WHO consolidated guidelines on tuberculosis

Module 4: Treatment and care

World Health Organization

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

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Abbreviations and acronyms

aDSM	active TB drug-safety monitoring and management
AFB	acid-fast bacilli
AIDS	acquired immunodeficiency syndrome
aIPD	adult individual patient data
aOR	adjusted odds ratio
aRR	adjusted risk ratio
ART	antiretroviral therapy
BMI	body mass index
BPaL	bedaquiline, pretomanid and linezolid
BPaLC	bedaquiline, pretomanid, linezolid and clofazimine
BPaLM	bedaquiline, pretomanid, linezolid and moxifloxacin
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
GTB	Global Programme on Tuberculosis & Lung Health
HIV	human immunodeficiency virus
HR	isoniazid–rifampicin
HREZ	isoniazid–rifampicin–ethambutol–pyrazinamide
(H)REZ	(isoniazid optional)–rifampicin–ethambutol–pyrazinamide
Hr-TB	rifampicin-susceptible, isoniazid-resistant tuberculosis
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
PICO	population, intervention, comparator and outcomes
PLHIV	people living with HIV
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)
SMS	short message service or text message
SRL	TB supranational reference laboratory
STREAM	Standard Treatment Regimen of Anti-tuberculosis Drugs for Patients with MDR-TB (trial)
TB	tuberculosis
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/GTB	Global Programme on Tuberculosis & Lung Health of the World Health Organization
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
PZA	pyrazinamide
R	rifampicin
Z	pyrazinamide

Definitions

Bacteriologically confirmed: when a biological specimen is positive by smear microscopy, culture or a rapid diagnostic test for tuberculosis (TB) recommended by the World Health Organization (WHO).

Clinically diagnosed: when a person who does not fulfil the criteria for bacteriological confirmation has been diagnosed with TB disease by a medical practitioner who has decided to give the person a full course of TB treatment.

Drug-resistant TB (DR-TB): TB disease caused by a strain of *Mycobacterium tuberculosis* complex that is resistant to any TB medicines.

Drug-susceptible TB (DS-TB): A bacteriologically confirmed or clinically diagnosed case of TB without evidence of infection with strains resistant to rifampicin and isoniazid.

Drug susceptibility testing (DST): in vitro testing using either molecular or 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): 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 (levofloxacin or moxifloxacin) and to at least one other "Group A" drug (bedaquiline or linezolid).

Extrapulmonary tuberculosis (EPTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs (e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges).

MDR/RR-TB: refers to either multidrug-resistant TB (MDR-TB) or rifampicin-resistant TB (RR-TB).

Multidrug-resistant TB (MDR-TB): TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin and isoniazid.

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.

Operational research or **implementation research**: "the use of systematic research techniques for programme decision-making to achieve a specific outcome".[1] In the context of this document, these terms are also applied to research that aims to develop the critical evidence base that informs the effective, sustained and embedded adoption of interventions within a health system, to improve health or patient outcomes. Such research deals with the knowledge gap between efficacy, effectiveness and current practice to produce the greatest gains in disease control.[2] Operational research also

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[1] Allotey P, Reidpath DD, Ghalib H, Pagnoni F, Skelly WC. Efficacious, effective, and embedded interventions: implementation research in infectious disease control. BMC Public Health. 2008;8:343. (https://doi.org/10.1186/1471–2458–8-343).

[2] Guide to operational research in programmes supported by the Global Fund. Geneva: Global Fund to Fight AIDS, Tuberculosis and Malaria; 2007.

provides decision-makers with information to enable them to improve the performance of their health programmes.[3]

Pulmonary tuberculosis (PTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree.

Pre-extensively drug-resistant TB (pre-XDR-TB): 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).

Rifampicin-resistant TB (RR-TB): TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin. These strains may be susceptible or resistant to isoniazid (i.e. multidrug-resistant TB [MDR-TB]), or resistant to other first-line or second-line TB medicines.

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

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. Adverse events that do not immediately result in one of these outcomes but that require an intervention to prevent such an outcome from happening are included. Serious adverse events may require a drastic intervention, such as termination of the drug suspected of having caused the event.

Severe extrapulmonary TB: 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.

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

Treatment support terminology in this document is used to describe an approach to supporting patients who are taking prescribed doses of TB medicines in order to help ensure adherence to treatment and maximize its efficacy. Treatment support needs to be provided in the context of people-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.

TB case: the occurrence of TB disease in a person.

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

[3] Expanding capacity for operations research in reproductive health: summary report of a consultative meeting WHO, Geneva, Switzerland, December 10–12, 2001. Geneva: World Health Organization; 2003 (https://iris.who.int/handle/10665/67936). Licence:WHO/RHR/02.18.

Executive summary

The Global Programme on Tuberculosis & Lung Health of the World Health Organization (WHO/GTB) is now combining all current recommendations into one overall set of consolidated guidelines on TB. The guidelines contain recommendations pertaining to all areas related to the programmatic management of TB (e.g. screening, preventive treatment, diagnostics, patient support, and the treatment of drug-susceptible TB and DR-TB). The consolidated guidelines contain modules specific to each programmatic area.

In this updated and consolidated Module 4. Treatment and care, stakeholders will be able to distinguish between previous recommendations that remain valid, previous recommendations that have been 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.

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

Target audience

These guidelines are primarily targeted at policy-makers in ministries of health, or managers of NTPs who formulate country-specific TB treatment guidelines or are involved in the planning of TB treatment programmes. It is expected that these updated recommendations will also be used by health professionals, including doctors, nurses and educators working in governmental and nongovernmental organizations, and by technical agencies involved in treating patients and organizing treatment services.

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 recent 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; while using it, about 85% of patients will have 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 current document 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 most recent round of guidelines development in 2021 – the recommendations for 4-month treatments of DS-TB.

This chapter of the consolidated guidelines includes recommendations related to the treatment of DS-TB in 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 in another dedicated chapter: *Tuberculosis care and support*. The recommendations specific for children and adolescents are consolidated in the module on management of tuberculosis in children and adolescents *(4)*.

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 most recent guideline update on DS-TB treatment in 2021 aimed to use the best available evidence on the treatment of DS-TB to inform policy decisions made in this technical area by national TB programme (NTP) managers, national policy-makers and medical practitioners in a variety of geographical, economic and social settings.

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 brings forward 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 to 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 extensive 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 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 and 2016, as expressed in the 2010 and 2017 guidelines update.

Structure of the chapter

The recommendations part of this chapter has four 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 anti-retroviral therapy (ART) in people living with HIV (PLHIV); and
- the use of adjuvant steroids in the treatment of TB meningitis and pericarditis.

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; web annexes provide more details on the methods, the GDGs, 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 *(6)*, which is a separate document that is designed to aid implementation efforts.

Summary of WHO recommendations on drug-susceptible TB treatment

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

No.	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).***
1.2	**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).***
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).***
1.4	**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).***

1.5	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).*

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

No.	Recommendation
2.1	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).*
2.2	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).*

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

No.	Recommendation
3.1	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).*
3.2	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).*

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

No.	Recommendation
4.1	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).*
4.2	In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used *(conditional recommendation, very low certainty of evidence).*

Recommendations

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

Recommendation 1.1

No.	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)***

Remarks

A: 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.

B: 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.

C: 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 *(7)*. 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.[4] 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 *(8)*.

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.

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

Monitoring and evaluation

This recommendation places high value on saving lives. Given both the high certainty of evidence for this benefit and the fact that the potential harm of acquired DR-TB can be mitigated by supervision of treatment. Periodic drug resistance surveys (or ongoing surveillance) in each country are essential for monitoring the impact of the regimen and the overall treatment programme.

Recommendation 1.2

No.	Recommendation
1.2	**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 *(7)*. 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 pan-susceptible new patients being treated with these dosing schedules. However, the use of a three times weekly intensive phase schedule in patients with pre-treatment isoniazid resistance was associated in another meta-analysis with a significantly higher risk of failure and acquired drug resistance *(9)*.

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 *(10)*. In developing

recommendations, this endpoint was ranked by the GDG 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 pre-treatment isoniazid resistance and for preventing acquired drug resistance in patients overall.

Recommendation 1.3

No.	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)***

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 *(7)*, this systematic review was updated with the most recent RCTs *(11–17)*.

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 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 co-infected 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. See WHO's 2014 guideline *Guidance for national tuberculosis programmes on the management of tuberculosis in children (18)* for recommendations on the daily dosing of children with DS-TB.

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.

Monitoring and evaluation

There are no new monitoring and evaluation recommendations as the standard of care (daily dosing of medications during the intensive and continuation phases of therapy) is being recommended.

Recommendation 1.4

No.	Recommendation
1.4	**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 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 co-morbidities (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.

Monitoring and evaluation

There are no specific new recommendations for monitoring and evaluation as the use of both types of drug formulation is already widespread.

Recommendation 1.5

No.	Recommendation
1.5	**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 under way (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.

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

Recommendation 2.1

No.	Recommendation
2.1	**People aged 12 years or older with drug-susceptible pulmonary TB, may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide[5]** ***(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 *(12, 13, 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 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[6] and culture-positive pulmonary DS-TB *[27]*. Study participants were recruited from 13 countries. The

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

[6] 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".

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)*.

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 1200 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, USA, Viet Nam and Zimbabwe) were randomly assigned to a treatment group. The microbiologically eligible population[7] 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[8] 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

[7] 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.

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

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 1200 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 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 treatment (ART). HIV-positive persons not on ART at enrollment, had planned initiation of efavirenz-based ART before or at study week 8. Persons with HIV were excluded from enrollment in the trial if, at the time of enrollment, 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 extra-pulmonary 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 breast-feeding 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[9] because no fixed dose combination tablet exists for the regimen and the dose of rifapentine is high (1200 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[10] 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[11] 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 1200 mg of rifapentine was dosed daily, with food. This was based on: 1) demonstration of the safety of rifapentine at 1200 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 *(12)*).

As described in the trial's statistical analysis plan, pharmacokinetic/pharmacodynamic modelling predicted that a rifapentine dose of 1200 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 900–1200 mg, the strategy proposed was a rifapentine dose of 1200 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.

Monitoring and evaluation

The current guidance on monitoring the response to DS-TB treatment stays the same. The panel did not recommend baseline electrocardiogram (ECG) monitoring for those receiving the shorter regimen (unless clinically indicated), and laboratory monitoring such as liver function tests would remain the same for both regimens. Some countries may have different requirements for liver function

[9] 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.

[10] Rifapentine 150mg and 300mg are both included in the WHO Model list of essential medicines: 22nd list (2021). See: https://apps.who.int/iris/bitstream/handle/10665/345533/WHO-MHP-HPS-EML-2021.02-eng.pdf (accessed 28 February 2021).

[11] Approximately 5 times (US$ 225–233 versus US$ 343), based on current estimates using weighted average prices of the Global Drug Facility.

monitoring due to the "black box" warnings for moxifloxacin and these should be followed according to the country's policies.

Recommendation 2.2

No.	Recommendation
2.2	**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)***

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 two months of treatment is recommended in settings with a high prevalence of HIV[12], or of isoniazid resistance[13].

Source of recommendation

This recommendation has been developed following advice from the Guidelines Development Group convened by the WHO Global Tuberculosis Programme 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 multi-centre, 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

[12] 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.

[13] 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.

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.

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);[14] 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 under three 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[15] 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 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

[14] 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.

[15] 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).

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.

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 treatment 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 sub-group 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 < 3kg: 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 (18)*. 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[16] and/or the prevalence of isoniazid resistance is high[17] should 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 2.1 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).

Monitoring and evaluation

The clinical monitoring requirements for the shorter regimen remain the same as for the six-month regimen and treatment outcomes are determined at the end of the four-month regimen.

Should there be insufficient clinical improvement after completion of the four-month regimen, the clinician may decide to extend treatment to six months while considering alternative diagnoses, including DR-TB.

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[16] 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.

[17] 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.

Monitoring for potential relapse is a priority for shorter regimens especially when they are introduced into programmatic settings. Therefore, follow-up of children and young adolescents for up to 12 months after completion of the four-month regimen is important.

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

Recommendation 3.1

No.	Recommendation
3.1	**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 6 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 3.2

No.	Recommendation
3.2	**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) *(11)*. In 2017, on the basis of a systematic review of evidence that earlier ART initiation resulted in reduced morbidity and mortality *(44)*, 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 *(44)* – with stated cautions for those with signs and symptoms of TB meningitis.

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

Recommendation 4.1

No.	Recommendation
4.1	**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 4.2

No.	Recommendation
4.2	**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 **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 *(45–49)* 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 *(50–56)* 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 *(52)* – 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 *(51)*. 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 *(52)*. 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.

Monitoring and evaluation

There are no additional recommendations beyond the standard of care.

Research gaps

The GDGs 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 *(53)*.

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 extra-pulmonary 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.

References (Chapter 1)

1. Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update (WHO/HTM/TB/2017.05). Geneva: World Health Organization; 2017 (https://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf).
2. Treatment of tuberculosis, guidelines for national programmes, fourth edition (WHO/HTM/TB/2009.420). Geneva: World Health Organization; 2010 (https://www.who.int/publications-detail-redirect/9789241547833).
3. Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946–1986, with relevant subsequent publications. Int J Tuberc Lung Dis. 1999;3:S231–79 (https://www.ncbi.nlm.nih.gov/pubmed/10529902).
4. WHO consolidated guidelines on tuberculosis. Module 5: Management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022 (https://www.who.int/publications/i/item/9789240046764). Licence: CC BY-NC-SA 3.0 IGO.
5. The End TB Strategy. Geneva: World Health Organization; 2015 (https://www.who.int/teams/global-tuberculosis-programme/the-end-tb-strategy).
6. WHO consolidated guidelines on tuberculosis. Module 4: Treatment – tuberculosis care and support. Geneva: World Health Organization; 2022 (https://www.who.int/publications/i/item/9789240047716). Licence: CC BY-NC-SA 3.0 IGO.
7. Menzies D, Benedetti A, Paydar A, Martin I, Royce S, Pai M et al. Effect of duration and intermittency of rifampin on tuberculosis treatment outcomes: a systematic review and meta-analysis. PLoS Med. 2009;6:e1000146 (https://doi.org/10.1371/journal.pmed.1000146).
8. Updated recommendations on treatment of adolescents and children with chronic HCV infection, and HCV simplified service delivery and diagnostics. Geneva: World Health Organization; 2022 (https://www.who.int/publications/i/item/9789240052734). Licence: CC BY-NC-SA 3.0 IGO.
9. Menzies D, Benedetti A, Paydar A, Royce S, Madhukar P, Burman W et al. Standardized treatment of active tuberculosis in patients with previous treatment and/or with mono-resistance to isoniazid: a systematic review and meta-analysis. PLoS Med. 2009;6:e1000150 (https://doi.org/10.1371/journal.pmed.1000150).
10. Jindani A, Nunn AJ, Enarson DA. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. Lancet. 2004;364:1244–51 (https://doi.org/10.1016/S0140-6736(04)17141-9).
11. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach, 2nd edition. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf).
12. Gillespie SH, Crook AM, McHugh TD, Mendel CM, Meredith SK, Murray SR et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. N Engl J Med. 2014;371:1577–87 (https://doi.org/10.1056/NEJMoa1407426).
13. Merle CS, Fielding K, Sow OB, Gninafon M, Lo MB, Mthiyane T et al. A four-month gatifloxacin-containing regimen for treating tuberculosis. N Engl J Med. 2014;371:1588–98 (https://doi.org/10.1056/NEJMoa1315817).

14. Blanc FX, Sok T, Laureillard D, Borand L, Rekacewicz C, Nerrienet E et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. N Engl J Med. 2011;365:1471–81 (https://doi.org/10.1056/NEJMoa1013911).

15. Johnson JL, Hadad DJ, Dietze R, Maciel EL, Sewali B, Gitta P et al. Shortening treatment in adults with noncavitary tuberculosis and 2-month culture conversion. Am J Respir Crit Care Med. 2009;180:558–63 (https://doi.org/10.1164/rccm.200904-0536OC).

16. Lienhardt C, Cook SV, Burgos M, Yorke-Edwards V, Rigouts L, Anyo G et al. Efficacy and safety of a 4-drug fixed-dose combination regimen compared with separate drugs for treatment of pulmonary tuberculosis: the Study C randomized controlled trial. JAMA. 2011;305:1415–23 (https://doi.org/10.1001/jama.2011.436).

17. Swaminathan S, Narendran G, Venkatesan P, Iliayas S, Santhanakrishnan R, Menon PA et al. Efficacy of a 6-month versus 9-month intermittent treatment regimen in HIV-infected patients with tuberculosis: a randomized clinical trial. Am J Respir Crit Care Med. 2010;181:743–51 (https://doi.org/10.1164/rccm.200903-0439OC).

18. Guidance for national tuberculosis programmes on the management of tuberculosis in children (WHO/HTM/TB/2014.03). Geneva: World Health Organization; 2014 (https://apps.who.int/iris/bitstream/handle/10665/112360/9789241548748_eng.pdf).

19. Albanna AS, Smith BM, Cowan D, Menzies D. Fixed-dose combination antituberculosis therapy: a systematic review and meta-analysis. Eur Respir J. 2013;42:721–32 (https://doi.org/10.1183/09031936.00180612).

20. Gallardo CR, Rigau Comas D, Valderrama Rodriguez A, Roque i Figuls M, Parker LA, Cayla J et al. Fixed-dose combinations of drugs versus single-drug formulations for treating pulmonary tuberculosis. Cochrane Database Syst Rev. 2016;2016:CD009913 (https://doi.org/10.1002/14651858.CD009913.pub2).

21. Blomberg B, Spinaci S, Fourie B, Laing R. The rationale for recommending fixed-dose combination tablets for treatment of tuberculosis. Bull World Health Organ. 2001;79:61–8 (https://www.ncbi.nlm.nih.gov/pubmed/11217670).

22. Milan-Segovia RC, Dominguez-Ramirez AM, Jung-Cook H, Magana-Aquino M, Romero-Mendez MC, Medellin-Garibay SE et al. Relative bioavailability of rifampicin in a three-drug fixed-dose combination formulation. Int J Tuberc Lung Dis. 2010;14:1454–60 (https://pubmed.ncbi.nlm.nih.gov/20937187/).

23. Hao LH, Guo SC, Liu CC, Zhu H, Wang B, Fu L et al. Comparative bioavailability of rifampicin and isoniazid in fixed-dose combinations and single-drug formulations. Int J Tuberc Lung Dis. 2014;18:1505–12 (https://doi.org/10.5588/ijtld.13.0647).

24. Aung KJ, Declercq E, Ali MA, Naha S, Datta Roy SC, Taleb MA et al. Extension of the intensive phase reduces relapse but not failure in a regimen with rifampicin throughout. Int J Tuberc Lung Dis. 2012;16:455–61 (https://doi.org/10.5588/ijtld.11.0216).

25. Global tuberculosis report 2020. Geneva: World Health Organization; 2020 (https://www.who.int/publications-detail-redirect/9789240013131). Licence: CC BY-NC-SA 3.0 IGO.

26. Jindani A, Harrison TS, Nunn AJ, Phillips PP, Churchyard GJ, Charalambous S et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. N Engl J Med. 2014;371:1599–608 (https://doi.org/10.1056/NEJMoa1314210).

27. Dorman SE, Nahid P, Kurbatova EV, Phillips PPJ, Bryant K, Dooley KE et al. Four-month rifapentine regimens with or without moxifloxacin for tuberculosis. N Engl J Med. 2021;384:1705–18 (https://doi.org/10.1056/NEJMoa2033400).

28. Grace AG, Mittal A, Jain S, Tripathy JP, Satyanarayana S, Tharyan P et al. Shortened treatment regimens versus the standard regimen for drug-sensitive pulmonary tuberculosis. Cochrane Database Syst Rev. 2019;12:CD012918 (https://doi.org/10.1002/14651858.CD012918.pub2).

29. Ismail NA, Mvusi L, Nanoo A, Dreyer A, Omar SV, Babatunde S et al. Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: a national and sub-national cross-sectional survey. Lancet Infect Dis. 2018;18:779–87 (https://doi.org/10.1016/S1473-3099(18)30222-6).

30. Kayomo MK, Mbula VN, Aloni M, Andre E, Rigouts L, Boutachkourt F et al. Targeted next-generation sequencing of sputum for diagnosis of drug-resistant TB: results of a national survey in Democratic Republic of the Congo. Sci Rep. 2020;10:10786 (https://doi.org/10.1038/s41598-020-67479-4).

31. Lim DR, Dean AS, Taguinod-Santiago MR, Borbe-Reyes A, Cabibbe AM, Zignol M et al. Low prevalence of fluoroquinolone resistance among patients with tuberculosis in the Philippines: results of a national survey. Eur Respir J. 2018;51 (https://doi.org/10.1183/13993003.02571-2017).

32. Mesfin AB, Araia ZZ, Beyene HN, Mebrahtu AH, Suud NN, Berhane YM et al. First molecular-based anti-TB drug resistance survey in Eritrea. Int J Tuberc Lung Dis. 2021;25:43–51 (https://doi.org/10.5588/ijtld.20.0558).

33. Zignol M, Dean AS, Alikhanova N, Andres S, Cabibbe AM, Cirillo DM et al. Population-based resistance of Mycobacterium tuberculosis isolates to pyrazinamide and fluoroquinolones: results from a multicountry surveillance project. Lancet Infect Dis. 2016;16:1185–92 (https://doi.org/10.1016/S1473-3099(16)30190-6).

34. Zvada SP, Van Der Walt JS, Smith PJ, Fourie PB, Roscigno G, Mitchison D et al. Effects of four different meal types on the population pharmacokinetics of single-dose rifapentine in healthy male volunteers. Antimicrob Agents Chemother. 2010;54:3390–4 (https://doi.org/10.1128/AAC.00345-10).

35. Turkova A, Wills GH, Wobudeya E, Chabala C, Palmer M, Kinikar A et al. Shorter treatment for nonsevere tuberculosis in African and Indian children. N Engl J Med. 2022;386:911–22 (https://doi.org/10.1056/NEJMoa2104535).

36. Chabala C, Turkova A, Thomason MJ, Wobudeya E, Hissar S, Mave V et al. Shorter treatment for minimal tuberculosis (TB) in children (SHINE): a study protocol for a randomised controlled trial. Trials. 2018;19:237 (https://doi.org/10.1186/s13063-018-2608-5).

37. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. Geneva: World Health Organization; 2007 (https://iris.who.int/handle/10665/43699).

38. Guideline: updates on the management of severe acute malnutrition in infants and children. Geneva: World Health Organization; 2013 (https://www.who.int/publications-detail-redirect/9789241506328).

39. WHO consolidated guidelines on tuberculosis. Module 4: Treatment – drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/9789240007048). Licence: CC BY-NC-SA 3.0 IGO.

40. WHO consolidated guidelines on tuberculosis. Module 1: Prevention – tuberculosis preventive treatment. Geneva: World Health Organization; 2020 (https://www.who.int/publications-detail-redirect/9789240001503). Licence: CC BY-NC-SA 3.0 IGO.

41. Khan FA, Minion J, Pai M, Royce S, Burman W, Harries AD et al. Treatment of active tuberculosis in HIV-coinfected patients: a systematic review and meta-analysis. Clin Infect Dis. 2010;50:1288–99 (https://doi.org/10.1086/651686).

42. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: World Health Organization; 2021 (https://www.who.int/publications-detail-redirect/9789240031593). Licence: CC BY-NC-SA 3.0 IGO.

43. Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for a public health approach: 2010 revision. Geneva: World Health Organization; 2010 (https://apps.who.int/iris/bitstream/handle/10665/44379/9789241599764_eng.pdf).

44. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/handle/10665/255884). Licence: CC BY-NC-SA 3.0 IGO.

45. Chotmongkol V, Jitpimolmard S, Thavornpitak Y. Corticosteroid in tuberculous meningitis. J Med Assoc Thai. 1996;79:83–90 (https://pubmed.ncbi.nlm.nih.gov/8868018/).

46. Kumarvelu S, Prasad K, Khosla A, Behari M, Ahuja GK. Randomized controlled trial of dexamethasone in tuberculous meningitis. Tuber Lung Dis. 1994;75:203–7 (https://doi.org/10.1016/0962-8479(94)90009-4).

47. Malhotra HS, Garg RK, Singh MK, Agarwal A, Verma R. Corticosteroids (dexamethasone versus intravenous methylprednisolone) in patients with tuberculous meningitis. Ann Trop Med Parasitol. 2009;103:625–34 (https://doi.org/10.1179/000349809X12502035776315).

48. Schoeman JF, Van Zyl LE, Laubscher JA, Donald PR. Effect of corticosteroids on intracranial pressure, computed tomographic findings, and clinical outcome in young children with tuberculous meningitis. Pediatrics. 1997;99:226–31 (https://doi.org/10.1542/peds.99.2.226).

49. Thwaites GE, Nguyen DB, Nguyen HD, Hoang TQ, Do TT, Nguyen TC et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med. 2004;351:1741–51 (https://doi.org/10.1056/NEJMoa040573).

50. Critchley JA, Young F, Orton L, Garner P. Corticosteroids for prevention of mortality in people with tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis. 2013;13:223–37 (https://doi.org/10.1016/S1473-3099(12)70321-3).

51. Hakim JG, Ternouth I, Mushangi E, Siziya S, Robertson V, Malin A. Double blind randomised placebo controlled trial of adjunctive prednisolone in the treatment of effusive tuberculous pericarditis in HIV seropositive patients. Heart. 2000;84:183–8 (https://doi.org/10.1136/heart.84.2.183).

52. Mayosi BM, Ntsekhe M, Bosch J, Pandie S, Jung H, Gumedze F et al. Prednisolone and Mycobacterium indicus pranii in tuberculous pericarditis. N Engl J Med. 2014;371:1121–30 (https://doi.org/10.1056/NEJMoa1407380).

53. Mayosi BM, Ntsekhe M, Volmink JA, Commerford PJ. Interventions for treating tuberculous pericarditis. Cochrane Database Syst Rev. 2002:CD000526 (https://doi.org/10.1002/14651858.CD000526).

54. Reuter H, Burgess LJ, Louw VJ, Doubell AF. Experience with adjunctive corticosteroids in managing tuberculous pericarditis. Cardiovasc J S Afr. 2006;17:233–8 (https://pubmed.ncbi.nlm.nih.gov/17117227/).

55. Schrire V. Experience with pericarditis at Groote Schuur Hospital, Cape Town: an analysis of one hundred and sixty cases studied over a six-year period. S Afr Med J. 1959;33:810–7 (https://pubmed.ncbi.nlm.nih.gov/14443596/).

56. Strang JI, Kakaza HH, Gibson DG, Girling DJ, Nunn AJ, Fox W. Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. Lancet. 1987;2:1418–22 (https://doi.org/10.1016/s0140-6736(87)91127-5).

Chapter 2
Drug-resistant TB treatment

Introduction

Tuberculosis (TB) strains that are resistant to TB medicines are more difficult to treat than drug-susceptible ones, 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 1**). WHO has recently started to consolidate 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. 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,[18] 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 (BEAT-TB) and endTB trials. The inclusion of new recommendations in the current 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.

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 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 MDR-TB treatment and hepatitis C and MDR/RR-TB treatment co-administration. Additionally, to inform the global community of the major gaps and research areas to be addressed and to inform the development of evidence-based recommendations, this document outlines the research priorities that will help to generate knowledge on evidence-based and attainable standards of health.

[18] Pretomanid is a new chemical entity and a member of a class of compounds known as nitroimidazo-oxazines, which possess significant anti-TB activity and a unique mechanism of action.

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.

Drug-resistant tuberculosis (DR-TB) remains a significant public health challenge, impacting patients, communities, and healthcare systems profoundly. In 2023, global estimates suggest there were around 400 000 new cases of multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB), yet less than half of these cases were officially reported and began treatment *(5)*. Treatment success rates have improved, rising from 50% in 2012 to 68% in 2021, but still, nearly 15% of those with MDR/RR-TB 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 drugs with more severe side effects, leading to significant adverse events and less favorable outcomes. However, a breakthrough came in 2022 with the introduction of the first 6-month treatment regimen using three or four medications.

This current chapter concerns TB treatment and care; it presents WHO recommendations that have been newly developed and are published here for the first time, and existing recommendations that have been published in other WHO guidelines that applied the Grading of Recommendations Assessment, Development and Evaluation (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 drug-resistant TB using 6-month regimens
  - the 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen;
  - the 6-month bedaquiline, delamanid, linezolid, levofloxacin and clofazimine (BDLLfxC) regimen
- Treatment of drug-resistant TB using 9-month regimens
  - the 9-month all-oral regimens;
  - the modified 9-month all-oral regimens;
- Treatment of drug-resistant TB using longer regimens;
- Treatment of rifampicin-susceptible and isoniazid-resistant TB (Hr-TB);
- Monitoring of the patient response to MDR/RR-TB treatment;
- Starting Antiretroviral therapy (ART) for people on MDR/RR-TB regimen;
- Surgery for people on MDR/RR-TB treatment;
- Hepatitis C virus (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, and monitoring and evaluation. Research gaps identified for each of the sections are then presented. Annexes provide more details on the methods, the Guideline Development Groups (GDGs), PICO 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)*. The detailed recommendations presented here replace all of those in previous WHO guidelines on the treatment of DR-TB.

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) continued to be an option for patients who were not eligible for the shorter option. Subsequent modifications to these treatment regimens led WHO to assess new evidence, which in turn resulted in revised recommendations, balancing 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 or do not have additional resistance to second-line 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 have prompted further advances in the development of new treatments such as 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 extensive drug-resistance profiles, has been the driver for several studies and initiatives to test more effective and novel treatment regimens, 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 pre-XDR-TB patients, under operational research conditions.

In preparation for the 2022 guidelines update, WHO/GTB received data from another trial – the Newer and Emerging Treatment for MDR/RR-TB (NExT) trial – which was a Phase 2–3 open-label

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 discussion on the population, intervention, comparator and outcome (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 randomized controlled trials (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 BPaLM/BPaL regimen for treatment of MDR/RR-TB and pre-XDR-TB, and two variations of the 9-month regimen for those without fluoroquinolone resistance. The latest evidence-based guidelines for the treatment of drug-resistant TB, including MDR/RR-TB and pre-XDR-TB, were published by WHO in December 2022 – "WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment".

In 2024, two clinical trials, BEAT-TB 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.

Scope of the 2025 update and available evidence

This chapter provides specific recommendations on the treatment of DR-TB, including the use of regimens for rifampicin-susceptible, isoniazid-resistant TB (Hr-TB), shorter and longer regimens for MDR/RR-TB, monitoring patient response to MDR/RR-TB treatment, starting 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.

The 2024 GDG meeting convened by WHO resulted in two new recommendations: the use of a new 6-month regimen and modified 9-month regimens.

Access to the new evidence was achieved through close collaboration and engagement with national TB programmes (NTPs), researchers, and not-for-profit organizations investigating the effectiveness and safety of these interventions.

The new evidence appraised during the 2024 GDG meeting included a new 6-month regimen based on bedaquiline (B), delamanid (D), and linezolid (L) in combination with either levofloxacin (Lfx) or clofazimine (C) or both (BEAT-TB clinical trial in South Africa, NCT04062201) and a group of modified 9-month regimens for the treatment of patients with MDR/RR-TB without fluoroquinolone resistance (endTB clinical trial, NCT02754765).

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

Table A. Evidence available for the guidelines updates

Trial (setting)	Population	Intervention regimen(s)	Comparator regimen(s)
BEAT-TB 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 $_{L600}$ for two months ($_{(}$for fluoroquinolone susceptible) • 18–20-month all-oral individualized regimen (for fluoroquinolone-resistant)
endTB trial (Georgia, India, Kazakhstan, Lesotho, Pakistan, Peru, South Africa)	15 years and older with documented pulmonary tuberculosis 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 300mg daily or 600mg 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 1200 mg daily for 6 months (option of 9 months for subjects who remain culture positive at month 4)[19]	No standard of care control group
ZeNix (South Africa, Georgia, Moldova and the Russian Federation) ***(25)***	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 $BPaL_{1200–26\ weeks}$ $BPaL_{1200–9\ weeks}$ $BPaL_{600–26\ weeks}$ $BPaL_{600–9\ weeks}$ Treatment extended if culture positive in weeks 16–26	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

[19] 21 patients in the Nix-TB study received linezolid 600 mg per day, at the beginning of the recruitment period.

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 Bdq & Lzd (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 Open-label RCT	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

BPaL: bedaquiline, pretomanid and linezolid; BPaLC: bedaquiline, pretomanid, linezolid and clofazimine; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; BLMZ: bedaquiline, linezolid, moxifloxacin and pyrazinamide; BLLfxCZ: bedaquiline, linezolid, levofloxacin, clofazimine and pyrazinamide; BDLLfxZ: bedaquiline, delamanid, linezolid, levofloxacin and pyrazinamide; DCLLfxZ: delamanid, clofazimine, linezolid, levofloxacin and pyrazinamide; DCMZ: delamanid, clofazimine, moxifloxacin and pyrazinamide BDLLfxC: bedaquiline, delamanid, linezolid, levofloxacin and clofazimine; HIV: human immunodeficiency virus; IPD: individual patient dataset; *M. tuberculosis; Mycobacterium tuberculosis;* MDR-TB: multidrug-resistant TB; RCT: randomized controlled trial; TB: tuberculosis; WHO: World Health Organization; pre-XDR-TB: pre-extensively drug-resistant TB.

Summary of WHO recommendations on drug-resistant 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 1**), and a WHO guideline development conducted in June 2024. These recommendations supersede the *WHO consolidated guidelines on tuberculosis. Module 4: Treatment – drug-resistant tuberculosis treatment*, that were published in 2022 *(3)*.

Box 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) *(26)*.
- 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) *(27)*.
- WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update. Geneva: World Health Organization; 2018 (WHO/CDS/TB/2018.15) *(28)*.
- 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) *(29)*.
- 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 *(30)*.
- WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2022 update (ISBN 978–92–4–006312–9) *(3)*.

The recommendations are presented in **Table B** below and labelled as either a new recommendation (where based on a review of new evidence) or a reprinted recommendation (where no new evidence was available or searched for the review).

Table B. List of recommendations in the 2025 edition, where (a) is a new recommendation based on review of the new evidence and (b) is a reprinted recommendation where no new evidence was available or searched for the review

1. Treatment of drug-resistant TB using 6-month regimens	
1.1	**The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for MDR/RR-TB and pre-XDR-TB (b)** 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)*
1.2	**The 6-month bedaquiline, delamanid, linezolid, levofloxacin and clofazimine (BDLLfxC) regimen (a)** 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)*
2. Treatment of drug-resistant TB using 9-month regimens	
2.1	**The 9-month all-oral regimen for MDR/RR-TB (b)** 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)*
2.2	**The modified 9-month all-oral regimens for MDR/RR-TB (a)** 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)*
2.3	WHO suggests against using 9-month DCLLfxZ or DCMZ regimens compared with currently recommended longer (>18 months) regimens in patients with fluoroquinolone-susceptible MDR/RR-TB. *(Conditional recommendation, very low certainty of evidence)*
3. Treatment of drug-resistant TB using longer regimens (b)	
3.1	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)*

3.2	**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)*
3.3	**Levofloxacin or moxifloxacin** should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)*
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 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)*
3.5	**Linezolid** should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)*
3.6	**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)*
3.7	**Ethambutol** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
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)* 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)*
3.9	**Pyrazinamide** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.10	**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]
3.11	**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 in the estimates of effect)*

[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.

3.12 **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 against use, very low certainty of evidence)

3.13 ***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 against use, very low certainty of evidence)

3.14 **Clavulanic acid** should not be included in the treatment of MDR/RR-TB patients on longer regimens.

(Strong recommendation against use, low certainty of evidence)[20]

3.15 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)

3.16 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)

3.17 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)

4. Regimen for rifampicin-susceptible and isoniazid-resistant TB (b)

4.1 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 in the estimates of effect)

4.2 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)

5. Monitoring patient response to MDR/RR-TB treatment using culture (b)

5.1 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)

6. Starting ART in patients on MDR/RR-TB regimens (b)

6.1 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)

7. Surgery for patients on MDR/RR-TB treatment (b)	
7.1	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)*
8. Hepatitis C virus (HCV) and MDR/RR-TB treatment co-administration (a)	
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)*

Target audience

These guidelines are primarily targeted at policy-makers in ministries of health, or managers of NTPs who formulate country-specific TB treatment guidelines or are involved in the planning of TB treatment programmes. It is expected that these updated recommendations will also be used by health professionals, including doctors, nurses and educators working in governmental and nongovernmental organizations, and by technical agencies involved in treating patients and organizing treatment services.

Recommendations

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

Recommendation 1.1 The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen

No.	Recommendation
1.1	WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) 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)*

Remarks

1. Drug susceptibility testing (DST) for fluoroquinolones is strongly encouraged in people with MDR/RR-TB, and although it should not delay initiation of the BPaLM, 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 without moxifloxacin would be initiated or continued.
2. This recommendation applies to the following:
   a) People with MDR/RR-TB or with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR-TB).
   b) People with confirmed pulmonary TB and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular or disseminated forms of TB with multiorgan involvement.[21]
   c) Adults and adolescents aged 14 years and older.
   d) All people regardless of HIV status.
   e) Patients with less than 1-month previous exposure to bedaquiline, linezolid, pretomanid or delamanid. When exposure is greater than 1 month, these patients may still receive these regimens if resistance to the specific medicines with such exposure has been ruled out.
3. This recommendation does not apply to pregnant and breastfeeding women owing to limited evidence on the safety of pretomanid.[22]
4. The recommended dose of linezolid is 600 mg once daily, both for the BPaLM and the BPaL regimen.[23]

[21] See subgroup considerations.

[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.

Rationale

The rationale for this recommendation is based on the evidence and considerations described in detail in the following two subsections. Briefly, data from an RCT (stage 2 of TB-PRACTECAL, corresponds to a Phase 3 trial) showed much improved treatment success rates with the BPaLM regimen (89%) of 6 months duration compared with the current SoC regimens (52%), as well as lower levels of treatment failure, death and loss to follow-up (LTFU). 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 currently 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.

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**).

PICO questions

The recommendation in this section is a result of assessments of the PICO questions listed below. Because of the different intervention and comparator groups used, PICOs 3, 5, and 6 have been split into several sub-PICO questions (details are given in the text and in **Table 1.3**).

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 BPaL regimen?

PICO question 4–2022 (MDR/RR-TB, 2022): Should 6-month regimen using bedaquiline, pretomanid, 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 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 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)?

Data and studies considered

The review of this group of PICO questions during the GDG meeting convened by WHO in February–March 2022 was based on new evidence provided by MSF from the TB-PRACTECAL clinical trial and by the TB Alliance from the ZeNix trial. For several assessments under this PICO question, the data from the 2021 WHO individual patient dataset (IPD) were used. Patient populations included in two trials were recruited following strict inclusion and exclusion criteria; the populations had many similarities and few notable differences. The highlights of the criteria used by these trials are presented in **Table 1.1**. For a complete list of the exclusion criteria, see published trial protocols.[24]

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

Table 1.1. High-level summary of main inclusion and exclusion criteria: TB-PRACTECAL and ZeNix trials

	TB-PRACTECAL	ZeNix *(25)*
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 (with the exception of 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 msec, 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 MAO Inhibitors

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

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

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

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.

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 and 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 and 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: 1200 mg 26 weeks, 1200 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) *(31)*. Safety monitoring included scheduled testing and assessments of laboratory parameters, ECG, vital

signs and other physical examinations *(32)*. Microbiological monitoring included smear microscopy, molecular testing and liquid culture from sputum at baseline and liquid culture at all patient visits thereafter *(32)*.

Table 1.2. 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 (B) 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 (B) 200 mg once daily for the first 8 weeks of treatment followed by 100 mg once daily for 18 weeks (off-label)
Pretomanid (Pa) 200 mg once daily for 24 weeks	Pretomanid (Pa) 200 mg once daily for 26 weeks
Linezolid (L) 600 mg daily for 16 weeks then 300 mg daily for the remaining 8 weeks	Linezolid (L) 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

Box 2. Bedaquiline dosing approach in ZeNix trial

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 *(31)* 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:

- The exposures (C_{max}, 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 WHO (*2018*) all-oral treatment regimen containing at least bedaquiline and linezolid.

The individual datasets that are included in this cohort are described in detail in the statistical analysis plan (**Annex 6**). 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:

- 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.

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 dataset or cohorts, outcomes were presented as unadjusted and adjusted risk ratios (RR). Adjusted risk ratios (aRR) were calculated using a log-binomial generalized linear regression (binomial error distribution with log link function). Pre-specified 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, aRR were not calculated, and unadjusted RR 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, it was important for follow-up time between two groups in a comparison to be equivalent, 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 *(33)*.
- 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 to allow for relapse to be captured.

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

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 a total of 419 of 423 participants who were enrolled in four arms of the TB-PRACTECAL 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 BPaLM/BPaL regimen. Even though 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 to the BPaLM arm (sub-PICOs 6.2 to 6.6) were performed to aid the panel in making final decisions.

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

Sub-PICO 3.2

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

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 1200 mg linezolid is suggested as part of the BPaL regimen in adults with MDR/RR-TB or pre-XDR-TB.

Sub-PICO 3.4

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 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 600–9 (*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 1200 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 – 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

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 – 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

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 but no comparison could be done 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

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 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

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 – 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

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 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, a 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

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

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

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);
- 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).

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).

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.

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);
- 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 – 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.

Summary of other evidence

Additional data reviewed by the 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 data based on the development of a pharmacokinetic 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.

Pharmacokinetic data

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

The pharmacokinetics 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 adverse effects 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 for 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 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.

Resources required and cost–effectiveness

Estimated regimen costs (in adults) at GDF prices[29] are about US$ 688 for BPaL (600–26), US$ 716 for BPaLM (600–26), an average of US$ 771 for longer regimens (depends on length and composition) and US$ 535–557 for 9-month regimens. 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 *(34, 35)* and one compared the BPaL, BPaLM and BPaLC regimens with longer (18-month) regimens and with the 9-month regimen with ethionamide *(36)*. 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 BPaLM/BPaL would probably to lead to large savings when replacing the longer (18-month) regimens and moderate savings when replacing the 9-month regimens.

[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.

The cost–effectiveness study *(36)* found that, in most settings, BPaLM/BPaL 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 BPaLM/BPaL.

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 BPaLM/BPaL regimen owing to its reduced complexity and shorter duration. Therefore, the panel judged that use of the BPaLM/BPaL regimen would probably increase equity.

A study on the acceptability and feasibility of the BPaL regimen from the provider perspective *(37)* 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 *(38)* 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 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 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, either due to ineligibility or unavailability of its components, can instead be treated with 6-month BDLLfxC (see Recommendation 1.2) or one of the 9-month regimens (see **Treatment of drug-resistant TB using 9-month regimens**). The use of the longer regimens is reserved (see **Treatment of drug-resistant TB using longer regimens**) 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 who would then receive a longer regimen designed with remaining effective medicines from Groups A, B and C, according to their drug susceptibility profile and other parameters.

[30] Unpublished, courtesy of Beverley Stringer, Manson unit, Médecins Sans Frontières.

Table 1.3 lists the comparisons and decisions on each of the sub-PICO-questions that were eventually used by the GDG to conclude with this summary recommendation. Throughout the discussion, the GDG panel 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 it to be higher than that of other (indirect or between-trial or cohort) comparisons.

Although assessments of PICO questions 3, 4, 5 and 6 have all contributed to the summary recommendation, the main assessment that defined the overall decision was that of sub-PICO 6.1 on the comparison of the BPaLM regimen of the stage 2 (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). Even though 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 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 resulted in the conditional recommendation for use of 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 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 resulted in the conditional recommendation for use of the BPaLM regimen of the TB-PRACTECAL trial over the comparator, 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 and 6.6 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 and 6.5 resulted in the conditional recommendations for BPaLM and BPaL over BPaLC; based on these assessments the GDG concluded that BPaLC should not be recommended as a regimen.

f) The assessment of sub-PICO 6.2 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.

Table 1.3. PICO questions and decisions of the GDG panel

#	PICO	Population	Intervention	Comparator [data source]	Sub-PICO	Recommendation
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-TB or pre-XDR-TB	BPaL (1200 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	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	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

#	PICO	Population	Intervention	Comparator [data source]	Sub-PICO	Recommendation
6	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)?	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

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-resistant or rifampicin-resistant TB; PICO: population, intervention, comparator and outcome; TB: tuberculosis; pre-XDR-TB: pre-extensively drug-resistant TB.

[a] ZeNix trial.

[b] 2021 IPD.

[c] TB-PRACTECAL.

The GDG panel 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 have been used in children except for pretomanid. New data on bedaquiline has been recently reviewed and its use has been expanded to all ages (see additional recommendation in the section on longer regimens and *(30)*). The lack of safety data on pretomanid in children aged below 14 years was the main barrier for potential extrapolation of the BPaLM/BPaL recommendation to the threshold of being aged below 14 years. Thus, the recommendation of the BPaLM/BPaL 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; however, it was impossible to perform any adjusted stratified analyses for people living with HIV (PLHIV), owing to the small sample size in sub-PICO comparisons 3.2, 3.3, 3.4 and 3.5. PLHIV 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 in the list of TB-PRACTECAL exclusion criteria, and PLHIV represented 27% of those enrolled. The median CD4 count among PLHIV 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 BPaLM/BPaL regimen applies to all people 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 **Treatment of drug-resistant TB using longer regimens**). Breastfeeding is not recommended for women taking pretomanid *(39)*. Thus, the recommendation of the BPaLM/BPaL regimen does not apply to pregnant and breastfeeding women. While 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 central nervous system (CNS) penetration of bedaquiline or pretomanid are limited. Although all forms of extrapulmonary TB were excluded from the clinical trials, 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 BPaLM/BPaL 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.

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 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.

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 BPaLM/BPaL 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 resistance testing should also be done before the start of treatment. However, fluoroquinolone resistance 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, moxifloxacin should be dropped 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 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 *(40, 41)*. The WHO has recently endorsed the use of targeted next-generation sequencing (NGS) for the detection of drug resistance, as outlined in the "WHO consolidated guidelines on tuberculosis. Module 3: Diagnosis – rapid diagnostics for tuberculosis detection, third edition" (Geneva: World Health Organization; 2024). 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 drug susceptibility testing (DST) criteria have been set. Countries implementing programs to manage drug-resistant TB (DR-TB) should develop lab infrastructure to perform culture-based phenotypic DST for drugs used in multidrug-resistant/rifampicin-resistant TB (MDR/RR-TB) treatments, 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 *(42)*.

Currently, there is limited capacity globally for DST for bedaquiline and linezolid. As these medicines and regimens containing these medicines become more widely used, laboratory capacity in this area must be strengthened. National and reference laboratories will need to have 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 sequencing of *M. tuberculosis* can provide a strong and future-proof platform for DST. If resistance to any of the component medicines in the BPaL regimen is detected, treatment with another recommended regimen should be started. The WHO TB Supranational Reference Laboratory (SRL) Network is available to support national TB reference laboratories in performing quality-assured DST. A WHO technical consultation in established critical concentrations for DST for the fluoroquinolones, bedaquiline, delamanid, clofazimine, pretomanid and linezolid *(42, 43)*. 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 can also protect against 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 *(44)*. Efavirenz reduces pretomanid exposures significantly; therefore, an alternative antiretroviral agent should be considered if pretomanid forms part of the BPaLM/BPaL regimen *(39)*. The preferred ART regimens for co-administration with BPaLM/BPaL are dolutegravir-based regimens in combination with two nucleoside reverse transcriptase inhibitors.

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) more than 500 ms, or 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 this to be the best option despite these contraindications and where adequate monitoring is available.

Regimen composition, dosing of component medicines and frequency

The BPaLM/BPaL regimen consists of bedaquiline, pretomanid and linezolid, with or without moxifloxacin 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. 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 assessments, the replacement of moxifloxacin with levofloxacin or any other fluoroquinolone cannot be recommended at this stage. The frequency of dosing should be 7 days a week with treatment support or using 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 *(31)*. 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; and
- 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 *(45)*. The 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 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 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. 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 where resistance to fluoroquinolones is identified before or after treatment initiation, moxifloxacin can be discontinued. 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 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 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). Ideally, 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, 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 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;
- 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 total of a maximum 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 1.2 The 6-month bedaquiline, delamanid, linezolid, levofloxacin and clofazimine (BDLLfxC) regimen

No.	Recommendation (NEW)
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).
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).

Rationale

The rationale for this recommendation is based on the evidence and considerations described in detail in the following two subsections. Data from an RCT (BEAT Tuberculosis trial: NCT04062201) showed that the efficacy and safety of the BDLLfxC regimen was similar to that of the control arm regimen (WHO-recommended 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 PLHIV.

Summary of evidence

This section provides the PICO question, 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 the web annex containing the GRADE evidence summary tables and GRADE EtD tables (**Annex 5**).

PICO question

The recommendation in this section is a result of assessments of the PICO question 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 (BDLLfxC) – be used in patients with pulmonary RR-TB (with or without fluoroquinolone resistance) over the currently recommended 9-month regimen?*

Data and studies considered

The review of this group of PICO questions during the GDG meeting convened by WHO in June 2024 was based on the new evidence from the BEAT-TB 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. Patient populations included in this trial were recruited based on the criteria shown in **Table 1.4**.

