phase have outcomes similar to daily dosing in the continuation phase in patients with drug-susceptible pulmonary tuberculosis patients?

Population	Intervention	Comparator	Outcomes
Pulmonary tuberculosis patients on continuation phase of treatment for drug-susceptible TB	3-times-weekly dosing of drugs throughout duration of treatment	Daily dosing of drugs throughout duration of treatment	• Cure or treatment completion • Treatment failure • Disease relapse • Death • Acquired drug resistance among patients who failed or relapsed

PICO question (Recommendation A.1.4.)

In patients with active TB, is the use of fixed-dose combination (FDC) formulations as effective as the use of separate drug formulations?

Population	Intervention	Comparator	Outcomes
Pulmonary tuberculosis patients treated with first-line drugs (2HRZE/ 4HR)	FDC formulation with isoniazid plus rifampicin plus pyrazinamide plus ethambutol	Separate drug formulation: isoniazid, rifampicin, pyrazinamide and ethambutol	• Cure or completion of treatment • Treatment failure or disease relapse • Death • Smear conversion after 2 months of treatment • Acquired drug resistance • Adverse drug reaction • Patient adherence and satisfaction

PICO question (Recommendation A.4.1.)

Does the use of adjuvant corticosteroids in tuberculous meningitis provide mortality and morbidity benefits?

Population	Intervention	Comparator	Outcomes
Patients with tuberculous meningitis	First-line oral agents plus systemic corticosteroid therapy	First-line oral agents plus placebo	• Death • Adherence • Constrictive pericarditis

PICO question (Recommendation A.4.2.)

Does the use of adjuvant corticosteroids in tuberculous pericarditis provide mortality and morbidity benefits?

Population	Intervention	Comparator	Outcomes
Patients with tuberculous pericarditis	First-line oral agents plus systemic corticosteroid therapy	First-line oral agents plus placebo	• Cure or treatment completion • Survival • Staying disease free after treatment; sustaining a cure • Acquisition or amplification of drug resistance • Smear or culture conversion during treatment • Drug adverse events

4.1.3. Guideline update 2022

PICO question (Recommendation A.2.1.)

In patients aged ≥ 12 years with drug-susceptible pulmonary TB, is a 4-month regimen composed of rifapentine, isoniazid, pyrazinamide and moxifloxacin as effective and safe as the standard drug-susceptible TB regimen composed according to WHO guidelines?

Population	Intervention	Comparator	Outcomes
Patients aged ≥ 12 years with drug-susceptible pulmonary TB, stratified by sub-populations: **a. with signs of extensive disease (i.e. bilateral cavitary disease or extensive parenchymal damage on radiography)*** **b. adults ≥20 years and adolescents aged 12–19 years** **c. persons with HIV (+/- ARVs)** **d. with comorbidities (e.g. diabetes mellitus; malnutrition)**	A 17-week regimen composed of two months of rifapentine, isoniazid, pyrazinamide and moxifloxacin followed by two months of rifapentine, pyrazinamide and moxifloxacin**	The currently WHO recommended standard drug-susceptible TB treatment regimen composed of two months of rifampicin, isoniazid, pyrazinamide and ethambutol followed by four months of rifampicin and isoniazid	• Cure (favourable outcome)*** • Absence of cure (unfavourable outcome)*** • Death • Adherence to treatment (or treatment interruption due to non-adherence) • Severe adverse events (defined as grade 3 or higher) • Acquisition (amplification) of drug resistance

* WHO defines extensive or advanced TB disease as: presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged under 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest radiography.

** Standard doses (i.e. those that are currently recommended, and weight based, where relevant) of pyrazinamide, isoniazid and moxifloxacin were used and the dose of rifapentine used was 1 200 mg.

*** In Study 31, a participant was classified as having a favourable outcome if any one of the following conditions was met and an unfavourable outcome did not occur:

1. Participants whose last culture result during the Month 12 analysis visit window was *M. tuberculosis* negative.
2. Participants who were seen during the Month 12 analysis visit window and were clinically without symptoms/signs of ongoing active TB (indicated by absence of initiation of possible poor treatment response (PPTR) evaluation or PPTR that did not indicate presence of symptoms/signs of ongoing active TB), and had achieved culture conversion prior to Month 12, and
   a) Were unable to produce a sputum specimen at any point during the Month 12 analysis visit window; or
   b) Produced a sputum specimen that was contaminated or unevaluable without evidence of *M. tuberculosis*, and no sputum specimens yielded positive or negative culture results during the Month 12 analysis visit window.

A participant was classified as having an unfavourable outcome if any one of the following conditions is met:

1. A participant was considered to have absence of bacteriological cure if he/she had a sputum sample, obtained at or after Week 17 and no later than the end of the Month 12 analysis visit window, that is *M. tuberculosis* Culture Positive that was indistinguishable from the initial isolate (see separate sequencing plan for definitions), and this was confirmed by a second sample that was *M. tuberculosis* culture positive. A second confirmatory sample, on a different day without an intervening *M. tuberculosis* negative culture result, was required, as a single positive sputum culture result in isolation was not considered absence of bacteriological cure. If results from strain analysis were inconclusive or unavailable, it was assumed that strains were indistinguishable.
2. Participants who died from any cause during study treatment ('study treatment phase' is defined in the protocol), except from violent or accidental cause (e.g. road traffic accident). Suicide during study treatment was classified as an unfavourable outcome.

3. Participants who were withdrawn from follow-up or lost to follow-up prior to the scheduled end of treatment of study treatment, except for pregnancies and violent or accidental death that were instead classified as having a Not Assessable outcome (see protocol for definition).
4. Participants who had an M. tuberculosis positive culture result when last seen during or prior to the Month 12 analysis visit window, whether confirmed by a second sample or not, unless determined to have been re-infected.
5. Participants receiving any one or more of the following, except when given for failure or recurrence subsequently shown to be a reinfection with a strain of *M. tuberculosis*, different from that or those identified at study entry through genotyping methods):
   a) Extension of treatment beyond that permitted by the protocol; excepting
      a. temporary drug re-challenge;
      b. over-treatment with drugs from assigned study kits;
      c. twenty-one days or fewer of non-study anti-TB medications given for treatment of active TB; or
      d. secondary isoniazid preventative therapy in HIV infected participants.
   b) Re-start of treatment for active TB;
   c) Change in treatment (including frequency or dosage) for any reason except re-infection, pregnancy, or temporary drug challenge.
6. Participants who died during the follow-up phase (as defined in the protocol) where the cause of death was considered related to TB.

PICO question (Recommendation A.2.2.)

In children and adolescents aged below 20 years with presumed or bacteriologically confirmed drug-susceptible TB meningitis, should a 6-month intensive regimen, compared to the 12-month regimen that conforms to WHO guidelines be used?

Population	Intervention	Comparator	Outcome/s
Children and adolescents aged below 20 years with presumed or bacteriologically confirmed rifampicin-susceptible TB meningitis Sub-populations: • Children living with HIV • Children with severe acute malnutrition Stratify by age: • 0-12 months • 1-4 years • 5-9 years • 10-19 years	A 6-month intensive regimen composed of rifampicin, isoniazid, pyrazinamide and ethionamide	A 12-month regimen composed of 2HRZE/10HR at standard doses (current WHO recommendation)	TB treatment outcomes: treatment success, treatment failure, death, loss to follow up Relapse Serious adverse events Disability/sequelae/ neurodevelopmental outcomes

* Notes: children in whom the diagnosis of non-severe TB was established by a committee.

Non-severe TB is defined as sputum smear-negative TB, extrathoracic lymph node TB, intrathoracic lymph node TB with no significant airway obstruction, or uncomplicated forms of pulmonary TB, confined to one lobe and with no cavities.

4.2. Drug-resistant TB

4.2.1. Guideline update 2022

Summary of PICO questions and comparisons on shorter (6-month or 9-month) regimens

PICO #	PICO question	Population	Intervention regimen	Comparator [data source]	Comparison #
1	Should a shorter all-oral regimen (less than 12 months) containing at least three Group A medicines be used in patients with MDR/RR-TB and fluoroquinolone resistance excluded?	MDR/RR	SA_new	WHO_short [SA_old]	1.1
				WHO_long [IPD]	1.2
2	Should a 6-to-9-month shorter all-oral regimen containing Lzd, Bdq, Lfx, Z, Eto/Hh/Trd be used in patients with MDR/RR-TB and fluoroquinolone resistance excluded?	MDR/RR	NExT	mix of SOC [NExT]	2.1
				WHO_short [SA_old]	2.2
				WHO_long [IPD]	2.3
				SA_new	2.4
3	Should BPaL regimens with lower linezolid exposure (dose or duration) be used instead of the original BPaL regimen in patients who are eligible for BPaL regimen?	MDR/RR and pre-XDR	BPaL (all 3 modified)	BPaL 1200–26 [Nix, ZeNix]	3.1
			BPaL 1200–9		3.2
			BPaL 600–26		3.3
			BPaL 600–9		3.4
			BPaL 600–300		3.5

PICO #	PICO question	Population	Intervention regimen	Comparator [data source]	Comparison #
4	Should 6-month regimen using bedaquiline, pretomanid, linezolid be used in patients with pulmonary pre-XDR-TB (MDR/RR-TB with fluoroquinolone resistance)?	pre-XDR	BPaL (all 5)	WHO_long [IPD]	4.1
5	Should 6-month regimen using bedaquiline, pretomanid and linezolid be used in patients with pulmonary MDR/RR-TB and without fluoroquinolone resistance?	MDR/RR	BPaL (all 5)	WHO_short [SA_old]	5.1
				WHO_long [IPD]	5.2
				SA_new	5.3
				NeXT	5.4
6	Should 6-month regimen using bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) be used in patients with pulmonary MDR/RR-TB (with or without fluoroquinolone resistance)?	MDR/RR and pre-XDR	BPaLM	trial-internal mix of SOC [PRACTECAL]	6.1
				trial-SOC 1 [PRACTECAL]	6.2
				trial-SOC 2 [PRACTECAL]	6.3
				trial-SOC 3 [PRACTECAL]	6.4
				trial-SOC 4 [PRACTECAL]	6.5
7	Should 6-month regimen using bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) be used in patients with pulmonary pre-XDR-TB (MDR/RR-TB with fluoroquinolone resistance)?	pre-XDR		WHO_long [IPD]	7.1
				BPaL (all 5)	7.2
				BPaLC [PRACTECAL]	7.3

PICO #	PICO question	Population	Intervention regimen	Comparator [data source]	Comparison #
8	Should 6-month regimen using bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) be used in patients with pulmonary MDR/RR-TB and without fluoroquinolone resistance?	MDR/RR	BPaLM	WHO_short [SA_old]	8.1
				WHO_long [IPD]	8.2
				SA_new	8.3
				NeXT	8.4
				BPaL (all 5)	8.5
				BPaLC [PRACTECAL]	8.6
9	Should 6-month regimen using bedaquiline, pretomanid, linezolid and clofazimine (BPaLC) be used in patients with pulmonary pre-XDR-TB (MDR/RR-TB with fluoroquinolone resistance)?	pre-XDR	BPaLC	WHO_long [IPD]	9.1
				BPaL (all 5)	9.2
10	Should 6-month regimen using bedaquiline, pretomanid, linezolid and clofazimine (BPaLC) be used in patients with pulmonary MDR/RR-TB and without fluoroquinolone resistance?	MDR/RR	BPaLC	WHO_short [SA_old]	10.1
				WHO_long [IPD]	10.2
				SA_new	10.3
				NeXT	10.4
				BPaL (all 5)	10.5

Question 1 (SA_new regimen)

Should a shorter all-oral regimen (less than 12 months) containing at least three Group A medicines be used in patients with **MDR/RR-TB** (fluoroquinolone resistance excluded)?

Population	Intervention*	Comparator**	Outcome
Patients with MDR/RR-TB (FQ resistance excluded, plus other inclusion criteria as for SA_new) *Stratified by:* • Adults, adolescents, children • PTB, EXPTB • Comorbidities: HIV, diabetes	SA_new	– WHO_short – WHO_long***	1. Treatment success 2. Failure and recurrence 3. LTFU 4. Death 5. Adverse events (DDIs for HIV-infected patients, if data available) 6. Amplification of drug resistance

* *Data sources: South Africa + OR in other countries (public call)*

** *Data sources:*
- Shorter regimen: SA (provided by country & 2 comparator regimens in TB-PRATECAL) & other countries (public call or OR studies)
- Longer regimens: Belarus, Republic of Moldova, Georgia, the Russian Federation, and others (public call)

*** If eligibility criteria for the SA_new is aligned and restricted to the same criteria as WHO_short then comparisons with the WHO_long becomes less relevant but if sufficient data we do this comparison (we may not have sufficient numbers of records with truly WHO-long, restricted to the same population as SA_new)

Note: *public call for additional data is required for both intervention and comparator*

Question 2 (NeXT study regimen)

- Should a 6-to-9-month shorter all-oral regimen containing **Lzd, Bdq, Lfx, Z, Eto/Hh/Trd** be used in patients with **MDR/RR-TB** (fluoroquinolone resistance excluded)?

Population	Intervention*	Comparator	Outcome
Patients with MDR/RR-TB and FQ resistance excluded (plus other inclusion criteria as in NeXT trial) *Stratified by:* • Adults, adolescents, children • PTB, EXPTB • Comorbidities: HIV, diabetes	NeXT	Injectable-based longer or shorter regimen (within trial comparison)	• Treatment success (24 months after initiation of treatment)
		External comparators**: – WHO_short – SA_new – WHO_long***	1. Treatment success 2. Failure and Recurrence 3. LTFU 4. Death 5. Adverse events (DDIs for HIV-infected patients) 6. Amplification of drug resistance

* *Source of data: NExT Clinical TRial – SA.* Six to nine months of all-oral regimen: Linezolid 600 mg daily (reduce to 300 mg if toxicity occurs), Bedaquiline 400 mg for 2 weeks, followed by 200 mg three times per week, Levofloxacin 750 mg (<50 kg) or 1 000 mg (>50 kg) daily, PZA 1 000–1 750 mg (40–50 kg) or 1 750–2 000 mg (51–70 kg) or 2 000–2 500 mg (71–90 kg) daily, Ethionamide 15 mg/kg (max 900 mg) daily, or high-dose Isoniazid 500 mg (40–50 kg) or 750 mg (51–70 kg) or 750–1 000 mg (71–90 kg) daily, or Terizidone 750 mg (40–70 kg) or 750–1 000 mg (71–90 kg) daily. Trd is used only for patients with KatG mutation (Eto and Hh no more effective)

** Data sources:
- Shorter regimens: SA (provided by NTP) & other countries (public call or OR studies)
- Longer regimens: Belarus, Republic of Moldova, Georgia, the Russian Federation, and others (public call, if available)

*** If eligibility criteria for the NeXT is aligned and restricted to the same criteria as WHO_short then comparisons with the WHO_long becomes less relevant but if sufficient data we do this comparison (we may not have sufficient numbers of records with truly WHO-long, restricted to the same population as NeXT)

Background Question 1 (ZeNix and TB-PRACTECAL study regimens)

What is the safety profile of BPaL regimens with different levels of exposure to linezolid when used in MDR-TB patients?

Population	Intervention	Comparator	Outcome
Patients with pulmonary MDR-TB (with or without fluoroquinolone resistance) *Stratified by:* • HIV • Site[1]	All BPaL regimens combined and stratified: 1. Lzd 1 200 mg x 26 weeks + Pa + Bdq 2. Lzd 1 200 mg x 9 weeks + Pa + Bdq 3. Lzd 600 mg x 26 weeks + Pa + Bdq 4. Lzd 600 mg x 9 weeks + Pa + Bdq 5. Lzd (600 mg x 16 weeks, 300 mg x 8 weeks) + Pa + Bdq[2]		Adverse events • SAEs • AEs of special interest: QT prolongation, peripheral neuropathy, optic neuritis, myelosuppression, hepatotoxicity.

[1] There is significant difference in AEs between sites in ZeNix study.

[2] TB-PRACTECAL arm 3 regimen.

Question 3 (The BPaL regimens with lower Lzd exposure – ZeNix and TB-PRACTECAL regimens)

Should BPaL regimens with lower linezolid exposure (dose or duration) be used instead of the original BPaL regimen in patients who are eligible for BPaL regimen?

Population	Intervention	Comparator	Outcome
Patients with pulmonary pre-XDR-TB (MDR/RR-TB and fluoroquinolone resistance) and treatment intolerant or non-responsive MDR-TB[1] *Stratified by:* • MDR/RR-TB with FQ resistance • MDR/RR-TB without FQ resistance • Adults, adolescents (17–19 yrs old) • Comorbidities: HIV, diabetes *If data available:* • Smear positivity • Culture positivity • Cavitation on chest x-ray • Smoker status	Modified BPaL regimen with lower Lzd exposure: 1. Lzd 1 200 mg x 9 weeks + Pa + Bdq 2. Lzd 600 mg x 26 weeks + Pa + Bdq 3. Lzd 600 mg x 9 weeks + Pa + Bdq 4. **External data** (compare if useful) Lzd (600 mg x 16 weeks and 300 mg x 8 weeks) + Pa + Bdq[2]	The BPaL regimen[3]: Lzd 1 200 mg x 26 weeks + Pa + Bdq 1. *BPaL cohort in ZeNix study; and* 2. ***External data*** *(compare if useful)* *Nix and ZeNix cohorts combined.*	1. Treatment success 2. Failure and Recurrence 3. Death 4. Lost to follow up 5. Adverse events (DDIs for HIV-infected patients) 6. Amplification of drug resistance

[1] *ZeNix study population also includes MDR/RR-TB patients with additional resistance to fluoroquinolone or injectable agents. Patients with treatment intolerant or non-responsive MDR-TB in the study are mainly intolerant or nonresponsive to the previously WHO recommended regimens (prior to the 2 020 recommendation).*

[2] *TB-PRACTECAL arm 3 regimen – external comparator, non-randomized.*

[3] *Data source: 1) BPaL cohort in ZeNix study; and 2) Nix and ZeNix cohorts combined. There is a difference in Bdq dosing between NiX and ZeNix studies.*

Question 4. Should 6-month regimen using bedaquiline, pretomanid, linezolid be used in patients with pulmonary pre-XDR-TB (MDR/RR-TB with fluoroquinolone resistance)?

Population	Intervention	Comparator	Outcome
Patients with microbiologically confirmed pulmonary MDR/RR-TB and **with FQ resistance** *Stratified by:* • Smear positivity • Culture positivity • Cavitation on chest x-ray • Smoker status • HIV status • Diabetes status	• **BPaL**[1] – **Combined but if possible stratified by regimen** – 6–9 Lzd 1 200 mg x 26 weeks + Pa + B – 6–9 Lzd 1 200 mg x 9 weeks + Pa + Bdq – 6–9 Lzd 600 mg x 26 weeks + Pa + Bdq – 6–9 Lzd 600 mg x 9 weeks + Pa + Bdq – 6–9 Lzd 600–300 mg + Pa+ Bdq	WHO_long[2]	1. Treatment success 2. Failure and Recurrence 3. Death 4. Lost to follow up 5. Adverse events (DDIs for HIV-infected patients, if available) 6. Amplification of drug resistance

[1] *Nix & Zenix & PRACTECAL studies*

[2] *Data sources:*
- Data contributed by countries (public call – for LR);
- EndTB regimens (IPD);

Question 5. Should 6-month regimen using bedaquiline, pretomanid and linezolid be used in patients with pulmonary MDR/RR-TB and without fluoroquinolone resistance?

Population	Intervention	Comparator	Outcome
Patients with pulmonary MDR/RR-TB and **without FQ resistance** *Stratified by:* • Smear positivity • Culture positivity • Cavitation on chest x-ray • Smoker status • HIV status • Diabetes status	• **BPaL**[1] – **Combined but if possible stratified by regimen** – 6–9 Lzd 1 200 mg x 26 weeks + Pa + B – 6–9 Lzd 1 200 mg x 9 weeks + Pa + Bdq – 6–9 Lzd 600 mg x 26 weeks + Pa + Bdq – 6–9 Lzd 600 mg x 9 weeks + Pa + Bdq – 6–9 Lzd 600–300 mg + Pa+ Bdq	Other regimens conforming to WHO guidelines[2] – Shorter regimen – Longer regimens Other regimens: – NeXT – SA_new	1. Treatment success 2. Failure and Recurrence 3. Death 4. Lost to follow up 5. Adverse events (DDIs for HIV-infected patients, if data available) 6. Amplification of drug resistance

[1] *Nix & Zenix & PRACTECAL studies*

[2] *Data sources:*
- Data contributed by countries (public call – for both SR & LR);
- IPD: all-oral SR (from SA), EndTB regimens;

Internal TB-PRACTECAL trial comparison

Question 6. Should 6-month regimen using bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) be used in patients with pulmonary MDR/RR-TB (with or without fluoroquinolone resistance)?

Population	Intervention	Comparator	Outcome
Patients with microbiologically confirmed pulmonary MDR/RR-TB (regardless of FQ resistance status) *Stratified by:* • **Fluoroquinolone resistance** • Smear positivity • Culture positivity • Cavitation on chest x-ray • Smoker status • HIV status • Diabetes status • Study site	BPaLM[a]	1. TB-PRACTECAL control regimens – Standard of Care (SOC) regimens – all combined 2. SOC regimen stratification: • 9–11 month shorter injectable regimen • 18–24 month conventional regimen (pre-2019) • 9–11 month shorter all oral regimen (SA) • 18–20 month longer all oral regimen	1. Unfavourable treatment outcome (failure, discontinuation, death, recurrence, loss to follow-up) at 72 weeks post-randomisation 2. Adverse events (SAEs or Grade 3 or higher AEs at 72 weeks post randomisation; DDIs for HIV-infected pa\ tients) 3. Amplification of drug resistance

[a] *TB-PRACTECAL intervention arm 1: Bedaquiline: 400 mg once daily for 2 weeks followed by 200 mg 3 times per week for 22 weeks, Pretomanid: 200 mg once daily for 24 weeks, Moxifloxacin: 400 mg once daily for 24 weeks, Linezolid: 600 mg daily for 16 weeks then 300 mg daily for the remaining 8 weeks or earlier when moderately tolerated.*

TB-PRACTECAL intervention regimens vs external comparators

Question 7. Should 6-month regimen using bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) be used in patients with pulmonary pre-XDR-TB (MDR/RR-TB with fluoroquinolone resistance)?

Population	Intervention	Comparator	Outcome
Patients with microbiologically confirmed pulmonary MDR/RR-TB and **with FQ resistance** *Stratified by:* • Smear positivity • Culture positivity • Cavitation on chest x-ray • Smoker status • HIV status • Diabetes status	**BPaLM**: 6 Bdq-Pa-Lzd-Mfx[1]	• **WHO_long**[2] • **BPaL**[3]**-Combined but if possible stratified by regimen** – 6–9 Lzd 1 200 mg x 26 weeks + Pa + B – 6–9 Lzd 1 200 mg x 9 weeks + Pa + Bdq – 6–9 Lzd 600 mg x 26 weeks + Pa + Bdq – 6–9 Lzd 600 mg x 9 weeks + Pa + Bdq – 6–9 Lzd 600–300 mg + Pa+ Bdq • **BPaLC**	1. Treatment Success 2. Failure and recurrence 3. Death 4. LTFU 5. Adverse events (DDIs for HIV-infected patients, if data are available) 6. Amplification of drug resistance

[1] *TB-PRACTECAL intervention arm 1: Bedaquiline: 400 mg once daily for 2 weeks followed by 200 mg 3 times per week for 22 weeks Pretomanid: 200 mg once daily for 24 weeks Moxifloxacin: 400 mg once daily for 24 weeks Linezolid: 600 mg daily for 16 weeks then 300 mg daily for the remaining 8 weeks or earlier when moderately tolerated.*

[2] *Data sources:*
- Data contributed by countries (public call – for LR);
- EndTB regimens (IPD);

[3] *Nix & Zenix & PRACTECAL studies*

Question 8. Should 6-month regimen using bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) be used in patients with pulmonary MDR/RR-TB and without fluoroquinolone resistance?

Population	Intervention	Comparator	Outcome
Patients with microbiologically confirmed pulmonary MDR/RR-TB and **without FQ resistance** *Stratified by:* • Smear positivity • Culture positivity • Cavitation on chest x-ray • Smoker status • HIV status • Diabetes status	TB-PRACTECAL Arm 1 regimen (BPaLM)[a]: 6 Bdq-Pa-Lzd-Mfx	Other regimens conforming to WHO guidelines[b] – WHO_short – WHO_long Other regimens: – NeXT regimen – SA_new – BPaL – BPaLC	1. Treatment success 2. Failure and Recurrence 3. Death 4. Lost to follow up 5. Adverse events (DDIs for HIV-infected patients, if data are available) 6. Amplification of drug resistance

[a] *TB-PRACTECAL intervention arm 1: Bedaquiline: 400 mg once daily for 2 weeks followed by 200 mg 3 times per week for 22 weeks, Pretomanid: 200 mg once daily for 24 weeks Moxifloxacin: 400 mg once daily for 24 weeks, Linezolid: 600 mg daily for 16 weeks then 300 mg daily for the remaining 8 weeks or earlier when moderately tolerated.*

[b] *Data sources:*
- Data contributed by countries (public call – for both SR & LR);
- IPD: all-oral SR (from SA), EndTB regimens;

Question 9. Should 6-month regimen using bedaquiline, pretomanid, linezolid and clofazimine (BPaLC) be used in patients with pulmonary pre-XDR-TB (MDR/RR-TB with fluoroquinolone resistance)?

Population	Intervention	Comparator	Outcome
Patients with microbiologically confirmed pulmonary MDR/RR-TB and **with FQ resistance** *Stratified by:* • Smear positivity • Culture positivity • Cavitation on chest x-ray • Smoker status • HIV status • Diabetes status	BPaLC: 6 Bdq-Pa-Lzd-Cfz[1]	• WHO_long[2] • **BPaL[3]-Combined but if possible stratified by regimen** – 6–9 Lzd 1 200 mg x 26 weeks + Pa + B – 6–9 Lzd 1 200 mg x 9 weeks + Pa + Bdq – 6–9 Lzd 600 mg x 26 weeks + Pa + Bdq – 6–9 Lzd 600 mg x 9 weeks + Pa + Bdq – 6–9 Lzd 600–300 mg + Pa+ Bdq	1. Treatment success 2. Failure and Recurrence 3. Death 4. Lost to follow up 5. Adverse events (DDIs for HIV-infected patients, if data are available) 6. Amplification of drug resistance

[1] *TB-PRACTECAL intervention arm 2. Linezolid use: 600 mg daily for 16 weeks then 300 mg daily for the remaining 8 weeks or earlier when moderately tolerated.*

[2] *Data sources:*
- Data contributed by countries (public call – for LR);
- EndTB regimens (IPD);

[3] *Nix & Zenix & PRACTECAL studies*

Question 10. Should 6-month regimen using bedaquiline, pretomanid, linezolid and clofazimine (BPaLC) be used in patients with pulmonary MDR/RR-TB and without fluoroquinolone resistance?

Population	Intervention	Comparator	Outcome
Patients with pulmonary MDR/RR-TB and **without FQ resistance** *Stratified by:* • Smear positivity • Culture positivity • Cavitation on chest x-ray • Smoker status • HIV status • Diabetes status	BPaLC[a]: 6 Bdq-Pa-Lzd-Cfz	Other regimens conforming to WHO guidelines[b] – Shorter regimen – Longer regimens Other regimens: – 6–9 Lzd Bdq Lfx Z Eto/Hh/Trd (NeXT regimen) – All-oral shorter regimen containing 3 group A medicines (SA regimen 2019) – 6–9 Lzd 600–300 mg + Pa+ Bdq (PRATECAL arm) – BPaL regimens (Nix/Zenix)	1. Treatment success 2. Failure and Recurrence 3. Death 4. Lost to follow up 5. Adverse events (DDIs for HIV-infected patients if data are available) 6. Amplification of drug resistance

[a] *TB-PRACTECAL intervention arm 2, with Linezolid 600 mg daily for 16 weeks then 300 mg daily (or 600 mg x3/wk) for the remaining 8 weeks or earlier when moderately tolerated.*

[b] *Data sources:*
- Data contributed by countries (public call – for both SR & LR);
- IPD: all-oral SR (from SA), EndTB regimens;

Question 11 (Use of bedaquiline for treatment of MDR/RR-TB in children below 6 years)

In MDR/RR-TB patients aged below 6 years, should an all-oral treatment regimen containing bedaquiline versus other regimens conforming to WHO guidelines without bedaquiline be used?

Population	Intervention	Comparator	Outcome/s
Children aged below 6 years with rifampicin-resistant or multidrug-resistant TB (MDR/RR-TB) *Stratify by:* • FQ resistance (child or most likely source case)	An all-oral second-line treatment regimen that includes bedaquiline *Sub-analyses:* • Shorter regimen (9–12 months) • Longer regimen (>12 months) • Concurrent use with delamanid	An all-oral second-line treatment regimen that includes NO bedaquiline conforming to WHO guidelines	• Successful completion of treatment • For children with bacteriological confirmation: Bacteriological cure by end of treatment • Adherence to treatment (or treatment interruption due to non-adherence) • Treatment failure or relapse • Survival (or death) • Adverse reactions from anti-TB medicines • Acquisition (amplification) of drug resistance

Question 12 (Use of delamanid for treatment of MDR/RR-TB in children below 3 years)

In MDR/RR-TB patients aged below 3 years, should an all-oral treatment regimen containing delamanid versus other regimens conforming to WHO guidelines without delamanid be used?

Population	Intervention	Comparator	Outcome/s
Children aged below 3 years with rifampicin-resistant or multidrug-resistant TB (MDR/RR-TB) *Stratify by:* • FQ resistance (child or most likely source case)	An all-oral second-line treatment regimen that includes delamanid *Sub-analyses:* • Shorter regimen (9–12 months) • Longer regimen (>12 months) • Concurrent use with bedaquiline	An all-oral second-line treatment regimen that includes NO delamanid conforming to WHO guidelines	• Successful completion of treatment • For children with bacteriological confirmation: Bacteriological cure by end of treatment • Adherence to treatment (or treatment interruption due to non-adherence) • Treatment failure or relapse • Survival (or death) • Adverse reactions from anti-TB medicines • Acquisition (amplification) of drug resistance

4.2.2. Guideline update 2025

Question 1 (BEAT-TB 6-month regimen)

Should a 6-month regimen using bedaquiline, delamanid, and linezolid with or without the addition of levofloxacin or clofazimine or both (BDLLfx/C) be used in patients with pulmonary RR-TB (with or without fluoroquinolone resistance) over the currently recommended 9-month regimen?

Population	Intervention	Comparator	Outcome
Patients with microbiologically confirmed pulmonary MDR/RR-TB and **with or without FQ resistance**	BDLLfx/C regimen[a]: 6 Bdq-Dlm-Lzd-Lfx/Cfz (and/or)	BEAT-Tuberculosis comparator regimens: • 9 Bdq(6)-Lzd(2)-Lfx-Cfz-Hh-Z-E (for Fq-susceptible) • WHO currently recommended longer regimens (18–20 months) (for Fq-resistant)	• Sustained treatment success • Failure and recurrence • Death • Lost to follow up • Adverse events • Amplification (acquisition) of drug resistance

[a] *BEAT-Tuberculosis trial intervention arm (6 months or 24 weeks)*

Question 2 (endTB modified 9-month regimens)

Should any 9-month endTB trial regimens be used in patients with pulmonary RR-TB (without fluoroquinolone resistance) over the currently recommended longer regimens?

Population	Intervention[a]	Comparator	Outcome
Patients with microbiologically confirmed pulmonary MDR/RR-TB and **without FQ resistance**	endTB 1 regimen: 9 Bdq-Lzd-Mfx-Z endTB 2 regimen: 9 Bdq-Lzd-Cfz-Lfx-Z endTB 3 regimen: 9 Bdq-Lzd-Dlm-Lfx-Z endTB 4 regimen: 9 Dlm-Cfz-Lzd-Lfx-Z endTB 5 regimen: 9 Dlm-Cfz-Mfx-Z	WHO currently recommended longer regimens (18–20 months)	• Sustained treatment success • Failure and recurrence • Death • Lost to follow up • Adverse events • Amplification (acquisition) of drug resistance

[a] *endTB trial intervention arms (9 months or 39 weeks)*

4.2.3. Guideline update 2026

PICO Question 1 (based on BEAT Tuberculosis[80] and endTB-Q[81] trial meta-analysis)

Should a BDLC regimen be used in patients with pulmonary pre-XDR-TB over the longer 18-month regimens?

Population	Intervention	Comparator	Outcome
Patients with microbiologically confirmed pulmonary pre-XDR-TB, stratified by severity	**BDLC regimen[a]:** **6 Bdq-Dlm-Lzd-Cfz**	**Currently recommended WHO longer regimens[a]**	7. Sustained treatment success 8. Failure and recurrence 9. Death 10. Lost to follow up 11. Adverse events 12. Amplification (acquisition) of drug resistance

[a] *BEAT Tuberculosis and endTB-Q meta-analysis*

PICO Question 2 (based on TB-PRACTECAL trial[82])

Should a BPaL regimen be used in patients with pulmonary pre-XDR-TB over the TB-PRACTECAL comparator regimens?

Population	Intervention	Comparator	Outcome
Patients with microbiologically confirmed pulmonary pre-XDR-TB or MDR/RR-TB *a*, stratified by severity	**BPaL regimen[b]** **6 Bdq-Pa-Lzd**	**currently recommended WHO longer regimens[a]** (Note: excluding any 9-month regimens in the trial comparator group)	13. Sustained treatment success 14. Failure and recurrence 15. Death 16. Lost to follow up 17. Adverse events 18. Amplification (acquisition) of drug resistance

[a] *Use data from participants with either MDR/RR-TB or pre-XDR-TB in the BPaL arm of the trial and extrapolate to pre-XDR-TB*

[b] *Updated dataset of TB-PRACTECAL with more records*

[80] https://www.medrxiv.org/content/10.1101/2025.05.04.25326549v1

[81] Bedaquiline, delamanid, linezolid, and clofazimine for rifampicin-resistant and fluoroquinolone-resistant tuberculosis (endTB-Q): an open-label, multicentre, stratified, non-inferiority, randomised, controlled, phase 3 trial - The Lancet Respiratory Medicine

[82] Short oral regimens for pulmonary rifampicin-resistant tuberculosis (TB-PRACTECAL): an open-label, randomised, controlled, phase 2B-3, multi-arm, multicentre, non-inferiority trial – The Lancet Respiratory Medicine

Background question 2.1 (based on operational research and observational data collected through the public call)

What are the outcomes of patients receiving BPaL?

Population	Intervention	Comparator	Outcome
Patients with microbiologically confirmed pulmonary Pre-XDR-TB or MDR/RR-TB	BPaL[a]	no comparator	19. Sustained treatment success 20. Failure and recurrence 21. Death 22. Lost to follow up 23. Adverse events 24. Amplification (acquisition) of drug resistance

[a] *Data source: all available, including operational research studies and programmatic implementation*

PICO Question 3 (based on TB-PRACTECAL trial)

Should a BPaLC regimen be used in patients with pulmonary pre-XDR-TB over the TB-PRACTECAL comparator regimens?

Population	Intervention	Comparator	Outcome
Patients with microbiologically confirmed pulmonary Pre-XDR-TB or MDR/RR-TB[a], stratified by severity	**BPaLC regimen**[b] **6 Bdq-Pa-Lzd-Cfz**	**WHO currently recommended longer regimens**[a]	25. Sustained treatment success 26. Failure and recurrence 27. Death 28. Lost to follow up 29. Adverse events 30. Amplification (acquisition) of drug resistance

[a] *Use data from participants with either MDR/RR-TB or pre-XDR-TB in the BPaL arm of the trial and extrapolate to pre-XDR-TB*

[b] *Updated dataset of TB-PRACTECAL with more records*

Background question 3.1 (based on operational research and observational data collected through the public call) What are the outcomes of patients receiving BPaLC?

Population	Intervention	Comparator	Outcome
Patients with microbiologically confirmed pulmonary Pre-XDR-TB or MDR/RR-TB	BPaLC[a]	no comparator	31. Sustained treatment success 32. Failure and recurrence 33. Death 34. Lost to follow up 35. Adverse events 36. Amplification (acquisition) of drug resistance

PICO Questions 4–6 (based on TB-PRACTECAL trial)

PICO	Population	Intervention	Comparator	Outcome
Should a BPaL regimen be used in patients with pulmonary pre-XDR-TB over the BPaLM regimen?	Patients with microbiologically confirmed pulmonary Pre-XDR-TB	BPaL[b]	BPaLM[b]	37. Sustained treatment success 38. Failure and recurrence 39. Death 40. Lost to follow up 41. Adverse events 42. Amplification (acquisition) of drug resistance
Should a BPaLC regimen be used in patients with pulmonary pre-XDR-TB over the BPaLM regimen?	Patients with microbiologically confirmed pulmonary Pre-XDR-TB	BPaLC[b]	BPaLM[b]	
Should a BPaLC regimen be used in patients with pulmonary pre-XDR-TB over the BPaL regimen?	Patients with microbiologically confirmed pulmonary Pre-XDR-TB	BPaLC[b]	BPaL[b]	

[a] *Data source: all available, including operational research studies and programmatic implementation*

[b] *Updated dataset of TB-PRACTECAL with more records*

4.3. TB care and support

Care and support interventions for all people with TB (Guideline update 2017)

Question 1. In patients with TB, are any interventions to promote adherence to TB treatment more or less likely to lead to the outcomes listed below?

Population	Intervention	Comparator	Outcome
Patients on treatment for DS-TB Patients on treatment for MDR-TB Children (0–14 years) and adults HIV-infected and HIV-uninfected TB patients	Any intervention to promote treatment adherence • Supervision of treatment (treatment support, virtual (video-) supported therapy) • Measures to improve treatment adherence (e.g. medication monitors and/or SMS or telephone call reminders) • Social support (educational, psychological, material) • Combinations of the above interventions	Routine practice[83]	• Adherence to treatment (or treatment interruption due to non-adherence) • Conventional TB treatment outcomes: cure or treatment completion, failure, relapse, survival/death • Adverse reactions from TB drugs (severity, type, organ class) • Cost to the patient (including direct medical costs as well as others such as transportation, lost wages due to disability) • Cost to health services

[83] Routine practice: regular TB drugs pick-up and consultations with physician or other health-care workers are available when necessary; TB treatment is free of charge; essential information/health education in relation to TB treatment is provided.

Models of care for people with drug-resistant TB (Guideline updates 2011 and 2017)

Question 2. Among patients with MDR-TB, is ambulatory therapy compared with inpatient treatment, more or less likely to lead to better outcomes?

