

# WHO consolidated guidelines on tuberculosis

Module 4: Treatment

**Drug-resistant  
tuberculosis treatment**



World Health  
Organization

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Module 4: Treatment

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## Recommendations for the management and care of drug-resistant tuberculosis, 2020 update

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## WHO Guideline Steering Committee

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# Abbreviations and acronyms

<b>aDSM</b>	active TB drug safety monitoring and management
<b>AFB</b>	acid-fast bacilli
<b>AIDS</b>	acquired immunodeficiency syndrome
<b>aIPD</b>	adult individual patient data
<b>aOR</b>	adjusted odds ratio
<b>ART</b>	antiretroviral therapy
<b>AST</b>	aspartate aminotransferase
<b>ATS</b>	American Thoracic Society
<b>BID</b>	twice a day
<b>BPaL</b>	bedaquiline, pretomanid and linezolid
<b>CI</b>	confidence interval
<b>CL</b>	confidence limits
<b>CNS</b>	central nervous system
<b>DALY</b>	disability adjusted life year
<b>DELIBERATE</b>	DELamanId Bedaquiline for ResistAnt Tuberculosis (trial)
<b>DOT</b>	directly observed treatment
<b>DR-TB</b>	drug-resistant tuberculosis
<b>DST</b>	drug susceptibility testing
<b>ECG</b>	electrocardiogram
<b>EDRWeb</b>	Electronic Drug-Resistant Tuberculosis Register (South Africa)
<b>FDC</b>	fixed-dose combination (medicines)
<b>GDF</b>	Global Drug Facility
<b>GDG</b>	Guideline Development Group
<b>GRADE</b>	Grading of Recommendations Assessment, Development and Evaluation
<b>HIV</b>	human immunodeficiency virus
<b>HR</b>	isoniazid–rifampicin
<b>HREZ</b>	isoniazid–rifampicin–ethambutol–pyrazinamide
<b>(H)REZ</b>	(isoniazid optional)–rifampicin–ethambutol–pyrazinamide
<b>Hr-TB</b>	rifampicin-susceptible, isoniazid-resistant tuberculosis
<b>IPD</b>	individual patient data (or dataset)
<b>IPD-MA</b>	individual patient data meta-analysis
<b>IQR</b>	interquartile range
<b>LPA</b>	line probe assay
<b>LTBI</b>	latent tuberculosis infection

<b>MDR-TB</b>	multidrug-resistant tuberculosis
<b>MDR/RR-TB</b>	multidrug- or rifampicin-resistant tuberculosis
<b>MIC</b>	minimum inhibitory concentration
<b>MSF</b>	Médecins Sans Frontières
<b>NTP</b>	national TB control programme
<b>PICO</b>	population, intervention, comparator and outcomes
<b>PLHIV</b>	people living with HIV
<b>QD</b>	once a day
<b>QTcF</b>	corrected QT interval by Fredericia
<b>RCT</b>	randomized controlled trial
<b>REZ</b>	rifampicin–ethambutol–pyrazinamide
<b>RR-TB</b>	rifampicin-resistant TB
<b>SAT</b>	self-administered therapy (also meaning unsupervised treatment)
<b>SMS</b>	short message service (mobile phone text message)
<b>SRL</b>	TB Supranational Reference Laboratory
<b>STREAM</b>	Standard Treatment Regimen of Anti-tuberculosis Drugs for Patients with MDR-TB (trial)
<b>TB</b>	tuberculosis
<b>USA</b>	United States of America
<b>USAID</b>	United States Agency for International Development
<b>US CDC</b>	United States Centers for Disease Control and Prevention
<b>US FDA</b>	United States Food and Drug Administration
<b>VOT</b>	video-observed treatment
<b>WHO</b>	World Health Organization
<b>XDR-TB</b>	extensively drug-resistant tuberculosis

# Definitions

**Drug susceptibility testing (DST):** in vitro testing using either molecular, genotypic techniques to detect resistance-conferring mutations, or phenotypic methods to determine susceptibility to a medicine.<sup>1</sup>

**Extensive (or advanced) tuberculosis (TB) disease:** 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.

**Extensively drug resistant TB (XDR-TB):** TB that is resistant to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance.<sup>2</sup>

**Longer multidrug-resistant TB (MDR-TB) regimens:** used for treatment of multidrug- or rifampicin-resistant TB (MDR/RR-TB), these regimens last 18 months or more, and are designed using a hierarchy of recommended medicines, including a minimum number of medicines considered to be effective based on drug-resistance patterns or patient history. The features and indications of these regimens are further elaborated in the Recommendations in these guidelines.

**MDR-TB:** TB caused by *Mycobacterium Tuberculosis* (*M. tuberculosis*) strains that are resistant to at least both rifampicin and isoniazid.

**New case:** a newly registered episode of TB in a patient who has never been treated for TB or has taken anti-TB medicines 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”.<sup>3</sup> In the context of this document, it is also applied 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.<sup>4</sup> Operational research also provides decision-makers with information to enable them to improve the performance of their health programmes.<sup>5</sup>

**Previously treated:** patients who have received 1 month or more of anti-TB medicines in the past. Previously treated cases may have been treated with a first-line regimen for drug-susceptible TB or a second-line regimen for drug-resistant forms (e.g. shorter MDR-TB regimen).

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<sup>1</sup> Implementing tuberculosis diagnostics: a policy framework. Geneva: World Health Organization; 2015 (WHO/HTM/TB/2015.11; [http://apps.who.int/iris/bitstream/10665/162712/1/9789241508612\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/162712/1/9789241508612_eng.pdf), accessed 15 February 2019).

<sup>2</sup> The current definition of XDR-TB will probably need to be changed, given the phasing out of injectables, anticipated patterns of resistance that are more relevant to current and future regimens, and advances in diagnostic methods and drug susceptibility testing (DST). Changes to the definition of XDR-TB will be the subject of future expert consultation, and will be included in revised WHO surveillance and reporting guides. Choosing appropriate regimens for patients with strains showing multidrug-resistant TB (MDR-TB) plus additional resistance to fluoroquinolones (so-called “pre-XDR”) are becoming more important and feasible, thanks to rapid advances in molecular DST.

<sup>3</sup> Allotey P, Reidpath DD, Ghalib H, Pagnoni F, Skelly WC (2008) Efficacious, effective, and embedded interventions: implementation research in infectious disease control. BMC Public Health 8: 343.

<sup>4</sup> The Global Fund and World Health Organization. Guide to operational research in programmes supported by the Global Fund. Geneva: The Global Fund; 2007.

<sup>5</sup> Expanding capacity for operations research in reproductive health: summary report of a consultative meeting, World Health Organization, Geneva, Switzerland, December 10–12, 2001. Geneva: World Health Organization; 2003.

**Rifampicin-resistant TB (RR-TB):** TB caused by *M. tuberculosis* strains resistant to rifampicin. These strains may be susceptible or resistant to isoniazid (i.e. MDR-TB), or resistant to other first-line or second-line TB medicines. In these guidelines and elsewhere, MDR-TB and RR-TB cases are often grouped together as MDR/RR-TB and are eligible for treatment with MDR-TB regimens.

**Rifampicin-susceptible, isoniazid-resistant TB (Hr-TB):** caused by *M. tuberculosis* strains resistant to isoniazid and susceptible to rifampicin.

**Second-line TB medicine (or drug):** an agent used for the treatment of drug-resistant TB. First-line TB medicines used to treat drug-susceptible TB – ethambutol, isoniazid and pyrazinamide – may also be used in MDR-TB regimens. Streptomycin is now considered a second-line TB medicine and is used only as a substitute for amikacin in the following situations: when amikacin is not available, when there is confirmed resistance to amikacin but confirmed susceptibility to streptomycin, and when an all-oral regimen cannot be constituted.

**Serious adverse events:** is 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. Serious 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 or TB meningitis. In children aged under 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are considered as severe.

**Shorter MDR/RR-TB regimen:** a course of treatment for MDR/RR-TB lasting 9–12 months, which is largely standardized, and whose composition and duration follows closely the one for which there is documented evidence from different settings.

**Treatment outcomes and relapse:** the categories for treatment outcomes used in these guidelines and the term relapse were applied according to the definitions agreed for use by TB programmes, unless otherwise specified.<sup>6</sup>

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<sup>6</sup> Definitions and reporting framework for tuberculosis – 2013 revision. Geneva: World Health Organization; 2013 (WHO/HTM/TB/2013.2; [http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf), accessed 15 February 2019). Laserson KF, Thorpe LE, Leimane V, Weyer K, Mitnick CD, Riekstina V et al. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis.* 2005;9(6):640–5.

# Executive summary

Tuberculosis (TB) strains with drug resistance 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 threatens global progress towards the targets set by the End TB Strategy<sup>7</sup> 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 drug-resistant 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 drug-resistant TB, published in a range of documents (see **Box 1**). More recently, WHO has 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.<sup>8</sup> The consolidation of WHO recommendations on TB and drug-resistant TB has now 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 drug-resistant TB treatment.

The guidance provided in this module 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 WHO-convened Guideline Development Groups (GDGs), using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to summarize the evidence, and formulate policy recommendations and accompanying remarks. However, it also incorporates new recommendations that were made in November 2019, based on new evidence that was available to WHO on the following: shorter regimens for MDR/RR-TB; the use of the bedaquiline, pretomanid and linezolid (BPaL) regimen for patients with MDR/RR-TB and additional fluoroquinolone resistance; the use of bedaquiline beyond 6 months; the use of bedaquiline in pregnancy; and the use of bedaquiline and delamanid together. In particular, this module focuses on public health recommendations on the use of effective treatment regimens for drug-resistant TB; specifically, regimens for isoniazid-resistant TB, all-oral shorter regimens for MDR/RR-TB, longer regimens for MDR/RR-TB, monitoring patient response to MDR/RR-TB treatment, starting antiretroviral therapy (ART) in patients on second-line anti-TB regimens, surgery for patients on MDR-TB treatment, and care and support measures for patients with MDR/RR-TB. Additionally, in an effort to inform the global community of the major gaps and research areas to be addressed to help inform the development of evidence-based recommendations, this document outlines the research priorities that will help us generate knowledge on evidence-based and attainable standards of health.

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<sup>7</sup> End TB Strategy. Global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva: World Health Organization; 2014 (<https://www.who.int/tb/strategy/en/>, accessed 20 March 2020).

<sup>8</sup> WHO consolidated guidelines on drug-resistant tuberculosis treatment (WHO/CDS/TB/2019.7). Geneva: World Health Organization; 2019 (<https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/>, accessed 6 March 2020).

### Box 1. WHO treatment recommendations incorporated into the present module on management and care of drug-resistant TB treatment

- Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Geneva: World Health Organization; 2011 (WHO/HTM/TB/2011.6).
- The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance. Geneva: World Health Organization; 2013 (WHO/HTM/TB/2013.6).
- The use of delamanid in the treatment of multidrug-resistant tuberculosis: interim policy guidance. Geneva: World Health Organization; 2014 (WHO/HTM/TB/2014.23).
- 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).
- WHO treatment guidelines for drug resistant tuberculosis: 2016 update. Geneva: World Health Organization; 2016 (WHO/HTM/TB/2016.4).
- Guidelines for the treatment of drug-susceptible tuberculosis and patient care: 2017 update. Geneva: World Health Organization; 2017 (WHO/HTM/TB/2017.05).
- 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).
- WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update. Geneva: World Health Organization; 2018 (WHO/CDS/TB/2018.15).
- WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019 (WHO/CDS/TB/2019.7).

The objective of the present update is to provide evidence-based information on critical areas that will help to inform the use of novel all-oral regimens and potential label expansion for new TB medicines – for example, concomitant bedaquiline and delamanid use, extended bedaquiline use, and assessment of bedaquiline use in special populations – and that will supersede earlier guidance. In this updated document, stakeholders will be able to distinguish between previous recommendations that remain valid, those that have been updated, and those that have been newly 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 recommendations included herein are a component of the WHO consolidated guidelines on tuberculosis, and are primarily intended for use by national TB control programmes (NTPs), public health agencies, and other key constituencies involved in the planning, implementation and monitoring of activities for the programmatic management of drug-resistant TB.

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.

# Current WHO recommendations on treatment and care for drug-resistant TB

The present recommendations for the treatment and care of drug-resistant TB have been derived from earlier WHO guideline documents (**Box 1**), and a recent WHO guideline development exercise conducted at the end of 2019. The current recommendations supersede the WHO consolidated guidelines on drug-resistant tuberculosis treatment that were published in 2019.<sup>9</sup>

This module contains policy recommendations on treatment regimens for rifampicin-susceptible, isoniazid-resistant TB (Hr-TB) and MDR/RR-TB, including all-oral shorter and longer regimens for MDR/RR-TB, monitoring of patients on treatment, the timing of ART in MDR/RR-TB patients infected with HIV, the use of surgery for patients receiving MDR-TB treatment, and models of patient support and care. The recommendations are presented below.

## 1. Regimen for rifampicin-susceptible and isoniazid-resistant tuberculosis

**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)*

**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)*

## 2. Shorter all-oral bedaquiline-containing regimen for multidrug- or rifampicin-resistant tuberculosis

**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)*

## 3. Longer regimens for multidrug- or rifampicin-resistant tuberculosis

**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)*

<sup>9</sup> WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva, Switzerland: World Health Organization; 2019 (<https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf?ua=1>, accessed 20 March 2020).

**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)*

**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)*

**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)*

**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)*

**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)*

**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)*

**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)*

**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)*

**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)<sup>10</sup>*

**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)*

**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)*

**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)*

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<sup>10</sup> 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.