Table 1.4. High-level summary of main inclusion and exclusion criteria: BEAT-TB trial

	BEAT-TB
Inclusion	1. Male or female, aged 6 years or older, including breastfeeding and pregnant women 2. Weigh more than or equal to 16 kg 3. 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 last three months 4. 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 5. Participants who are pregnant should have an ultrasound done to confirm a viable intrauterine pregnancy before enrolment 6. Willing to have an HIV test, and if positive, willing to be treated with appropriate ART

	BEAT-TB
Exclusion	1. Had taken more than 28 days, but less than 24 weeks, of second-line TB drugs including bedaquiline, linezolid, clofazimine, FQs or delamanid. 2. Has complicated or severe extra-pulmonary manifestations of TB, including osteoarticular, pericardial and CNS infection, as per the investigator's opinion. 3. 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. 4. 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. a) Haemoglobin level of <8.0 g/dL b) Platelet count <75 000/mm^3 c) Absolute neutrophil count <1000/mm^3 d) An estimated creatinine clearance <30 mL/min as calculated by the National Health Laboratory Service equation e) Alanine aminotransferase ≥3 × ULN f) Total bilirubin grade 3 or greater (>2.0 × ULN, or >1.50 × ULN when accompanied by any increase in other liver function test) g) Serum potassium <3.2 mmol/L

CNS: central nervous system; ECG: electrocardiogram; FQ: fluoroquinolone; HIV: human immunodeficiency virus; RR-TB: rifampicin-resistant TB; P: QTcF: corrected QT interval by Fredericia formula ; TB: tuberculosis; UNL: upper normal limit.

BEAT Tuberculosis trial

This 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 with 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 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 FQ DST results: BDLLfxC initiated without delay in the case of unknown FQ-resistance at the time of RR-TB diagnosis (and continued with both levofloxacin and clofazimine if FQ-DST results could not be obtained); or BDLLfx continued for FQ-susceptible TB; or BDLC for FQ-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, PLHIV, children aged 8 and above, 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.

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. 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 they 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.
- Loss to follow-up 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 1.5. Cross-tabulation of outcomes from the BEAT-TB trial and WHO

BEAT-TB trial outcomes	WHO Week 76 outcomes				
	Sustained treatment success	Not sustained treatment success			
		Failure or recurrence	Death	LTFU	Total
Favourable[a]	346				346
Unfavourable		31	20	6	57
On treatment			11		
Death					
LTFU on treatment				6	
Treatment failure (no culture conversion or reversion)		17			
Post-treatment					
Death			9		
Recurrence		14			
Total	346	31	20[b]	6	402

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] Three participants experienced treatment failure and then subsequently died.

Decision thresholds

This recommendation was developed using a new method for determining the magnitude of the health effects. 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. GDG members deemed these outcomes 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 understanding of the outcomes by the GDG members during their 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) *(46)*. 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 *(47)* to calculate suggested utility-adjusted absolute effect thresholds for the health outcomes. The calculated thresholds were as follows *(48)*:

- 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)*.

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 those thresholds to inform their judgements about magnitude of health effects in the GRADE EtD frameworks. Figures were created to visually depict absolute effects and 95% confidence intervals (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 (Fig. A1.3). The same thresholds were used to inform the group's judgements about imprecision, in line with GRADE guidance for decision-making *(49)*.

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

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

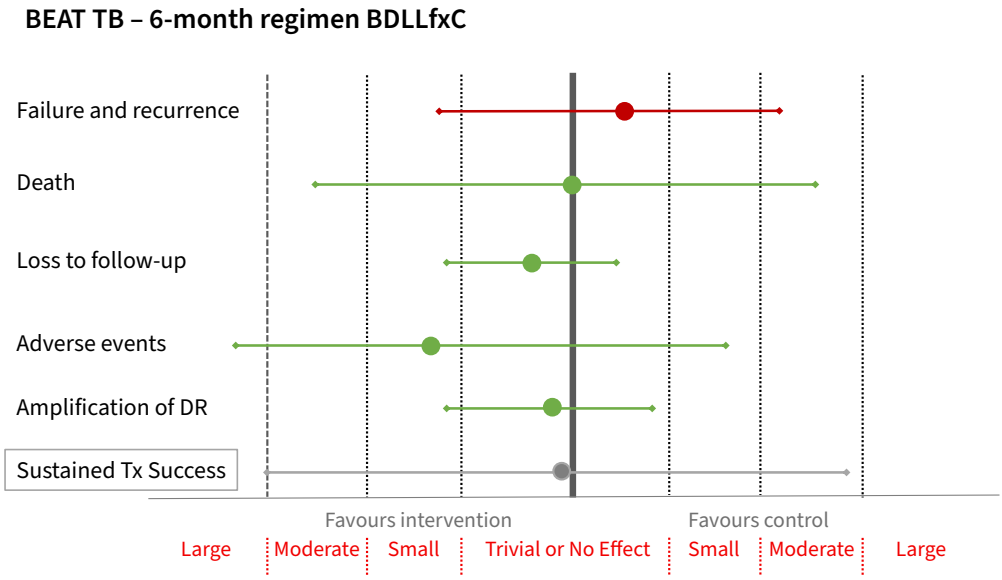
Participants with MDR/RR-TB (with or without quinolone resistance) receiving the BDLLfxC regimen (n=202) compared to participants receiving WHO-recommended SoC regimens used in the BEAT-TB trial (n=200) experienced:

- 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 with the intervention and comparator regimens. The intervention regimen is 24 weeks (5.5 months), so treatment duration is reduced compared with the control arm by 3–18 months. 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 BDLLfxC regimen.

Fig. 1.1. Visual depiction of absolute effects in relation to the decision thresholds used by the GDG



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, decision thresholds 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.

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 *(50)* on 20 June 2024.

Table 1.6. Regimen cost estimates

	Regimen	Estimated regimen price (US$)
BEAT-TB trial regimens	6BDLLfx (FQ-S)	1374
	6BDLC (FQ-R)	1460
	6BDLLfxC (FQ – unknown)	1479
WHO-recommended regimens	9-month regimen	418
	9-month regimen (with Lzd)	396
	Longer regimen ($18B_6LLC$)	632

BDLLfx: bedaquiline, delamanid, linezolid and levofloxacin; 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 modeling analysis in Ryckman et al. (*2024*) *(51)*. Costs may vary depending on the composition of the regimen being used.

Table 1.7. Patient-borne and health system costs

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 may decrease with generic development. It was highlighted that there are costs to a longer duration of treatment (especially for patients and families but also 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, underserviced settings and disadvantaged populations).

The GDG highlighted that health equity would probably increase for particular 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). On the other hand, 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 as 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-TB 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 the 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 hemoglobin levels in the BEAT-TB 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 hemoglobin levels.

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

Conclusion

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

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 BDLLfxC regimen rather than the 9-month or longer (18-month) regimens in MDR/RR-TB patients. The BDLLfxC 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.

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 PLHIV, children, pregnant and breastfeeding women, patients with extrapulmonary TB and patients with extensive TB disease and resistance to fluoroquinolones. The recent new recommendation for the use of bedaquiline in children with MDR/RR-TB aged below 6 years was considered *(30)*. 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 study, 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 (1 case each of anemia, 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 BDLLfxC regimen have been used in children and adolescents, have well-documented safety and efficacy profiles, and have sufficient pharmacokinetic and pharmacodynamic data. Thus, the recommendation of the BDLLfxC regimen applies to adults, adolescents and children of any age.

People living with HIV

All participants of the BEAT-TB trial were required to undergo an HIV test, but the test result and their CD4+ count, or whether they were receiving ART at the time of randomization, did not affect their eligibility for the trial. 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-nucleoside reverse transcriptase inhibitors were prohibited. In BEAT-TB, 202 PLHIV 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 vs the control was observed (risk difference 2.1% (95% CI: –7.9%, +12.2%). Thus, the recommendation for the BDLLfxC regimen applies to all people, regardless of HIV status or degree of immunosuppression and appeared preferable to the comparator.

Pregnant and breastfeeding women

The components of BDLLfxC have been used in pregnancy in women with MDR/RR-TB. Pregnant women could be enrolled in the BEAT-TB trial in any trimester of pregnancy. Also, women who become pregnant during the trial could continue their treatment without any changes. Of the 10 pregnant women (4 to the trial regimen) enrolled, 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 BDLLfxC regimen's component drugs, the trial data and other currently recommended alternatives, the BDLLfxC regimen is recommended for use in pregnant and breastfeeding women.

Extrapulmonary TB

Patients with complicated extrapulmonary TB involving the CNS, osteoarticular and pericardial forms of TB were not included in the BEAT-TB trial. 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 BDLLfxC regimen applies to people with pulmonary TB and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular or disseminated forms of TB with multiorgan involvement.

Extensive TB disease and resistance to fluoroquinolones

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).

Implementation considerations

The high treatment success rates shown for the BDLLfxC regimen in the BEAT-TB 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 BDLLfxC regimen should generally align with the criteria outlined in the BEAT-TB trial. 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

A comprehensive history of prior exposure to the regimen's components and the outcomes of previous episodes of TB should be taken. 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 *(52)*.

DST for FQ is strongly advised, although it should not delay the initiation of the BDLLfxC. When DST results confirm FQ susceptibility, clofazimine should be stopped, then BDLLfx can continue. When DST results confirm FQ resistance, levofloxacin should be stopped, then BDLC can continue. If DST is not done or is unavailable, then all five drugs should be given.

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) and linezolid for more than a month should have recent DST results confirming susceptibility before being enrolled on the BDLLfxC regimen. In settings where DST for bedaquiline, delamanid and linezolid can be done and resistance to any of these medicines is confirmed, the regimens 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 coadministration with BDLLfxC are dolutegravir-based in combination with two nucleoside reverse transcriptase inhibitors (NRTIs). The NRTI zidovudine should be avoided because of the overlapping toxicity of myelosuppression. The non-NRTIs (efavirenz) is contraindicated with bedaquiline. For newer agents, package inserts should be consulted.

Other considerations

There was no exclusion based on BMI. Eighty-five (42%) patients randomized to BDLLfxC had a BMI below 18.5 g/m^2. No major effect of a low BMI was noted on the efficacy of the BDLLfxC 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-TB 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 BDLLfxC 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-TB 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 BDLLfxC regimen comprises bedaquiline, delamanid and linezolid with levofloxacin and/or clofazimine throughout the duration of the regimen, depending on quinolone susceptibility. Delamanid was administered twice daily for 8 weeks and then daily for 16 weeks.

Bedaquiline dosing schemes

The dosing strategy used in the BEAT-TB trial was daily as a loading dose of 400mg for 2 weeks, then 200mg three times weekly for 22 weeks. As an alternative, it is possible to use the daily dosing strategy (i.e. loading dose daily of 200) for the first 2 months and then continue daily 100mg for the next 4 months.

Dosing of linezolid

For adults, the prescribed dose of linezolid was 600 mg for the entire duration of therapy, without any planned dose reductions. These patients continued their treatment with BDLfx or BDLfxC. Clinicians assessed the response to treatment, and if they determined that the response was satisfactory, the patients were allowed to continue with their treatment regimen.

Regimen duration, changes and extensions

Treatment may be extended to nine months if culture conversion is not sustained by week 16. In the BEAT-TB 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 the 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 BDLLfxC without interruptions. Eighteen patients had their linezolid treatment permanently discontinued owing to AEs: three patients experienced anemia, six developed optic neuritis and nine had peripheral neuropathy. The time of linezolid discontinuation was earliest at 6 weeks and latest at 22 weeks. The BDLLfxC regimen has been studied as a standardized course of treatment. Therefore, modifying the regimen through early discontinuation or replacement of any component medicines, except linezolid-related adverse events, 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 due to adverse events 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 one month should be made up for by extending the treatment duration (for the number of missed doses).

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

Recommendation 2.1 The 9-month all-oral regimen for MDR/RR-TB

No.	Recommendation
2.1	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

1. 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).
2. A 9-month regimen with linezolid instead of ethionamide may be used in pregnant women, unlike the regimen with ethionamide.
3. This recommendation applies to:
    a. people with MDR/RR-TB and without resistance to fluoroquinolones;
    b. patients without extensive TB disease[32] and without severe extrapulmonary TB;[33]
    c. 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;
    d. all people regardless of HIV status;
    e. 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).

Rationale

The rationale for this recommendation is based on the evidence and considerations described in detail in the following two subsections. 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 of DR-TB or other eligibility criteria not compatible with the 6-month regimen has driven the assessments presented in this section.

Briefly, two assessments have been performed: first, comparing the outcomes of the 9-month regimen including linezolid for 2 months and the identical regimen that included ethionamide for 4 months; and second, comparing 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. Data on most of 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%), loss to follow-up (15% vs 12%) and amplification of drug resistance (0.6% vs 0%). 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 compared with longer regimens also showed lower levels of treatment success (64% vs 74%), failure or recurrence (1% vs 3%) or amplification of drug resistance (1% vs 2%); and higher levels of deaths

[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, 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.

(20% vs 11%) or loss to follow-up (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 on 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 *(29)*. 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, 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 evidence-to-decision 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?*

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 *(53)*. In August 2019, WHO issued a public call for IPD on the use of all-oral shorter regimens of 9–12 months *(54)*, 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

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

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 *(55)* 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 treatment 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 1–2019

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 PLHIV 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 PLHIV 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.

PICO 1–2022

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

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];
- 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

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);

[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.

- 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 *(50)* 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

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 2.1 lists the comparisons and decisions on each of the sub-PICO questions that were assessed by the GDG 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 *(29)*.

Table 2.1. PICO questions and decisions of the GDG panel

#	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-resistant or rifampicin-resistant TB; PICO: population, intervention, comparator and outcome; TB: tuberculosis; WHO: World Health Organization.

Sub-PICO 1.1

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 (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 PLHIV 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 2.2**).

Table 2.2. 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

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

The GDG 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 PLHIV, 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 *(30)*. 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 PLHIV (>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 PLHIV. 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) *(56–58)*. Neuropathy, liver enzyme elevations and CNS side-effects can be attributed to HIV or TB drugs or their interactions *(59)*.

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 *(30)*.

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 *(60, 61)*. 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 *(62)*. 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 *(43)*.

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, using moxifloxacin in a shorter regimen with injectables and levofloxacin in an all-oral shorter regimen. Levofloxacin is often preferred because of moxifloxacin's slightly higher potential for cardiotoxicity; however, levofloxacin has been associated with musculoskeletal disorders in paediatric populations. Therefore, irrespective of the choice of fluoroquinolone, NTPs need to implement aDSM in all patients enrolled on treatment of DR-TB *(64, 65)*.

Assessment of TB disease

To determine regimen options, it is important to know the extent of TB disease, in addition to the DST results and other considerations mentioned above. Extensive 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 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.

[36] See the list of high-confidence resistance-conferring mutations in the WHO guide on the use of next-generation sequencing technologies, WHO (*2018*) *(63)*.

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 2.2 and 2.3 The modified 9-month all-oral regimens for MDR/RR-TB

No.	Recommendation (NEW)
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. Among these regimens, using BLMZ is suggested over using BLLfxCZ, and BLLfxCZ is suggested over BDLLfxZ. *(Conditional recommendation, very low certainty of evidence)*
2.3	WHO suggests against using 9-month DCLLfxZ or DCMZ regimens compared with currently recommended longer (>18 months) regimens in patients with fluoroquinolone-susceptible MDR/RR-TB. *(Conditional recommendation, very low certainty of evidence)*

Remarks

1. The recommended modified 9-month all-oral regimens comprise bedaquiline, linezolid and pyrazinamide in different combinations with levofloxacin/moxifloxacin, clofazimine and delamanid.
2. This recommendation applies to the following:
    a. People with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded.
    b. People with diagnosed pulmonary TB, including children, adolescents, PLHIV, and pregnant and breastfeeding women.
    c. People with extensive TB disease and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular TB or disseminated forms of TB with multiorgan involvement.
    d. 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.
    e. 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 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) *(66)* 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 2.4**). 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; 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 2.3**.

> *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)?*

> *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)?*

*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)?*

*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)?*

*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 2.3. 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: fluoroquinolone; MDR/RR-TB: multidrug-resistant 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 *(66)*. 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.

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 2.4**). 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 2.4. 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. 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 2.5. 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
Favorable	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

endTB W104 outcomes	WHO W104 outcomes				
	Sustained treatment success	Not sustained treatment success			
		Failure or recurrence	Death	LTFU	Total
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; 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 2.6. High-level summary of main inclusion and exclusion criteria: endTB trial

	endTB
Inclusion	1. Has documented pulmonary TB due to strains of *M. tuberculosis* resistant to rifampin (RIF) and susceptible to FQ, diagnosed by validated rapid molecular test. 2. Is ≥15 years of age. 3. Is willing to use contraception: pre-menopausal 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	1. Is known to be pregnant or is unwilling or unable to stop breastfeeding an infant. 2. 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. 3. Has received second-line drugs for 15 days or more prior to screening visit date in the current MDR/RR-TB treatment episode. 4. 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. 5. Unless otherwise specified, Grade 4 result as defined by the MSF severity scale on any of the screening laboratory tests. 6. Has cardiac risk factors defined QTcF intervals of ≥450 ms.

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) *(46)*. 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 *(47)* to calculate suggested utility-adjusted absolute effect thresholds for the health outcomes. The calculated thresholds were as follows *(48)*:

- 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 (Fig. A1.3). The same thresholds were used to inform the group's judgements about imprecision, in line with GRADE guidance for decision-making *(49)*.

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

Sub-PICO 2.1

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

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

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 BLLfxCZ 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

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

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 *(50)*, as shown in **Table 2.7**.

Table 2.7. Regimen cost estimates[a]

	Regimen	Estimated regimen price (US$)
endTB trial regimens	BLMZ	297
	BLLfxCZ	455
	BDLLfxZ	2219
WHO-recommended regimens	Longer regimen ($18B_6$LfxLC)	632

GDP: global domestic product; WHO: World Health Organization.

[a] Prices are based on the GDF online catalogue on [ADD DATE] *(50)*.

As shown in **Table 2.8**, 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 modeling analysis in Ryckman et al. 2024 *(51)*. Costs may vary, depending on the composition of the regimen being used.

Table 2.8. 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 *(51)*, 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 judgment 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 discoloration), 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 above, 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 2.9**).

Table 2.9. Multiple comparisons of three recommended endTB trial regimens[a]

	BLMZ	BLLfxCZ	BDLLfxZ
Balance of effects	★★★★	★★★	★★★
Resources required	★★★★★	★★★★★	★★
Cost–effectiveness	★★★★	★★★	★★
Equity	★★★★	★★★★	★★★
Acceptability	★★★★	★★★	★★
Feasibility	★★★★★	★★★★★	★★★★

[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 PLHIV regardless of their immunologic 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 *(67, 68)*. Close monitoring and systematic collection of data from pregnant, breastfeeding and post-partum 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 *(69)*).

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 PLHIV (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 2.10**. All of the modified 9-month regimens have bedaquiline, linezolid, pyrazinamide and a fluoroquinolone as core, with one or two other additional drugs.

Table 2.10. 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 adverse events 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**.

3. Treatment of drug-resistant TB using longer regimens

Recommendations 3.1–3.17 Longer regimens

No.	Recommendation
3.1	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)*
3.2	**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)*
3.3	**Levofloxacin or moxifloxacin** should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)*
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 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)*
3.5	**Linezolid** should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)*
3.6	**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)*
3.7	**Ethambutol** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
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)* 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)*
3.9	**Pyrazinamide** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*

No.	Recommendation
3.10	**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)*[37]
3.11	**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)*
3.12	**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 against use, very low certainty of evidence)*
3.13	***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 against use, very low certainty of evidence)*
3.14	**Clavulanic acid** should not be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation against use, low certainty of evidence)*[37]
3.15	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)*
3.16	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)*
3.17	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 3.1 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
- 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.

[37] 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.

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?*[38]
>
> ***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 *(30)*:

> ***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?*

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)*.

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[38] 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.

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. 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 *(70–73)*. 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 *(74)*{, 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 *(70–72)*. 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 *(75, 76)* 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, and Annex 6 for the analysis plan). 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 *(77)*.[39] 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[40] 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 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

[39] These countries are Armenia, Bangladesh, Belarus, the Democratic People's Republic of Korea, Ethiopia, Georgia, Indonesia, Kazakhstan, Kenya, Lesotho, Myanmar, Pakistan and Peru.

[40] 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.

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 *(71)*. 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. TMC207-C211 is a Phase 2, open-label, single-arm study to evaluate the pharmacokinetics, 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 aged 0–17 years who have bacteriologically confirmed or clinically diagnosed pulmonary and selected forms of extrapulmonary MDR-TB.[41] IMPAACT P1108 is a Phase 1–2 dose finding modified age de-escalation study to evaluate the pharmacokinetics, safety and tolerability of bedaquiline in combination with optimized individualized MDR-TB regimens in children living with HIV and HIV-uninfected children with clinically diagnosed or confirmed pulmonary (intrathoracic) and selected forms of extrapulmonary MDR-TB.[42]

[41] 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).

[42] 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).

Data reviewed from TMC207-C211 corresponded to children aged 5–18 years and data from IMPAACT P1108 included children aged 0–6 years; therefore, the review of pharmacokinetics 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 aged 0–6 years, cardiac safety signals were not distinct from those reported in adults. Population pharmacokinetic 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 aOR of injectable TB drug use. There was no statistically significant difference in successful treatment outcomes between children aged below 6 years receiving an all-oral bedaquiline-based regimen and 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 and will also soon be used in an updated protocol of the IMPAACT study P1108 (to date, this study has used the 100 mg formulation in all age groups). No head-to-head studies were conducted to examine the bioequivalence of the 20 mg and the 100 mg formulation of bedaquiline. 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 *(78)* also showed that the bioavailability of bedaquiline tablets suspended in water was the same as for tablets swallowed whole.

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.

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[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).

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 3.1**, **Table 3.2** and **Table 3.3**).

- **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.
- **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; see **Annex 6**) 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, 26)*. 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 3.1. 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
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid[e]	Dlm
	Pyrazinamide[f]	Z
	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 (see Annex 6).

[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 *(79)*. 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 *(79)*. 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 3.2. 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)

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)
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 3.3** and **Annex 5** and **Annex 6** 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 3.1**.

[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 3.3**) *(80)*; 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 *(81)*, whereas haematological toxicity was reported regardless of duration of use.

Table 3.3. 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]

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 *(80)* 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 3.1**.

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) *(61)*. 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) *(61)*. 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) *(61)*. 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 *(61)*. 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 *(61)*. 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) *(61)*.

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 3.1**.

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 adverse event and 7.4% for a Grade 2 QT adverse event. No patients experienced Grade 3 or 4 QT adverse events. 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 adverse events 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.

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

[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).

should be made to ensure access to approved rapid molecular tests. Until the capacity for second-line 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 *(82)*. 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 *(71)*. 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 *(30)*. 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 *(83)*, as do ethionamide or prothionamide, cycloserine or terizidone, linezolid and imipenem–cilastatin *(84, 85)*. 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 *(86–88)*. 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 is sparse. 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 *(61)*. 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) *(61)*. 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 *(61)*. In such cases, it is recommended that a longer regimen be individualized to include components with a better established safety profile. 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 PLHIV. 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 *(44)*).

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.

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[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. *(89)*

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 *(90)*.[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 adverse events.

The 2021 WHO model list of essential medicines *(91)* 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 *(90)*.

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 an extensive consultation with other specialists in different fields. It was based on the latest knowledge available about the optimal use of the medicines involved *(92)*. 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 *(93)*.

Monitoring and evaluation

Patients on longer MDR-TB treatment regimens need to be monitored for response to treatment and for safety, using reasonable schedules of relevant clinical and laboratory testing *(15, 65)*. The WHO framework for aDSM needs to be applied to patients on any type of MDR/RR-TB regimen, to ensure appropriate action and an acceptable level of monitoring for adverse events and prompt response to such events – alongside monitoring for treatment outcomes. ECG may be indicated as more regimens in the future may have two or three agents that are expected to prolong the QT interval. Audiometry

[50] This is particularly problematic with the delamanid tablet, the contents of which are most unpalatable (*see* summaries of unpublished data for the 2018 guidelines update in **Annex 6**).

and specific biochemical tests should also be made available whenever certain agents are included in the regimens. Treatment in pregnancy with postpartum surveillance for congenital anomalies will help to inform future recommendations for MDR/RR-TB treatment during pregnancy.

A separate recommendation on the use of culture and microscopy to monitor bacteriological response during treatment was made in the 2018 update of the guidelines (see **Monitoring patient response to MDR/RR-TB treatment** regarding PICO question 11 MDR/RR-TB, 2018). Access to DST of medicines for which there are reliable methods and the development of other methods for newer medicines (e.g. sequencing) are critical (and in the case of DST, necessary) accompaniments to the treatment recommendations in these guidelines.

Patients on longer MDR-TB treatment regimens need to be monitored for treatment response and for safety, using reasonable schedules of relevant clinical and laboratory testing *(15, 65)*. Response to treatment and toxicity are monitored through regular history-taking, physical examination and chest radiography; special tests such as audiometry, visual acuity tests and electrocardiography; and laboratory monitoring. Using smear microscopy or culture to assess conversion of bacteriological status is an important way to assess response, and most patients are expected to have converted to a sputum-negative status within the first few months of starting treatment. Persistence of culture positivity beyond that point, or close to the expected end of the intensive phase when injectable agents are in use, should trigger a review of the regimen and performance of DST. NTPs should also aim for complete registration of patients with MDR/RR-TB, through follow-up and monitoring of treatment outcomes as part of national surveillance. Regular review of MDR/RR-TB cohort data is essential.

Frameworks for the surveillance of bacteriological status, drug resistance and assignment of outcomes have been standardized in recent years *(94)*. In contrast, systematic monitoring of adverse events during and after the end of treatment needs to be strengthened in most NTPs, given the relative novelty of active pharmacovigilance within NTPs *(64, 65)*. The rationale for aDSM is largely supported by the increasing use worldwide of combinations of new and repurposed medications in MDR/RR-TB treatment regimens. The toxicity of certain agents may increase with the duration of use (e.g. nerve damage with linezolid), and may limit their continued use in a patient, sometimes resulting in complete cessation of treatment. The prospective collection of accurate data for key variables at the case-based level, using an electronic register, is strongly advised in the best interests of the individual patient, and to inform revisions of local and global policies *(95)*.

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

Recommendations 4.1–4.2 Treatment of Hr-TB

No.	Recommendation
4.1	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)*
4.2	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) *(96–98)*. 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) *(99)*.[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 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.

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[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).

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 adverse events were not evaluated owing to a lack of standardization (dissimilar reporting). The GDG also considered two reports containing data from patients from the United States of America (USA) in whom a detailed assessment of adverse events suggested a risk of excess hepatotoxicity with the 6(H)REZ combination *(100)*. 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 *(101)*. 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 (see **Annex 6**). 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 adverse events *(102–104)*. 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 *(105)*. 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 *(41, 106)*. 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 *(107)*.

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.

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.

[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.

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 *(108)*. Prolongation of treatment may increase the risk of adverse events in some cases (see **Implementation considerations**).

People living with HIV

The effect of longer duration TB treatment among PLHIV with and without ART has been studied among patients with drug-susceptible TB *(109)*. In these cases, relapse has been reported to be 2.4 times higher in PLHIV 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 drug-susceptible TB initiated on ART, no significant benefit from prolonging rifampicin-containing regimens for over 6 months has been observed *(93)*. 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 *(110)*. The 6(H)REZ–levofloxacin regimen is therefore recommended in PLHIV.

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 *(41, 111)*.

Surveillance of DR-TB indicates that fluoroquinolone resistance among patients with rifampicin-susceptible TB is generally low worldwide *(112)*. However, national data on the prevalence of fluoroquinolone resistance – including targeted or whole-genome sequencing to detect specific mutations associated with resistance to fluoroquinolones *(62)* – 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 *(113)*, the same effect has not been reported for levofloxacin, possibly because levofloxacin undergoes limited metabolism in humans and is excreted unchanged in the urine *(114)*. Third, although levofloxacin may interfere with lamivudine clearance, in contrast to moxifloxacin, there are no contraindications for its use with other antiretroviral agents *(44)*.

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]

[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.

[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.

- 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 *(115)*.[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 *(27, 93, 116)*. 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 *(44)*. Co-administration of levofloxacin with oral divalent cation-containing compounds (e.g. antacids) may 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

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[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 *(115)*.

[58] Studies included in this IPD analysis involved the use of regimens containing levofloxacin (usually at a dose of 750–1000 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.

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 4.1** 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 *(50)*. 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 4.1. 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; 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 *(50)*.

Source: Stop TB Partnership (*2020*) *(50)*.

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 *(93)*. In contrast to regimens for drug-susceptible 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.

Monitoring and evaluation

Patients who receive the (H)REZ–levofloxacin regimen need to be monitored during treatment, using schedules of clinical and laboratory testing. The definitions to use when assigning outcomes are the same as those used for drug-susceptible TB *(94)*. Signs of non-response or treatment failure should be followed up with DST for rifampicin resistance and, if possible, for fluoroquinolones and pyrazinamide. To limit the risk of acquisition of additional resistance, the addition of single TB medicines should be avoided in patients who remain smear positive or culture positive after month 2 of treatment, those who do not show a favourable clinical response and those without recent DST results.

As with any other TB medicine and regimen, safety precautions are required to ensure the rapid identification and proper management of any serious adverse event. Close clinical monitoring is essential for all patients receiving this regimen, particularly liver function tests, given the hepatotoxic potential of prolonged pyrazinamide use. If possible, all patients should be tested each month for levels of AST (also known as serum glutamic oxaloacetic transaminase, SGOT). If resources are not available to monitor all patients on the Hr-TB treatment regimen, monthly monitoring of patients at high risk (e.g. patients coinfected with viral hepatitis or with a history of heavy alcohol use) is strongly advised. Additionally, to prevent and manage the potential toxic effects of ethambutol in children (e.g. retrobulbar neuritis), it is necessary to adhere to the correct doses recommended for paediatric populations. Early signs of ethambutol toxicity can be tested in older children through red–green colour discrimination. Monitoring for retrobulbar neuritis can be undertaken early when appropriate *(117)*.

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

People who receive MDR/RR-TB regimens need to be monitored during treatment using relevant clinical and laboratory testing schedules. Response to treatment and toxicity are monitored through regular history taking, physical examination and CXR; special tests (e.g. audiometry, visual acuity tests, peripheral neurological examination and electrocardiography); and laboratory monitoring. Using smear microscopy or culture to assess the conversion of bacteriological status is an important way to assess treatment response.

NTPs should aim for complete registration of patients with MDR/RR-TB through follow-up and monitoring of treatment outcomes as part of national surveillance. Regular review of MDR/RR-TB cohort data is essential. The prospective collection of accurate data for key variables at the case-based level, using an electronic register, is strongly advised, both for the benefit of the individual patient, and to inform revisions of local and global policies.

The WHO framework for aDSM needs to be applied to patients on any type of MDR/RR-TB regimen, to ensure appropriate action and an acceptable level of monitoring for AEs and prompt response to such events, alongside monitoring for treatment outcomes. The rationale for aDSM is largely supported by the increasing use worldwide of combinations of new and repurposed medications in MDR/RR-TB treatment regimens. Additional evidence generated on AEs will be important to build the evidence base on the safety of the new regimens in varied settings.

Access to reliable DST for bedaquiline, linezolid and all medicines composing the regimen is essential to investigate reasons for lack of bacteriological and clinical improvement – in an ideal situation, the DST for all second-line medicines used in regimens would be available. This should not, however, delay the initiation of life-saving treatment. Before starting a 9-month regimen, the patient's bacteriological status should be available, with confirmation of TB disease, MDR/RR-TB (as a minimum) and FQ susceptibility. Country programmes need to strengthen and increase access to FQ DST and undertake surveillance for emerging drug resistance, including for bedaquiline and all second-line medicines for which reliable DST is available. The FQ DST is also important to support the prescription of the relevant combination of 6-month regimens – BPaLM, BPaL, BDLLfxC, BDLLfx or BDLC – to maximize efficacy and prevent unnecessary potential toxicity. The need for FQ DST should not be a barrier to starting treatment with 6-month regimens, because each regimen has a combination that can be started even though the FQ DST is not yet available.

Country programmes are also strongly encouraged to establish the DST capacity to test for resistance to bedaquiline and linezolid at baseline (particularly in cases demonstrating FQ resistance), and to test samples from patients with no bacteriological conversion after 4 months or recurrences while on the 6-month regimens. The implementation of 9-month regimens requires the use of routine DST to

FQ, not only for patient selection but also to monitor the acquisition of resistance (collection of strains for sequencing should be considered). Critical accompaniments to the treatment recommendations in these guidelines are access to DST for medicines for which there are reliable methods and the development of other methods for newer medicines (e.g. sequencing).

ECG may be indicated because in the future, more regimens may have two or three agents that are expected to prolong the QT interval. When QTc prolongation is identified, it is adviseable to check whether the serum potassium, calcium and magnesium are abnormal (and correct if necessary). Treating clinicians are also advised to obtain an ECG before initiation of treatment.

Audiometry and specific biochemical tests should also be made available whenever certain agents are included in the regimens. Treatment in pregnancy with postpartum surveillance for congenital anomalies will help to inform future recommendations for MDR/RR-TB treatment during pregnancy.

It is good practice to assess patients for symptoms and signs of liver disease (e.g. fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness and hepatomegaly); and to conduct laboratory tests such as ALT, AST, alkaline phosphatase and bilirubin. More frequent monitoring of indicators of hepatic toxicity is strongly advised for all MDR/RR-TB regimens.

Monitoring changes in dosing and duration of linezolid, in particular (when needed), will be important, to inform the future evidence base on the wider use of the 6-month or 9-month regimens, and the tolerability of linezolid in these regimens.

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 CXR 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. Where feasible, it is also important to follow up patients 12 months after the completion of treatment for possible relapse, including with sputum culture and smear. 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 (69)*.

Recommendation 5.1 Monitoring patient response

No.	Recommendation
5.1	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 and was conditionally recommended by WHO in 2011 as the preferred approach *(13, 118, 119)*. 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 response to treatment in both drug-susceptible 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. These 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 to address PICO question 11 (MDR/RR-TB, 2018). About 60% of these patients were PLHIV. The analysis focused on whether monthly culture versus monthly smear microscopy or culture every 2 months is needed to not miss 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 was also discussed (see **Implementation considerations** and **Table 5.1**). The data could not address the outcome on acquisition (amplification) of additional drug resistance, nor could it assess directly 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 11 (MDR/RR-TB, 2018). 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 missed true negativity. The added inconvenience to the patient and programme is considered relatively small, given that taking sputum and many other biological specimens is usually 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 upon 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 45 at the eighth month when using culture (**Table 5.1**). 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 5.1. Crude odds ratios (95% CLs) 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 for PICO question 7 MDR/RR-TB, 2018 (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 limits; IPD: individual patient data; MDR/RR-TB: multidrug-resistant or rifampicin-resistant tuberculosis; PICO: population, intervention, comparator and outcome.

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, such as 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 HIV coinfected, 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 analysed for PICO question 11 (MDR/RR-TB, 2018). 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. However, 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 joint 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 *(120)*. 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 *(121, 122)*.

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, at times, 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 *(94)*. 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, 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.

6. Starting antiretroviral therapy in patients on MDR/RR-TB regimens

Recommendation 6.1 Starting ART

No.	Recommendation
6.1	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 *(123–132)*, 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.

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-quality 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 *(133)* particularly in highly immunocompromised patients (CD4 cell count <50 cells/mm^3) *(134, 135)*. 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 *(133, 136)*. 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 *(110)*.

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 adverse events and case-holding throughout

[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.

treatment will necessitate more resources. Updated information on drug–drug interactions between antiretroviral and antituberculosis medicines is now available online *(44)*.

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.

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

Recommendation 7.1 Surgery for MDR/RR-TB patients

No.	Recommendation
7.1	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 *(137)*, and a systematic review and study-level meta-analysis *(138)*. 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) *(70)*. 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

[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).

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 PLHIV 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.

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.

Monitoring and evaluation

The rates of death in the IPD for surgical outcomes did not differ significantly between patients who underwent surgery and those who received medical treatment only. There were not enough data on adverse events, surgical complications or long-term sequelae – some of which may be fatal – to allow a meaningful analysis. Despite the unknown magnitude of perioperative complications, the GDG assumed that, overall, there is a net benefit from surgery.

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

Recommendation 8.1 HCV and MDR/RR-TB treatment

No.	Recommendation (NEW)
8.1	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)*

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) *(139)*.

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) *(140)*. 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 co-infection. 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 *(141)*.

Expert evidence has been defined as the observations or experience obtained from a person who is knowledgeable about or skilful in a particular area *(142)*. 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 co-infected 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 South-East Asia at 7.9% (95% CI: 3.5–13.9), the Americas at 7.5% (95% CI: 5.2–10.1), the Western Pacific at 6.2% (95% CI: 3.6–9.5), the Eastern Mediterranean at 5.7% (95% CI: 3.1–8.9) and Africa at 3.5% (95% CI: 0–16.1) *(142, 143)*.

As a follow-up to this review, an online survey was designed to gather expert evidence on treatment strategies for patients co-infected 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 *(142, 143)*. 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 co-infection, 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 *(144)*. The estimate of heterogeneity was calculated using the restricted maximum-likelihood method *(145)* and the standard error of the pooled effect estimate was derived from the Hartung-Knapp-Sidik-Jonkman method *(146)*. Extensive simulations have shown that these methods are less biased than the alternatives, and more robust to changes in the heterogeneity variance estimate *(147)*. 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 *(148)*. Between-study heterogeneity was assessed using Cochran's Q test *(149)*, with a 0.10 significance threshold and the I-squared metric *(150)* (>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 adverse events 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 co-infected 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 co-infected 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, PLHIV, 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 PLHIV, 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 *(151)*.

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 *(140)*.

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 (152)* and in the chapter 3 of this consolidated document.

Monitoring and evaluation

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 *(153)*.
- **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, aDSM systems must be functional to conduct rigorous active monitoring of adverse events 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 *(2, 16)* persist. 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 BPaLM 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 BPaLM/BPaL regimen for subpopulations for whom current data are limited or missing; that is, children aged below 14 years, patients with extrapulmonary TB, PLHIV 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 of the full AE profile of pretomanid and the frequency of relevant AEs, with a focus on hepatotoxicity and reproductive toxicity in humans (studies ongoing);
- 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);
- 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;
- 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.

[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 *(154)*.

The 6-month bedaquiline, delamanid, linezolid, levofloxacin and clofazimine (BDLLfxC) 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 PLHIV 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 *(155)*;
  - *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), PLHIV 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) *(92)*;
- 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 *(72)*. 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 in the estimates of effect; 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 PLHIV;
- 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 patient response to MDR/RR-TB treatment using culture

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 intravenous drug users, children, pregnant women and PLHIV;
- 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;
- bedaquiline concentrations in breast milk and its effects on newborns;
- 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 regimen 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.

References (Chapter 2)

1. The End TB Strategy. Geneva: World Health Organization; 2015 (https://www.who.int/teams/global-tuberculosis-programme/the-end-tb-strategy).
2. WHO consolidated guidelines on drug resistant tuberculosis treatment. Geneva: World Health Organization; 2019 (https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf). Licence: CC BY-NC-SA 3.0 IGO.
3. WHO consolidated guidelines on tuberculosis. Module 4: Treatment – tuberculosis care and support. Geneva: World Health Organization; 2022 (https://www.who.int/publications/i/item/9789240047716). Licence: CC BY-NC-SA 3.0 IGO.
4. Key updates to the treatment of drug-resistant tuberculosis: rapid communication, June 2024. Geneva: World Health Organization; 2024 (https://iris.who.int/handle/10665/378472). Licence: CC BY-NC-SA 3.0 IGO.
5. Global tuberculosis report 2024. Geneva: World Health Organization; 2024 (https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2024). Licence: CC BY-NC-SA 3.0 IGO.
6. Global tuberculosis report 2019 (WHO/CDS/TB/2019.15). Geneva: World Health Organization; 2019 (https://www.who.int/tb/publications/global_report/en/).
7. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis (WHO/HTM/TB/2014.11). Geneva: World Health Organization; 2014 (https://apps.who.int/iris/bitstream/handle/10665/130918/9789241548809_eng.pdf).
8. WHO operational handbook on tuberculosis. Module 4: Treatment – drug-resistant tuberculosis treatment, 2022 update. Geneva: World Health Organization; 2022 (https://www.who.int/publications/i/item/9789240065116). Licence: CC BY-NC-SA 3.0 IGO.
9. Guidelines for the management of drug-resistant tuberculosis (WHO/TB/96.210 Rev.1). Geneva: World Health Organization; 1997 (https://apps.who.int/iris/bitstream/handle/10665/63465/WHO_TB_96.210_(Rev.1).pdf).
10. Guidelines for establishing DOTS-Plus pilot projects for the management of multidrug-resistant tuberculosis (MDR-TB) (WHO/CDS/TB/2000.279). Geneva: World Health Organization; 2000 (https://iris.who.int/bitstream/handle/10665/66368/WHO_CDS_TB_2000.279_eng.pdf).
11. Guidelines for the programmatic management of drug-resistant tuberculosis (WHO/HTM/TB/2006.361). Geneva: World Health Organization; 2006 (https://apps.who.int/iris/handle/10665/246249).
12. Guidelines for the programmatic management of drug-resistant tuberculosis – emergency update (WHO/HTM/TB/2008.402). Geneva: World Health Organization; 2008 (https://apps.who.int/iris/handle/10665/43965).
13. Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update (WHO/HTM/TB/2011.6). Geneva: World Health Organization; 2011 (https://www.who.int/publications/i/item/9789241501583).
14. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis. Interim policy guidance (WHO/HTM/TB/2013.6). Geneva: World Health Organization; 2013 (https://apps.who.int/iris/handle/10665/84879).
15. The use of delamanid in the treatment of multidrug-resistant tuberculosis. Interim policy guidance (WHO/HTM/TB2014.23). Geneva: World Health Organization; 2014 (https://iris.who.int/handle/10665/137334).

16. WHO treatment guidelines for drug-resistant tuberculosis, 2016 update (WHO/HTM/TB/2016.4). Geneva: World Health Organization; 2016 (https://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-eng.pdf).
17. Van Deun A, Maug AKJ, Salim MAH, Das PK, Sarker MR, Daru P et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. Am J Respir Crit Care Med. 2010;182:684–92 (https://doi.org/10.1164/rccm.201001-0077OC).
18. Kuaban C, Noeske J, Rieder HL, Aït-Khaled N, Abena Foe JL, Trébucq A. High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon. Int J Tuberc Lung Dis. 2015;19:517–24 (https://doi.org/10.5588/ijtld.14.0535).
19. Trébucq A, Schwoebel V, Kashongwe Z, Bakayoko A, Kuaban C, Noeske J et al. Treatment outcome with a short multidrug-resistant tuberculosis regimen in nine African countries. Int J Tuberc Lung Dis. 2018;22:17–25 (https://doi.org/10.5588/ijtld.17.0498).
20. Piubello A, Harouna SH, Souleymane MB, Boukary I, Morou S, Daouda M et al. High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: no relapses. Int J Tuberc Lung Dis. 2014;18:1188–94 (https://doi.org/10.5588/ijtld.13.0075).
21. Nunn AJ, Phillips PP, Meredith SK, Chiang C-Y, Conradie F, Dalai D et al. A trial of a shorter regimen for rifampin-resistant tuberculosis. N Engl J Med. 2019;380:1201–13 (https://doi.org/10.1056/NEJMoa1811867).
22. Position statement on the continued use of the shorter MDR-TB regimen following an expedited review of the STREAM Stage 1 preliminary results (WHO/CDS/TB/2018.2). Geneva: World Health Organization; 2018 (https://www.who.int/publications/m/item/WHO-CDS-TB-2018.2).
23. Conradie F, Diacon AH, Ngubane N, Howell P, Everitt D, Crook AM et al. Treatment of highly drug-resistant pulmonary tuberculosis. N Engl J Med. 2020;382:893–902 (https://doi.org/10.1056/NEJMoa1901814).
24. Esmail A, Oelofse S, Lombard C, Perumal R, Mbuthini L, Goolam Mahomed A et al. An all-oral 6-month regimen for multidrug-resistant tuberculosis: a multicenter, randomized controlled clinical trial (the NExT Study). Am J Respir Crit Care Med. 2022;205:1214–27 (https://doi.org/10.1164/rccm.202107-1779OC).
25. Conradie F, Bagdasaryan TR, Borisov S, Howell P, Mikiashvili L, Ngubane N et al. Bedaquiline–pretomanid–linezolid regimens for drug-resistant tuberculosis. N Engl J Med. 2022;387:810–23 (https://doi.org/10.1056/NEJMoa2119430).
26. The use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents: interim policy guidance (WHO/HTM/TB/2016.14). Geneva: World Health Organization; 2016 (https://apps.who.int/iris/bitstream/handle/10665/250614/9789241549899-eng.pdf).
27. WHO treatment guidelines for isoniazid-resistant tuberculosis. Supplement to the WHO treatment guidelines for drug-resistant tuberculosis (WHO/CDS/TB/2018.7). Geneva: World Health Organization; 2018 (https://apps.who.int/iris/bitstream/handle/10665/260494/9789241550079-eng.pdf).
28. WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update. Geneva: World Health Organization; 2018 (https://www.who.int/news-room/events/detail/2018/07/16/default-calendar/who-treatment-guidelines-for-rifampicin--and-multidrug-resistant-tuberculosis-2018-update).
29. WHO consolidated guidelines on tuberculosis. Module 4: Treatment – drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/9789240007048). Licence: CC BY-NC-SA 3.0 IGO.
30. WHO consolidated guidelines on tuberculosis. Module 5: Management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022 (https://www.who.int/publications/i/item/9789240046764). Licence: CC BY-NC-SA 3.0 IGO.
31. Salinger DH, Nedelman JR, Mendel C, Spigelman M, Hermann DJ. Daily dosing for bedaquiline in patients with tuberculosis. Antimicrob Agents Chemother. 2019;63 (https://doi.org/10.1128/AAC.00463-19).

32. Protocol title: 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 participants with pulmonary infection of either extensively drug-resistant tuberculosis (XDR-TB), pre-XDR-TB or treatment intolerant or non-responsive multi-drug resistant tuberculosis (MDR-TB). 2020.

33. Nunn AJ, Phillips PP, Mitchison DA. Timing of relapse in short-course chemotherapy trials for tuberculosis. Int J Tuberc Lung Dis. 2010;14:241–2 (https://www.ncbi.nlm.nih.gov/pubmed/20074418).

34. Gomez GB, Siapka M, Conradie F, Ndjeka N, Garfin AMC, Lomtadze N et al. Cost-effectiveness of bedaquiline, pretomanid and linezolid for treatment of extensively drug-resistant tuberculosis in South Africa, Georgia and the Philippines. BMJ Open. 2021;11 (https://doi.org/10.1136/bmjopen-2021-051521).

35. Mulder C, Rupert S, Setiawan E, Mambetova E, Edo P, Sugiharto J et al. Budgetary impact of using BPaL for treating extensively drug-resistant tuberculosis. BMJ Global Health. 2022;7 (https://doi.org/10.1136/bmjgh-2021-007182).

36. Sweeney S. TB-PRACTECAL innovating MDR-TB treatment – preliminary cost-effectiveness analysis 2022.

37. van de Berg SEJ, Pelzer PT, van der Land AJ, Abdrakhmanova E, Ozi AM, Arias M et al. Acceptability, feasibility, and likelihood of stakeholders implementing the novel BPaL regimen to treat extensively drug-resistant tuberculosis patients. BMC Public Health. 2021;21 (https://doi.org/10.1186/s12889-021-11427-y).

38. Stringer B, Lowton K, James N, Nyang'wa BT. Capturing patient-reported and quality of life outcomes with use of shorter regimens for drug-resistant tuberculosis: mixed-methods substudy protocol, TB PRACTECAL-PRO. BMJ Open. 2021;11 (https://doi.org/10.1136/bmjopen-2020-043954).

39. Drug approval package: pretomanid [website]. Maryland, United States of America: US Food and Drug Administration; 2019 (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212862Orig1s000TOC.cfm).

40. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children (WHO/HTM/TB/2013.16). Geneva: World Health Organization; 2013 (https://apps.who.int/iris/bitstream/handle/10665/112472/9789241506335_eng.pdf).

41. The use of molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs: policy guidance (WHO/HTM/TB/2016.07). Geneva: World Health Organization; 2016 (https://apps.who.int/iris/bitstream/handle/10665/246131/9789241510561-eng.pdf).

42. WHO consolidated guidelines on tuberculosis. Module 3: Diagnosis – rapid diagnostics for tuberculosis detection, third edition. Geneva: World Health Organization; 2024 (https://www.who.int/publications/i/item/9789240089488). Licence: CC BY-NC-SA 3.0 IGO.

43. Technical report on critical concentrations for TB drug susceptibility testing of medicines used in the treatment of drug-resistant TB (WHO/CDS/TB/2018.5). Geneva: World Health Organization; 2018 (https://www.who.int/publications/i/item/WHO-CDS-TB-2018.5).

44. HIV drug interactions [website]. Liverpool, United Kingdom: University of Liverpool; 2020 (https://www.hiv-druginteractions.org/checker).

45. ZYVOX®. New York: Pfizer; 2010 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021130s022lbl.pdf).

46. Park HY, Cheon HB, Choi SH, Kwon JW. Health-related quality of life based on EQ-5D utility score in patients with tuberculosis: a systematic review. Front Pharmacol. 2021;12:659675 (https://doi.org/10.3389/fphar.2021.659675).