Question 3. Is decentralized treatment and care for MDR-TB patients more or less likely to lead to the outcomes listed below?

Population	Intervention	Comparator	Outcome
Patients on treatment for MDR-TB	Decentralized treatment and care (provided by non-specialized or periphery health centres; by community health workers, community volunteers or treatment supporters) • Treatment and patient support • Injection during the intensive phase • Specialist care for co-morbidities (e.g. HIV, diabetes, chronic lung diseases, or other conditions such as auditory function, renal function, liver function, neurology, ophthalmology)	Treatment and care provided solely by centres or teams specialized in drug-resistant TB	• Adherence to treatment (or treatment interruption due to non-adherence) • Conventional TB treatment outcomes: cure or treatment completion, failure, relapse, survival/ death • Adverse reactions from TB drugs (severity, type, organ class) • Acquisition (amplification) of drug resistance • Cost to the patient (including direct medical costs as well as others such as transportation, lost wages due to disability) • Cost to health services

Models of care for children and adolescents (Guideline update 2022)

Question 4. Models of care for TB case detection and TB prevention settings with a prevalence of TB in the general population of 100 per 100 000 or more:

a. In children and adolescents with signs and symptoms of TB, should the decentralization of child and adolescent TB services versus centralized child and adolescent TB services (at referral or tertiary hospital level) be used?

b. In children and adolescents exposed to TB, should the decentralization of child and adolescent TB prevention and care services versus centralized prevention and care services (at referral or tertiary hospital level) be used to increase coverage of TB preventive treatment in eligible children and adolescents?

c. In children and adolescents with signs and symptoms of TB, should family-centred, integrated services versus standard, non-family-centred, non-integrated services be used?

In children and adolescents exposed to TB, should family-centred, integrated services versus standard, non-family-centred, non-integrated services be used to increase coverage of TB preventive treatment in eligible children and adolescents?

Palliative care intervention (Guideline update 2026)

Should nurse-led palliative care interventions[84], in addition to effective treatment, be used in patients with pulmonary RR/MDR-TB over effective treatment without such interventions?

[84] https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(25)00173-1/fulltext

Population	Intervention	Comparator	Outcome
Patients with MDR/RR-TB: • *People with confirmed rifampicin-resistant or multidrug-resistant tuberculosis following a GeneXpert confirmation test for diagnosis (i.e. resistant to rifampicin or both isoniazid and rifampicin).* • *Adults aged at least 18 years* • *Able to give informed consent.*	**MDR/RR-TB treatment and nurse-led palliative care interventions[a]** Nurse-led palliative care interventions (based on African Palliative Care Association standards) spanning physical, psychological, social, and spiritual domains + DR-TB treatment: The intervention group received a novel multisectoral palliative care intervention, which was in line with the Global Plan to End TB 2023–30 and patients received care from a local voluntary sector hospice alongside the government-provided tuberculosis service. The palliative care intervention was modelled following the African Palliative Care Association's Standards for Palliative Care in Africa. The hospice-delivered palliative care component was nurse-led, in line with evidence that nurses are well placed to deliver specific components of care to patients with multidrug-resistant tuberculosis, including treatment; management of stigma, adherence, and side effects; and to support patients and families at the end of life.	**MDR/RR-TB treatment without palliative care interventions** This consisted of either an outpatient consultation or short admission duration of between 2 weeks and 4 weeks after initiation of treatment, and depending on the patient's condition, the remaining care and clinical assessment were conducted at a monthly clinic nurse-led appointment. However, patients could come back to the clinic for clinical assessment or medicine refill if problems occurred before the appointed review date.	1. Primary outcome: palliative care-related symptoms and concerns measured monthly for 4 months using the African Palliative Care Association Integrated Palliative Outcome Scale (APOS), 2. Secondary outcomes: a. Psychological morbidity measured monthly for 4 months with the General Health Questionnaire-12 (GHQ-12). b. Quality of life was measured monthly for 4 months using the 26-item WHO QoL-BREF. c. Treatment adherence: we asked whether the participant had missed any doses of their tuberculosis treatment in the previous month d. Alcohol consumption: We asked a single item about whether they had used alcohol in the previous month (Yes or No)

Population	Intervention	Comparator	Outcome
	MDR-TB patients in the intervention group received the additional palliative care at the tuberculosis clinic (for those admitted) or at home, as appropriate. First, nurses conducted a detailed person-centred holistic assessment with the patient (addressing physical, psychological, social, and spiritual concerns focused on the concerns of both the patient and their family. Nurses delivered support responsive to the assessment (eg, pain and symptom control, care planning), and referral for specific concerns beyond the scope of nursing provision (eg, spiritual or financial support). After the initial detailed assessment, for those admitted to a tuberculosis ward, the palliative care nurse followed up with the patient weekly; for those at home this was a fortnightly home visit, with a telephone call on alternate weeks to address any symptoms and concerns that might have arisen during the time between home visits. Palliative care intervention nurses were existing hospice nursing staff, and for the purposes of this study, were provided with an initial 2-day training course on multidrug resistant tuberculosis, palliative care needs	Referral to hospice for palliative and end-of life care was permittable from within all government health services for patient with advanced disease, although referrals for patients with tuberculosis are rare. No formal palliative care training had been provided to the government nurses for tuberculosis who were providing standard care	e. Service Receipt: We administered The Client Services Receipt Inventory questionnaire is a 23-item self-report measure monthly for 4 months

Population	Intervention	Comparator	Outcome
	and management, infection control, and the Uganda national multidrug-resistant tuberculosis standard operating procedures. Intervention nurses also had usual access to hospice clinical officers and doctors for further advice on cases. Drugs not commonly available at the government sites (eg, oral liquid morphine and Bisacodyl) were provided to patients in the intervention group by the hospice, as needed. The intervention lasted for 3 months.		

Annex 5. Summary of evidence, GRADE evidence profiles and evidence-to-decision tables

5.1 Drug-susceptible TB

5.1.1 Guidelines update 2010 to 2022

Evidence profiles and evidence-to-decision tables:

Refer to *WHO consolidated guidelines on tuberculosis: module 4: treatment: drug-susceptible tuberculosis treatment: Web annexes*. Web annex 4

https://iris.who.int/handle/10665/353398

Refer to WHO consolidated guidelines on tuberculosis: module 5: Management of tuberculosis in children and adolescents: Web annexes. Web annexes 2 and 3

Web annex 2: GRADE summary of findings tables: https://iris.who.int/handle/10665/352508

Web annex 3: GRADE evidence to decision tables: https://iris.who.int/handle/10665/352509

5.2 Drug-resistant TB

5.2.1 Guidelines update 2011 to 2022

Evidence profiles and evidence-to-decision tables:

Refer to *WHO consolidated guidelines on tuberculosis: module 4: treatment: drug-resistant tuberculosis treatment: Web annexes, 2022 update*. Web annexes 3 and 4

https://iris.who.int/handle/10665/365284

5.2.2 Guideline update 2025–26

Evidence profiles and evidence-to-decision tables:

For all PICOs from 2022, refer to *WHO consolidated guidelines on tuberculosis: module 4: treatment: drug-resistant tuberculosis treatment: Web annexes, 2022 update*. Web annexes 3 and 4

https://iris.who.int/handle/10665/365284

For all PICOs from 2025, refer to Module 4: treatment and care. Geneva: World Health Organization; 2025, Annex 5. GRADE evidence profiles and evidence-to-decision tables

https://iris.who.int/handle/10665/380799

For all PICOs from 2026, refer to GRADE evidence profiles and evidence-to-decision tables at the end of this Annex.

PICO 1a evidence profile

A BDLC regimen compared to the longer 18-month regimens in patients with non-severe pulmonary pre-XDR-TB (PICO 1a)

Bibliography:											
Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With the longer 18-month regimens	With a BDLC regimen	Relative effect (95% CI)	Risk with the longer 18-month regimens	Risk difference with a BDLC regimen
Failure and relapse (non-severe disease only) (follow-up: 18 months)											
153 (2 RCTs)	not serious	not serious	not serious	extremely serious[a]	none	⨁◯◯◯ Very low[a]	7/64 (10.9%)	10/89 (11.2%)	**RR 1.19** (0.48 to 2.96)	7/64 (10.9%)	**20 more per 1000** (from 80 fewer to 119 more)[b]
Death (non-severe disease only) (follow-up: 18 months)											
153 (2 RCTs)	not serious	not serious	not serious	extremely serious[a]	none	⨁◯◯◯ Very low[a]	2/64 (3.1%)	1/89 (1.1%)	**RR 0.36** (0.05 to 2.70)	2/64 (3.1%)	**20 fewer per 1000** (from 97 fewer to 34 more)[c]
Lost to follow up during treatment (non-severe disease only) (follow-up: 18 months)											
153 (2 RCTs)	serious[d]	not serious	not serious	serious[a]	none	⨁⨁◯◯ Low[a,d]	0/64 (0.0%)	0/89 (0.0%)	not estimable	0/64 (0.0%)	**0 fewer per 1000** (from 57 fewer to 42 more)[c]
Adverse events (Grade 3–4) (non-severe disease only) (follow-up: 18 months)											
153 (2 RCTs)	serious[d]	not serious	not serious	extremely serious[a]	none	⨁◯◯◯ Very low[a,d]	39/64 (60.9%)	53/89 (59.6%)	**RR 0.92** (0.71 to 1.19)	39/64 (60.9%)	**48 fewer per 1000** (from 205 fewer to 109 more)[b]
Amplification of resistance to drugs (non-severe disease only) (follow-up: 18 months)											
153 (2 RCTs)	not serious	not serious	not serious	extremely serious[a]	none	⨁◯◯◯ Very low[a]	5/64 (7.8%)	8/89 (9.0%)	**RR 1.31** (0.46 to 3.74)	5/64 (7.8%)	**23 more per 1000** (from 63 fewer to 109 more)[c]

CI: confidence interval; **RR:** risk ratio

Explanations

a. Certainty was downgraded by one, two or three levels depending upon the number of thresholds crossed by the confidence limits for each outcome.

b. Adjusted for baseline severity, trial, prior TB, body mass index, age and HIV status

c. Unadjusted due to low event rate.

d. Participants and study staff were unblinded to group allocation. Certainty was downgraded one level. for outcomes where unblinding may influence measurement.

PICO 1a evidence-to-decision

Question	
Should a BDLC regimen vs. the longer 18-month regimens be used for patients with non-severe pulmonary pre-XDR-TB (PICO 1a)?	
POPULATION:	patients with non-severe pulmonary pre-XDR-TB (PICO 1a)
INTERVENTION:	a BDLC regimen
COMPARISON:	the longer 18-month regimens
MAIN OUTCOMES:	Failure and relapse (non-severe disease only); Death (non-severe disease only); Lost to follow up during treatment (non-severe disease only); Adverse events (Grade 3–4) (non-severe disease only); Amplification of resistance to drugs (non-severe disease only); Failure and recurrence (both non-severe and severe); Death (both non-severe and severe); Lost to follow up during treatment (both non-severe and severe); Adverse events (Grade 3–4) during treatment (both non-severe and severe); Amplification of resistance to study drugs (both non-severe and severe);
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	This question addresses the effectiveness and safety of a 6-month BDLC treatment regimen in patients with non-severe pulmonary pre-XDR-TB versus the current standard of care.
CONFLICT OF INTERESTS:	The WHO GTB Program applied the WHO conflict of interest declaration and management policy, and the following were GDG members involved in decision-making for this recommendation: Ashna Ashesh (WHO Civil Society Task Force – TB; Survivors Against TB, India), Erlina Burhan (Persahabatan Hospital Jakarta; Faculty of Medicine – Universitas Indonesia), Muhwa Chakaya (National Tuberculosis Programme of Kenya), Gerry Davies (University of Liverpool, United Kingdom), Fernanda Dockhorn Costa Johansen (Ministry of Health MDR-TB referral centre, Brazil), Kelly Dooley (Vanderbilt University Medical Center, USA), Sobia Faisal (Greenstar Social Marketing, Pakistan), Elmira Gurbanova (Lung Clinic, University of Tartu, Estonia), Eric Krakauer (Harvard Medical School, USA), Christoph Lange (Research Center Borstel, Germany), Yuhong Liu (Beijing Chest Hospital, China), Andrey Maryandyshev (Phthisiopulmonology Department of the Northern State Medical University, Arkhangelsk, Russian Federation), Graeme Meintjes (University of Cape Town, South Africa), Mahshid Nasehi (National Tuberculosis Programme of the Islamic Republic of Iran), Mamel Quelapio (Independent consultant, the Philippines), Moorine Sekkade (National Tuberculosis Programme of Uganda), Wei Sha (Shanghai Pulmonary Hospital, China), Urvashi Singh (National TB Programme, Ministry of Health, India), Shaheed Vally Omar (South Africa Supranational TB Reference Laboratory), Luan Vo (Friends for International Tuberculosis Relief, Viet Nam). No member of the GDG had important conflicts precluding participation.

Assessment

Problem

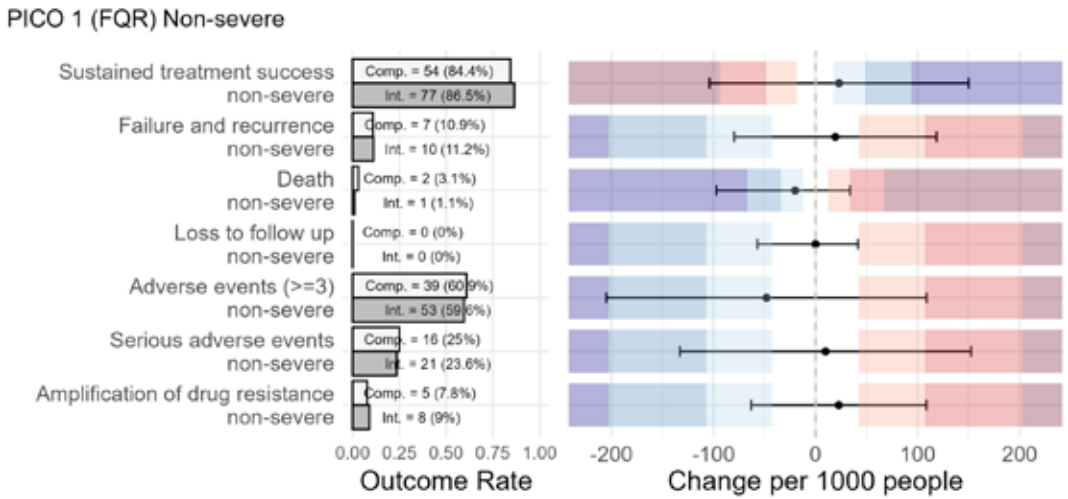
Is the problem a priority?

○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Tuberculosis (TB) remains a threat to global public health and is one of the topmost infectious causes of death in the world. In 2024, an estimated 10.7 million people developed TB, and 1.23 million died from the disease. About 390,000 new patients with rifampicin-resistant or multidrug-resistant tuberculosis (MDR/RR-TB) were estimated to emerge in 2024. While all of these patients would have been eligible for a second-line TB treatment regimen, only 165,650 enrolments on treatment were reported by countries in the same year. In recent years, substantial progress has been made with the introduction of improved diagnostics and more effective medicines, enabling earlier detection and boosting treatment success rates among MDR/RR-TB patients in many national programs, with a 71% success rate reported for those enrolled in 2022. MDR-/RR-TB is treatable but requires different treatment regimen combinations that used to be longer than regimens for drug-susceptible TB and include medicines that are potentially more toxic. The interest in reducing the duration of treatment for MDR/RR-TB motivated a continuous search for shorter and safer regimens. The regimens for the treatment of MDR/RR-TB have changed dramatically in the past ten years. Before 2016, DR-TB regimens were 24 months or longer and included six or more months of daily intramuscular injections with significant adverse events. In 2016, based on data from observational studies of the shorter regimens in different Asian and African countries, WHO, for the first time, recommended a standardized 9-month regimen containing an injectable agent providing shorter than the extant 18–20 months standard of care for the eligible patients. Evidence of permanent effects attributed to the toxicity of injectable agents has prompted further advances in the development of new treatments, such as shorter injectable-sparing regimens. The all-oral 9-month bedaquiline-containing regimen was reviewed and recommended by WHO in 2019. The pressing need for more effective treatment regimens for patients with MDR/RR-TB, including those with fluoroquinolone resistance and more extensive drug-resistance profiles, has driven several studies and initiatives to test more effective and novel treatment regimens, including newer and repurposed medicines. The Nix-TB study conducted by TB Alliance pioneered the 6-month regimen that included bedaquiline and a new medicine – pretomanid, and the BPaL combination successfully received regulatory approval from the FDA. Two randomized controlled trials (RCTs) that concluded in 2021 (TB-PRACTECAL and ZeNix) provided new evidence and prompted assessment by WHO to develop new recommendations for wide programmatic use of the BPaLM/BPaL regimen for treatment MDR/RR-TB with or without resistance to fluoroquinolones. The latest evidence-based guidelines for the treatment and care of TB and drug-resistant TB, including MDR/RR-TB and pre-XDR-TB, were published by WHO in April 2025 – "WHO consolidated guidelines on tuberculosis: module 4: treatment and care". The WHO has combined all recommendations on the treatment of drug-resistant TB, drug-susceptible TB, and TB care and support in three separate chapters of the consolidated guidelines. The recommendation for use of another 6-month BDLLfxC regimen based on the evidence from the BEAT Tuberculosis trial in South Africa was included in the 2025 update.	**ADDITIONAL CONSIDERATIONS** In the context of this new recommendation, prior relevant recommendations state: WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, delamanid, linezolid (600 mg), levofloxacin, and clofazimine (BDLLfxC) in MDR/RR-TB patients **with or without fluoroquinolone resistance.** *(Conditional recommendation, very low certainty of evidence)* **Remarks** 1. Drug susceptibility testing (DST) for fluoroquinolones is strongly encouraged in people with MDR/RR-TB. Although it should not delay the initiation of the BDLLfxC, the test results should guide the decision on whether levofloxacin or clofazimine should be retained. 2. This recommendation applies to the following: a. People with MDR/RR-TB or pre-XDR-TB (i.e. MDR/RR-TB and resistance to fluoroquinolones). b. Patients with less than 1 month of previous exposure to bedaquiline, linezolid, delamanid or clofazimine. When exposure is greater than 1 month, these patients may still receive the regimen if resistance to the specific medicines involved in such exposure has been ruled out. c. People with diagnosed pulmonary TB of all ages, including children, adolescents, PLHIV, and pregnant and breastfeeding women. d. People with all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular TB, or disseminated forms of TB with multiorgan involvement. e. Children and adolescents who do not have bacteriological confirmation of TB or resistance patterns but who do have a high likelihood of MDR/RR-TB (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB).

	Following the recent update of the WHO recommendations on DR-TB treatment, new or more complete evidence has become available from clinical trials or operational research on using combinations of medicines to treat MDR/RR-TB or pre-XDR-TB that a WHO-convened Guideline Development Group has not yet appraised. These regimens include the use of a new 6-month regimen including bedaquiline, delamanid, linezolid and clofazimine (endTB-Q and BEAT-TB South Africa trials) and the use of 6-month BPaL and BPaLC regimens (more complete data from the TB-PRATECAL trial and additional data from the operational research studies or programmatic implementation) for the treatment of patients with MDR/RR-TB with quinolone resistance. The evidence from these trials has been shared with WHO, and this guideline development group (GDG) is convened to review new evidence on the treatment and palliative care for patients with MDR/RR-TB or pre-XDR-TB to ensure that the latest treatment and care options are reflected in the WHO policy.	3. When resistance to fluoroquinolones is unknown, the regimen should be started as BDLLfxC and then adjusted based on the DST results. In cases of quinolone susceptibility, clofazimine should be dropped and the regimen started or continued as bedaquiline, delamanid, linezolid and levofloxacin (BDLLfx). **In cases of resistance to fluoroquinolones, levofloxacin should be dropped and the regimen started or continued as bedaquiline, delamanid, linezolid and clofazimine (BDLC).**

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Outcomes among patients with pre-XDR-TB receiving the BDLC regimen were compared to those receiving the SoC 18–20 month all-oral regimens for patients with pre-XDR-TB used in the BEAT-TB and endTB-Q trials. Primary analysis was undertaken at 76 weeks post treatment initiation. The patient cohort was stratified into those with non-severe (labelled "mild" in the studies) and severe pre-XDR-TB. Participants with non-severe pre-XDR-TB receiving the BDLC regimen (n=87) compared to participants receiving WHO-recommended SoC regimens used in the BEAT-TB and endTB-Q trials (n=61) experienced: • higher levels of failure or recurrence: 11.2% vs 10.9%; RD=20 more per 1000, 95% CI: 80 fewer to 119 more per 1000) • lower levels of death: 1.1% vs 3.1%; RD= 20 fewer per 1000 (95% CI: from 97 fewer to 34 more per 1000); • similar levels of LTFU: 0.0% vs 0.0%; RD= 0 fewer per 1000 (95% CI: from 57 fewer to 42 more per 1000); • lower levels of grade 3–5 AEs: 59.6% vs 60.9%; RD=48 fewer per 1000 (95% CI: 205 fewer to 109 more per 1000); and • higher levels of amplified resistance: 9.0% vs 7.8%; RD=23 more per 1000 (95% CI: 63 fewer to 109 more per 1000). **Fig. Visual depiction of absolute effects in relation to the decision thresholds used by the GDG**  	**Based on the research evidence and the additional considerations, the GDG discussed the absolute effects in relation to the decision thresholds described below and judged that BDLC may have small desirable effects in non-severe pulmonary pre-XDR-TB.** Decision Thresholds considered by the GDG during the discussion: **Death** • Trivial or no important Effect:: ≤12 fewer or more events per 1000 people • Small Effect: 12 to 34 fewer or more events per 1000 people • Moderate Effect: 34 to 67 fewer or more events per 1000 people • Large Effect: >67 fewer or more events per 1000 people **Treatment Failure or Recurrence, lost to follow-up, adverse events and amplification (acquisition) of drug resistance** • Trivial or no important Effect:: ≤41 fewer or more events per 1000 people • Small Effect: 41 to 107 fewer or more events per 1000 people • Moderate Effect: 107 to 202 fewer or more events per 1000 people • Large Effect: >202 fewer or more events per 1000 people Note: The GDG did not consider sustained treatment success as a separate outcome for this judgment. This is because treatment success is mathematically simply the complement of the three unfavourable treatment outcomes (failure, death and lost-to-follow) and thus does not carry any additional or independent information.

Summary of Findings for a BDLC regimen Versus the longer 18-month regimens for patients with non-severe pulmonary pre-XDR-TB (PICO 1a)							
Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			the longer 18-month regimens	[a] BDLC regimen	Difference		
Failure and relapse (non-severe disease only) Follow-up: 18 months	153 (2 RCTs)	**RR = 1.19** (0.48 to 2.96)	109 per 1000	**112 per 1000 (-- to --)[a]**	**20 more per 1000** (from 80 fewer to 119 more)[a]	⨁◯◯◯ Very low[b]	
Death (non-severe disease only) Follow-up: 18 months	153 (2 RCTs)	**RR = 0.36** (0.05 to 2.70)	31 per 1000	**11 per 1000 (-- to --)[c]**	**20 fewer per 1000** (from 97 fewer to 34 more)[c]	⨁◯◯◯ Very low[b]	
Lost to follow up during treatment (non-severe disease only) Follow-up: 18 months	153 (2 RCTs)	not estimable	0 per 1000	**-- per 1000 (-- to --)[c]**	**0 fewer per 1000** (from 57 fewer to 42 more)[c]	⨁⨁◯◯ Low[b,d]	
Adverse events (Grade 3–4) (non-severe disease only) Follow-up: 18 months	153 (2 RCTs)	**RR = 0.92** (0.71 to 1.19)	609 per 1000	**596 per 1000 (-- to --)[a]**	**48 fewer per 1000** (from 205 fewer to 109 more)[a]	⨁◯◯◯ Very low[b,d]	
Amplification of resistance to drugs (non-severe disease only) Follow-up: 18 months	153 (2 RCTs)	**RR = 1.31** (0.46 to 3.74)	78 per 1000	**90 per 1000 (-- to --)[c]**	**23 more per 1000** (from 63 fewer to 109 more)[c]	⨁◯◯◯ Very low[b]	

CI: confidence interval; **RR:** risk ratio

a. Adjusted for baseline severity, trial, prior TB, body mass index, age and HIV status.

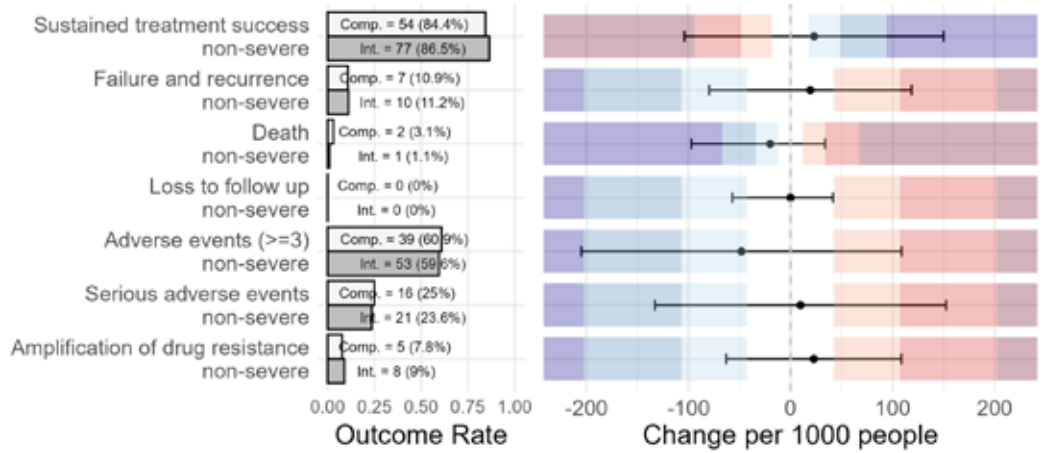
b. Certainty was downgraded by one, two or three levels depending upon the number of thresholds crossed by the confidence limits for each outcome.

Treatment Duration

Beyond the health outcomes included in the research evidence presented above, the WHO 'Target Regimen Profiles for Tuberculosis Treatment' (WHO, 2023) identified certain regimen characteristics as having desirable anticipated effects. These include a shorter treatment duration and reduced pill burden.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	PICO 1 (FQR) Non-severe 	**Based on this research evidence and the additional considerations, the GDG discussed the absolute effects in relation to the decision thresholds described below and judged that BDLC may have trivial undesirable effects in non-severe patients.** The panel noted the observed differences between people with mild and severe disease. The undesirable effects more pronounced in those with severe disease. Decision Thresholds considered by the GDG during the discussion: **Treatment Failure or Recurrence and Amplification (acquisition) of drug resistance** • Trivial or no important Effect:: ≤41 fewer or more events per 1000 people • Small Effect: 41 to 107 fewer or more events per 1000 people • Moderate Effect: 107 to 202 fewer or more events per 1000 people • Large Effect: >202 fewer or more events per 1000 people Note: The GDG did not consider sustained treatment success as a separate outcome for this judgment. This is because treatment success is mathematically simply the complement of the three unfavourable treatment outcomes (failure, death and lost-to-follow) and thus does not carry any additional or independent information.

Summary of Findings for a BDLC regimen Versus the longer 18-month regimens for patients with non-severe pulmonary pre-XDR-TB (PICO 1a)							
Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			the longer 18-month regimens	[a] BDLC regimen	Difference		
Failure and relapse (non-severe disease only) Follow-up: 18 months	153 (2 RCTs)	**RR = 1.19** (0.48 to 2.96)	109 per 1000	**112 per 1000 (-- to --)[a]**	**20 more per 1000** (from 80 fewer to 119 more)[a]	⨁◯◯◯ Very low[b]	
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Lost to follow up during treatment (non-severe disease only) Follow-up: 18 months	153 (2 RCTs)	not estimable	0 per 1000	**-- per 1000 (-- to --)[c]**	**0 fewer per 1000** (from 57 fewer to 42 more)[c]	⨁⨁◯◯ Low[b,d]	
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CI: confidence interval; **RR:** risk ratio

a. Adjusted for baseline severity, trial, prior TB, body mass index, age and HIV status.

b. Certainty was downgraded by one, two or three levels depending upon the number of thresholds crossed by the confidence limits for each outcome.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		The overall certainty of evidence was judged to be very low based on the critical outcomes failure and recurrence and death.

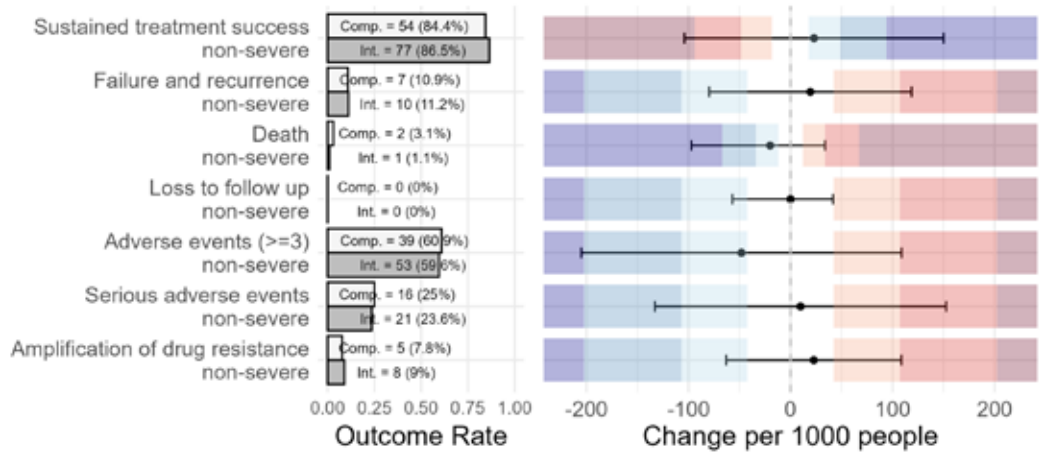
Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence was sought for.	The GDG noted that higher treatment efficacy, shorter duration of treatment, lower pill burden and less adverse events are usually valued by patients.

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	PICO 1 (FQR) Non-severe 	In patients with non-severe pre-XDR-TB, the GDG judged the desirable effects to be small and the undesirable effects of BDLC to be trivial compared with the WHO-recommended SoC regimens used in the BEAT-TB and endTB-Q trials. The certainty of evidence was judged to be very low. The balance of health effects was judged to be in favour of BDLC, with a small net benefit in people with non-severe disease (or small net harm for longer regimens in this population), favouring the intervention (BDLC), although there was very low certainty evidence due to indirectness and severe imprecision, in particular for the subgroup with non-severe disease.

Summary of Findings for a BDLC regimen Versus the longer 18-month regimens for patients with non-severe pulmonary pre-XDR-TB (PICO 1a)							
Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
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Lost to follow up during treatment (non-severe disease only) Follow-up: 18 months	153 (2 RCTs)	not estimable	0 per 1000	**-- per 1000 (-- to --)[c]**	**0 fewer per 1000** (from 57 fewer to 42 more)[c]	⨁⨁◯◯ Low[b,d]	
Adverse events (Grade 3–4) (non-severe disease only) Follow-up: 18 months	153 (2 RCTs)	**RR = 0.92** (0.71 to 1.19)	609 per 1000	**596 per 1000 (-- to --)[a]**	**48 fewer per 1000** (from 205 fewer to 109 more)[a]	⨁◯◯◯ Very low[b,d]	
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CI: confidence interval; **RR:** risk ratio

a. Adjusted for baseline severity, trial, prior TB, body mass index, age and HIV status.

b. Certainty was downgraded by one, two or three levels depending upon the number of thresholds crossed by the confidence limits for each outcome.

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	**Assumptions for BDLC regimen:** • Drug prices obtained from Stop TB Partnership Global Drug Facility • Duration of 24 weeks • BDQ using "regular" dosing – 2-week load and then either 22 or 37 weeks of 3x/weekly dosing • DLM full dosing through the entire 24 or 39 weeks • LZD dosed 600 mg daily for 16 weeks then either 300 mg daily or 600 mg 3x/week (price difference between the two dosing schemes is negligible) • Dosing based on weight > 50 kg (per protocol) • Daily dosing for • Linezolid • Levofloxacin • Clofazimine • "Standard" dosing for bedaquiline – 400 mg daily x 14 days then 200 mg 3x/week for weeks 3–24 • Delamanid 100 mg twice daily x 8 weeks, then 200 mg daily x 16 weeks **Assumptions for 18m regimen:** • 18B(6)LLC +/- D • Drug prices obtained from Stop TB Partnership Global Drug Facility • BDQ using "regular" dosing – 2-week load and then 22 weeks of 3x/weekly dosing • DLM used for 24 weeks • LZD dosed 600 mg daily for the 18 months (unlikely this would be tolerated for the full duration). **Non-drug cost estimates based on the following each month:** • 1 outpatient visit • 1 smear, 1 culture • safety monitoring cost (1 LFT, 1 FBC, 1 ECG, 1 neuropathy screen) • 1m treatment support **Caveats** • Medicine prices are average prices across all suppliers as per GDF market share allocation • Medicine prices may change with 2024 GDF tenders The GDG considered the following example of country-specific patient-borne and health system costs over a 3-month span (excluding drug costs) (based on modelling analysis in Ryckman et al, 2024). Note that the costs may vary depending on the composition of the regimen being used. REF: WHO. Target regimen profiles for tuberculosis treatment, 2023 update. 2023	**Previous GDG:** The GDG noted that affordability will vary depending on country (and resources available), health system differences, and the population the regimen would be used for and accordingly judged that there would be moderate savings with BDLC. Delamanid cost is one of the cost drivers in BDLC. With the drug being off patent, prices have decreased due to generic development (for certain countries) and may change further. Within the regimen it was also highlighted that there is a diagnostic cost involved for assessing resistance. A longer duration of treatment bears costs (especially for patients and families but also the health system) and some estimates were available and discussed by the group. Considering these costs together with the drug costs may attenuate some of the increased costs for the health system and lead to cost savings from the patient perspective. It was noted, however, that countries looking to implement a specific treatment regimen typically focus on the drug cost.

Drug cost

BDLC	
6m	US$ 975
9m	US$ 1570

18M regimen	
without Dlm	US$ 795
with Dlm	US$ 1195

Non-drug cost

	per 12 months		
	Patient	Health system	Total
India	1536	348	**1884**
Philippines	3096	936	**4032**
South Africa	1368	2568	**3936**

	per 9 months		
	Patient	Health system	Total
India	1152	261	**1413**
Philippines	2322	702	**3024**
South Africa	1026	1926	**2952**

Cost difference in DRUG COST			Comment
From	US$ 775	more	(BDLC for 9m vs 18m regimen w/o Dlm)
To	US$ -220	less	(BDLC for 6m vs 18m regimen w Dlm)

Cost difference in non-DRUG COST			Comment
From	US$ 261	less	health systems cost only; 9m BDLC; India
To	US$ 4032	less	health systems + patient cost; 6m BDLC; Philippines

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The drug prices for the regimens were elicited from the Stop TB Partnership Global Drug Facility and health system and patient costs in the three settings were estimated based on data from an economic modelling analysis (Ryckman et al. 2024) and extrapolated to the 3-month time period for the difference in the treatment durations. The estimated costs from the economic modelling analysis do not account for possible imprecision in the cost estimates and provide indirect data for other settings where the BEAT-TB treatment regimen would be used. Thus, the certainty in this evidence is low.	

Cost effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ No included studies	No research evidence searched for.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence searched for.	**Previous GDG:** The GDG considered the treatment duration and the ability to decentralize treatment (to enable access for remote, underserviced settings and disadvantaged populations) to affect equity.The GDG highlighted that health equity would probably increase given parts of the population that would have access to the shorter regimen and the medications included, in particular pregnant women and children and this may apply to other groups as well. On the other hand, it was also noted that there are populations that might not be able to afford the regimen, and between-country differences in impact on health equity may exist because of availability of medications. Despite not being able to identify relevant research evidence, the panel used their collective experience to judge that there would likely be advantages associated with the use of the BDLC regimen due to its reduced complexity and shorter duration. The panel judged that use of the BDLC regimen would probably increase equity.

Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence searched for.	Based on considerations of the previous GDG and new assessments, the GDG considered patients, health care providers and the health system as key interest-holders. For people living with Tb, acceptability of the BDLC and the longer 18-month regimen regimen will vary on the basis of disease severity. The panel judged that the BDLC regimen would probably be acceptable for those with non-severe disease. In people with more severe disease, longer regimens will be acceptable. The panel considered the following aspects as critical with regards to acceptability: regimen duration and drug safety monitoring needs (both relating to necessary travel, loss of income and general disruption of the life of patients; workload for the health care system), needs for drug susceptibility testing. With a shorter regiment overall quality of life may be improved.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**Previous GDG:** No research evidence was systematically searched for. However, the BDLLfxC regimen was additionally studied in operational research studies performed in three regions: Kazakhstan (STEM-TB cohort, n=23), Lesotho (STEM-TB, n=101), Europe (EURO STR 2, n=75), although given for 9 months instead of the 6 months used in the BEAT-TB trial. Favourable treatment outcomes (cure or treatment completion) were reported as 100%, 95%, and 75%, respectively. Additionally, BDLC **(BEAT-TB study regimen in those with pre-XDR-TB)** was also additionally studied in two studies: India (BEAT-TB cohort study, BDLC given for 6 months, n=152) and Nigeria (TDR SHORTT initiative, BDLC given for 9 months, n=38). Treatment success was reported as 91% in the BEAT-TB India cohort study with no data available yet from Nigeria.	There were different interpretations and opinions among panel members given the small amount of research data.

Summary of judgements

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	•	○

Conclusions

Recommendation
The use of the 6-month treatment regimen composed of bedaquiline, delamanid, linezolid, and clofazimine (BDLC) rather than the WHO-recommended SoC regimens used in the BEAT-TB and endTB-Q trials is suggested in patients with non-severe pre-XDR-TB, who have either had no previous exposure to the medicines in this regimen or have been exposed for less than 1 month *(conditional recommendation, very low certainty of evidence)*.