**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)*

**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)*

**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)*

**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)*

## **4. The bedaquiline, pretomanid and linezolid (BPaL) regimen for multidrug-resistant tuberculosis with additional fluoroquinolone resistance**

**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)*

## **5. Monitoring patient response to MDR-TB treatment using culture**

**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.**

## **6. Starting antiretroviral therapy in patients on second-line anti-TB regimens**

**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).*

## 7. Surgery for patients on multidrug-resistant TB treatment.

**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)*

## 8. Care and support for patients with multidrug- or rifampicin-resistant tuberculosis

**8.1 Health education and counselling on the disease and treatment adherence should be provided to patients on tuberculosis (TB) treatment.**

*(Strong recommendation, moderate certainty in the evidence)*

**8.2 A package of treatment adherence interventions<sup>11</sup> may be offered to patients on TB treatment in conjunction with the selection of a suitable treatment administration option.<sup>12</sup>**

*(Conditional recommendation, low certainty in the evidence)*

**8.3 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<sup>13</sup> and/or digital medication monitor<sup>14</sup> *(conditional recommendation, very low certainty in the evidence);*
- b) material support<sup>15</sup> to the patient *(conditional recommendation, moderate certainty in the evidence);*
- c) psychological support<sup>16</sup> to the patient *(conditional recommendation, low certainty in the evidence);*
- d) staff education<sup>17</sup> *(conditional recommendation, low certainty in the evidence).*

**8.4 The following treatment administration options may be offered to patients on TB treatment:**

- a) Community- or home-based directly observed treatment (DOT) is recommended over health facility-based DOT or unsupervised treatment *(conditional recommendation, moderate certainty in the evidence).*
- b) DOT administered by trained lay providers or health care workers is recommended over DOT administered by family members or unsupervised treatment *(conditional recommendation, very low certainty in the evidence).*
- c) Video-observed treatment (VOT) may replace DOT 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 in the evidence)*

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<sup>11</sup> Treatment adherence interventions include social support such as material support (e.g. food, financial incentives or transport fees), psychological support, tracers such as home visits or digital health communications (e.g. SMS or telephone calls), medication monitor and staff education. The interventions should be selected based on the assessment of the individual patient's needs, the provider's resources and conditions for implementation.

<sup>12</sup> Treatment administration options include DOT, non-daily DOT, VOT or unsupervised treatment.

<sup>13</sup> "Tracers" refer to the communication with the patient, including home visits or via SMS or telephone (voice) call.

<sup>14</sup> A digital medication monitor is a device that can measure the time between openings of the pill box. The medication monitor can have audio reminders or send an SMS to remind the patient to take medications, along with recording when the pill box is opened.

<sup>15</sup> 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 the indirect costs incurred by patients or their attendants in order to access health services, and may try to mitigate the consequences of income loss related to the disease.

<sup>16</sup> Psychological support can be counselling sessions or peer-group support.

<sup>17</sup> Staff education can be adherence education, chart or visual reminders, educational tools and desktop aids for decision-making and reminders.

**8.5 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 quality evidence)*

**8.6 A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment.**

*(Conditional recommendation, very low certainty in the evidence)*

**Main changes to the guidance in the current update**

*(see also [Supplementary table](#))*

- ➔ One recommendation on shorter regimens to treat MDR/RR-TB has been updated. The shorter regimen conditionally recommended in this update comprises 6 Bdq with 4–6 Lfx/Mfx-Cfz-Z-E-Hh-Eto/ 5 Lfx/Mfx-Cfz-Z-E (in previous guidance, the shorter regimen comprised 4–6 Am-Mfx-Cfz-Eto-Z-E-Hh/ 5 Mfx-Cfz-Z-E). The new shorter regimen is recommended as a standardized package. New information has been included in these guidelines (Recommendations – [Section 2](#)) on the use of this shorter regimen, including implementation considerations for national TB programmes.
- ➔ A new 6–9-month regimen composed of bedaquiline, pretomanid and linezolid (BPaL) has been conditionally recommended for use in patients with MDR/RR-TB and additional fluoroquinolone resistance, under operational research conditions only. A new section (Recommendations – [Section 4](#)) has been added to these guidelines to describe the evidence that was assessed in relation to this regimen, the eligible population and the conditions of use as part of operational research studies.
- ➔ Additional guidance on the safety of extended bedaquiline use (beyond 6 months), the concurrent use of bedaquiline and delamanid, and the use of bedaquiline during pregnancy has been provided in the section on longer regimens for MDR/RR-TB (Recommendations – [Section 3](#)). The grouping of medicines into Groups A, B and C has not changed since the previous guidelines were issued by WHO in 2018.
- ➔ The content of the guidelines has been updated, citing current references and the latest available evidence, including unpublished data on cost-effectiveness, safety and patient preferences for treatment.
- ➔ The research gaps have been updated to reflect the latest evidence reviewed.

# Introduction

Drug-resistant tuberculosis (TB) continues to be a public health problem, taking a heavy toll on patients, communities and health care systems. Recent global estimates indicate that there were about half a million new cases of multidrug- or rifampicin-resistant TB (MDR/RR-TB) in 2018, with less than 40% of the estimated burden being notified and 32% reported to have started second-line treatment (1). Current treatment regimens for MDR/RR-TB patients are far from satisfactory. Compared with treatments for drug-susceptible TB forms, these regimens require a longer course of treatment, a higher pill burden and the use of medicines with a higher toxicity profile; in addition, patients may develop significant adverse events and have poorer treatment outcomes. Globally, although treatment success rates have increased, almost 15% of MDR/RR-TB patients die from the disease, and 26% of those deaths are in patients with extensively drug-resistant TB (XDR-TB) (1).

The Global TB Programme of the World Health Organization (WHO) is now combining all current recommendations into one overall set of consolidated guidelines on TB. The guidelines will 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 and drug-resistant TB). The consolidated guidelines will contain modules specific to each programmatic area. This current module is on the treatment of drug-resistant TB; it presents WHO recommendations that have been newly developed and are published here for the first time, and existing recommendations that have been previously published in other WHO guidelines that applied the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

## Structure of the document

The Recommendations part of this document has eight main sections that cover aspects of the treatment of drug-resistant TB. The aspects covered are:

- the treatment of rifampicin-susceptible and isoniazid-resistant TB (Section 1);
- shorter all-oral bedaquiline-containing regimens for MDR/RR-TB (Section 2);
- the composition and duration of longer regimens for MDR/RR-TB (Section 3);
- the bedaquiline, pretomanid and linezolid (BPaL) regimen for MDR-TB with additional fluoroquinolone resistance (Section 4);
- monitoring of the patient response to MDR-TB treatment (Section 5);
- the use of antiretroviral therapy (ART) for people living with HIV infection (Section 6);
- the role of surgery for patients on MDR-TB treatment (Section 7); and
- the vital role of care and support for patients with MDR/RR-TB (Section 8).

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 monitoring and evaluation and implementation. Research gaps identified for each of the sections are presented at the end of this document, while online annexes provide more details on the methods, the Guideline Development Groups (GDGs), the analyses, unpublished data and statistical analysis plans. Each section reflects discussions held at GDG meetings over recent years. Additional information on the management of MDR/RR-TB is presented in the relevant chapter of the *WHO operational handbook on tuberculosis*, a separate document that is designed to aid implementation efforts. Eventually,

the operational handbook will replace the *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis (2)*.

## 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. The development of new TB drugs and the use of repurposed drugs such as linezolid and clofazimine has set a positive course; however, regimens for drug-resistant TB continue to present safety concerns, require long duration and put a significant burden on health care systems. Since the 1990s, WHO has regularly evaluated evidence on the use of specific drug compositions and combinations of different regimen durations (3–12). Patients with 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, while 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 effectiveness and harms on, for example:

- the use of all-oral longer treatment regimens; and
- the replacement of drugs associated with increased risk of treatment failure and relapse in the standardized shorter regimen.

## Rationale for the update

The latest WHO evidence-based guidelines for the treatment of drug-resistant TB were released in December 2018 and incorporated into consolidated guidelines published in March 2019 (77). Subsequently, new evidence on treatment for MDR/RR-TB and XDR-TB became available to WHO through national programmes, researchers and technical partners, and from a public call for data from WHO in August 2019 (73). New data from patients on both longer (>18 months) and shorter (<12 months) MDR-TB regimens were validated and incorporated into the set of individual patient data (IPD) that had been established earlier to help inform development of WHO guidelines on drug-resistant TB (this dataset covers patients who have been treated for MDR/RR-TB, as of November 2019 it contains >13 000 patient records from 55 different studies or centres in 38 countries overall). International standards for meta-analysis were followed to assess the relative contributions of treatment regimens or combinations of medicines to patient treatment outcomes. WHO convened an independent GDG on 12–14 November 2019, to assess the results of these analyses using the GRADE system. The detailed recommendations presented here replace all previous and current WHO guidelines on the treatment of drug-resistant TB.

## Scope of the 2020 update

This current module on drug-resistant TB management and care provides specific recommendations on the management and care of drug-resistant TB, including use of regimens for isoniazid-resistant TB, all-oral shorter regimens for MDR/RR-TB, longer regimens for MDR/RR-TB, monitoring patient response to MDR/RR-TB treatment, starting ART in patients on second-line anti-TB regimens, surgery for patients on MDR-TB treatment, and care and support measures for patients with MDR/RR-TB.

These updated recommendations resulted from the 2019 GDG meeting, convened by WHO to review and discuss results on the following:

- use of all-oral shorter regimens (9–12 months duration);
- use of BPaL in combination for patients with MDR/RR-TB with additional fluoroquinolone resistance;

- use of bedaquiline for longer than 6 months;
- concurrent use of bedaquiline and delamanid; and
- use of bedaquiline-containing regimens in pregnant women.

Access to these data was achieved through close collaboration and engagement with national TB control programmes (NTPs), researchers, and a not-for-profit product-development partnership (TB Alliance) investigating the effectiveness and safety of these interventions (see **Annex 1**).

The text clearly indicates where recommendations are new.

## 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 who 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

## Section 1. Regimen for rifampicin-susceptible, isoniazid-resistant tuberculosis

### 1.1 Recommendations

No.	Recommendation
1.1	<b>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.</b> <i>(Conditional recommendation, very low certainty in the estimates of effect)</i>
1.2	<b>In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen.</b> <i>(Conditional recommendation, very low certainty in the estimates of effect)</i>

### 1.2 Justification and evidence

The recommendations in this section address one PICO (population, intervention, comparator and outcomes) question:

**PICO question 1** (*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) (14–16). The evidence reviewed for this guideline compared treatment regimens with isoniazid, rifampicin, ethambutol, pyrazinamide ((H)REZ)<sup>18</sup> 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) (17).<sup>19</sup> In the IPD

<sup>18</sup> "(H)" indicates that isoniazid is optional.

<sup>19</sup> 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).



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). Since data were not included on intermittent dosing of the 6(H)REZ and >6(H)REZ regimens, 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 (adjusted odds ratio [aOR]: 0.4; 95% confidence limits [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 (interquartile range [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 a fluoroquinolone.

**Acquisition of drug resistance.** The analysis suggested that amplification of resistance to rifampicin was lower in patients receiving the 6(H)REZ regimen (0.6%) than in those receiving >6(H)REZ (4.3%). This observation could be due to the effect of 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 (78). 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 latent TB infection (LTBI) – in such individuals, a much higher occurrence of hepatotoxicity has been observed than in those receiving only isoniazid preventive therapy (79). 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 drug susceptibility testing (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. Addition of streptomycin did not reduce mortality significantly (see **Annex 3** and **Annex 4**). 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, allocation to treatment with specific regimens and their relationship with disease severity. Outcomes appeared to be worse in patients with cavitory 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 3**). 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 3** and **Annex 4** for more 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 for 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 (20–22). 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 do so (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* 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 (23). 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 drug-resistant TB treatment settings, and that the use of a regimen based on medicines that are fully 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 drug-resistant 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 (24, 25). 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 [Section 1.4](#)).

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; pregnancy or during breastfeeding (not an absolute contraindication). In Hr-TB cases 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 (*katG* or *inhA*). In addition, knowledge about overall host acetylator<sup>20</sup> status at country or regional level will be useful, given that these may have implications for regimen design (26).

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<sup>20</sup> 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.

Under development are high-throughput diagnostic platforms (as an alternative to line probe assay [LPA]) that can simultaneously detect TB, and resistance to rifampicin and isoniazid. Evaluation studies of these diagnostics are underway.

### 1.3 Subgroup considerations

**Children.** In the IPD review, only 2% of Hr-TB patients were children; thus, a separate estimate of effect for paediatric patients was not possible. However, there is no reason why the results and recommendations cannot be extrapolated from adults to children, considering that the regimen components have been standard paediatric TB medicines for many years.

**Patients with extensive disease.** Although the IPD analysis did not provide evidence for duration of treatment extension, the prolongation of the 6(H)REZ–levofloxacin regimen to more than 6 months could be considered on an individual basis for patients with extensive disease (27). Prolongation of treatment may increase the risk of adverse events in some cases (see [Section 1.5](#)).

**HIV-positive individuals.** The effect of longer duration TB treatment among HIV-positive patients with and without ART has been studied among patients with drug-susceptible TB (28). In these cases, relapse has been reported to be 2.4 times higher in HIV-infected patients 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 (29). 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 (30). The 6(H)REZ–levofloxacin regimen is therefore recommended in HIV-positive patients.

**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.

### 1.4 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 ahead of 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. Should the DST results taken at the start eventually show susceptibility to isoniazid, then levofloxacin is stopped, and the patient continues treatment in order 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 at the start 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 subsequent sections of these guidelines.

**Diagnostic capabilities.** The overall aim of TB treatment is to achieve cure without relapse in all patients, interrupting *Mycobacterium 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.<sup>21</sup> 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 and LPAs are preferred, to guide patient selection for the (H)REZ–levofloxacin regimen (25, 31).

Drug-resistant TB surveillance indicates that fluoroquinolone resistance among patients with rifampicin-susceptible TB is generally low worldwide (32). However, national data on the prevalence of fluoroquinolone resistance – including targeted or whole-genome sequencing to detect specific mutations associated with resistance to fluoroquinolones (33) – 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 in order 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/RIF or LPA, is indicated. 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 accordingly.

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 (34), the same effect has not been reported for levofloxacin, possibly because levofloxacin undergoes limited metabolism in humans and is excreted unchanged in the urine (35). Third, although levofloxacin may interfere with lamivudine clearance, in contrast to moxifloxacin, there are no contraindications for its use with other antiretroviral agents (36).

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/RIF);
- known or suspected resistance to levofloxacin;
- known intolerance to fluoroquinolones;

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<sup>21</sup> The association between previous TB treatment history and Hr-TB is less strong than that of MDR-TB. As a result, previous TB treatment is less reliable as a proxy for Hr-TB and a laboratory diagnosis is therefore important.