47. Morgano GP, Mbuagbaw L, Santesso N, Xie F, Brozek JL, Siebert U et al. Defining decision thresholds for judgments on health benefits and harms using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence to decision (EtD) frameworks: a protocol for a randomised methodological study (GRADE-THRESHOLD). BMJ Open. 2022;12:e053246 (https://doi.org/10.1136/bmjopen-2021-053246).

48. Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M et al. GRADE evidence to decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. BMJ. 2016;353:i2089 (https://doi.org/10.1136/bmj.i2089).

49. Schunemann HJ, Neumann I, Hultcrantz M, Brignardello-Petersen R, Zeng L, Murad MH et al. GRADE guidance 35: update on rating imprecision for assessing contextualized certainty of evidence and making decisions. J Clin Epidemiol. 2022;150:225–42 (https://doi.org/10.1016/j.jclinepi.2022.07.015).

50. Global Drug Facility (GDF) products catalog. Geneva: Stop TB Partnership; 2024 (https://www.stoptb.org/global-drug-facility-gdf/gdf-product-catalog).

51. Ryckman TS, Schumacher SG, Lienhardt C, Sweeney S, Dowdy DW, Mirzayev F et al. Economic implications of novel regimens for tuberculosis treatment in three high-burden countries: a modelling analysis. Lancet Glob Health. 2024;12:e995–1004 (https://doi.org/10.1016/S2214-109X(24)00088-3).

52. Liang R, Maartens G, Meintjes G, Wasserman S, Gandhi NR, Warren R et al. Bedaquiline and clofazimine resistance following an interruption in treatment for rifampicin-resistant TB [Conference abstract]. Presented at the Union World Conference on Lung Health 2024, Bali, Indonesia. 2024.

53. Ndjeka N, Campbell JR, Meintjes G, Maartens G, Schaaf HS, Hughes J et al. Treatment outcomes 24 months after initiating short, all-oral bedaquiline-containing or injectable-containing rifampicin-resistant tuberculosis treatment regimens in South Africa: a retrospective cohort study. Lancet Infect Dis. 2022;22:1042–51 (https://doi.org/10.1016/S1473-3099(21)00811-2).

54. Public call for individual patient data on treatment of drug-resistant tuberculosis. Geneva, World Health Organization. 2019 (https://www.who.int/news-room/articles-detail/public-call-for-individual-patient-data-on-treatment-of-drug-resistant-tuberculosis).

55. Public call for individual patient data on treatment of drug-resistant tuberculosis. Geneva, World Health Organization. 2021 (https://www.who.int/news-room/articles-detail/public-call-for-individual-patient-data-on-treatment-of-drug-resistant-tuberculosis_06292021#_ftn1).

56. Brill MJE, Svensson EM, Pandie M, Maartens G, Karlsson MO. Confirming model-predicted pharmacokinetic interactions between bedaquiline and lopinavir/ritonavir or nevirapine in patients with HIV and drug-resistant tuberculosis. Int J Antimicrob Agents. 2017;49:212–7 (https://doi.org/10.1016/j.ijantimicag.2016.10.020).

57. Svensson EM, Dooley KE, Karlsson MO. Impact of lopinavir-ritonavir or nevirapine on bedaquiline exposures and potential implications for patients with tuberculosis-HIV coinfection. Antimicrob Agents Chemother. 2014;58:6406–12 (https://doi.org/10.1128/AAC.03246-14).

58. Svensson EM, Aweeka F, Park J-G, Marzan F, Dooley KE, Karlsson MO. Model-based estimates of the effects of efavirenz on bedaquiline pharmacokinetics and suggested dose adjustments for patients coinfected with HIV and tuberculosis. Antimicrob Agents Chemother. 2013;57:2780–7 (https://doi.org/10.1128/AAC.00191-13).

59. Cerrone M, Bracchi M, Wasserman S, Pozniak A, Meintjes G, Cohen K et al. Safety implications of combined antiretroviral and anti-tuberculosis drugs. Expert Opin Drug Saf. 2020;19:23–41 (https://doi.org/10.1080/14740338.2020.1694901).

60. Acquah R, Mohr-Holland E, Daniels J, Furin J, Loveday M, Mudaly V et al. Outcomes of children born to pregnant women with drug-resistant tuberculosis treated with novel drugs in Khayelitsha, South Africa: a report of five patients. Pediatr Infect Dis J. 2021;40:e191–e2 (https://doi.org/10.1097/inf.0000000000003069).

61. Loveday M, Hughes J, Sunkari B, Master I, Hlangu S, Reddy T et al. Maternal and infant outcomes among pregnant women treated for multidrug/rifampicin-resistant tuberculosis in South Africa. Clin Infect Dis. 2020;72:1158–68 (https://doi.org/10.1093/cid/ciaa189).

62. The use of molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs: policy guidance (WHO/HTM/TB/2016.07). Geneva: World Health Organization; 2016 (https://apps.who.int/iris/bitstream/handle/10665/246131/9789241510561-eng.pdf).

63. The use of next-generation sequencing technologies for the detection of mutations associated with drug resistance in Mycobacterium tuberculosis complex: technical guide (WHO/CDS/TB/2018.19). Geneva: World Health Organization; 2018 (https://apps.who.int/iris/bitstream/handle/10665/274443/WHO-CDS-TB-2018.19-eng.pdf).

64. Borisov S, Danila E, Maryandyshev A, Dalcolmo M, Miliauskas S, Kuksa L et al. Surveillance of adverse events in the treatment of drug-resistant tuberculosis: first global report. Eur Respir J. 2019;54:1901522 (https://doi.org/10.1183/13993003.01522-2019).

65. ShORRT (Short, all-Oral Regimens for Rifampicin-resistant Tuberculosis) research package. Geneva: World Health Organization and the Special Programme for Research and Training in Tropical Diseases; 2015 (https://tdr.who.int/docs/librariesprovider10/brochures/all_oral_str_or_information_sheet_final.pdf?sfvrsn=59ffefbb_1).

66. Guglielmetti L, Khan U, Velásquez GE, Gouillou M, Abubakirov A, Baudin E et al. Oral Regimens for Rifampin-Resistant, Fluoroquinolone-Susceptible Tuberculosis. New England Journal of Medicine. 2025;392:468-82 (doi:10.1056/NEJMoa2400327).

67. Gupta A, Mathad JS, Abdel-Rahman SM, Albano JD, Botgros R, Brown V et al. Toward earlier inclusion of pregnant and postpartum women in tuberculosis drug trials: consensus statements from an international expert panel. Clin Infect Dis. 2016;62:761–9 (https://doi.org/10.1093/cid/civ991).

68. Alene KA, Murray MB, van de Water BJ, Becerra MC, Atalell KA, Nicol MP et al. Treatment outcomes among pregnant patients with multidrug-resistant tuberculosis: a systematic review and meta-analysis. JAMA Netw Open. 2022;5:e2216527 (https://doi.org/10.1001/jamanetworkopen.2022.16527).

69. WHO consolidated operational handbook on tuberculosis. Module 4: Treatment and care. Geneva: World Health Organization; 2025. Licence: CC BY-NC-SA 3.0 IGO.

70. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9153 patients. PLoS Med. 2012;9:e1001300 (https://doi.org/10.1371/journal.pmed.1001300).

71. 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:e1002591 (https://doi.org/10.1371/journal.pmed.1002591).

72. Ahmad N, Ahuja SD, Akkerman OW, Alffenaar J-WC, Anderson LF, Baghaei P et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet. 2018;392:821–34 (https://doi.org/10.1016/S0140-6736(18)31644-1).

73. Seddon JA, Hesseling AC, Godfrey-Faussett P, Schaaf HS. High treatment success in children treated for multidrug-resistant tuberculosis: an observational cohort study. Thorax. 2014;69:458–64 (https://doi.org/10.1136/thoraxjnl-2013-203900).

74. Public call for individual patient data on treatment of rifampicin and multidrug-resistant (MDR/RR-TB) tuberculosis [website]. Geneva: World Health Organization; 2018 (https://www.who.int/news-room/articles-detail/public-call-for-individual-patient-data-on-treatment-of-rifampicin-and-multidrug-resistant-(mdr-rr-tb)-tuberculosis).

75. Safety and efficacy trial of delamanid for 6 months in patients with multidrug resistant tuberculosis. Otsuka Pharmaceutical Development & Commercialization, Inc.; 2016 (https://clinicaltrials.gov/ct2/show/NCT01424670).

76. von Groote-Bidlingmaier F, Patientia R, Sanchez E, Balanag V, Ticona E, Segura P et al. Efficacy and safety of delamanid in combination with an optimised background regimen for treatment of multidrug-resistant tuberculosis: a multicentre, randomised, double-blind, placebo-controlled, parallel group Phase 3 trial. Lancet Respir Med. 2019;7:249–59 (https://doi.org/10.1016/S2213-2600(18)30426-0).

77. Khan U, Huerga H, Khan AJ, Mitnick CD, Hewison C, Varaine F et al. The endTB observational study protocol: treatment of MDR-TB with bedaquiline or delamanid containing regimens. BMC Infect Dis. 2019;19 (https://doi.org/10.1186/s12879-019-4378-4).

78. Svensson EM, du Bois J, Kitshoff R, de Jager VR, Wiesner L, Norman J et al. Relative bioavailability of bedaquiline tablets suspended in water: implications for dosing in children. Br J Clin Pharmacol. 2018;84:2384–92 (https://doi.org/10.1111/bcp.13696).

79. WHO best-practice statement on the off-label use of bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis (WHO/HTM/TB/2017.20). Geneva: World Health Organization; 2017 (https://apps.who.int/iris/bitstream/handle/10665/258941/WHO-HTM-TB-2017.20-eng.pdf).

80. Lan Z, Ahmad N, Baghaei P, Barkane L, Benedetti A, Brode SK et al. Drug-associated adverse events in the treatment of multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet Respir Med. 2020;8:383–94 (https://doi.org/10.1016/S2213-2600(20)30047-3).

81. Tang S, Yao L, Hao X, Zhang X, Liu G, Liu X et al. Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China. Eur Respir J. 2015;45:161–70 (https://doi.org/10.1183/09031936.00035114).

82. Dooley KE, Miyahara S, von Groote-Bidlingmaier F, Sun X, Hafner R, Rosenkranz SL et al. Early bactericidal activity of different isoniazid doses for drug resistant TB (INHindsight): a randomized open-label clinical trial. Am J Respir Crit Care Med. 2020;201:1416–24 (https://doi.org/10.1164/rccm.201910-1960OC).

83. Thwaites GE, Bhavnani SM, Chau TTH, Hammel JP, Torok ME, Van Wart SA et al. Randomized pharmacokinetic and pharmacodynamic comparison of fluoroquinolones for tuberculous meningitis. Antimicrob Agents Chemother. 2011;55:3244–53 (https://doi.org/10.1128/AAC.00064-11).

84. Donald PR. The chemotherapy of tuberculous meningitis in children and adults. Tuberculosis. 2010;90:375–92 (https://doi.org/10.1016/j.tube.2010.07.003).

85. Sun F, Ruan Q, Wang J, Chen S, Jin J, Shao L et al. Linezolid manifests a rapid and dramatic therapeutic effect for patients with life-threatening tuberculous meningitis. Antimicrob Agents Chemother. 2014;58:6297–301 (https://doi.org/10.1128/AAC.02784-14).

86. Akkerman OW, Odish OF, Bolhuis MS, de Lange WC, Kremer HP, Luijckx G-JR et al. Pharmacokinetics of bedaquiline in cerebrospinal fluid and serum in multidrug-resistant tuberculous meningitis. Clin Infect Dis. 2016;62:523–4 (https://doi.org/10.1093/cid/civ921).

87. Tucker EW, Pieterse L, Zimmerman MD, Udwadia ZF, Peloquin CA, Gler MT et al. Delamanid central nervous system pharmacokinetics in tuberculous meningitis in rabbits and humans. Antimicrob Agents Chemother. 2019;63:e00913–19 (https://doi.org/10.1128/AAC.00913-19).

88. Holdiness MR. Cerebrospinal fluid pharmacokinetics of the antituberculosis drugs. Clin Pharmacokinet. 1985;10:532–4 (https://doi.org/10.2165/00003088-198510060-00006).

89. Linh NN, Viney K, Gegia M, Falzon D, Glaziou P, Floyd K et al. World Health Organization treatment outcome definitions for tuberculosis: 2021 update. Eur Respir J. 2021;58 (https://doi.org/10.1183/13993003.00804-2021).

90. United States Food and Drug Administration. Sirturo (bedaquiline) label [website]. Maryland, United States of America: United States Food and Drug Administration; 2012 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/204384s000lbl.pdf).

91. WHO model list of essential medicines – 22nd list, 2021. Geneva: World Health Organization; 2021 (https://www.who.int/medicines/publications/essentialmedicines/en/).

92. Mao Y, Dai D, Jin H, Wang Y. The risk factors of linezolid-induced lactic acidosis: a case report and review. Med. 2018;97:e12114 (https://doi.org/10.1097/MD.0000000000012114).

93. Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update (WHO/HTM/TB/2017.05). Geneva: World Health Organization; 2017 (https://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf).

94. Hornik CP, Herring AH, Benjamin DK, Capparelli EV, Kearns GL, van den Anker J et al. Adverse events associated with meropenem versus imipenem/cilastatin therapy in a large retrospective cohort of hospitalized infants. Pediatr Infect Dis J. 2013;32:748–53 (https://doi.org/10.1097/INF.0b013e31828be70b).

95. Electronic recording and reporting for tuberculosis care and control (WHO/HTM/TB/2011.22). Geneva: World Health Organization; 2012 (https://apps.who.int/iris/handle/10665/44840).

96. Escalante P, Graviss EA, Griffith DE, Musser JM, Awe RJ. Treatment of isoniazid-resistant tuberculosis in southeastern Texas. Chest. 2001;119:1730–6 (https://doi.org/10.1378/chest.119.6.1730).

97. Nolan C, Goldberg S. Treatment of isoniazid-resistant tuberculosis with isoniazid, rifampin, ethambutol, and pyrazinamide for 6 months. Int J Tuberc Lung Dis. 2002;6:952–8 (https://pubmed.ncbi.nlm.nih.gov/12475140/).

98. Kim YH, Suh GY, Chung MP, Kim H, Kwon OJ, Lim SY et al. Treatment of isoniazid-resistant pulmonary tuberculosis. BMC Infect Dis. 2008;8 (https://doi.org/10.1186/1471-2334-8-6).

99. Fregonese F, Ahuja SD, Akkerman OW, Arakaki-Sanchez D, Ayakaka I, Baghaei P et al. Comparison of different treatments for isoniazid-resistant tuberculosis: an individual patient data meta-analysis. Lancet Respir Med. 2018;6:265–75 (https://doi.org/10.1016/S2213-2600(18)30078-X).

100. Andrade RJ, Tulkens PM. Hepatic safety of antibiotics used in primary care. J Antimicrob Chemother. 2011;66:1431–46 (https://doi.org/10.1093/jac/dkr159).

101. Centers for Disease Control and Prevention. Update. Fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC recommendations-United States, 2001. MMWR Morb Mortal Wkly. 2001;50:733–5 (https://pubmed.ncbi.nlm.nih.gov/11787580/).

102. Voogt GR, Schoeman HS. Ototoxicity of aminoglycoside drugs in tuberculosis treatment. S Afr J Commun Disord. 1996;43:3–6 (https://pubmed.ncbi.nlm.nih.gov/9265840/).

103. Gülbay BE, Gürkan ÖU, Yıldız ÖA, Önen ZP, Erkekol FÖ, Baççıoğlu A et al. Side effects due to primary antituberculosis drugs during the initial phase of therapy in 1149 hospitalized patients for tuberculosis. Respir Med. 2006;100:1834–42 (https://doi.org/10.1016/j.rmed.2006.01.014).

104. Bloss E, Kukša L, Holtz TH, Riekstina V, Skripčonoka V, Kammerer S et al. Adverse events related to multidrug-resistant tuberculosis treatment, Latvia, 2000–2004. Int J Tuberc Lung Dis. 2010;14:275–81 (https://pubmed.ncbi.nlm.nih.gov/20132617/).

105. Oxlade O, Falzon D, Menzies D. The impact and cost-effectiveness of strategies to detect drug-resistant tuberculosis. Eur Respir J. 2012;39:626–34 (https://doi.org/10.1183/09031936.00065311).

106. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children (WHO/HTM/TB/2013.16). Geneva: World Health Organization; 2013 (https://apps.who.int/iris/bitstream/handle/10665/112472/9789241506335_eng.pdf).

107. Bollela VR, Namburete NI, Feliciano CS, Macheque D, Harrison LH, Caminero J. Detection of katG and inhA mutations to guide isoniazid and ethionamide use for drug-resistant tuberculosis. Int J Tuberc Lung Dis. 2016;20:1099–104 (https://doi.org/10.5588/ijtld.15.0864).

108. Blumberg HM, Burman WJ, Chaisson RE, Daley CL, Etkind S, LN F et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med. 2003;167:603–62 (https://doi.org/10.1164/rccm.167.4.603).

109. Ahmad Khan F, Minion J, Al-Motairi A, Benedetti A, Harries AD, Menzies D. An updated systematic review and meta-analysis on the treatment of active tuberculosis in patients with HIV infection. Clin Infect Dis. 2012;55:1154–63 (https://doi.org/10.1093/cid/cis630).

110. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach, 2nd edition. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf).

111. Lan Z, Ahmad N, Baghaei P, Barkane L, Benedetti A, Brode SK et al. Drug-associated adverse events in the treatment of multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet Respir Med. 2020;

112. Zignol M, Dean AS, Alikhanova N, Andres S, Cabibbe AM, Cirillo DM et al. Population-based resistance of Mycobacterium tuberculosis isolates to pyrazinamide and fluoroquinolones: results from a multicountry surveillance project. Lancet Infect Dis. 2016;16:1185–92 (https://doi.org/10.1016/S1473-3099(16)30190-6).

113. Ramachandran G, Kumar AKH, Srinivasan R, Geetharani A, Sugirda P, Nandhakumar B et al. Effect of rifampicin & isoniazid on the steady state pharmacokinetics of moxifloxacin. Indian J Med Res. 2012;136:979 (https://pubmed.ncbi.nlm.nih.gov/23391793/).

114. Fish DN, Chow AT. The clinical pharmacokinetics of levofloxacin. Clin Pharmacokinet. 1997;32:101–19 (https://doi.org/10.2165/00003088-199732020-00002).

115. Lempens P, Meehan CJ, Vandelannoote K, Fissette K, de Rijk P, Van Deun A et al. Isoniazid resistance levels of Mycobacterium tuberculosis can largely be predicted by high-confidence resistance-conferring mutations. Sci Rep. 2018;8 (https://doi.org/10.1038/s41598-018-21378-x).

116. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. Clin Infect Dis. 2016;63:e147–e95 (https://doi.org/10.1093/cid/ciw376).

117. Guidance for national tuberculosis programmes on the management of tuberculosis in children (WHO/HTM/TB/2014.03). Geneva: World Health Organization; 2014 (https://apps.who.int/iris/bitstream/handle/10665/112360/9789241548748_eng.pdf).

118. Kurbatova EV, Gammino VM, Bayona J, Becerra M, Danilovitz M, Falzon D et al. Frequency and type of microbiological monitoring of multidrug-resistant tuberculosis treatment. Int J Tuberc Lung Dis. 2011;15:1553–5 (https://doi.org/10.5588/ijtld.11.0101).

119. Mitnick CD, White RA, Lu C, Rodriguez CA, Bayona J, Becerra MC et al. Multidrug-resistant tuberculosis treatment failure detection depends on monitoring interval and microbiological method. Eur Respir J. 2016;48:1160–70 (https://doi.org/10.1183/13993003.00462-2016).

120. Tuberculosis laboratory biosafety manual (WHO/HTM/ TB/2012.11). Geneva: World Health Organization; 2012 (https://apps.who.int/iris/bitstream/handle/10665/77949/9789241504638_eng.pdf).

121. Friedrich SO, Rachow A, Saathoff E, Singh K, Mangu CD, Dawson R et al. Assessment of the sensitivity and specificity of Xpert MTB/RIF assay as an early sputum biomarker of response to tuberculosis treatment. Lancet Respir Med. 2013;1:462–70 (https://doi.org/10.1016/S2213-2600(13)70119-X).

122. Jayakumar A, Savic RM, Everett CK, Benator D, Alland D, Heilig CM et al. Xpert MTB/RIF assay shows faster clearance of Mycobacterium tuberculosis DNA with higher levels of rifapentine exposure. J Clin Microbiol. 2016;54:3028–33 (https://doi.org/10.1128/JCM.01313-16).

123. Burgos M, Gonzalez LC, Paz EA, Gournis E, Kawamura LM, Schecter G et al. Treatment of multidrug-resistant tuberculosis in San Francisco: an outpatient-based approach. Clin Infect Dis. 2005;40:968–75 (https://doi.org/10.1086/428582).

124. Dheda K, Shean K, Zumla A, Badri M, Streicher EM, Page-Shipp L et al. Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study. Lancet. 2010;375:1798–807 (https://doi.org/10.1016/S0140-6736(10)60492-8).

125. Eker B, Ortmann J, Migliori GB, Sotgiu G, Muetterlein R, Centis R et al. Multidrug- and extensively drug-resistant tuberculosis, Germany. Emerg Infect Dis. 2008;14:1700–6 (https://doi.org/10.3201/eid1411.080729).

126. El Sahly H, Teeter L, Pawlak R, Musser J, Graviss E. Drug-resistant tuberculosis: a disease of target populations in Houston, Texas. J Infect. 2006;53:5–11 (https://doi.org/10.1016/j.jinf.2005.10.002).

127. Jamal L, Guibu I, Tancredi M, Ramalho M, Vasconcelos G, Cota I et al. Reliability and usefulness of TB/HIV co-infection data proceeding from developing countries. Bangkok, Thailand: International Conference on AIDS; 2004.

128. Leimane V, Dravniece G, Riekstina V, Sture I, Kammerer S, Chen MP et al. Treatment outcome of multidrug/extensively drug-resistant tuberculosis in Latvia, 2000–2004. Eur Respir J. 2010;36:584–93 (https://doi.org/10.1183/09031936.00003710).

129. Migliori GB, Besozzi G, Girardi E, Kliiman K, Lange C, Toungoussova OS et al. Clinical and operational value of the extensively drug-resistant tuberculosis definition. Eur Respir J. 2007;30:623–6 (https://doi.org/10.1183/09031936.00077307).

130. Palmero D, Ritacco V, Ambroggi M, Poggi S, Güemes Gurtubay J, Alberti F et al. Multidrug-resistant tuberculosis in AIDS patients at the beginning of the millennium. Medicina. 2006;66:399–404 (https://pubmed.ncbi.nlm.nih.gov/17137168/).

131. Shean KP, Willcox PA, Siwendu SN, Laserson KF, Gross L, Kammerer S et al. Treatment outcome and follow-up of multidrug-resistant tuberculosis patients, West Coast/Winelands, South Africa, 1992–2002. Int J Tuberc Lung Dis. 2008;12:1182–9 (https://pubmed.ncbi.nlm.nih.gov/18812049/).

132. Varma JK, Nateniyom S, Akksilp S, Mankatittham W, Sirinak C, Sattayawuthipong W et al. HIV care and treatment factors associated with improved survival during TB treatment in Thailand: an observational study. BMC Infect Dis. 2009;9 (https://doi.org/10.1186/1471-2334-9-42).

133. Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for a public health approach: 2010 revision. Geneva: World Health Organization; 2010 (https://apps.who.int/iris/bitstream/handle/10665/44379/9789241599764_eng.pdf).

134. Abdool Karim SS, Naidoo K, Grobler A, Padayatchi N, Baxter C, Gray A et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. N Engl J Med. 2010;362:697–706 (https://doi.org/10.1056/NEJMoa0905848).

135. Havlir D, Ive P, Kendall M, Luetkemeyer A, Swindells S, Kumwenda J et al. International randomized trial of Immediate vs. early ART in HIV+ patients treated for TB: ACTG 5221 STRIDE study. Boston, United States of America 8th Conference on Retroviruses and Opportunistic Infections; 2011 (CROI conference abstracts prior to 2014 are no longer available online).

136. Blanc F, Sok T, Laureillard D, Borand L, Rekacewicz C, Nerrienet E et al. Significant enhancement in survival with early (2 weeks) vs. late (8 weeks) initiation of highly active antiretroviral treatment (HAART) in severely immunosuppressed HIV-infected adults with newly diagnosed tuberculosis: "34% reduction in mortality in early arm". Vienna, Austria: 18th International AIDS Conference; 2010 (www.natap.org/2010/IAS/IAS_91.htm).

137. Fox GJ, Mitnick CD, Benedetti A, Chan ED, Becerra M, Chiang C-Y et al. Surgery as an adjunctive treatment for multidrug-resistant tuberculosis: an individual patient data metaanalysis. Clin Infect Dis. 2016;62:887–95 (https://doi.org/10.1093/cid/ciw002).

138. Harris RC, Khan MS, Martin LJ, Allen V, Moore DAJ, Fielding K et al. The effect of surgery on the outcome of treatment for multidrug-resistant tuberculosis: a systematic review and meta-analysis. BMC Infect Dis. 2016;16 (https://doi.org/10.1186/s12879-016-1585-0).

139. Olaru ID, Beliz Meier M, Mirzayev F, Prodanovic N, Kitchen PJ, Schumacher SG et al. Global prevalence of hepatitis B or hepatitis C infection among patients with tuberculosis disease: systematic review and meta-analysis. EClinicalMedicine. 2023;58:101938 (https://doi.org/10.1016/j.eclinm.2023.101938).

140. Zoratti MJ, Siddiqua A, Morassut RE, Zeraatkar D, Chou R, van Holten J et al. Pangenotypic direct acting antivirals for the treatment of chronic hepatitis C virus infection: a systematic literature review and meta-analysis. EClinicalMedicine. 2020;18:100237 (https://doi.org/10.1016/j.eclinm.2019.12.007).

141. Olaru ID, Beliz Meier M, Schumacher SG, Prodanovic N, Kitchen PJ, Mirzayev F et al. Co-administration of treatment for drug-resistant TB and hepatitis C. Int J Tuberc Lung Dis. 2023;27:66–8 (https://doi.org/10.5588/ijtld.22.0403).

142. Schunemann HJ, Zhang Y, Oxman AD, Expert Evidence in Guidelines G. Distinguishing opinion from evidence in guidelines. BMJ. 2019;366:l4606 (https://doi.org/10.1136/bmj.l4606).

143. Mustafa RA, Garcia CAC, Bhatt M, Riva JJ, Vesely S, Wiercioch W et al. GRADE notes: How to use GRADE when there is "no" evidence? A case study of the expert evidence approach. J Clin Epidemiol. 2021;137:231–5 (https://doi.org/10.1016/j.jclinepi.2021.02.026).

144. Emerson JD. Combining estimates of the odds ratio: the state of the art. Stat Methods Med Res. 1994;3:157–78 (https://doi.org/10.1177/096228029400300204).

145. Raudenbush SW. Analyzing effect sizes: random-effects models. In: Cooper H, Hedges L & Valentine J (eds.), In: The handbook of research synthesis and meta-analysis (2nd edition). New York, NY: Russell Sage Foundation; 2009:295–316.

146. Hartung J, Knapp G. A refined method for the meta-analysis of controlled clinical trials with binary outcome. Stat Med. 2001;20:3875–89 (https://doi.org/10.1002/sim.1009).

147. Langan D, Higgins JPT, Jackson D, Bowden J, Veroniki AA, Kontopantelis E et al. A comparison of heterogeneity variance estimators in simulated random-effects meta-analyses. Res Synth Methods. 2019;10:83–98 (https://doi.org/10.1002/jrsm.1316).

148. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med. 2004;23:1351–75 (https://doi.org/10.1002/sim.1761).

149. Cochran W. The combination of estimates from different experiments. Biometrics. 1954;10:101–29 (https://doi.org/10.2307/3001666).

150. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539–58 (https://doi.org/10.1002/sim.1186).

151. Melikyan N, Huerga H, Atshemyan H, Kirakosyan O, Sargsyants N, Aydinyan T et al. Concomitant treatment of chronic hepatitis C with direct-acting antivirals and multidrug-resistant tuberculosis is effective and safe. Open Forum Infect Dis. 2021;8:ofaa653 (https://doi.org/10.1093/ofid/ofaa653).

152. WHO operational guidelines on tuberculosis. Module 4: Treatment – tuberculosis care and support. Geneva: World Health Organization; 2022 (https://www.who.int/publications/i/item/9789240053519). Licence: CC BY-NC-SA 3.0 IGO.

153. Updated recommendations on treatment of adolescents and children with chronic HCV infection, and HCV simplified service delivery and diagnostics. Geneva: World Health Organization; 2022 (https://www.who.int/publications/i/item/9789240052734). Licence: CC BY-NC-SA 3.0 IGO.

154. Bateson A, Ortiz Canseco J, McHugh TD, Witney AA, Feuerriegel S, Merker M et al. Ancient and recent differences in the intrinsic susceptibility of Mycobacterium tuberculosis complex to pretomanid. J Antimicrob Chemother. 2022;77:1685–93 (https://doi.org/10.1093/jac/dkac070).

155. Boston University. Efficacy and safety of levofloxacin for the treatment of MDR-TB (Opti-Q) [website]. Maryland, USA: US National Library of Medicine; 2022 (https://clinicaltrials.gov/show/NCT01918397).

Chapter 3
Tuberculosis care and support

Introduction

WHO aims to use the best available evidence on interventions to ensure adequate patient care and support and in order to inform policy decisions made by national TB control programme managers, national policy-makers and medical practitioners in a variety of geographical, economic and social settings.

This chapter of the *WHO consolidated guidelines. Module 4: Treatment and care* aims to provide a summary of existing WHO recommendations on care and support during tuberculosis treatment.

The recommendations included in this chapter were developed by three Guidelines Development Groups (GDGs) convened by the WHO Global Tuberculosis Programme in 2011, 2016 and 2021 *(1–3)* in order to review the evidence available on key aspects of TB care and support (see **Annex 7**). The GDGs were composed of a multidisciplinary group of TB experts external to WHO.

The recommendations were formulated by the GDGs using the GRADE approach. The recommendations were then reviewed by external review groups which were composed of experts and end-users from all WHO regions.

The Global TB Programme (GTB) of the World Health Organization (WHO) has been combining all current recommendations into one overall set of consolidated guidelines on TB. The guidelines contain recommendations regarding all areas related to the programmatic management of TB (e.g. screening, preventive treatment, diagnostics, the treatment of drug-susceptible and drug-resistant TB, patient care and support). The consolidated guidelines contain modules specific to each programmatic area.

The consolidated WHO evidence-based guidelines for the treatment of drug-resistant TB *(4)*, for the treatment of drug-susceptible TB (DS-TB) *(5)*, and for the management of tuberculosis in children and adolescents *(3)* were published in 2020 and 2022. The recommendations on tuberculosis care and support contained in these guidelines were developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method for assessment of the quality of evidence.

People-centred care is an important element of the End TB Strategy which recommends treatment and patient support for all people with TB. Several interventions to support patients in their adherence to TB treatment have been implemented by national TB programmes for many years (e.g. treatment support with observation of medicine intake and social support), while others have been introduced recently (e.g. digital health interventions such as SMS messages, telephone calls or other reminders, and video-supported treatment, or VST). These interventions and models of care have been assessed using the GRADE method and WHO has issued guidelines with evidence-based recommendations for a variety of interventions for TB care and support. This chapter presents all WHO's recommendations on TB care and support that are either newly developed or are existing recommendations that have been published previously in other WHO guidelines that applied the GRADE approach.

Structure of the chapter

The Recommendations part of this chapter has three 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.
3. Models of care for children and adolescents exposed to TB or with TB disease.

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, the Guideline Development Groups (GDGs), 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 implementation of patient care interventions is presented in the relevant chapter of the *WHO consolidated operational handbook on tuberculosis. Module 4: Treatment and care* which is, a separate document that is designed to aid implementation efforts.

Summary of WHO recommendations on TB care and support

The recommendations on TB care and support are as follows:

1. Care and support interventions for all people with TB

No.	Recommendation
1.1	**Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment *(strong recommendation, moderate certainty of evidence).***
1.2	**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).***
1.3	**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);***

[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.

No.	Recommendation
	c. psychological support[67] to patient *(conditional recommendation, low certainty of evidence);*
	d. staff education[68] *(conditional recommendation, low certainty of evidence).*
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).*

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

No.	Recommendation
2.1	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).*
2.2	A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment *(conditional recommendation, very low certainty of evidence).*

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

No.	Recommendation
3.1	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).*
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).*

[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.

It is critical that national TB programmes and public health leaders consider these recommendations in the context of countries' TB epidemics, the strengths and weaknesses of health systems, and the availability of financial, human and other essential resources. In adapting these guidelines, care must be exercised to protect access for the populations most in need in order to achieve the greatest impact for the greatest number of people and to ensure sustainability. It is similarly important to ensure that the adaptation of these guidelines does not stifle ongoing or planned research; the new recommendations reflect the current state of knowledge and new information will be needed for sustainability and future modifications of the existing guidelines.

Recommendations

1. Care and support interventions for all people with TB

Recommendations 1.1–1.4

No.	Recommendation
1.1	Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment. *(Strong recommendation, moderate certainty of evidence)*
1.2	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)*
1.3	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
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 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 in order to help ensure adherence to treatment and maximize its efficacy. Treatment support needs to be provided in the context of people-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 *(6, 7)*, 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 > 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 *(8–15)* and from observational studies *(16–29)*, with preference given to the results of randomized controlled trials. 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 focused preferentially on randomized controlled trial data from the systematic review. When the data from randomized controlled trials 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 *(30–46)*, and many of these studies were conducted in the pre-ART era prior to antiretroviral treatment (ART) or shortly after the introduction of this treatment for HIV-positive TB patients *(30, 31, 36, 39)*. 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 *(33)*. 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

Randomized controlled trials *(10, 12–14)* and observational studies *(17, 18, 21, 23, 28, 32, 34–36, 42, 46)* 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 *(18, 21, 32, 47–51)*. 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

Randomized controlled trials *(10, 12, 14, 28, 52–55)* and observational studies *(16, 23, 32, 34, 36, 42, 56–89)* 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 randomized controlled trials. 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 *(90, 91)*. 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 randomized controlled trials. 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 randomized controlled trials *(91–96)* and observational studies *(56–62, 97)* 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 1**). 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 1. 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.

Tracers and digital health interventions rather than VST

Varied tracers were included in randomized controlled trials *(98–105)* and observational studies *(90, 91, 106–110)*. 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 randomized controlled trial *(99)* 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-centered 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 randomized controlled trials *(69–72)* and observational studies *(78, 111–118)*. 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 randomized controlled trials *(64–67)* and observational studies *(75)*. 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 randomized controlled trials *(68, 69, 118)* and observational studies *(119)*. 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 *(56, 74, 120)*. 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 *(121)* 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 non-medical 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 *(121)*.

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.

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

Recommendations 2.1–2.2

No.	Recommendation
2.1	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)*
2.2	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] *(122)*, Peru *(123)* and Philippines *(124)*.The design of these observational studies did not allow direct comparison of effects between models of care. Because none of the studies were randomized controlled trials, 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 *(125)*.

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 randomized controlled trials and observational studies were analysed, with the majority being from low- and middle-income countries *(120, 121, 126–133)*. 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 *(4)*.

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 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 *(134)*. 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.

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

Recommendations 3.1–3.2

No.	Recommendation
3.1	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)*
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)*

Remarks

1. These recommendations relate to TB services along the full range of care with a focus on case detection and provision of TPT.
2. 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.
3. 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.

4. Decentralization should be prioritized for settings and populations with poor access to existing services and/or in high TB-prevalence areas.
5. 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).
6. Family-centred care is a cross-cutting principle of child care 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 TB preventive treatment (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 *(135, 136)*. 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 *(136)*. 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 *(137)*. 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 (136)*. 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 *(136)*.

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 co-morbidities (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 *(136)*.

The set of PICO 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 *(138)*. Of the remaining studies that were included, 16 had elements of decentralization, 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.

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[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 co-morbidities (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.

Studies in which the primary intervention was decentralization chiefly assessed diagnosis or case notification outcomes (n=16) *(139–154)*, with fewer assessing TPT outcomes (n=3) *(59, 145, 155)*. 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 *(156, 157)* 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 *(158, 159)* 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 observed that two trials *(148, 150)* and one observational study of home-based screening (without facility-based strengthening) *(153)* 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 *(160)*. Available data from the global TB database *(161)* 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 *(121)* 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, co-infections and co-morbidities *(162)*. 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.

Research gaps

The GDGs discussed research priorities and highlighted a number of priorities.

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, as 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 – i.e. does treatment centered on hospital care or outpatient clinics pose a higher risk of transmission?
- Additional cost-effectiveness studies of decentralized versus centralized care.
- Many programmes are providing decentralized care, but very few have published the data. Programmes should be encouraged to publish – or 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/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 providers.
- Costs and catastrophic costs.

- Cost-effectiveness evaluations of family-centred, integrated and/or decentralized approaches, considering currently available resources (N.B. 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/non-randomized 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.

References (Chapter 3)

1. Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update (WHO/HTM/TB/2011.6). Geneva: World Health Organization; 2011 (https://www.who.int/tb/areas-of-work/drug-resistant-tb/programmatic_guidelines_for_mdrtb/en/).
2. Guidelines for treatment of drug-susceptible tuberculosis and patient care – 2017 update (WHO/HTM/TB/2017.05). Geneva: World Health Organization; 2017 (https://www.who.int/publications/i/item/9789241550000).
3. WHO consolidated guidelines on tuberculosis. Module 5: Co-morbidities, vulnerable populations and people-centred care. Management of tuberculosis in children and adolescents, 2022. Geneva: World Health Organization; 2022 (https://www.who.int/publications/i/item/9789240046764). Licence: CC BY-NC-SA 3.0 IGO.
4. WHO consolidated guidelines on tuberculosis. Module 4: Treatment – drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.
5. WHO consolidated guidelines on tuberculosis. Module 4: Treatment – drug-susceptible tuberculosis treatment Geneva: World Health Organization; 2022 (https://www.who.int/publications/i/item/9789240048126). Licence: CC BY-NC-SA 3.0 IGO.
6. Guidance on ethics of tuberculosis prevention, care and control. Geneva: World Health Organization; 2010 (https://www.who.int/publications/i/item/9789241500531).
7. Ethics guidance for the implementation of the End TB strategy. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/handle/10665/254820). Licence: CC BY-NC-SA 3.0 IGO.
8. Bayer R, Wilkinson D. Directly observed therapy for tuberculosis: history of an idea. Lancet. 1995;345:1545–8 (https://doi.org/10.1016/s0140-6736(95)91090-5).
9. Kamolratanakul P, Sawert H, Lertmaharit S, Kasetjaroen Y, Akksilp S, Tulaporn C et al. Randomized controlled trial of directly observed treatment (DOT) for patients with pulmonary tuberculosis in Thailand. Trans R Soc Trop Med Hyg. 1999;93:552–7 (https://doi.org/10.1016/s0035-9203(99)90379-6).
10. MacIntyre CR, Goebel K, Brown GV, Skull S, Starr M, Fullinfaw RO. A randomised controlled clinical trial of the efficacy of family-based direct observation of anti-tuberculosis treatment in an urban, developed-country setting. Int J Tuberc Lung Dis. 2003;7:848–54 (https://www.ncbi.nlm.nih.gov/pubmed/12971668).
11. A controlled clinical trial of oral short-course regimens in the treatment of sputum-positive pulmonary tuberculosis. Tuberculosis Research Centre. Int J Tuberc Lung Dis. 1997;1:509–17 (https://pubmed.ncbi.nlm.nih.gov/9487448/).
12. Walley JD, Khan MA, Newell JN, Khan MH. Effectiveness of the direct observation component of DOTS for tuberculosis: a randomised controlled trial in Pakistan. Lancet. 2001;357:664–9 (https://doi.org/10.1016/S0140-6736(00)04129-5).
13. Zwarenstein M, Schoeman JH, Vundule C, Lombard CJ, Tatley M. Randomised controlled trial of self-supervised and directly observed treatment of tuberculosis. Lancet. 1998;352:1340–3 (https://doi.org/10.1016/S0140-6736(98)04022-7).

14. Zwarenstein M, Schoeman JH, Vundule C, Lombard CJ, Tatley M. A randomised controlled trial of lay health workers as direct observers for treatment of tuberculosis. Int J Tuberc Lung Dis. 2000;4:550–4 (https://www.ncbi.nlm.nih.gov/pubmed/10864186).

15. Tandon M, Gupta M, Tandon S, Gupta KB. DOTS versus self administered therapy (SAT) for patients of pulmonary tuberculosis: a randomised trial at a tertiary care hospital. Indian J Med Sci. 2002;56:19–21 (https://www.ncbi.nlm.nih.gov/pubmed/12508627).

16. Akkslip S, Rasmithat S, Maher D, Sawert H. Direct observation of tuberculosis treatment by supervised family members in Yasothorn Province, Thailand. Int J Tuberc Lung Dis. 1999;3:1061–5 (https://www.ncbi.nlm.nih.gov/pubmed/10599008).

17. Balasubramanian VN, Oommen K, Samuel R. DOT or not? Direct observation of anti-tuberculosis treatment and patient outcomes, Kerala State, India. Int J Tuberc Lung Dis. 2000;4:409–13 (https://www.ncbi.nlm.nih.gov/pubmed/10815733).

18. Mathema B, Pande SB, Jochem K, Houston RA, Smith I, Bam DS et al. Tuberculosis treatment in nepal: a rapid assessment of government centers using different types of patient supervision. Int J Tuberc Lung Dis. 2001;5:912–9 (https://www.ncbi.nlm.nih.gov/pubmed/11605884).

19. Ormerod LP, Horsfield N, Green RM. Tuberculosis treatment outcome monitoring: Blackburn 1988-2000. Int J Tuberc Lung Dis. 2002;6:662–5 (https://www.ncbi.nlm.nih.gov/pubmed/12150476).

20. Tsuchida K, Koyanagi H. Outcome of directly observed therapy for tuberculosis in Yokohama City, Japan. Int J Tuberc Lung Dis. 2003;7:730–4 (https://www.ncbi.nlm.nih.gov/pubmed/12921148).

21. Nirupa C, Sudha G, Santha T, Ponnuraja C, Fathima R, Chandrasekharam VK et al. Evaluation of directly observed treatment providers in the revised National Tuberculosis Control Programme. Indian J Tuberc. 2005;52:73–7 (https://imsear.searo.who.int/handle/123456789/146953).

22. Daniel OJ. Pre- and post-directly observed treatment era in the management of TB: a teachiing hospital experience. Trop Doct. 2006;36:163–5 (https://doi.org/10.1258/004947506777978280).

23. Okanurak K, Kitayaporn D, Wanarangsikul W, Koompong C. Effectiveness of DOT for tuberculosis treatment outcomes: a prospective cohort study in Bangkok, Thailand. Int J Tuberc Lung Dis. 2007;11:762–8 (https://www.ncbi.nlm.nih.gov/pubmed/17609051).

24. Abassi A, Mansourian AR. Efficacy of DOTS strategy in treatment of respiratory tuberculosis in Gorgan, Islamic Republic of Iran. East Mediterr Health J. 2007;13:664–9 (https://www.ncbi.nlm.nih.gov/pubmed/17687840).

25. Siemion-Szcześniak I. KJ. [Treatment outcomes in culture-positive pulmonary tuberculosis]. Pneumonol Alergol Pol. 2009;77:11–22 (https://pubmed.ncbi.nlm.nih.gov/19308905/).

26. Caylà JA, Rodrigo T, Ruiz-Manzano J, Caminero JA, Vidal R, García JM et al. Tuberculosis treatment adherence and fatality in Spain. Respir Res. 2009;10:121 (https://doi.org/10.1186/1465-9921-10-121).

27. Zvavamwe Z, Ehlers VJ. Experiences of a community-based tuberculosis treatment programme in Namibia: a comparative cohort study. Int J Nurs Stud. 2009;46:302–9 (https://doi.org/10.1016/j.ijnurstu.2008.09.013).

28. Xu W, Lu W, Zhou Y, Zhu L, Shen H, Wang J. Adherence to anti-tuberculosis treatment among pulmonary tuberculosis patients: a qualitative and quantitative study. BMC Health Serv Res. 2009;9:169 (https://doi.org/10.1186/1472-6963-9-169).

29. Abuaku B, Tan H, Li X, Chen M, Huang X. Treatment default and death among tuberculosis patients in Hunan, China. Scand J Infect Dis. 2010;42:281–7 (https://doi.org/10.3109/00365540903493723).

30. Alvarez-Uria G, Midde M, Pakam R, Naik PK. Directly-observed intermittent therapy versus unsupervised daily regimen during the intensive phase of antituberculosis therapy in HIV infected patients. Biomed Res Int. 2014;2014:937817 (https://doi.org/10.1155/2014/937817).

31. Alwood K, Keruly J, Moore-Rice K, Stanton DL, Chaulk CP, Chaisson RE. Effectiveness of supervised, intermittent therapy for tuberculosis in HIV-infected patients. AIDS. 1994;8:1103–8 (https://doi.org/10.1097/00002030-199408000-00010).

32. Anuwatnonthakate A, Limsomboon P, Nateniyom S, Wattanaamornkiat W, Komsakorn S, Moolphate S et al. Directly observed therapy and improved tuberculosis treatment outcomes in Thailand. PLoS One. 2008;3:e3089 (https://doi.org/10.1371/journal.pone.0003089).

33. Bashar M, Alcabes P, Rom WN, Condos R. Increased incidence of multidrug-resistant tuberculosis in diabetic patients on the Bellevue Chest Service, 1987 to 1997. Chest. 2001;120:1514–9 (https://doi.org/10.1378/chest.120.5.1514).

34. Cavalcante SC, Soares EC, Pacheco AG, Chaisson RE, Durovni B, Team DE. Community DOT for tuberculosis in a Brazilian favela: comparison with a clinic model. Int J Tuberc Lung Dis. 2007;11:544–9 (https://www.ncbi.nlm.nih.gov/pubmed/17439679).

35. Caylà JA, Caminero JA, Rey R, Lara N, Vallés X, Galdós-Tangüis H et al. Current status of treatment completion and fatality among tuberculosis patients in Spain. Int J Tuberc Lung Dis. 2004;8:458–64 (https://www.ncbi.nlm.nih.gov/pubmed/15141739).

36. Das M, Isaakidis P, Armstrong E, Gundipudi NR, Babu RB, Qureshi IA et al. Directly-observed and self-administered tuberculosis treatment in a chronic, low-intensity conflict setting in India. PLoS One. 2014;9:e92131 (https://doi.org/10.1371/journal.pone.0092131).

37. Ershova JV, Podewils LJ, Bronner LE, Stockwell HG, Dlamini SS, Mametja LD. Evaluation of adherence to national treatment guidelines among tuberculosis patients in three provinces of South Africa. S Afr Med J. 2014;104:362–8 (https://doi.org/10.7196/samj.7655).

38. Jasmer RM, Seaman CB, Gonzalez LC, Kawamura LM, Osmond DH, Daley CL. Tuberculosis treatment outcomes: directly observed therapy compared with self-administered therapy. Am J Respir Crit Care Med. 2004;170:561–6 (https://doi.org/10.1164/rccm.200401-095OC).

39. Juan G, Lloret T, Perez C, Lopez P, Navarro R, Ramón M et al. Directly observed treatment for tuberculosis in pharmacies compared with self-administered therapy in Spain. Int J Tuberc Lung Dis. 2006;10:215–21 (https://www.ncbi.nlm.nih.gov/pubmed/16499264).

40. Kapella BK, Anuwatnonthakate A, Komsakorn S, Moolphate S, Charusuntonsri P, Limsomboon P et al. Directly observed treatment is associated with reduced default among foreign tuberculosis patients in Thailand. Int J Tuberc Lung Dis. 2009;13:232–7 (https://pubmed.ncbi.nlm.nih.gov/19146753/).

41. Ollé-Goig JE, Alvarez J. Treatment of tuberculosis in a rural area of Haiti: directly observed and non-observed regimens. The experience of H pital Albert Schweitzer. Int J Tuberc Lung Dis. 2001;5:137–41 (https://www.ncbi.nlm.nih.gov/pubmed/11258507).

42. Ong'ang'o JR, Mwachari C, Kipruto H, Karanja S. The effects on tuberculosis treatment adherence from utilising community health workers: a comparison of selected rural and urban settings in Kenya. PLoS One. 2014;9:e88937 (https://doi.org/10.1371/journal.pone.0088937).

43. Pungrassami P, Johnsen SP, Chongsuvivatwong V, Olsen J. Has directly observed treatment improved outcomes for patients with tuberculosis in southern Thailand? Trop Med Int Health. 2002;7:271–9 (https://doi.org/10.1046/j.1365-3156.2002.00849.x).

44. Radilla-Chávez P, Laniado-Laborín R. Results of directly observed treatment for tuberculosis in Ensenada, Mexico: not all DOTS programs are created equally. Int J Tuberc Lung Dis. 2007;11:289–92 (https://www.ncbi.nlm.nih.gov/pubmed/17352094).

45. Vieira AA, Ribeiro SA. Compliance with tuberculosis treatment after the implementation of the directly observed treatment, short-course strategy in the city of Carapicuíba, Brazil. J Bras Pneumol. 2011;37:223–31 (https://doi.org/10.1590/s1806-37132011000200013).