Remarks

Severity in pulmonary pre-XDR-TB for this regimen selection is defined by the presence of cavitary lesions on chest radiography and high bacillary load shown by sputum smear results of 1+ or higher positivity, and smear results of 2+ or higher (or an equivalent result on WHO-recommended molecular tests) even when cavities are not present. In children younger than 10 years, severe pulmonary pre-XDR-TB can manifest differently and may include extensive intrathoracic lymph node disease with airway obstruction, cavitary disease, or signs of extensive pulmonary involvement on imaging and severe respiratory compromise even without cavitation. Non-severe, in this context, refers to all situations not covered by the above definition of severe pulmonary pre-XDR-TB

Justification
In patients with non-severe pre-XDR-TB, the GDG judged the desirable effects to be small and the undesirable effects of BDLC to be trivial compared with the WHO-recommended SoC regimens used in the BEAT-TB and endTB-Q trials. The certainty of evidence was judged to be very low. The balance of health effects was judged to be in favour of BDLC, with a small net benefit in people with non-severe disease (or small net harm for longer regimens in this population), favouring the intervention (BDLC), although there was very low certainty evidence due to indirectness and severe imprecision, in particular for the subgroup with non-severe disease.

Subgroup considerations
The panel noted specific considerations for the subpopulations listed below.

People living with HIV

No restrictions were identified for the use of the intervention among people living with HIV.

Children and adolescents

Trial evidence included participants aged ≥14 years. Extrapolation to younger children and adolescents is considered acceptable, consistent with prior guideline decisions.

Pregnant and breastfeeding women

No restrictions were identified for the drug Delamanid. Use of the drug Pretomanid is restricted due to limited safety data in this population.

Extensive TB disease (based on the endTB-Q trial definition)

Patients with DR-TB who have extensive disease face greater challenges in treatment across all regimens and are at a higher risk of unfavourable outcomes and amplification of drug resistance. This risk is further elevated in those infected with pathogens that have advanced resistance profiles, particularly with additional resistance to fluoroquinolones. These patients may experience slightly worse outcomes compared to those without pre-XDR and develop resistance to regimen components. In the BEAT-TB trial among patients with pre-XDR-TB, the outcomes also appeared worse than among those who were fluoroquinolone susceptible. This reduction in the proportion with successful treatment outcomes was numerically greater in the BDLLfxC arm than in the control arm (14.3% vs 3.3%); however, this difference was within the range of statistical uncertainty, and the GDG judged that this should not affect the recommendation or remarks. The rate of acquisition of resistance to bedaquiline was similar between the two groups (11% in BDLLfxC and 9.1% in control). The evidence from the BEAT-TB trial is insufficient to draw definitive conclusions due to the small sample when stratified by fluoroquinolone resistance and related imprecision. Nonetheless, clinicians should remain vigilant and closely monitor the treatment response in this group of patients and promptly take relevant actions (extending the duration of treatment or changing the regimen).

Hepatitis C co-infectionA prior WHO recommendation, based on expert evidence, applies to patients with MDR/RR-TB and hepatitis C virus (HCV) co-infection. WHO suggests co-administration of HCV and TB treatments rather than delaying HCV treatment until completion of MDR/RR-TB therapy *(conditional recommendation, very low certainty of evidence)*.

Malnutrition and underweight Patients with severe undernutrition, including those with a body mass index (BMI) below 15, were included in the trials. No subgroup-specific restrictions were identified based on nutritional status. (The trials did not include overweight participants).

Other causes of immunosuppression For patients with immunosuppression due to causes other than HIV, careful interpretation of the conditional recommendation is warranted, taking into account the underlying condition and clinical context.

Implementation considerations
Paediatric formulations Availability of appropriate drug formulations for children should be ensured.
Regimen transitions
Clear programmatic guidance is needed to support transitions between regimens where clinically indicated.
Drug susceptibility testing
DST for fluoroquinolones is strongly encouraged in people with MDR/RR-TB. While DST should not delay initiation of the BDLLfxC regimen, results should inform decisions on whether levofloxacin or clofazimine is retained in the regimen.
Linezolid dosing
Clear guidance and clinical expertise are required for appropriate linezolid dosing, and dose adjustments may be necessary.
Assessment of TB disease
Availability of chest radiography (CXR) should be ensured to support disease and severity assessment.
Capacity building Health-care worker training is needed to support standardized assessment of disease severity.
Drug–drug interactions Potential drug–drug interactions should be systematically assessed and managed.
Medicine supply Reliable availability of all regimen components, including adequate buffer stocks, is required to prevent stock-outs and treatment interruptions.
Severity assessment Standardized severity definition and assessment should be incorporated into implementation guidance.
Safety monitoring Systems for routine monitoring and management of adverse events should be in place.
Additional considerations For delamanid-based regimens, assessment of serum albumin levels should be considered.
Patient-centred approach
Efforts are required to provide patient support to enable full adherence to treatment.
Access to mental health and psychosocial support services should be ensured. Consideration should also be given to insurance coverage and financing mechanisms.
Monitoring and evaluation
Systems should be in place to monitor disease recurrence and the emergence of drug resistance, particularly in cases of treatment failure or relapse.
Routine monitoring and management of adverse events are required.
For patients receiving BDLLC-containing regimens, regular QTc interval monitoring should be conducted.

Research priorities
The GDG discussed and identified the following research priorities relating to this recommendation:
Interventions, populations and the balance of desirable and undesirable health effects:
Further research is needed to refine definitions of disease severity and the risk assessment model (RAM) which will help to better understand the baseline risk for the outcomes of interest.
Direct comparative trials of BDLC versus BPaLC in patients with severe disease are a priority, including evaluation of optimal treatment duration in this subgroup.
Additional evidence is required in children, including the safety and dosing of pretomanid (Pa) in those younger than 14 years.
More programmatic and real-world data are needed, including outcomes in key subpopulations such as individuals with malnutrition.
Research should identify reliable biomarkers for outcomes to individualize treatment duration irrespective of drug resistance profile or regimen.
Assessment of the efficacy and safety of lower linezolid doses.
Identification of predictors of disease recurrence.
Larger trials and programmatic data for BPAL and BPALC regimens are required.
Studies assessing treatment completion, adherence support needs, and quality-of-life outcomes.
Values: Additional research is needed to obtain higher certainty in patient values related to the outcomes of interest.
Equity: Judgments about equity will be better informed by studies that capture both direct and indirect patient costs to better understand the financial burden of treatment, alongside the evaluation of equitable access to newer TB regimens across different populations
Resources: Effectiveness data from direct comparisons of regimens will be essential to inform cost-effectiveness and extended cost-effectiveness analyses, including the potential to reduce catastrophic costs for patients and households.
Acceptability: Studies assessing the acceptability of newer TB regimens among both patients and health-care providers, in conjunction with exploration of reasons for delayed uptake and implementation despite guideline recommendations, are needed.
Feasibility: Key feasibility concerns include barriers related to procurement and supply chains, regulatory approvals, and limitations in diagnostic and monitoring capacity.

PICO 1b evidence profile

A BDLC regimen compared to the longer 18-month regimens in patients with severe pulmonary pre-XDR-TB (PICO 1b)

Bibliography:											
Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With the longer 18-month regimens	With a BDLC regimen		Risk with the longer 18-month regimens	Risk difference with a BDLC regimen
Failure and relapse (severe disease only)											
172 (2 RCTs)	not serious	not serious	not serious	very serious[a]	none	⨁⨁◯◯ Low[a]	1/58 (1.7%)	14/114 (12.3%)	**RR 7.12** (1.27 to 42.02)	1/58 (1.7%)	**106 more per 1000** (from 22 more to 182 more)[b]
Death (severe disease only)											
172 (2 RCTs)	not serious	not serious	not serious	extremely serious[a]	none	⨁◯◯◯ Very low[a]	1/58 (1.7%)	4/114 (3.5%)	**RR 2.04** (0.32 to 13.43)	1/58 (1.7%)	**18 more per 1000** (from 59 fewer to 73 more)[b]
Loss to follow up (severe disease only)											
172 (2 RCTs)	serious[c]	not serious	not serious	serious[a]	none	⨁⨁◯◯ Low[a,c]	1/58 (1.7%)	1/114 (0.9%)	**RR 0.51** (0.05 to 4.84)	1/58 (1.7%)	**9 fewer per 1000** (from 84 fewer to 33 more)[b]
Adverse events (Grade 3–4) (severe disease only)											
172 (2 RCTs)	serious[c]	not serious	not serious	extremely serious[a]	none	⨁◯◯◯ Very low[a,c]	41/58 (70.7%)	72/114 (63.2%)	**RR 0.88** (0.71 to 1.08)	41/58 (70.7%)	**88 fewer per 1000** (from 230 fewer to 54 more)[d]
Amplification of resistance to drugs (severe disease only)											
172 (2 RCTs)	not serious	not serious	not serious	very serious[a]	none	⨁⨁◯◯ Low[a]	2/58 (3.4%)	11/114 (9.6%)	**RR 2.80** (0.73 to 11.08)	2/58 (3.4%)	**62 more per 1000** (from 29 fewer to 137 more)[d]

CI: confidence interval; **RR:** risk ratio

Explanations

a. Certainty was downgraded by one, two or three levels depending upon the number of thresholds crossed by the confidence limits for each outcome.

b. Unadjusted due to low event rate.

c. Participants and study staff were unblinded to group allocation. Certainty was downgraded one level. for outcomes where unblinding may influence measurement.

d. Adjusted for baseline severity, trial, prior TB, body mass index, age and HIV status

PICO 1b evidence-to-decision

Question	
Should a BDLC regimen vs. the longer 18-month regimens be used for patients with severe pulmonary pre-XDR-TB (PICO 1b)?	
POPULATION:	patients with severe pulmonary pre-XDR-TB (PICO 1b)
INTERVENTION:	a BDLC regimen
COMPARISON:	the longer 18-month regimens
MAIN OUTCOMES:	Failure and relapse (severe disease only); Death (severe disease only); Loss to follow up (severe disease only); Adverse events (Grade 3–4) (severe disease only); Amplification of resistance to drugs (severe disease only);
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	This question addresses the effectiveness and safety of a 6-month BDLC treatment regimen in patients with severe pulmonary pre-XDR-TB versus the current standard of care.
CONFLICT OF INTERESTS:	The WHO GTB Program applied the WHO conflict of interest declaration and management policy, and the following were GDG members involved in decision-making for this recommendation: Ashna Ashesh (WHO Civil Society Task Force – TB; Survivors Against TB, India), Erlina Burhan (Persahabatan Hospital Jakarta; Faculty of Medicine – Universitas Indonesia), Muhwa Chakaya (National Tuberculosis Programme of Kenya), Gerry Davies (University of Liverpool, United Kingdom), Fernanda Dockhorn Costa Johansen (Ministry of Health MDR-TB referral centre, Brazil), Kelly Dooley (Vanderbilt University Medical Center, USA), Sobia Faisal (Greenstar Social Marketing, Pakistan), Elmira Gurbanova (Lung Clinic, University of Tartu, Estonia), Eric Krakauer (Harvard Medical School, USA), Christoph Lange (Research Center Borstel, Germany), Yuhong Liu (Beijing Chest Hospital, China), Andrey Maryandyshev (Phthisiopulmonology Department of the Northern State Medical University, Arkhangelsk, Russian Federation), Graeme Meintjes (University of Cape Town, South Africa), Mahshid Nasehi (National Tuberculosis Programme of the Islamic Republic of Iran), Mamel Quelapio (Independent consultant, the Philippines), Moorine Sekkade (National Tuberculosis Programme of Uganda), Wei Sha (Shanghai Pulmonary Hospital, China), Urvashi Singh (National TB Programme, Ministry of Health, India), Shaheed Vally Omar (South Africa Supranational TB Reference Laboratory), Luan Vo (Friends for International Tuberculosis Relief, Viet Nam). No member of the GDG had important conflicts precluding participation.

Assessment

Problem

Is the problem a priority?

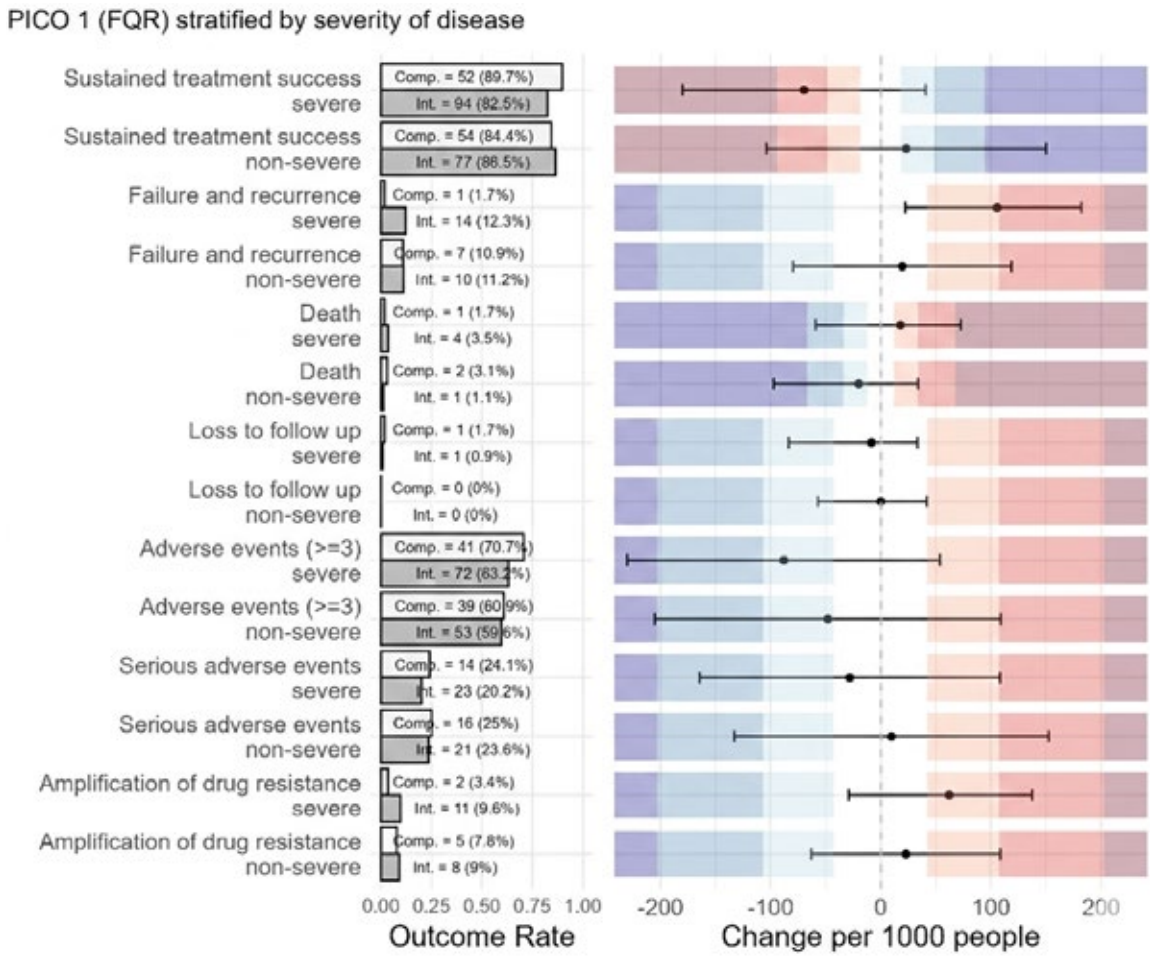
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Tuberculosis (TB) remains a threat to global public health and is one of the topmost infectious causes of death in the world. In 2024, an estimated 10.7 million people developed TB, and 1.23 million died from the disease. About 390,000 new patients with rifampicin-resistant or multidrug-resistant tuberculosis (MDR/RR-TB) were estimated to emerge in 2024. While all of these patients would have been eligible for a second-line TB treatment regimen, only 165,650 enrolments on treatment were reported by countries in the same year. In recent years, substantial progress has been made with the introduction of improved diagnostics and more effective medicines, enabling earlier detection and boosting treatment success rates among MDR/RR-TB patients in many national programs, with a 71% success rate reported for those enrolled in 2022. MDR-/RR-TB is treatable but requires different treatment regimen combinations that used to be longer than regimens for drug-susceptible TB and include medicines that are potentially more toxic. The interest in reducing the duration of treatment for MDR/RR-TB motivated a continuous search for shorter and safer regimens. The regimens for the treatment of MDR/RR-TB have changed dramatically in the past ten years. Before 2016, DR-TB regimens were 24 months or longer and included six or more months of daily intramuscular injections with significant adverse events. In 2016, based on data from observational studies of the shorter regimens in different Asian and African countries, WHO, for the first time, recommended a standardized 9-month regimen containing an injectable agent providing shorter than the extant 18–20 months standard of care for the eligible patients. Evidence of permanent effects attributed to the toxicity of injectable agents has prompted further advances in the development of new treatments, such as shorter injectable-sparing regimens. The all-oral 9-month bedaquiline-containing regimen was reviewed and recommended by WHO in 2019. The pressing need for more effective treatment regimens for patients with MDR/RR-TB, including those with fluoroquinolone resistance and more extensive drug-resistance profiles, has driven several studies and initiatives to test more effective and novel treatment regimens, including newer and repurposed medicines. The Nix-TB study conducted by TB Alliance pioneered the 6-month regimen that included bedaquiline and a new medicine – pretomanid, and the BPaL combination successfully received regulatory approval from the FDA. Two randomized controlled trials (RCTs) that concluded in 2021 (TB-PRACTECAL and ZeNix) provided new evidence and prompted assessment by WHO to develop new recommendations for wide programmatic use of the BPaLM/BPaL regimen for treatment MDR/RR-TB with or without resistance to fluoroquinolones. The latest evidence-based guidelines for the treatment and care of TB and drug-resistant TB, including MDR/RR-TB and pre-XDR-TB, were published by WHO in April 2025 – "WHO consolidated guidelines on tuberculosis: module 4: treatment and care". The WHO has combined all recommendations on the treatment of drug-resistant TB, drug-susceptible TB, and TB care and support in three separate chapters of the consolidated guidelines. The recommendation for use of another 6-month BDLLfxC regimen based on the evidence from the BEAT Tuberculosis trial in South Africa was included in the 2025 update. Following the recent update of the WHO recommendations on DR-TB treatment, new or more complete evidence has become available from clinical trials or operational research on using combinations of medicines to treat MDR/RR-TB or pre-XDR-TB that a WHO-convened Guideline Development Group has not yet appraised. These regimens include the use of a new 6-month regimen including bedaquiline, delamanid, linezolid and clofazimine (endTB-Q and BEAT-TB South Africa trials) and the use of 6-month BPaL and BPaLC regimens (more complete data from the TB-PRATECAL trial and additional data from the operational research studies or programmatic implementation) for the treatment of patients with MDR/RR-TB with quinolone resistance.	Current recommendation: 1.2 WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, delamanid, linezolid (600 mg), levofloxacin, and clofazimine (BDLLfxC) in MDR/RR-TB patients **with or without fluoroquinolone resistance.** *(Conditional recommendation, very low certainty of evidence)* **Remarks** 1. Drug susceptibility testing (DST) for fluoroquinolones is strongly encouraged in people with MDR/RR-TB. Although it should not delay the initiation of the BDLLfxC, the test results should guide the decision on whether levofloxacin or clofazimine should be retained. 2. This recommendation applies to the following: a. People with MDR/RR-TB or pre-XDR-TB (i.e. MDR/RR-TB and resistance to fluoroquinolones). b. Patients with less than 1 month of previous exposure to bedaquiline, linezolid, delamanid or clofazimine. When exposure is greater than 1 month, these patients may still receive the regimen if resistance to the specific medicines involved in such exposure has been ruled out. c. People with diagnosed pulmonary TB of all ages, including children, adolescents, PLHIV, and pregnant and breastfeeding women. d. People with all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular TB, or disseminated forms of TB with multiorgan involvement. e. Children and adolescents who do not have bacteriological confirmation of TB or resistance patterns but who do have a high likelihood of MDR/RR-TB (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB).

	The evidence from these trials has been shared with WHO, and this guideline development group (GDG) is convened to review new evidence on the treatment and palliative care for patients with MDR/RR-TB or pre-XDR-TB to ensure that the latest treatment and care options are reflected in the WHO policy.	3. When resistance to fluoroquinolones is unknown, the regimen should be started as BDLLfxC and then adjusted based on the DST results. In cases of quinolone susceptibility, clofazimine should be dropped and the regimen started or continued as bedaquiline, delamanid, linezolid and levofloxacin (BDLLfx). **In cases of resistance to fluoroquinolones, levofloxacin should be dropped and the regimen started or continued as bedaquiline, delamanid, linezolid and clofazimine (BDLC).**

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Outcomes among patients with MDR/RR-TB with quinolone resistance (pre-XDR-TB) receiving the BDLC regimen were compared to those receiving the SoC 18–20 month all-oral regimens for patients with pre-XDR-TB. Primary analysis was undertaken at 76 weeks post treatment initiation. The patient cohort was stratified into those with non-severe and severe pre-XDR-TB. Participants with severe pre-XDR-TB receiving the BDLC regimen (n=114) compared to participants receiving WHO-recommended SoC regimens used in the BEAT-TB and endTB-Q trials (n=58) experienced: • higher levels of failure or recurrence: 12.3% vs 1.7%; RD=106 more per 1000, 95% CI: 22 more to 182 more per 1000) • higher levels of death: 3.5% vs 1.7%; RD= 18 more per 1000 (95% CI: from 59 fewer to 73 more per 1000); • lower levels of LTFU: 0.9% vs 1.7%; RD= 9 fewer per 1000 (95% CI: from 84 fewer to 33 more per 1000); • lower levels of grade 3–5 AEs: 63.2% vs 70.7%; RD=88 fewer per 1000 (95% CI: 230 fewer to 54 more per 1000); and • higher levels of amplified resistance: 9.6% vs 3.4%; RD=62 more per 1000 (95% CI: 29 fewer to 137 more per 1000).	**Based on this research evidence and the additional considerations, the GDG discussed the absolute effects in relation to the decision thresholds described below and judged that BDLC may have small desirable effects.** Decision Thresholds considered by the GDG during the discussion: **Death** • Trivial Effect: ≤12 fewer or more events per 1000 people • Small Effect: 12 to 34 fewer or more events per 1000 people • Moderate Effect: 34 to 67 fewer or more events per 1000 people • Large Effect: >67 fewer or more events per 1000 people



Treatment Failure or Recurrence, lost to follow-up, adverse events and amplification (acquisition) of drug resistance

- Trivial Effect: ≤41 fewer or more events per 1000 people
- Small Effect: 41 to 107 fewer or more events per 1000 people
- Moderate Effect: 107 to 202 fewer or more events per 1000 people
- Large Effect: >202 fewer or more events per 1000 people

Note: The GDG did not consider sustained treatment success as a separate outcome for this judgment. This is because treatment success is mathematically simply the complement of the three unfavourable treatment outcomes (failure, death and lost-to-follow) and thus does not carry any additional or independent information.

Summary of Findings for a BDLC regimen Versus the longer 18-month regimens for patients with severe pulmonary pre-XDR-TB (PICO 1b)							
Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			the longer 18-month regimens	[a] BDLC regimen	Difference		
Failure and relapse (severe disease only)	172 (2 RCTs)	**RR = 7.12** (1.27 to 42.02)	17 per 1000	**123 per 1000 (-- to --)[a]**	**106 more per 1000** (from 22 more to 182 more)[a]	⨁⨁◯◯ Low[b]	
Death (severe disease only)	172 (2 RCTs)	**RR = 2.04** (0.32 to 13.43)	17 per 1000	**35 per 1000 (-- to --)[a]**	**18 more per 1000** (from 59 fewer to 73 more)[a]	⨁◯◯◯ Very low[b]	
Loss to follow up (severe disease only)	172 (2 RCTs)	**RR = 0.51** (0.05 to 4.84)	17 per 1000	**9 per 1000 (-- to --)[a]**	**9 fewer per 1000** (from 84 fewer to 33 more)[a]	⨁⨁◯◯ Low[b,c]	
Adverse events (Grade 3–4) (severe disease only)	172 (2 RCTs)	**RR = 0.88** (0.71 to 1.08)	707 per 1000	**632 per 1000 (-- to --)[d]**	**88 fewer per 1000** (from 230 fewer to 54 more)[d]	⨁◯◯◯ Very low[b,c]	
Amplification of resistance to drugs (severe disease only)	172 (2 RCTs)	**RR = 2.80** (0.73 to 11.08)	34 per 1000	**96 per 1000 (-- to --)[d]**	**62 more per 1000** (from 29 fewer to 137 more)[d]	⨁⨁◯◯ Low[b]	

CI: confidence interval; **RR:** risk ratio

a. Unadjusted due to low event rate.

b. Certainty was downgraded by one, two or three levels depending upon the number of thresholds crossed by the confidence limits for each outcome.

c. Participants and study staff were unblinded to group allocation. Certainty was downgraded one level. for outcomes where unblinding may influence measurement.

d. Adjusted for baseline severity, trial, prior TB, body mass index, age and HIV status

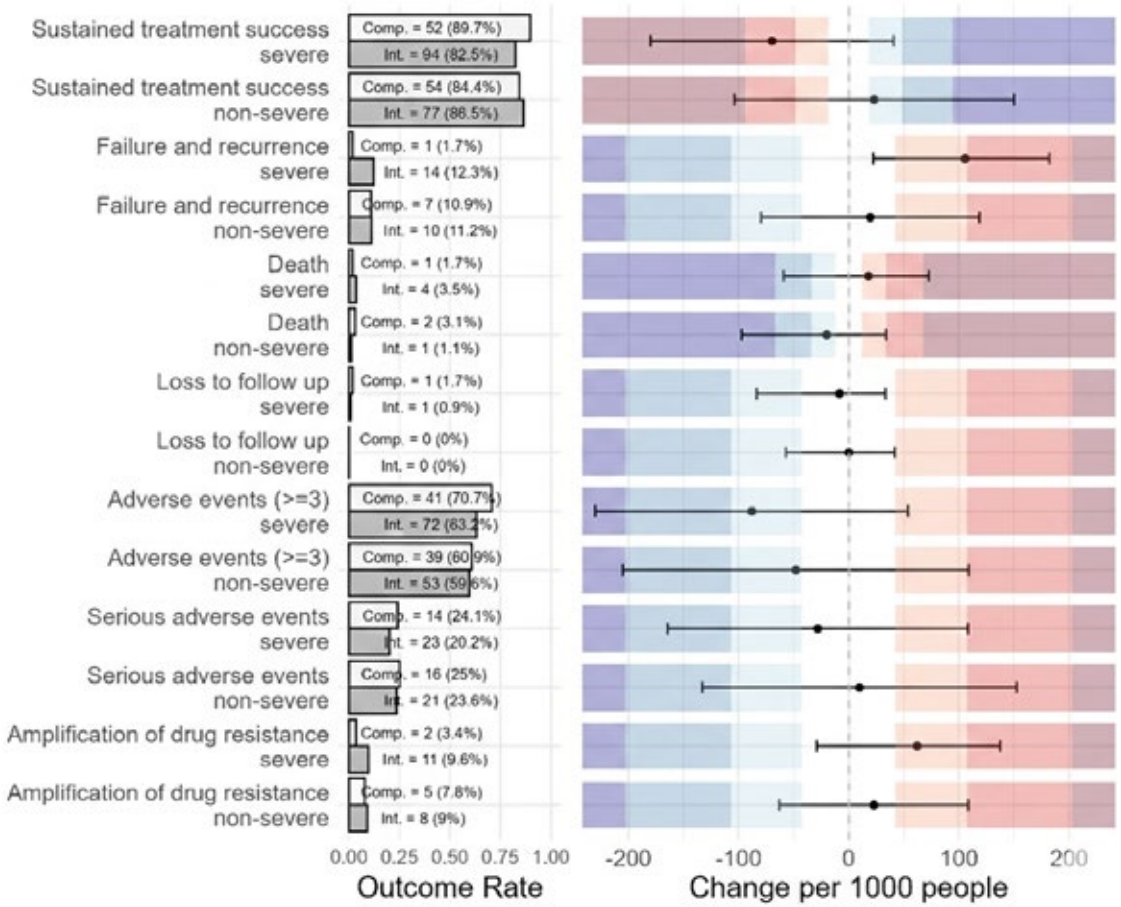
Treatment Duration

Beyond the health outcomes included in the research evidence presented above, the WHO 'Target Regimen Profiles for Tuberculosis Treatment' (WHO, 2023) identified certain regimen characteristics as having desirable anticipated effects. These include a shorter treatment duration and reduced pill burden.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	PICO 1 (FQR) stratified by severity of disease	**Based on this research evidence and the additional considerations, the GDG discussed the absolute effects in relation to the decision thresholds described below and judged that BDLC may have small undesirable effects in severe patients.** The panel noted the observed differences between people with mild and severe disease. Undesirable effects more pronounced and judged as small in those with severe disease. The overall judgement of small was also influenced by uncertainties to the degree to which risk stratification as applied in the trials could be applied across programmatic settings. Note: The GDG did not consider sustained treatment success as a separate outcome for this judgment. This is because treatment success is mathematically simply the complement of the three unfavourable treatment outcomes (failure, death and lost-to-follow) and thus does not carry any additional or independent information.



Summary of Findings for a BDLC regimen Versus the longer 18-month regimens for patients with severe pulmonary pre-XDR-TB (PICO 1b)							
Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			the longer 18-month regimens	[a] BDLC regimen	Difference		
Failure and relapse (severe disease only)	172 (2 RCTs)	**RR = 7.12** (1.27 to 42.02)	17 per 1000	**123 per 1000 (-- to --)[a]**	**106 more per 1000** (from 22 more to 182 more)[a]	⨁⨁◯◯ Low[b]	
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CI: confidence interval; **RR:** risk ratio

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c. Participants and study staff were unblinded to group allocation. Certainty was downgraded one level. for outcomes where unblinding may influence measurement.

d. Adjusted for baseline severity, trial, prior TB, body mass index, age and HIV status

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		The overall certainty of evidence was judged to be very low based on the critical outcomes failure and recurrence and death.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence was sought for.	The GDG noted that higher treatment efficacy, shorter duration of treatment, lower pill burden and less adverse events are usually valued by patients.

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

JUDGEMENT

○ Favours the comparison
● Probably favours the comparison
○ Does not favour either the intervention or the comparison
○ Probably favours the intervention
○ Favours the intervention
○ Varies
○ Don't know

RESEARCH EVIDENCE

Summary of Findings for a BDLC regimen Versus the longer 18-month regimens for patients with severe pulmonary pre-XDR-TB (PICO 1b)

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			the longer 18-month regimens	[a] BDLC regimen	Difference		
Failure and relapse (severe disease only)	172 (2 RCTs)	**RR = 7.12** (1.27 to 42.02)	17 per 1000	**123 per 1000 (-- to --)[a]**	**106 more per 1000** (from 22 more to 182 more)[a]	⨁⨁◯◯ Low[b]	
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c. Participants and study staff were unblinded to group allocation. Certainty was downgraded one level. for outcomes where unblinding may influence measurement.

d. Adjusted for baseline severity, trial, prior TB, body mass index, age and HIV status.

ADDITIONAL CONSIDERATIONS

In patients with severe pre-XDR-TB, the GDG judged both the desirable and undesirable effects of BDLC to be small when compared to those of the WHO-recommended SoC regimens used in the BEAT-TB and endTB-Q trials. The certainty of evidence was judged to be very low. The balance of health effects was judged to favour longer regimens, supporting the comparison, although the evidence certainty was very low due to indirectness and severe imprecision, particularly for the subgroup with non-severe disease.

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	**Assumptions for BDLC regimen:** • Drug prices obtained from Stop TB Partnership Global Drug Facility • Duration of 24 weeks • BDQ using "regular" dosing – 2-week load and then either 22 or 37 weeks of 3x/weekly dosing • DLM full dosing through the entire 24 or 39 weeks • LZD dosed 600 mg daily for 16 weeks then either 300 mg daily or 600 mg 3x/week (price difference between the two dosing schemes is negligible) • Dosing based on weight > 50 kg (per protocol) • Daily dosing for • Linezolid • Levofloxacin • Clofazimine • "Standard" dosing for bedaquiline – 400 mg daily x 14 days then 200 mg 3x/week for weeks 3–24 • Delamanid 100 mg twice daily x 8 weeks, then 200 mg daily x 16 weeks **Assumptions for 18m regimen:** • 18B(6)LLC +/- D • Drug prices obtained from Stop TB Partnership Global Drug Facility • BDQ using "regular" dosing – 2-week load and then 22 weeks of 3x/weekly dosing • DLM used for 24 weeks • LZD dosed 600 mg daily for the 18 months (unlikely this would be tolerated for the full duration). **Non-drug cost estimates based on the following each month:** • 1 outpatient visit • 1 smear, 1 culture • safety monitoring cost (1 LFT, 1 FBC, 1 ECG, 1 neuropathy screen) • 1m treatment support **Caveats** • Medicine prices are average prices across all suppliers as per GDF market share allocation • Medicine prices may change with 2024 GDF tenders The GDG considered the following example of country-specific patient-borne and health system costs over a 3-month span (excluding drug costs) (based on modelling analysis in Ryckman et al, 2024). Note that the costs may vary depending on the composition of the regimen being used.	**Previous GDG:** The GDG noted that affordability will vary depending on country (and resources available), health system differences, and the population the regimen would be used for and accordingly judged that there would be moderate savings with BDLC. Delamanid cost is one of the cost drivers in BDLC. With the drug being off patent, prices have decreased due to generic development (for certain countries) and may change further. Within the regimen it was also highlighted that there is a diagnostic cost involved for assessing resistance. It was highlighted that a longer duration of treatment bears costs (especially for patients and families but also the health system) and some estimates were available and discussed by the group. Considering these costs together with the drug costs may attenuate some of the increased costs for the health system and lead to cost savings from the patient perspective. It was noted, however, that countries looking to implement a specific treatment regimen typically focus on the drug cost.

Drug cost

BDLC	
6m	US$ 975
9m	US$ 1570

18M regimen	
without Dlm	US$ 795
with Dlm	US$ 1195

Non-drug cost

	per 12 months		
	Patient	Health system	Total
India	1536	348	**1884**
Philippines	3096	936	**4032**
South Africa	1368	2568	**3936**

	per 9 months		
	Patient	Health system	Total
India	1152	261	**1413**
Philippines	2322	702	**3024**
South Africa	1026	1926	**2952**

Cost difference in DRUG COST			Comment
From	US$ 775	more	(BDLC for 9m vs 18m regimen w/o Dlm)
To	US$ -220	less	(BDLC for 6m vs 18m regimen w Dlm)

Cost difference in non-DRUG COST			Comment
From	US$ 261	less	health systems cost only; 9m BDLC; India
To	US$ 4032	less	health systems + patient cost; 6m BDLC; Philippines

REF: WHO. Target regimen profiles for tuberculosis treatment, 2023 update. 2023

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The drug prices for the regimens were elicited from the Stop TB Partnership Global Drug Facility and health system and patient costs in the three settings were estimated based on data from an economic modelling analysis (Ryckman et al. 2024) and extrapolated to the 3-month time period for the difference in the treatment durations. The estimated costs from the economic modelling analysis do not account for possible imprecision in the cost estimates and provide indirect data for other settings where the BEAT-TB treatment regimen would be used. Thus, the certainty in this evidence is low.	

Cost effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ No included studies	No research evidence searched for.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence searched for.	**Based on prior recommendations,** the GDG considered the treatment duration and the ability to decentralize treatment (to enable access for remote, underserviced settings and disadvantaged populations) to affect equity. The GDG highlighted that health equity would probably increase given parts of the population that would have access to the shorter regimen and the medications included, in particular pregnant women and children and this may apply to other groups as well. On the other hand, it was also noted that there are populations that might not be able to afford the regimen, and between-country differences in impact on health equity may exist because of availability of medications. Despite not being able to identify relevant research evidence, the panel used their collective experience to judge that there would likely be advantages associated with the use of the BDLC regimen due to its reduced complexity and shorter duration. The panel judged that use of the BDLC regimen would probably increase equity.

Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence searched for.	Based on considerations of the previous GDG and new assessments, the GDG considered patients, health care providers and the health system as key interest-holders. For people living with Tb, acceptability of the BDLC and the longer 18-month regimen regimen will vary on the basis of disease severity. The panel judged that the BDLC regimen would probably be acceptable for those with non-severe disease. In people with more severe disease, longer regimens will be acceptable. The panel considered the following aspects as critical with regards to acceptability: regimen duration and drug safety monitoring needs (both relating to necessary travel, loss of income and general disruption of the life of patients; workload for the health care system), needs for drug susceptibility testing. With a shorter regiment overall quality of life may be improved.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**Previous GDG:** No research evidence was systematically searched for. However, the BDLLfxC regimen was additionally studied in operational research studies performed in three regions: Kazakhstan (STEM-TB cohort, n=23), Lesotho (STEM-TB, n=101), Europe (EURO STR 2, n=75), although given for 9 months instead of the 6 months used in the BEAT-TB trial. Favourable treatment outcomes (cure or treatment completion) were reported as 100%, 95%, and 75%, respectively. Additionally, BDLC **(BEAT-TB study regimen in those with pre-XDR-TB)** was also additionally studied in two studies: India (BEAT-TB cohort study, BDLC given for 6 months, n=152) and Nigeria (TDR SHORTT initiative, BDLC given for 9 months, n=38). Treatment success was reported as 91% in the BEAT-TB India cohort study with no data available yet from Nigeria.	There were different interpretations and opinions among panel members given the small amount of research data.