- known or suspected risk for prolonged QT interval;<sup>22</sup>
- 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<sup>23</sup> 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 because there was 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 *inhA* mutations are detected (and when *katG* 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 *katG* mutations, which usually confer a higher level resistance, the use of isoniazid even at a higher dose is less likely to be effective (37).<sup>24</sup>

**Dosage.** Although the IPD analysis did not provide evidence to address the frequency of dosing, it is best to avoid intermittent or divided dosing of the 6(H)REZ–levofloxacin regimen (29, 38, 39). In the absence of full information about optimal drug doses, a weight-band dosing scheme for levofloxacin is recommended.<sup>25</sup>

**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 (36). Co-administration of levofloxacin with oral divalent cation-containing compounds (e.g. antacids) may impair its absorption and should be avoided (9). Restriction of concomitant use of milk products is not necessary.

**Treatment prolongation beyond 6 months.** This may be considered for patients with extensive disease or in those slow to convert to smear or culture negative. In the latter, acquisition of additional resistance to rifampicin must be ruled out, as must resistance to fluoroquinolones and pyrazinamide, if possible. Such patients require careful monitoring and follow-up.

<sup>22</sup> Baseline-corrected QT. Prolongation of the QT interval and isolated cases of *torsade de pointes* have been reported. Avoid use in patients with known prolongation, those with hypokalaemia, and with other drugs that prolong the QT interval.

<sup>23</sup> Although most countries currently procure the four-drug FDC via the Stop TB Partnership’s Global Drug Facility (GDF), in settings where only the three-drug combination FDC (i.e. HRZ) is available, ethambutol has to be administered separately.

<sup>24</sup> An isolated *katG* or *inhA* mutation can correspond to variable minimum inhibitory concentration (MIC) levels. This implies that *inhA* mutations do not always indicate low-level isoniazid resistance, or that *katG* mutations are not necessarily correlated with high-level isoniazid resistance. The presence of both mutations is usually an indication of high-level resistance (37).

<sup>25</sup> 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 drug-resistant TB. Gatifloxacin is currently unavailable in quality-assured formulations, and ciprofloxacin and ofloxacin are no longer recommended for use in drug-resistant TB care.

**Cost.** Cost–effectiveness analysis was not performed for this review. [Table 1.1](#) presents approximate prices for a full course of medicines with the different regimens in adults, based on the cost of products available from the Global Drug Facility (GDF) (40). 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.

**Adherence.** The IPD analysis contained limited data on the treatment adherence strategies used, such as directly observed treatment (DOT) 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 (29). 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.

**Table 1.1. Illustrative costs of regimens used to treat Hr-TB compared with the 6-month first-line TB regimen**

Regimen	Average weighted prices, US\$ <sup>a</sup>
2HREZ/4HR	36
6HREZ	55
6REZ–Lfx	99
6HREZ–Lfx	76
9HREZ–Lfx	113

HR: isoniazid, rifampicin; HREZ: isoniazid, rifampicin, ethambutol, pyrazinamide; Lfx: levofloxacin; REZ: rifampicin, ethambutol, pyrazinamide.

<sup>a</sup> Prices are as of 15 March 2020 for a 60 kg adult, and 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 (40).

Source: Stop TB Partnership (2020) (40).

## 1.5 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 (41). 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 aspartate aminotransferase (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 coinfecting 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 (42).



## Section 2. Shorter all-oral bedaquiline-containing regimen for multidrug- or rifampicin-resistant tuberculosis

### 2.1 Recommendation

NEW RECOMMENDATION

No.	Recommendation
2.1	<p><b>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.</b></p> <p><i>(Conditional recommendation, very low certainty in the evidence)</i></p>

### 2.2 Remarks

- The evidence review focused on the shorter regimen where the injectable agent was replaced by bedaquiline<sup>26</sup> (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.
- After taking into account patient preference and clinical judgement, this regimen can be a preferred option for patients in whom all of the following apply: confirmed MDR/RR-TB (with at least confirmed resistance to rifampicin), with resistance to fluoroquinolones ruled out, exposure to previous treatment with second-line medicines for no more than 1 month, no extensive TB disease and no severe extrapulmonary TB (see Definitions).
- The evidence reviewed supports the use of this regimen in patient subgroups such as people living with HIV (PLHIV) (see Section 2.4).
- Implementation of this regimen requires access to rapid DST against fluoroquinolones.

### 2.3 Justification and evidence

Interest in reducing the duration of treatment for MDR/RR-TB has driven a number of initiatives in recent years to treat patients with shorter regimens under programmatic and trial conditions (43–48). When used in carefully selected MDR/RR-TB patients who have not been previously exposed or do not have additional resistance to second-line medicines, these regimens have been reported to achieve relapse-free cure in about 80% of cases or more, even under programmatic conditions (43, 47). In 2016, on the basis of data from observational studies of the standardized shorter regimens in different Asian and African countries, WHO for the first time recommended a standardized 9–12 month shorter MDR-TB regimen for eligible patients (70). Subsequently, 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 in 2018, following an evidence assessment and ranking of benefits and harms attributed to specific drugs; the revision included a recommendation to replace the injectable agent, kanamycin (or capreomycin), with amikacin (77). As debate about the excessive adverse effects of injectable agents (especially

<sup>26</sup> Bedaquiline is usually administered 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).

hearing loss) became more prominent through patient advocacy, and new and repurposed oral anti-TB drugs became available, the evaluation of new evidence on injectable-free shorter regimens from programmatic settings became pivotal, to provide better and safer standards of care for patients with drug-resistant TB.

Availability of data on the programmatic implementation of a shorter, injectable-free treatment regimen including bedaquiline in South Africa since 2017 prompted WHO to evaluate the following PICO question:

**PICO question 2 (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?*

**Evidence base and analyses.** Following close communication with key stakeholders and NTPs, the South African Department of Health provided WHO with access to programmatic data on injectable-free regimens that have been phased in since 2017, when a majority of eligible patients were enrolled on a shorter regimen, with bedaquiline replacing the injectable (personal communication, Dr Norbert Ndjeka, South African Department of Health, November 2019). In August 2019, WHO issued a public call for individual patient data on the use of all-oral shorter regimens of 9–12 months duration (73), but this call yielded no additional evidence on the implementation of such regimens. Consequently, the evidence review 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 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. As mentioned earlier, the IPD is 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 overall. The evidence review focused on the performance of a standardized shorter regimen in which the injectable agent was replaced by bedaquiline, in combination with levofloxacin (or moxifloxacin), clofazimine, and high-dose isoniazid, ethambutol, pyrazinamide and ethionamide (or prothionamide). Patients on this regimen did not receive any injectable agents, nor were they administered cycloserine, terizidone, *p*-aminosalicylic acid, delamanid or linezolid. According to the clinical guidance issued by the Department of Health of South Africa, at the time of regimen roll-out (2016–2017), patients were not enrolled on the all-oral shorter regimen if they had extensive disease and severe extrapulmonary TB, with fluoroquinolone resistance and previous exposure to second-line treatment for more than 1 month, or had LPA-based DST showing mutations in both *inhA* and *katG* genes.

As part of the primary analysis, the all-oral shorter regimen detailed above was compared with the following treatment regimens: standardized shorter regimen with the inclusion of an injectable agent; longer regimens in which at least one new TB drug was used, particularly bedaquiline; and additional comparison to longer regimens without use of new drugs (based on WHO guidelines issued in 2016). No data on all-oral longer regimens recommended by WHO in 2018 were available for analysis and comparison. 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.

A total of 10 152 records of patients with MDR/RR-TB initiating TB treatment anytime between January and June 2017<sup>27</sup> were considered, of which the following were included for primary<sup>28</sup> analyses: 891 patients who received a shorter all-oral bedaquiline-containing regimen (intervention), 987 patients treated with a shorter regimen that included an injectable agent, 1437 patients treated with longer (2016) regimens, and 474 treated with longer regimens that included at least bedaquiline.

<sup>27</sup> Data extraction from EDRWeb was limited to the first semester of 2017, to allow for patients to have reached at least a 2-year post-treatment follow-up.

<sup>28</sup> Primary analysis was conducted using EDRWeb data from South African patients who started treatment in 2017 and for whom there was information on end-of-treatment outcome, and data from the Civil Registration and Vital Statistics database to evaluate or cross-check mortality data.



The primary analysis comparing South African programmatic data 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, aOR for success versus failure/recurrence: 2.1, 95% confidence interval [CI]: 1.1–4.0; aOR success versus death: 1.6, 95% CI: 1.2–2.1; aOR success versus failure/recurrence/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 HIV-positive and negative patients was observed with the use of the shorter all-oral bedaquiline-containing regimen.

The analysis also suggested that when the shorter all-oral bedaquiline-containing regimen was compared to an injectable-free longer<sup>29</sup> 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/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 seemed to indicate that there were consistent differences in treatment outcomes, as observed in primary analyses among subgroups, in particular among AFB smear-positive patients and in HIV-positive individuals 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 to longer regimens without any new drugs. The all-oral shorter regimen performed significantly better across all outcomes and all subgroups in this comparison.

**GDG considerations.** The GDG acknowledged that, during the analysis, the intervention and comparator groups were made as comparable as possible. However, the GDG considered possible unmeasured confounding due to a lack of systematic collection of information on comorbidities and radiological findings through the EDRWeb system, as well as methodological challenges, such as a potential selection bias. However, apart from the selection criteria listed, the risk of major selection bias was considered low, given that this intervention represented a complete and comprehensive switch in the countrywide programmatic approach.

The GDG further discussed modifications to the shorter all-oral bedaquiline-containing regimen, which was adjusted in 2018 by removing ethionamide<sup>30</sup> and including linezolid for countrywide enrolment (50).<sup>31</sup> However, in the patient records for 2017 provided for this guideline development process, only 0.5% of patients received linezolid, and no treatment outcomes were available for these patients. Given the incomplete data and inability to analyse these data separately owing to the small numbers, the GDG decided to exclude all patients who received linezolid. A further sensitivity analysis within subgroups defined by the use of specific combinations of drugs was attempted, to explore whether the addition of medicines such as linezolid to bedaquiline-containing regimens would improve treatment outcomes. No data on this combination were available in the data source used for the primary analysis; therefore, longer regimens containing both bedaquiline and linezolid were compared to longer regimens in which other companion drugs plus bedaquiline only were used. Results of this analysis suggested that regimens containing both bedaquiline and linezolid were associated with significantly lower rates of death (aOR: 1.6; 95% CI: 1.1–2.3) as well as a significantly better composite outcome of success versus all unfavourable outcomes (aOR: 1.5; 95% CI: 1.1–2.0).

<sup>29</sup> Recommendations released by WHO in December 2018 emphasized that fully oral longer regimens should be prioritized and become the preferred option for most patients, and that injectable agents were no longer among the priority medicines to consider when designing longer MDR-TB regimens (7).

<sup>30</sup> The decision to modify this regimen followed results from a National TB Drug Resistance Survey conducted in South Africa in 2012–2014, and published in 2018. The survey found that 44.7% of *M. tuberculosis* isolates were resistant to ethionamide (95% CI: 25.9–63.6%) (49).

<sup>31</sup> Linezolid was to be included routinely within the regimen up front, to protect bedaquiline in the early stages of treatment, particularly in MDR/RR-TB cases where resistance to fluoroquinolones was yet to be detected.

Owing to the evidence being insufficient and indirect, the GDG was unable to use these data and consider the value of further modification of the all-oral shorter regimen at this stage.

During the evidence assessment process, members of the GDG further assessed the overall certainty in the quality of evidence, the balance between benefits and harms of the shorter all-oral bedaquiline-containing regimen in addition to treatment outcomes, values and preferences, as well as considerations on equity, acceptability and feasibility (51, 52). One of the areas that required further discussion was related to potential for confounding and generalizability. Even though confounding was reduced through double-adjustment in propensity score matching,<sup>32</sup> members of the GDG remained concerned about the risk of unmeasured or residual confounding and potential selection bias by indication. In addition, the GDG acknowledged that although well-collected and unbiased programmatic data hold promise and may better reflect real-world practices, these data typically lead to a low-quality grading of evidence and have important shortcomings compared with more robust randomized controlled trial (RCT) generated data. It is also important to consider the extent to which these findings could be applied in other settings; factors that may limit the generalizability of the study findings to other settings include high prevalence of HIV, use of ART, specific *M. tuberculosis* strains and drug-resistance patterns, and the quality of health care services, including adherence strategies in South Africa.

Overall, the GDG agreed that the certainty in the evidence on the efficacy of all-oral shorter regimens was “very low” due to concerns about unmeasured or residual confounding and potential risk of bias. The GDG considered all outcomes of interest, without any prioritization; the outcome for *success versus failure/relapse/death* was considered the primary indicator of regimen efficacy, whereas the *lost to follow-up* outcome was considered more indicative of feasibility and treatment adherence. Reduced toxicity (compared with injectable use), patient preference and programmatic simplicity were major perceived benefits of the shorter all-oral bedaquiline-containing regimen. Regarding generalizability, the GDG deliberated on whether the genetic diversity of *M. tuberculosis* strains in South Africa was globally representative, and concluded that there is a fair distribution of common strains 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 HIV-positive and negative individuals. The GDG agreed that results of the STREAM Stage 2 trial – a large-scale, multicountry Phase III trial examining a shorter all-oral bedaquiline-containing regimen – will provide additional important insight into the efficacy and safety of this regimen, and increase the certainty in the evidence.

A clear limitation emphasized by the GDG was the lack of data on adverse events in the EDRWeb, with only death being accounted for. Despite the strong preference expressed by patient surveys and patient advocates for injectable-free regimens, the GDG could not fully ascertain all relevant undesirable effects, although bedaquiline-containing shorter and longer regimens seemed to be the equivalent for death, with a significant reduction of loss to follow-up when using shorter regimens. A major concern is the risk of bedaquiline resistance, which is amplified if treatment regimens are inadequate or treatment adherence is low (which is why adherence and adequacy should be closely monitored). During Stage 1 of the STREAM trial, safety of the standardized shorter regimen with injectables – which consists of the same medicines as the intervention regimen, except for replacement of the injectable with bedaquiline – was carefully assessed and was considered similar to the safety of the longer regimen (47). Replacement of the injectable with bedaquiline removes serious safety concerns related to injectables.