46. Weis SE, Slocum PC, Blais FX, King B, Nunn M, Matney GB et al. The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. N Engl J Med. 1994;330:1179–84 (https://doi.org/10.1056/NEJM199404283301702).

47. Colvin M, Gumede L, Grimwade K, Maher D, Wilkinson D. Contribution of traditional healers to a rural tuberculosis control programme in Hlabisa, South Africa. Int J Tuberc Lung Dis. 2003;7:S86–91 (https://www.ncbi.nlm.nih.gov/pubmed/12971659).

48. Singh AA, Parasher D, Shekhavat GS, Sahu S, Wares DF, Granich R. Effectiveness of urban community volunteers in directly observed treatment of tuberculosis patients: a field report from Haryana, North India. Int J Tuberc Lung Dis. 2004;8:800–2 (https://www.ncbi.nlm.nih.gov/pubmed/15182154).

49. Kingkaew N, Sangtong B, Amnuaiphon W, Jongpaibulpatana J, Anuwatnonthakate A. Effectiveness of and results from directly observed treatment of tuberculosis patients by health-care workers vs. family members, Vachira Phuket Hospital, 2005–2006. 2010;2 (https://kb.hsri.or.th/dspace/bitstream/handle/11228/133/hsri-journal-v2n2-sup5-p189-196.pdf).

50. Tripathy SK, Kumar P, Sagili KD, Enarson DA. Effectiveness of a community-based observation of anti-tuberculosis treatment in Bangalore City, India, 2010-2011. Public Health Action. 2013;3:230–4 (https://doi.org/10.5588/pha.13.0043).

51. Wilkinson D, Davies GR. Coping with Africa's increasing tuberculosis burden: are community supervisors an essential component of the DOT strategy? Directly observed therapy. Trop Med Int Health. 1997;2:700–4 (https://doi.org/10.1046/j.1365-3156.1997.d01-358.x).

52. Lwilla F, Schellenberg D, Masanja H, Acosta C, Galindo C, Aponte J et al. Evaluation of efficacy of community-based vs. institutional-based direct observed short-course treatment for the control of tuberculosis in Kilombero district, Tanzania. Trop Med Int Health. 2003;8:204–10 (https://doi.org/10.1046/j.1365-3156.2003.00999.x).

53. Wandwalo E, Kapalata N, Egwaga S, Morkve O. Effectiveness of community-based directly observed treatment for tuberculosis in an urban setting in Tanzania: a randomised controlled trial. Int J Tuberc Lung Dis. 2004;8:1248–54 (https://pubmed.ncbi.nlm.nih.gov/15527158/).

54. Wright J, Walley J, Philip A, Pushpananthan S, Dlamini E, Newell J et al. Direct observation of treatment for tuberculosis: a randomized controlled trial of community health workers versus family members. Trop Med Int Health. 2004;9:559–65 (https://doi.org/10.1111/j.1365-3156.2004.01230.x).

55. Newell JN, Baral SC, Pande SB, Bam DS, Malla P. Family-member DOTS and community DOTS for tuberculosis control in Nepal: cluster-randomised controlled trial. Lancet. 2006;367:903–9 (https://doi.org/10.1016/S0140-6736(06)68380-3).

56. Farmer P, Robin S, Ramilus SL, Kim JY. Tuberculosis, poverty, and "compliance": lessons from rural Haiti. Semin Respir Infect. 1991;6:254–60 (https://www.ncbi.nlm.nih.gov/pubmed/1810004).

57. Jasmer RM, Bozeman L, Schwartzman K, Cave MD, Saukkonen JJ, Metchock B et al. Recurrent tuberculosis in the United States and Canada: relapse or reinfection? Am J Respir Crit Care Med. 2004;170:1360–6 (https://doi.org/10.1164/rccm.200408-1081OC).

58. Soares EC, Vollmer WM, Cavalcante SC, Pacheco AG, Saraceni V, Silva JS et al. Tuberculosis control in a socially vulnerable area: a community intervention beyond DOT in a Brazilian favela. Int J Tuberc Lung Dis. 2013;17:1581–6 (https://doi.org/10.5588/ijtld.13.0152).

59. Yassin MA, Datiko DG, Tulloch O, Markos P, Aschalew M, Shargie EB et al. Innovative community-based approaches doubled tuberculosis case notification and improve treatment outcome in Southern Ethiopia. PLoS One. 2013;8:e63174 (https://doi.org/10.1371/journal.pone.0063174).

60. Chan PC, Huang SH, Yu MC, Lee SW, Huang YW, Chien ST et al. Effectiveness of a government-organized and hospital-initiated treatment for multidrug-resistant tuberculosis patients--a retrospective cohort study. PLoS One. 2013;8:e57719 (https://doi.org/10.1371/journal.pone.0057719).

61. Gärden B, Samarina A, Stavchanskaya I, Alsterlund R, Övregaard A, Taganova O et al. Food incentives improve adherence to tuberculosis drug treatment among homeless patients in Russia. Scand J Caring Sci. 2013;27:117–22 (https://doi.org/10.1111/j.1471-6712.2012.01009.x).

62. Davidson BL. A controlled comparison of directly observed therapy vs self-administered therapy for active tuberculosis in the urban United States. Chest. 1998;114:1239–43 (https://doi.org/10.1378/chest.114.5.1239).

63. Puchalski Ritchie LM, Schull MJ, Martiniuk AL, Barnsley J, Arenovich T, van Lettow M et al. A knowledge translation intervention to improve tuberculosis care and outcomes in Malawi: a pragmatic cluster randomized controlled trial. Implement Sci. 2015;10:38 (https://doi.org/10.1186/s13012-015-0228-y).

64. Datiko DG, Lindtjørn B. Health extension workers improve tuberculosis case detection and treatment success in southern Ethiopia: a community randomized trial. PLoS One. 2009;4:e5443 (https://doi.org/10.1371/journal.pone.0005443).

65. Clark PM, Karagoz T, Apikoglu-Rabus S, Izzettin FV. Effect of pharmacist-led patient education on adherence to tuberculosis treatment. Am J Health Syst Pharm. 2007;64:497–505 (https://doi.org/10.2146/ajhp050543).

66. Janmeja AK, Das SK, Bhargava R, Chavan BS. Psychotherapy improves compliance with tuberculosis treatment. Respiration. 2005;72:375–80 (https://doi.org/10.1159/000086251).

67. Liefooghe R, Suetens C, Meulemans H, Moran MB, De Muynck A. A randomised trial of the impact of counselling on treatment adherence of tuberculosis patients in Sialkot, Pakistan. Int J Tuberc Lung Dis. 1999;3:1073–80 (https://www.ncbi.nlm.nih.gov/pubmed/10599010).

68. Baral SC, Aryal Y, Bhattrai R, King R, Newell JN. The importance of providing counselling and financial support to patients receiving treatment for multi-drug resistant TB: mixed method qualitative and pilot intervention studies. BMC Public Health. 2014;14:46 (https://doi.org/10.1186/1471-2458-14-46).

69. Martins N, Morris P, Kelly PM. Food incentives to improve completion of tuberculosis treatment: randomised controlled trial in Dili, Timor-Leste. BMJ. 2009;339:b4248 (https://doi.org/10.1136/bmj.b4248).

70. Lutge E, Lewin S, Volmink J, Friedman I, Lombard C. Economic support to improve tuberculosis treatment outcomes in South Africa: a pragmatic cluster-randomized controlled trial. Trials. 2013;14:154 (https://doi.org/10.1186/1745-6215-14-154).

71. Jahnavi G, Sudha CH. Randomised controlled trial of food supplements in patients with newly diagnosed tuberculosis and wasting. Singapore Med J. 2010;51:957–62 (https://www.ncbi.nlm.nih.gov/pubmed/21221502).

72. Sinclair D, Abba K, Grobler L, Sudarsanam TD. Nutritional supplements for people being treated for active tuberculosis. Cochrane Database Syst Rev. 2011:CD006086 (https://doi.org/10.1002/14651858.CD006086.pub3).

73. Álvarez Gordillo G, Alvarez Gordillo J, Dorantes Jimenez J. [Educational strategy to increase compliance with the anti-tuberculosis regimen in Chiapas, Mexico]. Pan Am J Public Heal. 2003;14:402–8 (https://iris.paho.org/handle/10665.2/8297).

74. Demissie M, Getahun H, Lindtjørn B. Community tuberculosis care through "TB clubs" in rural North Ethiopia. Soc Sci Med. 2003;56:2009–18 (https://doi.org/10.1016/s0277-9536(02)00182-x).

75. Dick J, Lombard C. Shared vision – a health education project designed to enhance adherence to anti-tuberculosis treatment. Int J Tuberc Lung Dis. 1997;1:181–6 (https://pubmed.ncbi.nlm.nih.gov/9441085/).

76. Banerjee A, Harries AD, Mphasa N, Nyirenda TE, Veen J, Ringdal T et al. Evaluation of a unified treatment regimen for all new cases of tuberculosis using guardian-based supervision. Int J Tuberc Lung Dis. 2000;4:333–9 (https://pubmed.ncbi.nlm.nih.gov/10777082/).

77. Becx-Bleumink M, Wibowo H, Apriani W, Vrakking H. High tuberculosis notification and treatment success rates through community participation in central Sulawesi, Republic of Indonesia. Int J Tuberc Lung Dis. 2001;5:920–5 (https://pubmed.ncbi.nlm.nih.gov/11605885/).

78. Dobler CC, Korver S, Batbayar O, Oyuntsetseg S, Tsolmon B, Wright C et al. Success of community-based directly observed anti-tuberculosis treatment in Mongolia. Int J Tuberc Lung Dis. 2015;19:657–62 (https://doi.org/10.5588/ijtld.14.0927).

79. Dudley L, Azevedo V, Grant R, Schoeman JH, Dikweni L, Maher D. Evaluation of community contribution to tuberculosis control in Cape Town, South Africa. Int J Tuberc Lung Dis. 2003;7:S48–55 (https://pubmed.ncbi.nlm.nih.gov/12971654/).

80. Maciel EL, Guidoni LM, Brioshi AP, do Prado TN, Fregona G, Hadad DJ et al. Household members and health care workers as supervisors of tuberculosis treatment. Rev Saude Publica. 2010;44:339–43 (https://doi.org/10.1590/s0034-89102010000200015).

81. Miti S, Mfungwe V, Reijer P, Maher D. Integration of tuberculosis treatment in a community-based home care programme for persons living with HIV/AIDS in Ndola, Zambia. Int J Tuberc Lung Dis. 2003;7:S92–8 (https://pubmed.ncbi.nlm.nih.gov/12971660/).

82. Moalosi G, Floyd K, Phatshwane J, Moeti T, Binkin N, Kenyon T. Cost-effectiveness of home-based care versus hospital care for chronically ill tuberculosis patients, Francistown, Botswana. Int J Tuberc Lung Dis. 2003;7:S80–5 (https://pubmed.ncbi.nlm.nih.gov/12971658/).

83. Niazi AD, Al-Delaimi AM. Impact of community participation on treatment outcomes and compliance of DOTS patients in Iraq. East Mediterr Health J. 2003;9:709–17 (https://pubmed.ncbi.nlm.nih.gov/15748068/).

84. Wares DF, Akhtar M, Singh S. DOT for patients with limited access to health care facilities in a hill district of eastern Nepal. Int J Tuberc Lung Dis. 2001;5:732–40 (https://pubmed.ncbi.nlm.nih.gov/11495264/).

85. Arora V, Neeta Singla N, Gupta R. Community mediated domiciliary DOTS execution – a study from New Delhi. Ind. J Tub. 2003;50:143.

86. Kironde S, Meintjies M. Tuberculosis treatment delivery in high burden settings: does patient choice of supervision matter? Int J Tuberc Lung Dis. 2002;6:599–608 (https://pubmed.ncbi.nlm.nih.gov/12102299/).

87. van den Boogaard J, Lyimo R, Irongo CF, Boeree MJ, Schaalma H, Aarnoutse RE et al. Community vs. facility-based directly observed treatment for tuberculosis in Tanzania's Kilimanjaro Region. Int J Tuberc Lung Dis. 2009;13:1524–9 (https://pubmed.ncbi.nlm.nih.gov/19919771/).

88. Manders AJ, Banerjee A, van den Borne HW, Harries AD, Kok GJ, Salaniponi FM. Can guardians supervise TB treatment as well as health workers? A study on adherence during the intensive phase. Int J Tuberc Lung Dis. 2001;5:838–42 (https://pubmed.ncbi.nlm.nih.gov/11573895/).

89. Akhtar S, Rozi S, White F, Hasan R. Cohort analysis of directly observed treatment outcomes for tuberculosis patients in urban Pakistan. Int J Tuberc Lung Dis. 2011;15:90–6 (https://pubmed.ncbi.nlm.nih.gov/21276303/).

90. Chuck C, Robinson E, Macaraig M, Alexander M, Burzynski J. Enhancing management of tuberculosis treatment with video directly observed therapy in New York City. Int J Tuberc Lung Dis. 2016;20:588–93 (https://doi.org/10.5588/ijtld.15.0738).

91. Wade VA, Karnon J, Eliott JA, Hiller JE. Home videophones improve direct observation in tuberculosis treatment: a mixed methods evaluation. PLoS One. 2012;7:e50155 (https://doi.org/10.1371/journal.pone.0050155).

92. Khortwong P, Kaewkungwal J. Thai health education program for improving TB migrant's compliance. J Med Assoc Thai. 2013;96:365–73 (https://pubmed.ncbi.nlm.nih.gov/23539943/).

93. Morisky DE, Malotte CK, Choi P, Davidson P, Rigler S, Sugland B et al. A patient education program to improve adherence rates with antituberculosis drug regimens. Health Educ Q. 1990;17:253–67 (https://doi.org/10.1177/109019819001700303).

94. Drabo M, Zerbo R, Berthe A, Ouedrago L, Konfe S, Mugishe E et al. [Community involvement in tuberculosis care in three rural health districts of Burkina Faso]. Sante Publique. 2009;21:485–97 (https://pubmed.ncbi.nlm.nih.gov/20229641/).

95. Thiam S, LeFevre AM, Hane F, Ndiaye A, Ba F, Fielding KL et al. Effectiveness of a strategy to improve adherence to tuberculosis treatment in a resource-poor setting: a cluster randomized controlled trial. Jama. 2007;297:380–6 (https://doi.org/10.1001/jama.297.4.380).

96. Hsieh CJ, Lin LC, Kuo BI, Chiang CH, Su WJ, Shih JF. Exploring the efficacy of a case management model using DOTS in the adherence of patients with pulmonary tuberculosis. J Clin Nurs. 2008;17:869–75 (https://doi.org/10.1111/j.1365-2702.2006.01924.x).

97. Atkins S, Lewin S, Jordaan E, Thorson A. Lay health worker-supported tuberculosis treatment adherence in South Africa: an interrupted time-series study. Int J Tuberc Lung Dis. 2011;15:84–9 (https://pubmed.ncbi.nlm.nih.gov/21276302/).

98. Iribarren S, Chirico C, Echevarria M, Cardinali D. TextTB: A parallel design randomized control pilot study to evaluate acceptance and feasibility of a patient-driven mobile phone based intervention to support adherence to TB treatment. J Mob Technol Med. 2012;1:23–4 (https://doi.org/10.7309/jmtm.46).

99. Krishnaswami KV, Somasundaram PR, Tripathy SP, Vaidyanathan B, Radhakrishna S, Fox W. A randomised study of two policies for managing default in out-patients collecting supplies of drugs for pulmonary tuberculosis in a large city in South India. Tubercle. 1981;62:103–12 (https://pubmed.ncbi.nlm.nih.gov/6171080/).

100. Kunawararak P, Pongpanich S, Chantawong S, Pokaew P, Traisathit P, Srithanaviboonchai K et al. Tuberculosis treatment with mobile-phone medication reminders in northern Thailand. Southeast Asian J Trop Med Public Health. 2011;42:1444–51 (https://pubmed.ncbi.nlm.nih.gov/22299414/).

101. Mohan A, Nassir H, Niazi A. Does routine home visiting improve the return rate and outcome of DOTS patients who delay treatment? East Mediterr Health J. 2003;9:702–8 (https://pubmed.ncbi.nlm.nih.gov/15748067/).

102. Paramasivan R, Parthasarathy RT, Rajasekaran S. Short course chemotherapy: a controlled study of indirect defaulter retrieval method. Indian J Tuberc. 1993;40:185–90

103. Tanke ED, Leirer VO. Automated telephone reminders in tuberculosis care. Med Care. 1994;32:380–9 (https://doi.org/10.1097/00005650-199404000-00006).

104. Moulding TS, Caymittes M. Managing medication compliance of tuberculosis patients in Haiti with medication monitors. Int J Tuberc Lung Dis. 2002;6:313–9 (https://pubmed.ncbi.nlm.nih.gov/11936740/).

105. Liu X, Lewis JJ, Zhang H, Lu W, Zhang S, Zheng G et al. Effectiveness of electronic reminders to improve medication adherence in tuberculosis patients: a cluster-randomised trial. PLoS Med. 2015;12:e1001876 (https://doi.org/10.1371/journal.pmed.1001876).

106. Bronner LE, Podewils LJ, Peters A, Somnath P, Nshuti L, van der Walt M et al. Impact of community tracer teams on treatment outcomes among tuberculosis patients in South Africa. BMC Public Health. 2012;7:621 (https://doi.org/10.1186/1471-2458-12-621).

107. Snidal SJ, Barnard G, Atuhairwe E, Amor YB. Use of eCompliance, an innovative biometric system for monitoring of tuberculosis treatment in rural Uganda. Am J Trop Med Hyg. 2015;92:1271–9 (https://doi.org/10.4269/ajtmh.14-0413).

108. Thomson KA, Cheti EO, Reid T. Implementation and outcomes of an active defaulter tracing system for HIV, prevention of mother to child transmission of HIV (PMTCT), and TB patients in Kibera, Nairobi, Kenya. Trans R Soc Trop Med Hyg. 2011;105:320–6 (https://doi.org/10.1016/j.trstmh.2011.02.011).

109. Al-Hajjaj MS, Al-Khatim IM. High rate of non-compliance with anti-tuberculosis treatment despite a retrieval system: a call for implementation of directly observed therapy in Saudi Arabia. Int J Tuberc Lung Dis. 2000;4:345–9 (https://pubmed.ncbi.nlm.nih.gov/10777084/).

110. Broomhead S, Mars M. Retrospective return on investment analysis of an electronic treatment adherence device piloted in the Northern Cape Province. Telemed e-Health. 2012;18:24–31 (https://doi.org/10.1089/tmj.2011.0143).

111. Ngamvithayapong-Yanai J, Luangjina S, Nedsuwan S, Kantipong P, Wongyai J, Ishikawa N. Engaging women volunteers of high socioeconomic status in supporting socioeconomically disadvantaged tuberculosis patients in Chiang Rai, Thailand. WPSAR. 2013;4:34–8 (https://pubmed.ncbi.nlm.nih.gov/23908953/).

112. Zou G, Wei X, Witter S, Yin J, Walley J, Liu S et al. Incremental cost-effectiveness of improving treatment results among migrant tuberculosis patients in Shanghai. Int J Tuberc Lung Dis. 2013;17:1056–64 (https://pubmed.ncbi.nlm.nih.gov/23827030/).

113. Lu H, Yan F, Wang W, Wu L, Ma W, Chen J et al. Do transportation subsidies and living allowances improve tuberculosis control outcomes among internal migrants in urban Shanghai, China? Western Pac Surveill Response J. 2013;4:19–24 (https://pubmed.ncbi.nlm.nih.gov/23908951/).

114. Wei X, Zou G, Yin J, Walley J, Yang H, Kliner M et al. Providing financial incentives to rural-to-urban tuberculosis migrants in Shanghai: an intervention study. Infect Dis Poverty. 2012;1:9 (https://doi.org/10.1186/2049-9957-1-9).

115. Cantalice Filho JP. Food baskets given to tuberculosis patients at a primary health care clinic in the city of Duque de Caxias, Brazil: effect on treatment outcomes. J Bras Pneumol. 2009;35:992–7 (https://pubmed.ncbi.nlm.nih.gov/19918632/).

116. Sripad A, Castedo J, Danford N, Zaha R, Freile C. Effects of Ecuador's national monetary incentive program on adherence to treatment for drug-resistant tuberculosis. Int J Tuberc Lung Dis. 2014;18:44–8 (https://pubmed.ncbi.nlm.nih.gov/24365551/).

117. Tsai W-C, Kung P-T, Khan M, Campbell C, Yang W-T, Lee T-F et al. Effects of pay-for-performance system on tuberculosis default cases control and treatment in Taiwan. J Infect. 2010;61:235–43 (https://pubmed.ncbi.nlm.nih.gov/20624421/).

118. Bock NN, Sales RM, Rogers T, DeVoe B. A spoonful of sugar...: improving adherence to tuberculosis treatment using financial incentives. Int J Tuberc Lung Dis. 2001;5:96–8 (https://pubmed.ncbi.nlm.nih.gov/11263524/).

119. Safdar N, Hinderaker SG, Baloch NA, Enarson DA, Khan MA, Morkve O. Childhood tuberculosis deskguide and monitoring: An intervention to improve case management in Pakistan. BMC Health Serv Res. 2011;1:187 (https://doi.org/10.1186/1472-6963-11-187).

120. Shin S, Livchits V, Connery HS, Shields A, Yanov S, Yanova G et al. Effectiveness of alcohol treatment interventions integrated into routine tuberculosis care in Tomsk, Russia. Addiction. 2013;108:1387–96 (https://doi.org/10.1111/add.12148).

121. The End TB Strategy. Global strategy and targets for tuberculosis prevention, care and control after 2015 (WHO/HTM/TB/2015.19). Geneva: World Health Organization; 2015 (https://www.who.int/tb/strategy/en/).

122. Floyd K, Hutubessy R, Kliiman K, Centis R, Khurieva N, Jakobowiak W et al. Cost and cost-effectiveness of multidrug-resistant tuberculosis treatment in Estonia and Russia. Eur Respir J. 2012;40:133–42 (https://doi.org/10.1183/09031936.00169411).

123. Suárez PG, Floyd K, Portocarrero J, Alarcón E, Rapiti E, Ramos G et al. Feasibility and cost-effectiveness of standardised second-line drug treatment for chronic tuberculosis patients: a national cohort study in Peru. Lancet. 2002;359:1980–9 (https://doi.org/10.1016/S0140-6736(02)08830-X).

124. Tupasi TE, Gupta R, Quelapio MID, Orillaza RB, Mira NR, Mangubat NV et al. Feasibility and cost-effectiveness of treating multidrug-resistant tuberculosis: a cohort study in the Philippines. PLoS Med. 2006;3:e352 (https://doi.org/10.1371/journal.pmed.0030352).

125. Fitzpatrick C, Floyd K. A systematic review of the cost and cost effectiveness of treatment for multidrug-resistant tuberculosis. PharmacoEconomics. 2012;30:63–80 (https://doi.org/10.2165/11595340-000000000-00000).

126. Chan P-C, Huang S-H, Yu M-C, Lee S-W, Huang Y-W, Chien S-T et al. Effectiveness of a government-organized and hospital-initiated treatment for multidrug-resistant tuberculosis patients – a retrospective cohort study. PLoS One. 2013;8:e57719 (https://doi.org/10.1371/journal.pone.0057719).

127. Cox H, Hughes J, Daniels J, Azevedo V, McDermid C, Poolman M et al. Community-based treatment of drug-resistant tuberculosis in Khayelitsha, South Africa. Int J Tuberc Lung Dis. 2014;18:441–8 (https://pubmed.ncbi.nlm.nih.gov/24670700/).

128. Gler MT, Podewils LJ, Munez N, Galipot M, Quelapio MID, Tupasi TE. Impact of patient and program factors on default during treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2012;16:955–60 (https://pubmed.ncbi.nlm.nih.gov/22584124/).

129. Loveday M, Wallengren K, Brust J, Roberts J, Voce A, Margot B et al. Community-based care vs. centralised hospitalisation for MDR-TB patients, KwaZulu-Natal, South Africa. Int J Tuberc Lung Dis. 2015;19:163–71 (https://pubmed.ncbi.nlm.nih.gov/25574914/).

130. Musa BM, John D, Habib AG, Kuznik A. Cost- optimization in the treatment of multidrug resistant tuberculosis in Nigeria. Trop Med Int Health. 2016;21:176–82 (https://pubmed.ncbi.nlm.nih.gov/26610176/).

131. Sinanovic E, Ramma L, Vassall A, Azevedo V, Wilkinson L, Ndjeka N et al. Impact of reduced hospitalisation on the cost of treatment for drug-resistant tuberculosis in South Africa. Int J Tuberc Lung Dis. 2015;19:172–8 (https://pmc.ncbi.nlm.nih.gov/articles/PMC4447891/).

132. Narita M, Alonso P, Lauzardo M, Hollender ES, Pitchenik AE, Ashkin D. Treatment experience of multidrug-resistant tuberculosis in Florida, 1994–1997. Chest. 2001;120:343–8 (https://pubmed.ncbi.nlm.nih.gov/11502627/).

133. Ho J, Byrne AL, Linh NN, Jaramillo E, Fox GJ. Decentralized care for multidrug-resistant tuberculosis: a systematic review and meta-analysis. Bull World Health Organ. 2017;95:584–93 (https://pmc.ncbi.nlm.nih.gov/articles/PMC5537756/).

134. WHO policy on TB infection control in health-care facilities, congregate settings and households (WHO/HTM/TB/2009.419). Geneva: World Health Organization; 2009 (https://apps.who.int/iris/bitstream/handle/10665/44148/9789241598323_eng.pdf).

135. Roadmap for childhood tuberculosis: towards zero deaths (WHO/HTM/TB/2013.12). Geneva: World Health Organization; 2013 (https://www.who.int/publications/i/item/9789241506137).

136. Roadmap towards ending TB in children and adolescents. Geneva: World Health Organization; 2018 (https://apps.who.int/iris/bitstream/handle/10665/275422/9789241514798-eng.pdf). Licence: CC BY-NC-SA 3.0 IGO.

137. Public–private mix for TB prevention and care: a roadmap (WHO/CDS/TB/2018.32). Geneva: World Health Organization; 2018 (https://iris.who.int/bitstream/handle/10665/333885/WHO-CDS-TB-2018.32-eng.pdf).

138. WHO consolidated guidelines on tuberculosis. Module 4: Treatment – care and support during tuberculosis treatment Geneva: World Health Organization; 2022.

139. Talukder K, Salim MA, Jerin I, Sharmin F, Talukder MQ, Marais BJ et al. Intervention to increase detection of childhood tuberculosis in Bangladesh. Int J Tuberc Lung Dis. 2012;16:70–5 (https://doi.org/10.5588/ijtld.11.0060).

140. Khan AJ, Khowaja S, Khan FS, Qazi F, Lotia I, Habib A et al. Engaging the private sector to increase tuberculosis case detection: an impact evaluation study. Lancet Infect Dis. 2012;12:608–16 (https://doi.org/10.1016/s1473-3099(12)70116-0).

141. Malik AA, Amanullah F, Codlin AJ, Siddiqui S, Jaswal M, Ahmed JF et al. Improving childhood tuberculosis detection and treatment through facility-based screening in rural Pakistan. Int J Tuberc Lung Dis. 2018;22:851–7 (https://doi.org/10.5588/ijtld.17.0736).

142. Zawedde-Muyanja S, Nakanwagi A, Dongo JP, Sekadde MP, Nyinoburyo R, Ssentongo G et al. Decentralisation of child tuberculosis services increases case finding and uptake of preventive therapy in Uganda. Int J Tuberc Lung Dis. 2018;22:1314–21 (https://doi.org/10.5588/ijtld.18.0025).

143. Maha A, Majumdar SS, Main S, Phillip W, Witari K, Schulz J et al. The effects of decentralisation of tuberculosis services in the East New Britain Province, Papua New Guinea. Public Health Action. 2019;9:S43–s9 (https://doi.org/10.5588/pha.18.0070).

144. Islam Z, Sanin KI, Ahmed T. Improving case detection of tuberculosis among children in Bangladesh: lessons learned through an implementation research. BMC Public Health. 2017;17:131 (https://doi.org/10.1186/s12889-017-4062-9).

145. Catalyzing Pediatric TB Innovation (CaP-TB) project. Unpublished data. 2021.

146. Oshi DC, Chukwu JN, Nwafor CC, Meka AO, Madichie NO, Ogbudebe CL et al. Does intensified case finding increase tuberculosis case notification among children in resource-poor settings? A report from Nigeria. Int J Mycobacteriol. 2016;5:44–50 (https://doi.org/10.1016/j.ijmyco.2015.10.007).

147. Joshi B, Chinnakali P, Shrestha A, Das M, Kumar AM, Pant R et al. Impact of intensified case-finding strategies on childhood TB case registration in Nepal. Public Health Action. 2015;5:93–8 (https://doi.org/10.5588/pha.15.0004).

148. Hanrahan CF, Nonyane BAS, Mmolawa L, West NS, Siwelana T, Lebina L et al. Contact tracing versus facility-based screening for active TB case finding in rural South Africa: A pragmatic cluster-randomized trial (Kharitode TB). PLoS Med. 2019;16:e1002796 (https://doi.org/10.1371/journal.pmed.1002796).

149. Moyo S, Verver S, Hawkridge A, Geiter L, Hatherill M, Workman L et al. Tuberculosis case finding for vaccine trials in young children in high-incidence settings: a randomised trial. Int J Tuberc Lung Dis. 2012;16:185–91 (https://doi.org/10.5588/ijtld.11.0348).

150. Davis JL, Turimumahoro P, Meyer AJ, Ayakaka I, Ochom E, Ggita J et al. Home-based tuberculosis contact investigation in Uganda: a household randomised trial. ERJ Open Res. 2019;5 (https://doi.org/10.1183/23120541.00112-2019).

151. Fatima R, Qadeer E, Yaqoob A, Haq Mu, Majumdar SS, Shewade HD et al. Extending 'contact tracing' into the community within a 50-metre radius of an index tuberculosis patient using Xpert MTB/RIF in urban, Pakistan: did it increase case detection. PLoS One. 2016;11:e0165813 (https://doi.org/10.1371/journal.pone.0165813).

152. Reddy KK, Ananthakrishnan R, Jacob AG, Das M, Isaakidis P, Kumar AMV. Intensified tuberculosis case finding amongst vulnerable communities in southern India. Public health action. 2015;5:246–8 (https://doi.org/10.5588/pha.15.0048).

153. Bayona J, Chavez-Pachas AM, Palacios E, Llaro K, Sapag R, Becerra MC. Contact investigations as a means of detection and timely treatment of persons with infectious multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2003;7:S501–9 (https://pubmed.ncbi.nlm.nih.gov/14677844/).

154. Sachdeva KS, Raizada N, Sreenivas A, van't Hoog AH, van den Hof S, Dewan PK et al. Use of Xpert MTB/RIF in decentralized public health settings and its effect on pulmonary TB and DR-TB case finding in India. PLoS One. 2015;10:e0126065 (https://doi.org/10.1371/journal.pone.0126065).

155. Zachariah R, Spielmann MP, Harries AD, Gomani P, Graham SM, Bakali E et al. Passive versus active tuberculosis case finding and isoniazid preventive therapy among household contacts in a rural district of Malawi. Int J Tuberc Lung Dis. 2003;7:1033–9 (https://pubmed.ncbi.nlm.nih.gov/14598961/).

156. Ketema L, Dememew ZG, Assefa D, Gudina T, Kassa A, Letta T et al. Evaluating the integration of tuberculosis screening and contact investigation in tuberculosis clinics in Ethiopia: A mixed method study. PLoS One. 2020;15:e0241977 (https://doi.org/10.1371/journal.pone.0241977).

157. Miyano S, Dube C, Kayama N, Ishikawa N, Nozaki I, Syakantu G. Association between tuberculosis treatment outcomes and the mobile antiretroviral therapy programme in Zambia. Int J Tuberc Lung Dis. 2013;17:540–5 (https://doi.org/10.5588/ijtld.12.0432).

158. Wingfield T, Tovar MA, Huff D, Boccia D, Montoya R, Ramos E et al. A randomized controlled study of socioeconomic support to enhance tuberculosis prevention and treatment, Peru. Bull World Health Organ. 2017;95:270–80 (https://doi.org/10.2471/BLT.16.170167).

159. Rocha C, Montoya R, Zevallos K, Curatola A, Ynga W, Franco J et al. The Innovative Socio-economic Interventions Against Tuberculosis (ISIAT) project: an operational assessment. Int J Tuberc Lung Dis. 2011;15 Suppl 2:50–7 (https://doi.org/10.5588/ijtld.10.0447).

160. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management (WHO/CDS/TB/2018.4). Geneva: World Health Organization; 2018 (https://www.who.int/publications/i/item/9789241550239).

161. Global tuberculosis report 2020. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf). Licence: CC BY-NC-SA 3.0 IGO.

162. Updated recommendations on service delivery for the treatment and care of people living with HIV. Geneva: World Health Organization; 2021 (https://www.who.int/publications/i/item/9789240023581). Licence: CC BY-NC-SA 3.0 IGO.

Annex 1. Summary of recommendations

Notes:

a. The *WHO consolidated guidelines on tuberculosis. Module 4: Treatment and care* include new recommendations developed in 2024–25 and all valid recommendations that had been previously published.

b. Recommendations on the use of bedaquiline and delamanid in children aged below 3 and 6 years were added from the *WHO consolidated guidelines on tuberculosis. Module 5. Management of tuberculosis in children and adolescents*.

c. Recommendations on drug-susceptible TB treatment are grouped in Chapter 1 of the *WHO consolidated guidelines on tuberculosis. Module 4: Treatment and care*.

d. Recommendations on drug-resistant TB treatment are grouped in Chapter 2 of the *WHO consolidated guidelines on tuberculosis. Module 4: Treatment and care*.

e. Recommendations on TB care and support are grouped in Chapter 3 of the WHO consolidated guidelines on tuberculosis. Module 4: Treatment and care.

Annex 1.1. Summary of changes to the World Health Organization (WHO) treatment recommendations for drug-susceptible TB (DS-TB) between 2010 and the update and consolidation in 2025

Treatment of DS-TB using 6-month regimen			
Treatment of tuberculosis, guidelines for national programmes, fourth edition 2010 *(1)*	**Guidelines for treatment of drug-susceptible tuberculosis and patient care. 2017 *(2)***	**Consolidated guidelines on tuberculosis Module 4: Treatment** **Drug-susceptible tuberculosis treatment. 2022**	**Consolidated guidelines on tuberculosis Module 4: Treatment and care. 2025**
(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)*	Remained valid	**Recommendation is copied without modification into this consolidated document and appears exactly as in the 2010 guidelines.** **Recommendation 1**	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 1.2) The 2HRZE/6HE treatment regimen should be phased out *(strong recommendation, high certainty of evidence)*	Remained valid	**Redundant. The 2HRZE/6HE regimen is not 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)*	Remained valid	**Recommendation is copied without modification into this consolidated document and appears exactly as in the 2010 guidelines.** **Recommendation 2**	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 2.1A) 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)*	UPDATED (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 is copied without modification into this consolidated document and appears exactly as in the 2017 guidelines update. This recommendation complements recommendation 2** **Recommendation 3**	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 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			
No recommendation	NEW RECOMMENDATION (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 is copied without modification into this consolidated document and appears exactly as in the 2010 guidelines.** **Recommendation 4**	Recommendation 1.4. 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)*
(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)*	Remained valid	**Recommendation is copied without modification into this consolidated document and appears exactly as in the 2010 guidelines. It remains valid for 6 months regimens due to evidence used for review. Extension of the 4-month regimens is not part of pertinent recommendations** **Recommendation 5**	Recommendation 1.5. 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)*

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 (expert opinion based)	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 (expert opinion based)	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)	UPDATED (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 4-month regimens			
No recommendation	NEW RECOMMENDATION (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)*	**UPDATED AND NEW RECOMMENDATION** **Patients 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 6**	Recommendation 2.1 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)*
No recommendation	No recommendation	**NEW RECOMMENDATION** **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 7**	Recommendation 2.2 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)*

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)*	Remained valid	**Recommendation is copied without modification into this consolidated document and appears exactly as in the 2012 guidelines.** **Recommendation 8**	Recommendation 3.1 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)*

DS-TB treatment and ART in people living with HIV			
No recommendation	NEW RECOMMENDATION (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)*			
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)*	**UPDATED. Recommendation is copied without modification from Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach 2021** **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). *(6)*** Recommendation 9	Recommendation 3.2 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)*
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/mm3) 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			
No recommendation	NEW RECOMMENDATION (Recommendation 1.6.1) 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 is copied without modification into this consolidated document and appears exactly as in the 2017 guidelines.** **Recommendation 10**	Recommendation 4.1 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)*
No recommendation	NEW RECOMMENDATION (Recommendation 1.6.2) In patients with **tuberculous pericarditis**, an initial adjuvant corticosteroid therapy may be used *(conditional recommendation, very low certainty of evidence)*	**Recommendation is copied without modification into this consolidated document and appears exactly as in the 2017 guidelines.** **Recommendation 11**	Recommendation 4.2 In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used *(conditional recommendation, very low certainty of evidence)*

TB treatment in children and adolescents		
	Guidance for national tuberculosis programmes on the management of tuberculosis in children. **2014 *(8)*.**	
	(Recommendation 8) The following dosages of anti-TB medicines should be used daily for the treatment of TB in children: isoniazid (H) 10 mg/kg (range 7–15 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 (range 30–40 mg/kg) ethambutol (E) 20 mg/kg (range 15–25 mg/kg) *(strong recommendation, moderate certainty of evidence)*	**Recommendations that are not redundant and are valid, in addition to all other recommendations relevant to children and adolescents, are featured in the guidelines on childhood TB treatment that are published in the module on management of tuberculosis in children and adolescents of this series of consolidated guidelines.**
	(Recommendation 9) Children with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis who live in settings with low HIV prevalence 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 the dosages specified in Recommendation 8 *(strong recommendation, moderate certainty of evidence)*	

TB treatment in children and adolescents	
	(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 high 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)*
	(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 pediatric TB *(strong recommendation, low certainty of evidence)*

TB treatment in children and adolescents	
	(Recommendation 12) During the continuation phase of treatment, thrice-weekly regimens can be considered for children known not to be HIV-infected and living in settings with well-established directly observed therapy *(conditional recommendation, very low certainty of evidence for use of intermittent treatment of children in specific settings)*
	(Recommendation 13) Streptomycin should not be used as part of first-line treatment regimens for children with pulmonary TB or tuberculous peripheral lymphadenitis *(strong recommendation, moderate certainty of 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)*

Annex 1.2. Summary of changes to the World Health Organization (WHO) treatment recommendations for multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB) between 2019 and the update and consolidation in 2025

Recommendations in the 2019 update	Recommendations in the 2020 update	Recommendations in the 2022 update	Recommendations in the 2025 update and consolidation
Not included in the 2019 guidelines	**Section 4: The bedaquiline, pretomanid and linezolid (BPaL) regimen for MDR-TB with additional fluoroquinolone resistance**	**Section 1: The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen**	**Recommendation 1.1: The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen**
Not included the in 2019 guidelines	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 in the estimates of effect)* ***(New 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)* ***(New recommendation, replacing 4.1 in the 2020 update)***	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)* ***(no change)***

Recommendations in the 2019 update	Recommendations in the 2020 update	Recommendations in the 2022 update	Recommendations in the 2025 update and consolidation
Not included	*Not included*	*Not included*	**Recommendation 1.2: The 6-month bedaquiline, delamanid, linezolid, levofloxacin and clofazimine (BDLLfxC) regimen**
Not included	*Not included*	*Not included*	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)* ***(New recommendation)***

Recommendations in the 2019 update	Recommendations in the 2020 update	Recommendations in the 2022 update	Recommendations in the 2025 update and consolidation
Section 4: Use of the standardized shorter MDR-TB regimen	**Section 2: Shorter, all-oral, bedaquiline-containing regimen for multidrug-/ rifampicin-resistant tuberculosis**	**Section 2: The 9-month all-oral regimen for MDR/RR-TB**	**Recommendation 2.1: 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 in the estimates of effect)*	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 in the evidence)* *(Updated recommendation)*	2.1 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)* ***(New recommendation, replacing 2.1 in the 2020 update)***	2.1 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)* ***(no change)***
Not included	*Not included*	*Not included*	**Recommendation 2.2: The modified 9-month all-oral regimens for MDR/RR-TB**

Recommendations in the 2019 update	Recommendations in the 2020 update	Recommendations in the 2022 update	Recommendations in the 2025 update and consolidation
Not included	*Not included*	*Not included*	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)* ***(New 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)* ***(New recommendation)***

Recommendations in the 2019 update	Recommendations in the 2020 update	Recommendations in the 2022 update	Recommendations in the 2025 update and consolidation
Section 2: The composition of longer MDR-TB regimens	**Section 3: Longer regimens for multidrug-/ rifampicin-resistant tuberculosis**	**Section 3: Longer regimens for MDR/RR-TB**	**3. Treatment of drug-resistant TB using longer regimens** **Recommendations 3.1–3.17**
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 in the estimates of effect)*	3.1 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 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 in the estimates of effect)* ***(Editing of the word "after" to "if" with reference to stopping bedaquiline)***	3.1 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)* ***(No change)***	3.1 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)* ***(No change)***

[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**).

Recommendations in the 2019 update	Recommendations in the 2020 update	Recommendations in the 2022 update	Recommendations in the 2025 update and consolidation
Kanamycin and capreomycin are not to be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty in the estimates of effect)*	3.2 Kanamycin and capreomycin are not to be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty in the estimates of effect)* *(No change)*	3.2 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)* *(No change)*	3.2 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)* *(No change)*
Levofloxacin or moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty in the estimates of effect)*	3.3 Levofloxacin or moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty in the estimates of effect)* *(No change)*	3.3 Levofloxacin or moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)* *(No change)*	3.3 Levofloxacin or moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)* *(No change)*

Recommendations in the 2019 update	Recommendations in the 2020 update	Recommendations in the 2022 update	Recommendations in the 2025 update and consolidation
Bedaquiline should be included in longer MDR-TB regimens for patients aged 18 years or more. *(Strong recommendation, moderate certainty in the estimates of effect)* Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years. *(Conditional recommendation, very low certainty in the estimates of effect)*	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 in the estimates of effect)* Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years. *(Conditional recommendation, very low certainty in the estimates of effect)* *(No change)*	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 of evidence)* *(No change)* Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years. *(Conditional recommendation, very low certainty of evidence)* *(No change)* 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)* *(New and additional 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 of evidence)* *(No change)* Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years. *(Conditional recommendation, very low certainty of evidence)* *(No change)* 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)* *(No change)*
Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty in the estimates of effect)*	3.5 Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty in the estimates of effect)* *(No change)*	3.5 Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)* *(No change)*	3.5 Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)* *(No change)*

Recommendations in the 2019 update	Recommendations in the 2020 update	Recommendations in the 2022 update	Recommendations in the 2025 update and consolidation
Clofazimine and cycloserine or terizidone may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty in the estimates of effect)*	3.6 Clofazimine and cycloserine or terizidone may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty in the estimates of effect)* *(No change)*	3.6 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)* *(No change)*	3.6 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)* *(No change)*
Ethambutol may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty in the estimates of effect)*	3.7 Ethambutol may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty in the estimates of effect)* *(No change)*	3.7 Ethambutol may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)* *(No change)*	3.7 Ethambutol may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)* *(No change)*
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 the estimates of effect)*	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 in the estimates of effect)* *(No change)*	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)* *(No change)* 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)* *(New and additional 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)* *(No change)* 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)* *(No change)*

Recommendations in the 2019 update	Recommendations in the 2020 update	Recommendations in the 2022 update	Recommendations in the 2025 update and consolidation
Pyrazinamide may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty in the estimates of effect)*	3.9 Pyrazinamide may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty in the estimates of effect)* *(No change)*	3.9 Pyrazinamide may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)* *(No change)*	3.9 Pyrazinamide may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)* *(No change)*
Imipenem–cilastatin or meropenem may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty in the estimates of effect)*	3.10 Imipenem–cilastatin or meropenem may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty in the estimates of effect)*[79] *(No change)*	3.10 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] *(No change)*	3.10 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] *(No change)*
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 in the estimates of effect)*	3.11 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 in the estimates of effect)* *(No change)*	3.11 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)* *(No change)*	3.11 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)* *(No change)*

[79] 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.

Recommendations in the 2019 update	Recommendations in the 2020 update	Recommendations in the 2022 update	Recommendations in the 2025 update and consolidation
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 against use, very low certainty in the estimates of effect)*	3.12 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 against use, very low certainty in the estimates of effect)* *(No change)*	3.12 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 against use, very low certainty of evidence)* *(No change)*	3.12 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 against use, very low certainty of evidence)* *(No change)*
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 against use, very low certainty in the estimates of effect)*	3.13 *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 against use, very low certainty in the estimates of effect)* *(No change)*	3.13 *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 against use, very low certainty of evidence)* *(No change)*	3.13 *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 against use, very low certainty of evidence)* ***(No change)***

Recommendations in the 2019 update	Recommendations in the 2020 update	Recommendations in the 2022 update	Recommendations in the 2025 update and consolidation
Clavulanic acid should not be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation against use, low certainty in the estimates of effect)*[80]	3.14 Clavulanic acid should not be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation against use, low certainty in the estimates of effect)*[1] *(No change)*	3.14 Clavulanic acid should not be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation against use, low certainty of evidence)*[80] *(No change)*	3.14 Clavulanic acid should not be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation against use, low certainty of evidence)*[1] ***(No change)***
Section 3: The duration of longer MDR-TB regimens	**Section 3: Longer regimens for multidrug-/ rifampicin-resistant tuberculosis**	**Section 3: Longer regimens for MDR/RR-TB**	**3. Treatment of drug-resistant TB using longer regimens** **Recommendations 3.1–3.17**
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 in the estimates of effect)*	3.15 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 in the estimates of effect)* *(No change to wording but combined with section above called: Section 3: Recommendations on the use of longer regimens for multidrug-/ rifampicin-resistant tuberculosis)*	3.15 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)* *(No change)*	3.15 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)* ***(No change)***

[80] 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.

Recommendations in the 2019 update	Recommendations in the 2020 update	Recommendations in the 2022 update	Recommendations in the 2025 update and consolidation
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 in the estimates of effect)*	3.16 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 in the estimates of effect)* *(No change to wording but combined with section above called: Section 3: Recommendations on the use of longer regimens for multidrug-/ rifampicin-resistant tuberculosis)*	3.16 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)* *(No change)*	3.16 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)* ***(No change)***
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 in the estimates of effect)*	3.17 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 in the estimates of effect)* *(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)*	3.17 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)* *(No change)*	3.17 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)* ***(No change)***

Recommendations in the 2019 update	Recommendations in the 2020 update	Recommendations in the 2022 update	Recommendations in the 2025 update and consolidation
Section 1: Regimens for isoniazid-resistant tuberculosis	**Section 1: Regimen for rifampicin-susceptible and isoniazid-resistant tuberculosis**	**Section 4: Regimen for rifampicin-susceptible and isoniazid-resistant tuberculosis**	**4. 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 in the estimates of effect)*	1.1 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 in the estimates of effect)* *(No change)*	4.1 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)* *(No change)*	4.1 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)* ***(No change)***
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 in the estimates of effect)*	1.2. 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 in the estimates of effect)* *(No change)*	4.2. 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)* *(No change)*	4.2. 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)* ***(No change)***

Recommendations in the 2019 update	Recommendations in the 2020 update	Recommendations in the 2022 update	Recommendations in the 2025 update and consolidation
Section 5: Monitoring patient response to MDR-TB treatment using culture	**Section 5: Monitoring patient response to MDR-TB treatment using culture**	**Section 5: Monitoring patient response to MDR/RR-TB treatment using culture**	**5. Monitoring patient response to MDR/RR-TB treatment using culture**
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)*	5.1. 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. *(No change)*	5.1. 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. *(No change)*	5.1. 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. ***(No change)***

Recommendations in the 2019 update	Recommendations in the 2020 update	Recommendations in the 2022 update	Recommendations in the 2025 update and consolidation
Section 6: Start of antiretroviral therapy in patients on second-line antituberculosis regimens	**Section 6: Start of antiretroviral therapy in patients on second-line antituberculosis regimens**	**Section 6: Start of antiretroviral therapy in patients on MDR/RR-TB regimens**	**6. 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-quality evidence)*	6.1. 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 quality evidence)* *(No change)*	6.1. 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)* *(No change)*	6.1. 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)* ***(No change)***
Section 7: Surgery for patients on MDR-TB treatment	**Section 7: Surgery for patients on MDR-TB treatment**	**Section 7: Surgery for patients on MDR/RR-TB treatment**	**7. 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 in the evidence)*	7.1. 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 in the evidence)* *(No change)*	7.1. 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)* *(No change)*	7.1. 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)* ***(No change)***

Recommendations in the 2019 update	Recommendations in the 2020 update	Recommendations in the 2022 update	Recommendations in the 2025 update and consolidation
Not included	*Not included*	*Not included*	**8. Hepatitis C virus (HCV) and MDR/RR-TB treatment co-administration**
Not included	*Not included*	*Not included*	**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)* ***(New recommendation)***
Section 8: Care and support for patients with MDR/RR-TB	**Section 8: Care and support for patients with MDR/RR-TB**	**Presented in a separate sub-module of the *WHO consolidated guidelines on tuberculosis. Module 4. Treatment – Tuberculosis care and support (1)***	**Presented in Chapter 3. *Tuberculosis care and support***

Annex 1.3. Summary of changes to the World Health Organization (WHO) treatment recommendations for Tuberculosis care and support between 2011 and the update and consolidation in 2025

Recommendations in the Guidelines for the programmatic management of drug-resistant tuberculosis. 2011	Recommendations in the Guidelines for treatment of drug-susceptible tuberculosis and patient care 2017	Recommendations in the 2020–2021 update and consolidation	Recommendations in the 2025 update and consolidation
Care and support interventions for all people with TB			
No recommendation	NEW RECOMMENDATION (Recommendation 1.1) Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment *(strong recommendation, moderate certainty of evidence)*		1.1 Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment *(strong recommendation, moderate certainty of evidence)*
	NEW RECOMMENDATION (Recommendation 1.2) 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)*		1.2 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)*

Recommendations in the Guidelines for the programmatic management of drug-resistant tuberculosis. 2011	Recommendations in the Guidelines for treatment of drug-susceptible tuberculosis and patient care 2017	Recommendations in the 2020–2021 update and consolidation	Recommendations in the 2025 update and consolidation
	NEW RECOMMENDATION (Recommendation 1.3) 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 or digital medication monitor *(conditional recommendation, very low certainty in the evidence)* b) material support to patient *(conditional recommendation, moderate certainty evidence)*; c) psychological support to patient *(conditional recommendation, low certainty of evidence)*; d) staff education *(conditional recommendation, low certainty of evidence)*.		1.3 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 or digital medication monitor *(conditional recommendation, very low certainty in the evidence)* b) material support to patient *(conditional recommendation, moderate certainty evidence)*; c) psychological support to patient *(conditional recommendation, low certainty of evidence)*; d) staff education *(conditional recommendation, low certainty of evidence)*.