Summary of judgements

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favours the comparison	**Probably favours the comparison**	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	•	○	○	○

Conclusions

Recommendation
The use of the WHO-recommended SoC regimens used in the BEAT-TB and endTB-Q trials rather than the 6-month treatment regimen composed of bedaquiline, delamanid, linezolid, and clofazimine (BDLC), is suggested in patients with severe pre-XDR-TB, who have either had no previous exposure to the medicines in this regimen or have been exposed for less than 1 month *(conditional recommendation, very low certainty of evidence)*.
Remarks
Severity in pulmonary pre-XDR-TB for this regimen selection is defined by the presence of cavitary lesions on chest radiography and high bacillary load shown by sputum smear results of 1+ or higher positivity, and smear results of 2+ or higher (or an equivalent result on WHO-recommended molecular tests) even when cavities are not present. In children younger than 10 years, severe pulmonary pre-XDR-TB can manifest differently and may include extensive intrathoracic lymph node disease with airway obstruction, cavitary disease, or signs of extensive pulmonary involvement on imaging and severe respiratory compromise even without cavitation. Non-severe, in this context, refers to all situations not covered by the above definition of severe pulmonary pre-XDR-TB.
Justification
In patients with severe pre-XDR-TB, the GDG judged both the desirable and undesirable effects of BDLC to be small when compared to those of the WHO-recommended SoC regimens used in the BEAT-TB and endTB-Q trials. The certainty of evidence was judged to be very low. The balance of health effects was judged to favour longer regimens, supporting the comparison, although the evidence was very low due to indirectness and severe imprecision, particularly for the subgroup with non-severe disease.
Subgroup considerations
The panel noted specific considerations for the subpopulations listed below.
People living with HIV
No restrictions were identified for the use of the intervention among people living with HIV.
Children and adolescents
Trial evidence included participants aged ≥14 years. Extrapolation to younger children and adolescents is considered acceptable, consistent with prior guideline decisions.
Pregnant and breastfeeding women
No restrictions were identified for the drug Delamanid. Use of the drug Pretomanid is restricted due to limited safety data in this population.
Extensive TB disease (based on the endTB-Q trial definition)
Patients with DR-TB who have extensive disease face greater challenges in treatment across all regimens and are at a higher risk of unfavourable outcomes and amplification of drug resistance. This risk is further elevated in those infected with pathogens that have advanced resistance profiles, particularly with additional resistance to fluoroquinolones. These patients may experience slightly worse outcomes compared to those without pre-XDR and develop resistance to regimen components. In the BEAT-TB trial among patients with pre-XDR-TB, the outcomes also appeared worse than among those who were fluoroquinolone susceptible. This reduction in the proportion with successful treatment outcomes was numerically greater in the BDLLfxC arm than in the control arm (14.3% vs 3.3%); however, this difference was within the range of statistical uncertainty, and the GDG judged that this should not affect the recommendation or remarks. The rate of acquisition of resistance to bedaquiline was similar between the two groups (11% in BDLLfxC and 9.1% in control). The evidence from the BEAT-TB trial is insufficient to draw definitive conclusions due to the small sample when stratified by fluoroquinolone resistance and related imprecision. Nonetheless, clinicians should remain vigilant and closely monitor the treatment response in this group of patients and promptly take relevant actions (extending the duration of treatment or changing the regimen).
Hepatitis C co-infectionA prior WHO recommendation, based on expert evidence, applies to patients with MDR/RR-TB and hepatitis C virus (HCV) co-infection. WHO suggests co-administration of HCV and TB treatments rather than delaying HCV treatment until completion of MDR/RR-TB therapy *(conditional recommendation, very low certainty of evidence)*.
Malnutrition and underweight Patients with severe undernutrition, including those with a body mass index (BMI) below 15, were included in the trials. No subgroup-specific restrictions were identified based on nutritional status. (The trials did not include overweight participants).
Other causes of immunosuppression For patients with immunosuppression due to causes other than HIV, careful interpretation of the conditional recommendation is warranted, taking into account the underlying condition and clinical context.

Implementation considerations
Paediatric formulations Availability of appropriate drug formulations for children should be ensured.
Regimen transitions
Clear programmatic guidance is needed to support transitions between regimens where clinically indicated.
Drug susceptibility testing
DST for fluoroquinolones is strongly encouraged in people with MDR/RR-TB. While DST should not delay initiation of the BDLLfxC regimen, results should inform decisions on whether levofloxacin or clofazimine is retained in the regimen.
Linezolid dosing
Clear guidance and clinical expertise are required for appropriate linezolid dosing, and dose adjustments may be necessary.
Assessment of TB disease
Availability of chest radiography (CXR) should be ensured to support disease and severity assessment.
Capacity building Health-care worker training is needed to support standardized assessment of disease severity.
Drug–drug interactions Potential drug–drug interactions should be systematically assessed and managed.
Medicine supply Reliable availability of all regimen components, including adequate buffer stocks, is required to prevent stock-outs and treatment interruptions.
Severity assessment Standardized severity definition and assessment should be incorporated into implementation guidance.
Safety monitoring Systems for routine monitoring and management of adverse events should be in place.
Additional considerations For delamanid-based regimens, assessment of serum albumin levels should be considered.
Patient-centred approach
Efforts are required to provide patient support to enable full adherence to treatment.
Access to mental health and psychosocial support services should be ensured. Consideration should also be given to insurance coverage and financing mechanisms.
Monitoring and evaluation
Systems should be in place to monitor disease recurrence and the emergence of drug resistance, particularly in cases of treatment failure or relapse.
Routine monitoring and management of adverse events are required.
For patients receiving BDLLC-containing regimens, regular QTc interval monitoring should be conducted.

Research priorities
The GDG discussed and identified the following research priorities relating to this recommendation: **Interventions, populations and the balance of desirable and undesirable health effects:** Further research is needed to refine definitions of disease severity and the risk assessment model (RAM) which will help to better understand the baseline risk for the outcomes of interest. Direct comparative trials of BDLC versus BPaLC in patients with severe disease are a priority, including evaluation of optimal treatment duration in this subgroup. Additional evidence is required in children, including the safety and dosing of pretomanid (Pa) in those younger than 14 years. More programmatic and real-world data are needed, including outcomes in key subpopulations such as individuals with malnutrition. Research should identify reliable biomarkers for outcomes to individualize treatment duration irrespective of drug resistance profile or regimen. Assessment of the efficacy and safety of lower linezolid doses. Identification of predictors of disease recurrence. Larger trials and programmatic data for BPAL and BPALC regimens are required. Studies assessing treatment completion, adherence support needs, and quality-of-life outcomes. **Values:** Additional research is needed to obtain higher certainty in patient values related to the outcomes of interest. **Equity:** Judgments about equity will be better informed by studies that capture both direct and indirect patient costs to better understand the financial burden of treatment, alongside the evaluation of equitable access to newer TB regimens across different populations **Resources:** Effectiveness data from direct comparisons of regimens will be essential to inform cost-effectiveness and extended cost-effectiveness analyses, including the potential to reduce catastrophic costs for patients and households. **Acceptability:** Studies assessing the acceptability of newer TB regimens among both patients and health-care providers, in conjunction with exploration of reasons for delayed uptake and implementation despite guideline recommendations, are needed. **Feasibility:** Key feasibility concerns include barriers related to procurement and supply chains, regulatory approvals, and limitations in diagnostic and monitoring capacity.

PICO 2 evidence profile

A BPaL regimen compared to TB-PRACTECAL comparator regimens in patients with pulmonary pre-XDR-TB (PICO 2)

Bibliography:											
Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With TB-PRACTECAL comparator regimens	With a BPaL regimen		Risk with TB-PRACTECAL comparator regimens	Risk difference with a BPaL regimen
Failure and recurrence (both non-severe and severe) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)											
254 (1 RCT)	not serious	not serious	serious[a]	serious[b]	none	⨁⨁◯◯ Low[a,b]	40/143 (28.0%)	12/111 (10.8%)	**RR 0.39** (0.21 to 0.70)	40/143 (28.0%)	**172 fewer per 1000** (from 265 fewer to 78 fewer)[c]
Death (both non-severe and severe) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)											
254 (1 RCT)	not serious	not serious	serious[a]	very serious[b]	none	⨁◯◯◯ Very low[a,b]	6/143 (4.2%)	2/111 (1.8%)	**RR 0.43** (0.10 to 1.82)	6/143 (4.2%)	**24 fewer per 1000** (from 73 fewer to 26 more)[d]
Lost to follow up during treatment (both non-severe and severe) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)											
254 (1 RCT)	serious[e,fg]	not serious[h]	serious[a]	not serious[b]	none	⨁⨁◯◯ Low[a,b,e,fg,h]	6/143 (4.2%)	7/111 (6.3%)	**RR 1.50** (0.52 to 4.35)	6/143 (4.2%)	**21 more per 1000** (from 35 fewer to 77 more)[d]
Adverse events (Grade 3–4) during treatment (both non-severe and severe) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)											
254 (1 RCT)	serious[e,fg]	not serious[h]	serious[a]	very serious[b]	none	⨁◯◯◯ Very low[a,b,e,fg,h]	69/143 (48.3%)	24/111 (21.6%)	**RR 0.44** (0.30 to 0.66)	69/143 (48.3%)	**267 fewer per 1000** (from 378 fewer to 155 fewer)[c]
Amplification of resistance to study drugs (both non-severe and severe) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)											
254 (1 RCT)	not serious	not serious[h]	serious[a]	serious[b]	none	⨁⨁◯◯ Low[a,b,h]	0/143 (0.0%)	3/111 (2.7%)	not estimable	0/143 (0.0%)	**27 more per 1000** (from 0 more to 77 more)[d]

CI: confidence interval; **RR:** risk ratio

Explanations

a. A single trial. Serious indirectness (i) Populations: Differences in population of a trial and population to which guidelines will apply. (ii) Comparator: Some comparator regimens are sub-optimal, not according with the WHO standard of care (at the time or presently), and vary by country. Downgraded one level.

b. The number of participants in both intervention and comparator groups was small. Very few events in the outcomes of interest, causing serious or very serious imprecision. We downgraded between 0 and 3 levels depending upon how many decision thresholds were crossed by the 95 % confidence interval.

c. Adjusted for baseline severity, prior TB, body mass index, age, HIV status and study site.

d. Not adjusted owing to small numbers of events.

e. An imbalance in measured covariates (gender, past DR-TB treatment, smear status, FQ-resistance) likely arises from the small number of participants in each group. While the adjusted analyses will account for measured confounding, unmeasured confounding is also likely.

f. Small numbers of events in some outcomes precludes adjustment in some comparisons.

g. A lack of blinding of patients, caregivers and those adjudicating outcomes may introduce bias in the conduct of the trial. Slightly higher loss to follow-up was noted in the comparator group, which is an outcome that may be influenced by patient or clinician knowledge of the regimen.

h. Multiple comparator regimens were used, varying across site. This may explain some of the substantial inconsistency in the point estimates for treatment outcomes seen between countries (Belarus, South Africa and Uzbekistan). The decision whether to downgrade is a difficult decision. We did not downgrade for inconsistency as the issue of comparators was addressed under indirectness

PICO 2 evidence-to-decision

Question	
Should a BPaL regimen vs. TB-PRACTECAL comparator regimens be used for patients with pulmonary pre-XDR-TB (PICO 2)?	
POPULATION:	patients with pulmonary pre-XDR-TB (PICO 2)
INTERVENTION:	a BPaL regimen
COMPARISON:	TB-PRACTECAL comparator regimens
MAIN OUTCOMES:	Failure and recurrence (both non-severe and severe) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R); Death (both non-severe and severe) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R); Lost to follow up during treatment (both non-severe and severe) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R); Adverse events (Grade 3–4) during treatment (both non-severe and severe) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R); Amplification of resistance to study drugs (both non-severe and severe) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R); Failure and relapse (both non-severe and severe, for MDR-TB (FQ-S and FQ-R) in BPaL arm and MDR-TB (FQ-R only) in SOC – 18 months; Death (both non-severe and severe TB, for MDR-TB (FQ-S and FQ-R) in BPaL arm and MDR-TB (FQ-R only) in SOC – 18 months; Loss to follow-up during treatment (both non-severe and severe TB, for MDR-TB (FQ-S and FQ-R) in BPaL arm and MDR-TB (FQ-R only) in SOC – 18 months; Adverse events (Grade 3–4 during treatment, both non-severe and severe TB, for MDR-TB (FQ-S and FQ-R) in BPaL arm and MDR-TB (FQ-R only) in SOC – 18 months; Amplification of resistance (both non-severe and severe TB, for MDR-TB (FQ-S and FQ-R) in BPaL arm and MDR-TB (FQ-R only) in SOC – 18 months;
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	This question addresses the effectiveness and safety of a 6-month BPaL treatment regimen in patients with pulmonary pre-XDR-TB versus the current standard of care.
CONFLICT OF INTERESTS:	The WHO GTB Program applied the WHO conflict of interest declaration and management policy, and the following were GDG members involved in decision-making for this recommendation: Ashna Ashesh (WHO Civil Society Task Force – TB; Survivors Against TB, India), Erlina Burhan (Persahabatan Hospital Jakarta; Faculty of Medicine – Universitas Indonesia), Muhwa Chakaya (National Tuberculosis Programme of Kenya), Gerry Davies (University of Liverpool, United Kingdom), Fernanda Dockhorn Costa Johansen (Ministry of Health MDR-TB referral centre, Brazil), Kelly Dooley (Vanderbilt University Medical Center, USA), Sobia Faisal (Greenstar Social Marketing, Pakistan), Elmira Gurbanova (Lung Clinic, University of Tartu, Estonia), Eric Krakauer (Harvard Medical School, USA), Christoph Lange (Research Center Borstel, Germany), Yuhong Liu (Beijing Chest Hospital, China), Andrey Maryandyshev (Phthisiopulmonology Department of the Northern State Medical University, Arkhangelsk, Russian Federation), Graeme Meintjes (University of Cape Town, South Africa), Mahshid Nasehi (National Tuberculosis Programme of the Islamic Republic of Iran), Mamel Quelapio (Independent consultant, the Philippines), Moorine Sekkade (National Tuberculosis Programme of Uganda), Wei Sha (Shanghai Pulmonary Hospital, China), Urvashi Singh (National TB Programme, Ministry of Health, India), Shaheed Vally Omar (South Africa Supranational TB Reference Laboratory), Luan Vo (Friends for International Tuberculosis Relief, Viet Nam). No member of the GDG had important conflicts precluding participation.

Assessment

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Tuberculosis (TB) remains a threat to global public health and is one of the topmost infectious causes of death in the world. In 2024, an estimated 10.7 million people developed TB, and 1.23 million died from the disease. About 390,000 new patients with rifampicin-resistant or multidrug-resistant tuberculosis (MDR/RR-TB) were estimated to emerge in 2024. While all of these patients would have been eligible for a second-line TB treatment regimen, only 165,650 enrolments on treatment were reported by countries in the same year. In recent years, substantial progress has been made with the introduction of improved diagnostics and more effective medicines, enabling earlier detection and boosting treatment success rates among MDR/RR-TB patients in many national programs, with a 71% success rate reported for those enrolled in 2022. MDR-/RR-TB is treatable but requires different treatment regimen combinations that used to be longer than regimens for drug-susceptible TB and include medicines that are potentially more toxic. The interest in reducing the duration of treatment for MDR/RR-TB motivated a continuous search for shorter and safer regimens. The regimens for the treatment of MDR/RR-TB have changed dramatically in the past ten years. Before 2016, DR-TB regimens were 24 months or longer and included six or more months of daily intramuscular injections with significant adverse events. In 2016, based on data from observational studies of the shorter regimens in different Asian and African countries, WHO, for the first time, recommended a standardized 9-month regimen containing an injectable agent providing shorter than the extant 18–20 months standard of care for the eligible patients. Evidence of permanent effects attributed to the toxicity of injectable agents has prompted further advances in the development of new treatments, such as shorter injectable-sparing regimens. The all-oral 9-month bedaquiline-containing regimen was reviewed and recommended by WHO in 2019. The pressing need for more effective treatment regimens for patients with MDR/RR-TB, including those with fluoroquinolone resistance and more extensive drug-resistance profiles, has driven several studies and initiatives to test more effective and novel treatment regimens, including newer and repurposed medicines. The Nix-TB study conducted by TB Alliance pioneered the 6-month regimen that included bedaquiline and a new medicine – pretomanid, and the BPaL combination successfully received regulatory approval from the FDA. Two randomized controlled trials (RCTs) that concluded in 2021 (TB-PRACTECAL and ZeNix) provided new evidence and prompted assessment by WHO to develop new recommendations for wide programmatic use of the BPaLM/BPaL regimen for treatment MDR/RR-TB with or without resistance to fluoroquinolones. The latest evidence-based guidelines for the treatment and care of TB and drug-resistant TB, including MDR/RR-TB and pre-XDR-TB, were published by WHO in April 2025 – "WHO consolidated guidelines on tuberculosis: module 4: treatment and care". The WHO has combined all recommendations on the treatment of drug-resistant TB, drug-susceptible TB, and TB care and support in three separate chapters of the consolidated guidelines. The recommendation for use of another 6-month BDLLfxC regimen based on the evidence from the BEAT Tuberculosis trial in South Africa was included in the 2025 update.	**Information from a prior GDG (2022) meeting on sub-PICOs 6.6 and 4.1 stated the following and this information still applies:** **Sub-PICO 6.6** The BPaL arm of the TB-PRACTECAL trial with a population including patients with **MDR/RR-TB with or without fluoroquinolone resistance (MDR/RR-TB or pre-XDR-TB)** was compared with the comparator arm of the TB-PRACTECAL trial that comprised MDR/RR-TB or pre-XDR-TB patients treated with multiple local SoC regimens (including a 9–12-month injectable-containing regimen, an 18–24-month WHO regimen [pre-2019], a 9–12-month all-oral regimen and an 18–20-month all-oral regimen). Primary analysis was undertaken at 72 weeks post treatment initiation. Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving BPaL (*n*=60) compared with participants receiving WHO-recommended SoC regimens used in the TB-PRACTECAL trial (*n*=66) experienced: • higher levels of treatment success (77% vs 52%); that is, a 47% relative increase (aRR=1.47, 95% CI: 1.09 to 1.99); • lower levels of failure and recurrence (13% vs 26%); that is, a 48% relative reduction (aRR=0.52, 95% CI: 0.22 to 1.18); • lower levels of deaths (0% vs 3.0%); that is, a 3% absolute reduction (RD= –0.03, 95% CI: –0.10 to 0.03);

Following the recent update of the WHO recommendations on DR-TB treatment, new or more complete evidence has become available from clinical trials or operational research on using combinations of medicines to treat MDR/RR-TB or pre-XDR-TB that a WHO-convened Guideline Development Group has not yet appraised. These regimens include the use of a new 6-month regimen including bedaquiline, delamanid, linezolid and clofazimine (endTB-Q and BEAT-TB South Africa trials) and the use of 6-month BPaL and BPaLC regimens (more complete data from the TB-PRATECAL trial and additional data from the operational research studies or programmatic implementation) for the treatment of patients with MDR/RR-TB with quinolone resistance.

The evidence from these trials has been shared with WHO, and this guideline development group (GDG) is convened to review new evidence on the treatment and palliative care for patients with MDR/RR-TB or pre-XDR-TB to ensure that the latest treatment and care options are reflected in the WHO policy.

- lower levels of LTFU (10% vs 20%); that is, a 40% relative reduction (aRR=0.60, 95% CI: 0.24 to 1.56);
- lower levels of AEs (20% vs 51%); that is, a 62% relative reduction (RR=0.38, 95% CI: 0.24 to 0.60); and
- higher levels of amplification of drug resistance (2.9% vs 1.9%); that is, a 59% relative increase (RR=1.59, 95% CI: 0.32 to 7.84).

The GDG judged the benefits of BPaL to be large and the undesirable effects to be trivial compared with WHO-recommended SoC regimens. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours the BPaL regimen.

Conclusion

The use of the 6-month treatment regimen composed of bedaquiline, pretomanid and linezolid (BPaL) rather than a 9-month or longer (18-month) regimen is suggested in patients with MDR/RR-TB with or without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month.

Sub-PICO 4.1

The BPaL 600–26 arm of the ZeNix trial (where linezolid 600 mg daily was used for 26 weeks and the population included patients **with MDR/RR-TB with fluoroquinolone resistance**) was compared with a cohort of MDR/RR-TB patients with fluoroquinolone resistance from the 2021 IPD who were receiving longer regimens for treatment of MDR/RR-TB, designed in line with 2020 WHO guidelines. Primary analysis was undertaken at 18 months post treatment initiation.

Participants with pulmonary pre-XDR-TB (MDR/RR-TB with fluoroquinolone resistance) receiving BPaL 600–26 (n=33) compared with participants receiving longer regimens for MDR/RR-TB (n=839) experienced:

higher levels of treatment success (100% vs 75%); that is, a 34% relative increase (RR=1.34, 95% CI: 1.20 to 1.40);

lower levels of failure and recurrence (0% vs 6.6%); that is, a 7% absolute reduction (RD= –0.07, 95% CI: –0.08 to –0.04);

lower levels of deaths (0% vs 9.9%); that is, a 10% absolute reduction (RD= –0.10, 95% CI: –0.12 to –0.01);

lower levels of LTFU (0% vs 9.1%); that is, a 9% absolute reduction (RD= –0.09, 95% CI: –0.11 to –0.01); higher levels of AEs (15% vs 4.4%); that is, a 3.4-fold increase (RR=3.44, 95% CI: 1.44 to 8.17); and

lower levels of amplification of drug resistance (0% vs 7.4%); that is, a 7% absolute reduction (RD= –0.07, 95% CI: –0.09 to –0.03).

The GDG judged the benefits of BPaL with linezolid 600–26 to be large and the undesirable effects to be moderate compared with longer regimens recommended by WHO. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaL with linezolid 600–26.

Conclusion

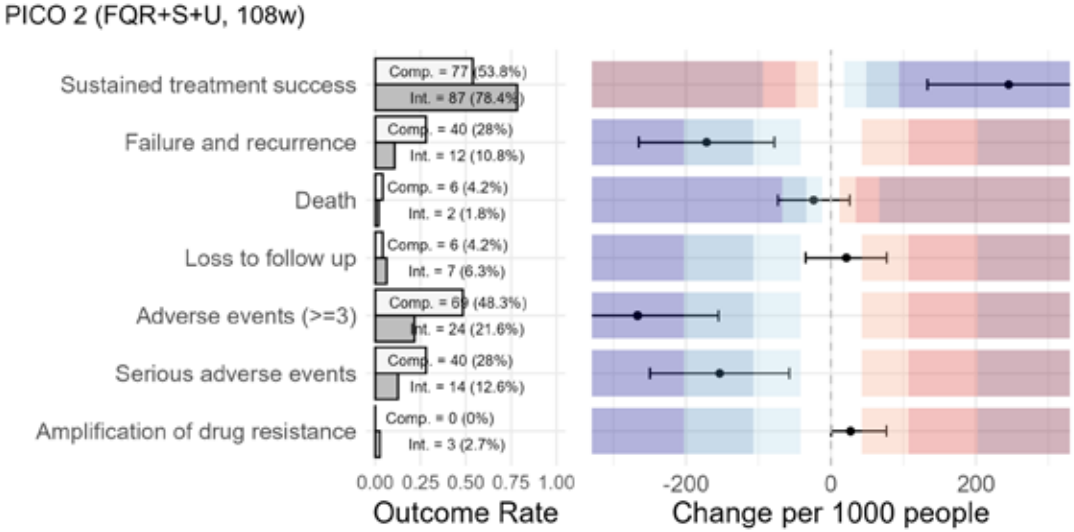
The use of the 6-month treatment regimen composed of bedaquiline, pretomanid and linezolid (BPaL) rather than a longer (18-month) regimen is suggested in patients with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR-TB), who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	The BPaL regimen arm of the TB-PRACTECAL trial, with a population including patients with MDR/RR-TB with or without fluoroquinolone resistance (MDR/RR-TB or pre-XDR-TB), was compared to the comparator arm comprised of MDR/RR-TB or pre-XDR-TB patients treated with multiple local SoC regimens recommended by WHO at the time of trial conduct (including a 9–12-month injectable-containing regimen; 18–24-month WHO-recommended regimen [pre-2019]; 9–12-month all-oral regimen; and 18–20-month all-oral regimen). Although the research question focused explicitly on pre-XDR-TB patients, the analysis included both MDR/RR and pre-XDR-TB patients in both groups to increase the sample size and improve statistical precision, as excluding fluoroquinolone-susceptible cases would have resulted in insufficiently small cohorts. In the intervention group, use of the BPaL regimen, which does not include a fluoroquinolone, meant that fluoroquinolone susceptibility had no effect on treatment benefit, whereas in the comparator group, inclusion of fluoroquinolone susceptible patients allowed regimens that could potentially perform better, thereby biasing the comparison against the intervention rather than in its favour, which was acceptable given the objective to demonstrate the added benefit of the BPaLC regimen Primary analysis was undertaken at 108 weeks post-treatment initiation. Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving BPaL (n=111) compared with participants receiving WHO-recommended SoC regimens used in the TB-PRACTECAL trial (n=143) experienced: • lower levels of failure and recurrence (10.8% vs 28%); RD=172 fewer per 1000, 95% CI: 265 fewer to 78 fewer per 1000); • lower levels of deaths (1.8% vs 4.2%); RD=24 fewer per 1000, 95% CI: 73 fewer to 26 more per 1000); • higher levels of LTFU (6.3% vs 4.2%); RD=21 more per 1000, 95% CI: 35 fewer to 77 more per 1000); • lower levels of AEs (21.6% vs 48.3%); RD=267 fewer per 1000, 95% CI: 378 fewer to 155 fewer per 1000); and • higher levels of amplification of drug resistance (2.7% vs 0%); RD=27 more per 1000, 95% CI: 0 fewer to 77 more per 1000).	Based on the thresholds for the prioritized outcomes listed below, the GDG judged the desirable effects of BPaL compared to the TB-PRACTECAL comparator regimen to be large. Additional benefits include that: Treatment duration is reduced by 12–18 months, i.e. to 1/3 to 1/2 of duration of comparator regimen (6–9 months vs 18–24 months). Pill burden is significantly decreased, 5–6 times (on average from 3'400 to 530). **Death** • Trivial Effect: ≤12 fewer or more events per 1000 people • Small Effect: 12 to 34 fewer or more events per 1000 people • Moderate Effect: 34 to 67 fewer or more events per 1000 people • Large Effect: >67 fewer or more events per 1000 people **Treatment Failure or Recurrence, lost to follow-up, adverse events and amplification (acquisition) of drug resistance** • Trivial Effect: ≤41 fewer or more events per 1000 people • Small Effect: 41 to 107 fewer or more events per 1000 people • Moderate Effect: 107 to 202 fewer or more events per 1000 people • Large Effect: >202 fewer or more events per 1000 people

Fig. Visual depiction of absolute effects in relation to the decision thresholds used by the GDG



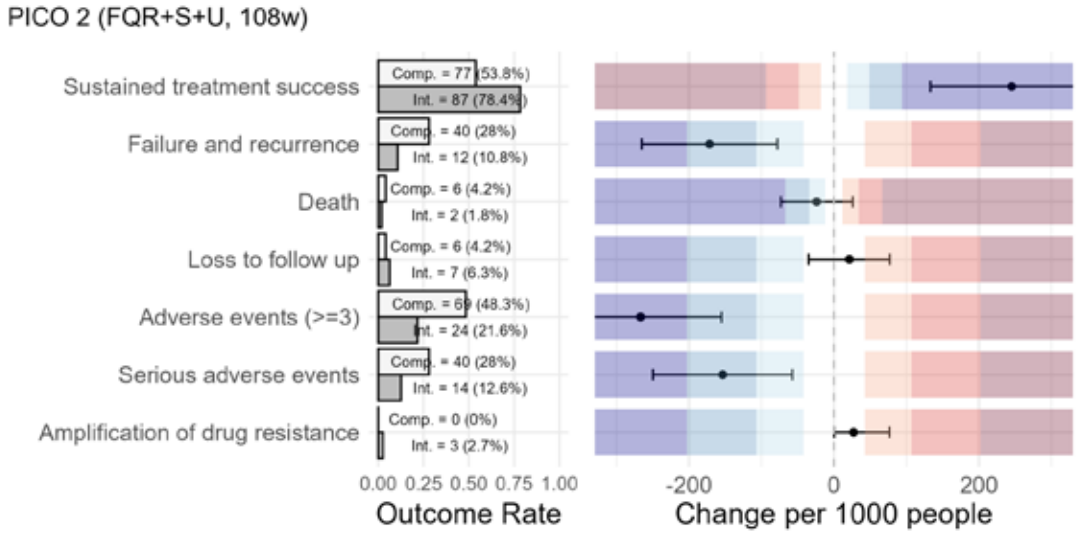
Decision threshold diagram

All (non severe + severe)

The GDG judged the benefits of BPaL to be large and the undesirable effects to be small compared with the WHO-recommended SoC regimens used in the TB-PRACTECAL trial. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours the BPaL regimen.

Undesirable Effects

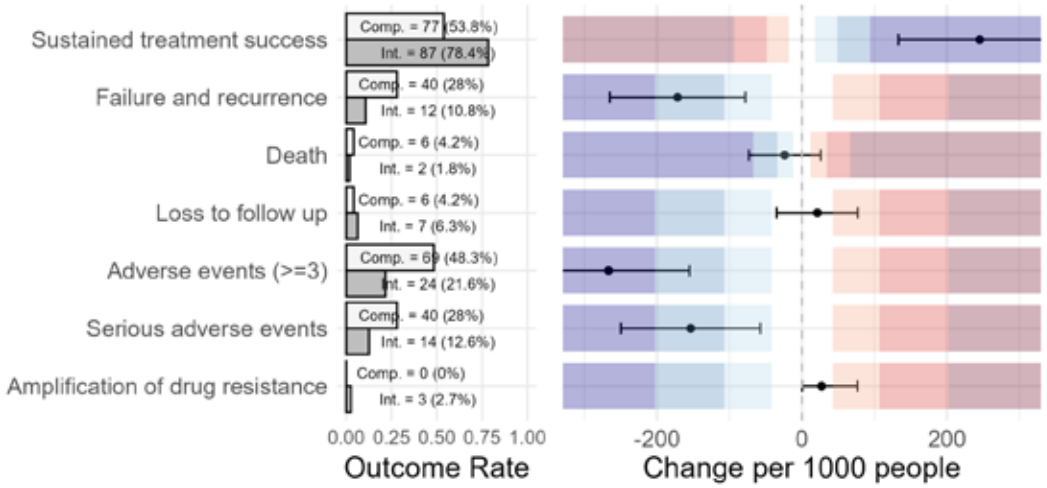
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	**All (severe + non-severe)** 	Based on the thresholds for the prioritized outcomes listed below, the GDG judged the undesirable health effects of BPaLC compared to the TB-PRACTECAL comparator regimen to be small.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	PICO 2 (FQR+S+U, 108w)	There was risk of bias due to lack of blinding of patients and caregivers, indirectness and very serious imprecision that lower the certainty in the evidence for several outcomes.



Summary of Findings for a BPaL regimen Versus TB-PRACTECAL comparator regimens for patients with pulmonary pre-XDR-TB (PICO 2)							
Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			TB-PRACTECAL comparator regimens	[a] BPaL regimen	Difference		
Failure and recurrence (both non-severe and severe) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	254 (1 RCT)	**RR = 0.39** (0.21 to 0.70)	280 per 1000	**108 per 1000 (-- to --)[a]**	**172 fewer per 1000** (from 265 fewer to 78 fewer)[a]	⨁⨁◯◯ Low[b,c]	
Death (both non-severe and severe) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	254 (1 RCT)	**RR = 0.43** (0.10 to 1.82)	42 per 1000	**18 per 1000 (-- to --)[d]**	**24 fewer per 1000** (from 73 fewer to 26 more)[d]	⨁◯◯◯ Very low[b,c]	
Lost to follow up during treatment (both non-severe and severe) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	254 (1 RCT)	**RR = 1.50** (0.52 to 4.35)	42 per 1000	**63 per 1000 (-- to --)[d]**	**21 more per 1000** (from 35 fewer to 77 more)[d]	⨁⨁◯◯ Low[b,c,e,f,g,h]	
Adverse events (Grade 3–4) during treatment (both non-severe and severe) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	254 (1 RCT)	**RR = 0.44** (0.30 to 0.66)	483 per 1000	**216 per 1000 (-- to --)[a]**	**267 fewer per 1000** (from 378 fewer to 155 fewer)[a]	⨁◯◯◯ Very low[b,c,e,f,g,h]	
Amplification of resistance to study drugs (both non-severe and severe) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	254 (1 RCT)	not estimable	0 per 1000	**27 per 1000 (-- to --)[d]**	**27 more per 1000** (from 0 more to 77 more)[d]	⨁⨁◯◯ Low[b,c,h]	

CI: confidence interval; **RR:** risk ratio

a. Adjusted for baseline severity, prior TB, body mass index, age, HIV status and study site.

b. A single trial. Serious indirectness (i) Populations: Differences in population of a trial and population to which guidelines will apply. (ii) Comparator: Some comparator regimens are sub-optimal, not according with the WHO standard of care (at the time or presently), and vary by country. Downgraded one level.

c. The number of participants in both intervention and comparator groups was small. Very few events in the outcomes of interest, causing serious or very serious imprecision. We downgraded between 0 and 3 levels depending upon how many decision thresholds were crossed by the 95 % confidence interval.

d. Not adjusted owing to small numbers of events.

	e. An imbalance in measured covariates (gender, past DR-TB treatment, smear status, FQ-resistance) likely arises from the small number of participants in each group. While the adjusted analyses will account for measured confounding, unmeasured confounding is also likely. f. Small numbers of events in some outcomes precludes adjustment in some comparisons. g. A lack of blinding of patients, caregivers and those adjudicating outcomes may introduce bias in the conduct of the trial. Slightly higher loss to follow-up was noted in the comparator group, which is an outcome that may be influenced by patient or clinician knowledge of the regimen. h. Multiple comparator regimens were used, varying across site. This may explain some of the substantial inconsistency in the point estimates for treatment outcomes seen between countries (Belarus, South Africa and Uzbekistan). The decision whether to downgrade is a difficult decision. We did not downgrade for inconsistency as the issue of comparators was addressed under indirectness	

Values

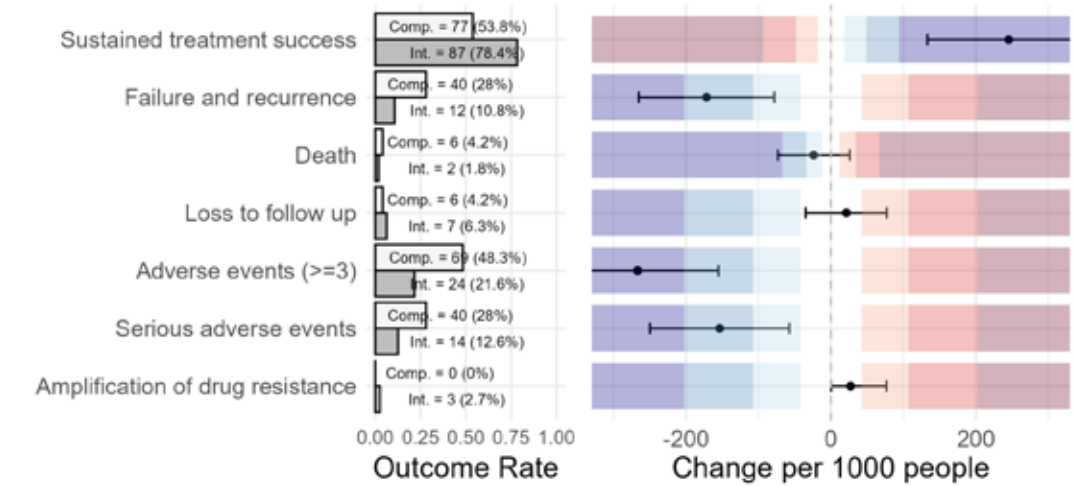
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence was sought for.	The GDG noted that higher treatment efficacy, shorter duration of treatment, lower pill burden and less adverse events are usually valued by patients.

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	PICO 2 (FQR+S+U, 108w)	The GDG judged the benefits of BPaL to be large and the undesirable effects to be small compared with the WHO-recommended SoC regimens used in the TB-PRACTECAL trial. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours the BPaL regimen.



Summary of Findings for a BPaL regimen Versus TB-PRACTECAL comparator regimens for patients with pulmonary pre-XDR-TB (PICO 2)							
Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			TB-PRACTECAL comparator regimens	[a] BPaL regimen	Difference		
Failure and recurrence (both non-severe and severe) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	254 (1 RCT)	**RR = 0.39** (0.21 to 0.70)	280 per 1000	**108 per 1000 (-- to --)[a]**	**172 fewer per 1000** (from 265 fewer to 78 fewer)[a]	⨁⨁◯◯ Low[b,c]	
Death (both non-severe and severe) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	254 (1 RCT)	**RR = 0.43** (0.10 to 1.82)	42 per 1000	**18 per 1000 (-- to --)[d]**	**24 fewer per 1000** (from 73 fewer to 26 more)[d]	⨁◯◯◯ Very low[b,c]	
Lost to follow up during treatment (both non-severe and severe) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	254 (1 RCT)	**RR = 1.50** (0.52 to 4.35)	42 per 1000	**63 per 1000 (-- to --)[d]**	**21 more per 1000** (from 35 fewer to 77 more)[d]	⨁⨁◯◯ Low[b,c,e,f,g,h]	
Adverse events (Grade 3–4) during treatment (both non-severe and severe) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	254 (1 RCT)	**RR = 0.44** (0.30 to 0.66)	483 per 1000	**216 per 1000 (-- to --)[a]**	**267 fewer per 1000** (from 378 fewer to 155 fewer)[a]	⨁◯◯◯ Very low[b,c,e,f,g,h]	
Amplification of resistance to study drugs (both non-severe and severe) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	254 (1 RCT)	not estimable	0 per 1000	**27 per 1000 (-- to --)[d]**	**27 more per 1000** (from 0 more to 77 more)[d]	⨁⨁◯◯ Low[b,c,h]	

CI: confidence interval; **RR:** risk ratio

a. Adjusted for baseline severity, prior TB, body mass index, age, HIV status and study site.

b. A single trial. Serious indirectness (i) Populations: Differences in population of a trial and population to which guidelines will apply. (ii) Comparator: Some comparator regimens are sub-optimal, not according with the WHO standard of care (at the time or presently), and vary by country. Downgraded one level.

c. The number of participants in both intervention and comparator groups was small. Very few events in the outcomes of interest, causing serious or very serious imprecision. We downgraded between 0 and 3 levels depending upon how many decision thresholds were crossed by the 95 % confidence interval.

d. Not adjusted owing to small numbers of events.

e. An imbalance in measured covariates (gender, past DR-TB treatment, smear status, FQ-resistance) likely arises from the small number of participants in each group. While the adjusted analyses will account for measured confounding, unmeasured confounding is also likely.

f. Small numbers of events in some outcomes precludes adjustment in some comparisons.

g. A lack of blinding of patients, caregivers and those adjudicating outcomes may introduce bias in the conduct of the trial. Slightly higher loss to follow-up was noted in the comparator group, which is an outcome that may be influenced by patient or clinician knowledge of the regimen.

h. Multiple comparator regimens were used, varying across site. This may explain some of the substantial inconsistency in the point estimates for treatment outcomes seen between countries (Belarus, South Africa and Uzbekistan). The decision whether to downgrade is a difficult decision. We did not downgrade for inconsistency as the issue of comparators was addressed under indirectness

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ● Large savings ○ Varies ○ Don't know	Cost of medicines: • 6BPaL (the current recommended regimen) – $259 • Assumes LZD 600 mg daily through the entire treatment • Usual dosing for all other meds • 26 weeks duration • 9BPaL – $ 382 • Assumes 9 months of BDQ using "usual" dosing and LZD 600 mg daily through the entire treatment • Usual dosing for pretomanid • 39 weeks duration **Assumptions for 18m regimen:** • 18B(6)LLC +/- D • Drug prices obtained from Stop TB Partnership Global Drug Facility • BDQ using "regular" dosing – 2-week load and then 22 weeks of 3x/weekly dosing • DLM used for 24 weeks • LZD dosed 600 mg daily for the 18 months (unlikely this would be tolerated for the full duration). **Non-drug cost estimates based on the following each month:** • - 1 outpatient visit • - 1 smear, 1 culture • - safety monitoring cost (1 LFT, 1 FBC, 1 ECG, 1 neuropathy screen) • - 1m treatment support **Caveats** • Medicine prices are average prices across all suppliers as per GDF market share allocation • Medicine prices may change with future GDF tenders The GDG considered the following example of country-specific patient-borne and health system costs over a 3-month span (excluding drug costs) (based on modelling analysis in Ryckman et al, 2024). Note that the costs may vary depending on the composition of the regimen being used.	The GDG judged the differentially associated cost of BPaL compared to the 18-month regimen to lead to large savings for health systems.