The GDG also discussed data on potential costs and cost-effectiveness. Modelling of the cost-effectiveness of the shorter all-oral bedaquiline-containing regimen showed robust cost savings relative to either a longer oral regimen or a short injectable-containing regimen. The use of the standardized shorter regimens, which included injectable agents, carried the additional costs of

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<sup>32</sup> In the matching algorithm, the intervention and control groups were matched according to AFB smear status, resistance to isoniazid, previous treatment, HIV status (antiretroviral use), gender and age. To further reduce imbalance, matching without replacement was employed, using a caliper width of 0.5; this required an exact match for HIV status, AFB and culture status, and propensity score match for age, gender, resistance to isoniazid and previous treatment.

management of dose-related adverse events (e.g. nephrotoxicity and ototoxicity) associated with second-line injectables drugs. With the implementation of the shorter all-oral bedaquiline-containing regimen, additional costs for electrocardiogram (ECG) monitoring had to be factored in; nevertheless, expenses related to quality audiometry and regular assessment of renal toxicity biomarkers would decrease. In addition, it was possible to achieve improved treatment outcomes and, more importantly, avoid lifelong disability and reduced economic losses as a result of patients' ability to regain employment. The cost-effectiveness model presented to the GDG estimated that a 9–12 all-oral regimen was both cost saving and cost effective, relative to either a longer all-oral or a shorter injectable-containing regimen (see **Annex 2**, **Annex 4** and **Annex 5**). However, the GDG acknowledged that implementing the all-oral shorter regimen does not automatically and immediately eliminate or reduce costs. In absolute terms, looking at overall benefits and potential harms, the use of the all-oral shorter regimen is believed to outweigh the harms (i.e. lower risk of mortality) for most patients.

Another issue was variability in how much end-users (in particular, patients) value the outcomes associated with the use of the all-oral bedaquiline-containing regimen. The GDG, driven by the results of the qualitative study on values and preferences (see **Annex 2**, **Annex 3** and **Annex 5**), concurred that it is important to prevent the outcome of death, and to reduce the frequency and seriousness of adverse events, particularly those attributed to second-line injectable agents, especially hearing loss, nephrotoxicity and vestibular toxicity. A qualitative study on patients' values, preferences and perspectives, based on interviews involving 16 former drug-resistant TB patients drawn globally from high burden countries, indicated that the most acceptable regimen is one that has few to no physical and mental health side-effects, is short and is all-oral (in that order of preference); added value was given to a low pill burden.

Data on feasibility could not be retrieved to help inform these recommendations; therefore, a collaborative decision-making approach was used to assess the judgements of the GDG on whether there were specific feasibility considerations. Such considerations mostly centred on the need for DST to guide safe implementation of the shorter all-oral bedaquiline-containing regimen, together with bedaquiline resistance monitoring. The GDG emphasized the crucial need to improve laboratory capacity for early drug-resistant TB detection, expanded drug-resistance testing and ongoing monitoring of drug-resistance acquisition or amplification.

## 2.4 Subgroup considerations

Following the GDG's assessment of the current evidence and judgements, the considerations were discussed for specific subgroups, as outlined in this section.

**People living with HIV.** The data evaluated corresponded to a setting with a high prevalence of HIV (slightly above 70% in the dataset). More than 95% of PLHIV initiated on the all-oral bedaquiline-containing regimen were on 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. 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 (they 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) (53–55). Neuropathy, liver enzyme elevations and central nervous system (CNS) side-effects can be attributed to HIV or TB drugs or their interactions (56).

**Children.** Although the analysis attempted to provide further insights into the use of the all-oral bedaquiline-containing regimen in special populations, the limited sample of children aged under 14 years in the database ( $n=6$ ) meant that no direct outcome estimations could be drawn for this

population. However, because the components of the all-oral bedaquiline-containing regimen have been used in children, extrapolation was deemed reasonable, provided that considerations for the implementation of bedaquiline in children are followed (11). Earlier recommendations on the composition of *longer* regimens indicated that bedaquiline could also be included in such regimens for patients aged 6–17 years (11); hence, the all-oral bedaquiline-containing regimen may be used in *eligible* children aged 6 years<sup>33</sup> and above, taking into account considerations for specific medications.

**Pregnant and lactating women.** The intervention regimen contains ethionamide, which 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. Although more compelling evidence is needed on toxicity causes attributed to the use of specific anti-TB drugs during pregnancy and lactation, individualized longer regimens can be designed to avoid known toxicities until better safety profiles are established.

**Extrapulmonary TB.** The evaluated shorter all-oral bedaquiline-containing regimen was also implemented in individuals confirmed with MDR/RR-TB and with uncomplicated extrapulmonary TB disease. No evidence was available to discern the impact of this regimen in patients with extensive TB disease or severe forms of extrapulmonary TB.

## 2.5 Implementation considerations

**Decisions to start the shorter all-oral bedaquiline-containing regimen** in newly diagnosed patients should be made through an informed decision-making process that includes patient preference and clinical judgement, and with several DST results available before the start of treatment. Patients should be informed on the advantages and possible disadvantages, and make an informed decision on the regimen of choice. Previous exposure of less than 1 month duration to the second-line medicines used in the regimen needs to be ascertained, and can be considered along with any additional DST results available. Based on the available evidence, this regimen can be a preferred option for patients with confirmed MDR/RR-TB (with at least confirmed resistance to rifampicin), for whom resistance to fluoroquinolones has been ruled out, in the following situations;

- without resistance or suspected ineffectiveness of a medicine in the shorter regimen (except isoniazid resistance<sup>34</sup>);
- without exposure to previous treatment with second-line medicines in the regimen for more than 1 month (unless susceptibility to these medicines is confirmed);
- with no extensive TB disease and with no severe extrapulmonary TB;
- not pregnant; and
- if a child, aged 6 years or more.

Those who may benefit from the all-oral longer regimen, designed according to the principles outlined in **Section 3** of this document, are as follows: all MDR/RR-TB patients who have been exposed to treatment with second-line TB medicines including bedaquiline (for >1 month), patients in whom resistance to fluoroquinolones has not been excluded, and patients with extensive TB disease or severe extrapulmonary TB.

One of the exclusion criteria for all shorter regimens (whether with injectables or all oral) in South Africa in 2016–2017 was mutations in both *inhA* promoter and *katG* regions, confirmed using LPA. This means that patients with only *inhA* or only *katG* mutations were not excluded. DST results for pyrazinamide were not available for most of the patients in the dataset extracted from EDRWeb and used for the analysis.

<sup>33</sup> Based on the results of an RCT conducted by the manufacturer, the US FDA has extended approval for the use of bedaquiline for children aged 5 years and above. However, these data have not yet been assessed by WHO.

<sup>34</sup> Determined by mutations in either *inhA* or *katG* genes (not both) or phenotypic DST. The presence of mutations in both the *inhA* promoter and *katG* suggests that isoniazid at high dose and thioamides are not effective, and that the shorter regimen should not therefore be used.

**Drug susceptibility testing.** DST is an important implementation consideration that will need to be enhanced in many countries, given the increasing potential use of bedaquiline 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 shorter, all-oral, bedaquiline-containing MDR-TB regimen. Baseline DST will confirm eligibility for different regimen options; therefore, the establishment and strengthening of DST services is a vital consideration for implementation. In patients with bacteriologically confirmed MDR/RR-TB,<sup>35</sup> the second-line LPA (MTBDRsl) may be used as the initial test, in preference to culture and phenotypic DST, to detect resistance to fluoroquinolones (33). A first-line LPA (MTBDRplus) can determine mutations in the *inhA* promoter or *katG* regions; both mutations confer resistance to isoniazid, with the resistance being low level when *inhA* mutations alone are present, or high level when mutations in the *katG* gene alone or mutations in *inhA* promoter and *katG* gene are combined. Mutations at the *inhA* promoter are also associated with resistance to ethionamide and prothionamide. The presence of mutations in both the *inhA* promoter and *katG* suggests that isoniazid at high dose and thioamides are not effective, and that the shorter regimen should 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 in this epidemiological setting (33). Phenotypic DST for some medicines included in the regimen (i.e. ethambutol and ethionamide) is not considered reliable and reproducible; therefore, it should be employed with caution to inform the use of this regimen.<sup>36</sup>

Since bedaquiline and fluoroquinolones are the backbone of the regimen, it is vital to monitor resistance to these medicines during treatment if there is no culture conversion by month 6. NTPs need to rapidly establish DST for bedaquiline, to monitor bedaquiline resistance; if possible, it is highly desirable that this testing is carried out at baseline. If DST is not immediately available, NTPs may consider storing culture isolates for future analysis.

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 medicine powders available to enable DST to be carried out, and will need data on the minimum inhibitory concentration (MIC) distribution of all *M. tuberculosis* lineages that are circulating globally. 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 2017 established critical concentrations for susceptibility testing for the fluoroquinolones, bedaquiline, delamanid, clofazimine and linezolid (58).

**Selection of fluoroquinolones** may take into account the evidence from South Africa available for the review – 83% of patients analysed using this dataset received levofloxacin, and the rest received moxifloxacin at standard dose. Both levofloxacin and moxifloxacin have shown similar efficacy for treating drug-resistant 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

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<sup>35</sup> MDR/RR-TB is usually confirmed by rapid molecular tests that detect resistance to rifampicin and *M. tuberculosis*. Current WHO recommendations state that Xpert MTB/RIF should be used rather than conventional microscopy, culture and DST as the initial diagnostic test in adults suspected of having MDR-TB or HIV-associated TB (strong recommendation, high-quality evidence). Xpert MTB/RIF should be used rather than conventional microscopy, culture and DST as the initial diagnostic test in children suspected of having MDR-TB or HIV-associated TB (strong recommendation, very low quality evidence) (24). A recent WHO rapid communication reinforced the high diagnostic accuracy and improved patient outcomes of rapid molecular diagnostic tests such as Xpert MTB/RIF, Xpert MTB/RIF Ultra and TrueNat (31).

<sup>36</sup> See list of high-confidence resistance-conferring mutations in WHO guide on the use of next generation sequencing technologies, WHO (2018) (57).



in paediatric populations. Therefore, irrespective of the choice of fluoroquinolone, NTPs need to implement active TB drug safety monitoring and management (aDSM) in all patients enrolled on treatment of drug-resistant TB (59, 60).

**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 chest radiography. In children aged under 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest radiography. This highlights the importance of chest radiography as part of the diagnostic work-up for patients, together with the usual patient–clinician interaction.

**Regimen duration.** The all-oral bedaquiline-containing regimen consists of an intensive phase of 4 months that may be extended to 6 months, and a continuation phase of 5 months, giving a total duration of 9–11 months. In the EDRWeb dataset analysed, bedaquiline use was restricted to the on-label duration of 6 months.

**Use of linezolid.** The evidence made available to inform this recommendation focused on the assessment of a regimen composed of bedaquiline, either levofloxacin or moxifloxacin, ethionamide, ethambutol, high-dose isoniazid, clofazimine and pyrazinamide. In 2018, South Africa transitioned to an all-oral bedaquiline-containing regimen, further modifying it by replacing ethionamide with 2 months of linezolid.

Secondary analyses determined that a bedaquiline-containing shorter regimen was comparable to an all-oral longer regimen containing both bedaquiline and linezolid, in terms of death and failure outcomes; however, the shorter regimen seemed to have significantly less loss to follow-up. Further sensitivity analyses (albeit in the longer regimens containing bedaquiline–linezolid versus longer regimens containing bedaquiline only) determined that the addition of linezolid to bedaquiline-containing regimens would, overall, improve outcomes. Nevertheless, the GDG concurred that, because of the lack of direct data for shorter regimens, no general conclusions could be drawn at the time.

Until new evidence is forthcoming and available to WHO, the shorter all-oral bedaquiline-containing regimen advised to be used does not include linezolid. In settings with a high probability of resistance to, or confirmed resistance to, ethionamide, ethambutol, pyrazinamide, clofazimine and high-dose isoniazid, further modifications of the regimen using priority grouping of second-line oral medicines may be implemented; however, the efficacy, safety and tolerability of additionally modified shorter regimens are unknown and should be evaluated under operational research conditions.

## 2.6 Monitoring and evaluation

Patients who receive a shorter MDR-TB treatment regimen need to be monitored during treatment using schedules of relevant clinical and laboratory testing, which have been successfully applied in previous studies of shorter regimens under field conditions and in the programmatic setting in South Africa.

The GDG emphasized the need to strengthen and increase access to DST, and the need to monitor and undertake surveillance for emerging drug resistance, including for bedaquiline and for all second-line medicines in the shorter regimen for which reliable DST are available. This should not delay implementation of the shorter regimen; however, monitoring and surveillance will become increasingly necessary as the use of the shorter regimen increases, as does the use of bedaquiline as part of the longer regimens. Resistance mutations to fluoroquinolones detected using MTBDRs/ should be considered a contraindication for the shorter regimen.

The WHO framework for aDSM needs to be applied, to ensure appropriate action and prompt response to adverse events, and an acceptable level of monitoring for such events, alongside monitoring for treatment outcomes. Additional information about aDSM is available in the relevant chapter of the operational handbook.

If feasible, it is also important to follow up patients after the completion of treatment, for possible relapse. Although this was not carried out routinely in the programmatic setting in South Africa, the data used to inform this PICO question were from 2017, and the EDRWeb data were reviewed again in 2019, which allowed detection of TB recurrence. Therefore, some post-treatment outcomes were available, even though follow-up post-treatment completion was not routinely carried out. Of the 653 patients who received the shorter all-oral bedaquiline-containing regimen in South Africa, 22 (3.4%) had an outcome of failure and recurrence combined. Although evidence from the STREAM trial did not inform this PICO question, the interim results from the STREAM trial indicated that relapse occurred in 3.3% of those in the study arm – a figure that was higher than that inferred from observational studies. However, the final results of the STREAM trial did not demonstrate a statistically significant higher rate of reversion, relapse or lack of conversion in patients using the shorter regimen.

The schedule of bacteriological monitoring in South Africa included both smear and culture, carried out on a monthly basis. Therefore, the response to treatment should be monitored by using monthly sputum smear microscopy, and culture (ideally at the same frequency). This is similar to the schedule of bacteriological monitoring recommended for the longer regimens ([Section 5](#)).

## Section 3. Longer regimens for multidrug- or rifampicin-resistant tuberculosis

Table 3.1 gives details of the grouping of medicines recommended for use in longer MDR-TB regimens, but 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.