Recommendations in the Guidelines for the programmatic management of drug-resistant tuberculosis. 2011	Recommendations in the Guidelines for treatment of drug-susceptible tuberculosis and patient care 2017	Recommendations in the 2020–2021 update and consolidation	Recommendations in the 2025 update and consolidation
	NEW RECOMMENDATION (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 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)*.		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)*.

Recommendations in the Guidelines for the programmatic management of drug-resistant tuberculosis. 2011	Recommendations in the Guidelines for treatment of drug-susceptible tuberculosis and patient care 2017	Recommendations in the 2020–2021 update and consolidation	Recommendations in the 2025 update and consolidation
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)*	Remained valid	(Recommendation 2.1) 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)*	2.1 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)*
No recommendation	NEW RECOMMENDATION (Recommendation 2.2) A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment *(conditional recommendation, very low certainty of evidence)*	(Recommendation 2.2) A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment *(conditional recommendation, very low certainty of evidence)*	2.2 A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment *(conditional recommendation, very low certainty of evidence)*

Recommendations in the Guidelines for the programmatic management of drug-resistant tuberculosis. 2011	Recommendations in the Guidelines for treatment of drug-susceptible tuberculosis and patient care 2017	Recommendations in the 2020–2021 update and consolidation	Recommendations in the 2025 update and consolidation
Models of care for children and adolescents exposed to TB or with TB disease			
		(Recommendation 3.1) 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)*	3.1. 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 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)*	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)*

Annex 2. Methods and expert panels

2.1 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 such as the GRADE approach [Grading of Recommendations Assessment, Development, and Evaluation], to support a structured and transparent methodology for policy-making. The policy recommendations presented in the guideline document were developed following the standards and updated procedures as described in the WHO Handbook for Guideline Development.

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. The Guideline Development Group comprises researchers, epidemiologists, end-users (clinicians and national TB control programme officers), community representatives, and experts in evidence synthesis. In compliance with the procedures and practices established by the GRC, declarations of interest (DOI) were managed according to the WHO Conflict of Interest Policy, including 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 Guideline Development Group 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 Guideline Development Group meeting, the members of the GDG reached decisions through a process of discussion and consensus. Where consensus through discussion could not be reached, the GDG voted on decisions. In these cases, decisions were made based on the vote of the majority.

Preparation for evidence assessment

The GRADE approach (Grading of Recommendations Assessment, Development, and Evaluation) was used to rate the certainty in the estimate of effect (quality 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 Guideline Review Committee. Details about the preparatory work ahead of the update were released to the public through public comment, focusing on the following: (i) rationale for providing up-to-date guidance, including the scope of the updates; (ii) prioritization and formulation of key questions; as well as (iii) the list, affiliations, and constituencies of potential members of the Guideline Development Group, undergoing conflict of interest assessments, as per the WHO Office of Compliance, Risk Management and Ethics policies. In preparation for the Guideline Development Group meeting, four webinars (via Zoom) were held with members of the Group to finalize the scoping and PICO (Patients, Intervention, Comparator and

Outcomes) questions, score outcomes of interest, and discuss preliminary data analysis results. The PICO questions, including sub-populations, treatment regimen composition, duration, and outcomes, were agreed upon by members of the Guideline Development Group. 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-tuberculosis agents.

The PICO questions looked at the following six distinct outcomes: (i) sustained treatment success; (ii) treatment failure and recurrence; (iii) death (due to any cause); (iv) loss to follow-up; (v) serious adverse event or adverse events of special interest; (vi) amplification (acquisition) of drug resistance. Members of the Guideline Development Group 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 quality of evidence, several factors can increase or decrease the quality of evidence. The highest quality rating is usually assigned to evidence gathered from randomized control trials, while evidence from observational studies, including programmatic data, may usually assigned a low or very low-quality value. The higher the quality of evidence, the more likely a strong recommendation can be made (**Table A2.1**). The criteria used by the Guideline Development Group to determine the quality of available evidence are summarized in the Summary of Evidence tables. The certainty in the estimates of effect (quality of evidence) was assessed and either rated down or up based on: risk of bias; inconsistency or heterogeneity; indirectness; imprecision; and other considerations.

Table A2.1. Certainty of evidence and strength of recommendations

Certainty in the 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 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 system, 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 A2.2**).

Table A2.2. 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.	Recognise 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.

Assessment of the quality of the evidence

The WHO Guideline Development process uses specific criteria to assess the characteristics of a body of evidence, such as within-study bias (methodological quality), consistency, precision, directness or applicability of the evidence, and others.

Publication, implementation, evaluation and expiry

These guidelines were prepared in accordance with the requirements of the Guideline Review Committee. The guidelines will be published on the WHO website for free download as part of comprehensive WHO consolidated guidelines on tuberculosis 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. National programmes will be supported by WHO and technical and funding partners to prepare a national plan for the programmatic management of drug-resistant 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. Training of frontline healthcare staff and students on critical areas such as diagnosis, designing a regimen, patient support, monitoring response to treatment and management of adverse reactions is important. National programmes 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.

2.2 Expert panels

Drug-susceptible TB treatment

Participants in the Guideline Development group meeting on Drug-susceptible TB in 2009

Guideline Development Group

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

Anthony D. Harries, Senior Consultant, International Union Against Tuberculosis and Lung Disease, Winchester, Hants, England

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

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, England

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 Director, International Council of Nurses, Suffolk, England

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

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

Participants in the Guideline Development Group meeting in 2016

Guideline Development Group

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Drug-resistant TB treatment

WHO guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update

Refer to Annex 1: GRADE evidence summary tables in the WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment. Online annexes. 9789240007062-eng.pdf (who.int), accessed 10 October 2022).

WHO treatment guidelines for isoniazid-resistant tuberculosis, 2018 update

Refer to Annex 1: GRADE evidence summary tables in the WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment. Online annexes. (9789240007062-eng.pdf, accessed 10 October 2022).

WHO treatment guidelines for rifampicin- and multidrug-resistant tuberculosis, 2018 update

Refer to Annex 1: GRADE evidence summary tables in the WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment. Online annexes. (9789240007062-eng.pdf, accessed 10 October 2022).

WHO treatment guidelines for drug-resistant TB treatment, 2020 update

Refer to Annex 1: A2 Expert panels in the WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment. Online annexes. (9789240007062-eng.pdf, accessed 13 September 2022).

WHO treatment guidelines for drug-resistant TB treatment, 2022 update

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WHO treatment guidelines for drug-resistant TB treatment, 2025 update

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Tuberculosis care and support

Guidelines on tuberculosis care and support update, 2017

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Guidelines on management of tuberculosis in children and adolescents, 2022

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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, United States of America.

Gail Kennedy, George Rutherford, Karen Steingart, University of California (San Francisco), California, United States of America. Matthew Arentz, David Horne, Patricia Pavlinac, Judd L. Walson, University of Washington, Seattle, Washington WA, United States of America.

Melissa Bauer, Richard (Dick) Menzies, Olivia Oxlade, McGill University, Montreal, Quebec, Canada. Consultant: Patricia Whyte, Griffith University, Queensland, Australia (guideline development).

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://apps.who.int/iris/bitstream/handle/10665/44597/9789241501583_eng.pdf.

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 US 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/bitstream/handle/10665/250125/9789241549639-eng.pdf.

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, United States of America; and Lelia CHAISSON, Johns Hopkins Bloomberg School of Public Health, Baltimore, United States of America. 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://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf.

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 (WHO treatment guidelines for rifampicin- and multidrug-resistant tuberculosis, 2018 update). 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 US 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 (US) 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 US 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 US 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 US 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 (WHO treatment guidelines for rifampicin- and multidrug-resistant tuberculosis, 2018 update).

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 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: WHO treatment guidelines for isoniazid-resistant tuberculosis: supplement to the WHO treatment guidelines for drug-resistant tuberculosis.

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/news-room/events/detail/2019/09/27/default-calendar/guideline-development-group-meeting-to-update-the-who-guidelines-on-drug-resistant-tuberculosis). 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, Vietnam 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, Vietnam. 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 Vietnam clinical trial units in Hanoi and HCMC 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 U.S. FDA. Drug donation from TB Alliance (pretomanid) and Pfizer (rifabutin). No salary support. Participation as investigator on trials sponsored by the NIH, FDA, the U.S. 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 U.S. 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 U.S. FDA Antimicrobial Drugs Advisory Committee in response to a request for comments. 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 U.S. CDC as temporary voting members within the U.S. 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 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-whoconsolidated-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 US 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 US 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. US 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: 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: 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 UK MRC, 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 topic of the lecture and the 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-scale, multi-country clinical trial to examine 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.

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

Recommendation 1. PICO question

Should new pulmonary TB patients be treated with the 6-month or the 2-month rifampicin regimen?

Recommendation 2. PICO question

When a country selects 2HRZE/4HR, should patients be treated daily or three times weekly during the intensive phase?

Recommendation 5. PICO question

In new pulmonary TB patients, how effective is extension of treatment for preventing failure or relapse?

Recommendation 8. PICO question

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

Recommendation 3. PICO questions

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

Recommendation 4. PICO question

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

Recommendation 10. PICO question

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

Recommendation 11. PICO question

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

Recommendation 7. PICO question

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 1200mg.

*** In Study 31, a participant was classified as having a favorable outcome if any one of the following conditions was met and an unfavorable 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 unfavorable 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 unfavorable 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.

Recommendation 8. PICO question

In children and adolescents with non-severe TB*, should a 4-month intervention regimen versus the standard 6-month regimen conforming to WHO guidelines be used?

Population	Intervention	Comparator	Outcomes
Children and adolescents with non-severe tuberculosis* Sub-populations: • children living with HIV; • children with lymph node TB (extrathoracic and intrathoracic). Stratify by age: • Infants aged 0–12 months; • Children aged 1–4 years; • Children aged 5–9 years; • Adolescents aged 10–14 years • Adolescents aged 15–19 years.	4 months of TB treatment comprised of 8 weeks of HRZ(E), followed by 8 weeks of HR	Currently recommended treatment regimen for drug susceptible TB comprised of 8 weeks HRZ(E), followed by 16 weeks of HR	• Treatment outcomes (treatment success, treatment failure, mortality, loss to follow-up) • Relapse • Treatment adherence • Adverse events

* 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

WHO PICO questions and comparisons

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, Russia 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 600mg daily (reduce to 300mg if toxicity occurs), Bedaquiline 400mg for 2 weeks, followed by 200mg three times per week, Levofloxacin 750mg (<50kg) or 1 000mg (>50kg) daily, PZA 1 000–1 750mg (40–50kg) or 1 750–2 000mg (51–70kg) or 2 000–2 500mg (71–90kg) daily, Ethionamide 15mg/kg (max 900mg) daily, or high-dose Isoniazid 500mg (40–50kg) or 750mg (51–70kg) or 750–1 000mg (71–90kg) daily, or Terizidone 750mg (40–70kg) or 750–1 000mg (71–90kg) 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, Russia 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 1200mg x 26 weeks + Pa + Bdq 2. Lzd 1200 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 (600mg x 16 weeks, 300mg 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 300mg x 8 weeks) + Pa + Bdq[2]	The BPaL regimen[3]: Lzd 1 200mg 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 1200mg x 26 weeks + Pa + B – 6–9 Lzd 1200 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 1200mg x 26 weeks + Pa + B – 6–9 Lzd 1200 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 patients) 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: 200mg once daily for 24 weeks, Moxifloxacin: 400 mg once daily for 24 weeks, Linezolid: 600mg daily for 16 weeks then 300mg 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 1200mg x 26 weeks + Pa + B – 6–9 Lzd 1200 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: 200mg once daily for 24 weeks Moxifloxacin: 400 mg once daily for 24 weeks Linezolid: 600mg daily for 16 weeks then 300mg 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: 200mg once daily for 24 weeks Moxifloxacin: 400 mg once daily for 24 weeks, Linezolid: 600mg daily for 16 weeks then 300mg 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 1200mg x 26 weeks + Pa + B – 6–9 Lzd 1200 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: 600mg daily for 16 weeks then 300mg 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 600mg daily for 16 weeks then 300mg daily (or 600mg 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;

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)*

4.3. 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[81]	• 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

[81] 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?

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 coverage of TB preventive treatment in eligible children and adolescents?

Annex 5. GRADE evidence profiles and evidence-to-decision tables

5.1 Drug-susceptible TB

5.1.1 Guidelines update 2010 to 2022

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

5.2 Drug-resistant TB

5.2.1 Guidelines update 2011 to 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

5.2.2 Guideline update 2025

PICO 1

Question: Should a 6-month regimen using bedaquiline, delamanid, and linezolid with or without the addition of levofloxacin or clofazimine or both (BDLLfx/C) vs. the currently recommended standard of care, i.e. either the 9-month regimen (for patients without fluoroquinolone resistance) or an individualized long regimen (for patients with fluoroquinolone resistance) be used in patients with pulmonary RR-TB (with or without fluoroquinolone resistance)?

Certainty assessment							№ of patients		Effect			
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**a 6-month regimen using bedaquiline, delamanid, and linezolid with or without the addition of levofloxacin or clofazimine or both (BDLLfx/C)**	**the currently recommended standard of care, i.e. either the 9-month regimen (for patients without fluoroquinolone resistance) or an individualized long regimen (for patients with fluoroquinolone resistance)**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**	**Importance**
Sustained Treatment Success (follow-up: 76 weeks; assessed with: successful treatment outcome at end of treatment and at end of follow-up)												
1	randomised trials	not serious	not serious	not serious[a]	extremely serious[b]	none	174/202 (86.1%)	172/200 (86.0%)	**RR 1.00** (0.93 to 1.08)	**1 more per 1,000** (from 66 fewer to 69 more)[c]	⨁◯◯◯ VERY LOW	CRITICAL
Failure and Recurrence (follow-up: 76 weeks)												
1	randomised trials	not serious	not serious	not serious[a]	extremely serious[d]	none	17/202 (8.4%)	14/200 (7.0%)	**RR 1.20** (0.61 to 2.37)	**14 more per 1,000** (from 38 fewer to 66 more)[c]	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect			
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**a 6-month regimen using bedaquiline, delamanid, and linezolid with or without the addition of levofloxacin or clofazimine or both (BDLLfx/C)**	**the currently recommended standard of care, i.e. either the 9-month regimen (for patients without fluoroquinolone resistance) or an individualized long regimen (for patients with fluoroquinolone resistance)**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**	**Importance**
Death (follow-up: 76 weeks)												
1	randomised trials	not serious	not serious	not serious[a]	extremely serious[e]	none	10/202 (5.0%)	10/200 (5.0%)	**RR 0.99** (0.42 to 2.33)	**0 fewer per 1,000** (from 43 fewer to 42 more)[c]	⨁◯◯◯ VERY LOW	CRITICAL
Lost to Follow-up (assessed with: missed 28 consecutive days of treatment not directed by the clinician)												
1	randomised trials	not serious	not serious	not serious[a]	serious[f]	none	2/202 (1.0%)	4/200 (2.0%)	**RR 0.50** (0.09 to 2.67)	**10 fewer per 1,000** (from 34 fewer to 14 more)[c]	⨁⨁◯◯ MODERATE	CRITICAL
Adverse Events (assessed with: any Grade 3–5 adverse event during treatment and follow-up)												
1	randomised trials	not serious	not serious	not serious[a]	extremely serious[g]	none	69/202 (34.2%)	76/200 (38.0%)	**RR 0.90** (0.69 to 1.17)	**38 fewer per 1,000** (from 132 fewer to 55 more)[c]	⨁◯◯◯ VERY LOW	CRITICAL
Amplification (acquisition) of Drug-Resistance (follow-up: 76 weeks; assessed with: any new drug resistance detected after baseline)												
1	randomised trials	not serious	not serious	not serious[a]	serious[f]	none	5/202 (2.5%)	6/200 (3.0%)	**RR 0.83** (0.26 to 2.66)	**5 fewer per 1,000** (from 37 fewer to 27 more)[c]	⨁⨁◯◯ MODERATE	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. In the BEAT TB trial, those in the intervention group who had established fluoroquinolone (FQ) resistance (22%) did not receive levofloxacin and those with established FQ sensitivity (60%) did not receive clofazimine. In the control group, those who had established FQ resistance (22%) received an individualized regimen with bedaquiline, linezolid, delamanid and other drugs and those with established FQ sensitivity (60%) continued the standard of care (South African RR TB regimen). Those in whom FQ sensitivity was not established continued with the BEAT TB regimen in the intervention group (17%) or continued standard of care in the control group (16%). A subgroup analysis according to FQ sensitivity and resistance showed a difference in the risk difference between groups, but with overlapping 95% confidence intervals and the test for interaction was not statistically significant. We did not downgrade for indirectness due to uncertainty in the subgroup effect.

b. Sustained treatment success: The 95% CI for the absolute effect crosses three thresholds, from moderate harm to large benefit. We, therefore, downgraded the certainty by three levels due to extremely serious imprecision.

c. For the absolute effect we used the risk difference and 95% CI calculated from the trial data.

d. Failure and recurrence: The 95% CI for the absolute effect crosses three thresholds, from small benefit to moderate harm. We, therefore, downgraded the certainty by three levels due to extremely serious imprecision.

e. Death: The 95% CI for the absolute effect crosses three thresholds, from moderate benefit to moderate harm. We, therefore, downgraded the certainty by three levels due to extremely serious imprecision.

f. Lost to follow up/Amplification (acquisition) of drug-resistance: The 95% CI for the absolute effect crosses one threshold, from small benefit to trivial harm. We, therefore, downgraded the certainty by one level due to serious imprecision.

g. Adverse events: The 95% CI for the absolute effect crosses four thresholds, from large benefit to small harm. We, therefore, downgraded the certainty by three levels due to extremely serious imprecision.

PICO 1

Question	
Should a 6-month regimen using bedaquiline, delamanid, and linezolid with or without the addition of levofloxacin or clofazimine or both (BDLLfx/C) vs. the currently recommended standard of care, i.e. either the 9-month regimen (for patients without fluoroquinolone resistance) or an individualized long regimen (for patients with fluoroquinolone resistance) be used for patients with pulmonary RR-TB (with or without fluoroquinolone resistance)?	
POPULATION:	patients with pulmonary RR-TB (with or without fluoroquinolone resistance)
INTERVENTION:	a 6-month regimen using bedaquiline, delamanid, and linezolid with or without the addition of levofloxacin or clofazimine or both (BDLLfx/C)
COMPARISON:	the currently recommended standard of care, i.e. either the 9-month regimen (for patients without fluoroquinolone resistance) or an individualized long regimen (for patients with fluoroquinolone resistance)
MAIN OUTCOMES:	Sustained Treatment Success; Failure and Recurrence; Death; Lost to Follow-up; Adverse Events; Amplification (acquisition) of Drug-Resistance;
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	This question addresses the effectiveness and safety of a 6-month treatment regimen using bedaquiline, delamanid, and linezolid with or without the addition of levofloxacin or clofazimine or both 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: • Fernanda Dockhorn Costa Johansen, Muhwa Chakaya, Gopalan Narendran, Daniela Cirillo, Charles Daley, Gerry Davies, Elmira Gurbanova, Anneke Hesseling, Christoph Lange, Ashna Ashesh, Kim Cuong Nguyen, Andrew Vernon, Mahshid Nasehi, Erlina Burhan, Raymond Byaruhanga, Wenhong Zhang The following were GDG members recused from decision-making for this recommendation: • Graeme Meintjes

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 2022, an estimated 10.6 million people developed TB, and 1.3 million died from the disease. About 410,000 new patients with rifampicin-resistant or multidrug-resistant tuberculosis (MDR/RR-TB) were estimated to emerge in 2022. While all of these patients would have been eligible for a second-line TB treatment regimen, only 175,650 enrolments on treatment were reported by countries in the same year. Significant improvements in the availability of enhanced diagnostics and more effective medicines have occurred in recent years and have led to earlier detection and higher success rates among patients with MDR/RR-TB in many national programs. 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 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 treating drug-resistant TB, including MDR/RR-TB and pre-XDR-TB, were published by WHO in December 2022 – "WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment". WHO recommends the BPaLM, a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg), and moxifloxacin, for all eligible MDR/RR-TB patients (14 years or older) with or without resistance to fluoroquinolones rather than the 9-month or longer (18-month) regimens. BPaLM was the first standardized regimen for the treatment of drug-resistant TB that is as short as the first-line TB regimens but has limitations in use for children and adolescents below 14 years of age and during pregnancy.	

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 or without quinolone resistance (MDR/RR-TB or pre-XDR-TB) receiving the BDLLfxC regimen were compared to those receiving the SoC regimens (9–12 month all oral regimen with linezolid for patients with MDR/RR-TB; 18–20 month all oral regimen 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 standard of care regimens used in the BEAT-TB trial (n=200) experienced: • lower levels of death: 5.0% vs 5.0%; RD= 0.5 fewer per 1,000 (95%CI from 43 fewer to 42 more per 1,000); • lower levels of loss to follow-up: 1.0% vs 2.0%; RD= 10 fewer per 1,000 (95%CI from 34 fewer to 14 more per 1,000); • lower levels of grade 3 to 5 adverse events: 34% vs 38%; RD=38 fewer per 1,000 (95%CI from 132 fewer to 55 more per 1,000); and • lower levels of amplified resistance: 2.5% vs 3.0%; RD=5 fewer per 1,000 (95%CI from 37 fewer to 27 more per 1,000). Implementing BDLLfxC may lead to improvements in the outcomes of death, loss to follow-up, amplification of drug-resistance and adverse events but the evidence is very uncertain.	The GDG also considered the duration and pill burden with the intervention and comparator regimens. The duration of the intervention regimen is 24 weeks (5.5 months) so treatment duration is reduced compared to the control arm by between 3–18 months. 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. **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 BDLLfxC may have small desirable effects.** Decision Thresholds considered by the GDG during the discussion: **Death** • Trivial Effect: ≤14 fewer or more events per 1000 people • Small Effect: 15 to 32 fewer or more events per 1000 people • Moderate Effect: 33 to 63 fewer or more events per 1000 people • Large Effect: ≥64 fewer or more events per 1000 people **For lost to follow-up, adverse events and amplification (acquisition) of drug resistance** • Trivial Effect: ≤30 fewer or more events per 1000 people • Small Effect: 31 to 59 fewer or more events per 1000 people • Moderate Effect: 60 to 119 fewer or more events per 1000 people • Large Effect: ≥120 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 currently recommended standard of care	Risk difference with a 6-month regimen using bedaquiline, delamanid, and linezolid with or without the addition of levofloxacin or clofazimine or both (BDLLfx/C)
Death follow-up: 76 weeks	402 (1 RCT)	⨁◯◯◯ Very low[a,b]	**RR 0.99** (0.42 to 2.33)	Study population	
				50 per 1,000	**0 fewer per 1,000** (43 fewer to 42 more)
Lost to Follow-up assessed with: missed 28 consecutive days of treatment not directed by the clinician	402 (1 RCT)	⨁⨁⨁◯ Moderate[a,c]	**RR 0.50** (0.09 to 2.67)	Study population	
				20 per 1,000	10 fewer per 1,000 (34 fewer to 14 more)
Adverse Events assessed with: any Grade 3-5 adverse event during treatment and follow-up	402 (1 RCT)	⨁◯◯◯ Very low[a,d]	**RR 0.90** (0.69 to 1.17)	Study population	
				380 per 1,000	**38 fewer per 1,000** (132 fewer to 55 more)
Amplification (acquisition) of Drug-Resistance assessed with: any new drug resistance detected after baseline follow-up: 76 weeks	402 (1 RCT)	⨁⨁⨁◯ Moderate[a,c]	**RR 0.83** (0.26 to 2.66)	Study population	
				30 per 1,000	**5 fewer per 1,000** (37 fewer to 27 more)

a. Outcomes among patients with MDR/RR-TB with or without quinolone resistance (MDR/RR-TB or pre-XDR-TB) receiving the BDLLfxC regimen with linezolid were compared to those receiving the SoC regimens (9–12 month all oral regimen for patients with MDR/RR-TB; 18–20 month all oral regimen for patients with pre-XDR-TB). In the BEAT Tuberculosis trial, those in the intervention group who had established fluoroquinolone (FQ) resistance (22%) did not receive levofloxacin and those with established FQ sensitivity (60%) did not receive clofazimine. In the control group, those who had established FQ resistance (22%) received an individualized regimen with bedaquiline, linezolid, delamanid and other drugs and those with established FQ sensitivity (60%) continued the standard of care (South African 9-month RR TB regimen with Linezolid). Those with unknown FQ DST status continued with the full BDLLfxC regimen with all five drugs in the intervention group (17%) or continued standard of care in the control group (16%). A subgroup analysis according to FQ sensitivity and resistance showed a difference in the risk difference between groups, but with overlapping 95% confidence intervals and the test for interaction was not statistically significant. We did not downgrade for indirectness due to uncertainty in the subgroup effect..

b. Death: The 95% CI for the absolute effect crosses three thresholds, from moderate benefit to moderate harm. We, therefore, downgraded the certainty by three levels due to extremely serious imprecision.

c. Lost to follow up/Amplification (acquisition) of drug-resistance: The 95% CI for the absolute effect crosses one threshold, from small benefit to trivial harm. We, therefore, downgraded the certainty by one level due to serious imprecision.

d. Adverse events: The 95% CI for the absolute effect crosses four thresholds, from large benefit to small harm. We, therefore, downgraded the certainty by three levels due to extremely serious imprecision.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with the currently recommended standard of care	Risk difference with a 6-month regimen using bedaquiline, delamanid, and linezolid with or without the addition of levofloxacin or clofazimine or both (BDLLfx/C)
Sustained Treatment Success assessed with: successful treatment outcome at end of treatment and at end of follow-up follow-up: 76 weeks	402 (1 RCT)	⨁◯◯◯ Very low[a,b]	**RR 1.00** (0.93 to 1.08)	Study population	
				860 per 1,000	**1 more per 1,000** (66 fewer to 69 more)

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 unfavorable treatment outcomes (failure, death and lost-to-follow) and thus does not carry any additional or independent information.

a. Outcomes among patients with MDR/RR-TB with or without quinolone resistance (MDR/RR-TB or pre-XDR-TB) receiving the BDLLfxC regimen with linezolid were compared to those receiving the SoC regimens (9–12 month all oral regimen for patients with MDR/RR-TB; 18–20 month all oral regimen for patients with pre-XDR-TB). In the BEAT Tuberculosis trial, those in the intervention group who had established fluoroquinolone (FQ) resistance (22%) did not receive levofloxacin and those with established FQ sensitivity (60%) did not receive clofazimine. In the control group, those who had established FQ resistance (22%) received an individualized regimen with bedaquiline, linezolid, delamanid and other drugs and those with established FQ sensitivity (60%) continued the standard of care (South African 9-month RR TB regimen with Linezolid). Those with unknown FQ DST status continued with the full BDLLfxC regimen with all five drugs in the intervention group (17%) or continued standard of care in the control group (16%). A subgroup analysis according to FQ sensitivity and resistance showed a difference in the risk difference between groups, but with overlapping 95% confidence intervals and the test for interaction was not statistically significant. We did not downgrade for indirectness due to uncertainty in the subgroup effect.

b. Sustained treatment success: The 95% CI for the absolute effect crosses three thresholds, from moderate harm to large benefit. We, therefore, downgraded the certainty by three levels due to extremely serious imprecision.

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

- ● Trivial
- ○ Small
- ○ Moderate
- ○ Large
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

Outcomes among patients with MDR/RR-TB with or without quinolone resistance (MDR/RR-TB or pre-XDR-TB) receiving the BDLLfxC regimen were compared to those receiving the SoC regimens (9–12 month all oral regimen with linezolid for patients with MDR/RR-TB; 18–20 month all oral regimen 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 standard of care regimens used in the BEAT-TB trial (n=200) experienced

- higher levels of failure/recurrence: 8.4% vs 7.0%; RD=14 more per 1,000 (95%CI from 38 fewer to 66 more per 1,000)

Implementing BDLLxC may lead to worsening in the outcome of failure/recurrence but the evidence is very uncertain.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with the currently recommended standard of care	Risk difference with a 6-month regimen using bedaquiline, delamanid, and linezolid with or without the addition of levofloxacin or clofazimine or both (BDLLfx/C)
Failure and Recurrence follow-up: 76 weeks	402 (1 RCT)	⨁◯◯◯ Very low[a,b]	**RR 1.20** (0.61 to 2.37)	Study population	
				70 per 1,000	**14 more per 1,000** (38 fewer to 66 more)

a. Outcomes among patients with MDR/RR-TB with or without quinolone resistance (MDR/RR-TB or pre-XDR-TB) receiving the BDLLfxC regimen with linezolid were compared to those receiving the SoC regimens (9–12 month all oral regimen for patients with MDR/RR-TB; 18–20 month all oral regimen for patients with pre-XDR-TB). In the BEAT Tuberculosis trial, those in the intervention group who had established fluoroquinolone (FQ) resistance (22%) did not receive levofloxacin and those with established FQ sensitivity (60%) did not receive clofazimine. In the control group, those who had established FQ resistance (22%) received an individualized regimen with bedaquiline, linezolid, delamanid and other drugs and those with established FQ sensitivity (60%) continued the standard of care (South African 9-month RR TB regimen with Linezolid). Those with unknown FQ DST status continued with the full BDLLfxC regimen with all five drugs in the intervention group (17%) or continued standard of care in the control group (16%). A subgroup analysis according to FQ sensitivity and resistance showed a difference in the risk difference between groups, but with overlapping 95% confidence intervals and the test for interaction was not statistically significant. We did not downgrade for indirectness due to uncertainty in the subgroup effect

b. Failure and recurrence: The 95% CI for the absolute effect crosses three thresholds, from small benefit to moderate harm. We, therefore, downgraded the certainty by three levels due to extremely serious imprecision.

ADDITIONAL CONSIDERATIONS

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 BDLLfxC may have trivial or no undesirable effects.

The GDG discussed applicability issues related to the research evidence, noting the baseline risk in the target population may be different than that in the trial. Applying different baseline risks would lead to different absolute effects but the group decided to base their judgements on the baseline risks observed in the trial.

Furthermore, the GDG discussed that there is a distinction between treatment failure and recurrence, while the outcome was synthesized in aggregate. Details of who specifically had recurrence and time to recurrence, as well as type of recurrence were reviewed, noting that failures were more common in the control arm and recurrences more common in the intervention arms (although overall numbers were very small). Acquired drug resistance was common among those experiencing failure but uncommon among those experiencing relapse.

Decision Thresholds considered by the GDG during the discussion:

Treatment Failure or Recurrence

Trivial Effect: ≤30 fewer or more events per 1000 people

Small Effect: 31 to 59 fewer or more events per 1000 people

Moderate Effect: 60 to 119 fewer or more events per 1000 people

Large Effect: ≥120 fewer or more events per 1000 people

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 very low, primarily due to imprecision in the effect estimates.

Values

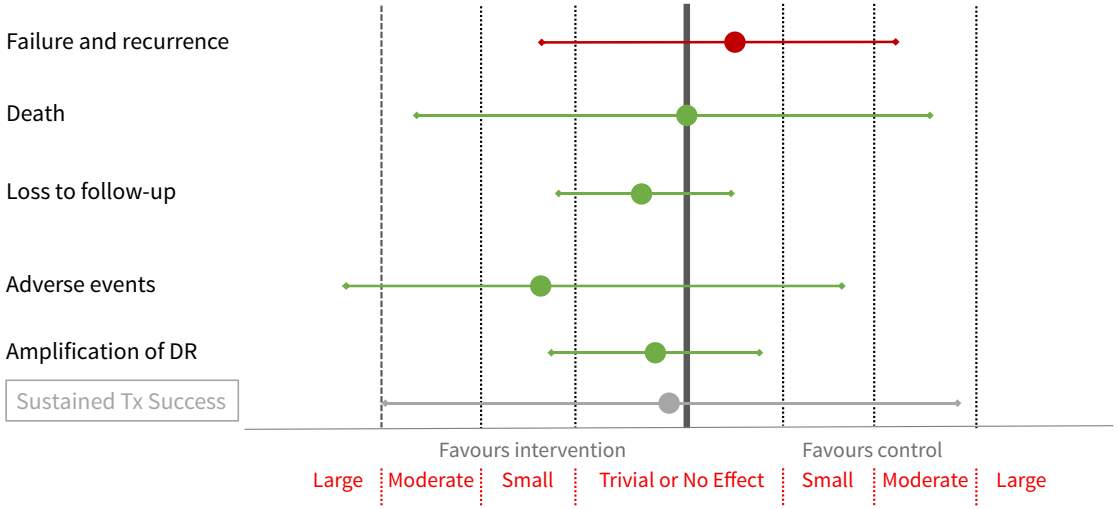
Is there important uncertainty about or variability in how much people value the main outcomes?

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 systematically searched for. Higher treatment efficacy, shorter duration of treatment, lower pill burden and less adverse events are usually valued by patients. A recent systematic review of health-related quality of life based on EQ-5D utility scores in patients with tuberculosis (Park et al, 2021) reported based on one identified study (Kitikraisak et al, 2012; prospective cohort study with 222 patients from Thailand) that the EQ-5D value for MDR-TB was 0.51, which increased to 0.88 after completion of treatment.	The GDG noted that there would probably be no important uncertainty about how much people value the outcomes, and that patients may prefer a shorter treatment duration because of the outcomes associated with it. The GDG also noted important additional outcomes such as disability during and after treatment and quality of life were not assessed.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**BEAT TB – 6-month regimen BDLL/C**	The GDG judged the benefits of BDLLfxC to be small and the undesirable effects to be trivial compared to WHO recommended standard of care 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 BDLLfxC regimen.



Note: The positioning of point estimates and CIs is indicative and for illustration purposes only and exact figures are available in the GRADE evidence profiles. As indicated above in the sections on desirable and undesirable effects, decision thresholds vary for some of the outcomes and therefore only the descriptive labels (trivial or no effect, small, moderate, large) are used for the x-axis rather than numerical values themselves.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	We considered the following estimated regimen prices (from Stop TB Partnership Global Drug Facility):	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 costs would vary between moderate and a large cost. Delamanid cost is one of the cost drivers in BDLLfxC. With the drug being off patent, prices may change with generic development. 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.

	Regimen	Estimated Regimen Price
Beat – Tuberculosis Trial Regimens	6BDLL (FQ-S)	$1374
	6BDLC (FQ-R)	$1460
	6BDLLC (FQ – Unknown)	$1479
WHO-Recommended Regimens	BPaLM	$443
	BPaL	$415
	Shorter Regimen	$418
	Shorter Regimen (with Lzd)	$396
	Longer Regimen ($18B_6LLC$)	$632

Assumptions for BEATTB treatment:

- Duration of 24 weeks
- Dosing based on weight > 50kg (per protocol)
- Daily dosing for
- Linezolid
- Levofloxacin
- Clofazimine
- "Standard" dosing for bedaquiline – 400mg daily x 14 days then 200mg 3x/week for weeks 3–24
- Delamanid 100mg twice daily x 8 weeks, then 200mg daily x 16 weeks

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.

RR			
	Costs over 3 months		
Country	**Patient**	**Health System**	**Total**
India	$384	$87	$471
Philippines	$774	$234	$1008
South Africa	$342	$642	$984

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.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors 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.	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. Voting for a decision on the judgement took place: • 13 GDG members voted 'probably increased' • 3 GDG member voted 'increased' 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 BDLLfxC regimen due to its reduced complexity and shorter duration. The panel judged that use of the BDLLfxC regimen would probably increase equity.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence searched for.	The GDG considered patients and health care providers as key stakeholders. 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 BDLLfxC regimen would probably be acceptable.

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 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.	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 drug susceptibility testing. BEAT-Tuberculosis was a pragmatic trial, and similar intervention regimens have been given in other studies across a range of countries, increasing the likelihood that 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, and alternative regimens may not always be available. Access to some of the medications is hampered by licensing differences. A few patients with low hemoglobin levels in the BEAT-TB trial received a blood transfusion before initiating treatment. The need for blood transfusion before initiating treatment may be a limiting factor in some settings for patients with low hemoglobin levels. However, given the reduced duration, complexity and associated workload, the GDG judged that implementation is probably feasible.

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	**Trivial**	Small	Moderate	Large		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	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors 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	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors 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
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. This recommendation applies to the following:
   a. People with MDR/RR-TB or pre-XDR-TB (MDR/RR-TB and resistance to fluoroquinolones).
   b. People with MDR/RR-TB and less than one month of previous exposure to bedaquiline, linezolid, delamanid, or clofazimine. When exposure is greater than one month, these patients may still receive the regimen if resistance to the specific medicines with such exposure has been ruled out.
   c. People with diagnosed pulmonary TB, including children, adolescents, PLHIV, pregnant and breastfeeding women.
   d. People with most forms of extrapulmonary TB except for TB involving the CNS, osteoarticular, or disseminated forms of TB with multi-organ 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).

2. 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 or dropped from the regimen.

3. When resistance to fluoroquinolones is unknown, the regimen can be started as BDLLfxC and then adjusted based on the DST results. In cases of quinolone susceptibility, the regimen can include four medicines – bedaquiline, delamanid, linezolid and levofloxacin (BDLLfx). In cases of resistance to fluoroquinolones, the regimen with bedaquiline, delamanid, linezolid and clofazimine (BDLC) can be used.

4. During the randomized controlled trial, the BDLLfxC regimen group was compared to the group of participants who received either a previously recommended 9-month shorter regimen with linezolid or the longer(>18 months) WHO-recommended regimens. The majority of controls were on the 9-month regimen.

Justification
The GDG issued a conditional recommendation, rather than a strong recommendation, based on the very low certainty evidence (due to imprecision in the absolute effect estimates) that the balance of effects probably favours the intervention, as well as the resource considerations. While the included trial was designed as a non-inferiority trial the GDG considered the magnitude of effects in relation to specific thresholds the group agreed on for the desirable and undesirable effects. There was additionally a lack of information on the value that people place on outcomes associated with the interventions.
Subgroup considerations
Participants with severe forms of the EPTB like its disseminated forms or TB with CNS involvement were not included in the trial but some participants with less severe forms as were included.
Implementation considerations
Drug susceptibility testing (DST) for fluoroquinolones is strongly encouraged in people with MDR/ RR-TB, and although it should not delay initiation of the BDLLfxC regimen, results of the test should guide the decision on whether linezolid can be retained or should be dropped from the regimen – in cases of documented resistance to fluoroquinolones, BDLLC without linezolid would be initiated or continued. The GDG acknowledged access issues related to the lack of DST testing and for some medications in the regimen. The GDG also noted that with the use of bedaquiline, bedaquiline concentrations in breast milk may be high, with implications for breastfeeding. The GDG noted that patient support may increase adherence to the 6-month regimen (e.g. Delamanid needs to be taken twice daily).
Monitoring and evaluation
The importance of monitoring for drug-drug interactions with other medications was noted by the GDG.

Research priorities
The GDG discussed and identified the following research priorities relating to this recommendation: • Research on choice of quinolones for 6-month regimens and treatment outcomes. (e.g. moxifloxacin/levofloxacin) • Cost-effectiveness studies Cross-cutting research priorities: • Research on dose reduction strategies of linezolid within 6-month regimens and treatment outcomes • Research on early and practical markers of linezolid toxicity • Bedaquiline concentrations in breast milk and its effects on newborns. • Research on component drug interactions with a view on drugs used for other frequent co-morbidities • Research on values people place on outcomes • Research on quality of life outcomes in TB treatment trials • Operational research including strategies on testing • Research on the efficacy of the regimen in patients with disseminated forms of TB • Research on the effects of QT-prolonging drugs in elderly patients that are clinically significant

PICO 2.1

Question: A 9-month regimen using bedaquiline, linezolid, moxifloxacin, and pyrazinamide (BLMZ) compared to currently recommended longer WHO regimens in patients with pulmonary RR-TB (without fluoroquinolone resistance)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**a 9-month regimen using bedaquiline, linezolid, moxifloxacin, and pyrazinamide (BLMZ)**	**currently recommended longer WHO regimens**	**Relative (95% CI)**	**Absolute (95% CI)**		
Sustained Treatment Success (follow-up: 104 weeks)												
1	randomised trials	not serious	not serious	not serious[a]	very serious[b]	none	105/118 (89.0%)	92/119 (77.3%)	**RR 1.15** (1.02 to 1.29)	**117 more per 1,000** (from 23 more to 211 more)[c]	⨁⨁◯◯ LOW	CRITICAL
Failure and Recurrence (follow-up: 104 weeks)												
1	randomised trials	not serious	not serious	not serious[a]	very serious[d]	none	4/118 (3.4%)	3/119 (2.5%)	**RR 1.34** (0.31 to 5.88)	**9 more per 1,000** (from 34 fewer to 52 more)[c]	⨁⨁◯◯ LOW	CRITICAL
Death (follow-up: 104 weeks)												
1	randomised trials	not serious	not serious	not serious[a]	extremely serious[e]	none	2/118 (1.7%)	4/119 (3.4%)	**RR 0.50** (0.09 to 2.70)	**17 fewer per 1,000** (from 57 fewer to 23 more)[c]	⨁◯◯◯ VERY LOW	CRITICAL
Lost to Follow-up (follow-up: 104 weeks; assessed with: discontinuation of treatment, consent withdrawal, use of prohibited concomitant, or outcomes not assessable after treatment completion)												
1	randomised trials	not serious	not serious	not serious[a]	very serious[f]	none	7/118 (5.9%)	20/119 (16.8%)	**RR 0.35** (0.16 to 0.80)	**109 fewer per 1,000** (from 188 fewer to 29 fewer)[c]	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**a 9-month regimen using bedaquiline, linezolid, moxifloxacin, and pyrazinamide (BLMZ)**	**currently recommended longer WHO regimens**	**Relative (95% CI)**	**Absolute (95% CI)**		
Adverse Events (follow-up: 104 weeks; assessed with: any Grade 3–5 adverse event during treatment and follow-up)												
1	randomised trials	not serious	not serious	not serious[a]	extremely serious[g]	none	70/126 (55.6%)	82/126 (65.1%)	**RR 0.85** (0.70 to 1.04)	**95 fewer per 1,000** (from 216 fewer to 25 more)[c]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse Events (follow-up: 104 weeks; assessed with: participants with one or more serious adverse events)												
1	randomised trials	not serious	not serious	not serious[a]	extremely serious[h]	none	20/126 (15.9%)	24/126 (19.0%)	**RR 0.83** (0.49 to 1.43)	**32 fewer per 1,000** (from 125 fewer to 62 more)[c]	⨁◯◯◯ VERY LOW	CRITICAL
Amplification (acquisition) of Drug-Resistance (follow-up: 104 weeks)												
1	randomised trials	not serious	not serious	not serious[a]	not serious	none	0/127 (0.0%)	0/130 (0.0%)	not estimable	**0 fewer per 1,000** (from 29 fewer to 29 more)[i]	⨁⨁⨁⨁ HIGH	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Standard of care for the treatment of rifampicin-resistant and fluoroquinolone-susceptible tuberculosis was composed according to latest World Health Organization guidelines, as they evolved during the trial. In this group 82% of participants were treated with the longer (18–24 month) all-oral regimen. After Dec 18, 2018 the first change in WHO Guidelines (ending use of injectables) was applied to the trial control regimen. A sensitivity analysis did not show important differences, with overlap in 95% confidence intervals, when excluding the 18% randomized during the period when injectables were prescribed. We therefore did not downgrade for indirectness.

b. Sustained treatment success: The 95% CI for the absolute effect crosses two thresholds, from small benefit to large benefit. We therefore downgraded the certainty by two levels due to serious imprecision.

c. For the absolute effect we used the risk difference and 95% CI calculated from the trial data.

d. Failure and recurrence: The 95% CI for the absolute effect crosses two thresholds, from small benefit to small harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

e. Death: The 95% CI for the absolute effect crosses three thresholds, from small benefit to moderate harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

f. Lost to follow-up: The 95% CI for the absolute effect crosses two thresholds, from small benefit to large benefit. We therefore downgraded the certainty by two levels due to very serious imprecision.

g. Adverse events (Grade 3–5): The 95% CI for the absolute effect crosses three thresholds, from large benefit to trivial harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

h. Adverse events (serious adverse events): The 95% CI for the absolute effect crosses three thresholds, from moderate benefit to moderate harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

i. Risk ratios could not be calculated because there was no acquired resistance in the control arm. The risk difference was 0% (95% CI, -2.9% to 2.9%).

PICO 2.1

Question	
Should a 9-month regimen using bedaquiline, linezolid, moxifloxacin, and pyrazinamide (BLMZ) vs. currently recommended longer WHO regimens be used for patients with pulmonary RR-TB (without fluoroquinolone resistance)?	
POPULATION:	patients with pulmonary RR-TB (without fluoroquinolone resistance)
INTERVENTION:	a 9-month regimen using bedaquiline, linezolid, moxifloxacin, and pyrazinamide (BLMZ)
COMPARISON:	currently recommended longer WHO regimens
MAIN OUTCOMES:	Sustained Treatment Success; Failure and Recurrence; Death; Lost to Follow-up; Adverse Events; Adverse Events; Amplification (acquisition) of Drug-Resistance;
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	This question addresses the effectiveness and safety of a 9-month regimen using bedaquiline, linezolid, fluoroquinolone (moxifloxacin), and pyrazinamide (BLMZ) versus the currently recommended longer regimens.
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: • Fernanda Dockhorn Costa Johansen, Muhwa Chakaya, Gopalan Narendran, Daniela Cirillo, Charles Daley, Gerry Davies, Elmira Gurbanova, Anneke Hesseling, Christoph Lange, Ashna Ashesh, Kim Cuong Nguyen, Andrew Vernon, Mahshid Nasehi, Graeme Meintjes, Erlina Burhan, Raymond Byaruhanga, Wenhong Zhang The following were GDG members recused from decision-making for this recommendation: • None

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 2022, an estimated 10.6 million people developed TB, and 1.3 million died from the disease. About 410,000 new patients with rifampicin-resistant or multidrug-resistant tuberculosis (MDR/RR-TB) were estimated to emerge in 2022. While all of these patients would have been eligible for a second-line TB treatment regimen, only 175,650 enrolments on treatment were reported by countries in the same year. Significant improvements in the availability of enhanced diagnostics and more effective medicines have occurred in recent years and have led to earlier detection and higher success rates among patients with MDR/RR-TB in many national programs. 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 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 treating drug-resistant TB, including MDR/RR-TB and pre-XDR-TB, were published by WHO in December 2022 – "WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment". WHO recommends the BPaLM, a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg), and moxifloxacin, for all eligible MDR/RR-TB patients (14 years or older) with or without resistance to fluoroquinolones rather than the 9-month or longer (18-month) regimens. BPaLM was the first standardized regimen for the treatment of drug-resistant TB that is as short as the first-line TB regimens but has limitations in use for children and adolescents below 14 years of age and during pregnancy.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

○ Trivial
○ Small
● Moderate
○ Large
○ Varies
○ Don't know

RESEARCH EVIDENCE

Patients with MDR/RR-TB receiving the BLMZ regimen (n=118 for death and loss to follow-up; n=126 for adverse events and n=127 for amplification of drug resistance) compared to those receiving the currently recommended longer WHO regiments (n=119 for death and loss to follow up; 126 for adverse events and n=130 for amplification of drug resistance) experienced:

- lower levels of death: 1.7% vs 3.4%; RD=17 fewer per 1,000 (95%CI from 57 fewer to 23 more per 1,000);
- lower levels of loss to follow-up: 5.9% vs 16.8%; RD=109 fewer per 1,000 (95%CI from 188 fewer to 29 fewer per 1,000);
- lower levels of grade 3 to 5 adverse events: 55.6% vs 65.1%; RD=95 fewer per 1,000 (95%CI from 216 fewer to 25 more per 1,000);
- lower levels of people with at least one serious adverse event: 15.9% vs 19.0%; RD=32 fewer per 1,000 (95%CI from 125 fewer to 62 more per 1,000); and
- similar levels of amplified resistance: 0.0% vs 0.0%; RD=0 fewer per 1,000 (95%CI from 29 fewer to 29 more per 1,000).