Drug cost

BPaL	
6m	US$ 259
9m	US$ 382

18M regimen	
without Dlm	US$ 795
with Dlm	US$ 1195

Non-drug cost

	BPaL per 6 months		
	Patient	Health system	Total
India	966	174	**1140**
Philippines	1043	468	**1511**
South Africa	824	1284	**2108**

	18M Regimen per 18 months		
	Patient	Health system	Total
India	2502	522	**3024**
Philippines	2951	1404	**4355**
South Africa	2192	3852	**6044**

Cost difference DRUG + NON-DRUG cost			Comment
From	US$ 761	less	BPaL for 9m vs 18m regimen w/o Dlm; health systems cost only; 9m BPaL; India
To	US$ 4872	less	BPaL for 6m vs 18m regimen w Dlm; health systems & patient cost; 6m BPaL; South Africa

Cost difference in DRUG cost			Comment
From	US$ 413	less	BPaL for 9m vs 18m regimen w/o Dlm
To	US$ 936	less	BPaL for 6m vs 18m regimen w Dlm

Cost difference in NON-DRUG cost			Comment
From	US$ 348	less	health systems cost only; 9m BPaL; India
To	US$ 3936	less	health systems cost & patient cost; 6m BPaL; South Africa

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The drug prices for the regimens were elicited from the Stop TB Partnership Global Drug Facility and health system and patient costs in the three settings were estimated based on data from an economic modelling analysis (Ryckman et al. 2024) and extrapolated to the 3-month time period for the difference in the treatment durations. The estimated costs from the economic modelling analysis do not account for possible imprecision in the cost estimates and provide indirect data for other settings where the BEAT-TB treatment regimen would be used. Thus, the certainty in this evidence is low.	

Cost effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ No included studies	**Sweeney et al., 2022.** Multi-country cost-effectiveness model. BPaL and BPaLM were likely cost-saving and more effective than standard of care in a range of settings. BPaL often the most cost-saving**. PMC** **James et al., 2024 / PubMed.** Modelled lifetime costs, found 6-month BPaLM cost-effective versus standard care, with substantial per-person cost reductions in base case**. PubMed** **Country economic analyses and modelling (examples**). India and Philippines analyses found BPaL/BPaLM cost-saving or highly cost-effective under local assumptions. See India modelling (2025) and Philippines study (2024)**. Cambridge Core** **PLOS Global Public Health, 2025.** Analysis of impact of fluoroquinolone resistance on cost-effectiveness. Concludes BPaLM can be cost-effective in empirical settings and may replace BPaL depending on resistance prevalence**. PLOS Journals**	Given the research evidence, and that the balance of effects probably favours the intervention and that BPaL leads to large savings, the GDG judged that the cost-effectiveness of the intervention probably favours the intervention.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence searched for.	The panel considered the treatment duration and the ability to decentralize treatment (to enable access for remote, underserviced settings and disadvantaged populations) to affect equity. Despite not being able to identify relevant research evidence, the panel used their collective experience to judge that there would likely be advantages associated with the use of the BPaL regimen due to its reduced complexity and shorter duration. The panel judged that use of the BPaL regimen would probably increase equity.

Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	One study found that acceptability: overall high and rated as acceptable by >80% across domains **van de Berg et al., BMC Public Health, 2021.** Multi-country qualitative study of stakeholders in Indonesia, Kyrgyzstan, Nigeria. Found high acceptability and willingness to implement BPaL despite system constraints. BioMed Central **KNCV / TB Alliance operational report, 2021.** Acceptability and feasibility study in three high-burden countries, similar conclusions: stakeholders and patients generally positive about BPaL adoption. kncvtbplus.com	Acceptability was considered by the 2022 GDG for related evidence. Based on considerations of the previous GDG and new assessments, the GDG considered patients, health care providers and the health system as key intest-holders. For people living with TB, the panel considered the following aspects as critical with regards to acceptability: regimen duration and drug safety monitoring needs (both relating to necessary travel, loss of income and general disruption of the life of patients; workload for the health care system), needs for drug susceptibility testing. The panel judged that the BPaL regimen would probably be acceptable for patients, providers and policy-makers.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	WHO received data from a small cohort of patients treated with the BPaL regimen under programmatic conditions at a single site in Italy. The cohort included a limited number of patients with MDR-TB in the WHO IPD dataset. None had pre-XDR-TB. Treatment outcomes were broadly consistent with those observed in the BPaL arm of the TB-PRACTECAL trial. These findings also support the feasibility of implementing the BPaL regimen in routine care settings.	Based on considerations of the previous GDG (2022) and new assessments, the GDG considered the following aspects to affect feasibility (i.e. to be potential barriers to implementation): requirements for drug safety monitoring and requirements for drug susceptibility testing. The panel noted limited availability of drugs in the BPaL regimen for use in DST as a potential barriers to implementation and also noted that data on the critical concentration of Pretomanid for use in DST is limited. However, given the reduced duration, complexity and associated workload, the panel judged that implementation is probably feasible.

Outcome	WHO IPD BPaL		TB-PRACTECAL BPaL		TB-PRACTECAL Control	
	n	*(%)*	*n*	*(%)*	*n*	*(%)*
Total included	**16**		**111**		**143**	
Treatment success	**14**	**(88)**	**96**	**(87)**	**85**	**(59)**
Cure	**6**	**(38)**	**0**	**(0)**	**0**	**(0)**
Treatment complete	**8**	**(50)**	**0**	**(0)**	**0**	**(0)**
Loss to follow up	**1**	**(6)**	**11**	**(11)**	**1**	**(1)**
Failure	**0**	**(0)**	**1**	**(1)**	**39**	**(27)**
Death	**1**	**(6)**	**3**	**(3)**	**5**	**(3)**

Summary of judgements

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	**Large savings**	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	•	○

Conclusions

Recommendation
The use of the 6-month treatment regimen composed of bedaquiline, pretomanid and linezolid (BPaL) rather than a longer (18-month) regimen is suggested in patients with pre-XDR-TB, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month *(conditional recommendation, very low certainty)*.
Justification
The GDG judged the benefits of BPaL to be large and the undesirable effects to be small compared with the WHO-recommended SoC regimens used in the TB-PRACTECAL trial. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours the BPaL regimen. A conditional recommendation was made because there is very low certainty and evidence of of acquired drug resistance in severe TB subgroup is still missing. However, cost-effectiveness and other factors are in favour of BPaL.
Subgroup considerations
The panel identified subpopulations of people who might be affected differently than most by this recommendation; these subpopulations were PLHIV, children, pregnant women, breastfeeding women, and patients with extensive TB disease. The recent new recommendation for the use of bedaquiline in children with MDR/RR-TB aged below 6 years was considered *(29)*. Thus, the panel noted specific considerations for the subpopulations listed below. **People living with HIV** No restrictions were identified for the use of the intervention among people living with HIV. **Children and adolescents** Trial evidence included participants aged ≥14 years. **Pregnant and breastfeeding women** No restrictions were identified for the drug Delamanid. Use of the drug Pretomanid is restricted due to limited safety data in this population **Extensive TB disease (based on the endTB-Q trial definition)** Patients with DR-TB who have extensive disease face greater challenges in treatment across all regimens and are at a higher risk of unfavourable outcomes and amplification of drug resistance. This risk is further elevated in those infected with pathogens that have advanced resistance profiles, particularly with additional resistance to fluoroquinolones. These patients may experience slightly worse outcomes compared to those without pre-XDR and develop resistance to regimen components. In the BEAT-TB trial among patients with pre-XDR-TB, the outcomes also appeared worse than among those who were fluoroquinolone susceptible. This reduction in the proportion with successful treatment outcomes was numerically greater in the BDLLfxC arm than in the control arm (14.3% vs 3.3%); however, this difference was within the range of statistical uncertainty, and the GDG judged that this should not affect the recommendation or remarks. The rate of acquisition of resistance to bedaquiline was similar between the two groups (11% in BDLLfxC and 9.1% in control). The evidence from the BEAT-TB trial is insufficient to draw definitive conclusions due to the small sample when stratified by fluoroquinolone resistance and related imprecision. Nonetheless, clinicians should remain vigilant and closely monitor the treatment response in this group of patients and promptly take relevant actions (extending the duration of treatment or changing the regimen). **Hepatitis C co-infection:** A prior WHO recommendation, based on expert evidence, applies to patients with MDR/RR-TB and hepatitis C virus (HCV) co-infection. WHO suggests co-administration of HCV and TB treatments rather than delaying HCV treatment until completion of MDR/RR-TB therapy *(conditional recommendation, very low certainty of evidence)*. **Malnutrition and underweight:** Patients with severe undernutrition, including those with a body mass index (BMI) below 15, were included in the trials. No subgroup-specific restrictions were identified based on nutritional status. (The trials did not include overweight participants) **Other causes of immunosuppression:** For patients with immunosuppression due to causes other than HIV, careful interpretation of the conditional recommendation is warranted, taking into account the underlying condition and clinical context

Implementation considerations
Programs should collect data while implementing the BPaL regimen.
Paediatric formulations
Availability of appropriate drug formulations for children should be ensured.
Regimen transitions
Clear programmatic guidance is needed to support transitions between regimens where clinically indicated.
Drug susceptibility testing
DST for fluoroquinolones is strongly encouraged in people with MDR/RR-TB. While DST should not delay initiation of the regimen, results should inform decisions on whether levofloxacin or clofazimine is retained in the regimen.
Linezolid dosing
Clear guidance and clinical expertise are required for appropriate linezolid dosing, and dose adjustments may be necessary.
Assessment of TB disease
Availability of chest radiography (CXR) should be ensured to support disease and severity assessment.
Capacity building
Health-care worker training is needed to support standardized assessment of disease severity.
Drug–drug interactions
Potential drug–drug interactions should be systematically assessed and managed.
Medicine supply
Reliable availability of all regimen components, including adequate buffer stocks, is required to prevent stock-outs and treatment interruptions.
Severity assessment
Standardized severity definition and assessment should be incorporated into implementation guidance.
Safety monitoring
Systems for routine monitoring and management of adverse events should be in place.
Additional considerations
For delamanid-based regimens, assessment of serum albumin levels should be considered.
Patient-centred approach
Efforts are required to provide patient support to enable full adherence to treatment. Access to mental health and psychosocial support services should be ensured. Consideration should also be given to insurance coverage and financing mechanisms.
Monitoring and evaluation
Systems should be in place to monitor disease recurrence and the emergence of drug resistance, particularly in cases of treatment failure or relapse.
Routine monitoring and management of adverse events are required.
For patients receiving BDLLC-containing regimens, regular QTc interval monitoring should be conducted.

Research priorities
The GDG discussed and identified the following research priorities relating to this recommendation
Interventions, populations and the balance of desirable and undesirable health effects:
Further research is needed to refine definitions of disease severity and the risk assessment model (RAM) to define severe and non-severe patients.
Additional evidence is required in children, including the safety and dosing of pretomanid (Pa) in those younger than 14 years.
More programmatic and real-world data are needed, including outcomes in key subpopulations such as individuals with malnutrition.
Research should evaluate biomarkers to individualize treatment duration irrespective of drug resistance profile or regimen.
Assessment of the efficacy and safety of lower linezolid doses
Identify predictors of disease recurrence.
Larger trials and programmatic data for BPaL and BPaLC regimens are required to further refine recommendations.
Studies assessing treatment completion, adherence support needs, and quality-of-life outcomes.
Values and preferences: Research is needed to evaluate patient values and preferences
Equity: There is a need for patient cost studies capturing both direct and indirect costs to better understand the financial burden of treatment, alongside the evaluation of equitable access to newer TB regimens across different populations
Resources: Effectiveness data from direct comparisons of regimens will be essential to inform cost-effectiveness and extended cost-effectiveness analyses, including the potential to reduce catastrophic costs for patients and households.
Acceptability: Studies assessing the acceptability of newer TB regimens among both patients and health-care providers, in conjunction with exploration of reasons for delayed uptake and implementation despite guideline recommendations, are needed.
Feasibility: Key feasibility concerns include barriers related to procurement and supply chains, implementation, and regulatory approvals

PICO 3 evidence profile

A BPaLC compared to the TB-PRACTECAL comparator regimens in patients with pulmonary pre-XDR-TB (PICO 3)

Bibliography:											
Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With the TB-PRACTECAL comparator regimens	With a BPaLC		Risk with the TB-PRACTECAL comparator regimens	Risk difference with a BPaLC
Failure and recurrence (both non-severe and severe) (follow-up: 108 weeks)											
258 (1 RCT)	not serious	not serious	serious[a]	very serious[b]	none	⨁◯◯◯ Very low[a,b]	40/143 (28.0%)	16/115 (13.9%)	**RR 0.50** (0.30 to 0.85)	40/143 (28.0%)	**138 fewer per 1000** (from 234 fewer to 41 fewer)[c]
Death (both non-severe and severe) (follow-up: 108 weeks)											
258 (1 RCT)	not serious	not serious	serious[a]	extremely serious[b]	none	⨁◯◯◯ Very low[a,b]	6/143 (4.2%)	1/115 (0.9%)	**RR 0.21** (0.03 to 1.28)	6/143 (4.2%)	**33 fewer per 1000** (from 81 fewer to 10 more)[d]
Lost to follow up during treatment (both non-severe and severe) (follow-up: 108 weeks)											
258 (1 RCT)	not serious	not serious	serious[a]	very serious[b]	none	⨁◯◯◯ Very low[a,b]	6/143 (4.2%)	10/115 (8.7%)	**RR 2.10** (0.78 to 5.64)	6/143 (4.2%)	**46 more per 1000** (from 16 fewer to 107 more)[d]
Adverse events (Grade 3–4) during treatment (both non-severe and severe) (follow-up: 108 weeks)											
258 (1 RCT)	serious[e]	not serious	serious[a]	very serious[b]	none	⨁◯◯◯ Very low[a,b,e]	69/143 (48.3%)	36/115 (31.3%)	**RR 0.64** (0.47 to 0.89)	69/143 (48.3%)	**172 fewer per 1000** (from 290 fewer to 55 fewer)[c]
Amplification of resistance to study drugs (both non-severe and severe) (follow-up: 108 weeks)											
258 (1 RCT)	not serious	not serious	serious[a]	not serious[b]	none	⨁⨁◯◯ Moderate[a,b]	0/143 (0.0%)	0/115 (0.0%)	not estimable	0/143 (0.0%)	**0 fewer per 1000** (from 26 fewer to 32 more)[d]

CI: confidence interval; **RR:** risk ratio

Explanations

a. A single trial. Serious indirectness (i) Populations: Differences in population of a trial and population to which guidelines will apply. (ii) Comparator: Some comparator regimens are sub-optimal, not according with the WHO standard of care (at the time or presently), and vary by country. Downgraded one level.

b. The number of participants in both intervention and comparator groups was small. Very few events in some outcomes of interest caused imprecision. We downgraded according to the number of decision thresholds crossed by the 95% confidence limits for each outcome.

c. Adjusted for baseline severity, prior TB, body mass index, age, HIV status and study site.

d. Not adjusted owing to small numbers of events.

e. Descriptive analyses were generally well-balanced. Small numbers of events in some outcomes precludes adjustment in some comparisons. We downgraded for risk of bias for outcomes where subjective assessment by unblinded individuals is possible (LTFU and AEs grade 3–4)

PICO 3 evidence-to-decision

Question	
Should a BPaLC vs. the TB-PRACTECAL comparator regimens be used for patients with pulmonary pre-XDR-TB (PICO 3)?	
POPULATION:	patients with pulmonary pre-XDR-TB (PICO 3)
INTERVENTION:	a BPaLC
COMPARISON:	the TB-PRACTECAL comparator regimens
MAIN OUTCOMES:	Failure and recurrence (both non-severe and severe) (follow-up: 108 weeks); Death (both non-severe and severe) (follow-up: 108 weeks); Lost to follow up during treatment (both non-severe and severe) (follow-up: 108 weeks); Adverse events (Grade 3–4) during treatment (both non-severe and severe) (follow-up: 108 weeks); Amplification of resistance to study drugs (both non-severe and severe) (follow-up: 108 weeks); Failure and relapse (both non-severe and severe, for MDR-TB (FQ-S and FQ-R) in BPaLC arm and MDR-TB (FQ-R only) in SOC (108 weeks); Death (both non-severe and severe TB, for MDR-TB (FQ-S and FQ-R) in BPaLC arm and MDR-TB (FQ-R only) in SOC (108 weeks); Loss to follow-up during treatment (both non-severe and severe TB, for MDR-TB (FQ-S and FQ-R) in BPaLC arm and MDR-TB (FQ-R only) in SOC (108 weeks); Adverse events (Grade 3–4 during treatment, both non-severe and severe TB, for MDR-TB (FQ-S and FQ-R) in BPaLC arm and MDR-TB (FQ-R only) in SOC (108 weeks); Amplification of resistance (both non-severe and severe TB, for MDR-TB (FQ-S and FQ-R) in BPaLC arm and MDR-TB (FQ-R only) in SOC (108 weeks);
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	This question addresses the effectiveness and safety of a 6-month BPaLC treatment regimen in patients with pulmonary pre-XDR-TB versus the current standard of care.
CONFLICT OF INTERESTS:	The WHO GTB Program applied the WHO conflict of interest declaration and management policy, and the following were GDG members involved in decision-making for this recommendation: Ashna Ashesh (WHO Civil Society Task Force – TB; Survivors Against TB, India), Erlina Burhan (Persahabatan Hospital Jakarta; Faculty of Medicine – Universitas Indonesia), Muhwa Chakaya (National Tuberculosis Programme of Kenya), Gerry Davies (University of Liverpool, United Kingdom), Fernanda Dockhorn Costa Johansen (Ministry of Health MDR-TB referral centre, Brazil), Kelly Dooley (Vanderbilt University Medical Center, USA), Sobia Faisal (Greenstar Social Marketing, Pakistan), Elmira Gurbanova (Lung Clinic, University of Tartu, Estonia), Eric Krakauer (Harvard Medical School, USA), Christoph Lange (Research Center Borstel, Germany), Yuhong Liu (Beijing Chest Hospital, China), Andrey Maryandyshev (Phthisiopulmonology Department of the Northern State Medical University, Arkhangelsk, Russian Federation), Graeme Meintjes (University of Cape Town, South Africa), Mahshid Nasehi (National Tuberculosis Programme of the Islamic Republic of Iran), Mamel Quelapio (Independent consultant, the Philippines), Moorine Sekkade (National Tuberculosis Programme of Uganda), Wei Sha (Shanghai Pulmonary Hospital, China), Urvashi Singh (National TB Programme, Ministry of Health, India), Shaheed Vally Omar (South Africa Supranational TB Reference Laboratory), Luan Vo (Friends for International Tuberculosis Relief, Viet Nam). No member of the GDG had important conflicts precluding participation.

Assessment

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Tuberculosis (TB) remains a threat to global public health and is one of the topmost infectious causes of death in the world. In 2024, an estimated 10.7 million people developed TB, and 1.23 million died from the disease. About 390,000 new patients with rifampicin-resistant or multidrug-resistant tuberculosis (MDR/RR-TB) were estimated to emerge in 2024. While all of these patients would have been eligible for a second-line TB treatment regimen, only 165,650 enrolments on treatment were reported by countries in the same year. In recent years, substantial progress has been made with the introduction of improved diagnostics and more effective medicines, enabling earlier detection and boosting treatment success rates among MDR/RR-TB patients in many national programs, with a 71% success rate reported for those enrolled in 2022. MDR-/RR-TB is treatable but requires different treatment regimen combinations that used to be longer than regimens for drug-susceptible TB and include medicines that are potentially more toxic. The interest in reducing the duration of treatment for MDR/RR-TB motivated a continuous search for shorter and safer regimens. The regimens for the treatment of MDR/RR-TB have changed dramatically in the past ten years. Before 2016, DR-TB regimens were 24 months or longer and included six or more months of daily intramuscular injections with significant adverse events. In 2016, based on data from observational studies of the shorter regimens in different Asian and African countries, WHO, for the first time, recommended a standardized 9-month regimen containing an injectable agent providing shorter than the extant 18–20 months standard of care for the eligible patients. Evidence of permanent effects attributed to the toxicity of injectable agents has prompted further advances in the development of new treatments, such as shorter injectable-sparing regimens. The all-oral 9-month bedaquiline-containing regimen was reviewed and recommended by WHO in 2019. The pressing need for more effective treatment regimens for patients with MDR/RR-TB, including those with fluoroquinolone resistance and more extensive drug-resistance profiles, has driven several studies and initiatives to test more effective and novel treatment regimens, including newer and repurposed medicines. The Nix-TB study conducted by TB Alliance pioneered the 6-month regimen that included bedaquiline and a new medicine – pretomanid, and the BPaL combination successfully received regulatory approval from the FDA. Two randomized controlled trials (RCTs) that concluded in 2021 (TB-PRACTECAL and ZeNix) provided new evidence and prompted assessment by WHO to develop new recommendations for wide programmatic use of the BPaLM/BPaL regimen for treatment MDR/RR-TB with or without resistance to fluoroquinolones. The latest evidence-based guidelines for the treatment and care of TB and drug-resistant TB, including MDR/RR-TB and pre-XDR-TB, were published by WHO in April 2025 – "WHO consolidated guidelines on tuberculosis: module 4: treatment and care". The WHO has combined all recommendations on the treatment of drug-resistant TB, drug-susceptible TB, and TB care and support in three separate chapters of the consolidated guidelines. The recommendation for use of another 6-month BDLLfxC regimen based on the evidence from the BEAT Tuberculosis trial in South Africa was included in the 2025 update.	**Information from a prior GDG (2022) meeting on sub-PICOs 6.4 stated the following and this information still applies:** The BPaLC regimen arm of the TB-PRACTECAL trial with population including patients with MDR/RR-TB with or without fluoroquinolone resistance (MDR/RR-TB or pre-XDR-TB) was compared to the comparator arm of the TB-PRACTECAL trial comprised of MDR/RR-TB or pre-XDR-TB patients treated with multiple local SoC regimens recommended by WHO at the time of trial conduct (including a 9–12-month injectable-containing regimen; 18–24-month WHO-recommended regimen [pre-2019]; 9–12-month all-oral regimen; and 18–20-month all-oral regimen). Primary analysis was undertaken at 72 weeks post treatment initiation. Participants with **MDR/RR-TB (with or without fluoroquinolone resistance)** receiving BPaLC (n=64) compared to participants receiving WHO-recommended SoC regimens used in the TB-PRACTECAL trial (n=66) experienced: • higher treatment success (81% vs 52%); that is, a 55% relative increase (aRR=1.55, 95% CI: 1.15 to 2.11); • lower levels of failure and recurrence (9.4% vs 26%); that is, a 66% relative reduction (aRR=0.34, 95% CI: 0.14 to 0.87); • lower levels of deaths (1.6% vs 3.0%); that is, a 48% relative reduction (RR=0.52, 95% CI: 0.07 to 3.85);

	Following the recent update of the WHO recommendations on DR-TB treatment, new or more complete evidence has become available from clinical trials or operational research on using combinations of medicines to treat MDR/RR-TB or pre-XDR-TB that a WHO-convened Guideline Development Group has not yet appraised. These regimens include the use of a new 6-month regimen including bedaquiline, delamanid, linezolid and clofazimine (endTB-Q and BEAT-TB South Africa trials) and the use of 6-month BPaL and BPaLC regimens (more complete data from the TB-PRATECAL trial and additional data from the operational research studies or programmatic implementation) for the treatment of patients with MDR/RR-TB with quinolone resistance. The evidence from these trials has been shared with WHO, and this guideline development group (GDG) is convened to review new evidence on the treatment and palliative care for patients with MDR/RR-TB or pre-XDR-TB to ensure that the latest treatment and care options are reflected in the WHO policy.	• lower levels of LTFU (7.8% vs 20%); that is, a 57% relative reduction (aRR=0.43, 95% CI: 0.15 to 1.23); • lower levels of grade 3 to 5 AEs (34% vs 51%); that is, a 33% relative reduction (aRR=0.67, 95% CI: 0.46 to 0.97); and • higher levels of amplified resistance (1.9% vs 1.9%); that is, a 4% relative increase (RR=1.04, 95% CI: 0.19 to 5.80). The GDG judged the benefits of BPaLC to be large and the undesirable effects to be trivial compared to WHO-recommended SoC regimens. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaLC. **Conclusion** The use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid and clofazimine (BPaLC) rather than a 9-month or longer (18-month) regimen is suggested in MDR/RR-TB patients with or without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month (overruled by conclusions of sub-PICO 6.5 and sub-PICO 6.6)

Desirable Effects

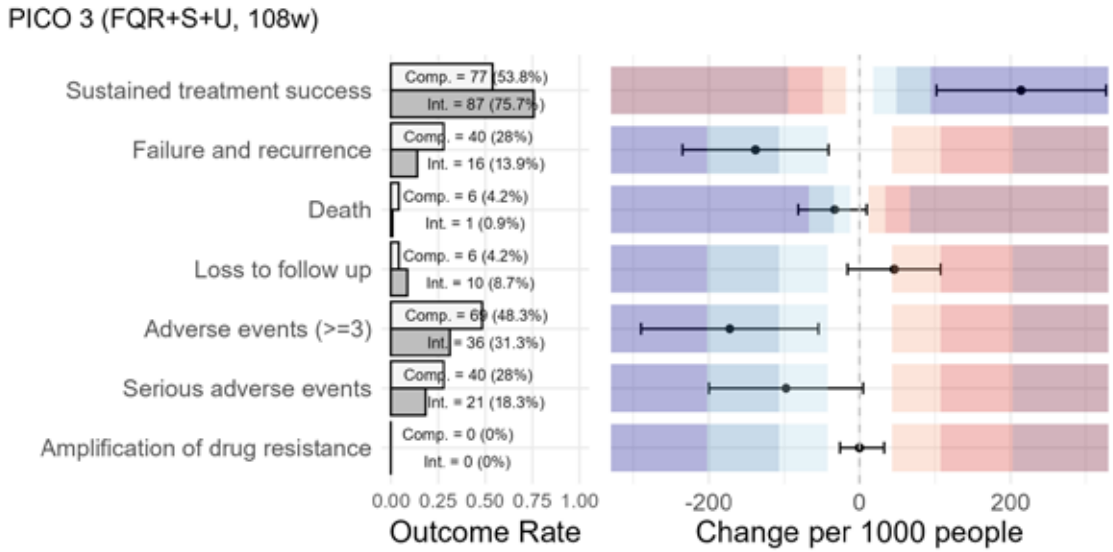
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	The BPaLC regimen arm of the TB-PRACTECAL trial, with a population including patients with MDR/RR-TB with or without fluoroquinolone resistance (MDR/RR-TB or pre-XDR-TB), was compared to the comparator arm comprised of MDR/RR-TB or pre-XDR-TB patients treated with multiple local SoC regimens recommended by WHO at the time of trial conduct (including a 9–12-month injectable-containing regimen; 18–24-month WHO-recommended regimen [pre-2019]; 9–12-month all-oral regimen; and 18–20-month all-oral regimen). Although the research question focused explicitly on pre-XDR-TB patients, the analysis included both MDR/RR and pre-XDR-TB patients in both groups to increase the sample size and improve statistical precision, as excluding fluoroquinolone-susceptible cases would have resulted in insufficiently small cohorts. In the intervention group, use of the BPaLC regimen, which does not include a fluoroquinolone, meant that fluoroquinolone susceptibility had no effect on treatment benefit, whereas in the comparator group, inclusion of fluoroquinolone susceptible patients allowed regimens that could potentially perform better, thereby biasing the comparison against the intervention rather than in its favour, which was acceptable given the objective to demonstrate the added benefit of the BPaLC regimen. Primary analysis was undertaken at 108 weeks post-treatment initiation. Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving BPaLC (n=115) compared to participants receiving WHO-recommended SoC regimens used in the TB-PRACTECAL trial (n=143) experienced: • lower levels of failure and recurrence (13.9% vs 28%); RD=138 fewer per 1000, 95% CI: 234 fewer to 41 fewer per 1000); • lower levels of deaths (0.9% vs 4.2%); RD=33 fewer per 1000, 95% CI: 81 fewer to 10 more per 1000); • higher levels of LTFU (8.7% vs 4.2%); RD=46 more per 1000, 95% CI: 16 fewer to 107 more per 1000); • lower levels of grade 3 to 5 AEs (31.3% vs 48.3%); RD=172 fewer per 1000, 95% CI: 290 fewer to 55 fewer per 1000); and • and similar levels of amplified resistance (0% vs 0%); RD=0 fewer per 1000, 95% CI: 26 fewer to 32 more per 1000).	Based on the thresholds for the prioritized outcomes listed below, the GDG judged the desirable effects of BPaLC compared to the TB-PRACTECAL regimento be large. Additional benefits include that: Treatment duration is reduced by 12–18 months, i.e. to 1/3 to 1/2 of duration of comparator regimen (6–9 months vs 18–24 months). Pill burden is significantly decreased 5–6 times (on average from 3'400 to 530). **Death** • Trivial Effect: ≤12 fewer or more events per 1000 people • Small Effect: 12 to 34 fewer or more events per 1000 people • Moderate Effect: 34 to 67 fewer or more events per 1000 people • Large Effect: >67 fewer or more events per 1000 people **Treatment Failure or Recurrence, lost to follow-up, adverse events and amplification (acquisition) of drug resistance** • Trivial Effect: ≤41 fewer or more events per 1000 people • Small Effect: 41 to 107 fewer or more events per 1000 people • Moderate Effect: 107 to 202 fewer or more events per 1000 people • Large Effect: >202 fewer or more events per 1000 people

Fig. Visual depiction of absolute effects in relation to the decision thresholds used by the GDG

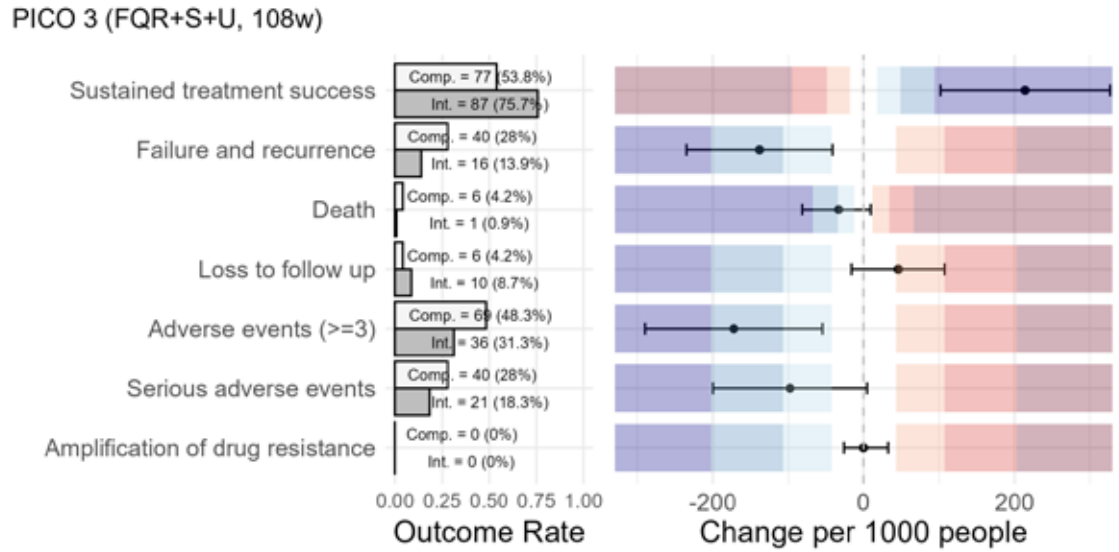
Decision threshold diagram

All



Undesirable Effects

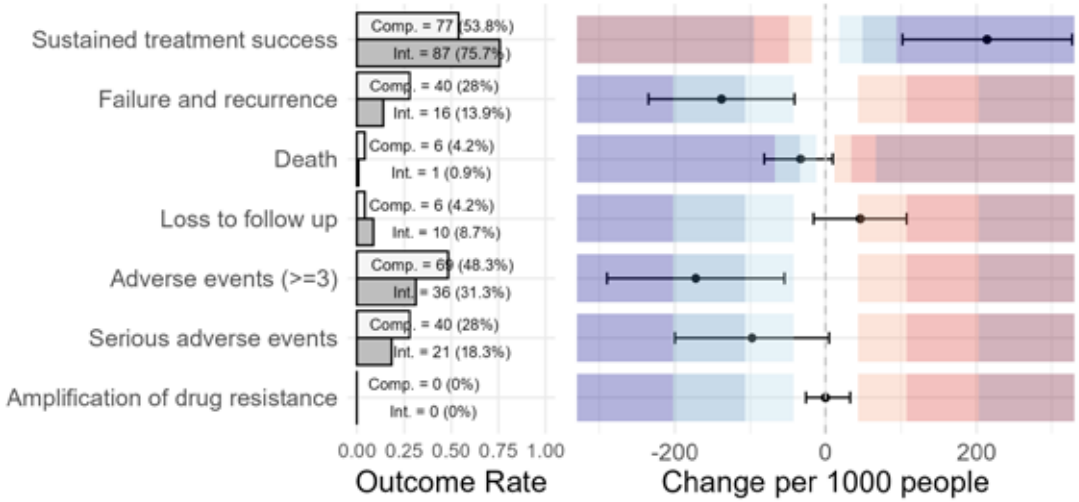
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	**All** 	Based on the thresholds for the prioritized outcomes listed below, the GDG judged the undesirable health effects of BPaLC compared to the TB-PRACTECAL regimen to be small.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	PICO 3 (FQR+S+U, 108w)	There was risk of bias due to lack of blinding of patients and caregivers, indirectness and very serious imprecision that lower the certainty in the evidence for several outcomes.



Summary of Findings for a BPaLC Versus the TB-PRACTECAL comparator regimens for patients with pulmonary pre-XDR-TB (PICO 3)							
Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			the TB-PRACTECAL comparator regimens	[a] BPaLC	Difference		
Failure and recurrence (both non-severe and severe) (follow-up: 108 weeks)	258 (1 RCT)	**RR = 0.50** (0.30 to 0.85)	280 per 1000	**139 per 1000 (-- to --)[a]**	**138 fewer per 1000** (from 234 fewer to 41 fewer) [a]	⨁◯◯◯ Very low[b,c]	
Death (both non-severe and severe) (follow-up: 108 weeks)	258 (1 RCT)	**RR = 0.21** (0.03 to 1.28)	42 per 1000	**9 per 1000 (-- to --)[d]**	**33 fewer per 1000** (from 81 fewer to 10 more)[d]	⨁◯◯◯ Very low[b,c]	
Lost to follow up during treatment (both non-severe and severe) (follow-up: 108 weeks)	258 (1 RCT)	**RR = 2.10** (0.78 to 5.64)	42 per 1000	**87 per 1000 (-- to --)[d]**	**46 more per 1000** (from 16 fewer to 107 more)[d]	⨁◯◯◯ Very low[b,c]	
Adverse events (Grade 3–4) during treatment (both non-severe and severe) (follow-up: 108 weeks)	258 (1 RCT)	**RR = 0.64** (0.47 to 0.89)	483 per 1000	**313 per 1000 (-- to --)[a]**	**172 fewer per 1000** (from 290 fewer to 55 fewer)[a]	⨁◯◯◯ Very low[b,c,e]	
Amplification of resistance to study drugs (both non-severe and severe) (follow-up: 108 weeks)	258 (1 RCT)	not estimable	0 per 1000	**-- per 1000 (-- to --)[d]**	**0 fewer per 1000** (from 26 fewer to 32 more)[d]	⨁⨁⨁◯ Moderate[b,c]	

CI: confidence interval; **RR:** risk ratio

a. Adjusted for baseline severity, prior TB, body mass index, age, HIV status and study site.

b. A single trial. Serious indirectness (i) Populations: Differences in population of a trial and population to which guidelines will apply. (ii) Comparator: Some comparator regimens are sub-optimal, not according with the WHO standard of care (at the time or presently), and vary by country. Downgraded one level.

c. The number of participants in both intervention and comparator groups was small. Very few events in some outcomes of interest caused imprecision. We downgraded according to the number of decision thresholds crossed by the 95% confidence limits for each outcome.

d. Not adjusted owing to small numbers of events.

e. Descriptive analyses were generally well-balanced. Small numbers of events in some outcomes precludes adjustment in some comparisons. We downgraded for risk of bias for outcomes where subjective assessment by unblinded individuals is possible (LTFU and AEs grade 3–4)

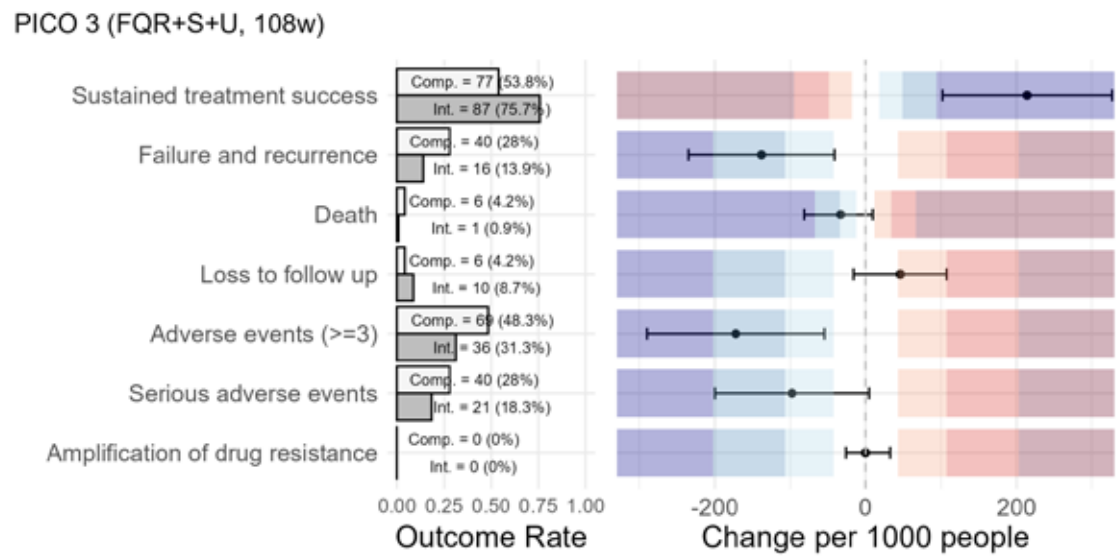
Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence was sought for.	The GDG noted that higher treatment efficacy, shorter duration of treatment, lower pill burden and less adverse events are usually valued by patients.