### 3.1 Recommendations

No.	Recommendation
3.1	<b>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.</b> <i>(Conditional recommendation, very low certainty in the estimates of effect)</i>
3.2	<b>Kanamycin and capreomycin are not to be included in the treatment of MDR/RR-TB patients on longer regimens.</b> <i>(Conditional recommendation, very low certainty in the estimates of effect)</i>
3.3	<b>Levofloxacin or moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens.</b> <i>(Strong recommendation, moderate certainty in the estimates of effect)</i>
3.4	<b>Bedaquiline should be included in longer multidrug-resistant TB (MDR-TB) regimens for patients aged 18 years or more.</b> <i>(Strong recommendation, moderate certainty in the estimates of effect)</i> <b>Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years.</b> <i>(Conditional recommendation, very low certainty in the estimates of effect)</i>
3.5	<b>Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens.</b> <i>(Strong recommendation, moderate certainty in the estimates of effect)</i>
3.6	<b>Clofazimine and cycloserine or terizidone may be included in the treatment of MDR/RR-TB patients on longer regimens.</b> <i>(Conditional recommendation, very low certainty in the estimates of effect)</i>
3.7	<b>Ethambutol may be included in the treatment of MDR/RR-TB patients on longer regimens.</b> <i>(Conditional recommendation, very low certainty in the estimates of effect)</i>
3.8	<b>Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens.</b> <i>(Conditional recommendation, moderate certainty in the estimates of effect)</i>



No.	Recommendation
3.9	<b>Pyrazinamide may be included in the treatment of MDR/RR-TB patients on longer regimens.</b> <i>(Conditional recommendation, very low certainty in the estimates of effect)</i>
3.10	<b>Imipenem–cilastatin or meropenem may be included in the treatment of MDR/RR-TB patients on longer regimens.</b> <i>(Conditional recommendation, very low certainty in the estimates of effect)<sup>37</sup></i>
3.11	<b>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.</b> <i>(Conditional recommendation, very low certainty in the estimates of effect)</i>
3.12	<b>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.</b> <i>(Conditional recommendation against use, very low certainty in the estimates of effect)</i>
3.13	<b><i>P</i>-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.</b> <i>(Conditional recommendation against use, very low certainty in the estimates of effect)</i>
3.14	<b>Clavulanic acid should not be included in the treatment of MDR/RR-TB patients on longer regimens.</b> <i>(Strong recommendation against use, low certainty in the estimates of effect)</i>
3.15	<b>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.</b> <i>(Conditional recommendation, very low certainty in the estimates of effect)</i>
3.16	<b>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.</b> <i>(Conditional recommendation, very low certainty in the estimates of effect)</i>
3.17	<b>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.</b> <i>(Conditional recommendation, very low certainty in the estimates of effect)</i>

## 3.2 Justification and evidence

This section refers to recommendations on MDR-TB treatment regimens that are of longer duration than the 9–12 month shorter MDR-TB regimen described in Section 2. The recommendations in this section address PICO questions formulated in 2018 and 2019. The questions formulated in 2018 were as follows:

<sup>37</sup> 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 question 3** (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?*<sup>38</sup>

**PICO question 4** (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** (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** (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** (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** (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** (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?*

Recommendations for the design of longer MDR-TB regimens have been issued by WHO for a number of years, and have been implemented in many countries worldwide (1, 7, 10, 11). The recommendations in this section cover all forms of MDR/RR-TB; they include treatment of patients with strains susceptible to isoniazid, or with additional resistance to isoniazid (i.e. MDR-TB), or with resistance to other medicines from the first-line group (polyresistant), or from the second-line group. WHO recommends that all patients with TB – children or adults – diagnosed with strains shown to be resistant to rifampicin be placed on an MDR-TB treatment regimen (11). The addition of high-dose isoniazid or ethambutol (or both) could be considered to further strengthen the regimen.

The likelihood of treatment success in MDR/RR-TB patients on longer regimens depends on patient-level and strain factors (including severity of disease, resistance patterns and comorbidities), as well as access to health care (e.g. regimens with sufficient effective agents, medications of good quality, management of adverse events 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 (61–64). 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 the 2011 WHO guidelines (7). 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.

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<sup>38</sup> 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.

**Evidence base and analyses.** Ahead of the GDG discussion, WHO made a public call for individual MDR/RR-TB patient data, complete with results of treatment (65). IPD meta-analysis in adults and children treated with longer MDR-TB regimens allows the study of useful correlates of outcome, including the regimen composition (61–63). The evidence base for the effectiveness of many of the medicines used in MDR-TB regimens relies on the IPD meta-analysis. In turn, the IPD meta-analysis relies heavily on observational studies, only a few of which have employed randomized controlled conditions (66); hence, the overall certainty in the evidence is often graded as low or very low. The sources of data used by the GDG to address the PICO questions in this section are summarized below.

**PICO question 3 (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 contains new datasets from recent years in several countries, including a large dataset from South Africa with many patients treated with bedaquiline-containing regimens. Second, to analyse adverse events resulting in permanent discontinuation of individual medicines in longer regimens, a subset of 5450 records from 17 studies in the IPD was used, supplemented with additional information from 10 other studies that only reported adverse events for either bedaquiline ( $n=130$ ), linezolid ( $n=508$ ) or carbapenems ( $n=139$ ).

In addition to these data, the GDG also assessed unpublished results from the Phase III Trial 213 of delamanid (67, 68), and safety and pharmacological exposure data from unpublished paediatric studies of bedaquiline (Phase II TMC207-C211 and Phase I/II IMPAACT P1108) and delamanid (Phase I 242–12–245, Phase I 242–12–232, Phase II 242–07–204 and Phase II 242–12–233) (see Annex 5). The GDG 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 (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 (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. As this question focused on the number of agents in the intensive phase, 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 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 3** and **Annex 4** for the GRADE tables, and **Annex 6** for the analysis plan). Patients followed up for relapse and the number reported with relapse were relatively small. The three IPD subsets for PICO questions 4, 5 and 6 are discussed below.

***The analysis for PICO question 5 (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 whom 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:  $n=165$ .

***The evidence to inform PICO question 6 (MDR/RR-TB, 2018) (on regimen duration)*** 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:  $n=90$ .

***The analysis to address PICO question 7 (MDR/RR-TB, 2018) (on treatment duration after culture conversion)*** 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 8 (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 (69).<sup>39</sup> 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 (the subject of PICO question 8), and among patients with treatment success, from those who received at least 17.5 months of treatment in total. A total of 515 patients met these criteria. The intervention group comprised 242 patients who received bedaquiline for more than 203 days<sup>40</sup> in total, and they were compared to 273 patients who received bedaquiline for a total of 168–203 days. Additional data sources considered by the GDG 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 a Médecins Sans Frontières (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.

<sup>39</sup> These countries are Armenia, Bangladesh, Belarus, Democratic People's Republic of Korea, Ethiopia, Georgia, Indonesia, Kazakhstan, Kenya, Lesotho, Myanmar, Pakistan and Peru.

<sup>40</sup> 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. It should be noted that the cut-off was not 6 months exactly, but 203 days.

**PICO question 9 (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 7. 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. Due to the limited data available, 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 South Africa and Peru. Eligible patients were aged 18 years or more, with pulmonary MDR-TB (or rifampicin mono-resistance) receiving treatment for MDR-TB, but without clofazimine, and with moxifloxacin replaced by levofloxacin and a baseline corrected QT interval by Fredericia (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 8 and 9, the GDG 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 rifampicin-resistant TB (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 to 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 considered the need for the guidelines to cater also 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 reduces the likelihood of death and the emergence of additional resistance while minimizing harms. The GDG 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 (62). Children with XDR-TB 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 to partly address PICO question 9; the overall certainty in the estimates of effect for this study was judged to be low.

### 3.3 Remarks

The GDG 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 (MDR/RR-TB, 2018; see **Annex 3** and **Annex 4** 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 and 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, and are therefore no longer recommended for use in MDR-TB regimens.
- **Gatifloxacin and high-dose isoniazid, and thioacetazone** – gatifloxacin and high-dose isoniazid were used in very few patients, and thioacetazone was not used at all. Quality-assured preparations of gatifloxacin are not currently 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 [Section 3.4](#)).
- **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 under 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 II trial TMC207-C211 and Phase I/II IMPAACT P1108; see **Annex 5**) 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 or more enrolled in the trials – who were all 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 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, but stressed the need for more data before considering an upgrade of this recommendation to a strong one.

With respect to the use of delamanid in children aged under 6 years, the GDG decided that on the basis of 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 under 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 or more, for whom past GDGs convened by WHO had already recommended the use of delamanid (9, 70). 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 is available (50 mg), which is not bioequivalent and presents challenges to manipulating its contents without compromising its effectiveness.

**Table 3.1. Grouping of medicines recommended for use in longer MDR-TB regimens<sup>a</sup>**

Groups and steps	Medicine	Abbreviation
Group A: Include all three medicines	Levofloxacin <i>or</i> moxifloxacin	Lfx Mfx
	Bedaquiline <sup>b,c</sup>	Bdq
	Linezolid <sup>d</sup>	Lzd
Group B: Add one or both medicines	Clofazimine	Cfz
	Cycloserine <i>or</i> terizidone	Cs Trd
	Ethambutol	E
	Delamanid <sup>e</sup>	Dlm
	Pyrazinamide <sup>f</sup>	Z
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Imipenem–cilastatin <i>or</i> meropenem <sup>g</sup>	Ipm–Cln Mpm
	Amikacin ( <i>or</i> streptomycin) <sup>h</sup>	Am (S)
	Ethionamide <i>or</i> prothionamide <sup>i</sup>	Eto Pto
	<i>P</i> -aminosalicylic acid <sup>i</sup>	PAS

DST: drug susceptibility testing; ECG: electrocardiogram; GDG: Guideline Development Group; IPD: individual patient data; LPA: line probe assay; MDR-TB: multidrug-resistant tuberculosis.

<sup>a</sup> 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 [Section 2](#)). 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 5**).

<sup>b</sup> Bedaquiline is usually administered 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). Evidence on the safety and effectiveness of bedaquiline use beyond 6 months and in children aged under 6 years was insufficient for review in 2018. Therefore, the use of bedaquiline beyond 6 months was implemented following best practices in “off-label” use (77). New evidence on the safety profile of bedaquiline use beyond 6 months was available to the GDG in 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. It is important to note that the use of bedaquiline beyond 6 months still remains as off-label use and, in this regard, best practices in off-label use still apply.

- <sup>c</sup> 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. With regard to 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, but owing to the limited evidence and potential residual confounding in the data, the GDG was unable to proceed with a recommendation on effectiveness.
- <sup>d</sup> 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 whole duration of treatment would optimize its effect (about 70% of patients on linezolid with data received it for more than 6 months and 30% for 18 months or the whole duration). No patient predictors for early cessation of linezolid could be inferred from the IPD subanalysis.
- <sup>e</sup> Evidence on the safety and effectiveness of delamanid beyond 6 months and in children aged under 3 years was insufficient for review. The use of delamanid beyond these limits should follow best practices in “off-label” use (71).
- <sup>f</sup> Pyrazinamide is counted as an effective agent only when DST results confirm susceptibility.
- <sup>g</sup> 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.
- <sup>h</sup> 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. 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.
- <sup>i</sup> 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)<sup>a</sup>**

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 <i>or</i> 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 <i>or</i> terizidone	5483	0.6 (0.4–0.9)	6160	0.6 (0.5–0.8)

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)	
C	Ethambutol	1163	0.4 (0.1–1.0)	1245	0.5 (0.1–1.7)
	Delamanid	289	1.1 (0.4–2.8) <sup>b</sup>	290	1.2 (0.5–3.0) <sup>b</sup>
	Pyrazinamide	1248	2.7 (0.7–10.9)	1272	1.2 (0.1–15.7)
	Imipenem–cilastatin <i>or</i> 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 <i>or</i> prothionamide	2582	1.6 (0.5–5.5)	2750	2.0 (0.8–5.3)
	<i>P</i> -aminosalicylic acid	1564	3.1 (1.1–8.9)	1609	1.0 (0.6–1.6)
Other medicines	Kanamycin	2946	1.9 (1.0–3.4)	3269	1.1 (0.5–2.1)
	Capreomycin	777	2.0 (1.1–3.5)	826	1.4 (0.7–2.8)
	Amoxicillin–clavulanic acid	492	1.7 (1.0–3.0)	534	2.2 (1.3–3.6)

CL: confidence limit; GDG: Guideline Development Group; IPD: individual patient data; MDR-TB: multidrug-resistant tuberculosis.

<sup>a</sup> See also text, [Table 3.3](#) and [Annex 3](#), [Annex 4](#) and [Annex 5](#) for more detail on how the estimates were derived and the additional factors considered by the GDG when reclassifying medicines for use in longer MDR-TB regimens as shown in [Table 3.1](#).

<sup>b</sup> The values are the unadjusted risk ratios, as defined by the study investigators of Trial 213 by month 24.

**Regarding PICO question 4 (MDR/RR-TB, 2018) (number of agents likely to be effective)**, 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 likely to be effective. The analysis 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 adverse events 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 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](#)) (72), meaning that for most of its duration, the regimen would contain two key agents fewer than at the start. While 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 in 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 over 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 over 30% received it for more than 18 months, and these patients had the lowest frequency of treatment failure, loss to follow-up and death. A plot of linezolid duration and treatment failure suggests that the optimal duration of use would be around 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 adverse event and duration of use, although a few cases were reported with optic neuropathy, known to be associated with long-term use of linezolid (73), whereas haematological toxicity was reported regardless of duration of use.

**Table 3.3. Serious adverse events in patients on longer MDR-TB regimens<sup>a</sup>**

Medicine	Absolute risk of serious adverse event	
	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]
<i>P</i> -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 tuberculosis; TB: tuberculosis.

<sup>a</sup> From an “arm-based network” meta-analysis of a patient subset from the 2016 IPD for which adverse events 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 (72) 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 in 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-TB patients, including those with additional resistance to fluoroquinolones or other medicines.

**Regarding PICO question 8 (MDR/RR-TB, 2020) (use of bedaquiline longer than 6 months),** the analysis yielded adjusted odds ratios 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 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 noted that the population included in the studies that were assessed comprised a highly selected population, 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 concluded that a statement on safety could be made. This information is included in [Section 3.5](#) and in a table note for [Table 3.1](#).