Implementing BLMZ may lead to improvements in the outcomes of death, loss to follow-up and adverse events without impact on amplification (acquisition) of drug resistance but the evidence is overall very uncertain.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with currently recommended longer WHO regimens	Risk difference with a 9-month regimen using bedaquiline, linezolid, moxifloxacin, and pyrazinamide (BLMZ)
Death follow-up: 104 weeks	237 (1 RCT)	⨁◯◯◯ Very low[a,b]	**RR 0.50** (0.09 to 2.70)	Study population 34 per 1,000	**17 fewer per 1,000** (57 fewer to 23 more)
Lost to Follow-up assessed with: discontinuation of treatment, consent withdrawal, use of prohibited concomitant, or outcomes not assessable after treatment completion follow-up: 104 weeks	237 (1 RCT)	⨁⨁◯◯ Low[a,c]	**RR 0.35** (0.16 to 0.80)	Study population 168 per 1,000	**109 fewer per 1,000** (188 fewer to 29 fewer)
Adverse Events assessed with: any Grade 3-5 adverse event during treatment and follow-up follow-up: 104 weeks	252 (1 RCT)	⨁◯◯◯ Very low[a,d]	**RR 0.85** (0.70 to 1.04)	Study population 651 per 1,000	**95 fewer per 1,000** (216 fewer to 25 more)
Adverse Events assessed with: participants with one or more serious adverse events follow-up: 104 weeks	252 (1 RCT)	⨁◯◯◯ Very low[a,e]	**RR 0.83** (0.49 to 1.43)	Study population 190 per 1,000	**32 fewer per 1,000** (125 fewer to 62 more)
Amplification (acquisition) of Drug-Resistance follow-up: 104 weeks	257 (1 RCT)	⨁⨁⨁⨁ High[a]	not estimable	Study population 0 per 1,000	**0 fewer per 1,000** (29 fewer to 29 more)

ADDITIONAL CONSIDERATIONS

The GDG also considered the duration and pill burden with the intervention and comparator regimens. The duration of the intervention regimen is 36 weeks (9 months) so treatment duration is reduced compared to the control arm by between 9 and 15 months. The exact magnitude of reduction in time on treatment depends on the specific comparator regimen (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.

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 BLMZ may have moderate desirable effects.

Specifically, the GDG considered that the desirable effects were small for the outcome of death, moderate for the outcome of loss-to-follow up, moderate for all adverse events and small for serious adverse events, and trivial or no effect for amplification of drug resistance. Additionally the GDG considered the shortening of the treatment duration and the reduction in pill burden as a desirable effect.

Decision Thresholds considered by the GDG during the discussion:

Death

Trivial Effect: ≤14 fewer or more events per 1000 people

Small Effect: 15 to 32 fewer or more events per 1000 people

Moderate Effect: 33 to 63 fewer or more events per 1000 people

Large Effect: ≥64 fewer or more events per 1000 people

a. Standard of care for the treatment of rifampicin-resistant and fluoroquinolone-susceptible tuberculosis was composed according to latest World Health Organization guidelines, as they evolved during the trial. In this group 82% of participants were treated with the longer (18–24 month) all-oral regimen. After Dec 18, 2018 the first change in WHO Guidelines (ending use of injectables) was applied to the trial control regimen. A sensitivity analysis did not show important differences, with overlap in 95% confidence intervals, when excluding the 18% randomized during the period when injectables were prescribed. We therefore did not downgrade for indirectness.

b. Death: The 95% CI for the absolute effect crosses three thresholds, from small benefit to moderate harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

c. Lost to Follow-up: The 95% CI for the absolute effect crosses two thresholds, from small benefit to large benefit. We therefore downgraded the certainty by two levels due to very serious imprecision.

d. Adverse events (Grade 3–5): The 95% CI for the absolute effect crosses three thresholds, from large benefit to trivial harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

e. Adverse events (serious adverse events): The 95% CI for the absolute effect crosses three thresholds, from moderate benefit to moderate harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with currently recommended longer WHO regimens	Risk difference with a 9-month regimen using bedaquiline, linezolid, moxifloxacin, and pyrazinamide (BLMZ)
Sustained Treatment Success follow-up: 104 weeks	237 (1 RCT)	⨁⨁◯◯ Low[a,b]	**RR 1.15** (1.02 to 1.29)	Study population	
				773 per 1,000	**117 more per 1,000** (23 more to 211 more)

a. Standard of care for the treatment of rifampicin-resistant and fluoroquinolone-susceptible tuberculosis was composed according to latest World Health Organization guidelines, as they evolved during the trial. In this group 82% of participants were treated with the longer (18–24 month) all-oral regimen. After Dec 18, 2018 the first change in WHO Guidelines (ending use of injectables) was applied to the trial control regimen. A sensitivity analysis did not show important differences, with overlap in 95% confidence intervals, when excluding the 18% randomized during the period when injectables were prescribed. We therefore did not downgrade for indirectness.

b. Sustained treatment success: The 95% CI for the absolute effect crosses two thresholds, from small benefit to large benefit. We therefore downgraded the certainty by two levels due to serious imprecision.

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.

For lost to follow-up, adverse events and amplification (acquisition) of drug resistance

Trivial Effect: ≤30 fewer or more events per 1000 people

Small Effect: 31 to 59 fewer or more events per 1000 people

Moderate Effect: 60 to 119 fewer or more events per 1000 people

Large Effect: ≥120 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 unfavorable treatment outcomes (failure, death and loss-to-follow) and thus does not carry any additional or independent information.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Patients with MDR/RR-TB receiving the BLMZ regimen (n=118) compared to those receiving the currently recommended longer WHO regiments (n=119) experienced: • higher levels of failure/recurrence: 3.4% vs 2.5%; RD=9 more per 1,000 (95%CI from 34 fewer to 52 more per 1,000) Implementing BLMZ may lead to worsening in the outcome of failure/recurrence but the evidence is uncertain.	**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 BLMZ may have trivial or no undesirable effects.** Specifically, the GDG considered that the undesirable effects were trivial or no effect for the outcome of failure and recurrence. Decision Thresholds considered by the GDG during the discussion: **Treatment failure or recurrence** Trivial Effect: ≤30 fewer or more events per 1000 people Small Effect: 31 to 59 fewer or more events per 1000 people Moderate Effect: 60 to 119 fewer or more events per 1000 people Large Effect: ≥120 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 currently recommended longer WHO regimens	Risk difference with a 9-month regimen using bedaquiline, linezolid, moxifloxacin, and pyrazinamide (BLMZ)
Failure and Recurrence follow-up: 104 weeks	237 (1 RCT)	⨁⨁◯◯ Low[a,b]	**RR 1.34** (0.31 to 5.88)	Study population	
				25 per 1,000	**9 more per 1,000** (34 fewer to 52 more)

a. Standard of care for the treatment of rifampicin-resistant and fluoroquinolone-susceptible tuberculosis was composed according to latest World Health Organization guidelines, as they evolved during the trial. In this group 82% of participants were treated with the longer (18–24 month) all-oral regimen. After Dec 18, 2018 the first change in WHO Guidelines (ending use of injectables) was applied to the trial control regimen. A sensitivity analysis did not show important differences, with overlap in 95% confidence intervals, when excluding the 18% randomized during the period when injectables were prescribed. We therefore did not downgrade for indirectness.

b. Failure and recurrence: The 95% CI for the absolute effect crosses two thresholds, from small benefit to small harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

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 very low, primarily due to imprecision in the effect estimates.

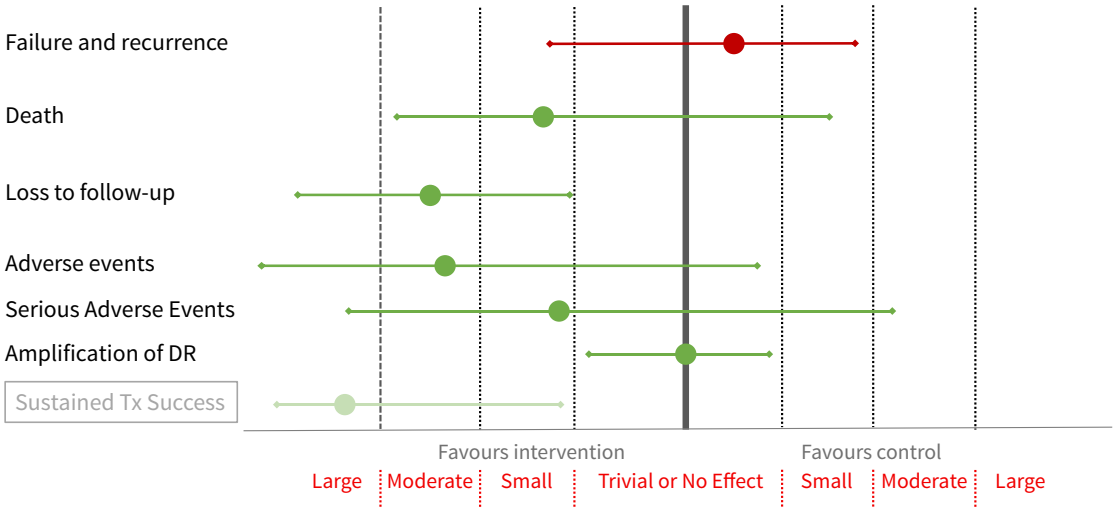
Values

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 systematically searched for. Higher treatment efficacy, shorter duration of treatment, lower pill burden and less adverse events are usually valued by patients. A recent systematic review of health-related quality of life based on EQ-5D utility scores in patients with tuberculosis (Park et al,2021) reported based on one identified study (Kitikraisak et al, 2012; prospective cohort study with 222 patients from Thailand) that the EQ-5D value for MDR-TB was 0.51, which increased to 0.88 after completion of treatment.	The GDG noted that there would probably be no important uncertainty about how much people value the outcomes, and that patients may prefer a shorter treatment duration because of the outcomes associated with it. The GDG also noted important additional outcomes such as disability during and after treatment and quality of life were not assessed.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**EndTB 1 – BLMZ**  Note: The positioning of point estimates and CIs is indicative and for illustration purposes only and exact figures are available in the GRADE evidence profiles. As indicated above in the sections on desirable and undesirable effects, decision thresholds vary for some of the outcomes and therefore only the descriptive labels (trivial, small, moderate, large) are used for the x-axis rather than numerical values themselves.	The GDG judged the benefits of BLMZ to be moderate and the undesirable effects to be trivial compared to 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. Based on this, the GDG determined that the balance of health effects probably favours the BLMZ regimen.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ● Large savings ○ Varies ○ Don't know	We considered the following estimated regimen prices (from Stop TB Partnership Global Drug Facility):	The GDG considered that as compared to the currently recommended longer WHO regimens, the BLMZ regimen would result in large savings.

	Regimen	Estimated Regimen Price
endTB Trial Regimens	endTB 1 9BLMZ	$297
	endTB 2 9BLLCZ	$455
	endTB 3 9BDLLZ	$2219
	endTB 4 9DLLCZ	$2192
	endTB 5 9DMCZ	$2170
WHO-Recommended Regimens	BPaLM	$443
	BPaL	$415
	Shorter Regimen	$418
	Shorter Regimen (with Lzd)	$396
	Longer Regimen ($18B_6$LLC)	$632

Assumptions for endTB treatment:

- Duration of 39 weeks
- Dosing based on weight > 55–70kg (per protocol)
- Daily dosing for
- Moxifloxacin
- Levofloxacin
- Clofazimine
- Pyrazinamide
- Bedaquiline dosing – 400mg daily x 14 days then 200mg 3x/week for weeks 3–39
- Delamanid dosing – 100mg twice daily x 39 weeks
- Linezolid dosing – 600mg daily x 16 weeks, then 600mg 3x/week for weeks 17–39

Caveats

- Medicine prices are average prices across all suppliers as per GDF market share allocation
- Medicine prices may change with 2024 GDF tenders

We 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.

RR			
	Cost over 9 months		
Country	Patient	Health System	Total
India	$1152	$261	$1413
Philippines	$2322	$702	$3024
South Africa	$1026	$1926	$2952

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 9-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 treatment regimen would be used.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No research evidence searched for.	Despite no research evidence to consider, the GDG discussed that given the moderate net benefit and cost savings with the BLMZ regimen, a judgement of cost-effectiveness favouring the intervention is appropriate. This judgment is based on logical arguments that a cheaper regiment with better health outcomes will be cost-effective although the exact savings are not known without such analyses.

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 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 at overall lower cost.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence searched for.	The GDG considered patients and healthcare providers as key stakeholders. The GDG considered the regiment duration as critical with regards to acceptability. Thus, the GDG judged that the BLMZ regimen would probably be acceptable.

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 searched for.	The BLMZ regimen was viewed as feasible given that it does not include delamanid. Bedaquiline is also not available in all settings, but this would not make a difference between the intervention and comparison.

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	**Trivial**	Small	Moderate	Large		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	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors 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	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors 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
WHO suggests using BLMZ over currently recommended longer (>18 months) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. *(Conditional recommendation, very low certainty of evidence)* **Remarks** 1. The recommended modified 9-month all-oral regimens comprise bedaquiline, linezolid and pyrazinamide in different combinations with levofloxacin/moxifloxacin, clofazimine and delamanid. 2. This recommendation applies to the following: a. People with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. b. People with diagnosed pulmonary TB, including children, adolescents, PLHIV, and pregnant and breastfeeding women. c. People with extensive TB disease and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular TB or disseminated forms of TB with multiorgan involvement. d. 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. e. 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).
Justification
The GDG issued a conditional recommendation based on very low certainty of evidence (due to imprecision in the effect estimates) based on a moderate benefit, with trivial harms, and cost savings. The GDG also highlighted the importance of a lower pill burden with the 9-month regimen.
Subgroup considerations
See information in summary EtD for PICO 2
Implementation considerations
See information in summary EtD for PICO 2
Monitoring and evaluation
See information in summary EtD for PICO 2
Research priorities
See information in summary EtD for PICO 2

PICO 2.2

Question: A 9-month regimen using bedaquiline, clofazimine, linezolid, levofloxacin, and pyrazinamide (BLLfxCZ) compared to currently recommended longer WHO regimens in patients with pulmonary RR-TB (without fluoroquinolone resistance)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a 9-month regimen using bedaquiline, clofazimine, linezolid, levofloxacin, and pyrazinamide (BLLfxCZ)	currently recommended longer WHO regimens	Relative (95% CI)	Absolute (95% CI)		
Sustained Treatment Success (follow-up: 104 weeks)												
1	randomised trials	not serious	not serious	not serious[a]	very serious[b]	none	102/115 (88.7%)	92/119 (77.3%)	**RR 1.15** (1.02 to 1.29)	**114 more per 1,000** (from 19 more to 209 more)[c]	⨁⨁◯◯ LOW	CRITICAL
Failure and Recurrence (follow-up: 104 weeks)												
1	randomised trials	not serious	not serious	not serious[a]	very serious[d]	none	7/115 (6.1%)	3/119 (2.5%)	**RR 2.41** (0.64 to 9.12)	**36 more per 1,000** (from 16 fewer to 88 more)[c]	⨁⨁◯◯ LOW	CRITICAL
Death (follow-up: 104 weeks)												
1	randomised trials	not serious	not serious	not serious[a]	very serious[e]	none	1/115 (0.9%)	4/119 (3.4%)	**RR 0.26** (0.03 to 2.28)	**25 fewer per 1,000** (from 62 fewer to 12 more)[c]	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**a 9-month regimen using bedaquiline, clofazimine, linezolid, levofloxacin, and pyrazinamide (BLLfxCZ)**	**currently recommended longer WHO regimens**	**Relative (95% CI)**	**Absolute (95% CI)**		
Lost to Follow-up (follow-up: 104 weeks; assessed with: discontinuation of treatment, consent withdrawal, use of prohibited concomitant, or outcomes not assessable after treatment completion)												
1	randomised trials	not serious	not serious	not serious[a]	very serious[b]	none	5/115 (4.3%)	20/119 (16.8%)	**RR 0.26** (0.10 to 0.67)	**125 fewer per 1,000** (from 201 fewer to 48 fewer)[c]	⨁⨁◯◯ LOW	CRITICAL
Adverse Events (follow-up: 104 weeks; assessed with: any Grade 3–5 adverse event during treatment and follow-up)												
1	randomised trials	not serious	not serious	not serious[a]	extremely serious[f]	none	72/122 (59.0%)	82/126 (65.1%)	**RR 0.91** (0.75 to 1.10)	**61 fewer per 1,000** (from 181 fewer to 60 more)[c]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse Events (follow-up: 104 weeks; assessed with: participants with one or more serious adverse events)												
1	randomised trials	not serious	not serious	not serious[a]	extremely serious[g]	none	18/122 (14.8%)	24/126 (19.0%)	**RR 0.77** (0.44 to 1.35)	**43 fewer per 1,000** (from 136 fewer to 50 more)[c]	⨁◯◯◯ VERY LOW	CRITICAL
Amplification (acquisition) of Drug-Resistance (follow-up: 104 weeks)[h]												
1	randomised trials	not serious	not serious	not serious[a]	serious[i]	none	2/124 (1.6%)	0/130 (0.0%)	not estimable	**16 more per 1,000** (from 13 fewer to 56 more)[h]	⨁⨁⨁◯ MODERATE	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Standard of care for the treatment of rifampicin-resistant and fluoroquinolone-susceptible tuberculosis was composed according to latest World Health Organization guidelines, as they evolved during the trial. In this group 82% of participants were treated with the longer (18–24 month) all-oral regimen. After Dec 18, 2018 the first change in WHO Guidelines (ending use of injectables) was applied to the trial control regimen. A sensitivity analysis did not show important differences, with overlap in 95% confidence intervals, when excluding the 18% randomized during the period when injectables were prescribed. We therefore did not downgrade for indirectness.

b. Sustained treatment success, Lost to follow-up: The 95% CI for the absolute effect crosses two thresholds, from small benefit to large benefit. We therefore downgraded the certainty by two levels due to very serious imprecision.

c. For the absolute effect we used the risk difference and 95% CI calculated from the trial data.

d. Failure and recurrence: The 95% CI for the absolute effect crosses three thresholds, from trivial benefit to large harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

e. Death: The 95% CI for the absolute effect crosses three thresholds, from moderate benefit to moderate harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

f. Adverse events (Grade 3–5): The 95% CI for the absolute effect crosses three thresholds, from large benefit to moderate harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

g. Adverse events (serious adverse events): The 95% CI for the absolute effect crosses three thresholds, from moderate benefit to moderate harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

h. Risk ratios could not be calculated because there was no acquired resistance in the control arm. The risk difference was 1.6% (95% CI, -1.3% to 5.6%).

i. Amplification (acquisition) of drug-resistance: The 95% CI for the absolute effect crosses one threshold, from trivial benefit to small harm. We therefore downgraded the certainty by one level due to serious imprecision.

PICO 2.2

Question	
Should a 9-month regimen using bedaquiline, clofazimine, linezolid, levofloxacin, and pyrazinamide (BLLfxCZ) vs. currently recommended longer WHO regimens be used for patients with pulmonary RR-TB (without fluoroquinolone resistance)?	
POPULATION:	patients with pulmonary RR-TB (without fluoroquinolone resistance)
INTERVENTION:	a 9-month regimen using bedaquiline, clofazimine, linezolid, levofloxacin, and pyrazinamide (BLLfxCZ)
COMPARISON:	currently recommended longer WHO regimens
MAIN OUTCOMES:	Sustained Treatment Success; Failure and Recurrence; Death; Lost to Follow-up; Adverse Events; Adverse Events; Amplification (acquisition) of Drug-Resistance;
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	This question addresses the effectiveness and safety of a 9-month regimen using bedaquiline, clofazimine, linezolid, fluoroquinolone (levofloxacin), and pyrazinamide (BLLfxCZ) versus the currently recommended longer regimens.
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: • Fernanda Dockhorn Costa Johansen, Muhwa Chakaya, Gopalan Narendran, Daniela Cirillo, Charles Daley, Gerry Davies, Elmira Gurbanova, Anneke Hesseling, Christoph Lange, Ashna Ashesh, Kim Cuong Nguyen, Andrew Vernon, Mahshid Nasehi, Graeme Meintjes, Erlina Burhan, Raymond Byaruhanga, Wenhong Zhang The following were GDG members recused from decision-making for this recommendation: • None

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 2022, an estimated 10.6 million people developed TB, and 1.3 million died from the disease. About 410,000 new patients with rifampicin-resistant or multidrug-resistant tuberculosis (MDR/RR-TB) were estimated to emerge in 2022. While all of these patients would have been eligible for a second-line TB treatment regimen, only 175,650 enrolments on treatment were reported by countries in the same year. Significant improvements in the availability of enhanced diagnostics and more effective medicines have occurred in recent years and have led to earlier detection and higher success rates among patients with MDR/RR-TB in many national programs. 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 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 treating drug-resistant TB, including MDR/RR-TB and pre-XDR-TB, were published by WHO in December 2022 – "WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment". WHO recommends the BPaLM, a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg), and moxifloxacin, for all eligible MDR/RR-TB patients (14 years or older) with or without resistance to fluoroquinolones rather than the 9-month or longer (18-month) regimens. BPaLM was the first standardized regimen for the treatment of drug-resistant TB that is as short as the first-line TB regimens but has limitations in use for children and adolescents below 14 years of age and during pregnancy.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

○ Trivial
○ Small
● Moderate
○ Large
○ Varies
○ Don't know

RESEARCH EVIDENCE

Patients with MDR/RR-TB receiving the BLLfxCZ regimen (n=115 for death and loss to follow and n=122 for adverse events) compared to those receiving the currently recommended longer WHO regiments (n=119 for death and loss to follow up and n=126 for adverse events) experienced:

- lower levels of death: 0.9% vs 3.4%; RD=25 fewer per 1,000 (95%CI from 62 fewer to 12 more per 1,000);
- lower levels of loss to follow-up: 4.3% vs 16.8%; RD=125 fewer per 1,000 (95%CI from 201 fewer to 48 fewer per 1,000);
- lower levels of grade 3 to 5 adverse events: 59.0% vs 65.1%; RD=61 fewer per 1,000 (95%CI from 181 fewer to 60 more per 1,000); and
- lower levels of people with at least one serious adverse event: 14.8% vs 19.0%; RD=43 fewer per 1,000 (95%CI from 136 fewer to 50 more per 1,000).

Implementing BLLfxCZ may lead to improvements in the outcomes of death, loss to follow-up and adverse events but the evidence is overall very uncertain.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with currently recommended longer WHO regimens	Risk difference with a 9-month regimen using bedaquiline, clofazimine, linezolid, levofloxacin, and pyrazinamide (BLLfxCZ)
Death follow-up: 104 weeks	234 (1 RCT)	⨁⨁◯◯ Low[a,b]	**RR 0.26** (0.03 to 2.28)	Study population	
				34 per 1,000	**25 fewer per 1,000** (62 fewer to 12 more)
Lost to Follow-up assessed with: discontinuation of treatment, consent withdrawal, use of prohibited concomitant, or outcomes not assessable after treatment completion follow-up: 104 weeks	234 (1 RCT)	⨁⨁◯◯ Low[a,c]	**RR 0.26** (0.10 to 0.67)	Study population	
				168 per 1,000	**125 fewer per 1,000** (201 fewer to 48 fewer)
Adverse Events assessed with: any Grade 3-5 adverse event during treatment and follow-up follow-up: 104 weeks	248 (1 RCT)	⨁◯◯◯ Very low[a,d]	**RR 0.91** (0.75 to 1.10)	Study population	
				651 per 1,000	**61 fewer per 1,000** (181 fewer to 60 more)
Adverse Events assessed with: participants with one or more serious adverse events follow-up: 104 weeks	248 (1 RCT)	⨁◯◯◯ Very low[a,e]	**RR 0.77** (0.44 to 1.35)	Study population	
				190 per 1,000	**43 fewer per 1,000** (136 fewer to 50 more)

ADDITIONAL CONSIDERATIONS

The GDG also considered the duration and pill burden with the intervention and comparator regimens. The duration of the intervention regimen is 36 weeks (9 months) so treatment duration is reduced compared to the control arm by between 9 and 15 months. The exact magnitude of reduction in time on treatment depends on the specific comparator regimen (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.

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 BLLfxCZ may have moderate desirable effects.

Specifically, the GDG considered that the desirable effects were small for the outcome of death, large for the outcome of loss-to-follow up, moderate for all adverse events, and small for serious adverse events. Additionally the GDG considered the shortening of the treatment duration and the reduction in pill burden as a desirable effect.

Decision Thresholds considered by the GDG during the discussion:

a. Standard of care for the treatment of rifampicin-resistant and fluoroquinolone-susceptible tuberculosis was composed according to latest World Health Organization guidelines, as they evolved during the trial. In this group 82% of participants were treated with the longer (18–24 month) all-oral regimen. After Dec 18, 2018 the first change in WHO Guidelines (ending use of injectables) was applied to the trial control regimen. A sensitivity analysis did not show important differences, with overlap in 95% confidence intervals, when excluding the 18% randomized during the period when injectables were prescribed. We therefore did not downgrade for indirectness

b. Death: The 95% CI for the absolute effect crosses three thresholds, from moderate benefit to moderate harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

c. Lost to Follow-up: The 95% CI for the absolute effect crosses two thresholds, from small benefit to large benefit. We therefore downgraded the certainty by two levels due to very serious imprecision.

d. Adverse Events (Grade 3–5): The 95% CI for the absolute effect crosses three thresholds, from large benefit to moderate harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

e. Adverse Events (serious adverse events): The 95% CI for the absolute effect crosses three thresholds, from moderate benefit to moderate harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with currently recommended longer WHO regimens	Risk difference with a 9-month regimen using bedaquiline, clofazimine, linezolid, levofloxacin, and pyrazinamide (BLLfxCZ)
Sustained Treatment Success follow-up: 104 weeks	234 (1 RCT)	⨁⨁◯◯ Low[a,b]	**RR 1.15** (1.02 to 1.29)	Study population	
				773 per 1,000	**114 more per 1,000** (19 more to 209 more)

a. Standard of care for the treatment of rifampicin-resistant and fluoroquinolone-susceptible tuberculosis was composed according to latest World Health Organization guidelines, as they evolved during the trial. In this group 82% of participants were treated with the longer (18–24 month) all-oral regimen. After Dec 18, 2018 the first change in WHO Guidelines (ending use of injectables) was applied to the trial control regimen. A sensitivity analysis did not show important differences, with overlap in 95% confidence intervals, when excluding the 18% randomized during the period when injectables were prescribed. We therefore did not downgrade for indirectness

b. Sustained treatment success: The 95% CI for the absolute effect crosses two thresholds, from small benefit to large benefit. We therefore downgraded the certainty by two levels due to very serious imprecision.

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.

Death

Trivial Effect: ≤14 fewer or more events per 1000 people

Small Effect: 15 to 32 fewer or more events per 1000 people

Moderate Effect: 33 to 63 fewer or more events per 1000 people

Large Effect: ≥64 fewer or more events per 1000 people

For lost to follow-up and adverse events

Trivial Effect: ≤30 fewer or more events per 1000 people

Small Effect: 31 to 59 fewer or more events per 1000 people

Moderate Effect: 60 to 119 fewer or more events per 1000 people

Large Effect: ≥120 fewer or more events per 1000 people

Note: The GDG did not consider treatment success as a separate outcome for this judgment. This is because treatment success is mathematically simply the complement of the three unfavorable treatment outcomes (failure, death and loss-to-follow) and thus does not carry any additional or independent information.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Patients with MDR/RR-TB receiving the BLLfxCZ regimen (n=115 for failure and recurrence and n=124 for amplification of drug resistance) compared to those receiving the currently recommended longer WHO regiments (n=119 for failure and recurrence and n=130 for amplification of drug resistance) experienced: • higher levels of failure/recurrence: 6.1% vs 2.5%; RD=36 more per 1,000 (95%CI from 16 fewer to 123 more per 1,000); and • higher levels of amplified resistance: 1.6% vs 0%; RD=16 more per 1,000 (95%CI from 13 fewer to 56 more per 1,000). Implementing BLLfxCZ may lead to worsening in the outcomes of failure and recurrence and amplification (acquisition) of drug resistance but the evidence is overall very uncertain.	**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 BLLfxCZ may have small undesirable effects.** Specifically, the GDG considered that the undesirable effects were small for the outcome of failure and recurrence and trivial or no effect for amplification of drug resistance. Decision Thresholds considered by the GDG during the discussion: **For treatment failure or recurrence and amplification (acquisition) of drug resistance** Trivial Effect: ≤30 fewer or more events per 1000 people Small Effect: 31 to 59 fewer or more events per 1000 people Moderate Effect: 60 to 119 fewer or more events per 1000 people Large Effect: ≥120 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 currently recommended longer WHO regimens	Risk difference with a 9-month regimen using bedaquiline, clofazimine, linezolid, levofloxacin, and pyrazinamide (BLLfxCZ)
Failure and Recurrence follow-up: 104 weeks	234 (1 RCT)	⨁◯◯◯ Very low[a,b]	**RR 2.41** (0.64 to 9.12)	Study population	
				25 per 1,000	**36 more per 1,000** (16 fewer to 88 more)
Amplification (acquisition) of Drug-Resistance follow-up: 104 weeks[c]	254 (1 RCT)	⨁⨁◯◯ Moderate[a,d]	not estimable	Study population	
				0 per 1,000	**16 more per 1,000** (13 fewer to 56 more)

a. Standard of care for the treatment of rifampicin-resistant and fluoroquinolone-susceptible tuberculosis was composed according to latest World Health Organization guidelines, as they evolved during the trial. In this group 82% of participants were treated with the longer (18–24 month) all-oral regimen. After Dec 18, 2018 the first change in WHO Guidelines (ending use of injectables) was applied to the trial control regimen. A sensitivity analysis did not show important differences, with overlap in 95% confidence intervals, when excluding the 18% randomized during the period when injectables were prescribed. We therefore did not downgrade for indirectness

b. Failure and recurrence: The 95% CI for the absolute effect crosses three thresholds, from trivial benefit to large harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

c. Risk ratios could not be calculated because there was no acquired resistance in the control arm. The risk difference was 1.6% (95% CI, -1.3% to 5.6%).

d. Amplification (acquisition) of drug-resistance: The 95% CI for the absolute effect crosses one threshold, from trivial benefit to small harm. We therefore downgraded the certainty by one level due to serious imprecision.

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 very low, primarily due to imprecision in the effect estimates.

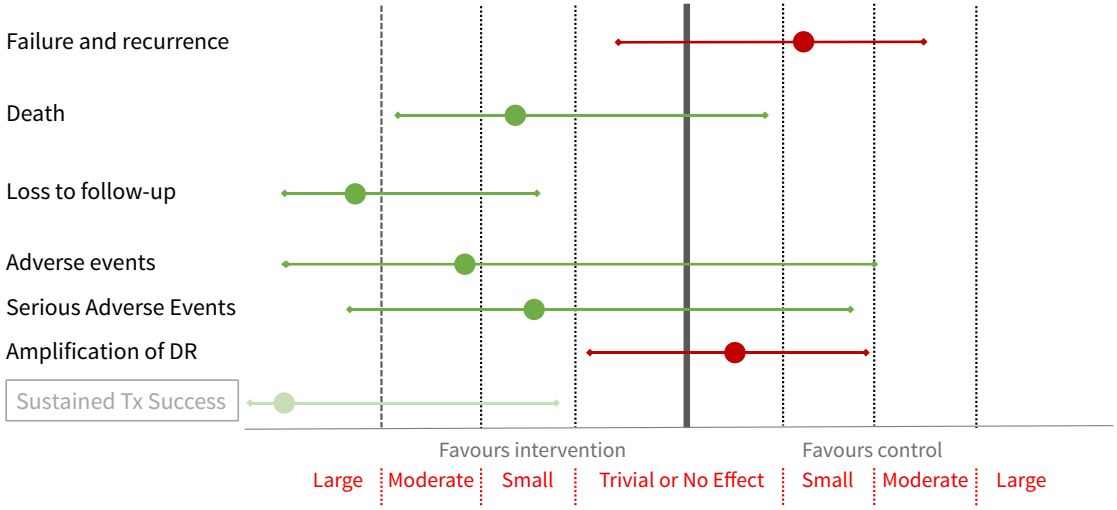
Values

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 systematically searched for. Higher treatment efficacy, shorter duration of treatment, lower pill burden and less adverse events are usually valued by patients. A recent systematic review of health-related quality of life based on EQ-5D utility scores in patients with tuberculosis (Park et al,2021) reported based on one identified study (Kitikraisak et al, 2012; prospective cohort study with 222 patients from Thailand) that the EQ-5D value for MDR-TB was 0.51, which increased to 0.88 after completion of treatment.	The GDG noted that there would probably be no important uncertainty about how much people value the outcomes, and that patients may prefer a shorter treatment duration because of the outcomes associated with it.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**EndTB 2 – BLLfxCZ**  Note: The positioning of point estimates and CIs is indicative and for illustration purposes only and exact figures are available in the GRADE evidence profiles. As indicated above in the sections on desirable and undesirable effects, decision thresholds vary for some of the outcomes and therefore only the descriptive labels (trivial or no effect, small, moderate, large) are used for the x-axis rather than numerical values themselves.	The GDG judged the benefits of BLLfxCZ to be moderate and the undesirable effects to be small compared to 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. Based on this, the GDG determined that the balance of health effects probably favours the BLLfxCZ regimen.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT

○ Large costs
○ Moderate costs
○ Negligible costs and savings
○ Moderate savings
● Large savings
○ Varies
○ Don't know

RESEARCH EVIDENCE

We considered the following estimated regimen prices (from Stop TB Partnership Global Drug Facility):

	Regimen	Estimated Regimen Price
endTB Trial Regimens	endTB 1 9BLMZ	$297
	endTB 2 9BLLCZ	$455
	endTB 3 9BDLLZ	$2219
	endTB 4 9DLLCZ	$2192
	endTB 5 9DMCZ	$2170
WHO-Recommended Regimens	BPaLM	$443
	BPaL	$415
	Shorter Regimen	$418
	Shorter Regimen (with Lzd)	$396
	Longer Regimen ($18B_6LLC$)	$632

Assumptions for endTB treatment:

- Duration of 39 weeks
- Dosing based on weight > 55–70kg (per protocol)
- Daily dosing for
- Moxifloxacin
- Levofloxacin
- Clofazimine
- Pyrazinamide
- Bedaquiline dosing – 400mg daily x 14 days then 200mg 3x/week for weeks 3–39
- Delamanid dosing – 100mg twice daily x 39 weeks
- Linezolid dosing – 600mg daily x 16 weeks, then 600mg 3x/week for weeks 17–39

Caveats

- Medicine prices are average prices across all suppliers as per GDF market share allocation
- Medicine prices may change with 2024 GDF tenders

We 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.

ADDITIONAL CONSIDERATIONS

The GDG considered that as compared to the currently recommended longer WHO regimens, the BLLfxCZ regimen would result in large savings.

RR			
	Cost over 9 months		
Country	Patient	Health System	Total
India	$1152	$261	$1413
Philippines	$2322	$702	$3024
South Africa	$1026	$1926	$2952

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 9-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 treatment regimen would be used.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No research evidence searched for.	Despite no research evidence to consider, the GDG discussed that given the moderate net benefit and cost savings with the BLLfxCZ regimen, a judgement of cost-effectiveness favouring the intervention is appropriate. This judgment is based on logical arguments that a cheaper regiment with better health outcomes will be cost-effective although the exact savings are not known without such analyses.

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 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 at overall lower cost.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence searched for.	The GDG considered patients and health care providers as key stakeholders. The GDG considered the regiment duration as critical with regards to acceptability. The GDG also noted that clofazimine may be less acceptable, e.g. because of discoloration, and noted 4% discontinuation due to clofazimine in the intervention arm in the trial. There is also one additional drug (5 total) compared to the EndTB1 regimen. Despite this, GDG judged that the BLLfxCZ regimen would probably be acceptable.

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 searched for. The BLLfxCZ regimen was additionally studied within the SHORRT initiative in cohort studies performed in three countries: Vietnam (n=108), Ecuador (n=100), Lao (n=58). Favourable treatment outcomes (cure or treatment completion) were reported as 90%, 58%, and 75%, respectively, at 6-month follow-up. At the Ecuador study sites 92.8% treatment adherence was reported.	The BLLfxCZ regimen was viewed as feasible given that it does not include delamanid. Bedaquiline is also not available in all settings, but this would not make a difference between the intervention and comparison.

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	Trivial	**Small**	Moderate	Large		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	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors 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	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors 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
WHO suggests using the BLLfxCZ over currently recommended longer (>18 months) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. *(Conditional recommendation, very low certainty of evidence)* **Remarks** 1. The recommended modified 9-month all-oral regimens comprise bedaquiline, linezolid and pyrazinamide in different combinations with levofloxacin/moxifloxacin, clofazimine and delamanid. 2. This recommendation applies to the following: a. People with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. b. People with diagnosed pulmonary TB, including children, adolescents, PLHIV, and pregnant and breastfeeding women. c. People with extensive TB disease and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular TB or disseminated forms of TB with multiorgan involvement. d. 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. e. 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).
Justification
The GDG issued a conditional recommendation based on very low certainty of evidence (due to imprecision in the effect estimates) based on a moderate benefit, with small harms, and cost savings. The GDG also highlighted the importance of a lower pill burden with the 9-month BLLfxCZ regimen.
Subgroup considerations
See information in summary EtD for PICO 2
Implementation considerations
See information in summary EtD for PICO 2
Monitoring and evaluation
See information in summary EtD for PICO 2
Research priorities
See information in summary EtD for PICO 2

PICO 2.3

Question: A 9-month regimen using bedaquiline, delamanid, linezolid, levofloxacin, and pyrazinamide (BDLLfxZ) compared to currently recommended longer WHO regimens in patients with pulmonary RR-TB (without fluoroquinolone resistance)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**a 9-month regimen using bedaquiline, delamanid, linezolid, levofloxacin, and pyrazinamide (BDLLfxZ)**	**currently recommended longer WHO regimens**	**Relative (95% CI)**	**Absolute (95% CI)**		
Sustained Treatment Success (follow-up: 104 weeks)												
1	randomised trials	not serious	not serious	not serious[a]	very serious[b]	none	104/122 (85.2%)	92/119 (77.3%)	**RR 1.10** (0.98 to 1.25)	**79 more per 1,000** (from 19 fewer to 177 more)[c]	⨁⨁◯◯ LOW	CRITICAL
Failure and Recurrence (follow-up: 104 weeks)												
1	randomised trials	not serious	not serious	not serious[a]	serious[d]	none	2/122 (1.6%)	3/119 (2.5%)	**RR 0.65** (0.11 to 3.83)	**9 fewer per 1,000** (from 45 fewer to 27 more)[c]	⨁⨁⨁◯ MODERATE	CRITICAL
Death (follow-up: 104 weeks)												
1	randomised trials	not serious	not serious	not serious[a]	extremely serious[e]	none	3/122 (2.5%)	4/119 (3.4%)	**RR 0.73** (0.17 to 3.20)	**9 fewer per 1,000** (from 52 fewer to 33 more)[c]	⨁◯◯◯ VERY LOW	CRITICAL
Lost to Follow-up (follow-up: 104 weeks; assessed with: discontinuation of treatment, consent withdrawal, use of prohibited concomitant, or outcomes not assessable after treatment completion)												
1	randomised trials	not serious	not serious	not serious[a]	extremely serious[f]	none	13/122 (10.7%)	20/119 (16.8%)	**RR 0.63** (0.33 to 1.22)	**62 fewer per 1,000** (from 148 fewer to 25 more)[c]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse Events (follow-up: 104 weeks; assessed with: any Grade 3–5 adverse event during treatment and follow-up)												
1	randomised trials	not serious	not serious	not serious[a]	extremely serious[g]	none	80/127 (63.0%)	82/126 (65.1%)	**RR 0.97** (0.80 to 1.16)	**21 fewer per 1,000** (from 139 fewer to 97 more)[c]	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**a 9-month regimen using bedaquiline, delamanid, linezolid, levofloxacin, and pyrazinamide (BDLLfxZ)**	**currently recommended longer WHO regimens**	**Relative (95% CI)**	**Absolute (95% CI)**		
Adverse Events (follow-up: 104 weeks; assessed with: participants with one or more serious adverse events)												
1	randomised trials	not serious	not serious	not serious[a]	extremely serious[h]	none	20/127 (15.7%)	24/126 (19.0%)	**RR 0.83** (0.48 to 1.42)	**33 fewer per 1,000** (from 126 fewer to 60 more)[c]	⨁◯◯◯ VERY LOW	CRITICAL
Amplification (acquisition) of Drug-Resistance (follow-up: 104 weeks)												
1	randomised trials	not serious	not serious	not serious[a]	not serious	none	0/128 (0.0%)	0/130 (0.0%)	not estimable	**0 fewer per 1,000** (from 29 fewer to 29 more)[i]	⨁⨁⨁⨁ HIGH	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Standard of care for the treatment of rifampicin-resistant and fluoroquinolone-susceptible tuberculosis was composed according to latest World Health Organization guidelines, as they evolved during the trial. In this group 82% of participants were treated with the longer (18–24 month) all-oral regimen. After Dec 18, 2018 the first change in WHO Guidelines (ending use of injectables) was applied to the trial control regimen. A sensitivity analysis did not show important differences, with overlap in 95% confidence intervals, when excluding the 18% randomized during the period when injectables were prescribed. We therefore did not downgrade for indirectness.

b. Sustained treatment success: The 95% CI for the absolute effect crosses three thresholds, from small harm to large benefit. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

c. For the absolute effect we used the risk difference and 95% CI calculated from the trial data.

d. Failure and recurrence: The 95% CI for the absolute effect crosses two thresholds, from trivial benefit to moderate harm. We therefore downgraded the certainty by two levels due to very serious imprecision.

e. Death: The 95% CI for the absolute effect crosses three thresholds, from large harm to small benefit. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

f. Lost to follow-up: The 95% CI for the absolute effect crosses three thresholds, from moderate benefit to small harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

g. Adverse events (Grade 3–5): The 95% CI for the absolute effect crosses three thresholds, from large benefit to moderate harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

h. Adverse events (serious adverse events): The 95% CI for the absolute effect crosses three thresholds, from moderate benefit to moderate harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

i. Risk ratios could not be calculated because there was no acquired resistance in the control arm. The risk difference was 0% (95% CI, -2.9% to 2.9%).

PICO 2.3

Question	
Should a 9-month regimen using bedaquiline, delamanid, linezolid, levofloxacin, and pyrazinamide (BDLLfxZ) vs. currently recommended longer WHO regimens be used for patients with pulmonary RR-TB (without fluoroquinolone resistance)?	
POPULATION:	patients with pulmonary RR-TB (without fluoroquinolone resistance)
INTERVENTION:	a 9-month regimen using bedaquiline, delamanid, linezolid, levofloxacin, and pyrazinamide (BDLLfxZ)
COMPARISON:	currently recommended longer WHO regimens
MAIN OUTCOMES:	Sustained Treatment Success; Failure and Recurrence; Death; Lost to Follow-up; Adverse Events; Adverse Events; Amplification (acquisition) of Drug-Resistance
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	This question addresses the effectiveness and safety of a 9-month regimen using bedaquiline, delamanid, linezolid, fluoroquinolone (levofloxacin), and pyrazinamide (BDLLfxZ) versus the currently recommended longer regimens.
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: • Fernanda Dockhorn Costa Johansen, Muhwa Chakaya, Gopalan Narendran, Daniela Cirillo, Charles Daley, Gerry Davies, Elmira Gurbanova, Anneke Hesseling, Christoph Lange, Ashna Ashesh, Kim Cuong Nguyen, Andrew Vernon, Mahshid Nasehi, Graeme Meintjes, Erlina Burhan, Raymond Byaruhanga, Wenhong Zhang The following were GDG members recused from decision-making for this recommendation: • None

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 2022, an estimated 10.6 million people developed TB, and 1.3 million died from the disease. About 410,000 new patients with rifampicin-resistant or multidrug-resistant tuberculosis (MDR/RR-TB) were estimated to emerge in 2022. While all of these patients would have been eligible for a second-line TB treatment regimen, only 175,650 enrolments on treatment were reported by countries in the same year. Significant improvements in the availability of enhanced diagnostics and more effective medicines have occurred in recent years and have led to earlier detection and higher success rates among patients with MDR/RR-TB in many national programs. 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 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 treating drug-resistant TB, including MDR/RR-TB and pre-XDR-TB, were published by WHO in December 2022 – "WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment". WHO recommends the BPaLM, a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg), and moxifloxacin, for all eligible MDR/RR-TB patients (14 years or older) with or without resistance to fluoroquinolones rather than the 9-month or longer (18-month) regimens. BPaLM was the first standardized regimen for the treatment of drug-resistant TB that is as short as the first-line TB regimens but has limitations in use for children and adolescents below 14 years of age and during pregnancy.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Patients with MDR/RR-TB receiving the BDLLfxZ regimen (n=122 for failure and recurrence, death, and loss to follow; n=127 for adverse events and n=128 for amplification of drug resistance) compared to those receiving the currently recommended longer WHO regiments (n=119 for failure and recurrence, death, and loss to follow; n=126 for adverse events and n=130 for amplification of drug resistance) experienced: • lower levels of failure/recurrence: 1.6% vs 2.5%; RD=9 fewer per 1,000 (95%CI from 45 fewer to 27 more per 1,000); • lower levels of death: 2.5% vs 3.4%; RD=9 fewer per 1,000 (95%CI from 52 fewer to 33 more per 1,000); • lower levels of loss to follow-up: 10.7% vs 16.8%; RD=62 fewer per 1,000 (95%CI from 148 fewer to 25 more per 1,000); • lower levels of grade 3 to 5 adverse events: 63.0% vs 65.1%; RD=21 fewer per 1,000 (95%CI from 139 fewer to 97 more per 1,000); • lower levels of people with at least one serious adverse event: 15.7% vs 19.0%; RD=33 fewer per 1,000 (95%CI from 126 fewer to 60 more per 1,000); and • similar levels of amplified resistance: 0.0% vs 0.0%; RD=0 fewer per 1,000 (95%CI from 29 fewer to 29 more per 1,000). Implementing BDLLfxZ may lead to improvements in the outcomes of failure/recurrence, death, loss to follow-up, adverse events, and amplification (acquisition) of drug resistance but the evidence is overall very uncertain.	The GDG also considered the duration and pill burden with the intervention and comparator regimens. The duration of the intervention regimen is 36 weeks (9 months) so treatment duration is reduced compared to the control arm by between 9 and 15 months. The exact magnitude of reduction in time on treatment depends on the specific comparator regimen (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. **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 BDLLfxZ may have small desirable effects.**

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with currently recommended longer WHO regimens	Risk difference with a 9-month regimen using bedaquiline, delamanid, linezolid, levofloxacin, and pyrazinamide (BDLLfxZ)
Failure and Recurrence follow-up: 104 weeks	241 (1 RCT)	⨁⨁⨁◯ Moderate[a,b]	**RR 0.65** (0.11 to 3.83)	Study population	
				25 per 1,000	**9 fewer per 1,000** (45 fewer to 27 more)
Death follow-up: 104 weeks	241 (1 RCT)	⨁◯◯◯ Very low[a,c]	**RR 0.73** (0.17 to 3.20)	Study population	
				34 per 1,000	**9 fewer per 1,000** (52 fewer to 33 more)
Lost to Follow-up assessed with: discontinuation of treatment, consent withdrawal, use of prohibited concomitant, or outcomes not assessable after treatment completion follow-up: 104 weeks	241 (1 RCT)	⨁◯◯◯ Very low[a,d]	**RR 0.63** (0.33 to 1.22)	Study population	
				168 per 1,000	**62 fewer per 1,000** (148 fewer to 25 more)
Adverse Events assessed with: any Grade 3-5 adverse event during treatment and follow-up follow-up: 104 weeks	253 (1 RCT)	⨁◯◯◯ Very low[a,e]	**RR 0.97** (0.80 to 1.16)	Study population	
				651 per 1,000	**21 fewer per 1,000** (139 fewer to 97 more)
Adverse Events assessed with: participants with one or more serious adverse events follow-up: 104 weeks	253 (1 RCT)	⨁◯◯◯ Very low[a,f]	**RR 0.83** (0.48 to 1.42)	Study population	
				190 per 1,000	**33 fewer per 1,000** (126 fewer to 60 more)
Amplification (acquisition) of Drug-Resistance follow-up: 104 weeks	258 (1 RCT)	⨁⨁⨁⨁ High[a]	not estimable	Study population	
				0 per 1,000	**0 fewer per 1,000** (29 fewer to 29 more)

a. Standard of care for the treatment of rifampicin-resistant and fluoroquinolone-susceptible tuberculosis was composed according to latest World Health Organization guidelines, as they evolved during the trial. In this group 82% of participants were treated with the longer (18–24 month) all-oral regimen. After Dec 18, 2018 the first change in WHO Guidelines (ending use of injectables) was applied to the trial control regimen. A sensitivity analysis did not show important differences, with overlap in 95% confidence intervals, when excluding the 18% randomized during the period when injectables were prescribed. We therefore did not downgrade for indirectness.

b. Failure and recurrence: The 95% CI for the absolute effect crosses two thresholds, from trivial benefit to moderate harm. We therefore downgraded the certainty by two levels due to very serious imprecision.

c. Death: The 95% CI for the absolute effect crosses three thresholds, from large harm to small benefit. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

Specifically, the GDG considered that the desirable effects were trivial or no effect for the outcomes of death and failure and recurrence, moderate for the outcome of loss-to-follow up, trivial or no effect for all adverse events, small for serious adverse events, and trivial or no effect for for amplification of drug resistance. Additionally the GDG considered the shortening of the treatment duration and the reduction in pill burden as a desirable effect.