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know		The GDG judged the benefits of BPaLC to be large and the undesirable effects to be small compared to the WHO-recommended SoC regimens used in the TB-PRACTECAL trial. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaLC.

Summary of Findings for a BPaLC Versus the TB-PRACTECAL comparator regimens for patients with pulmonary pre-XDR-TB (PICO 3)							
Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			the TB-PRACTECAL comparator regimens	[a] BPaLC	Difference		
Failure and recurrence (both non-severe and severe) (follow-up: 108 weeks)	258 (1 RCT)	**RR = 0.50** (0.30 to 0.85)	280 per 1000	**139 per 1000 (-- to --)[a]**	**138 fewer per 1000** (from 234 fewer to 41 fewer) [a]	⨁◯◯◯ Very low[b,c]	
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Lost to follow up during treatment (both non-severe and severe) (follow-up: 108 weeks)	258 (1 RCT)	**RR = 2.10** (0.78 to 5.64)	42 per 1000	**87 per 1000 (-- to --)[d]**	**46 more per 1000** (from 16 fewer to 107 more)[d]	⨁◯◯◯ Very low[b,c]	
Adverse events (Grade 3–4) during treatment (both non-severe and severe) (follow-up: 108 weeks)	258 (1 RCT)	**RR = 0.64** (0.47 to 0.89)	483 per 1000	**313 per 1000 (-- to --)[a]**	**172 fewer per 1000** (from 290 fewer to 55 fewer)[a]	⨁◯◯◯ Very low[b,c,e]	
Amplification of resistance to study drugs (both non-severe and severe) (follow-up: 108 weeks)	258 (1 RCT)	not estimable	0 per 1000	**-- per 1000 (-- to --)[d]**	**0 fewer per 1000** (from 26 fewer to 32 more)[d]	⨁⨁⨁◯ Moderate[b,c]	

CI: confidence interval; **RR:** risk ratio

a. Adjusted for baseline severity, prior TB, body mass index, age, HIV status and study site.

b. A single trial. Serious indirectness (i) Populations: Differences in population of a trial and population to which guidelines will apply. (ii) Comparator: Some comparator regimens are sub-optimal, not according with the WHO standard of care (at the time or presently), and vary by country. Downgraded one level.

c. The number of participants in both intervention and comparator groups was small. Very few events in some outcomes of interest caused imprecision. We downgraded according to the number of decision thresholds crossed by the 95% confidence limits for each outcome.

d. Not adjusted owing to small numbers of events.

e. Descriptive analyses were generally well-balanced. Small numbers of events in some outcomes precludes adjustment in some comparisons. We downgraded for risk of bias for outcomes where subjective assessment by unblinded individuals is possible (LTFU and AEs grade 3–4)

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ● Large savings ○ Varies ○ Don't know	Cost of medicines: 6BPaLC – $338 • Assumes LZD 600 mg daily through the entire treatment • Usual dosing for all other meds • 26 weeks duration 9BPaLC – $499 • Assumes 9 months of BDQ using "usual" dosing and LZD 600 mg daily through the entire treatment • Usual dosing for pretomanid • 39 weeks duration Healthcare and patient costs:	The GDG judged the differentially associated cost of BPaLC compared to the 18-month regimen to lead to large savings for health systems.

Drug cost

BPaLC	
6m	US$ 338
9m	US$ 499

18M regimen	
without Dlm	US$ 795
with Dlm	US$ 1195

Non-drug cost

	BPaLC per 6 months		
	Patient	Health system	Total
India	966	174	**1140**
Philippines	1043	468	**1511**
South Africa	824	1,284	**2108**

	18M Regimen per 18 months		
	Patient	Health system	Total
India	2502	522	**3024**
Philippines	2951	1404	**4355**
South Africa	2192	3852	**6044**

Cost difference DRUG + NON-DRUG cost			Comment
From	US$ 644	less	BPaLC for 9m vs 18m regimen w/o Dlm; health systems cost only; 9m BPaL; India
To	US$ 4793	less	BPaLC for 6m vs 18m regimen w Dlm; health systems & patient cost; 6m BPaL; South Africa

Cost difference in DRUG cost			Comment
From	US$ 296	less	BPaLC for 9m vs 18m regimen w/o Dlm
To	US$ 857	less	BPaLC for 6m vs 18m regimen w Dlm

Cost difference in NON-DRUG cost			Comment
From	US$ 348	less	health systems cost only; 9m BPaLC; India
To	US$ 3936	less	health systems cost & patient cost; 6m BPaLC; South Africa

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The drug prices for the regimens were elicited from the Stop TB Partnership Global Drug Facility and health system and patient costs in the three settings were estimated based on data from an economic modelling analysis (Ryckman et al. 2024) and extrapolated to the 3-month time period for the difference in the treatment durations. The estimated costs from the economic modelling analysis do not account for possible imprecision in the cost estimates and provide indirect data for other settings where the BEAT-TB treatment regimen would be used. Thus, the certainty in this evidence is low.	

Cost effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ No included studies	**Sweeney et al., 2022.** Multi-country cost-effectiveness model. BPaL and BPaLM were likely cost-saving and more effective than standard of care in a range of settings. BPaL often the most cost-saving**. PMC** **James et al., 2024 / PubMed.** Modelled lifetime costs, found 6-month BPaLM cost-effective versus standard care, with substantial per-person cost reductions in base case**. PubMed** **Country economic analyses and modelling (examples**). India and Philippines analyses found BPaL/BPaLM cost-saving or highly cost-effective under local assumptions. See India modelling (2025) and Philippines study (2024)**. Cambridge Core** **PLOS Global Public Health, 2025.** Analysis of impact of fluoroquinolone resistance on cost-effectiveness. Concludes BPaLM can be cost-effective in empirical settings and may replace BPaL depending on resistance prevalence**. PLOS Journals**	Given that the balance of effects probably favours the intervention and that BPaLC leads to large savings, the GDG judged that the cost-effectiveness of the intervention probably favours the intervention.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence searched for.	The panel considered the treatment duration and the ability to decentralize treatment (to enable access for remote, underserviced settings and disadvantaged populations) to affect equity. Despite not being able to identify relevant research evidence, the panel used their collective experience to judge that there would likely be advantages associated with the use of the BPaLC regimen due to its reduced complexity and shorter duration. The panel judged that use of the BPaLC regimen would probably increase equity.

Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	One study found that acceptability: overall high and rated as acceptable by >80% across domains **van de Berg et al., BMC Public Health, 2021.** Multi-country qualitative study of stakeholders in Indonesia, Kyrgyzstan, Nigeria. Found high acceptability and willingness to implement BPaL despite system constraints. BioMed Central **KNCV / TB Alliance operational report, 2021.** Acceptability and feasibility study in three high-burden countries, similar conclusions: stakeholders and patients generally positive about BPaL adoption. kncvtbplus.com	Acceptability was considered by the 2022 GDG for related evidence. Based on considerations of the previous GDG and new assessments, the GDG considered patients, health care providers and the health system as key intest-holders. For people living with Tb, the panel considered the following aspects as critical with regards to acceptability: regimen duration and drug safety monitoring needs (both relating to necessary travel, loss of income and general disruption of the life of patients; workload for the health care system), needs for drug susceptibility testing. The panel judged that the BPaLC regimen would probably be acceptable for patients, providers and policy-makers.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The GDG also reviewed data from programmatic sites in Belarus (n=261) and Uzbekistan (n=42). The majority of patients had pre-XDR TB and were treated with the BPaLC regimen. Treatment was delivered under routine programmatic conditions. Outcomes were broadly consistent with those observed in clinical trial settings, supporting the feasibility of BPaLC implementation in routine care.	The GDG considered the following aspects to affect feasibility (i.e. to be potential barriers to implementation): requirements for drug safety monitoring and requirements for drug susceptibility testing. The panel noted limited availability of drugs in the BPaLC regimen for use in DST as a potential barriers to implementation and also noted that data on the critical concentration of Pretomanid for use in DST is limited. However, given the reduced duration, complexity and associated workload, the panel judged that implementation is probably feasible. Data from the MSF operational reasearch cohorts in Uzbekistan and Belarus to be added.

Outcome	Belarus		Uzbekistan	
	n	*(%)*	*n*	*(%)*
Total included	**261**	**(0)**	**42**	**(0)**
Treatment success	**220**	**(84)**	**36**	**(86)**
Cure	**193**	**(74)**	**35**	**(83)**
Treatment complete	**27**	**(10)**	**1**	**(2)**
Loss to follow up	**14**	**(5)**	**0**	**(0)**
Failure	**6**	**(2)**	**0**	**(0)**
Death	**17**	**(7)**	**2**	**(5)**

Summary of judgements

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	**Large savings**	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	•	○

Conclusions

Recommendation
The use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid and clofazimine (BPaLC) rather than a longer (18-month) regimen is suggested in pre-XDR-TB patients, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month *(conditional recommendation, very low certainty)*.
Justification
The GDG judged the benefits of BPaLC to be large and the undesirable effects to be small compared to the WHO-recommended SoC regimens used in the TB-PRACTECAL trial. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaLC.
Subgroup considerations
The panel identified subpopulations of people who might be affected differently than most by this recommendation; these subpopulations were PLHIV, children, pregnant women, breastfeeding women, and patients with extensive TB disease. The recent new recommendation for the use of bedaquiline in children with MDR/RR-TB aged below 6 years was considered *(29)*. The panel noted specific considerations for the subpopulations listed below.
People living with HIV
No restrictions were identified for the use of the intervention among people living with HIV.
Children and adolescents
Trial evidence included participants aged ≥14 years.
Pregnant and breastfeeding women
No restrictions were identified for the drug Delamanid. Use of the drug Pretomanid is restricted due to limited safety data in this population
Extensive TB disease (based on the endTB-Q trial definition)
Patients with DR-TB who have extensive disease face greater challenges in treatment across all regimens and are at a higher risk of unfavourable outcomes and amplification of drug resistance. This risk is further elevated in those infected with pathogens that have advanced resistance profiles, particularly with additional resistance to fluoroquinolones. These patients may experience slightly worse outcomes compared to those without pre-XDR and develop resistance to regimen components. In the BEAT-TB trial among patients with pre-XDR-TB, the outcomes also appeared worse than among those who were fluoroquinolone susceptible. This reduction in the proportion with successful treatment outcomes was numerically greater in the BDLLfxC arm than in the control arm (14.3% vs 3.3%); however, this difference was within the range of statistical uncertainty, and the GDG judged that this should not affect the recommendation or remarks. The rate of acquisition of resistance to bedaquiline was similar between the two groups (11% in BDLLfxC and 9.1% in control). The evidence from the BEAT-TB trial is insufficient to draw definitive conclusions due to the small sample when stratified by fluoroquinolone resistance and related imprecision. Nonetheless, clinicians should remain vigilant and closely monitor the treatment response in this group of patients and promptly take relevant actions (extending the duration of treatment or changing the regimen).
Hepatitis C co-infection
A prior WHO recommendation, based on expert evidence, applies to patients with MDR/RR-TB and hepatitis C virus (HCV) co-infection. WHO suggests co-administration of HCV and TB treatments rather than delaying HCV treatment until completion of MDR/RR-TB therapy *(conditional recommendation, very low certainty of evidence)*.
Malnutrition and underweight
Patients with severe undernutrition, including those with a body mass index (BMI) below 15, were included in the trials. No subgroup-specific restrictions were identified based on nutritional status. (The trials did not include overweight participants)
Other causes of immunosuppression
For patients with immunosuppression due to causes other than HIV, careful interpretation of the conditional recommendation is warranted, taking into account the underlying condition and clinical context

Implementation considerations
Paediatric formulations
Availability of appropriate drug formulations for children should be ensured.
Regimen transitions
Clear programmatic guidance is needed to support transitions between regimens where clinically indicated.
Drug susceptibility testing
DST for fluoroquinolones is strongly encouraged in people with MDR/RR-TB. While DST should not delay initiation of the BDLLfxC regimen, results should inform decisions on whether levofloxacin or clofazimine is retained in the regimen.
Linezolid dosing
Clear guidance and clinical expertise are required for appropriate linezolid dosing, and dose adjustments may be necessary.
Assessment of TB disease
Availability of chest radiography (CXR) should be ensured to support disease and severity assessment.
Capacity building
Health-care worker training is needed to support standardized assessment of disease severity.
Drug–drug interactions
Potential drug–drug interactions should be systematically assessed and managed.
Medicine supply
Reliable availability of all regimen components, including adequate buffer stocks, is required to prevent stock-outs and treatment interruptions.
Severity assessment
Standardized severity definition and assessment should be incorporated into implementation guidance.
Safety monitoring
Systems for routine monitoring and management of adverse events should be in place.
Additional considerations
For delamanid-based regimens, assessment of serum albumin levels should be considered.
Patient-centred approach
Efforts are required to provide patient support to enable full adherence to treatment. Access to mental health and psychosocial support services should be ensured. Consideration should also be given to insurance coverage and financing mechanisms.
Monitoring and evaluation
Systems should be in place to monitor disease recurrence and the emergence of drug resistance, particularly in cases of treatment failure or relapse.
Routine monitoring and management of adverse events are required.

Research priorities
The GDG discussed and identified the following research priorities relating to this recommendation.
Interventions, populations and the balance of desirable and undesirable health effects:
Further research is needed to refine definitions of disease severity and the risk assessment model (RAM) to define severe and non-severe patients.
Direct comparative trials of BDLC versus BPaLC in patients with severe disease are a priority, including evaluation of optimal treatment duration in this subgroup.
Additional evidence is required in children, including the safety and dosing of pretomanid (Pa) in those younger than 14 years.
More programmatic and real-world data are needed, including outcomes in key subpopulations such as individuals with malnutrition.
Research should evaluate biomarkers to individualize treatment duration irrespective of drug resistance profile or regimen.
Assessment of the efficacy and safety of lower linezolid doses.
Identify predictors of disease recurrence.
Larger trials and programmatic data for BPAL and BPALC regimens are required.
Studies assessing treatment completion, adherence support needs, and quality-of-life outcomes.
Values: Additional research is needed to obtain higher certainty in patient values related to the outcomes of interest.
Equity: Judgments about equity will be better informed by studies that capture both direct and indirect patient costs to better understand the financial burden of treatment, alongside the evaluation of equitable access to newer TB regimens across different populations.
Resources: Effectiveness data from direct comparisons of regimens will be essential to inform cost-effectiveness and extended cost-effectiveness analyses, including the potential to reduce catastrophic costs for patients and households.
Acceptability: Studies assessing the acceptability of newer TB regimens among both patients and health-care providers, in conjunction with exploration of reasons for delayed uptake and implementation despite guideline recommendations, are needed.
Feasibility: Key feasibility concerns include barriers related to procurement and supply chains, regulatory approvals, and limitations in diagnostic and monitoring capacity.

PICO 6a evidence profile

A BPaLC compared to the BPaL in patients with non-severe pulmonary pre-XDR-TB (PICO 6a)

Bibliography:											
Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With the BPaL	With a BPaLC		Risk with the BPaL	Risk difference with a BPaLC
Failure and recurrence (non-severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)											
91 (1 RCT)	not serious	not serious	serious[a]	serious[b]	none	⨁⨁◯◯ Low[a,b]	1/46 (2.2%)	9/45 (20.0%)	**RR 9.20** (1.61 to 55.15)	1/46 (2.2%)	**178 more per 1000** (from 59 more to 321 more)[c]
Death (non-severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)											
91 (1 RCT)	not serious	not serious	serious[a]	serious[b]	none	⨁⨁◯◯ Low[a,b]	1/46 (2.2%)	0/45 (0.0%)	**RR 0.00** (0.00 to 3.86)	1/46 (2.2%)	**22 fewer per 1000** (from 114 fewer to 59 more)[d]
Lost to follow up during treatment (non-severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)											
91 (1 RCT)	not serious	not serious	serious[a]	serious[b]	none	⨁⨁◯◯ Low[a,b]	4/46 (8.7%)	6/45 (13.3%)	**RR 1.53** (0.46 to 5.07)	4/46 (8.7%)	**46 more per 1000** (from 82 fewer to 175 more)[d]
Adverse events (Grade 3–4) during treatment (non-severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)											
91 (1 RCT)	not serious	not serious	serious[a]	serious[b]	none	⨁⨁◯◯ Low[a,b]	11/46 (23.9%)	15/45 (33.3%)	**RR 1.39** (0.72 to 2.70)	11/46 (23.9%)	**94 fewer per 1000** (from 91 fewer to 279 more)[d]
Amplification of resistance to study drugs (non-severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)											
91 (1 RCT)	not serious	not serious	serious[a]	serious[b]	none	⨁⨁◯◯ Low[a,b]	0/46 (0.0%)	0/45 (0.0%)	not estimable	0/46 (0.0%)	**0 fewer per 1000** (from 78 fewer to 80 more)[d]

CI: confidence interval; **RR:** risk ratio

Explanations

a. A single trial. Serious indirectness (i) Populations: Differences in population of a trial and population to which guidelines will apply. (ii) Comparator: Some comparator regimens are sub-optimal, not according with the WHO standard of care (at the time or presently), and vary by country. Downgraded one level.

b. The number of participants in both intervention and comparator groups was small. Very few events in the outcomes of interest, causing serious or very serious imprecision. We downgraded two levels for imprecision for some outcomes, and one level for others

c. Adjusted for baseline severity, prior TB, body mass index, age, HIV status and study site.

d. Not adjusted owing to small numbers of events.

PICO 6a evidence-to-decision

Question	
Should a BPaLC vs. the BPaL be used for patients with non-severe pulmonary pre-XDR-TB (PICO 6a)?	
POPULATION:	patients with non-severe pulmonary pre-XDR-TB (PICO 6a)
INTERVENTION:	a BPaLC
COMPARISON:	the BPaL
MAIN OUTCOMES:	Failure and recurrence (non-severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R); Death (non-severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R); Lost to follow up during treatment (non-severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R); Adverse events (Grade 3–4) during treatment (non-severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R); Amplification of resistance to study drugs (non-severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R); Failure and recurrence (both non-severe and severe) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R); Death (both non-severe and severe) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R); Lost to follow up during treatment (both non-severe and severe) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R); Adverse events (Grade 3–4) during treatment (both non-severe and severe) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R); Amplification of resistance to study drugs (both non-severe and severe) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R);
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation – population perspective
BACKGROUND:	This question addresses the effectiveness and safety of a 6-month BPaLC treatment regimen in patients with non-severe pulmonary pre-XDR-TB versus BPaL regimen.
CONFLICT OF INTERESTS:	The WHO GTB Program applied the WHO conflict of interest declaration and management policy, and the following were GDG members involved in decision-making for this recommendation: Ashna Ashesh (WHO Civil Society Task Force – TB; Survivors Against TB, India), Erlina Burhan (Persahabatan Hospital Jakarta; Faculty of Medicine – Universitas Indonesia), Muhwa Chakaya (National Tuberculosis Programme of Kenya), Gerry Davies (University of Liverpool, United Kingdom), Fernanda Dockhorn Costa Johansen (Ministry of Health MDR-TB referral centre, Brazil), Kelly Dooley (Vanderbilt University Medical Center, USA), Sobia Faisal (Greenstar Social Marketing, Pakistan), Elmira Gurbanova (Lung Clinic, University of Tartu, Estonia), Eric Krakauer (Harvard Medical School, USA), Christoph Lange (Research Center Borstel, Germany), Yuhong Liu (Beijing Chest Hospital, China), Andrey Maryandyshev (Phthisiopulmonology Department of the Northern State Medical University, Arkhangelsk, Russian Federation), Graeme Meintjes (University of Cape Town, South Africa), Mahshid Nasehi (National Tuberculosis Programme of the Islamic Republic of Iran), Mamel Quelapio (Independent consultant, the Philippines), Moorine Sekkade (National Tuberculosis Programme of Uganda), Wei Sha (Shanghai Pulmonary Hospital, China), Urvashi Singh (National TB Programme, Ministry of Health, India), Shaheed Vally Omar (South Africa Supranational TB Reference Laboratory), Luan Vo (Friends for International Tuberculosis Relief, Viet Nam). No member of the GDG had important conflicts precluding participation.

Assessment

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Tuberculosis (TB) remains a threat to global public health and is one of the topmost infectious causes of death in the world. In 2024, an estimated 10.7 million people developed TB, and 1.23 million died from the disease. About 390,000 new patients with rifampicin-resistant or multidrug-resistant tuberculosis (MDR/RR-TB) were estimated to emerge in 2024. While all of these patients would have been eligible for a second-line TB treatment regimen, only 165,650 enrolments on treatment were reported by countries in the same year. In recent years, substantial progress has been made with the introduction of improved diagnostics and more effective medicines, enabling earlier detection and boosting treatment success rates among MDR/RR-TB patients in many national programs, with a 71% success rate reported for those enrolled in 2022. MDR-/RR-TB is treatable but requires different treatment regimen combinations that used to be longer than regimens for drug-susceptible TB and include medicines that are potentially more toxic. The interest in reducing the duration of treatment for MDR/RR-TB motivated a continuous search for shorter and safer regimens. The regimens for the treatment of MDR/RR-TB have changed dramatically in the past ten years. Before 2016, DR-TB regimens were 24 months or longer and included six or more months of daily intramuscular injections with significant adverse events. In 2016, based on data from observational studies of the shorter regimens in different Asian and African countries, WHO, for the first time, recommended a standardized 9-month regimen containing an injectable agent providing shorter than the extant 18–20 months standard of care for the eligible patients. Evidence of permanent effects attributed to the toxicity of injectable agents has prompted further advances in the development of new treatments, such as shorter injectable-sparing regimens. The all-oral 9-month bedaquiline-containing regimen was reviewed and recommended by WHO in 2019. The pressing need for more effective treatment regimens for patients with MDR/RR-TB, including those with fluoroquinolone resistance and more extensive drug-resistance profiles, has driven several studies and initiatives to test more effective and novel treatment regimens, including newer and repurposed medicines. The Nix-TB study conducted by TB Alliance pioneered the 6-month regimen that included bedaquiline and a new medicine – pretomanid, and the BPaL combination successfully received regulatory approval from the FDA. Two randomized controlled trials (RCTs) that concluded in 2021 (TB-PRACTECAL and ZeNix) provided new evidence and prompted assessment by WHO to develop new recommendations for wide programmatic use of the BPaLM/BPaL regimen for treatment MDR/RR-TB with or without resistance to fluoroquinolones. The latest evidence-based guidelines for the treatment and care of TB and drug-resistant TB, including MDR/RR-TB and pre-XDR-TB, were published by WHO in April 2025 – "WHO consolidated guidelines on tuberculosis: module 4: treatment and care". The WHO has combined all recommendations on the treatment of drug-resistant TB, drug-susceptible TB, and TB care and support in three separate chapters of the consolidated guidelines. The recommendation for use of another 6-month BDLLfxC regimen based on the evidence from the BEAT Tuberculosis trial in South Africa was included in the 2025 update.	**Information from a prior GDG (2022) meeting on sub-PICOs 6.5 stated the following and this information still applies:** **Sub-PICO 6.5** The BPaLC regimen arm of the TB-PRACTECAL trial with a population including patients with MDR/RR-TB **with or without fluoroquinolone resistance (MDR/RR-TB or pre-XDR-TB**) was compared with the BPaL arm of the TB-PRACTECAL trial that comprised MDR/RR-TB or pre-XDR-TB patients. Primary analysis was undertaken at 72 weeks post treatment initiation. Participants with pulmonary MDR/RR-TB or pre-XDR-TB receiving BPaLC (n=64) compared with participants receiving BPaL 600–300 (n=60) experienced: • higher levels of treatment success (81% vs 77%); that is, a 4% relative increase (aRR=1.04, 95% CI: 0.84 to 1.30); • lower levels of failure and recurrence (9.4% vs 13%); that is, a 14% relative reduction (aRR=0.86, 95% CI: 0.28 to 2.69); • higher levels of deaths (1.6% vs 0%); that is, a 2% absolute increase (RD=0.02, 95% CI: –0.05 to 0.08); • lower levels of LTFU (7.8% vs 10%); that is, a 28% relative reduction (aRR=0.72, 95% CI: 0.21 to 2.47); • higher levels of AEs (34% vs 20%); that is, a 64% relative increase (aRR=1.64, 95% CI: 0.97 to 2.79); and • lower levels of amplification of drug resistance (1.9% vs 2.9%); that is, a 35% relative reduction (RR=0.65, 95% CI: 0.13 to 3.21).

Following the recent update of the WHO recommendations on DR-TB treatment, new or more complete evidence has become available from clinical trials or operational research on using combinations of medicines to treat MDR/RR-TB or pre-XDR-TB that a WHO-convened Guideline Development Group has not yet appraised. These regimens include the use of a new 6-month regimen including bedaquiline, delamanid, linezolid and clofazimine (endTB-Q and BEAT-TB South Africa trials) and the use of 6-month BPaL and BPaLC regimens (more complete data from the TB-PRATECAL trial and additional data from the operational research studies or programmatic implementation) for the treatment of patients with MDR/RR-TB with quinolone resistance.

The evidence from these trials has been shared with WHO, and this guideline development group (GDG) is convened to review new evidence on the treatment and palliative care for patients with MDR/RR-TB or pre-XDR-TB to ensure that the latest treatment and care options are reflected in the WHO policy.

The GDG judged both the desirable and the undesirable effects of BPaLC to be small compared with BPaL. The certainty of evidence was judged to be very low. The balance of health effects did not favour either the intervention or the comparator; however, taking into consideration the higher cost of the regimen, increased pill burden, reduced acceptability due to skin discolouration and other potential adverse effects related to clofazimine without noticeable net benefit in terms of health effects, the panel judged against the intervention.

Conclusion

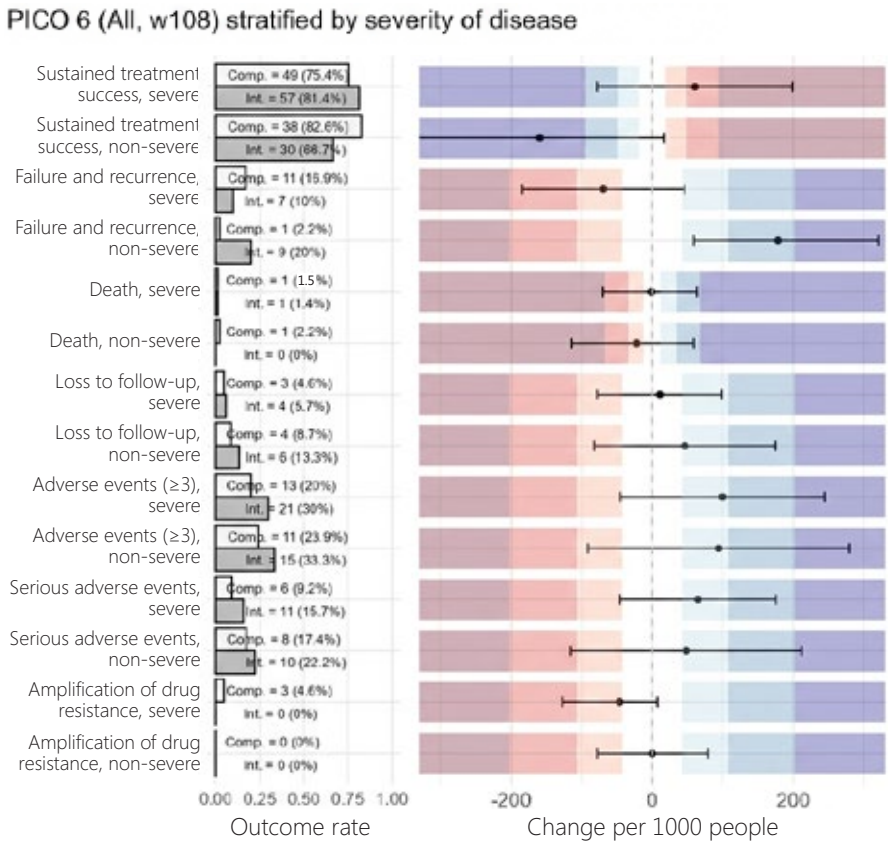
The use of the 6-month treatment regimen composed of bedaquiline, pretomanid and linezolid (BPaL) rather than BPaLC is suggested in MDR/RR-TB patients with or without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	The BPaLC regimen arm of the TB-PRACTECAL trial with a population including patients with MDR/RR-TB or pre-XDR-TB was compared with the BPaL arm of the TB-PRACTECAL trial that comprised MDR/RR-TB or pre-XDR-TB patients. Primary analysis was undertaken at 108 weeks post treatment initiation. The patient cohort was stratified into those with non-severe and severe pre-XDR-TB. Participants with non-severe pulmonary MDR/RR-TB or pre-XDR-TB receiving BPaLC (*n*=115) compared with participants receiving BPaL (*n*=111) experienced: Participants with non-severe pulmonary MDR/RR-TB or pre-XDR-TB receiving BPaLC (*n*=45) compared with participants receiving BPaL (*n*=46) experienced: • higher levels of failure and recurrence (20% vs 2.2%); RD=178 more per 1000, 95% CI: 59 more to 321 more per 1000); • lower levels of deaths (0% vs 2.2%); RD=22 fewer per 1000, 95% CI: 114 fewer to 59 more per 1000); • higher levels of LTFU (13.3% vs 8.7%); RD=46 more per 1000, 95% CI: 82 fewer to 175 more per 1000); • higher levels of AEs (33.3% vs 23.9%); RD=94 more per 1000, 95% CI: 91 fewer to 279 more per 1000); and • similar levels of amplification of drug resistance (0% vs 0%); RD=0 per 1000, 95% CI: 78 fewer to 80 more per 1000).	Based on the thresholds for the prioritized outcomes listed below, the GDG judged the undesirable health effects of BPaLC compared to BPaL to be trivial in patients with non-severe pre-XDR-TB. **Death** • Trivial Effect: ≤12 fewer or more events per 1000 people • Small Effect: 12 to 34 fewer or more events per 1000 people • Moderate Effect: 34 to 67 fewer or more events per 1000 people • Large Effect: >67 fewer or more events per 1000 people

Decision threshold diagram



Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with the BPaL	Risk difference with a BPaLC
Death (non-severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	91 (1 RCT)	⨁⨁◯◯ Low[a,b]	**RR 0.00** (0.00 to 3.86)	Study population	
				22 per 1000	**22 fewer per 1000** (22 fewer to 62 more)
Amplification of resistance to study drugs (non-severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	91 (1 RCT)	⨁⨁◯◯ Low[a,b]	not estimable	Study population	
				0 per 1000	**0 fewer per 1000** (0 fewer to 0 fewer)

Treatment Failure or Recurrence, lost to follow-up, adverse events and amplification (acquisition) of drug resistance

- Trivial Effect: ≤41 fewer or more events per 1000 people
- Small Effect: 41 to 107 fewer or more events per 1000 people
- Moderate Effect: 107 to 202 fewer or more events per 1000 people
- Large Effect: >202 fewer or more events per 1000 people

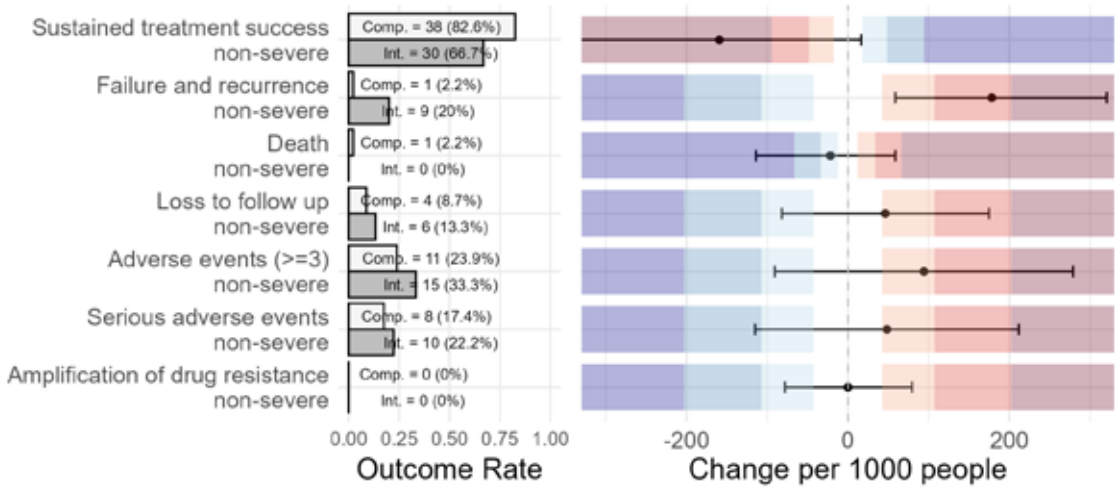
a. A single trial. Serious indirectness (i) Populations: Differences in population of a trial and population to which guidelines will apply. (ii) Comparator: Some comparator regimens are sub-optimal, not according with the WHO standard of care (at the time or presently), and vary by country. Downgraded one level.

b. The number of participants in both intervention and comparator groups was small. Very few events in the outcomes of interest, causing serious or very serious imprecision. We downgraded two levels for imprecision for some outcomes, and one level for others

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	PICO 6 (All, w108) Non-severe	Based on the thresholds for the prioritized outcomes listed below, the GDG judged the undesirable health effects of BPaLC compared to BPaL to be moderate for patients with non-severe pre-XDR-TB. **Treatment Failure or Recurrence, lost to follow-up, adverse events and amplification (acquisition) of drug resistance** • Trivial Effect: ≤41 fewer or more events per 1000 people • Small Effect: 41 to 107 fewer or more events per 1000 people • Moderate Effect: 107 to 202 fewer or more events per 1000 people • Large Effect: >202 fewer or more events per 1000 people



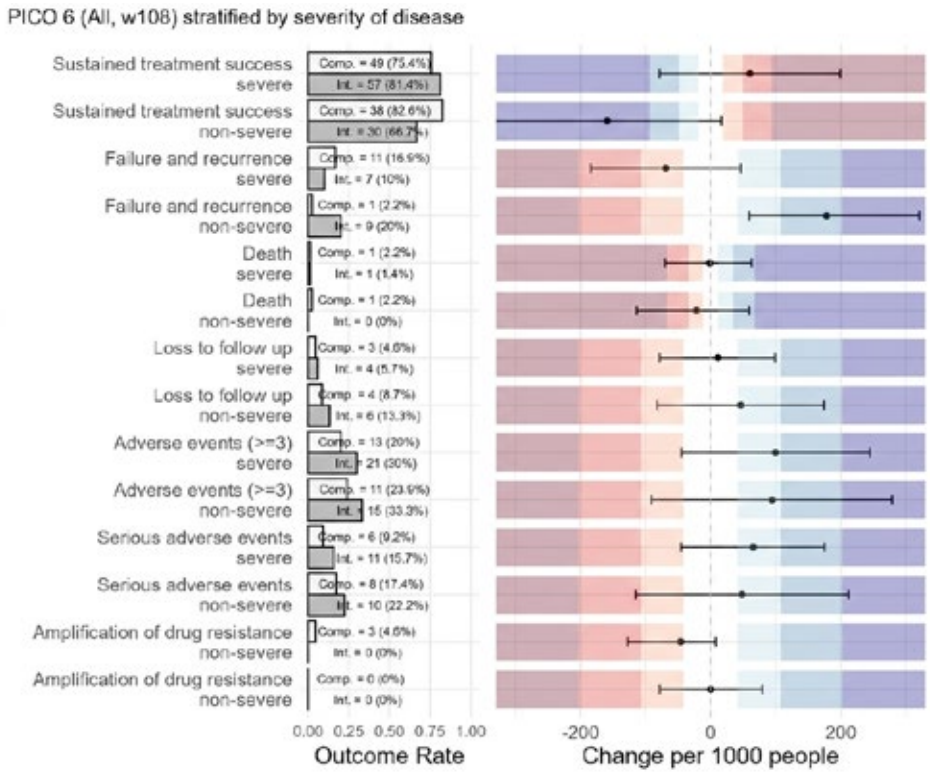
Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with the BPaL	Risk difference with a BPaLC
Failure and recurrence (non-severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	91 (1 RCT)	⨁⨁◯◯ Low[a,b]	**RR 9.20** (1.61 to 55.15)	Study population	
				22 per 1000	**178 more per 1000** (13 more to 1,177 more)
Lost to follow up during treatment (non-severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	91 (1 RCT)	⨁⨁◯◯ Low[a,b]	**RR 1.53** (0.46 to 5.07)	Study population	
				87 per 1000	**46 more per 1000** (47 fewer to 354 more)
Adverse events (Grade 3–4) during treatment (non-severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	91 (1 RCT)	⨁⨁◯◯ Low[a,b]	**RR 1.39** (0.72 to 2.70)	Study population	
				239 per 1000	**93 more per 1000** (67 fewer to 407 more)

a. A single trial. Serious indirectness (i) Populations: Differences in population of a trial and population to which guidelines will apply. (ii) Comparator: Some comparator regimens are sub-optimal, not according with the WHO standard of care (at the time or presently), and vary by country. Downgraded one level.

b. The number of participants in both intervention and comparator groups was small. Very few events in the outcomes of interest, causing serious or very serious imprecision. We downgraded two levels for imprecision for some outcomes, and one level for others

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		There was risk of bias due to lack of blinding of patients and caregivers, indirectness and very serious imprecision that lower the certainty in the evidence for several outcomes. Imprecision was exacerbated by dividing into subgroups of severe and non-severe.