With regard to adverse events, 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 adverse event (rate: 0.44 per 100 person-months of exposure), with 16 patients having this event classified as a serious adverse event (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 adverse events and 15 of the 16 serious adverse events occurred; the remaining six of the 26 drug-related adverse events and one of the 16 serious adverse events occurred subsequently. All patients who received bedaquiline for more than 203 days did not experience a drug-related adverse event (of any grade) in the first 203 days of treatment. Also, rates of treatment drug-related adverse events 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 adverse events 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 measures among people receiving bedaquiline increased by an average of 22 ms (from 397 ms to 419 ms) from measures 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 measures 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 adverse events 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 versus those who did not have this exposure ( $P=0.741$  for birth outcomes and  $P=0.312$  for pregnancy outcomes) (74). There were 45 live births (92% of total) in the bedaquiline exposed group versus 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) (74). The results of the study also demonstrated that treatment outcomes were favourable for pregnant women exposed to bedaquiline versus not exposed (71% versus 62%, respectively,  $P=0.349$ ) (74). Pregnancy outcomes included live births and unfavourable pregnancy outcomes (fetal and neonatal deaths, preterm births <37 weeks and low birth weight <2500 g) and infant outcomes included weight gain and developmental milestones and the diagnosis of TB (74). Of all pregnancy and infant outcomes assessed, only low birth weight was associated with bedaquiline exposure in utero (45% versus 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 (74). 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 ( $P=0.914$ ) (74).

**Regarding PICO question 9 (MDR/RR-TB, 2019) (use of bedaquiline and delamanid together)**, the analyses yielded adjusted odds ratios 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. With regard to adverse events, 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 adverse events and delamanid-related adverse events 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 adverse events 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 adverse events 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 measures among people receiving bedaquiline and delamanid increased by an average of 15 ms (from 398 ms to 413 ms) from measures 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 measures 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 adverse events 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 adverse event 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); also, another patient experienced a cardiac arrhythmia. Both of the 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 adverse events were absolute and not relative, the panel felt that this additional evidence was important for close monitoring in the future, 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 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 concomitant use of bedaquiline and delamanid; however, the GDG concluded that a statement on safety could be made. This information is included in [Section 3.5](#) 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 (Dooley K, unpublished data, Johns Hopkins Medicine, November 2019 – for this statement and the rest of this paragraph). Of the 27 patients who received both medicines, 10 (37.0%) experienced a Grade 1<sup>41</sup> QT prolongation adverse event, and two (7.4%) experienced a Grade 2 QT adverse event. In the bedaquiline arm, 32.0% and 3.6% of patients experienced Grade 1 and 2 QT adverse events; 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.

## 3.4 Subgroup considerations

**MDR/RR-TB alone or with additional resistance.** A longer regimen 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

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<sup>41</sup> 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 (Dooley K, unpublished data, Johns Hopkins Medicine, November 2019).



with resistance to isoniazid and ethionamide or prothionamide. Currently, there is no approved rapid test for pyrazinamide resistance, and phenotypic DST may require several weeks to produce a reliable result, implying that a DST-based decision to include or replace pyrazinamide could delay the start of treatment by several weeks, which is not desirable. 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 [Section 3.5](#)). NTPs should possess or rapidly build the capacity to undertake DST, and all efforts should be made to ensure access to approved, rapid molecular tests. Until the capacity for second-line 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 XDR-TB. 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 additional resistance, 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 [Section 2](#)). While 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 (75). High-dose isoniazid was shown to be an important component in paediatric regimens in a 2016 evidence review of the WHO guidelines, based on which its use in adults was extrapolated (62). In this analysis, high-dose isoniazid was associated with treatment success among children with confirmed MDR-TB (aOR: 5.9; 95% CL: 1.7–20.5,  $P=0.007$ ).

**Children.** 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 aged under 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 recommended the use of bedaquiline in children aged at least 6 years, and delamanid in children aged at least 3 years (see [Section 3.3](#)).<sup>42</sup> 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 in the foreseeable future (77). 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 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 2018 recommendation is primarily for adults).

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<sup>42</sup> Based on the results of an RCT conducted by the manufacturer, the US FDA has extended approval for the use of bedaquiline for children aged 5 years and above. However, these data have not yet been assessed by WHO.



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 (76), as do ethionamide/prothionamide, cycloserine/terizidone, linezolid and imipenem–cilastatin (77, 78). 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 may be useful if the strains are susceptible. *P*-aminosalicylic acid and ethambutol do not penetrate the CNS well, and 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 (79–81). In addition, cerebrospinal fluid concentrations may not mirror concentrations in the meninges or brain.

**Culture-negative TB.** Other durations of treatment may be appropriate for persons with culture-negative TB and Recommendation 3.16 does not apply. In such cases, if a longer regimen option is chosen, a total duration of 18–20 months of treatment is advised, and the response should be monitored by clinical parameters other than specimen bacteriology. A negative culture result may reflect poor laboratory performance rather than true sputum negativity, underscoring the importance of quality assurance in the laboratory.

**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 in 2019; it included information on 58 mothers who received bedaquiline during pregnancy (74). The results of this study indicated that fetal exposure to bedaquiline in utero was associated with low birth weight<sup>43</sup> (45% of babies exposed to bedaquiline had a low birth weight compared to 26% of babies not exposed,  $P=0.034$ ) (74). 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 (74). 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 (36)).

**Patients with extensive TB disease.** The duration of treatment post culture conversion may be modified according to the patient's response to therapy (e.g. culture conversion before 2 months of

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<sup>43</sup> Low birth weight was defined as less than 2500 g.

treatment) and other risk factors for treatment failure or relapse. This should be considered in patients with extensive TB disease.

**Patients on regimens without amikacin/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). This situation is expected to apply to an increasing proportion of patients in future 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.

### 3.5 Implementation considerations

The new recommendations signal an important departure from previous approaches to treating MDR/RR-TB. The implementation of MDR-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 (7). 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 (82).<sup>44</sup>

**Concurrent bedaquiline and delamanid use.** The GDG 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 with regard to 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.

With the exception of the carbapenems and bedaquiline in children, the latest WHO model list of essential medicines (83) includes all agents required for longer regimens.

<sup>44</sup> 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 (83).

**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, which could reliably identify resistance to fluoroquinolones, would help clinicians to decide whether the patient is eligible for the shorter MDR-TB regimen, and what agents to include in a longer MDR-TB regimen (the GenoType MTBDRs/ LPA may be used for this purpose). GenoType MTBDRs/ can be used in both children and adults for testing sputum specimens (direct testing) and cultured isolates of *M. tuberculosis* complex (indirect testing). The latter can be performed on culture isolates from both pulmonary and extrapulmonary sites. Direct testing on sputum specimens allows for the earlier initiation of appropriate treatment, and it can be applied irrespective of the smear status, although the indeterminate rate is higher when testing smear-negative sputum specimens than it is with smear-positive sputum specimens. Conventional phenotypic DST can still be used in the evaluation of patients with a negative GenoType MTBDRs/ result, particularly in populations with a high pretest probability for resistance to fluoroquinolones or if the patient is at high risk for fluoroquinolone resistance (or both). The new 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 based on DST results once they 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 a number of 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 take into account the relative benefits and harms to the individual patient, including drug–drug interactions.

**Bedaquiline use beyond 6 months.** It is generally agreed that most patients can be treated with four effective agents at the start of the therapy, one of which – usually bedaquiline – can usually be stopped at month 6. However, evidence assessed by the GDG in November 2019 supports the safety of using bedaquiline beyond 6 months in patients who receive appropriate schedules of baseline and follow-up monitoring. The GDG was not able to assess the relative effectiveness of prolonged bedaquiline use, owing to the limited evidence and to potential residual confounding in the data. The regimen needs to have at least three effective agents if bedaquiline is stopped at 6 months; thus, if another agent needs to be stopped because of toxicity, then that medicine would need to be replaced by another one.<sup>45</sup> The replacement medicine would be chosen from either Group B (unless both clofazimine and cycloserine or terizidone are already included) or Group C. The choice from Group C is determined by the order in which the medicines are ranked, and the individual circumstances of the patient and setting. Starting with five agents instead of four may be preferred in certain situations, to avoid the need to replace a medicine after treatment has started. Such situations include the following: two of the four agents are likely to be stopped before the end of treatment (e.g. if bedaquiline is stopped at month 6 and linezolid is stopped early because of toxicity); reliable DST is not available for one

<sup>45</sup> While replacement of one agent by another one because of toxicity may be acceptable, this should not be done if there are signs that the patient is not responding (e.g. persistent culture positivity or reversion to positive after culture has become negative). A need to replace two or more agents because of toxicity fulfils the definition of treatment failure (41).

or more of the agents on the regimen, but background resistance to the agent is known to be high; and the agents included in the regimen are unlikely to cure the patient (e.g. a total of only two of the agents from Group A and Group B are included in the regimen).

**Longer versus shorter regimens.** The conditionality of the recommendation for the use of the shorter MDR-TB regimen may require the patient and health care provider to decide on longer treatment in patients who are otherwise eligible for the shorter MDR-TB regimen, based on the individual circumstances. Such circumstances include uncertainty about DST results or lack of access to second-line LPA, unavailability of clofazimine or another component medicine, or the patient's condition requiring immediate start of treatment before all baseline testing can be completed. If the shorter MDR-TB regimen cannot be used, the patient needs to be reassessed with a view to starting a longer MDR-TB treatment regimen. Usually, a patient started on the shorter MDR-TB regimen can later be transferred to a longer regimen should the need arise. However, in general, patients who are placed on a longer regimen for at least 4 weeks can no longer be switched to the shorter regimen.

**Dosage and duration.** The guidelines update in 2018 concurrently revised the weight-based dosage schedules for medicines used in MDR-TB regimens for both children and adults (see the *Operational handbook on tuberculosis*). 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 (84). 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.<sup>46</sup>

In patients taking amikacin or streptomycin who are culture positive at the start of treatment, all three recommendations on the duration of treatment apply. For patients on an all-oral MDR-TB regimen, the length of treatment is determined by the recommendations on total duration and time after culture conversion (Recommendations 3.15 and 3.16, respectively). In patients with bacteriologically negative TB or most forms of extrapulmonary disease, Recommendation 3.15 on total duration is the only applicable recommendation.

The 6-month duration of use of bedaquiline and delamanid generally recommended in these guidelines reflects how these medicines have been used in most of the patient data reviewed, which is aligned to the prescribing recommendations that their manufacturers filed with regulatory authorities (e.g. (85–87)). New evidence on the safety profile of bedaquiline use beyond 6 months suggests that it is safe in patients who receive appropriate baseline and follow-up monitoring. However, in contrast to bedaquiline and delamanid, several of the other medicines included in MDR-TB regimens (e.g. fluoroquinolones and clofazimine) are used outside their licensed indication, and the recommended duration of use in MDR-TB regimens is often much longer than the one proposed for their original licensed purpose. Other medicines may need to be used for shorter durations because of toxicity associated with their long-term administration (particularly linezolid).

It is important to prevent treatment interruption, to increase the likelihood of treatment success. Measures that can help to increase retention include 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 (29).

## 3.6 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 (9, 60). The WHO framework for aDSM needs to be applied to patients on any type of MDR-TB regimen, to ensure

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<sup>46</sup> This is particularly problematic with the delamanid tablet, the contents of which are very unpalatable (see summaries of unpublished data for the 2018 guidelines update in Annex 5).

appropriate action and an acceptable level of monitoring for and prompt response to adverse events – alongside monitoring for treatment outcomes. Electrocardiography may be indicated as more regimens in the future may have two or three agents that are expected to prolong the QT interval. 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-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 [Section 5](#) 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 (9, 60). 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 (47). 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 (59, 60). In the case of this recommendation, it is important to monitor for hearing loss and kidney function, especially with the use of the aminoglycosides. The rationale for aDSM is largely supported by the increasing use worldwide of combinations of new and repurposed medications in MDR-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 local and global policy revisions (88).

## Section 4. The bedaquiline, pretomanid and linezolid (BPaL) regimen for multidrug-resistant tuberculosis with additional fluoroquinolone resistance

### 4.1 Recommendation

NEW RECOMMENDATION

No.	Recommendation
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- |     |  |
|-----|--|
| 4.1 | <b>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.</b><br><i>(Conditional recommendation, very low certainty in the estimates of effect)</i> |
|-----|--|

### 4.2 Remarks

- The bedaquiline, pretomanid<sup>47</sup> and linezolid (BPaL) regimen, which was used in the Nix-TB study<sup>48</sup> (89), may not be considered for *routine* programmatic use worldwide until additional evidence on efficacy and safety has been generated. However, in individual patients for whom the design of an effective regimen based on existing WHO recommendations is not possible, the BPaL regimen may be considered as a last resort under prevailing ethical standards.
- The evidence reviewed supports the use of this regimen in certain patient subgroups, such as PLHIV (see Section 4.4).

### 4.3 Justification and evidence

The recommendation in this section addresses the following question:

**PICO question 10** (MDR/RR-TB, 2020): *In XDR-TB patients or patients who are treatment intolerant or with non-responsive MDR-TB, does a treatment regimen lasting 6–9 months composed of bedaquiline, pretomanid and linezolid safely improve outcomes when compared with other regimens conforming to WHO guidelines?*

This is a new recommendation for a defined patient group; it is to be used under operational research conditions, and thus does not apply to routine programmatic use. Given these limitations, this recommendation complements other WHO recommendations on the use of longer regimens for patients with MDR/RR-TB (see Section 3) because individuals with MDR/RR-TB and additional fluoroquinolone resistance would usually receive a longer regimen comprising medicines from Groups A, B and C, according to their drug susceptibility profile and other parameters. Several conditions are therefore necessary for the implementation of this new recommendation on BPaL, and these are described in Section 4.5.

Treatment of XDR-TB presents multiple challenges to clinicians and NTPs, because of the limited range of medicines available and the life-threatening nature of the disease. Patients with MDR/RR-TB and additional fluoroquinolone resistance have typically experienced poor treatment outcomes since XDR-TB was first described in 2006 (90). Based on data reported by Member States to WHO, for the

<sup>47</sup> 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.