Decision Thresholds considered by the GDG during the discussion:

Death

Trivial Effect: ≤14 fewer or more events per 1000 people

Small Effect: 15 to 32 fewer or more events per 1000 people

Moderate Effect: 33 to 63 fewer or more events per 1000 people

Large Effect: ≥64 fewer or more events per 1000 people

For failure or recurrence, lost to follow-up, adverse events, and amplification (acquisition) of drug resistance

Trivial Effect: ≤30 fewer or more events per 1000 people

Small Effect: 31 to 59 fewer or more events per 1000 people

Moderate Effect: 60 to 119 fewer or more events per 1000 people

Large Effect: ≥120 fewer or more events per 1000 people

d. Lost to follow-up: The 95% CI for the absolute effect crosses three thresholds, from moderate benefit to small harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

e. Adverse events (Grade 3–5): The 95% CI for the absolute effect crosses three thresholds, from large benefit to moderate harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

f. Adverse events (serious adverse events): The 95% CI for the absolute effect crosses three thresholds, from moderate benefit to moderate harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with currently recommended longer WHO regimens	Risk difference with a 9-month regimen using bedaquiline, delamanid, linezolid, levofloxacin, and pyrazinamide (BDLLfxZ)
Sustained Treatment Success follow-up: 104 weeks	241 (1 RCT)	⨁⨁◯◯ Low[a,b]	**RR 1.10** (0.98 to 1.25)	Study population	
				773 per 1,000	**79 more per 1,000** (19 fewer to 177 more)

a. Standard of care for the treatment of rifampicin-resistant and fluoroquinolone-susceptible tuberculosis was composed according to latest World Health Organization guidelines, as they evolved during the trial. In this group 82% of participants were treated with the longer (18–24 month) all-oral regimen. After Dec 18, 2018 the first change in WHO Guidelines (ending use of injectables) was applied to the trial control regimen. A sensitivity analysis did not show important differences, with overlap in 95% confidence intervals, when excluding the 18% randomized during the period when injectables were prescribed. We therefore did not downgrade for indirectness.

b. Sustained treatment success: The 95% CI for the absolute effect crosses three thresholds, from small harm to large benefit. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

Note: The GDG did not consider treatment success as a separate outcome for this judgment. This is because treatment success is mathematically simply the complement of the three unfavorable treatment outcomes (failure, death and loss-to-follow) and thus does not carry any additional or independent information.

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
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know		Given that all of the health effects for the intervention were desirable effects, the GDG judged the undesirable effects as trivial.

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 very low, primarily due to imprecision in the effect estimates.

Values

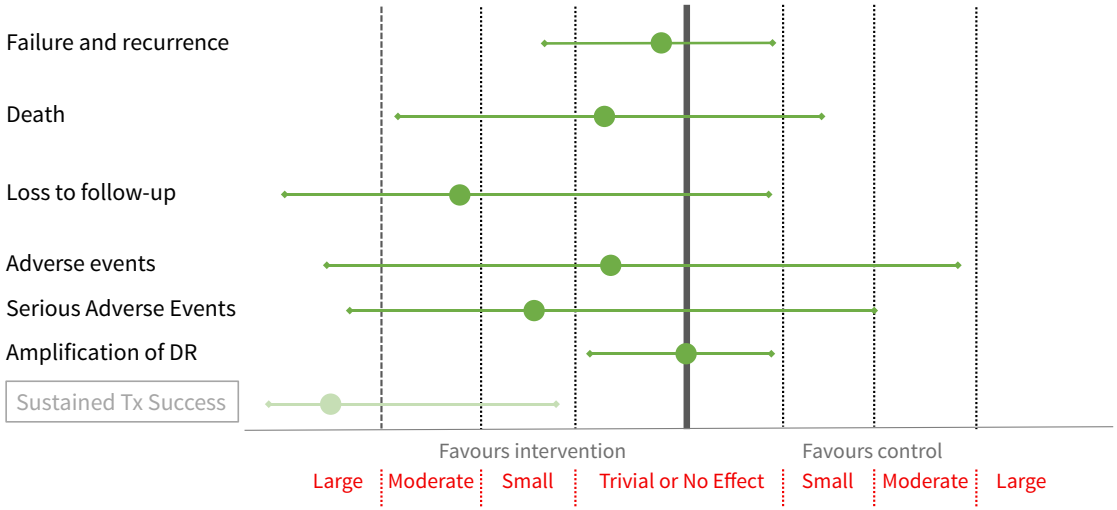
Is there important uncertainty about or variability in how much people value the main outcomes?

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 systematically searched for. Higher treatment efficacy, shorter duration of treatment, lower pill burden and less adverse events are usually valued by patients. A recent systematic review of health-related quality of life based on EQ-5D utility scores in patients with tuberculosis (Park et al,2021) reported based on one identified study (Kitikraisak et al, 2012; prospective cohort study with 222 patients from Thailand) that the EQ-5D value for MDR-TB was 0.51, which increased to 0.88 after completion of treatment.	The GDG noted that there would probably be no important uncertainty about how much people value the outcomes, and that patients may prefer a shorter treatment duration because of the outcomes associated with it.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**EndTB 3 – BDLLfxZ**	The GDG judged the benefits of BDLLfxZ to be small and the undesirable effects to be trivial compared to 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. Based on this, the GDG determined that the balance of health effects probably favours the BDLLfxZ regimen.



Note: The positioning of point estimates and CIs is indicative and for illustration purposes only and exact figures are available in the GRADE evidence profiles. As indicated above in the sections on desirable and undesirable effects, decision thresholds vary for some of the outcomes and therefore only the descriptive labels (trivial or no effect, small, moderate, large) are used for the x-axis rather than numerical values themselves.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT

○ Large costs
○ Moderate costs
○ Negligible costs and savings
○ Moderate savings
○ Large savings
● Varies
○ Don't know

RESEARCH EVIDENCE

We considered the following estimated regimen prices (from Stop TB Partnership Global Drug Facility):

	Regimen	Estimated Regimen Price
endTB Trial Regimens	endTB 1 9BLMZ	$297
	endTB 2 9BLLCZ	$455
	endTB 3 9BDLLZ	$2219
	endTB 4 9DLLCZ	$2192
	endTB 5 9DMCZ	$2170
WHO-Recommended Regimens	BPaLM	$443
	BPaL	$415
	Shorter Regimen	$418
	Shorter Regimen (with Lzd)	$396
	Longer Regimen ($18B_6LLC$)	$632

Assumptions for endTB treatment:

- Duration of 39 weeks
- Dosing based on weight > 55–70kg (per protocol)
- Daily dosing for
- Moxifloxacin
- Levofloxacin
- Clofazimine
- Pyrazinamide
- Bedaquiline dosing – 400mg daily x 14 days then 200mg 3x/week for weeks 3–39
- Delamanid dosing – 100mg twice daily x 39 weeks
- Linezolid dosing – 600mg daily x 16 weeks, then 600mg 3x/week for weeks 17–39

Caveats

- Medicine prices are average prices across all suppliers as per GDF market share allocation
- Medicine prices may change with 2024 GDF tenders

We 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.

RR			
	Cost over 9 months		
Country	**Patient**	**Health System**	**Total**
India	$1152	$261	$1413
Philippines	$2322	$702	$3024
South Africa	$1026	$1926	$2952

ADDITIONAL CONSIDERATIONS

Given the drugs included in the BDLLfxZ regimen, in particular delamanid, the cost would vary between moderate and large and may or may not be offset by the reduced non-drug health systems costs for BDLLfxZ compared to the longer regimen.

For the drug prices, cost would be large from the NTP perspective.

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 9-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 treatment regimen would be used.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors 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.	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.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence searched for.	The GDG considered patients and health care providers as key stakeholders. The GDG considered the regiment duration as critical with regards to acceptability. The GDG highlighted considerations about use of delamanid (required twice per day) in this regimen.

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 searched for. The 9-month BDLLfxZ regimen was additionally studied in the operational research STEM-TB cohort study in Kazakhstan (n=73). Treatment success was reported as reported as 89% in this cohort.	The GDG highlighted that the cost of the BDLLfxZ regimen (driven by delamanid) may affect feasibility for program managers in particular. Approval by regulators influences the feasibility of implementing the regimen, and alternative regimens may not always be available. Access to some of the medications is hampered by licensing differences.

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	**Trivial**	Small	Moderate	Large		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	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors 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	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors 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
WHO suggests using the 9-month all-oral regimens BDLLfxZ over currently recommended longer (>18 months) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. *(Conditional recommendation, very low certainty of evidence)* **Remarks** 1. The recommended modified 9-month all-oral regimens comprise bedaquiline, linezolid and pyrazinamide in different combinations with levofloxacin/moxifloxacin, clofazimine and delamanid. 2. This recommendation applies to the following: a. People with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. b. People with diagnosed pulmonary TB, including children, adolescents, PLHIV, and pregnant and breastfeeding women. c. People with extensive TB disease and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular TB or disseminated forms of TB with multiorgan involvement. d. 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. e. 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).
Justification
The GDG issued a conditional recommendation based on very low certainty of evidence (due to imprecision in the effect estimates) based on a small net benefit, and probably no uncertainty about patients' values, in particular with respect to the outcomes associated with a shorter duration regimen.
Subgroup considerations
See information in summary EtD for PICO 2
Implementation considerations
See information in summary EtD for PICO 2
Monitoring and evaluation
See information in summary EtD for PICO 2
Research priorities
See information in summary EtD for PICO 2

PICO 2.4

Question: A 9-month regimen using delamanid, clofazimine, linezolid, levofloxacin, and pyrazinamide (DCLLfxZ) compared to currently recommended longer WHO regimens in patients with pulmonary RR-TB (without fluoroquinolone resistance)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a 9-month regimen using delamanid, clofazimine, linezolid, levofloxacin, and pyrazinamide (DCLLfxZ)	currently recommended longer WHO regimens	Relative (95% CI)	Absolute (95% CI)		
Sustained Treatment Success (follow-up: 104 weeks)												
1	randomised trials	not serious	not serious	not serious[a]	extremely serious[b]	none	90/118 (76.3%)	92/119 (77.3%)	**RR 0.99** (0.86 to 1.13)	**10 fewer per 1,000** (from 118 fewer to 97 more)[c]	⨁◯◯◯ VERY LOW	CRITICAL
Failure and Recurrence (follow-up: 104 weeks)												
1	randomised trials	not serious	not serious	not serious[a]	extremely serious[d]	none	13/118 (11.0%)	3/119 (2.5%)	**RR 4.37** (1.28 to 14.95)	**85 more per 1,000** (from 22 more to 148 more)[c]	⨁◯◯◯ VERY LOW	CRITICAL
Death (follow-up: 104 weeks)												
1	randomised trials	not serious	not serious	not serious[a]	extremely serious[e]	none	3/118 (2.5%)	4/119 (3.4%)	**RR 0.76** (0.17 to 3.31)	**8 fewer per 1,000** (from 51 fewer to 35 more)[c]	⨁◯◯◯ VERY LOW	CRITICAL
Lost to Follow-up (follow-up: 104 weeks; assessed with: discontinuation of treatment, consent withdrawal, use of prohibited concomitant, or outcomes not assessable after treatment completion)												
1	randomised trials	not serious	not serious	not serious[a]	extremely serious[f]	none	12/118 (10.2%)	20/119 (16.8%)	**RR 0.61** (0.31 to 1.18)	**66 fewer per 1,000** (from 153 fewer to 20 more)[c]	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a 9-month regimen using delamanid, clofazimine, linezolid, levofloxacin, and pyrazinamide (DCLLfxZ)	currently recommended longer WHO regimens	Relative (95% CI)	Absolute (95% CI)		
Adverse Events (follow-up: 104 weeks; assessed with: any Grade 3–5 adverse event during treatment and follow-up)												
1	randomised trials	not serious	not serious	not serious[a]	extremely serious[g]	none	78/124 (62.9%)	82/126 (65.1%)	**RR 0.97** (0.80 to 1.16)	**22 fewer per 1,000** (from 141 fewer to 97 more)[c]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse Events (follow-up: 104 weeks; assessed with: participants with one or more serious adverse events)												
1	randomised trials	not serious	not serious	not serious[a]	extremely serious[h]	none	19/124 (15.3%)	24/126 (19.0%)	**RR 0.80** (0.46 to 1.39)	**37 fewer per 1,000** (from 131 fewer to 56 more)[c]	⨁◯◯◯ VERY LOW	CRITICAL
Amplification (acquisition) of Drug-Resistance (follow-up: 104 weeks)												
1	randomised trials	not serious	not serious	not serious[a]	very serious[i]	none	5/125 (4.0%)	0/130 (0.0%)	not estimable	**40 more per 1,000** (from 9 more to 87 more)[j]	⨁⨁◯◯ LOW	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Standard of care for the treatment of rifampicin-resistant and fluoroquinolone-susceptible tuberculosis was composed according to latest World Health Organization guidelines, as they evolved during the trial. In this group 82% of participants were treated with the longer (18–24 month) all-oral regimen. After Dec 18, 2018 the first change in WHO Guidelines (ending use of injectables) was applied to the trial control regimen. A sensitivity analysis did not show important differences, with overlap in 95% confidence intervals, when excluding the 18% randomized during the period when injectables were prescribed. We therefore did not downgrade for indirectness.

b. Sustained treatment success: The 95% CI for the absolute effect crosses three thresholds, from large harm to large benefit. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

c. For the absolute effect we used the risk difference and 95% CI calculated from the trial data.

d. Failure and recurrence: The 95% CI for the absolute effect crosses three thresholds, from trivial harm to large harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

e. Death: The 95% CI for the absolute effect crosses three thresholds, from small benefit to large harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

f. Lost to follow-up: The 95% CI for the absolute effect crosses two thresholds, from moderate benefit to small harm. We therefore downgraded the certainty by two levels due to very serious imprecision.

g. Adverse events (Grade 3–5): The 95% CI for the absolute effect crosses three thresholds, from large benefit to moderate harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

h. Adverse events (serious adverse events): The 95% CI for the absolute effect crosses three thresholds, from moderate benefit to moderate harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

i. Amplification (acquisition) of drug-resistance: The 95% CI for the absolute effect crosses two thresholds, from trivial harm to moderate harm. We therefore downgraded the certainty by two levels due to very serious imprecision.

j. Risk ratios could not be calculated because there was no acquired resistance in the control arm. The risk difference was 4.0% (95% CI, 0.9% to 8.7%).

PICO 2.4

Question	
Should a 9-month regimen using delamanid, clofazimine, linezolid, levofloxacin, and pyrazinamide (DCLLfxZ) vs. currently recommended longer WHO regimens be used for patients with pulmonary RR-TB (without fluoroquinolone resistance)?	
POPULATION:	patients with pulmonary RR-TB (without fluoroquinolone resistance)
INTERVENTION:	a 9-month regimen using delamanid, clofazimine, linezolid, levofloxacin, and pyrazinamide (DCLLfxZ)
COMPARISON:	currently recommended longer WHO regimens
MAIN OUTCOMES:	Sustained Treatment Success; Failure and Recurrence; Death; Lost to Follow-up; Adverse Events; Adverse Events; Amplification (acquisition) of Drug-Resistance;
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	This question addresses the effectiveness and safety of a 9-month regimen using delamanid, clofazimine, linezolid, fluoroquinolone (levofloxacin), and pyrazinamide (DCLLfxZ) versus the currently recommended longer regimens.
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: • Fernanda Dockhorn Costa Johansen, Muhwa Chakaya, Gopalan Narendran, Daniela Cirillo, Charles Daley, Gerry Davies, Elmira Gurbanova, Anneke Hesseling, Christoph Lange, Ashna Ashesh, Kim Cuong Nguyen, Andrew Vernon, Mahshid Nasehi, Graeme Meintjes, Erlina Burhan, Raymond Byaruhanga, Wenhong Zhang The following were GDG members recused from decision-making for this recommendation: • None Note: Anneke Hesseling and Wenhong Zhang away from discussion for this EtD

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 2022, an estimated 10.6 million people developed TB, and 1.3 million died from the disease. About 410,000 new patients with rifampicin-resistant or multidrug-resistant tuberculosis (MDR/RR-TB) were estimated to emerge in 2022. While all of these patients would have been eligible for a second-line TB treatment regimen, only 175,650 enrolments on treatment were reported by countries in the same year. Significant improvements in the availability of enhanced diagnostics and more effective medicines have occurred in recent years and have led to earlier detection and higher success rates among patients with MDR/RR-TB in many national programs. 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 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 treating drug-resistant TB, including MDR/RR-TB and pre-XDR-TB, were published by WHO in December 2022 – "WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment". WHO recommends the BPaLM, a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg), and moxifloxacin, for all eligible MDR/RR-TB patients (14 years or older) with or without resistance to fluoroquinolones rather than the 9-month or longer (18-month) regimens. BPaLM was the first standardized regimen for the treatment of drug-resistant TB that is as short as the first-line TB regimens but has limitations in use for children and adolescents below 14 years of age and during pregnancy.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

○ Trivial
● Small
○ Moderate
○ Large
○ Varies
○ Don't know

RESEARCH EVIDENCE

Patients with MDR/RR-TB receiving the DCLLfxZ regimen (n=118 for death and loss to follow and n=124 for adverse events) compared to those receiving the currently recommended longer WHO regiments (n=119 for death and loss to follow up and n=126 for adverse events) experienced:

- lower levels of death: 2.5% vs 3.4%; RD=8 fewer per 1,000 (95%CI from 51 fewer to 35 more per 1,000);
- lower levels of loss to follow-up: 10.2% vs 16.8%; RD=66 fewer per 1,000 (95%CI from 153 fewer to 20 more per 1,000);
- lower levels of grade 3 to 5 adverse events: 62.9% vs 65.1%; RD=22 fewer per 1,000 (95%CI from 141 fewer to 97 more per 1,000); and
- lower levels of people with at least one serious adverse event: 15.3% vs 19.0%; RD=37 fewer per 1,000 (95%CI from 131 fewer to 56 more per 1,000).

Implementing DCLLfxZ may lead to improvements in the outcomes of death, loss to follow-up and adverse events but the evidence is overall very uncertain.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with currently recommended longer WHO regimens	Risk difference with a 9-month regimen using delamanid, clofazimine, linezolid, levofloxacin, and pyrazinamide (DCLLfxZ)
Death follow-up: 104 weeks	237 (1 RCT)	⨁◯◯◯ Very low[a,b]	**RR 0.76** (0.17 to 3.31)	Study population 34 per 1,000	**8 fewer per 1,000** (51 fewer to 35 more)
Lost to Follow-up assessed with: discontinuation of treatment, consent withdrawal, use of prohibited concomitant, or outcomes not assessable after treatment completion follow-up: 104 weeks	237 (1 RCT)	⨁◯◯◯ Very low[a,c]	**RR 0.61** (0.31 to 1.18)	Study population 168 per 1,000	**66 fewer per 1,000** (153 fewer to 20 more)
Adverse Events assessed with: any Grade 3-5 adverse event during treatment and follow-up follow-up: 104 weeks	250 (1 RCT)	⨁◯◯◯ Very low[a,d]	**RR 0.97** (0.80 to 1.16)	Study population 651 per 1,000	**22 fewer per 1,000** (141 fewer to 97 more)
Adverse Events assessed with: participants with one or more serious adverse events follow-up: 104 weeks	250 (1 RCT)	⨁◯◯◯ Very low[a,e]	**RR 0.80** (0.46 to 1.39)	Study population 190 per 1,000	**37 fewer per 1,000** (131 fewer to 56 more)

ADDITIONAL CONSIDERATIONS

The GDG also considered the duration and pill burden with the intervention and comparator regimens. The duration of the intervention regimen is 36 weeks (9 months) so treatment duration is reduced compared to the control arm by between 9 and 15 months. The exact magnitude of reduction in time on treatment depends on the specific comparator regimen (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.

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 DCLLfxZ may have small desirable effects.

Specifically, the GDG considered that the desirable effects were trivial or no effect for the outcome of death, moderate for the outcome of loss-to-follow up, trivial or no effect for all adverse events, and small for serious adverse events. Additionally the GDG considered the shortening of the treatment duration and the reduction in pill burden as a desirable effect.

Decision Thresholds considered by the GDG during the discussion:

Death

Trivial Effect: ≤14 fewer or more events per 1000 people

Small Effect: 15 to 32 fewer or more events per 1000 people

Moderate Effect: 33 to 63 fewer or more events per 1000 people

Large Effect: ≥64 fewer or more events per 1000 people

a. Standard of care for the treatment of rifampicin-resistant and fluoroquinolone-susceptible tuberculosis was composed according to latest World Health Organization guidelines, as they evolved during the trial. In this group 82% of participants were treated with the longer (18–24 month) all-oral regimen. After Dec 18, 2018 the first change in WHO Guidelines (ending use of injectables) was applied to the trial control regimen. A sensitivity analysis did not show important differences, with overlap in 95% confidence intervals, when excluding the 18% randomized during the period when injectables were prescribed. We therefore did not downgrade for indirectness.

b. Death: The 95% CI for the absolute effect crosses three thresholds, from small benefit to large harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

c. Lost to follow-up: The 95% CI for the absolute effect crosses two thresholds, from moderate benefit to small harm. We therefore downgraded the certainty by two levels due to very serious imprecision.

d. Adverse events (Grade 3–5): The 95% CI for the absolute effect crosses three thresholds, from large benefit to moderate harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

e. Adverse events (serious adverse events): The 95% CI for the absolute effect crosses three thresholds, from moderate benefit to moderate harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

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.

For lost to follow-up and adverse events

Trivial Effect: ≤30 fewer or more events per 1000 people

Small Effect: 31 to 59 fewer or more events per 1000 people

Moderate Effect: 60 to 119 fewer or more events per 1000 people

Large Effect: ≥120 fewer or more events per 1000 people

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

○ Trivial
○ Small
● Moderate
○ Large
○ Varies
○ Don't know

RESEARCH EVIDENCE

Patients with MDR/RR-TB receiving the DCLLfxZ regimen (n=118 for failure and recurrence and n=125 for amplification of drug resistance) compared to those receiving the currently recommended longer WHO regiments (n=119 for failure and recurrence and n=130 for amplification of drug resistance) experienced:

- higher levels of failure/recurrence: 11.0% vs 2.5%; RD=85 more per 1,000 (95%CI from 22 more to 148 more per 1,000); and
- higher levels of amplified resistance: 4.0% vs 0%; RD=40 more per 1,000 (95%CI from 9 more to 87 more per 1,000).

Implementing DCLLfxZ may lead to worsening in the outcomes of failure and recurrence and amplification (acquisition) of drug resistance but the evidence is overall very uncertain.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with currently recommended longer WHO regimens	Risk difference with a 9-month regimen using delamanid, clofazimine, linezolid, levofloxacin, and pyrazinamide (DCLLfxZ)
Failure and Recurrence follow-up: 104 weeks	237 (1 RCT)	⨁◯◯◯ Very low[a,b]	**RR 4.37** (1.28 to 14.95)	Study population	
				25 per 1,000	**85 more per 1,000** (22 more to 148 more)
Amplification (acquisition) of Drug-Resistance follow-up: 104 weeks	255 (1 RCT)	⨁⨁◯◯ Low[a,c]	not estimable	Study population	
				0 per 1,000	**40 more per 1,000** (9 more to 87 more)

a. Standard of care for the treatment of rifampicin-resistant and fluoroquinolone-susceptible tuberculosis was composed according to latest World Health Organization guidelines, as they evolved during the trial. In this group 82% of participants were treated with the longer (18–24 month) all-oral regimen. After Dec 18, 2018 the first change in WHO Guidelines (ending use of injectables) was applied to the trial control regimen. A sensitivity analysis did not show important differences, with overlap in 95% confidence intervals, when excluding the 18% randomized during the period when injectables were prescribed. We therefore did not downgrade for indirectness.

b. Failure and recurrence: The 95% CI for the absolute effect crosses three thresholds, from trivial harm to large harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

c. Amplification (acquisition) of drug-resistance: The 95% CI for the absolute effect crosses two thresholds, from trivial harm to moderate harm. We therefore downgraded the certainty by two levels due to very serious imprecision.

ADDITIONAL CONSIDERATIONS

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 DCLLfxZ may have moderate undesirable effects.

Specifically, the GDG considered that the undesirable effects were moderate for the outcome of failure and recurrence and small for amplification of drug resistance.

Decision Thresholds considered by the GDG during the discussion:

For treatment failure or recurrence and amplification (acquisition) of drug resistance

Trivial Effect: ≤30 fewer or more events per 1000 people

Small Effect: 31 to 59 fewer or more events per 1000 people

Moderate Effect: 60 to 119 fewer or more events per 1000 people

Large Effect: ≥120 fewer or more events per 1000 people

Note: The GDG did not consider treatment success as a separate outcome for this judgment. This is because treatment success is mathematically simply the complement of the three unfavorable treatment outcomes (failure, death and loss-to-follow) and thus does not carry any additional or independent information.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with currently recommended longer WHO regimens	Risk difference with a 9-month regimen using delamanid, clofazimine, linezolid, levofloxacin, and pyrazinamide (DCLLfxZ)
Sustained Treatment Success follow-up: 104 weeks	237 (1 RCT)	⨁◯◯◯ Very low[a,b]	**RR 0.99** (0.86 to 1.13)	Study population	
				773 per 1,000	**10 fewer per 1,000** (118 fewer to 97 more)

a. Standard of care for the treatment of rifampicin-resistant and fluoroquinolone-susceptible tuberculosis was composed according to latest World Health Organization guidelines, as they evolved during the trial. In this group 82% of participants were treated with the longer (18–24 month) all-oral regimen. After Dec 18, 2018 the first change in WHO Guidelines (ending use of injectables) was applied to the trial control regimen. A sensitivity analysis did not show important differences, with overlap in 95% confidence intervals, when excluding the 18% randomized during the period when injectables were prescribed. We therefore did not downgrade for indirectness.

b. Sustained treatment success: The 95% CI for the absolute effect crosses three thresholds, from large harm to large benefit. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

Table. Frequency of new drug resistance among randomized endTB study participants (N=754) with at least one paired specimen (N=31) containing the same strain of *M. tuberculosis*, by drug and treatment arm, showing n new resistance/pairs tested (%)

	9DCLLfxZ	Control
Pairs tested	**11**	**3**
Bedaquiline	0 (0.0%)	0 (0.0%)
Clofazimine	0 (0.0%)	0 (0.0%)
Delamanid	3 (27.3%)	0 (0.0%)
Fluoroquinolone[a]	2 (18.2%)	0 (0.0%)
Linezolid	0 (0.0%)	0 (0.0%)
Total new resistance among randomized (%)	5/125 (4.0%)	0/130 (0.0%)

[a] moxifloxacin or levofloxacin.

Table. Acquired drug resistance# – Randomized population

	9DCLLfxZ	Control
Total in randomized population	125	130
Acquired drug resistance#	5 (4.0%)	0 (0.0%)
95% CI	1.3%;9.1%	0.0%;2.8%
Risk difference %[a]	4.0%	
95% CI[c]	0.9%;8.7%c	
Risk ratio[b]	-	
95% CI	-	

[a] Percent of patients with outcome in the experimental arm – percent of patients with outcome in the control arm

[b] Percent of patients with outcome in the experimental arm / percent of patients with in the control arm

[c] Confidence intervals calculated using the Miettinen-Nurminen method (binomial exact method)

To: bedaquiline, clofazimine, delamanid, levofloxacin, linezolid, or moxifloxacin

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 very low, primarily due to imprecision in the effect estimates.

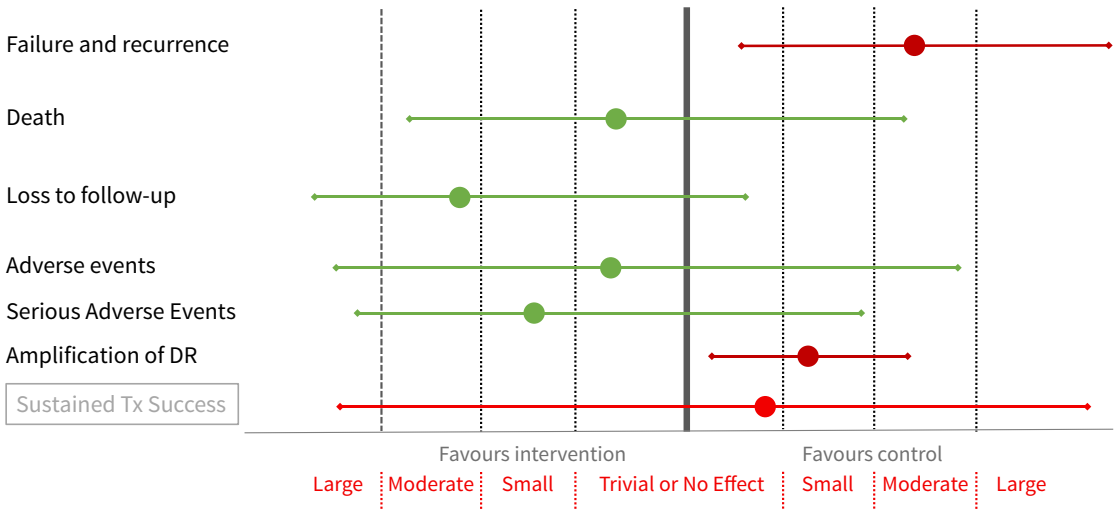
Values

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 systematically searched for. Higher treatment efficacy, shorter duration of treatment, lower pill burden and less adverse events are usually valued by patients. A recent systematic review of health-related quality of life based on EQ-5D utility scores in patients with tuberculosis (Park et al,2021) reported based on one identified study (Kitikraisak et al, 2012; prospective cohort study with 222 patients from Thailand) that the EQ-5D value for MDR-TB was 0.51, which increased to 0.88 after completion of treatment.	The GDG noted that there would probably be no important uncertainty about how much people value the outcomes, and that patients may prefer a shorter treatment duration because of the outcomes associated with it.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**EndTB 4 – DCLLfxZ**  Note: The positioning of point estimates and CIs is indicative and for illustration purposes only and exact figures are available in the GRADE evidence profiles. As indicated above in the sections on desirable and undesirable effects, decision thresholds vary for some of the outcomes and therefore only the descriptive labels (trivial or no effect, small, moderate, large) are used for the x-axis rather than numerical values themselves.	The GDG judged the benefits of DCLLfxZ to be small and the undesirable effects to be moderate compared to 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. Based on this, the GDG determined that the balance of health effects probably favours the WHO recommended longer regimens.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	We considered the following estimated regimen prices (from Stop TB Partnership Global Drug Facility):	Given the drugs included in the DCLLfxZ regimen, in particular delamanid, the cost would vary between moderate and large and may or may not be offset by the health systems costs for the longer regimen. For the drug prices, cost would be large from the NTP perspective.

	Regimen	Estimated Regimen Price
endTB Trial Regimens	endTB 1 9BLMZ	$297
	endTB 2 9BLLCZ	$455
	endTB 3 9BDLLZ	$2219
	endTB 4 9DLLCZ	$2192
	endTB 5 9DMCZ	$2170
WHO-Recommended Regimens	BPaLM	$443
	BPaL	$415
	Shorter Regimen	$418
	Shorter Regimen (with Lzd)	$396
	Longer Regimen ($18B_6LLC$)	$632

Assumptions for endTB treatment:

- Duration of 39 weeks
- Dosing based on weight > 55–70kg (per protocol)
- Daily dosing for
- Moxifloxacin
- Levofloxacin
- Clofazimine
- Pyrazinamide
- Bedaquiline dosing – 400mg daily x 14 days then 200mg 3x/week for weeks 3–39
- Delamanid dosing – 100mg twice daily x 39 weeks
- Linezolid dosing – 600mg daily x 16 weeks, then 600mg 3x/week for weeks 17–39

Caveats

- Medicine prices are average prices across all suppliers as per GDF market share allocation
- Medicine prices may change with 2024 GDF tenders

We 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.

RR			
	Cost over 9 months		
Country	**Patient**	**Health System**	**Total**
India	$1152	$261	$1413
Philippines	$2322	$702	$3024
South Africa	$1026	$1926	$2952

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 9-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 treatment regimen would be used.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No research evidence searched for.	Despite no research evidence to consider, the GDG discussed that given the small benefit, moderate harm, and moderate to large variable costs with DCLLfxZ regimen, a judgement of cost-effectiveness probably favouring the comparison is appropriate.

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.	Given the moderate to large costs, as well as the lack of net benefit, health equity would probably be reduced compared to the longer currently recommended WHO regimens.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence searched for.	The GDG considered patients and health care providers as key stakeholders. The DCLLfxZ regimen would not be acceptable to patients and healthcare workers given less benefit and net harm, as well as higher cost.

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 searched for.	Approval by regulators influences the feasibility of implementing the regimen, and alternative regimens may not always be available. Access to some of the medications is hampered by licensing differences.

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	Trivial	Small	**Moderate**	Large		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	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors 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	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors 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
WHO suggests against using the 9-month DCLLfxZ regimen compared with currently recommended longer regimens in patients with FQ susceptible RR-TB. (Conditional recommendation, based on very low certainty in the effects)
Justification
The GDG judged that there was net harm with moderate undesirable effects (including acquisition of drug resistance and treatment failures and recurrence that may be increased) and small desirable effects based on very low certainty evidence.
Subgroup considerations
NA
Implementation considerations
NA
Monitoring and evaluation
NA
Research priorities
NA

PICO 2.5

Question: A 9-month regimen using delamanid, clofazimine, moxifloxacin, and pyrazinamide (DCMZ) compared to currently recommended longer WHO regimens in patients with pulmonary RR-TB (without fluoroquinolone resistance)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**a 9-month regimen using delamanid, clofazimine, moxifloxacin, and pyrazinamide (DCMZ)**	**currently recommended longer WHO regimens**	**Relative (95% CI)**	**Absolute (95% CI)**		
Sustained Treatment Success (follow-up: 104 weeks)												
1	randomised trials	not serious	not serious	not serious[a]	extremely serious[b]	none	88/107 (82.2%)	92/119 (77.3%)	**RR 1.06** (0.93 to 1.21)	**49 more per 1,000** (from 55 fewer to 154 more)[c]	⨁◯◯◯ VERY LOW	CRITICAL
Failure and Recurrence (follow-up: 104 weeks)												
1	randomised trials	not serious	not serious	not serious[a]	extremely serious[d]	none	12/107 (11.2%)	3/119 (2.5%)	**RR 4.45** (1.29 to 15.34)	**87 more per 1,000** (from 21 more to 153 more)[c]	⨁◯◯◯ VERY LOW	CRITICAL
Death (follow-up: 104 weeks)												
1	randomised trials	not serious	not serious	not serious[a]	extremely serious[e]	none	3/107 (2.8%)	4/119 (3.4%)	**RR 0.83** (0.19 to 3.64)	**6 fewer per 1,000** (from 51 fewer to 39 more)[c]	⨁◯◯◯ VERY LOW	CRITICAL
Lost to Follow-up (follow-up: 104 weeks; assessed with: discontinuation of treatment, consent withdrawal, use of prohibited concomitant, or outcomes not assessable after treatment completion)												
1	randomised trials	not serious	not serious	not serious[a]	very serious[f]	none	4/107 (3.7%)	20/119 (16.8%)	**RR 0.22** (0.08 to 0.63)	**131 fewer per 1,000** (from 207 fewer to 54 fewer)[c]	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a 9-month regimen using delamanid, clofazimine, moxifloxacin, and pyrazinamide (DCMZ)	currently recommended longer WHO regimens	Relative (95% CI)	Absolute (95% CI)		
Adverse Events (follow-up: 104 weeks; assessed with: any Grade 3–5 adverse event during treatment and follow-up)												
1	randomised trials	not serious	not serious	not serious[a]	extremely serious[g]	none	72/120 (60.0%)	82/126 (65.1%)	**RR 0.92** (0.76 to 1.12)	**51 fewer per 1,000** (from 172 fewer to 70 more)[c]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse Events (follow-up: 104 weeks; assessed with: participants with one or more serious adverse events)												
1	randomised trials	not serious	not serious	not serious[a]	extremely serious[h]	none	21/120 (17.5%)	24/126 (19.0%)	**RR 0.92** (0.54 to 1.56)	**15 fewer per 1,000** (from 112 fewer to 81 more)[c]	⨁◯◯◯ VERY LOW	CRITICAL
Amplification (acquisition) of Drug-Resistance (follow-up: 104 weeks)												
1	randomised trials	not serious	not serious	not serious[a]	serious[i]	none	8/120 (6.7%)	0/130 (0.0%)	not estimable	**67 more per 1,000** (from 32 more to 119 more)[j]	⨁⨁⨁◯ MODERATE	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Standard of care for the treatment of rifampicin-resistant and fluoroquinolone-susceptible tuberculosis was composed according to latest World Health Organization guidelines, as they evolved during the trial. In this group 82% of participants were treated with the longer (18–24 month) all-oral regimen. After Dec 18, 2018 the first change in WHO Guidelines (ending use of injectables) was applied to the trial control regimen. A sensitivity analysis did not show important differences, with overlap in 95% confidence intervals, when excluding the 18% randomized during the period when injectables were prescribed. We therefore did not downgrade for indirectness.

b. Sustained treatment success: The 95% CI for the absolute effect crosses three thresholds, from moderate harm to large benefit. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

c. For the absolute effect we used the risk difference and 95% CI calculated from the trial data.

d. Failure and recurrence: The 95% CI for the absolute effect crosses three thresholds, from trivial harm to large harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

e. Death: The 95% CI for the absolute effect crosses three thresholds, from moderate benefit to moderate harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

f. Lost to follow-up: The 95% CI for the absolute effect crosses two thresholds, from large benefit to small benefit. We therefore downgraded the certainty by two levels due to very serious imprecision.

g. Adverse events (Grade 3–5): The 95% CI for the absolute effect crosses three thresholds, from large benefit to moderate harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

h. Adverse events (serious adverse events): The 95% CI for the absolute effect crosses three thresholds, from moderate benefit to moderate harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

i. Amplification (acquisition) of drug-resistance: The 95% CI for the absolute effect crosses one threshold, from small harm to moderate harm. We therefore downgraded the certainty by one level due to serious imprecision.

j. Risk ratios could not be calculated because there was no acquired resistance in the control arm. The risk difference was 6.7% (95% CI, 3.2% to 11.9%).

PICO 2.5

Question	
Should a 9-month regimen using delamanid, clofazimine, moxifloxacin, and pyrazinamide (DCMZ) vs. currently recommended longer WHO regimens be used for patients with pulmonary RR-TB (without fluoroquinolone resistance)?	
POPULATION:	patients with pulmonary RR-TB (without fluoroquinolone resistance)
INTERVENTION:	a 9-month regimen using delamanid, clofazimine, moxifloxacin, and pyrazinamide (DCMZ)
COMPARISON:	currently recommended longer WHO regimens
MAIN OUTCOMES:	Sustained Treatment Success; Failure and Recurrence; Death; Lost to Follow-up; Adverse Events; Adverse Events; Amplification (acquisition) of Drug-Resistance;
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	This question addresses the effectiveness and safety of a 9-month regimen using delamanid, clofazimine, fluoroquinolone (moxifloxacin), and pyrazinamide (DCMZ) versus the currently recommended longer regimens.
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: • Fernanda Dockhorn Costa Johansen, Muhwa Chakaya, Gopalan Narendran, Daniela Cirillo, Charles Daley, Gerry Davies, Elmira Gurbanova, Anneke Hesseling, Christoph Lange, Ashna Ashesh, Kim Cuong Nguyen, Andrew Vernon, Mahshid Nasehi, Graeme Meintjes, Erlina Burhan, Raymond Byaruhanga, Wenhong Zhang The following were GDG members recused from decision-making for this recommendation: • None

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 2022, an estimated 10.6 million people developed TB, and 1.3 million died from the disease. About 410,000 new patients with rifampicin-resistant or multidrug-resistant tuberculosis (MDR/RR-TB) were estimated to emerge in 2022. While all of these patients would have been eligible for a second-line TB treatment regimen, only 175,650 enrolments on treatment were reported by countries in the same year. Significant improvements in the availability of enhanced diagnostics and more effective medicines have occurred in recent years and have led to earlier detection and higher success rates among patients with MDR/RR-TB in many national programs. 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 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 treating drug-resistant TB, including MDR/RR-TB and pre-XDR-TB, were published by WHO in December 2022 – "WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment". WHO recommends the BPaLM, a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg), and moxifloxacin, for all eligible MDR/RR-TB patients (14 years or older) with or without resistance to fluoroquinolones rather than the 9-month or longer (18-month) regimens. BPaLM was the first standardized regimen for the treatment of drug-resistant TB that is as short as the first-line TB regimens but has limitations in use for children and adolescents below 14 years of age and during pregnancy.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

○ Trivial
○ Small
● Moderate
○ Large
○ Varies
○ Don't know

RESEARCH EVIDENCE

Patients with MDR/RR-TB receiving the DCMZ regimen (n=107 for death and loss to follow and n=120 for adverse events) compared to those receiving the currently recommended longer WHO regiments (n=119 for death and loss to follow up and n=126 for adverse events) experienced:

- lower levels of death: 2.8% vs 3.4%; RD=6 fewer per 1,000 (95%CI from 51 fewer to 39 more per 1,000);
- lower levels of loss to follow-up: 3.7% vs 16.8%; RD=131 fewer per 1,000 (95%CI from 207 fewer to 54 fewer per 1,000);
- lower levels of grade 3 to 5 adverse events: 60.0% vs 65.1%; RD=51 fewer per 1,000 (95%CI from 172 fewer to 70 more per 1,000); and
- lower levels of people with at least one serious adverse event: 17.5% vs 19.0%; RD=15 fewer per 1,000 (95%CI from 112 fewer to 81 more per 1,000).

Implementing DCMZ may lead to improvements in the outcomes of death, loss to follow-up and adverse events but the evidence is overall very uncertain.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with currently recommended longer WHO regimens	Risk difference with a 9-month regimen using delamanid, clofazimine, moxifloxacin, and pyrazinamide (DCMZ)
Death follow-up: 104 weeks	226 (1 RCT)	⨁◯◯◯ Very low[a,b]	**RR 0.83** (0.19 to 3.64)	Study population	
				34 per 1,000	**6 fewer per 1,000** (51 fewer to 39 more)
Lost to Follow-up assessed with: discontinuation of treatment, consent withdrawal, use of prohibited concomitant, or outcomes not assessable after treatment completion follow-up: 104 weeks	226 (1 RCT)	⨁⨁◯◯ Low[a,c]	**RR 0.22** (0.08 to 0.63)	Study population	
				168 per 1,000	**131 fewer per 1,000** (207 fewer to 54 fewer)
Adverse Events assessed with: any Grade 3-5 adverse event during treatment and follow-up follow-up: 104 weeks	246 (1 RCT)	⨁◯◯◯ Very low[a,d]	**RR 0.92** (0.76 to 1.12)	Study population	
				651 per 1,000	**51 fewer per 1,000** (172 fewer to 70 more)
Adverse Events assessed with: participants with one or more serious adverse events follow-up: 104 weeks	246 (1 RCT)	⨁◯◯◯ Very low[a,e]	**RR 0.92** (0.54 to 1.56)	Study population	
				190 per 1,000	**15 fewer per 1,000** (112 fewer to 81 more)

ADDITIONAL CONSIDERATIONS

The GDG also considered the duration and pill burden with the intervention and comparator regimens. The duration of the intervention regimen is 36 weeks (9 months) so treatment duration is reduced compared to the control arm by between 9 and 15 months. The exact magnitude of reduction in time on treatment depends on the specific comparator regimen (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.

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 DCMZ may have moderate desirable effects.

Specifically, the GDG considered that the desirable effects were trivial or no effect for the outcome of death, large for the outcome of loss to follow-up, small for all adverse events, and trivial or no effect for serious adverse events. Additionally the GDG considered the shortening of the treatment duration and the reduction in pill burden as a desirable effect.

Decision Thresholds considered by the GDG during the discussion:

a. Standard of care for the treatment of rifampicin-resistant and fluoroquinolone-susceptible tuberculosis was composed according to latest World Health Organization guidelines, as they evolved during the trial. In this group 82% of participants were treated with the longer (18–24 month) all-oral regimen. After Dec 18, 2018 the first change in WHO Guidelines (ending use of injectables) was applied to the trial control regimen. A sensitivity analysis did not show important differences, with overlap in 95% confidence intervals, when excluding the 18% randomized during the period when injectables were prescribed. We therefore did not downgrade for indirectness.

b. Death: The 95% CI for the absolute effect crosses three thresholds, from moderate benefit to moderate harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

c. Lost to follow-up: The 95% CI for the absolute effect crosses two thresholds, from large benefit to small benefit. We therefore downgraded the certainty by two levels due to very serious imprecision.

d. Adverse events (Grade 3–5): The 95% CI for the absolute effect crosses three thresholds, from large benefit to moderate harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

e. Adverse events (serious adverse events): The 95% CI for the absolute effect crosses three thresholds, from moderate benefit to moderate harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with currently recommended longer WHO regimens	Risk difference with a 9-month regimen using delamanid, clofazimine, moxifloxacin, and pyrazinamide (DCMZ)
Sustained Treatment Success follow-up: 104 weeks	226 (1 RCT)	⨁◯◯◯ Very low[a,b]	**RR 1.06** (0.93 to 1.21)	Study population	
				773 per 1,000	**49 more per 1,000** (55 fewer to 154 more)

a. Standard of care for the treatment of rifampicin-resistant and fluoroquinolone-susceptible tuberculosis was composed according to latest World Health Organization guidelines, as they evolved during the trial. In this group 82% of participants were treated with the longer (18–24 month) all-oral regimen. After Dec 18, 2018 the first change in WHO Guidelines (ending use of injectables) was applied to the trial control regimen. A sensitivity analysis did not show important differences, with overlap in 95% confidence intervals, when excluding the 18% randomized during the period when injectables were prescribed. We therefore did not downgrade for indirectness.

b. Sustained treatment success: The 95% CI for the absolute effect crosses three thresholds, from moderate harm to large benefit. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

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.

Death

Trivial Effect: ≤14 fewer or more events per 1000 people

Small Effect: 15 to 32 fewer or more events per 1000 people

Moderate Effect: 33 to 63 fewer or more events per 1000 people

Large Effect: ≥64 fewer or more events per 1000 people

For lost to follow-up and adverse events

Trivial Effect: ≤30 fewer or more events per 1000 people

Small Effect: 31 to 59 fewer or more events per 1000 people

Moderate Effect: 60 to 119 fewer or more events per 1000 people

Large Effect: ≥120 fewer or more events per 1000 people

Note: The GDG did not consider treatment success as a separate outcome for this judgment. This is because treatment success is mathematically simply the complement of the three unfavorable treatment outcomes (failure, death and loss-to-follow) and thus does not carry any additional or independent information.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

○ Trivial
○ Small
● Moderate
○ Large
○ Varies
○ Don't know

RESEARCH EVIDENCE

Patients with MDR/RR-TB receiving the DCMZ regimen (n=107 for failure and recurrence and n=120 for amplification of drug resistance) compared to those receiving the currently recommended longer WHO regiments (n=119 for failure and recurrence and n=130 for amplification of drug resistance) experienced:

- higher levels of failure/recurrence: 11.2% vs 2.5%; RD=87 more per 1,000 (95%CI from 21 more to 153 more per 1,000); and
- higher levels of amplified resistance: 6.7% vs 0%; RD=67 more per 1,000 (95%CI from 32 more to 119 more per 1,000).

Implementing DCMZ may lead to worsening in the outcomes of failure and recurrence and amplification (acquisition) of drug resistance but the evidence is overall very uncertain.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with currently recommended longer WHO regimens	Risk difference with a 9-month regimen using delamanid, clofazimine, moxifloxacin, and pyrazinamide (DCMZ)
Failure and Recurrence follow-up: 104 weeks	226 (1 RCT)	⨁◯◯◯ Very low[a,b]	**RR 4.45** (1.29 to 15.34)	Study population	
				25 per 1,000	**87 more per 1,000** (21 more to 153 more)
Amplification (acquisition) of Drug-Resistance follow-up: 104 weeks	250 (1 RCT)	⨁⨁⨁◯ Moderate[a,c]	not estimable	Study population	
				0 per 1,000	**67 more per 1,000** (32 more to 119 more)

a. Standard of care for the treatment of rifampicin-resistant and fluoroquinolone-susceptible tuberculosis was composed according to latest World Health Organization guidelines, as they evolved during the trial. In this group 82% of participants were treated with the longer (18–24 month) all-oral regimen. After Dec 18, 2018 the first change in WHO Guidelines (ending use of injectables) was applied to the trial control regimen. A sensitivity analysis did not show important differences, with overlap in 95% confidence intervals, when excluding the 18% randomized during the period when injectables were prescribed. We therefore did not downgrade for indirectness.

b. Failure and recurrence: The 95% CI for the absolute effect crosses three thresholds, from trivial harm to large harm. We therefore downgraded the certainty by three levels due to extremely serious imprecision.

c. Amplification (acquisition) of drug-resistance: The 95% CI for the absolute effect crosses one threshold, from small harm to moderate harm. We therefore downgraded the certainty by one level due to serious imprecision.