Summary of Findings for a BPaLC Versus the BPaL for patients with non-severe pulmonary pre-XDR-TB (PICO 6a)							
Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			the BPaL	a BPaLC	Difference		
Failure and recurrence (non-severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	91 (1 RCT)	**RR = 9.20** (1.61 to 55.15)	22 per 1000	**200 per 1000** (-- to --)[a]	**178 more per 1000** (from 59 more to 321 more)[a]	⨁⨁◯◯ Low[b,c]	
Death (non-severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	91 (1 RCT)	**RR = 0.00** (0.00 to 3.86)	22 per 1000	**-- per 1000** (-- to --)[d]	**22 fewer per 1000** (from 114 fewer to 59 more)[d]	⨁⨁◯◯ Low[b,c]	
Lost to follow up during treatment (non-severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	91 (1 RCT)	**RR = 1.53** (0.46 to 5.07)	87 per 1000	**133 per 1000** (-- to --)[d]	**46 more per 1000** (from 82 fewer to 175 more)[d]	⨁⨁◯◯ Low[b,c]	
Adverse events (Grade 3–4) during treatment (non-severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	91 (1 RCT)	**RR = 1.39** (0.72 to 2.70)	239 per 1000	**333 per 1000** (-- to --)[d]	**94 fewer per 1000** (from 91 fewer to 279 more)[d]	⨁⨁◯◯ Low[b,c]	
Amplification of resistance to study drugs (non-severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	91 (1 RCT)	not estimable	0 per 1000	**-- per 1000** (-- to --)[d]	**0 fewer per 1000** (from 78 fewer to 80 more)[d]	⨁⨁◯◯ Low[b,c]	

CI: confidence interval; **RR:** risk ratio

a. Adjusted for baseline severity, prior TB, body mass index, age, HIV status and study site.

b. A single trial. Serious indirectness (i) Populations: Differences in population of a trial and population to which guidelines will apply. (ii) Comparator: Some comparator regimens are sub-optimal, not according with the WHO standard of care (at the time or presently), and vary by country. Downgraded one level.

c. The number of participants in both intervention and comparator groups was small. Very few events in the outcomes of interest, causing serious or very serious imprecision. We downgraded two levels for imprecision for some outcomes, and one level for others

d. Not adjusted owing to small numbers of events.

e. An imbalance in measured covariates (gender, past DR-TB treatment, smear status, FQ-resistance) likely arises from the small number of participants in each group. While the adjusted analyses will account for measured confounding, unmeasured confounding is also likely.

f. Small numbers of events in some outcomes precludes adjustment in some comparisons.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence was sought for.	There is little doubt that the identified outcomes are important to people with XDR-TB but given that no evidence was searched for the judgment is somewhat uncertain.

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

JUDGEMENT

○ Favours the comparison
● Probably favours the comparison
○ Does not favour either the intervention or the comparison
○ Probably favours the intervention
○ Favours the intervention
○ Varies
○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with the BPaL	Risk difference with a BPaLC
Failure and recurrence (non-severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	91 (1 RCT)	⨁⨁◯◯ Low[a,b]	**RR 9.20** (1.61 to 55.15)	Study population	
				22 per 1000	**178 more per 1000 (13 more to 1,177 more)**
Death (non-severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	91 (1 RCT)	⨁⨁◯◯ Low[a,b]	**RR 0.00** (0.00 to 3.86)	Study population	
				22 per 1000	**22 fewer per 1000 (22 fewer to 62 more)**
Lost to follow up during treatment (non-severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	91 (1 RCT)	⨁⨁◯◯ Low[a,b]	**RR 1.53** (0.46 to 5.07)	Study population	
				87 per 1000	**46 more per 1000 (47 fewer to 354 more)**
Adverse events (Grade 3–4) during treatment (non-severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	91 (1 RCT)	⨁⨁◯◯ Low[a,b]	**RR 1.39** (0.72 to 2.70)	Study population	
				239 per 1000	**93 more per 1000 (67 fewer to 407 more)**
Amplification of resistance to study drugs (non-severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	91 (1 RCT)	⨁⨁◯◯ Low[a,b]	not estimable	Study population	
				0 per 1000	**0 fewer per 1000 (0 fewer to 0 fewer)**

a. A single trial. Serious indirectness (i) Populations: Differences in population of a trial and population to which guidelines will apply. (ii) Comparator: Some comparator regimens are sub-optimal, not according with the WHO standard of care (at the time or presently), and vary by country. Downgraded one level.

b. The number of participants in both intervention and comparator groups was small. Very few events in the outcomes of interest, causing serious or very serious imprecision. We downgraded two levels for imprecision for some outcomes, and one level for others

ADDITIONAL CONSIDERATIONS

The GDG judged the desirable effects to be trivial and the undesirable effects of BPaLC to be moderate compared with BPaL. The certainty of evidence was judged to be very low. The balance of health effects was judged to be in favour of BPaL, with a small net benefit in people with non-severe disease (or small net harm for BPaLC in this population), favouring the comparison (BPaL), although there was very low certainty evidence due to indirectness and severe imprecision, in particular for the subgroup with non-severe disease. There also was probably no important uncertainty or variability in values.

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		There is little difference in the cost given that cost of the additional drug are very low.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ● High ○ No included studies	Althouh no evidence was searched for, the additional cost for BPaLC are reported as: Estimated regimen costs (in adults) at GDF prices are about US$ 278 for BPaL, US$ 304 for BPaLM, US$ 365 for BPaLC, an average of US$ 475 for a longer regimen (depends on length and composition) and US$ 205–1 748 for a 9-month regimen.	Estimated regimen prices were calculated using the average weighted price for each medicine (average weighted price accounts for the different prices for each supplier of that medicine weighted by the market share allocation received from each GDF tender), the duration indicated (in months) and assuming 30 days of treatment per month. Actual final costs may differ based on the products delivered. https://www.stoptb.org/what-we-do/facilitate-access-tb-drugs-diagnostics/global-drug-facility-gdf/buyers/plan-order, accessed on 13 February 2026.

Cost effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ● No included studies	Amplification of drug resistance is not considered in the available cost-effectiveness analysis. Additional evidence has not been identified.	**Logical conclusion cannot be drawn because of the uncertainty in the effectiveness outcomes.** **Sweeney et al., 2022.** Multi-country cost-effectiveness model. BPaL and BPaLM were likely cost-saving and more effective than standard of care in a range of settings. BPaL often the most cost-saving**. PMC** **James et al., 2024 / PubMed.** Modelled lifetime costs, found 6-month BPaLM cost-effective versus standard care, with substantial per-person cost reductions in base case**. PubMed** **Country economic analyses and modelling (examples**). India and Philippines analyses found BPaL/BPaLM cost-saving or highly cost-effective under local assumptions. See India modelling (2025) and Philippines study (2024)**. Cambridge Core** **PLOS Global Public Health, 2025.** Analysis of impact of fluoroquinolone resistance on cost-effectiveness. Concludes BPaLM can be cost-effective in empirical settings and may replace BPaL depending on resistance prevalence**. PLOS Journals**

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		Clofazimine is widely available and would not have impact on equity.

Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know		Both regiments acceptable but influenced by severity of the disease (and the related consequences). For severe disease BPaLC would be more acceptable than BPaL and vice versa for non-severe disease.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The BPaLM regimen and its variants has been implemented in many programmatic settings. The data from programmatic sites in Belarus (n=261) and Uzbekistan (n=42) using BPaLC and the data from a site in Italy (n=16) using BPaL demonstrates the outcomes to be well aligned with those observed in clinical trial settings, and is supporting the feasibility of BPaL/C implementation in routine care.	Both regimens are feasible. BPaLC requires additional medicine – clofazimine, which adds to the procurement needs. It is a drug off patent, available through usual procurement channels in higher burden countries and inexpensive. There are availability issue in some EU countries but it is the case with many of the second-line medicines.

Summary of judgements

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favours the comparison	**Probably favours the comparison**	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies
COST EFFECTIVENESS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

Conclusions

Recommendation
The use of the 6-month treatment regimen composed of bedaquiline, pretomanid and linezolid (BPaL) rather than BPaLC is suggested in patients with non-severe pre-XDR-TB, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month *(conditional recommendation, very low certainty)*.

Remarks

Severity in pulmonary pre-XDR-TB for this regimen selection is defined by the presence of cavitary lesions on chest radiography and high bacillary load shown by sputum smear results of 1+ or higher positivity, and smear results of 2+ or higher (or an equivalent result on WHO-recommended molecular tests) even when cavities are not present. Non-severe, in this context, refers to all situations not covered by the definition of severe pulmonary pre-XDR-TB.

Justification
The GDG judged the desirable effects to be trivial and the undesirable effects of BPaLC to be moderate compared with BPaL. The certainty of evidence was judged to be very low. The balance of health effects was judged to be in favour of BPaL, with a small net benefit in people with non-severe disease (or small net harm for BPaLC in this population), favouring the comparison (BPaL), although there was very low certainty evidence due to indirectness and severe imprecision, in particular for the subgroup with non-severe disease. There also was probably no important uncertainty or variability in values.

Subgroup considerations

The panel identified subpopulations of people who might be affected differently than most by this recommendation; these subpopulations were PLHIV, children, pregnant women, breastfeeding women, and patients with extensive TB disease. The recent new recommendation for the use of bedaquiline in children with MDR/RR-TB aged below 6 years was considered *(29)*. The panel noted specific considerations for the subpopulations listed below.

People living with HIV

No restrictions were identified for the use of the intervention among people living with HIV.

Children and adolescents

Trial evidence included participants aged ≥14 years.

Pregnant and breastfeeding women

No restrictions were identified for the drug Delamanid. Use of the drug Pretomanid is restricted due to limited safety data in this population

Extensive TB disease (based on the endTB-Q trial definition)

Patients with DR-TB who have extensive disease face greater challenges in treatment across all regimens and are at a higher risk of unfavourable outcomes and amplification of drug resistance. This risk is further elevated in those infected with pathogens that have advanced resistance profiles, particularly with additional resistance to fluoroquinolones. These patients may experience slightly worse outcomes compared to those without pre-XDR and develop resistance to regimen components. In the BEAT-TB trial among patients with pre-XDR-TB, the outcomes also appeared worse than among those who were fluoroquinolone susceptible. This reduction in the proportion with successful treatment outcomes was numerically greater in the BDLLfxC arm than in the control arm (14.3% vs 3.3%); however, this difference was within the range of statistical uncertainty, and the GDG judged that this should not affect the recommendation or remarks. The rate of acquisition of resistance to bedaquiline was similar between the two groups (11% in BDLLfxC and 9.1% in control). The evidence from the BEAT-TB trial is insufficient to draw definitive conclusions due to the small sample when stratified by fluoroquinolone resistance and related imprecision. Nonetheless, clinicians should remain vigilant and closely monitor the treatment response in this group of patients and promptly take relevant actions (extending the duration of treatment or changing the regimen).

Hepatitis C co-infection

A prior WHO recommendation, based on expert evidence, applies to patients with MDR/RR-TB and hepatitis C virus (HCV) co-infection. WHO suggests co-administration of HCV and TB treatments rather than delaying HCV treatment until completion of MDR/RR-TB therapy *(conditional recommendation, very low certainty of evidence)*.

Malnutrition and underweight

Patients with severe undernutrition, including those with a body mass index (BMI) below 15, were included in the trials. No subgroup-specific restrictions were identified based on nutritional status. (The trials did not include overweight participants)

Other causes of immunosuppression

For patients with immunosuppression due to causes other than HIV, careful interpretation of the conditional recommendation is warranted, taking into account the underlying condition and clinical context

Implementation considerations
Paediatric formulations
Availability of appropriate drug formulations for children should be ensured.
Regimen transitions
Clear programmatic guidance is needed to support transitions between regimens where clinically indicated.
Drug susceptibility testing
DST for fluoroquinolones is strongly encouraged in people with MDR/RR-TB. While DST should not delay initiation of the BDLLfxC regimen, results should inform decisions on whether levofloxacin or clofazimine is retained in the regimen.
Linezolid dosing
Clear guidance and clinical expertise are required for appropriate linezolid dosing, and dose adjustments may be necessary.
Assessment of TB disease
Availability of chest radiography (CXR) should be ensured to support disease and severity assessment.
Capacity building
Health-care worker training is needed to support standardized assessment of disease severity.
Drug–drug interactions
Potential drug–drug interactions should be systematically assessed and managed.
Medicine supply
Reliable availability of all regimen components, including adequate buffer stocks, is required to prevent stock-outs and treatment interruptions.
Severity assessment
Standardized severity definition and assessment should be incorporated into implementation guidance.
Safety monitoring
Systems for routine monitoring and management of adverse events should be in place.
Additional considerations
For delamanid-based regimens, assessment of serum albumin levels should be considered.
Patient-centred approach
Efforts are required to provide patient support and to enable full adherence to treatment.
Access to mental health and psychosocial support services should be ensured.
Consideration should also be given to insurance coverage and financing mechanisms.
Monitoring and evaluation
Systems should be in place to monitor disease recurrence and the emergence of drug resistance, particularly in cases of treatment failure or relapse.
Routine monitoring and management of adverse events are required.
For patients receiving BDLLC-containing regimens, regular QTc interval monitoring should be conducted.

Research priorities
The GDG discussed and identified the following research priorities relating to this recommendation.
Interventions, populations and the balance of desirable and undesirable health effects:
Further research is needed to refine definitions of disease severity and the risk assessment model (RAM).
Direct comparative trials of BDLC versus BPaLC in patients with severe disease are a priority, including evaluation of optimal treatment duration in this subgroup.
Additional evidence is required in children, including the safety and dosing of pretomanid (Pa) in those younger than 14 years.
More programmatic and real-world data are needed, including outcomes in key subpopulations such as individuals with malnutrition.
Research should evaluate biomarkers to individualize treatment duration irrespective of drug resistance profile or regimen.
Assessment of the efficacy and safety of lower linezolid doses.
Identify predictors of disease recurrence.
Larger trials and programmatic data for BPAL and BPALC regimens are required.
Studies assessing treatment completion, adherence support needs, and quality-of-life outcomes.
Values: Additional research is needed to obtain higher certainty in patient values related to the outcomes of interest.
Equity: Judgments about equity will be better informed by studies that capture both direct and indirect patient costs to better understand the financial burden of treatment, alongside the evaluation of equitable access to newer TB regimens across different populations
Resources: Effectiveness data from direct comparisons of regimens will be essential to inform cost-effectiveness and extended cost-effectiveness analyses, including the potential to reduce catastrophic costs for patients and households.
Acceptability: Studies assessing the acceptability of newer TB regimens among both patients and health-care providers, in conjunction with exploration of reasons for delayed uptake and implementation despite guideline recommendations, are needed.
Feasibility: Key feasibility concerns include barriers related to procurement and supply chains, regulatory approvals, and limitations in diagnostic and monitoring capacity.

PICO 6b evidence profile

A BPaLC compared to the BPaL in patients with severe pulmonary pre-XDR-TB (PICO 6b)

Bibliography:											
Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With the BPaL	With a BPaLC		Risk with the BPaL	Risk difference with a BPaLC
Failure and recurrence (severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)											
135 (1 RCT)	not serious	not serious	serious[a]	very serious[b]	none	⨁◯◯◯ Very low[a,b]	11/65 (16.9%)	7/70 (10.0%)	**RR 0.59** (0.24 to 1.43)	11/65 (16.9%)	**69 fewer per 1000** (from 416 fewer to 211 fewer)[c]
Death (severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)											
135 (1 RCT)	not serious	not serious	serious[a]	very serious[b]	none	⨁◯◯◯ Very low[a,b]	1/65 (1.5%)	1/70 (1.4%)	**RR 0.93** (0.10 to 8.79)	1/65 (1.5%)	**1 fewer per 1000** (from 222 fewer to 267 more)[d]
Lost to follow up during treatment (severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)											
135 (1 RCT)	serious[e,f]	not serious	serious[a]	serious[b]	none	⨁◯◯◯ Very low[a,b,e,f]	3/65 (4.6%)	4/70 (5.7%)	**RR 1.24** (0.32 to 4.81)	3/65 (4.6%)	**11 more per 1000** (from 144 fewer to 384 more)[c]
Adverse events (Grade 3–4) during treatment (severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)											
135 (1 RCT)	serious[e,f]	not serious	serious[a]	very serious[b]	none	⨁◯◯◯ Very low[a,b,e,f]	13/65 (20.0%)	21/70 (30.0%)	**RR 1.50** (0.82 to 2.74)	13/65 (20.0%)	**100 more per 1000** (from 198 fewer to 463 more)[c]
Amplification of resistance to study drugs (severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)											
135 (1 RCT)	not serious	not serious	serious[a]	serious[b]	none	⨁⨁◯◯ Low[a,b]	3/65 (4.6%)	0/70 (0.0%)	**RR 1.70** (0.67 to 4.34)	3/65 (4.6%)	**46 fewer per 1000** (from 321 fewer to 205 more)[d]

CI: confidence interval; **RR:** risk ratio

Explanations

a. A single trial. Serious indirectness (i) Populations: Differences in population of a trial and population to which guidelines will apply. (ii) Comparator: Some comparator regimens are sub-optimal, not according with the WHO standard of care (at the time or presently), and vary by country. Downgraded one level.

b. The number of participants in both intervention and comparator groups was small. Very few events in the outcomes of interest, causing serious or very serious imprecision. We downgraded two levels for imprecision for some outcomes, and one level for others

c. Adjusted for baseline severity, prior TB, body mass index, age, HIV status and study site.

d. Not adjusted owing to small numbers of events.

e. An imbalance in measured covariates (gender, past DR-TB treatment, smear status, FQ-resistance) likely arises from the small number of participants in each group. While the adjusted analyses will account for measured confounding, unmeasured confounding is also likely.

f. Small numbers of events in some outcomes precludes adjustment in some comparisons.

PICO 6b evidence-to-decision

Question	
Should a BPaLC vs. the BPaL be used for patients with severe pulmonary pre-XDR-TB (PICO 6b)?	
POPULATION:	patients with severe pulmonary pre-XDR-TB (PICO 6b)
INTERVENTION:	a BPaLC
COMPARISON:	the BPaL
MAIN OUTCOMES:	Failure and recurrence (severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R); Death (severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R); Lost to follow up during treatment (severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R); Adverse events (Grade 3–4) during treatment (severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R); Amplification of resistance to study drugs (severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R);
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation – population perspective
BACKGROUND:	This question addresses the effectiveness and safety of a 6-month BPaLC treatment regimen in patients with severe pulmonary pre-XDR-TB versus BPaL regimen.
CONFLICT OF INTERESTS:	The WHO GTB Program applied the WHO conflict of interest declaration and management policy, and the following were GDG members involved in decision-making for this recommendation: Ashna Ashesh (WHO Civil Society Task Force – TB; Survivors Against TB, India), Erlina Burhan (Persahabatan Hospital Jakarta; Faculty of Medicine – Universitas Indonesia), Muhwa Chakaya (National Tuberculosis Programme of Kenya), Gerry Davies (University of Liverpool, United Kingdom), Fernanda Dockhorn Costa Johansen (Ministry of Health MDR-TB referral centre, Brazil), Kelly Dooley (Vanderbilt University Medical Center, USA), Sobia Faisal (Greenstar Social Marketing, Pakistan), Elmira Gurbanova (Lung Clinic, University of Tartu, Estonia), Eric Krakauer (Harvard Medical School, USA), Christoph Lange (Research Center Borstel, Germany), Yuhong Liu (Beijing Chest Hospital, China), Andrey Maryandyshev (Phthisiopulmonology Department of the Northern State Medical University, Arkhangelsk, Russian Federation), Graeme Meintjes (University of Cape Town, South Africa), Mahshid Nasehi (National Tuberculosis Programme of the Islamic Republic of Iran), Mamel Quelapio (Independent consultant, the Philippines), Moorine Sekkade (National Tuberculosis Programme of Uganda), Wei Sha (Shanghai Pulmonary Hospital, China), Urvashi Singh (National TB Programme, Ministry of Health, India), Shaheed Vally Omar (South Africa Supranational TB Reference Laboratory), Luan Vo (Friends for International Tuberculosis Relief, Viet Nam). No member of the GDG had important conflicts precluding participation.

Assessment

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Tuberculosis (TB) remains a threat to global public health and is one of the topmost infectious causes of death in the world. In 2024, an estimated 10.7 million people developed TB, and 1.23 million died from the disease. About 390,000 new patients with rifampicin-resistant or multidrug-resistant tuberculosis (MDR/RR-TB) were estimated to emerge in 2024. While all of these patients would have been eligible for a second-line TB treatment regimen, only 165,650 enrolments on treatment were reported by countries in the same year. In recent years, substantial progress has been made with the introduction of improved diagnostics and more effective medicines, enabling earlier detection and boosting treatment success rates among MDR/RR-TB patients in many national programs, with a 71% success rate reported for those enrolled in 2022. MDR-/RR-TB is treatable but requires different treatment regimen combinations that used to be longer than regimens for drug-susceptible TB and include medicines that are potentially more toxic. The interest in reducing the duration of treatment for MDR/RR-TB motivated a continuous search for shorter and safer regimens. The regimens for the treatment of MDR/RR-TB have changed dramatically in the past ten years. Before 2016, DR-TB regimens were 24 months or longer and included six or more months of daily intramuscular injections with significant adverse events. In 2016, based on data from observational studies of the shorter regimens in different Asian and African countries, WHO, for the first time, recommended a standardized 9-month regimen containing an injectable agent providing shorter than the extant 18–20 months standard of care for the eligible patients. Evidence of permanent effects attributed to the toxicity of injectable agents has prompted further advances in the development of new treatments, such as shorter injectable-sparing regimens. The all-oral 9-month bedaquiline-containing regimen was reviewed and recommended by WHO in 2019. The pressing need for more effective treatment regimens for patients with MDR/RR-TB, including those with fluoroquinolone resistance and more extensive drug-resistance profiles, has driven several studies and initiatives to test more effective and novel treatment regimens, including newer and repurposed medicines. The Nix-TB study conducted by TB Alliance pioneered the 6-month regimen that included bedaquiline and a new medicine – pretomanid, and the BPaL combination successfully received regulatory approval from the FDA. Two randomized controlled trials (RCTs) that concluded in 2021 (TB-PRACTECAL and ZeNix) provided new evidence and prompted assessment by WHO to develop new recommendations for wide programmatic use of the BPaLM/BPaL regimen for treatment MDR/RR-TB with or without resistance to fluoroquinolones. The latest evidence-based guidelines for the treatment and care of TB and drug-resistant TB, including MDR/RR-TB and pre-XDR-TB, were published by WHO in April 2025 – "WHO consolidated guidelines on tuberculosis: module 4: treatment and care". The WHO has combined all recommendations on the treatment of drug-resistant TB, drug-susceptible TB, and TB care and support in three separate chapters of the consolidated guidelines. The recommendation for use of another 6-month BDLLfxC regimen based on the evidence from the BEAT Tuberculosis trial in South Africa was included in the 2025 update.	**Information from a prior GDG (2022) meeting on sub-PICOs 6.5 stated the following and this information still applies:** **Sub-PICO 6.5** The BPaLC regimen arm of the TB-PRACTECAL trial with a population including patients with MDR/RR-TB **with or without fluoroquinolone resistance (MDR/RR-TB or pre-XDR-TB**) was compared with the BPaL arm of the TB-PRACTECAL trial that comprised MDR/RR-TB or pre-XDR-TB patients. Primary analysis was undertaken at 72 weeks post treatment initiation. Participants with pulmonary MDR/RR-TB or pre-XDR-TB receiving BPaLC (n=64) compared with participants receiving BPaL 600–300 (n=60) experienced: • higher levels of treatment success (81% vs 77%); that is, a 4% relative increase (aRR=1.04, 95% CI: 0.84 to 1.30); • lower levels of failure and recurrence (9.4% vs 13%); that is, a 14% relative reduction (aRR=0.86, 95% CI: 0.28 to 2.69); • higher levels of deaths (1.6% vs 0%); that is, a 2% absolute increase (RD=0.02, 95% CI: –0.05 to 0.08); • lower levels of LTFU (7.8% vs 10%); that is, a 28% relative reduction (aRR=0.72, 95% CI: 0.21 to 2.47); • higher levels of AEs (34% vs 20%); that is, a 64% relative increase (aRR=1.64, 95% CI: 0.97 to 2.79); and • lower levels of amplification of drug resistance (1.9% vs 2.9%); that is, a 35% relative reduction (RR=0.65, 95% CI: 0.13 to 3.21).

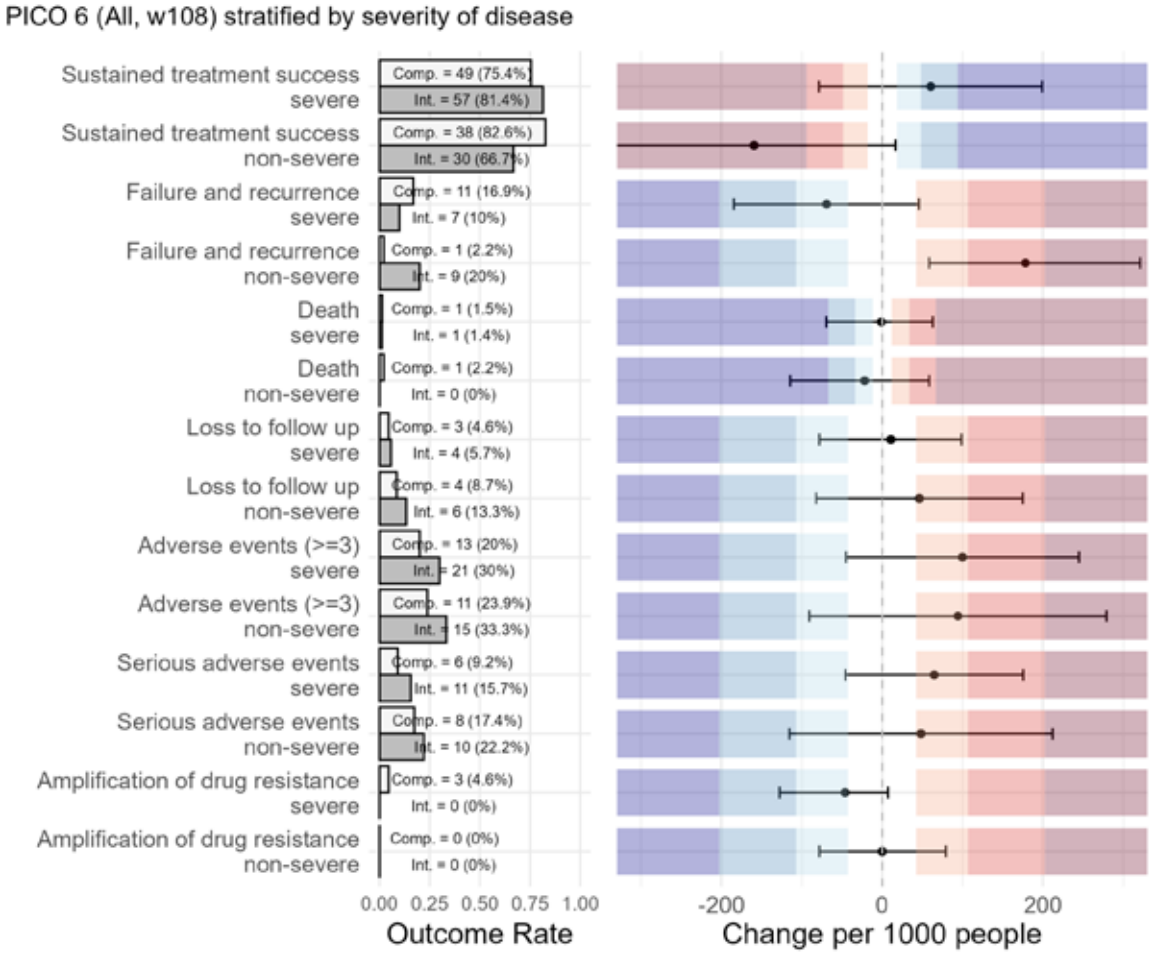
	Following the recent update of the WHO recommendations on DR-TB treatment, new or more complete evidence has become available from clinical trials or operational research on using combinations of medicines to treat MDR/RR-TB or pre-XDR-TB that a WHO-convened Guideline Development Group has not yet appraised. These regimens include the use of a new 6-month regimen including bedaquiline, delamanid, linezolid and clofazimine (endTB-Q and BEAT-TB South Africa trials) and the use of 6-month BPaL and BPaLC regimens (more complete data from the TB-PRATECAL trial and additional data from the operational research studies or programmatic implementation) for the treatment of patients with MDR/RR-TB with quinolone resistance. The evidence from these trials has been shared with WHO, and this guideline development group (GDG) is convened to review new evidence on the treatment and palliative care for patients with MDR/RR-TB or pre-XDR-TB to ensure that the latest treatment and care options are reflected in the WHO policy.	The GDG judged both the desirable and the undesirable effects of BPaLC to be small compared with BPaL. The certainty of evidence was judged to be very low. The balance of health effects did not favour either the intervention or the comparator; however, taking into consideration the higher cost of the regimen, increased pill burden, reduced acceptability due to skin discolouration and other potential adverse effects related to clofazimine without noticeable net benefit in terms of health effects, the panel judged against the intervention. **Conclusion** The use of the 6-month treatment regimen composed of bedaquiline, pretomanid and linezolid (BPaL) rather than BPaLC is suggested in MDR/RR-TB patients with or without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	The BPaLC regimen arm of the TB-PRACTECAL trial, including patients with MDR/RR-TB or pre-XDR-TB, was compared with the BPaL arm of the TB-PRACTECAL trial, which comprised MDR/RR-TB or pre-XDR-TB patients. Primary analysis was undertaken at 108 weeks post treatment initiation. The patient cohort was stratified into those with non-severe and severe pre-XDR-TB. Participants with severe pulmonary MDR/RR-TB or pre-XDR-TB receiving BPaLC (*n*=70) compared with participants receiving BPaL (*n*=65) experienced: • lower levels of failure and recurrence (10% vs 16.9%); RD=69 fewer per 1000, 95% CI: 416 fewer to 211 fewer per 1000); • lower levels of deaths (1.4% vs 1.5%); RD=1 fewer per 1000, 95% CI: 222 fewer to 267 more per 1000); • higher levels of LTFU (5.7% vs 4.6%); RD=11 more per 1000, 95% CI: 144 fewer to 384 more per 1000); • higher levels of AEs (30% vs 20%); RD=100 more per 1000, 95% CI: 198 fewer to 463 more per 1000); and • lower levels of amplification of drug resistance (0% vs 4.6%); RD=46 fewer per 1000, 95% CI: 321 fewer to 205 more per 1000).	Based on the thresholds for the prioritized outcomes listed below, the GDG judged the undesirable health effects of BPaLC compared to BPaL to be moderate in patients with severe pre-XDR-TB based on the combined effects on failure and amplifications of drug resistance. **Death** • Trivial Effect: ≤12 fewer or more events per 1000 people • Small Effect: 12 to 34 fewer or more events per 1000 people • Moderate Effect: 34 to 67 fewer or more events per 1000 people • Large Effect: >67 fewer or more events per 1000 people

Decision threshold diagram



Treatment Failure or Recurrence, lost to follow-up, adverse events and amplification (acquisition) of drug resistance

- Trivial Effect: ≤41 fewer or more events per 1000 people
- Small Effect: 41 to 107 fewer or more events per 1000 people
- Moderate Effect: 107 to 202 fewer or more events per 1000 people
- Large Effect: >202 fewer or more events per 1000 people

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with the BPaL	Risk difference with a BPaLC
Failure and recurrence (severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	135 (1 RCT)	⨁◯◯◯ Very low[a,b]	**RR 0.59** (0.24 to 1.43)	Study population	
				169 per 1000	**69 fewer per 1000** (129 fewer to 73 more)
Death (severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	135 (1 RCT)	⨁◯◯◯ Very low[a,b]	**RR 0.93** (0.10 to 8.79)	Study population	
				15 per 1000	**1 fewer per 1000** (14 fewer to 120 more)

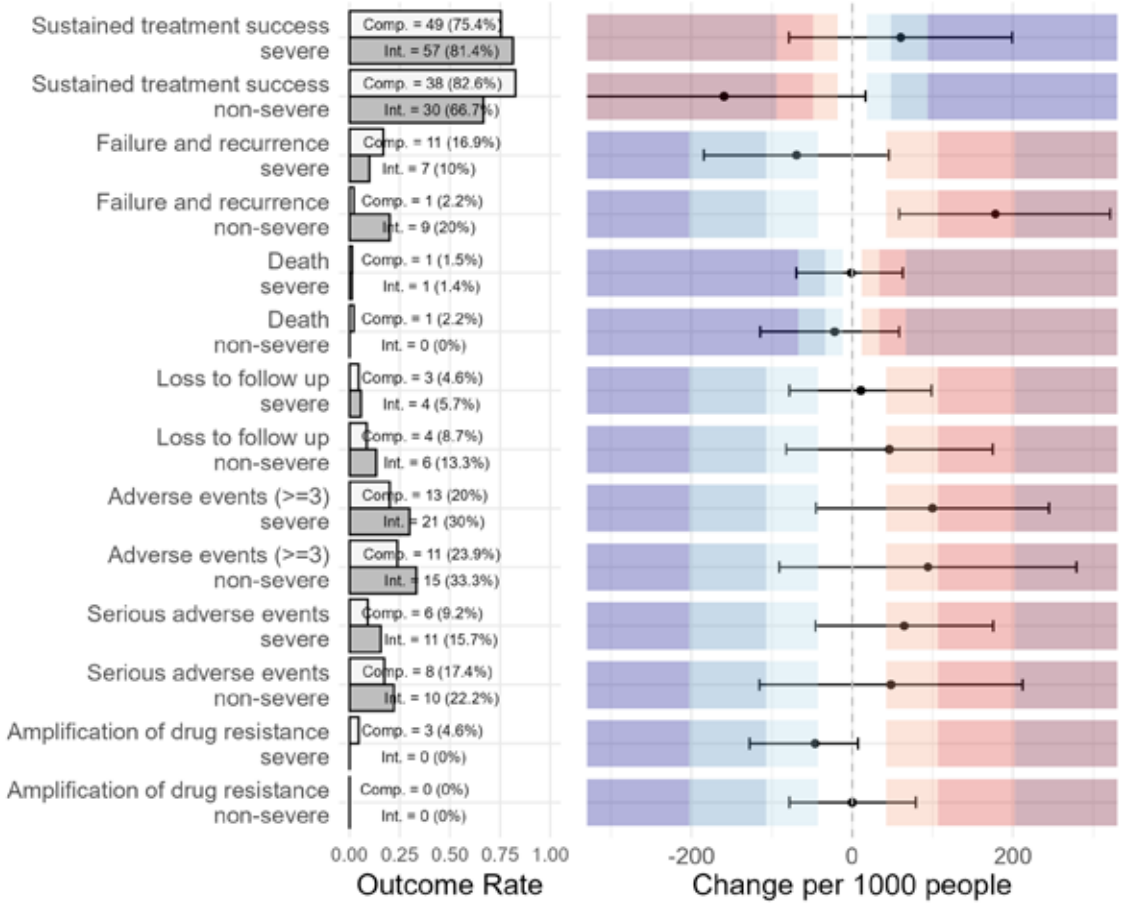
a. A single trial. Serious indirectness (i) Populations: Differences in population of a trial and population to which guidelines will apply. (ii) Comparator: Some comparator regimens are sub-optimal, not according with the WHO standard of care (at the time or presently), and vary by country. Downgraded one level.

b. The number of participants in both intervention and comparator groups was small. Very few events in the outcomes of interest, causing serious or very serious imprecision. We downgraded two levels for imprecision for some outcomes, and one level for others

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	PICO 6 (All, w108) stratified by severity of disease	Based on the thresholds for the prioritized outcomes listed below, the GDG judged the undesirable health effects of BPaLC compared to BPaL to be small for people with severe pre-XDR-TB. **Treatment Failure or Recurrence, lost to follow-up, adverse events and amplification (acquisition) of drug resistance** • Trivial Effect: ≤41 fewer or more events per 1000 people • Small Effect: 41 to 107 fewer or more events per 1000 people • Moderate Effect: 107 to 202 fewer or more events per 1000 people • Large Effect: >202 fewer or more events per 1000 people



Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with the BPaL	Risk difference with a BPaLC
Lost to follow up during treatment (severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	135 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d]	**RR 1.24** (0.32 to 4.81)	Study population	
				46 per 1000	**11 more per 1000 (31 fewer to 176 more)**
Adverse events (Grade 3–4) during treatment (severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	135 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d]	**RR 1.50** (0.82 to 2.74)	Study population	
				200 per 1000	**100 more per 1000 (36 fewer to 348 more)**
Amplification of resistance to study drugs (severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	135 (1 RCT)	⨁⨁◯◯ Low[c,d]	**RR 1.70** (0.67 to 4.34)	Study population	
				46 per 1000	**32 more per 1000 (15 fewer to 154 more)**

a. An imbalance in measured covariates (gender, past DR-TB treatment, smear status, FQ-resistance) likely arises from the small number of participants in each group. While the adjusted analyses will account for measured confounding, unmeasured confounding is also likely.

b. Small numbers of events in some outcomes precludes adjustment in some comparisons.