<sup>48</sup> The protocol for the Nix-TB study is available at <https://clinicaltrials.gov/ct2/show/NCT02333799>. <https://clinicaltrials.gov/ct2/show/NCT02333799>, and the results of the Nix-TB study have been published (90).



cohort of XDR-TB patients who started treatment in 2016 (and for whom treatment outcomes were available in 2018), only 39% completed treatment successfully, while 26% died, treatment failed for 18% and an additional 17% were lost to follow-up or were not evaluated (7).

**Evidence base and analyses.** 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 a number of studies and initiatives to test more effective and novel treatment regimens, including newer and repurposed medicines. One such study is the Nix-TB study, conducted by TB Alliance. The Nix-TB study was a one-arm, Phase III, open-label observational cohort study that assessed the safety, efficacy, tolerability and pharmacokinetic properties of a 6-month BPaL treatment regimen, extendable to 9 months for those who missed doses, or who remained culture positive or reverted from culture negative to positive between months 4 and 6 of treatment (89). The study was conducted between 2014 and 2019 at three study sites, all in South Africa, with the first patient enrolled in April 2015. Eligible patients were aged 14 years and above, weighed at least 35 kg, had a documented HIV result and had bacteriologically confirmed sputum culture positive XDR-TB or bacteriologically confirmed MDR/RR-TB, but were treatment intolerant or non-responsive to previous MDR/RR-TB treatment. A number of other inclusion criteria were applied (Box 2).

### Box 2. Inclusion criteria for the Nix-TB study, which used the BPaL regimen

The Nix-TB study's inclusion criteria were as follows:

1. Provide written, informed consent prior to all trial-related procedures (if under 18, include consent of legal guardian).
2. Body weight of  $\geq 35$  kg (in light clothing and no shoes).
3. Willingness and ability to attend scheduled follow-up visits and undergo study assessments.
4. Provide consent to HIV testing (if an HIV test was performed within 1 month prior to trial start, it should not be repeated as long as documentation can be provided [ELISA and/or Western Blot]). If HIV status is a confirmed known positive, repeated HIV test is not needed provided documentation is available.
5. Male or female, aged 14 years or above.
6. Subjects with one of the following pulmonary TB conditions:
  - a. XDR-TB with i. documented culture positive (for *M. tuberculosis*) results within 3 months prior to screening or *M. tuberculosis* confirmed in sputum based on molecular test within 3 months prior to or at screening; ii. documented resistance to isoniazid, rifamycins, a fluoroquinolone and an injectable historically at any time or at screening.
  - b. MDR-TB documented by culture positive results (for *M. tuberculosis*.) within 3 months prior to or at screening with documented non-response to treatment with the best available regimen for 6 months or more prior to enrolment who in the opinion of the investigator have been adherent to treatment and will be adherent to study regimen.
  - c. MDR-TB documented by culture positive (for *M. tuberculosis*) results within 3 months prior to or at screening who are unable to continue second-line drug regimen due to a documented intolerance to: i. *p*-aminosalicylic acid, ethionamide, aminoglycosides or fluoroquinolones; ii. current treatment not listed above that renders subject eligible for the study in the investigator's opinion.



7. Chest X-ray picture (taken within a year prior to screening) consistent with pulmonary TB in the opinion of the investigator.
8. Being of non-childbearing potential or using effective methods of birth control, as defined in the protocol.

Twenty exclusion criteria are listed in the protocol; they relate to medical history, specific medical treatments and laboratory abnormalities. For a complete list of the exclusion criteria, please see the protocol, available at: <https://clinicaltrials.gov/ct2/show/NCT02333799>.

Patients were followed up for a period of up to 24 months after completion of treatment. The primary outcome measure was the incidence of bacteriological failure, relapse or clinical failure (including TB-related deaths) through follow-up until 6 months after the end of treatment. Secondary outcome measures comprised:

- incidence of bacteriological failure or relapse or clinical failure through follow-up until 24 months after the end of treatment (as a confirmatory analysis);
- time to sputum culture conversion to negative status through the treatment period;
- the proportion of subjects with sputum culture conversion to negative status at 4, 6, 8, 12, 16 and 26 or 39 weeks;
- linezolid dosing (actual) and efficacy;
- change from baseline in TB symptoms;
- change from baseline in patient reported health status; and
- change from baseline in weight.

The Nix-TB study regimen comprised pretomanid administered at 200 mg once daily, bedaquiline administered at 400 mg once daily for the first 2 weeks of treatment (days 1–14) and then 200 mg three times a week thereafter, and linezolid commenced at 1200 mg per day (additional information on linezolid dosing is included in [Section 4.5](#)) (89). Close microbiological, clinical and adverse event monitoring were features of the Nix-TB study (89).

The evidence to inform PICO question 10 was derived from the Nix-TB study, and included information on 108 patients. The total study population was 109 patients, but one patient withdrew informed consent to participate in the study; this person was included in safety analyses but not in the analyses for effectiveness. These data were compared to a subset of data from the IPD, which overall included 13 273 individual patient records from 55 different studies or centres in 38 countries. For the primary analyses, the comparator group included patients from the IPD on longer treatment regimens (with a mean duration of treatment of 21.0–25.5 months), who received both bedaquiline and linezolid as part of the regimen (no patients received pretomanid in the IPD). This comparison group included data of 456 patients reported from Belarus, India, France, Russian Federation and South Africa, and from one study in a group of countries.<sup>49</sup> The intervention and comparison groups were matched exactly for XDR, MDR and fluoroquinolone resistance, and for HIV status, with propensity score matching for the variables of age, sex, baseline culture result, extent of disease (determined by baseline AFB smear or chest X-ray findings of cavitation or bilateral disease if the AFB smear result was missing) and country income level (using the World Bank Atlas method (91)). Treatment outcomes used in these analyses comprised the investigator-defined outcomes for the intervention group (i.e. for the Nix-TB study) and those largely based on WHO definitions<sup>50</sup> for the comparator group (i.e. for the patients included in the IPD). To allow an equal opportunity for treatment outcomes to occur from

<sup>49</sup> China, Philippines, Republic of Korea, Russian Federation, Thailand.

<sup>50</sup> These treatment outcomes conform to the definitions outlined in the paper by Laserson K.F. et al. (2005) (93) or in the WHO publication: Definitions and reporting framework for tuberculosis – 2013 revision (94).

the start of treatment when comparing the two groups, all outcomes were included from the start of treatment to 24 months after the start of treatment. Thus, in the intervention group, these outcomes occurred after completion of treatment and in the comparator group the outcomes were end-of-treatment outcomes (because patients in the IPD received a longer regimen and were not followed up after completion of treatment). Three other comparator groups from the IPD included patients on longer treatment regimens who received one of the following: a regimen that included bedaquiline, a regimen that included linezolid, or a regimen that included neither bedaquiline nor linezolid. The GDG's initial intention was to assess the intervention regimen against all three comparison groups; however, during their deliberations, the panel agreed that the judgements should be based on the comparison group who received bedaquiline and linezolid as part of their regimen, because these patients most closely resemble patients who would receive currently recommended longer regimens composed with medicines from Groups A, B and C. However, a direct comparison of BPaL with all-oral longer regimens constructed according to the most recent WHO recommendations issued in March 2019 was not possible, because these regimens may have only been in use since mid-2019, so treatment outcomes for these patients are not yet available. 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.

Additional data reviewed by the GDG relevant to PICO question 10 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 review of preclinical and early clinical data on pretomanid. The cost-effectiveness analysis, acceptability study and modelled pharmacokinetic studies were conducted along with the Nix-TB study and were sponsored by TB Alliance.

The aims of the cost-effectiveness study were twofold:

- to estimate the cost-effectiveness of a new regimen (BPaL) compared with the standard of care at a given price; and
- to estimate the maximum drug price at which the BPaL regimen could be considered cost effective or cost neutral in each setting.

There were two patient populations: XDR-TB patients; and XDR-TB patients combined with MDR-TB patients who failed treatment or who were treatment intolerant. The comparison treatment regimen was the standard of care in Georgia, the Philippines and South Africa, and the main outcome of interest was the incremental cost per disability adjusted life year (DALY) averted. A health service perspective was taken.

The objective of the acceptability study was to assess the acceptability and likelihood of implementation of the BPaL regimen as anticipated by key stakeholders based on a number of criteria including perceived benefits and challenges of implementation of BPaL and also longer individualized treatment regimens and other practical requirements of implementation. The study was a mixed-methods, multicountry, cross-sectional study conducted in 2018–2019 among stakeholders in Indonesia, Kyrgyzstan and Nigeria. A total of 188 participants offered their views; they included caregivers, programmatic stakeholders (including national and international programmatic stakeholders and patient advocacy groups), and public and private laboratory stakeholders.

Additional evidence presented included modelled pharmacokinetic data based on the development of a pharmacokinetic toxicodynamic model designed to quantify the relationship between pharmacokinetic features of linezolid and toxicity as part of a 6-month BPaL regimen. Modelled data from 88 patients who received linezolid as part of the Nix-TB study were presented. This patient population included information on seven patients who had died. A total of 21 individuals from the Nix-TB study were excluded from these analyses – 16 because they had incomplete dosing histories (i.e. they were receiving ongoing treatment at the time of analysis) and five because they had an unverifiable dosing history.

Additionally, the GDG was presented with an independent summary review of the preclinical and early clinical data on pretomanid. This review included background information, preclinical data and early phase clinical data detailing safety and efficacy, including data submitted to the United States Food and Drug Administration (US FDA) as part of the original new drug application or as supplemental information.

**GDG considerations.** The GDG considered the desirable effect of treatment success, which was higher in the intervention group than in the comparator, for all four treatment outcomes assessed. Overall, when comparing treatment success versus failure or recurrence, the treatment success rate was 97.0% in the Nix-TB study and 91.7% in the comparator group (resulting in 6 more outcomes of treatment success per 100 patients). For the comparison of treatment success versus death, treatment success was 93.2% in the Nix-TB study and 91.9% in the comparator group (resulting in 1 more outcome of treatment success per 100 patients). For the comparisons of treatment success versus failure, recurrence or death, and treatment success versus all unfavourable outcomes combined (i.e. failure, relapse or death, and loss to follow-up) the proportions of patients with treatment success in the intervention and comparator groups were 90.5% versus 84.8% (6 more outcomes of treatment success per 100 patients) and 88.9% versus 82.2% (2 more outcomes of treatment success per 100 patients), respectively. Based on these figures, the primary analysis yielded adjusted odds ratios of 3.3 for treatment success (versus the combined outcome of failure and recurrence; 95% CI: 0.8–13.7), 1.0 for success versus death (95% CI: 0.1–8.2), 1.8 for success versus failure, relapse or death (95% CI: 0.7–4.4), and 1.2 for success versus all unfavourable outcomes (95% CI: 0.5–3.1), with a mean duration of follow-up of 24 months (range 21.0–25.5 months), when BPaL was compared to longer regimens containing bedaquiline and linezolid. The GDG considered lower rates of loss to follow-up as a desirable effect; the proportion of patients who were lost to follow-up was lower in the intervention (BPaL) group (1.8%) than in the comparison group (3.1%); however, this difference was not considered by the panel to be large. The panel also considered that a shortened duration of treatment and less drug exposure were desirable effects of the intervention, and that both of these were components of the overall burden of a given MDR/RR-TB treatment regimen, which may not be wholly reflected in rates of loss to follow-up alone. Subgroup analyses could not be undertaken because of the small sample size.

The BPaL regimen was also associated with a high rate of adverse events, relative to the study drugs, which was a concern for GDG members. Of the 109 patients in the Nix-TB study, 28 (25.7%) experienced at least one serious adverse event. This included one (0.9%) death related to acute haemorrhagic pancreatitis, 29 (26.6%) other serious adverse events including hospitalizations and life-threatening events, and two (1.8%) adverse events that resulted in persistent or significant disability or incapacity. A total of 53 (49%) patients experienced at least one Grade 3–4 adverse event considered to be related to the study drugs; these comprised 25 with peripheral neuropathy (11 resolved), 16 with increased hepatic transaminases (13 resolved), nine with haematologic adverse events (all resolved), eight with increased pancreatic enzymes (7 resolved) and two with optic neuritis (both resolved). This led to all three drugs being discontinued in one patient, and linezolid (initial dose 1200 mg/day) being discontinued in another 35 (32%) patients. Only 20 (18%) patients completed a full course of linezolid at 1200 mg/day. The GDG discussed the difficulty of comparing these adverse event rates with other studies, owing to major and important differences in ascertaining, assessing and reporting adverse events. However, in the IPD studies (where 90% of patients received a linezolid dose of  $\leq 600$  mg/day), the pooled rate of permanent discontinuation of linezolid was 17.9%, and in the endTB observational study (where all patients received a linezolid dose of  $\leq 600$  mg/day), the rate of linezolid discontinuation was 13.1%. In both of these studies, more than 80% of patients received a starting dose of linezolid of 600 mg per day. In preliminary analyses of the endTB observational study, nine patients out of 1094 (0.8%) died of an adverse event that was possibly or probably drug related, including two individuals with sudden cardiac death; these two patients were receiving bedaquiline, clofazimine, capreomycin and *p*-aminosalicylic acid, and both had hypokalaemia.

Information from the independent review on the preclinical and early phase clinical data highlighted that pretomanid possesses activity against replicating and non-replicating bacilli that is both concentration and dose dependent. Safety signals were comprehensively described, many of which were observed at exposures that are higher than would be used in humans; however, safety signals of note included liver toxicities (hypertrophy of hepatocytes, transaminase elevation and increased liver weight, observed at higher doses in rodents and lower doses in monkeys) and reproductive toxicities in males observed in animal (murine and simian) models, which appear to be both time and dose dependent. The observations in monkeys may have been due to the general decline of health in these animals; however, the same signals were observed in rodent models, with some evidence that these effects may be irreversible. In mouse models, these effects were observed at exposures that would be used in humans, and in females, reproductive toxicities were also observed.