ADDITIONAL CONSIDERATIONS

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 DCMZ may have moderate undesirable effects.

Specifically, the GDG considered that the undesirable effects were moderate for the outcome of failure and recurrence and moderate for amplification of drug resistance.

Decision Thresholds considered by the GDG during the discussion:

For treatment failure or recurrence and amplification (acquisition) of drug resistance

Trivial Effect: ≤30 fewer or more events per 1000 people

Small Effect: 31 to 59 fewer or more events per 1000 people

Moderate Effect: 60 to 119 fewer or more events per 1000 people

Large Effect: ≥120 fewer or more events per 1000 people

Table. Frequency of new drug resistance among randomized endTB study participants (N=754) with at least one paired specimen (N=31) containing the same strain of *M. tuberculosis*, by drug and treatment arm, showing n new resistance/pairs tested (%)

	9DCMZ	Control
Pairs tested	**9**	**3**
Bedaquiline	1 (11.1%)	0 (0.0%)
Clofazimine	1 (11.1%)	0 (0.0%)
Delamanid	5 (55.6%)	0 (0.0%)
Fluoroquinolone[a]	7 (77.8%)	0 (0.0%)
Linezolid	0 (0.0%)	0 (0.0%)
Total new resistance among randomized (%)	**8/120 (6.7%)**	**0/130 (0.0%)**

[a] moxifloxacin or levofloxacin.

Table. Acquired drug resistance# – Randomized population

	9DCMZ	Control
Total in randomized population	120	130
Acquired drug resistance#	8 (6.7%)	0 (0.0%)
95% CI	2.9%;12.7%	0.0%;2.8%
Risk difference %[a]	6.7%	
95% CI[c]	3.2%;11.9%[c]	
Risk ratio[b]	-	
95% CI	-	

[a] Percent of patients with outcome in the experimental arm – percent of patients with outcome in the control arm

[b] Percent of patients with outcome in the experimental arm / percent of patients with in the control arm

[c] Confidence intervals calculated using the Miettinen-Nurminen method (binomial exact method)

To: bedaquiline, clofazimine, delamanid, levofloxacin, linezolid, or moxifloxacin

Certainty of evidence

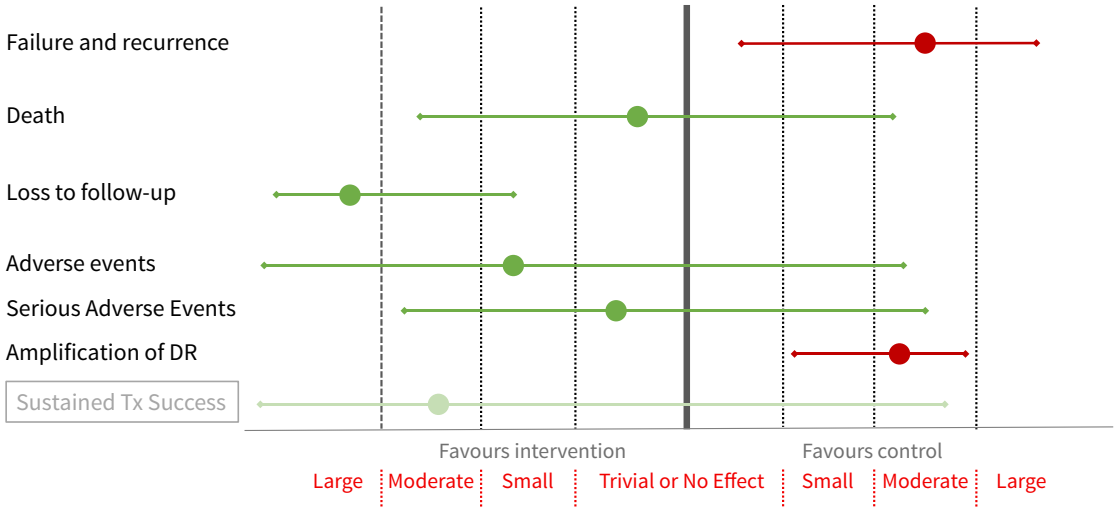
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		The overall certainty of evidence was very low, primarily due to imprecision in the effect estimates.

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 systematically searched for. Higher treatment efficacy, shorter duration of treatment, lower pill burden and less adverse events are usually valued by patients. A recent systematic review of health-related quality of life based on EQ-5D utility scores in patients with tuberculosis (Park et al,2021) reported based on one identified study (Kitikraisak et al, 2012; prospective cohort study with 222 patients from Thailand) that the EQ-5D value for MDR-TB was 0.51, which increased to 0.88 after completion of treatment.	The GDG noted that there would probably be no important uncertainty about how much people value the outcomes, and that patients may prefer a shorter treatment duration because of the outcomes associated with it.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**EndTB 5 – DCMZ**  Note: The positioning of point estimates and CIs is indicative and for illustration purposes only and exact figures are available in the GRADE evidence profiles. As indicated above in the sections on desirable and undesirable effects, decision thresholds vary for some of the outcomes and therefore only the descriptive labels (trivial or no effect, small, moderate, large) are used for the x-axis rather than numerical values themselves.	The GDG judged the benefits of DCMZ to be moderate and the undesirable effects to be moderate compared to 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. 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 that failed treatment. Based on this, the GDG determined that the balance of health effects probably favours the WHO recommended longer regimens.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT

○ Large costs
○ Moderate costs
○ Negligible costs and savings
○ Moderate savings
○ Large savings
● Varies
○ Don't know

RESEARCH EVIDENCE

We considered the following estimated regimen prices (from Stop TB Partnership Global Drug Facility):

	Regimen	Estimated Regimen Price
endTB Trial Regimens	endTB 1 9BLMZ	$297
	endTB 2 9BLLCZ	$455
	endTB 3 9BDLLZ	$2219
	endTB 4 9DLLCZ	$2192
	endTB 5 9DMCZ	$2170
WHO-Recommended Regimens	BPaLM	$443
	BPaL	$415
	Shorter Regimen	$418
	Shorter Regimen (with Lzd)	$396
	Longer Regimen ($18B_6LLC$)	$632

Assumptions for endTB treatment:

- Duration of 39 weeks
- Dosing based on weight > 55–70kg (per protocol)
- Daily dosing for
- Moxifloxacin
- Levofloxacin
- Clofazimine
- Pyrazinamide
- Bedaquiline dosing – 400mg daily x 14 days then 200mg 3x/week for weeks 3–39
- Delamanid dosing – 100mg twice daily x 39 weeks
- Linezolid dosing – 600mg daily x 16 weeks, then 600mg 3x/week for weeks 17–39

Caveats

- Medicine prices are average prices across all suppliers as per GDF market share allocation
- Medicine prices may change with 2024 GDF tenders

We 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.

ADDITIONAL CONSIDERATIONS

Given the drugs included in the DCMZ regimen, in particular delamanid, the cost would vary between moderate and large and may or may not be offset by the health systems costs for the longer regimen. There may also be savings in some settings.

For the drug prices, cost would be large from the NTP perspective.

RR			
	Cost over 9 months		
Country	Patient	Health System	Total
India	$1152	$261	$1413
Philippines	$2322	$702	$3024
South Africa	$1026	$1926	$2952

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 9-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 treatment regimen would be used.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors 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.	Given the moderate to large costs in most settings, as well as the lack of net benefit, health equity would probably be reduced compared to the longer currently recommended WHO regimens.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence searched for.	The GDG considered patients and healthcare providers as key stakeholders. The DCMZ regimen would probably not be acceptable to patients and healthcare workers given less benefit, as well as potentially higher cost.

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 searched for.	Approval by regulators influences the feasibility of implementing the regimen, and alternative regimens may not always be available. Access to some of the medications is hampered by licensing differences.

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	Trivial	Small	**Moderate**	Large		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	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors 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	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors 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
WHO suggests against using the 9-month DCMZ regimen compared with currently recommended longer regimens in patients with FQ susceptible RR-TB. (Conditional recommendation, based on very low certainty in the effects)
Justification
While both desirable and undesirable effects were judged to be moderate, the GDG judged that overall the harms outweigh the benefits. The main concerns being that there may be an increased acquisition of drug resistance as well as treatment failure and recurrence, based on very low certainty in the evidence.
Subgroup considerations
NA
Implementation considerations
NA
Monitoring and evaluation
NA
Research priorities
NA

PICO 8

Question: Should HCV treatment be co-administered with MDR-TB treatment in patients co-infected by MDR/RR-TB and HCV?

Background: We designed an online survey for collection of data about choice of treatment strategies when treating patients with MDR-TB and HCV co-infection and their health outcomes. Data collected from investigators (i.e. cohorts) who treated at least one patient with MDR-TB and HCV treatment co-administration (i.e., intervention arm) and at least one patient with MDR-TB treatment with delay of HCV treatment (i.e., comparator arm) were included in a comparative analysis, in which the risk ratio was calculated to assess treatment effects for the outcomes of interest.

Summary of findings:

MDR-TB and HCV treatment co-administration compared to MDR-TB treatment with delay of HCV treatment for adults with MDR-TB and HCV co-infection

Patient or population: adults with MDR-TB and HCV co-infection

Intervention: MDR-TB and HCV treatment co-administration

Comparison: MDR-TB treatment with delay of HCV treatment

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDR-TB and HCV treatment co-administration	MDR-TB treatment with delay of HCV treatment	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
MDR-TB treatment success[a]												
8	observational studies	very serious[b]	not serious	not serious	serious[c]	none	85/97 (87.6%)	150/230 (65.2%)	**RR 1.25** (1.07 to 1.46)	**163 more per 1,000** (from 46 more to 300 more)	⨁◯◯◯ VERY LOW	CRITICAL
MDR-TB treatment failure												
8	observational studies	very serious[b]	not serious	not serious	not serious	none	1/97 (1.0%)	9/230 (3.9%)[d]	**RR 0.30** (0.12 to 0.74)	**27 fewer per 1,000** (from 34 fewer to 10 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDR-TB and HCV treatment co-administration	MDR-TB treatment with delay of HCV treatment	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Death												
8	observational studies	very serious[b]	not serious	not serious	very serious[e]	none	5/97 (5.2%)	27/230 (11.7%)	**RR 0.98** (0.22 to 4.33)	**2 fewer per 1,000** (from 92 fewer to 391 more)	⨁◯◯◯ VERY LOW	CRITICAL
Loss to follow-up												
8	observational studies	very serious[b]	not serious	not serious	not serious	none	6/97 (6.2%)	41/230 (17.8%)	**RR 0.42** (0.24 to 0.73)	**103 fewer per 1,000** (from 135 fewer to 48 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events												
4	observational studies	very serious[b]	not serious	not serious	very serious[f]	none	50/81 (61.7%)	120/151 (79.5%)	**RR 0.72** (0.49 to 1.07)	**223 fewer per 1,000** (from 405 fewer to 56 more)	⨁◯◯◯ VERY LOW	CRITICAL
Hepatic adverse events (as a subset of adverse events)												
4	observational studies	very serious[b]	not serious	not serious	very serious[f]	none	24/81 (29.6%)	47/151 (31.1%)	**RR 1.19** (0.23 to 6.16)	**59 more per 1,000** (from 240 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
HCV treatment success												
1	observational studies	very serious[b]	not serious	not serious	very serious[f]	none	3/4 (75.0%)	3/3 (100.0%)	**RR 0.78** (0.48 to 1.27)	**220 fewer per 1,000** (from 520 fewer to 270 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDR-TB and HCV treatment co-administration	MDR-TB treatment with delay of HCV treatment	Relative (95% CI)	Absolute (95% CI)		
Amplification of drug resistance – not reported[g]												
-	-	-	-	-	-	-	-	-	-	-	-	
Drug-drug interactions – not reportedg[g]												
-	-	-	-	-	-	-	-	-	-	-	-	
MDR-TB treatment success (single cohorts)[h]												
24	observational studies	very serious[i]	not serious	not serious	not serious	none	In 12 cohorts of patients (n=135) receiving co-administration of MDR-TB and HCV treatments, the pooled estimate for MDR-TB treatment success was 88.1% (95% CI: 81.4% to 92.4%). In 12 cohorts of patients (n=439) receiving delayed HCV treatment the estimate was 70.8% (95% CI: 57.9% to 79.7%). Among the 8 cohorts included in the comparative analysis above, the pooled proportions were 87.6% (95% CI: 79.3% to 92.6%) and 65.2% (95% CI: 58.7% to 70.8%) in the co-administration and delayed treatment groups, respectively.				⨁◯◯◯ VERY LOW	CRITICAL
MDR-TB treatment failure (single cohorts)												
24	observational studies	very serious[i]	not serious	not serious	not serious	none	In 12 cohorts of patients (n=135) receiving co-administration of MDR-TB and HCV treatments, the pooled estimate for MDR-TB treatment failure was 3.0% (95% CI: 1.1% to 7.2%). In 12 cohorts of patients (n=439) receiving delayed HCV treatment the estimate was 3.7% (95% CI: 1.6% to 10.8%). Among the 8 cohorts included in the comparative analysis above, the pooled proportions were 1.0% (95% CI: 0.1% to 6.2%) and 4.5% (95% CI: 1.4% to 15.6%) in the co-administration and delayed treatment groups, respectively.				⨁◯◯◯ VERY LOW	CRITICAL
Death (single cohorts)												
24	observational studies	very serious[i]	not serious	not serious	serious[j]	none	In 12 cohorts of patients (n=135) receiving co-administration of MDR-TB and HCV treatments, the pooled estimate for death was 1.9% (95% CI: 0.1% to 28.6%). In 12 cohorts of patients (n=439) receiving delayed HCV treatment the estimate was 9.2% (95% CI: 4.4% to 18.0%). Among the 8 cohorts included in the comparative analysis above, the pooled proportions were 9.7% (95% CI: 1.0% to 45.1%) and 12.5% (95% CI: 5.1% to 27.8%) in the co-administration and delayed treatment groups, respectively.				⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDR-TB and HCV treatment co-administration	MDR-TB treatment with delay of HCV treatment	Relative (95% CI)	Absolute (95% CI)		
Loss to follow-up (single cohorts)												
24	observational studies	very serious[i]	not serious	not serious	serious[j]	none	In 12 cohorts of patients (n=135) receiving co-administration of MDR-TB and HCV treatments, the pooled estimate for loss to follow-up was 3.4% (95% CI: 0.5% to 19.0%). In 12 cohorts of patients (n=439) receiving delayed HCV treatment the estimate was 10.3% (95% CI: 5.2% to 19.2%). Among the 8 cohorts included in the comparative analysis above, the pooled proportions were 6.2% (95% CI: 2.8% to 12.5%) and 16.6% (95% CI: 10.1% to 25.3%) in the co-administration and delayed treatment groups, respectively.				⨁◯◯◯ VERY LOW	CRITICAL
Adverse events (single cohorts)												
18	observational studies	very serious[i]	not serious	not serious	serious[j]	none	In 8 cohorts of patients (n=123) receiving co-administration of MDR-TB and HCV treatments, the pooled estimate for adverse events was 3.6% (95% CI: 0.0% to 80.6%). In 10 cohorts of patients (n=428) receiving delayed HCV treatment the estimate was 48.5% (95% CI: 17.0% to 81.2%). Among the 4 cohorts included in the comparative analysis above, the pooled proportions were 57.4% (95% CI: 12.5% to 87.4%) and 65.8% (95% CI: 33.4% to 89.1%) in the co-administration and delayed treatment groups, respectively.				⨁◯◯◯ VERY LOW	CRITICAL
Hepatic adverse events (as a subset of adverse events) (single cohorts)												
18	observational studies	very serious[i]	not serious	not serious	serious[j]	none	In 8 cohorts of patients (n=123) receiving co-administration of MDR-TB and HCV treatments, the pooled estimate for hepatic adverse events, as a subset in those experiencing adverse events, was 4.5% (95% CI: 0.2% to 50.5%). In 10 cohorts of patients (n=428) receiving delayed HCV treatment the estimate was 23.2% (95% CI: 7.7% to 52.3%). Among the 4 cohorts included in the comparative analysis above, the pooled proportions were 34.1% (95% CI: 13.2% to 60.5%) and 34.7% (95% CI: 19.2% to 52.4%) in the co-administration and delayed treatment groups, respectively.				⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients	Effect				
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDR-TB and HCV treatment co-administration	MDR-TB treatment with delay of HCV treatment	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
HCV treatment success (single cohorts)												
11	observational studies	very serious[i]	not serious	not serious	serious[j]	none	In 9 cohorts of patients (n=124) receiving co-administration of MDR-TB and HCV treatments, the pooled estimate for MDR-TB treatment success was 95.1% (95% CI: 84.3% to 98.6%). In 2 cohorts of patients (n=4) receiving delayed HCV treatment the estimate was 100% (95% CI: 0.0% to 100%). Among the 1 cohort included in the comparative analysis above, the pooled proportions were 75.0% (95% CI: 19.4% to 99.4%) and 100% (95% CI: 29.2% to 100%) in the co-administration and delayed treatment groups, respectively.				⨁◯◯◯ VERY LOW	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Data collected from investigators (i.e. cohorts) who treated at least one patient with MDR-TB and HCV treatment co-administration (i.e., intervention arm) and at least one patient with MDR-TB treatment with delay of HCV treatment (i.e., comparator arm) were included in the comparative analysis.

b. The outcome data is based on records or recall by experts from an expert-evidence survey, for cohorts of patients receiving either co-administration of MDR-TB and HCV treatments, or delayed HCV treatment in their healthcare setting. The comparative analysis to calculate relative effects based on these cohorts does not control for any potential confounding. We downgraded the certainty of evidence due to very serious risk of bias.

c. The 95% CI includes both small but important benefit as well as large benefit.

d. Additionally, 1/97 patients receiving co-administration of treatments and 3/230 patients receiving delayed HCV treatment experienced TB recurrence.

e. The 95% CI includes both a large benefit and large harm. We therefore downgraded the certainty of evidence due to imprecision.

f. The 95% CI includes both large benefit and harm. We therefore downgraded the certainty of evidence due to imprecision.

g. There was insufficient data provided by the experts to allow a calculation of relative effects, and information about the time frame of amplification of drug resistance and occurrence of drug-drug interactions was not available.

h. The pooled proportions of the 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. Inferences should not be made by comparing the pooled proportions in the two different groups as they are a mix of comparative and non-comparative scenarios derived from non-randomized data, and are subject to bias and serious confounding. This analysis was performed for descriptive purposes.

i. The pooled proportions in the two groups are derived from the single cohorts of patients receiving co-administration of MDR-TB and HCV treatments or MDR-TB treatment only with delayed HCV treatment.

j. The 95% CIs around the pooled proportions are wide.

PICO 8

Question	
Should MDR-TB and HCV treatment co-administration vs. MDR-TB treatment with delay of HCV treatment be used for adults with MDR-TB and HCV co-infection?	
POPULATION:	adults with MDR-TB and HCV co-infection
INTERVENTION:	MDR-TB and HCV treatment co-administration
COMPARISON:	MDR-TB treatment with delay of HCV treatment
MAIN OUTCOMES:	MDR-TB treatment success; MDR-TB treatment failure; Death; Loss to follow-up; Adverse events; Hepatic adverse events (as a subset of adverse events); HCV treatment success; Amplification of drug resistance; Drug-drug interactions; MDR-TB treatment success (single cohorts); MDR-TB treatment failure (single cohorts); Death (single cohorts); Loss to follow-up (single cohorts); Adverse events (single cohorts); Hepatic adverse events (as a subset of adverse events) (single cohorts); HCV treatment success (single cohorts);
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation – population perspective
BACKGROUND:	This question addresses the efficacy and safety of co-administration of MDR-TB and HCV treatments as compared to MDR-TB treatment only with delay of HCV treatment in patients co-infected with MDR-TB and Hepatitis C.
CONFLICT OF INTERESTS:	None

Assessment

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	A systematic review (Olaru ID, Denkinger CM, *et al.*, 2022) 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 according to WHO region was highest in the European Region at 17.5% (95%CI 12.2–23.5) followed by South-East Asia at 7.9% (95%CI 3.5–13.9), the Americas at 7.5% (95%CI 5.2–10.1), Western Pacific at 6.2% (95%CI 3.6–9.5), Eastern Mediterranean at 5.7% (95%CI 3.1–8.9) and Africa at 3.5% (95%CI 0–16.1)."	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

- ○ Trivial
- ○ Small
- ● Moderate
- ○ Large
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with MDR-TB treatment with delay of HCV treatment	Risk difference with MDR-TB and HCV treatment co-administration
MDR-TB treatment success[a]	327 (8 observational studies)	⨁◯◯◯ Very low[b,c]	**RR 1.25** (1.07 to 1.46)	Study population 652 per 1,000	**163 more per 1,000** (46 more to 300 more)
MDR-TB treatment failure	327 (8 observational studies)[d]	⨁◯◯◯ Very low[c,e]	**RR 0.30** (0.12 to 0.74)	Study population 39 per 1,000[d]	**27 fewer per 1,000** (34 fewer to 10 fewer)
Death	327 (8 observational studies)	⨁◯◯◯ Very low[c,f]	**RR 0.98** (0.22 to 4.33)	Study population 117 per 1,000	**2 fewer per 1,000** (92 fewer to 391 more)
Loss to follow-up	327 (8 observational studies)	⨁◯◯◯ Very low[c]	**RR 0.42** (0.24 to 0.73)	Study population 178 per 1,000	**103 fewer per 1,000** (135 fewer to 48 fewer)
Adverse events	232 (4 observational studies)	⨁◯◯◯ Very low[c,g]	**RR 0.72** (0.49 to 1.07)	Study population 795 per 1,000	**223 fewer per 1,000** (405 fewer to 56 more)
Hepatic adverse events (as a subset of adverse events)	232 (4 observational studies)	⨁◯◯◯ Very low[c,g]	**RR 1.19** (0.23 to 6.16)	Study population 311 per 1,000	**59 more per 1,000** (240 fewer to 1,000 more)
HCV treatment success	7 (1 observational study)	⨁◯◯◯ Very low[c,g]	**RR 0.78** (0.48 to 1.27)	Study population 1,000 per 1,000	**220 fewer per 1,000** (520 fewer to 270 more)
Amplification of drug resistance - not reported	-	-	-	-	-
Drug-drug interactions - not reported	-	-	-	-	-

ADDITIONAL CONSIDERATIONS

The guideline development group noted that there is also possibly additional adherence support while being treated for MDR TB, to also treat for HCV.

a. Data collected from expert-evidence survey respondents who treated at least one patient with MDR-TB and HCV treatment co-administration (i.e., intervention arm) and at least one patient with MDR-TB treatment with delay of HCV treatment (i.e., comparator arm) were included in the comparative analysis.

b. The 95% CI includes both small but important benefit as well as large benefit. We downgraded the certainty of evidence due to very serious imprecision.

c. The health outcome data is based on records or recall by experts from the expert-evidence survey, for cohorts of patients receiving either co-administration of MDR-TB and HCV treatments, or delayed HCV treatment in their healthcare setting. The comparative analysis to calculate relative effects based on these cohorts does not control for any potential confounding. We downgraded the certainty of evidence due to very serious risk of bias.

d. Additionally, 1/97 patients receiving co-administration of treatments and 3/230 patients receiving delayed HCV treatment experienced TB recurrence.

e. Based on very few events and wide 95% confidence interval including important benefit and trivial benefit. We therefore downgraded the certainty of evidence due to serious imprecision.

f. The 95% CI includes both a large benefit and large harm. We therefore downgraded the certainty of evidence due to very serious imprecision.

g. The 95% CI includes both large benefit and harm. We therefore downgraded the certainty of evidence due to very serious imprecision.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

- ○ Large
- ○ Moderate
- ● Small
- ○ Trivial
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with MDR-TB treatment with delay of HCV treatment	Risk difference with MDR-TB and HCV treatment co-administration
MDR-TB treatment success[a]	327 (8 observational studies)	⨁◯◯◯ Very low[b,c]	**RR 1.25** (1.07 to 1.46)	Study population	
				652 per 1,000	**163 more per 1,000** (46 more to 300 more)
MDR-TB treatment failure	327 (8 observational studies)[d]	⨁◯◯◯ Very low[c,e]	**RR 0.30** (0.12 to 0.74)	Study population	
				39 per 1,000[d]	**27 fewer per 1,000** (34 fewer to 10 fewer)
Death	327 (8 observational studies)	⨁◯◯◯ Very low[c,f]	**RR 0.98** (0.22 to 4.33)	Study population	
				117 per 1,000	**2 fewer per 1,000** (92 fewer to 391 more)
Loss to follow-up	327 (8 observational studies)	⨁◯◯◯ Very low[c]	**RR 0.42** (0.24 to 0.73)	Study population	
				178 per 1,000	**103 fewer per 1,000** (135 fewer to 48 fewer)
Adverse events	232 (4 observational studies)	⨁◯◯◯ Very low[c,g]	**RR 0.72** (0.49 to 1.07)	Study population	
				795 per 1,000	**223 fewer per 1,000** (405 fewer to 56 more)
Hepatic adverse events (as a subset of adverse events)	232 (4 observational studies)	⨁◯◯◯ Very low[c,g]	**RR 1.19** (0.23 to 6.16)	Study population	
				311 per 1,000	**59 more per 1,000** (240 fewer to 1,000 more)
HCV treatment success	7 (1 observational study)	⨁◯◯◯ Very low[c,g]	**RR 0.78** (0.48 to 1.27)	Study population	
				1,000 per 1,000	**220 fewer per 1,000** (520 fewer to 270 more)
Amplification of drug resistance - not reported	-	-	-	-	-
Drug-drug interactions - not reported	-	-	-	-	-

ADDITIONAL CONSIDERATIONS

a. Data collected from expert-evidence survey respondents who treated at least one patient with MDR-TB and HCV treatment co-administration (i.e., intervention arm) and at least one patient with MDR-TB treatment with delay of HCV treatment (i.e., comparator arm) were included in the comparative analysis.

b. The 95% CI includes both small but important benefit as well as large benefit. We downgraded the certainty of evidence due to very serious imprecision.

c. The health outcome data is based on records or recall by experts from the expert-evidence survey, for cohorts of patients receiving either co-administration of MDR-TB and HCV treatments, or delayed HCV treatment in their healthcare setting. The comparative analysis to calculate relative effects based on these cohorts does not control for any potential confounding. We downgraded the certainty of evidence due to very serious risk of bias.

d. Additionally, 1/97 patients receiving co-administration of treatments and 3/230 patients receiving delayed HCV treatment experienced TB recurrence.

e. Based on very few events and wide 95% confidence interval including important benefit and trivial benefit. We therefore downgraded the certainty of evidence due to serious imprecision.

f. The 95% CI includes both a large benefit and large harm. We therefore downgraded the certainty of evidence due to very serious imprecision.

g. The 95% CI includes both large benefit and harm. We therefore downgraded the certainty of evidence due to very serious imprecision.

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 is very low, with the calculated estimates of effects based on outcome data from recall or records obtained from the expert evidence survey, with 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.	

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	Evidence not searched for.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The guideline development group discussed the substantial reduction in loss to follow-up against possible impact on HCV treatment success. The group highlighted the knowledge gap about HCV outcomes.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Results from Expert Evidence Survey:** Of 18 respondents to the expert evidence survey, 39% (n=7) indicated that co-administration of MDR-TB and HCV treatments incurrent additional costs, 11% (n=2) noted that there were no cost implications, and 28% (n=5) did not know about specific cost implications. Experts noted that MDR-TB treatment is provided at no cost to patients, whereas HCV treatment is often not covered. It was noted that overall costs do not change if HCV treatment is given concomitantly or sequentially. Further, one expert noted: "My main concern is the type of HCV treatment and the price of oral antivirals medications. We tend to avoid IFN-r based HCV treatment in active TB patients, thus delaying HCV treatment. For oral anti-HCV medications, if it is not covered by national health insurance, we will have to go for generic drugs to reduce financial burden on patients."	

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		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	**Results from Expert Evidence Survey:** Of 18 respondents to the expert evidence survey: • 5.5% (n=1) noted that cost-effectiveness favours MDR-TB treatment only with delay of HCV treatment • 11% (n=2) noted that cost-effectiveness probably favours MDR-TB treatment only with delay of HCV treatment • 22% (n=4) noted that cost-effectiveness probably favours co-administration of HCV and MDR-TB treatments • 50% (n=9) noted that cost-effectiveness favours co-administration of HCV and MDR-TB treatments • 11% (n=2) indicated that they do not know about the cost-effectiveness	

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	**Results from Expert Evidence Survey:** Of 18 respondents to the expert evidence survey: • 5.5% (n=1) noted that health equity will probably be reduced with co-administration of HCV and MDR-TB treatments • 5.5% (n=1) noted that health equity will probably not be impacted with co-administration of HCV and MDR-TB treatments • 16% (n=1) noted that health equity will probably be increased with co-administration of HCV and MDR-TB treatments • 44% (n=8) noted that health equity will be increased with co-administration of HCV and MDR-TB treatments	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**Results from Expert Evidence Survey:** Of 18 respondents to the expert evidence survey, 50% (n=9) indicated that co-administration of HCV and MDR-TB treatments would be acceptable to key stakeholders, 33% (n=6) indicated that it would probably be acceptable, and 16% (n=3) indicated that they do not know about the acceptability. Further, one expert noted, "Due to difficulties in the access to HCV treatment, only selected MDR-TB patients receive concomitant HCV treatment. The selection is based on concerns of MDR-TB-related hepatotoxicity, more than on subgroup considerations."	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**Results from Expert Evidence Survey:** Of 18 respondents to the expert evidence survey: • 11% (n=2) noted co-administration of HCV and MDR-TB treatments would not be feasible • 5.5% (n=1) noted co-administration of HCV and MDR-TB treatments would probably not be feasible • 27% (n=5) noted co-administration of HCV and MDR-TB treatments would probably be feasible • 50% (n=9) noted co-administration of HCV and MDR-TB treatments would be feasible • 5.5% (n=1) indicated that they do not know about the feasibility.	

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	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors 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	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors 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 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. In patients with MDR-TB and HCV co-infection, the WHO suggests the co-administration of HCV and MDR-TB treatment **over** delaying HCV treatment until after MDR treatment is completed (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 drug-drug interactions (DDI) and other co-morbidities.
Justification
The guideline development group judged that the balance of effects probably favours co-administration of MDR-TB and HCV treatments for MDR/RR-TB patients co-infected 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 guideline development group viewed that there is probably no important variability or uncertainty in how MDR/RR-TB patients co-infected 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 guideline development group 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 guideline development group issued the conditional recommendation suggesting co-administration of both MDR-TB and HCV treatments, over the delay of HCV treatment until after treatment of MDR/RR-TB is completed.
Subgroup considerations
Despite acknowledging the data limitations and very low certainty of the evidence, the guideline development group believed 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, PLHIV, younger children, and patients with liver cirrhosis) necessitates caution in extrapolating the findings to all patients. The guideline development group discussed whether the specific findings can be applied to individuals living with HIV, with reservations stemming from the absence of specific data on subgroups like older individuals, people with comorbidities, and other factors that we were unable to obtain through the expert evidence survey. The guideline development group underscored the lack of comprehensive data for these subgroups and emphasized the necessity of approaching such extrapolations with caution.
Implementation considerations
The guideline development group noted that clinicians should initiate co-administration of MDR-TB and HCV treatments in line with knowledge and consideration about drug-drug interactions and patients' co-morbidities. 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 in the decision-making process with patients. Finally, when considering implementation of the recommendation, it was highlighted that unavailability of HCV treatment should not delay MDR treatment.

Monitoring and evaluation
Patients receiving co-administration of HCV and MDR-TB treatments require vigilant monitoring throughout the treatment using schedules of relevant clinical and laboratory testing. This includes monitoring for hepatotoxicity. The guideline development group acknowledged the safety implications of shorter all-oral MDR-TB regimens, particularly the increased risk of hepatotoxicity associated with the co-administration of bedaquiline-containing shorter regimens. However, as bedaquiline remains the key component of all MDR-TB regimens, its exclusion significantly reduces the benefits for patients. The concomitant use of direct acting antivirals (DAA) with TB medicines used for MDR-TB treatment is generally well tolerated. Data on interactions between declatasvir (DCV), ledipasvir (LDV), and sofosbuvir (SOF) and second-line antituberculosis drugs are very limited. Theoretically, ethionamide/prothionamide and clofazimine can interact with declatasvir (DCV) because both are CYP3A4 inhibitors in vitro. However, the clinical relevance is unknown.
Research priorities
The guideline development group outlined several research priorities: • Conducting high-quality observational studies. • 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 intravenous drug users (IDUs), children, pregnant women, and people living with HIV (PLHIV). • Collecting comprehensive drug-drug interaction (DDI) data to better understand the potential interactions between HCV medicines and bedaquiline; a crucial component of the MDR-TB treatment regimen. • 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. • Furthermore, there is a need to identify barriers causing delays in initiating HCV treatment.

PICO 2.1–2.3 (Summary EtD with full notes on Conclusions)

Question	
Should the 9-month regimens BLMZ, BLLfxCZ, and BDLLfxZ vs. currently recommended longer WHO regimens be used for patients with pulmonary RR-TB (without fluoroquinolone resistance)?	
POPULATION:	patients with pulmonary RR-TB (without fluoroquinolone resistance)
INTERVENTION:	the 9-month regimens BLMZ, BLLfxCZ, and BDLLfxZ
COMPARISON:	currently recommended longer WHO regimens
MAIN OUTCOMES:	Sustained Treatment Success; Failure and Recurrence; Death; Lost to Follow-up; Adverse Events; Amplification (acquisition) of Drug-Resistance;
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	This evidence-to-decision framework addresses the effectiveness and safety of a 9-month regimen using bedaquiline, linezolid, fluoroquinolone (moxifloxacin), and pyrazinamide (BLMZ), the 9-month regimen using bedaquiline, clofazimine, linezolid, fluoroquinolone (levofloxacin), and pyrazinamide (BLLfxCZ), and the 9-month regimen using bedaquiline, delamanid, linezolid, fluoroquinolone (levofloxacin), and pyrazinamide (BDLLfxZ), versus the currently recommended longer regimens.
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: • Fernanda Dockhorn Costa Johansen, Muhwa Chakaya, Gopalan Narendran, Daniela Cirillo, Charles Daley, Gerry Davies, Elmira Gurbanova, Anneke Hesseling, Christoph Lange, Ashna Ashesh, Kim Cuong Nguyen, Andrew Vernon, Mahshid Nasehi, Graeme Meintjes, Erlina Burhan, Raymond Byaruhanga, Wenhong Zhang The following were GDG members recused from decision-making for this recommendation: • None

Assessment

Problem		
Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know		

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know		

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know		

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		

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		

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		

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		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies		

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		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know		

Feasibility		
Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know		

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	Trivial	Small	Moderate	Large		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	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors 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	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors 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
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)* **Remarks** 1. The recommended modified 9-month all-oral regimens comprise bedaquiline, linezolid and pyrazinamide in different combinations with levofloxacin/moxifloxacin, clofazimine and delamanid. 2. This recommendation applies to the following: a. People with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. b. People with diagnosed pulmonary TB, including children, adolescents, PLHIV, and pregnant and breastfeeding women. c. People with extensive TB disease and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular TB or disseminated forms of TB with multiorgan involvement. d. 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. e. 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).

Related recommendation(s)

1. Should a 9-month regimen using bedaquiline, linezolid, moxifloxacin, and pyrazinamide (BLMZ) vs. currently recommended longer WHO regimens be used in patients with pulmonary RR-TB (without fluoroquinolone resistance)?

WHO suggests using BLMZ over currently recommended longer (>18 months) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded.

(Conditional recommendation, very low certainty of evidence)

Remarks

1. The recommended modified 9-month all-oral regimens comprise bedaquiline, linezolid and pyrazinamide in different combinations with levofloxacin/moxifloxacin, clofazimine and delamanid.

2. This recommendation applies to the following:

   a. People with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded.

   b. People with diagnosed pulmonary TB, including children, adolescents, PLHIV, and pregnant and breastfeeding women.

   c. People with extensive TB disease and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular TB or disseminated forms of TB with multiorgan involvement.

   d. 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.

   e. 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).

2. Should a 9-month regimen using bedaquiline, clofazimine, linezolid, levofloxacin, and pyrazinamide (BLLfxCZ) vs. currently recommended longer WHO regimens be used in patients with pulmonary RR-TB (without fluoroquinolone resistance)?

WHO suggests using the BLLfxCZ over currently recommended longer (>18 months) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded.

(Conditional recommendation, very low certainty of evidence)

Remarks

1. The recommended modified 9-month all-oral regimens comprise bedaquiline, linezolid and pyrazinamide in different combinations with levofloxacin/moxifloxacin, clofazimine and delamanid.

2. This recommendation applies to the following:

   a. People with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded.

   b. People with diagnosed pulmonary TB, including children, adolescents, PLHIV, and pregnant and breastfeeding women.

   c. People with extensive TB disease and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular TB or disseminated forms of TB with multiorgan involvement.

   d. 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.

   e. 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).

3. Should a 9-month regimen using bedaquiline, delamanid, linezolid, levofloxacin, and pyrazinamide (BDLLfxZ) vs. currently recommended longer WHO regimens be used in patients with pulmonary RR-TB (without fluoroquinolone resistance)?

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

(Conditional recommendation, very low certainty of evidence)

Remarks

1. The recommended modified 9-month all-oral regimens comprise bedaquiline, linezolid and pyrazinamide in different combinations with levofloxacin/moxifloxacin, clofazimine and delamanid.

2. This recommendation applies to the following:

   a. People with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded.

   b. People with diagnosed pulmonary TB, including children, adolescents, PLHIV, and pregnant and breastfeeding women.

   c. People with extensive TB disease and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular TB or disseminated forms of TB with multiorgan involvement.

   d. 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.

   e. 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).

Justification

The GDG issued the conditional recommendations suggesting use of these 9-month regimens (BLMZ, BLLfxCZ, BDLLfxZ) over currently recommended longer regimens based on very low certainty of evidence (due to imprecision in the effect estimates). The balance of effects probably favoured the intervention for each of the 9-month regimens (moderate benefit and trivial harms for BLMZ; moderate benefit and small harms for BLLfxCZ; small benefit and trivial harms for BDLLfxZ). The GDG judged that there would be cost savings with the BLMZ and BLLfxCZ regimens, and that resources required for the BDLLfxZ would vary between settings due to the inclusion of higher-cost Delamanid in the regimen. The GDG also highlighted the importance of a lower pill burden with the 9-month regimens and judged that there would probably be no uncertainty about patients' values, in particular with respect to the outcomes associated with a shorter duration regimen.

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 PLHIV regardless of their immunologic 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 *(65, 66)*. Close monitoring and systematic collection of data from pregnant, breastfeeding and post-partum 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).

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 PLHIV (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 2.10. All of the modified 9-month regimens have bedaquiline, linezolid, pyrazinamide and a fluoroquinolone as core, with one or two other additional drugs.

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.

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 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.

Monitoring and evaluation

Patients who receive 9-month regimens need to be monitored during treatment using relevant clinical and laboratory testing schedules that have been successfully applied in trials and previous studies of shorter regimens under field conditions and in the programmatic setting in South Africa.

The patient's bacteriological status should be available before treatment initiation, with confirmation of MDR/RR-TB and FQ susceptibility. The GDG emphasized the need to strengthen and increase access to FQ DST and undertake surveillance for emerging drug resistance, including for bedaquiline and for all second-line medicines, in the shorter regimen for which reliable DST is available.

The CXR at the baseline and 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). If feasible, it is also important to follow up patients 12 months after the completion of treatment for possible relapse, including with sputum culture and smear.

Based on guidance in current literature and collective experience, the panel advised the following with regard to monitoring and evaluation of the safety and effectiveness of the 9-month regimens:

- the implementation of these regimens requires the use of routine DST to FQ, not only for patient selection but also to monitor the acquisition of resistance (collection of strains for sequencing should be considered);
- aDSM systems must be functional to conduct rigorous active monitoring of AEs and to detect, manage and report suspected or confirmed drug toxicities in a timely manner; and
- access to reliable DST for bedaquiline and linezolid is essential to investigate reasons for lack of bacteriological and clinical improvement after 4 months of treatment – in an ideal situation, the DST for all second-line medicines used in 9-month regimens would be available.

It is good practice to assess patients for symptoms and signs of liver disease (e.g. fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness and hepatomegaly); and to conduct laboratory tests such as ALT, AST, alkaline phosphatase and bilirubin, as well as anaemia (e.g. fatigue or increasing dyspnea), a complete blood count, and peripheral or optic neuropathy. More frequent monitoring of indicators of hepatic toxicity is strongly advised when using all 9-month regimens. When QTc prolongation is identified, it is suggested to check and correct if the serum potassium, calcium and magnesium is abnormal. Treating clinicians are also advised to obtain an ECG before initiation of treatment. . A suggested monitoring schedule is provided in the WHO consolidated operational handbook on tuberculosis. Module 4: Treatment and care. *(7)*.

Research priorities
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 those with diabetes; • research on the acceptability of the regimens; and • for the 9BDLLFxZ regimen, research about patient support and adherence to delamanid.

PICO 2.4–2.5 (Summary EtD with full notes on Conclusions)

Question	
Should the 9-month regimens DCLLfxZ and DCMZ vs. currently recommended longer WHO regimens be used for patients with pulmonary RR-TB (without fluoroquinolone resistance)?	
POPULATION:	patients with pulmonary RR-TB (without fluoroquinolone resistance)
INTERVENTION:	the 9-month regimens DCLLfxZ and DCMZ
COMPARISON:	currently recommended longer WHO regimens
MAIN OUTCOMES:	
SETTING:	Outpatient
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

Assessment

Problem		
Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know		

Desirable Effects		
How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know		

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know		

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		

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		

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		

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		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies		

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		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know		

Feasibility		
Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know		

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	Trivial	Small	Moderate	Large		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	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors 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	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors 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
WHO suggests against using 9-month DCLLfxZ or DCMZ regimens compared with currently recommended longer (>18 months) regimens in patients with fluoroquinolone-susceptible MDR/RR-TB. *(Conditional recommendation, very low certainty of evidence)*
Related recommendation(s)
1. Should a 9-month regimen using delamanid, clofazimine, linezolid, levofloxacin, and pyrazinamide (DCLLfxZ) vs. currently recommended longer WHO regimens be used in patients with pulmonary RR-TB (without fluoroquinolone resistance)? WHO suggests against using the 9-month DCLLfxZ regimen compared with currently recommended longer regimens in patients with FQ susceptible RR-TB. (Conditional recommendation, based on very low certainty in the effects) **2. Should a 9-month regimen using delamanid, clofazimine, moxifloxacin, and pyrazinamide (DCMZ) vs. currently recommended longer WHO regimens be used in patients with pulmonary RR-TB (without fluoroquinolone resistance)?** WHO suggests against using the 9-month DCMZ regimen compared with currently recommended longer regimens in patients with FQ susceptible RR-TB. (Conditional recommendation, based on very low certainty in the effects)
Justification
The GDG issued the conditional recommendations suggesting against the use of these 9-month regimens (DCLLfxZ and DCMZ) over currently recommended longer regimens based on very low certainty of evidence (due to imprecision in the effect estimates). The balance of effects did not favour these 9-month regimens (small benefit and moderate harms for DCLLfxZ; moderate benefit and moderate harms for DCMZ). The main concerns being that there may be an increased acquisition of drug resistance as well as treatment failure and recurrence, based on very low certainty in the evidence. The high cost of delamanid was an additional consideration for this recommendation against use of the 9-month DCLLfxZ and DCMZ regimens.
Subgroup considerations
NA
Implementation considerations
NA
Monitoring and evaluation
NA
Research priorities
NA

Comparison between BLMZ, BLLfxCZ and BDLLfxZ to support prioritization

Question 1: 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)?

Question 2: 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)?

Question 3: 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)?

Question 4: 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)?

Question 5: 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)?

Summary of judgements

	a 9-month regimen using bedaquiline, linezolid, moxifloxacin, and pyrazinamide (9BLMZ)/ currently recommended longer WHO regimens	**a 9-month regimen using bedaquiline, clofazimine, linezolid, levofloxacin, and pyrazinamide (9BLLfxCZ)/ currently recommended longer WHO regimens**	**a 9-month regimen using bedaquiline, delamanid, linezolid, levofloxacin, and pyrazinamide (9BDLLfxZ)/ currently recommended longer WHO regimens**	**a 9-month regimen using delamanid, clofazimine, linezolid, levofloxacin, and pyrazinamide (9DCLLfxZ)/ currently recommended longer WHO regimens**	**a 9-month regimen using delamanid, clofazimine, moxifloxacin, and pyrazinamide (9DCMZ)/ currently recommended longer WHO regimens**	**Importance for decision**
Balance of effects	Probably favors the intervention	Probably favors the intervention	Probably favors the intervention	Probably favors the comparison	Probably favors the comparison	**high**
Certainty of evidence	Very low	Very low	Very low	Very low	Very low	
Resources required	Large savings	Large savings	Varies	Varies	Varies	**high**
Cost effectiveness	Probably favors the intervention	Probably favors the intervention	No included studies	Probably favors the comparison	No included studies	**high**
Equity	Probably increased	Probably increased	Probably increased	Probably reduced	Probably reduced	**high**
Acceptability	Probably yes	Probably yes	Probably yes	No	Probably no	**high**
Feasibility	Yes	Yes	Probably yes	Probably yes	Probably yes	**high**

Review

	a 9-month regimen using bedaquiline, linezolid, moxifloxacin, and pyrazinamide (9BLMZ)	a 9-month regimen using bedaquiline, clofazimine, linezolid, levofloxacin, and pyrazinamide (9BLLfxCZ)	a 9-month regimen using bedaquiline, delamanid, linezolid, levofloxacin, and pyrazinamide (9BDLLfxZ)	Importance for decision	Comment
Balance of effects	★★★★	★★★	★★★	**high**	
Resources required	★★★★★	★★★★★	★★	**high**	
Cost effectiveness	★★★★	★★★	★★	**high**	
Equity	★★★★	★★★★	★★★	**high**	
Acceptability	★★★★	★★★	★★	**high**	
Feasibility	★★★★★	★★★★★	★★★★	**high**	

Recommendation

Strength of recommendation Conditional

WHO suggests using the 9-month all-oral regimens (BLMZ, BLLfxCZ and BDLLfxZ) over currently recommended longer (18-month) 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, based on very low certainty in the effects)

Remarks:

1. These 9-month all-oral regimens consist of bedaquiline in combination with levofloxacin/moxifloxacin, linezolid, clofazimine, delamanid, and pyrazinamide.

2. This recommendation applies to:

   a. People with MDR/RR-TB and without resistance to fluoroquinolones;

   b. People with diagnosed pulmonary TB, including children, adolescents, PLHIV, pregnant and breastfeeding women;

   c. People with extensive TB disease and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular, and disseminated TB with multi-organ involvement;

   d. Patients with less than one month of previous exposure to bedaquiline, fluoroquinolones, linezolid, and clofazimine; when exposure is greater than one month, these patients may still receive this regimen if resistance to the specific medicines with such exposure has been ruled out;

   e. 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).

Justification	Amongst 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 (see the 'Review' section above). Following this, the panel was asked to deliberate about the ranking of the three regimens considering their prior 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, with moderate desirable effects and trivial to no undesirable effects, compared to both BLLfxCZ and BDLLfxZ • It 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 to BDLLfxZ was deemed to have a similar but slightly preferable balance of health effects, given the overall desirable effects were judged as moderate for BLLfxCZ and small for BDLLfxZ • BLLfxCZ is also significantly lower cost and has a lower daily pill burden than BDLLfxZ • The much greater cost of BDLLfxZ was judged to have likely to have negative effects on equity, acceptability, and feasibility • Therefore, BLLfxCZ was deemed to be the preferable over BDLLfxZ
Subgroup considerations	**See information in summary EtD for PICO 2**
Implementation considerations	**See information in summary EtD for PICO 2**
Monitoring and evaluation	**See information in summary EtD for PICO 2**
Research priorities	**See information in summary EtD for PICO 2**

5.3 TB care and support

Refer to *WHO consolidated guidelines on tuberculosis: module 4: treatment: tuberculosis care and support: web annexes.*

Web Annexes 1 and 2 https://iris.who.int/handle/10665/352904

Annex 6. Statistical analysis plans

WHO treatment guidelines for drug-resistant TB treatment

WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update

Refer to Annex 10: Summaries of unpublished data and analysis plans used for the recommendations in the *WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update.*

https://iris.who.int/bitstream/handle/10665/311390/WHO-CDS-TB-2019.3-eng.pdf

WHO treatment guidelines for drug-resistant TB treatment, 2020 update

Refer to Annex 5: Summaries of unpublished data and statistical analysis plans in the *WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment. Online annexes.*

https://iris.who.int/bitstream/handle/10665/332678/9789240007062-eng.pdf

WHO treatment guidelines for drug-resistant TB treatment, 2022 update

Refer to Web Annex 5: Statistical analysis plan in the *WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. Web Annexes.*

https://iris.who.int/handle/10665/365284

Annex 7. Reports of the systematic reviews for Tuberculosis care and support

https://apps.who.int/iris/bitstream/handle/10665/352904/9789240047754-eng.pdf

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