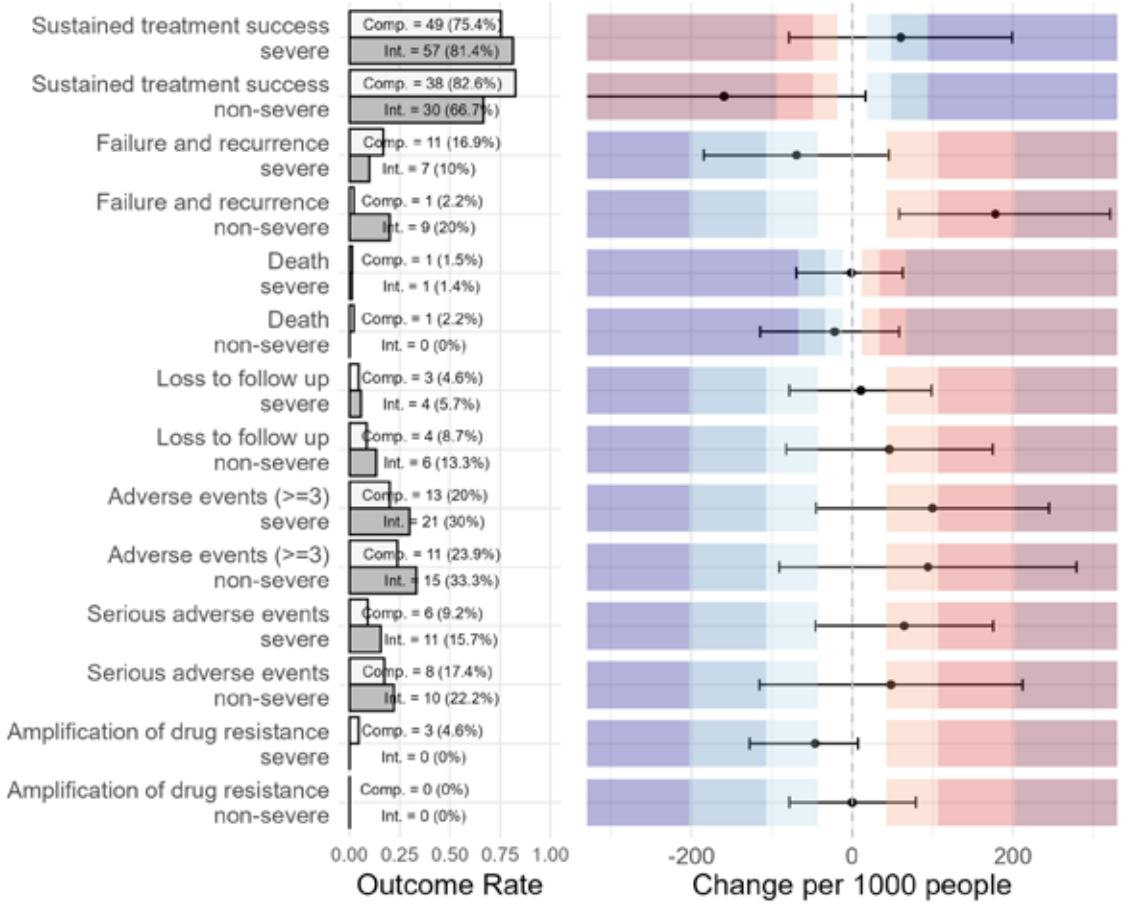
c. A single trial. Serious indirectness (i) Populations: Differences in population of a trial and population to which guidelines will apply. (ii) Comparator: Some comparator regimens are sub-optimal, not according with the WHO standard of care (at the time or presently), and vary by country. Downgraded one level.

d. The number of participants in both intervention and comparator groups was small. Very few events in the outcomes of interest, causing serious or very serious imprecision. We downgraded two levels for imprecision for some outcomes, and one level for others

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	PICO 6 (All, w108) stratified by severity of disease	There was risk of bias due to lack of blinding of patients and caregivers, indirectness and very serious imprecision that lower the certainty in the evidence for several outcomes.



Summary of Findings for a BPaLC Versus the BPaL for patients with severe pulmonary pre-XDR-TB (PICO 6b)							
Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			the BPaL	[a] BPaLC	Difference		
Failure and recurrence (severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	135 (1 RCT)	**RR = 0.59** (0.24 to 1.43)	169 per 1000	**100 per 1000** (-- to --)[a]	**69 fewer per 1000** (from 416 fewer to 211 fewer)[a]	⨁◯◯◯ Very low[b,c]	
Death (severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	135 (1 RCT)	**RR = 0.93** (0.10 to 8.79)	15 per 1000	**14 per 1000** (-- to --)[d]	**1 fewer per 1000** (from 222 fewer to 267 more)[d]	⨁◯◯◯ Very low[b,c]	
Lost to follow up during treatment (severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	135 (1 RCT)	**RR = 1.24** (0.32 to 4.81)	46 per 1000	**57 per 1000** (-- to --)[a]	**11 more per 1000** (from 144 fewer to 384 more)[a]	⨁◯◯◯ Very low[b,c,e,f]	
Adverse events (Grade 3–4) during treatment (severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	135 (1 RCT)	**RR = 1.50** (0.82 to 2.74)	200 per 1000	**300 per 1000** (-- to --)[a]	**100 more per 1000** (from 198 fewer to 463 more)[a]	⨁◯◯◯ Very low[b,c,e,f]	
Amplification of resistance to study drugs (severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	135 (1 RCT)	**RR = 1.70** (0.67 to 4.34)	46 per 1000	**-- per 1000** (-- to --)[d]	**46 fewer per 1000** (from 321 fewer to 205 more)[d]	⨁⨁◯◯ Low[b,c]	

CI: confidence interval; **RR:** risk ratio

a. Adjusted for baseline severity, prior TB, body mass index, age, HIV status and study site.

b. A single trial. Serious indirectness (i) Populations: Differences in population of a trial and population to which guidelines will apply. (ii) Comparator: Some comparator regimens are sub-optimal, not according with the WHO standard of care (at the time or presently), and vary by country. Downgraded one level.

c. The number of participants in both intervention and comparator groups was small. Very few events in the outcomes of interest, causing serious or very serious imprecision. We downgraded two levels for imprecision for some outcomes, and one level for others.

d. Not adjusted owing to small numbers of events.

e. An imbalance in measured covariates (gender, past DR-TB treatment, smear status, FQ-resistance) likely arises from the small number of participants in each group. While the adjusted analyses will account for measured confounding, unmeasured confounding is also likely.

f. Small numbers of events in some outcomes precludes adjustment in some comparisons.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence was sought for.	There is little doubt that the identified outcomes are important to people with XDR-TB but given that no evidence was searched for the judgment is somewhat uncertain.

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

JUDGEMENT

○ Favours the comparison
○ Probably favours the comparison
○ Does not favour either the intervention or the comparison
● Probably favours the intervention
○ Favours the intervention
○ Varies
○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with the BPaL	Risk difference with a BPaLC
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				200 per 1000	**100 more per 1000 (36 fewer to 348 more)**
Amplification of resistance to study drugs (severe disease) (follow-up: 24 months) for MDR-TB (FQ-S and FQ-R)	135 (1 RCT)	⨁⨁◯◯ Low[a,b]	**RR 1.70** (0.67 to 4.34)	Study population	
				46 per 1000	**32 more per 1000 (15 fewer to 154 more)**

a. A single trial. Serious indirectness (i) Populations: Differences in population of a trial and population to which guidelines will apply. (ii) Comparator: Some comparator regimens are sub-optimal, not according with the WHO standard of care (at the time or presently), and vary by country. Downgraded one level.

b. The number of participants in both intervention and comparator groups was small. Very few events in the outcomes of interest, causing serious or very serious imprecision. We downgraded two levels for imprecision for some outcomes, and one level for others

c. An imbalance in measured covariates (gender, past DR-TB treatment, smear status, FQ-resistance) likely arises from the small number of participants in each group. While the adjusted analyses will account for measured confounding, unmeasured confounding is also likely.

d. Small numbers of events in some outcomes precludes adjustment in some comparisons.

ADDITIONAL CONSIDERATIONS

The GDG judged the desirable effects to be moderate and the undesirable effects of BPaLC to be small compared with BPaL. The certainty of evidence was judged to be very low. The balance was judged to be in favour of BPaLC, with a small net benefit in people with severe disease, favouring the intervention (BPaLC), although the evidence was very low in certainty due to indirectness and severe imprecision. There was probably also no important uncertainty or variability in values.

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		There is little difference in the cost given that cost of the additional drug are very low.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ● High ○ No included studies	Althouh no evidence was searched for, the additional cost for BPaLC are reported as: Estimated regimen costs (in adults) at GDF prices are about US$ 278 for BPaL, US$ 304 for BPaLM, US$ 365 for BPaLC, an average of US$ 475 for a longer regimen (depends on length and composition) and US$ 205–1 748 for a 9-month regimen.	

Cost effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ● No included studies	Amplification of drug resistance is not considered in the available cost-effectiveness analysis. Additional evidence has not been identified.	**Logical conclusion cannot be drawn because of the uncertainty in the effectiveness outcomes.** **Sweeney et al., 2022.** Multi-country cost-effectiveness model. BPaL and BPaLM were likely cost-saving and more effective than standard of care in a range of settings. BPaL often the most cost-saving**. PMC** **James et al., 2024 / PubMed.** Modelled lifetime costs, found 6-month BPaLM cost-effective versus standard care, with substantial per-person cost reductions in base case**. PubMed** **Country economic analyses and modelling (examples**). India and Philippines analyses found BPaL/BPaLM cost-saving or highly cost-effective under local assumptions. See India modelling (2025) and Philippines study (2024)**. Cambridge Core** **PLOS Global Public Health, 2025.** Analysis of impact of fluoroquinolone resistance on cost-effectiveness. Concludes BPaLM can be cost-effective in empirical settings and may replace BPaL depending on resistance prevalence**. PLOS Journals**

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		C is widely available and would not have impact on equity.

Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		Both regiments acceptable but influenced by severity of the disease (and the related consequences). For severe disease BPaLC would be more acceptable than BPaL and vice versa for non-severe disease.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The BPaLM regimen and its variants has been implemented in many programmatic settings. The data from programmatic sites in Belarus (n=261) and Uzbekistan (n=42) using BPaLC and the data from a site in Italy (n=16) using BPaL demonstrates the outcomes to be well aligned with those observed in clinical trial settings, and is supporting the feasibility of BPaL/C implementation in routine care.	Both are feasible. Clofazimine (and other novel medicines) availability may add a slight complexity in countries with complex regulatory framework like EU countries. All medicines that are part of these regimens are available in countries with high-TB burden and the access is facilitated by Global Drug Facility.

Summary of judgements

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies
COST EFFECTIVENESS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	•	○

Conclusions

Recommendation
The use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid and clofazimine (BPaLC) rather than BPaL is suggested in patients with severe pre-XDR-TB, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month *(conditional recommendation, very low certainty)*
Remarks
Severity in pulmonary pre-XDR-TB for this regimen selection is defined by the presence of cavitary lesions on chest radiography and high bacillary load shown by sputum smear results of 1+ or higher positivity, and smear results of 2+ or higher (or an equivalent result on WHO-recommended molecular tests) even when cavities are not present. Non-severe, in this context, refers to all situations not covered by the definition of severe pulmonary pre-XDR-TB.
Justification
The GDG judged the desirable effects to be moderate and the undesirable effects of BPaLC to be small compared with BPaL. The certainty of evidence was judged to be very low. The balance was judged to be in favour of BPaLC, with a small net benefit in people with severe disease, favouring the intervention (BPaLC), although the evidence was very low in certainty due to indirectness and severe imprecision. There was probably also no important uncertainty or variability in values. Cost differences are neglibile. Both regimens do not differe in acceptability (except for patients who will find the appropriate regiment based on their severity to be more appropriate) and feasibility is given for both.
Subgroup considerations
The panel identified subpopulations of people who might be affected differently than most by this recommendation; these subpopulations were PLHIV, children, pregnant women, breastfeeding women, and patients with extensive TB disease. The recent new recommendation for the use of bedaquiline in children with MDR/RR-TB aged below 6 years was considered *(29)*. The panel noted specific considerations for the subpopulations listed below.
People living with HIV
No restrictions were identified for the use of the intervention among people living with HIV.
Children and adolescents
Trial evidence included participants aged ≥14 years.
Pregnant and breastfeeding women
No restrictions were identified for the drug Delamanid. Use of the drug Pretomanid is restricted due to limited safety data in this population
Extensive TB disease (based on the endTB-Q trial definition)
Patients with DR-TB who have extensive disease face greater challenges in treatment across all regimens and are at a higher risk of unfavourable outcomes and amplification of drug resistance. This risk is further elevated in those infected with pathogens that have advanced resistance profiles, particularly with additional resistance to fluoroquinolones. These patients may experience slightly worse outcomes compared to those without pre-XDR and develop resistance to regimen components. In the BEAT-TB trial among patients with pre-XDR-TB, the outcomes also appeared worse than among those who were fluoroquinolone susceptible. This reduction in the proportion with successful treatment outcomes was numerically greater in the BDLLfxC arm than in the control arm (14.3% vs 3.3%); however, this difference was within the range of statistical uncertainty, and the GDG judged that this should not affect the recommendation or remarks. The rate of acquisition of resistance to bedaquiline was similar between the two groups (11% in BDLLfxC and 9.1% in control). The evidence from the BEAT-TB trial is insufficient to draw definitive conclusions due to the small sample when stratified by fluoroquinolone resistance and related imprecision. Nonetheless, clinicians should remain vigilant and closely monitor the treatment response in this group of patients and promptly take relevant actions (extending the duration of treatment or changing the regimen).
Hepatitis C co-infection
A prior WHO recommendation, based on expert evidence, applies to patients with MDR/RR-TB and hepatitis C virus (HCV) co-infection. WHO suggests co-administration of HCV and TB treatments rather than delaying HCV treatment until completion of MDR/RR-TB therapy *(conditional recommendation, very low certainty of evidence)*.

Malnutrition and underweight

Patients with severe undernutrition, including those with a body mass index (BMI) below 15, were included in the trials. No subgroup-specific restrictions were identified based on nutritional status. (The trials did not include overweight participants)

Other causes of immunosuppression

For patients with immunosuppression due to causes other than HIV, careful interpretation of the conditional recommendation is warranted, taking into account the underlying condition and clinical context

Implementation considerations

Paediatric formulations

Availability of appropriate drug formulations for children should be ensured.

Regimen transitions

Clear programmatic guidance is needed to support transitions between regimens where clinically indicated.

Drug susceptibility testing

DST for fluoroquinolones is strongly encouraged in people with MDR/RR-TB. While DST should not delay initiation of the BDLLfxC regimen, results should inform decisions on whether levofloxacin or clofazimine is retained in the regimen.

Linezolid dosing

Clear guidance and clinical expertise are required for appropriate linezolid dosing, and dose adjustments may be necessary.

Assessment of TB disease

Availability of chest radiography (CXR) should be ensured to support disease and severity assessment.

Capacity building

Health-care worker training is needed to support standardized assessment of disease severity.

Drug–drug interactions

Potential drug–drug interactions should be systematically assessed and managed.

Medicine supply

Reliable availability of all regimen components, including adequate buffer stocks, is required to prevent stock-outs and treatment interruptions.

Severity assessment

Standardized severity definition and assessment should be incorporated into implementation guidance.

Safety monitoring

Systems for routine monitoring and management of adverse events should be in place.

Additional considerations

For delamanid-based regimens, assessment of serum albumin levels should be considered.

Patient-centred approach

Efforts are required to provide patient support and to enable full adherence to treatment.

Access to mental health and psychosocial support services should be ensured.

Consideration should also be given to insurance coverage and financing mechanisms.

Monitoring and evaluation
Systems should be in place to monitor disease recurrence and the emergence of drug resistance, particularly in cases of treatment failure or relapse.
Routine monitoring and management of adverse events are required.
For patients receiving BDLLC-containing regimens, regular QTc interval monitoring should be conducted.
Research priorities
The GDG discussed and identified the following research priorities relating to this recommendation.
Interventions, populations and the balance of desirable and undesirable health effects:
Further research is needed to refine definitions of disease severity and the risk assessment model (RAM).
Direct comparative trials of BDLC versus BPaLC in patients with severe disease are a priority, including evaluation of optimal treatment duration in this subgroup.
Additional evidence is required in children, including the safety and dosing of pretomanid (Pa) in those younger than 14 years.
More programmatic and real-world data are needed, including outcomes in key subpopulations such as individuals with malnutrition.
Research should evaluate biomarkers to individualize treatment duration irrespective of drug resistance profile or regimen.
Assessment of the efficacy and safety of lower linezolid doses.
Identify predictors of disease recurrence.
Larger trials and programmatic data for BPAL and BPALC regimens are required.
Studies assessing treatment completion, adherence support needs, and quality-of-life outcomes.
Values: Additional research is needed to obtain higher certainty in patient values related to the outcomes of interest.
Equity: Judgments about equity will be better informed by studies that capture both direct and indirect patient costs to better understand the financial burden of treatment, alongside the evaluation of equitable access to newer TB regimens across different populations
Resources: Effectiveness data from direct comparisons of regimens will be essential to inform cost-effectiveness and extended cost-effectiveness analyses, including the potential to reduce catastrophic costs for patients and households.
Acceptability: Studies assessing the acceptability of newer TB regimens among both patients and health-care providers, in conjunction with exploration of reasons for delayed uptake and implementation despite guideline recommendations, are needed.
Feasibility: Key feasibility concerns include barriers related to procurement and supply chains, regulatory approvals, and limitations in diagnostic and monitoring capacity.

PICO 7 evidence profile

Nurse-led palliative care interventions, in addition to effective treatment compared to effective treatment without such interventions in patients with pulmonary RR/MDR-TB (PICO 7)

Bibliography:											
Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With effective treatment without such interventions	With nurse-led palliative care interventions, in addition to effective treatment		Risk with effective treatment without such interventions	Risk difference with nurse-led palliative care interventions, in addition to effective treatment
Palliation (follow-up: 4 months; assessed with: African Palliative Outcome Scale)											
154 (1 RCT)	not serious[a]	not serious	not serious	very serious[b]	none	⨁⨁◯◯ Low[a,b]	78	76	-	-	SMD **0.61 SD higher** (0.35 higher to 0.86 higher)
Quality of life (Total) (follow-up: 4 months; assessed with: WHO-QOL BREF)											
154 (1 RCT)	not serious[c]	not serious	not serious	very serious[b]	none	⨁⨁◯◯ Low[b,c]	78	76	-	-	SMD **0.79 SD higher** (0.44 higher to 1.14 higher)
Psychological Well-being (lower scores indicate less psychological distress) (follow-up: 4 months; assessed with: GHQ-12)											
154 (1 RCT)	not serious[a]	not serious	not serious	serious[d]	none	⨁⨁⨁◯ Moderate[a,d]	78	76	-	-	SMD **0.49 SD lower** (0.68 lower to 0.3 lower)
TB Drug adherence (follow-up: 4 months; assessed with: number of patients with no missed doses in the past 30 days)											
135 (1 RCT)	not serious[a]	not serious	not serious	serious[e]	none	⨁⨁⨁◯ Moderate[a,e]	38/68 (55.9%)	62/67 (92.5%)	**OR 10.77** (3.99 to 35.10)	38/68 (55.9%)	**373 more per 1000** (from 276 more to 419 more)

Bibliography:											
Certainty assessment								Summary of findings			
Quality of life-Physical Domain (follow-up: 4 months; assessed with: WHOQoL BREF Tool; Scale from: 7 to 35)											
154 (1 RCT)	not serious[c]	not serious	not serious	very serious[f]	none	⨁⨁◯◯ Low[c,f]	78	76	-	-	SMD **0.45 SD higher** (0.15 higher to 0.76 higher)
Quality of life-Psychological Domain (follow-up: 4 months; assessed with: WHOQoL BREF Tool; Scale from: 6 to 30)											
154 (1 RCT)	not serious[c]	not serious	not serious	serious[g]	none	⨁⨁⨁◯ Moderate[c,g]	78	76	-	-	SMD **1.01 SD higher** (0.7 higher to 1.32 higher)
Quality of life-Social Domain (follow-up: 4 months; assessed with: WHOQoL BREF tool; Scale from: 3 to 15)											
154 (1 RCT)	not serious[c]	not serious	not serious	very serious[b]	none	⨁⨁◯◯ Low[b,c]	78	76	-	-	SMD **0.84 SD higher** (0.49 higher to 1.19 higher)
Quality of life -Environmental domain (follow-up: 4 months; assessed with: WHOQoL BREF tool; Scale from: 8 to 40)											
154 (1 RCT)	not serious[c]	not serious	not serious	very serious[b]	none	⨁⨁◯◯ Low[b,c]	78	76	-	-	SMD **0.6 SD higher** (0.21 higher to 0.99 higher)
Alcohol consumption (follow-up: 4 months; assessed with: Proportions of patients who had alcohol in the past month)											
135 (1 RCT)	not serious[a]	not serious	not serious	serious[h]	none	⨁⨁⨁◯ Moderate[a,h]	27/68 (39.7%)	10/67 (14.9%)	**OR 0.21** (0.08 to 0.51)	27/68 (39.7%)	**276 fewer per 1000** (from 347 fewer to 146 fewer)

CI: confidence interval; **OR:** odds ratio; **SMD:** standardised mean difference

Explanations

a. Low risk of bias: investigators were masked to each block size to reduce the possibility of predicting group allocation; Data collectors and statistician were masked to group assignment; however, the participants self-reported the outcome, which might introduce information bias

b. The optimal information size has not been met (total participants less than 400);2. From the confidence interval, it crosses moderate and large effect thresholds

c. Low risk of bias: investigators were masked to each block size to reduce the possibility of predicting group allocation; Data collectors and statistician were masked to group assignment.

d. The optimal information size has not been met (total participants less than 400); the confidence interval crossed one threshold (moderate effect)

e. The optimal information size has not been met (total events less than 300); the confidence interval does not cross the decision threshold

f. The optimal information size has not been met (total participants less than 400); the confidence interval crossed two thresholds (small and moderate effect)

g. The optimal information size has not been met (total participants less than 400); the confidence interval crossed one threshold (Large effect)

h. The optimal information size has not been met (total events less than 300); the confidence interval crossed the small effect threshold

PICO 7 evidence-to-decision

Question

Should nurse-led palliative care interventions, in addition to effective treatment vs. effective treatment without such interventions be used for patients with pulmonary RR/MDR-TB (PICO 7)?

POPULATION:	patients with pulmonary RR/MDR-TB (PICO 7)
INTERVENTION:	nurse-led palliative care interventions, in addition to effective treatment
COMPARISON:	effective treatment without such interventions
MAIN OUTCOMES:	Palliation; Quality of life (Total); Psychological Well-being (lower scores indicate less psychological distress); TB Drug adherence; Quality of life-Physical Domain; Quality of life-Psychological Domain; Quality of life-Social Domain; Quality of life -Environmental domain; Alcohol consumption;
SETTING:	Outpatient
PERSPECTIVE:	Population
BACKGROUND:	
CONFLICT OF INTERESTS:	The WHO GTB Program applied the WHO conflict of interest declaration and management policy, and the following were GDG members involved in decision-making for this recommendation: Ashna Ashesh (WHO Civil Society Task Force – TB; Survivors Against TB, India), Erlina Burhan (Persahabatan Hospital Jakarta; Faculty of Medicine – Universitas Indonesia), Muhwa Chakaya (National Tuberculosis Programme of Kenya), Gerry Davies (University of Liverpool, United Kingdom), Fernanda Dockhorn Costa Johansen (Ministry of Health MDR-TB referral centre, Brazil), Kelly Dooley (Vanderbilt University Medical Center, USA), Sobia Faisal (Greenstar Social Marketing, Pakistan), Elmira Gurbanova (Lung Clinic, University of Tartu, Estonia), Eric Krakauer (Harvard Medical School, USA), Christoph Lange (Research Center Borstel, Germany), Yuhong Liu (Beijing Chest Hospital, China), Andrey Maryandyshev (Phthisiopulmonology Department of the Northern State Medical University, Arkhangelsk, Russian Federation), Graeme Meintjes (University of Cape Town, South Africa), Mahshid Nasehi (National Tuberculosis Programme of the Islamic Republic of Iran), Mamel Quelapio (Independent consultant, the Philippines), Moorine Sekkade (National Tuberculosis Programme of Uganda), Urvashi Singh (National TB Programme, Ministry of Health, India), Wei Sha (Shanghai Pulmonary Hospital, China), Shaheed Vally Omar (South Africa Supranational TB Reference Laboratory), Luan Vo (Friends for International Tuberculosis Relief, Viet Nam). No member of the GDG had important conflicts precluding participation.

Assessment

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Tuberculosis (TB) remains a threat to global public health and is one of the topmost infectious causes of death in the world. In 2024, an estimated 10.7 million people developed TB, and 1.23 million died from the disease. About 390,000 new patients with rifampicin-resistant or multidrug-resistant tuberculosis (MDR/RR-TB) were estimated to emerge in 2024. While all of these patients would have been eligible for a second-line TB treatment regimen, only 165,650 enrolments on treatment were reported by countries in the same year. In recent years, substantial progress has been made with the introduction of improved diagnostics and more effective medicines, enabling earlier detection and boosting treatment success rates among MDR/RR-TB patients in many national programs, with a 71% success rate reported for those enrolled in 2022. The latest evidence-based guidelines for the treatment and care of TB and drug-resistant TB, including MDR/RR-TB and pre-XDR-TB, were published by WHO in April 2025 – "WHO consolidated guidelines on tuberculosis: module 4: treatment and care". The WHO Global TB Programme has combined all recommendations on the treatment of drug-resistant TB, drug-susceptible TB, and TB care and support in three separate chapters of the consolidated guidelines. Palliative care is the preventing and relieving of the suffering of people affected by TB during and after treatment and at the end-of-life. Many people with TB, and most with DR-TB, suffer in multiple ways: from physical symptoms such as pain or dyspnoea, from psychological symptoms such as anxiety or depression, and from social problems such as discrimination or homelessness. This suffering may be due to the disease, its treatment, physical or psychological comorbidities such as HIV/AIDS, diabetes, or mental health/substance use disorders, stigma and discrimination, or extreme poverty. People continue to die from both DR-TB and DS-TB, and their family members may suffer from the stress of caregiving, financial challenges, further stigma and grief. The RCT was conducted in Uganda to test whether nurse-led palliative care interventions improve patient-reported outcomes for patients with multidrug-resistant tuberculosis, compared with usual care. A total of 154 participants were recruited and randomly assigned to the intervention group (76 individuals) or the control group (78 individuals). Intervention group participants received nurse-led person-centred holistic assessment in line with WHO's definition of palliative care, care planning and palliative care support delivered on inpatient wards or at home. The research team made the trial data available to the WHO and presented it to the GDG for review at the meeting in November 2025. The evidence from this trial has been shared with WHO, and this guideline development group (GDG) is convened to review new evidence on the treatment and palliative care for patients with MDR/RR-TB or pre-XDR-TB to ensure that the latest treatment and care options are reflected in the WHO policy.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

○ Trivial
○ Small
● Moderate
○ Large
○ Varies
○ Don't know

RESEARCH EVIDENCE

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with effective treatment without such interventions	Risk with nurse-led palliative care interventions, in addition to effective treatment				
Palliation (PC) assessed with: African Palliative Outcome Scale follow-up: 4 months	The mean Palliation was **0** SD	SMD **0.61 SD higher** (0.35 higher to 0.86 higher)	-	154 (1 RCT)	⨁⨁◯◯ Low[a,b]	CRITICAL
Quality of life (Total) (QoL) assessed with: WHO-QOL BREF follow-up: 4 months	The mean quality of life (Total) was **0** SD	SMD **0.79 SD higher** (0.44 higher to 1.14 higher)	-	154 (1 RCT)	⨁⨁◯◯ Low[b,c]	CRITICAL
Psychological Well-being (lower scores indicate less psychological distress) assessed with: GHQ-12 follow-up: 4 months	The mean psychological Well-being (lower scores indicate better psychological well-being) was **0** SD	SMD **0.49 SD lower** (0.68 lower to 0.3 lower)	-	154 (1 RCT)	⨁⨁⨁◯ Moderate[a,d]	CRITICAL
TB Drug Adherence assessed with: number of patients with no missed doses in the past 30 days follow-up: 4 months	**Study population**		**OR 10.77** (3.99 to 35.10)	135 (1 RCT)	⨁⨁⨁◯ Moderate[a,e]	CRITICAL
	559 per 1000	**932 per 1000 (835 to 978)**				
Alcohol consumption assessed with: Proportions of patients who had alcohol in the past month follow-up: 4 months	**Study population**		**OR 0.21** (0.08 to 0.51)	135 (1 RCT)	⨁⨁⨁◯ Moderate[a,f]	IMPORTANT

a. Low risk of bias: investigators were masked to each block size to reduce the possibility of predicting group allocation; Data collectors and statistician were masked to group assignment; however, the participants self-reported the outcome, which might introduce information bias

b. The optimal information size has not been met (total participants less than 400);2. From the confidence interval, it crosses moderate and large effect thresholds

c. Low risk of bias: investigators were masked to each block size to reduce the possibility of predicting group allocation; Data collectors and statistician were masked to group assignment.

d. The optimal information size has not been met (total participants less than 400); the confidence interval crossed one threshold (moderate effect)

ADDITIONAL CONSIDERATIONS

Based on the thresholds for the prioritized outcomes listed below and the target of the certainty rating being a moderate effect, the GDG judged the desirable effcts to be moderate.

Continuous outcomes Palliation, Quality of Life and Psychological well being

- Trivial or no important Effect: <0.2 SMD
- Small Effect: 0.2 – 0.49 SMD
- Moderate Effect: 0.5 SMD – 0.79 SMD
- Large Effect: **> 0.8 SMD**

TB Drug Adherece

- Trivial or no important Effect: <58 fewer or more events per 1000 people
- Small Effect: 58 to 143 fewer or more events per 1000 people
- Moderate Effect: 144 to 269 fewer or more events per 1000 people
- Large Effect: ≥270 fewer or more events per 1000 people

These thresholds were derived from the panel and a utility estimates of 0.75 for TB Drug adherence. The panel expressed consensus for this threshold.

If the target of the certainty rating would be a small effect the certainty would even be higher.

e. The optimal information size has not been met (total events less than 300); the confidence interval does not cross the decision threshold

f. The optimal information size has not been met (total events less than 300); the confidence interval crossed the small effect threshold

Outcomes	With effective treatment without such interventions	With nurse-led palliative care interventions, in addition to effective treatment	Difference	Relative effect (95% CI)
Palliation assessed with: African Palliative Outcome Scale follow-up: 4 months	The mean Palliation was **0** SD	The mean Palliation in the intervention group was 0.61 standard deviations SD higher (0.35 higher to 0.86 higher)	SMD **0.61 SD higher** (0.35 higher to 0.86 higher) Moderate effect	-
Quality of life (Total) assessed with: WHO-QOL BREF follow-up: 4 months	The mean quality of life (Total) was **0** SD	The mean quality of life (Total) in the intervention group was 0.79 standard deviations SD higher (0.44 higher to 1.14 higher)	SMD **0.79 SD higher** (0.44 higher to 1.14 higher) Moderate effect	-
Psychological Well-being (lower scores indicate less psychological distress) assessed with: GHQ-12 follow-up: 4 months	The mean psychological Well-being (lower scores indicate less psychological distress) was **0** SD	The mean psychological Well-being (lower scores indicate less psychological distress) in the intervention group was 0.49 standard deviations SD lower (0.68 lower to 0.3 lower)	SMD **0.49 SD lower** (0.68 lower to 0.3 lower) Small effect	-
TB Drug adherence assessed with: number of patients with no missed doses in the past 30 days follow-up: 4 months	559 per 1000	**932 per 1000** (835 to 978)	**373 more per 1000** (276 more to 419 more) Large Effect	**OR 10.77** (3.99 to 35.10)

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	From the available evidence, there were no undesirable health effects identified.	However, the GDG notet that there was possible stigma with regards to confidentiality and privacy concerns when palliation interventions were delivered at home. There may also be cultural differences about the delivery and receiving palliative care.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	There was low overall certainty for moderate benefit and, thus, in the overall effect due to very severe imprecision (multiple thresholds crossed). If the target for the certainty rating of the desirable effects is a small effect, than it there is moderate overall certainty for small benefit and the resulting small net benefit due to severe imprecision (no thresholds crossed for main outcomes but the review information size not being met).	Panel noted that nurses in the country where the trial was done had prior training on how to deliver palliative care but agreed that this should not lead to downgrading for indirectness but that who can provide palliative care should rather be captured by specifying who can provide such care or what training would be required.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence was sought for.	There is little doubt that the identified outcomes are important to people with XDR-TB but given that no evidence was searched for the judgment is somewhat uncertain.

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ● Favours the intervention ○ Varies ○ Don't know	Moderate certainty in small net benefit, low certainty in moderate net benefit and probably no important uncertainty in the values.	The balance was judged to be in favour of the intervention.

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No available evidence from the systematic reviews. Two studies reported on the costs: **Buyinza et al 2025** provided the following information regarding the cost: Within the trial, the costs were: • $6 daily transport for the nurse x 5 days x 4 weeks = $120 • $16 daily professional allowance x 5 days x 4 weeks = $320 • $10 one-time off-airtime payment per month, Total =$330 • The full salary for a Hospice Africa Uganda nurse per month, including taxes, is about $685 per month • Cost savings range from 5–20% (such as place of care, reduction of beneficial treatment) **Gwyther 2025 et al** (*article in press*) provided costs for the Essential package of palliative care (EPPC)in a low-income country (Rwanda), a lower-middle-income country (Viet Nam), and upper upper-middle-income country (Mexico). The total costs for EPPC in LIC: USD 219; LMIC: USD 119, and UMIC: USD 796	There would be a requirement for a comprehensive package of care to make palliative care available to all patients.

Per Patient Cost of the Health Care Components of the Essential Package of Palliative Care adapted from the Lancet Commission of Palliative Care, 2018 USD 2015

	Rwanda	Viet Nam	Mexico
Medicines	52	27	122
Morphine (oral or injectable)	20	14	90
Equipment	31	5	31
Palliative care Team (HR)	121	78	584
Operational costs (8% of total)	16	9	59
Total[a]	**220**	**119**	**796**
% GDP required to fund EPPC for all patients in need	0.25	0.04	0.03
% total health expenditure required to fund the EPPC for all patients in need	3.35	0.56	0.50
% government expenditure on health required to fund the EPPC for all patients in need	8.79	1.04	0.97

[a] Total exclusive of Morphine costs, since costs covered in the medicines

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	There is imprecise information from limited settings leading to extremely serious indirectness.	

Cost effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ● No included studies	No research evidence was searched for systematically. Some studies were provided by the evidence review team.	Economic evaluations conducted by the following studies but they are not directly applicable to the information provided here. Thus, there are no included studies **1. Economic evaluations of palliative care models: A systematic review" by Mathew et al. (2020) (DOI: 10.1177/0269216319875906** **Key findings:** From an initial pool of 12,632 articles, only 5 studies met their inclusion criteria. • **Among the included studies:** • Two were modelling studies (from the USA and United Kingdom). • Three were economic evaluations from United Kingdom, Australia, and Italy. • **In terms of what was being compared:** • Two studies compared home-based palliative care vs. "usual care". • One compared a home-based PC to no care. • **Outcomes measured included:** • Prevention of hospital readmissions • Number of days at home (versus in hospital / institutional care), • Symptom severity under palliative care. • All five studies concluded that palliative care was cost-effective compared with usual care. **Conclusion:** The evidence suggests that palliative care *can* be a cost-effective model compared to usual care, but with current evidence – especially given methodological limitations (small sample sizes) – we should be cautious about generalising that conclusion broadly. More robust data are needed – ideally from large, well-designed studies that capture a full range of costs and patient-centred outcomes

		2. Reid et al 2019: (Is palliative care cost-effective in low-income and middle-income countries? A mixed-methods systematic review):https://pubmed.ncbi.nlm.nih.gov/30274970/ • Identified 10 eligible papers that reported both palliative-care outcomes and economic data in LMIC settings. • Four studies provided a "true cost-effectiveness analysis," meaning they compared palliative care vs. alternative care or usual care (no palliative care) and assessed costs relative to outcomes. • In those analyses, palliative care was associated with cost savings, favourable palliative (comfort, satisfaction, symptom relief, quality-of-life) outcomes, and positive feedback from patients and families.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was searched for	A recommendation in favour is likely to increase access to palliative care for the MDR-TB patients was the judgment by the GDG.

Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was searched for.	Because of the lack of research evidence nurse-led palliative care was judged as probably acceptable. **Patient:** Palliative care improves symptom management and patients' satisfaction. This intervention supports TB-patient-centred care **Providers or health care workers**: Expand the scope of work for the Nurses: training might be required, workload management, and compensation

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was searched for.	Because of the lack of research evidence nurse-led palliative care was judged as probably feasible. There was information from the trial investigating the effects as follows: Hospice Africa Uganda delivered the intervention Opened in 1993 and has been in operation without a break since then MDR-TB/TB patients would meet existing standard referral criteria to palliative care Strong network of clinical care services in the public and voluntary sector in Africa **Other considerations:** The GDG identified the importance of training needs for the nurses, workload of the nurses. The GDG judged that this intervention could be delivered by all trained health care providers

Summary of judgements

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	**Favours the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	•	○

Conclusions

Recommendation
In patients with pulmonary MDR/RR-TB, in addition to effective treatment, WHO GDG recommends integrating palliative care assessment and interventions by trained providers, as described in WHO palliative care guidance documents
(conditional recommendation, moderate certainty of evidence).
Remarks
Remarks:
While the underlying evidence stems from an RCT in Uganda involving nurses with advanced palliative care training delivering the intervention in addition to effective MDR/RR-TB treatment, the findings suggest that other appropriately trained providers could also deliver this care.
The interventions may be applicable to selected people with drug-susceptible TB who need palliative care interventions following needs assessment based on the WHO palliative care guidance documents.
Justification
Although there was only one trial, the balance of the effects generally favoured the intervention based on low and moderate certainty evidence depending on the target of the certainty rating for the benefits. There is little uncertainty about the values, but there is moderate cost and concerns about implementability which led to a conditional recommendation.
Subgroup considerations
There are no restrictions on the use of this intervention across population subgroups. Individuals with drug-susceptible tuberculosis (DS-TB) who meet the criteria outlined in the WHO model of palliative care are considered eligible.
Implementation considerations
Implementation of this recommendation requires careful attention to confidentiality and patient privacy. Individuals should be supported to choose their preferred place of care, whether at a health facility or at home, in line with their needs and circumstances.
Capacity building is essential to ensure high-quality palliative care delivery. This includes provision of basic training in palliative care for relevant health workers, aligned with the WHO model of palliative care.
A reliable medicine supply is critical, particularly the consistent availability of medications for pain relief and symptom control. Health systems should ensure uninterrupted access to these essential medicines.
Health system support and regulatory frameworks play a key role in implementation. Clear regulations are needed to define who is authorized to prescribe palliative care medications and under what conditions. Broader regulatory considerations should also address access to essential medicines.
Additional considerations include strengthening linkages with existing palliative care services and integrating palliative care with socio-economic support services where available.
Clinical decision-making regarding the choice and dosing of medicines should take into account individual patient factors, including organ function.
Monitoring and evaluation

Research priorities
Further research is needed to increase certainty in the evidence base, particularly to address the current imprecision.
Priority areas include evaluating the impact of palliative care on tuberculosis treatment outcomes, such as cure rates, sputum conversion, and mortality.
Economic evaluations are also required to assess the cost-effectiveness of integrating palliative care into tuberculosis services.
Implementation research should examine the acceptability and feasibility of palliative care for patients, caregivers, and health workers.
Research should explore different models of palliative care service delivery, including the involvement of additional provider cadres, and assess how these models perform across diverse geographical settings and contexts with varying tuberculosis burdens.
Further studies are needed to better understand which components of palliative care interventions are critical to achieving meaningful patient and health system outcomes.
Research should assess the potential risk of transmission of drug-resistant *Mycobacterium tuberculosis* strains within palliative care settings, with particular attention to the safety of caregivers and health workers.

Annex 6. Reports of the systematic reviews for tuberculosis care and support

https://iris.who.int/handle/10665/352904.



For further information, please contact:

Department for HIV, Tuberculosis, Hepatitis and Sexually Transmitted Infections
World Health Organization
Avenue Appia 20, 1211 Geneva 27, Switzerland
Website: www.who.int/tb