Additional information on adverse events presented to the GDG included the results of a pharmacokinetic toxicodynamic model (Savic R, unpublished data, University of California, San Francisco, November 2019). Based on these data, it was concluded that the pharmacokinetics of linezolid are nonlinear in XDR-TB patients, and that individual linezolid concentration–time profiles are the best predictor of toxicity. Higher toxicity rates were observed at higher total daily doses, with comparable toxicity rates for BID (twice a day) and QD (once a day) dosing schedules. The results of the modelled data highlighted that anaemia can be managed by closely monitoring changes in haemoglobin over the first 4 weeks of treatment (in particular, changes in haemoglobin >10% decrease from baseline should trigger a reduction in the dose of linezolid; haemoglobin levels recover well after dose reductions). Thrombocytopenia was not a major concern. The study investigators recommended that peripheral neuropathy should be closely monitored; based on the modelled data, when peripheral neuropathy did occur, for most patients, it was reversible within 3 months. The GDG was concerned that the two studies had different findings with regard to reversibility of peripheral neuropathy (i.e. one study found that it was largely reversible, the other study had different findings).

The panel considered at length the desirable and undesirable effects, and the balance of these effects, noting the very low certainty of the evidence and acknowledging the efforts to match patients in the intervention and comparator groups (through exact and propensity score-based matching). Overall, the GDG agreed that the BPaL regimen showed high rates of treatment success when used in XDR-TB patients in South Africa, and they noted the additional positive treatment outcomes resulting from the use of the regimen when compared with patients receiving longer regimens with bedaquiline and linezolid. However, there were important residual concerns about the likelihood and severity of adverse events, possible reproductive toxicity signals in the preclinical data, limitations in the study design and the overall very low certainty of the evidence. The GDG was concerned that the Nix-TB study was a one-arm study with no in-study comparison group, including 109 participants overall recruited from one country setting (South Africa), with the inclusion of a group of patients who were sputum culture negative at baseline, and many patients receiving second-line treatment of variable duration before being enrolled on BPaL. The GDG agreed that this might limit the generalizability of the study findings to all populations and to all regions.

The GDG was concerned about issue of serious adverse events, particularly those related to linezolid, and pretomanid-associated potential safety signals related to male infertility observed in animal models (murine and simian). They highlighted the potential difficulties in monitoring infertility in a programmatic setting. Additional human sperm studies recommended by the US FDA will be carried out by TB Alliance; however, these data were not available for the GDG to consider at the time of the meeting. The GDG determined that infertility is a serious issue because it affects both patients and their families. The GDG also acknowledged that, at the time the Nix-TB study started, treatment options for patients with MDR-TB and additional fluoroquinolone resistance were limited in South Africa, with an associated high case fatality rate, which meant that patients may have placed a different value on potential male infertility at that time than they might now. The judgement about the balance of the desirable and undesirable effects was therefore assessed as not favouring the intervention or the comparison.

With regard to how much patients might value the outcomes, no research evidence was available for the GDG to consider. Although no research evidence was identified, the GDG felt that there was possibly important uncertainty or variability in how much people would value the main outcomes. Fertility was raised as an outcome for which there is less information at the present time. The GDG thought that this issue would increase the complexity of the judgement about how much people would value the outcomes. They discussed the fact that there are other safety outcomes (e.g. other adverse events, including peripheral neuropathy) that may vary, and that people may value these outcomes differently. The GDG considered indirect evidence in the form of a separate qualitative study conducted among 16 drug-resistant TB patients from high burden countries (which informed the judgements on PICO question 2, described in [Section 2](#)). The aim of the study was to determine the most acceptable treatment regimen for drug-resistant TB from the patient perspective. Based on the results of this study, the preferred MDR/RR-TB treatment regimen from the perspective of the patients who were interviewed was a short, injectable-free regimen with few to no physical or mental health side-effects, and a low pill burden.

The cost-effectiveness study determined that the use of BPaL for the treatment of XDR-TB is likely to be cost saving at the proposed price (US\$ 364 per treatment course for pretomanid), in the settings in which it was studied. The study found that cost savings are a function of the cost of care and the magnitude of XDR-TB burden, and are about US\$ 4490 (not including ART costs) in South Africa, US\$ 4060 in Georgia and US\$ 3860 in the Philippines. In high HIV-TB prevalence settings, such as South Africa, related future costs such as those from the HIV programme (ART costs) reduce the magnitude of expected cost savings to US\$ 1400 per patient. Overall, when BPaL is introduced to a larger population (including MDR/RR-TB treatment failure and people with MDR-TB who are treatment intolerant), the GDG observed an increase in the incremental benefits, both in terms of deaths and DALYs averted, and incremental costs. The study investigators concluded that the impact of BPaL on costs and DALYs averted will depend on the overall performance of the NTP (e.g. considering rates of loss to follow-up or mortality). The GDG noted that food costs were not included in the cost-effectiveness analysis, and would need to be considered when BPaL is implemented. During the Nix-TB study, all study medications were administered with food (attributable to the administration of bedaquiline, which will also now feature as a core medicine in longer treatment regimens for MDR/RR-TB). The GDG noted that the cost-effectiveness analysis was not specific to the other evidence that was presented; most importantly, the undesirable effects were not considered according to the GDG's judgements. This made the cost-effectiveness analyses informative, but not directly based on the evidence that the GDG was assessing.

Although no research evidence was identified on equity, the GDG felt that the impact on health equity would be a probable increase, given the option of a shorter regimen that could be available to all patients, globally. The GDF identified a price for pretomanid and stated that it will make the BPaL regimen available to NTPs, depending on the recommendation from the panel. Children and pregnant women were ineligible for inclusion in the Nix-TB study, and therefore will not be an eligible population for BPaL at the present time.

Acceptability was higher for BPaL than for the longer MDR-TB regimens in six of the seven acceptability categories assessed (ranging from patient friendliness to treatment safety monitoring), with the exception of treatment safety monitoring, where the difference was negligible. The main drivers of the acceptability of BPaL were the shorter duration, absence of injectables, lower pill burden, anticipated patient preferences and lower financial burden for patients, anticipated higher treatment success, lower costs for the health system, minimal additional requirements for diagnostic processes, and a lower anticipated per patient burden to TB laboratories for bacteriological treatment monitoring. The GDG thought that the intervention was probably acceptable to key stakeholders. There were residual concerns about the acceptability of the intervention, given the potential reproductive toxicities (which were not specifically discussed with study participants because they were not known to the study investigators at the time) and the comparator that was used in this study (which was not the same



as the comparator assessed by the GDG). Therefore, the GDG felt that the acceptability study was informative, but was not based directly on the evidence that was assessed.

In line with the overall high acceptability of the BPaL regimen, the likelihood of implementing the BPaL regimen as a standard of care for the treatment of patients with XDR-TB and MDR-TB treatment failure or persons with MDR-TB who are treatment intolerant scored at 88%; only 1% of the 166 participants scored the implementation as “unlikely”, and 11% had a neutral opinion. The likelihood of implementation was similar for the BPaL regimen as a standard of care for MDR-TB patients with fluoroquinolone resistance, with a score of 84%, regardless of additional resistance to second-line injectables. This indicated that those interviewed generally felt that it may be feasible to implement the regimen.

The GDG noted that more research studies are needed in the future, which may allow a more closely aligned comparison group, with less potential for residual confounding and more certainty in the evidence overall. The GDG also emphasized that it will be necessary for WHO to review, revise or update this guidance, as additional substantive data on the efficacy and safety of the BPaL regimen become available. Therefore, as the evidence base on the use of BPaL increases, researchers and NTPs are encouraged to make these data available for international policy-making.

**Unpublished data.** After the GDG meeting, the TB Alliance shared with WHO an additional report (unpublished and confidential at the time of the release of the current guidelines) that included comparison of data from the Nix-TB study with a cohort of patients with XDR-TB, treated at one of the study sites. The comparison group in these analyses comprised 102 XDR-TB patients treated in a programmatic setting in South Africa, between November 2013 and April 2016. All patients in the comparison group had laboratory-confirmed XDR-TB, with TB isolates resistant to rifampicin, isoniazid, ofloxacin and amikacin. About half of the patients in the comparison group had HIV infection (51.0%). These comparative analyses were carried out by a data analyst under contract to the TB Alliance, who used a methodology that differed from that used for the analyses that informed the WHO recommendation on the use of BPaL presented in these guidelines, and no IPD were provided. Thus, the comparative analyses are not directly comparable to the analyses presented in **Annex 3**. Although this report could not be considered by the GDG during the November 2019 meeting (given that it was not made available until after the meeting), it was reviewed by the WHO Guideline Steering Group and the GDG before finalizing the guidelines document. The comparison in this report reinforces the positive treatment success rates that have been observed with the use of the BPaL regimen. In these analyses, the treatment success rate for patients receiving BPaL was 89.9% (98/109) versus 66.7% (56/84) for patients receiving another XDR-TB regimen that also contained bedaquiline and linezolid, yielding an adjusted risk ratio of 1.31 (95% CI: 1.11–1.55,  $P=0.0012$ ). The detailed data that supported this comparison, together with the results of operational research in other settings, may be useful for informing policy recommendations on the use of BPaL in the future.

## 4.4 Subgroup considerations

**Children.** Children (aged 0–13 years) were excluded from the Nix-TB study; therefore, no analysis specific to this subgroup of patients could be performed. It is recommended that children with pulmonary MDR/RR-TB with additional resistance to fluoroquinolones be given the same consideration for longer treatment regimens as adults, to include components with a safety profile that is better established. Bedaquiline is currently only recommended for children aged 6 years and above.<sup>51</sup> Additional data on the use of BPaL in eligible children would be useful, and this may be a feature of carefully planned and monitored future research.

**People living with HIV.** PLHIV represented half of those enrolled in the Nix-TB study; however, it was impossible to perform any adjusted stratified analyses for PLHIV, owing to the small sample size.

<sup>51</sup> Based on the results of an RCT conducted by the manufacturer, the US FDA has extended approval for the use of bedaquiline for children aged 5 years and above. However, these data have not yet been assessed by WHO.

PLHIV were eligible to enrol in the Nix-TB study if they had a CD4 count of more than 50 cells/ $\mu$ L and if they were using permitted antiretroviral medications.<sup>52</sup> It is important to note drug–drug interactions when administering TB and HIV medications in combination, including the documented interactions between bedaquiline and efavirenz (see also (36)). Efavirenz also reduces pretomanid exposures significantly – therefore, an alternative antiretroviral agent should be considered if pretomanid or the BPaL regimen is to be used (94). Regimens including zidovudine should be used with special caution because zidovudine and linezolid may both cause peripheral nerve toxicity, and they are known to have myelosuppression cross toxicity.

**Pregnant and lactating women** were excluded from the Nix-TB study; therefore, no analysis specific to this subgroup of patients could be performed. For pregnant and lactating women, a longer regimen should be individualized to include components with a safety profile that is better established. Where this is the case, the outcomes of treatment and pregnancy (including infant characteristics), and postpartum surveillance for congenital anomalies should be documented to help inform future recommendations for MDR-TB treatment during pregnancy. The use of bedaquiline in pregnancy has been shown to be associated with infants born with a lower mean birth weight, when compared with infants whose mothers did not take bedaquiline; however, this did not appear to be a clinically significant finding when infants were followed up over time (see Section 3.2). Breastfeeding is not recommended for women taking BPaL (94).

**Extrapulmonary TB.** Patients with extrapulmonary TB were excluded from the Nix-TB study; therefore, no analysis specific to this subgroup of patients could be performed. The WHO recommendations on MDR-TB regimens apply to patients with extrapulmonary disease, including for those with TB meningitis. There are few data on the CNS penetration of bedaquiline or pretomanid.

**Patients with very limited treatment options.** In some instances, patients will have extensive drug-resistance profiles that may make it difficult (or impossible) to construct a regimen based on existing WHO recommendations. In such situations, the patient’s life may be endangered. Therefore, for individual patients for whom it is not possible to design an effective regimen based on existing recommendations,<sup>53</sup> the BPaL regimen may be considered as a last resort under prevailing ethical standards. In such patients, the use of BPaL should be accompanied by individual patient informed consent, adequate counselling on the potential benefits and harms, and active monitoring and management of adverse events. Patients should also be advised that reproductive toxicities have been observed in animal studies, and that the potential effects on human male fertility have not been adequately evaluated at this time.

## 4.5 Implementation considerations

Given the paucity of evidence on the use of BPaL, and the concerns mentioned above, members of the GDG suggested that it should be implemented only in the context of operational research. The GDG emphasized that, despite the promising treatment success rates observed in the Nix-TB study, the regimen may not be considered for programmatic use worldwide until additional evidence on efficacy and safety has been generated. The group emphasized the need for this research to take the form of RCTs as well as observational studies. Given the conditionality of this recommendation in the context of additional research, certain standards and principles are prerequisites for the implementation of BPaL. Further, the GDG emphasized that the principles of good clinical practice should apply in any operational research study involving BPaL.

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<sup>52</sup> These permitted antiretroviral treatments were: 1. nevirapine in combination with any nucleoside reverse transcriptase inhibitors (NRTIs), 2. lopinavir/ritonavir in combination with any NRTIs, 3. tenofovir/lamivudine/abacavir (if normal renal function), 4. triple NRTI therapy consisting of zidovudine, lamivudine and abacavir (however, noting the increased risk of peripheral nerve toxicity with zidovudine and linezolid), and 5. raltegravir in combination with NRTIs.

<sup>53</sup> Usually this group of patients would include those with an extensive drug-resistance profile who have very limited treatment options as part of a longer treatment regimen.



**Patient selection.** Overall, to reproduce the treatment success rates observed in the Nix-TB study, all efforts need to be made to carefully select eligible patients. Once those patients are enrolled, it is also important to provide effective patient support to enable adherence to treatment, and close monitoring for adverse events, response to treatment and emerging drug resistance. As outlined below, all efforts should be made to ensure proper patient inclusion; obtain signed patient informed consent; administer treatment under closely monitored conditions; and ensure active pharmacovigilance and proper management of adverse drug reactions, and prevention of complications from drug–drug interactions.

*Ensure proper patient inclusion* – use is not advised in pregnant and lactating women and in children, and the Nix-TB study gives other inclusion and exclusion criteria. Although DST is an important component of patient selection for the BPaL regimen (described below), another key implementation consideration is prior TB treatment history. Patients are eligible for the BPaL regimen if they have not received bedaquiline or linezolid for 2 weeks or more previously, and this was an eligibility criterion of the Nix-TB study. Given that the current WHO recommendation for longer treatment regimens for MDR/RR-TB includes bedaquiline and linezolid as priority medicines in Group A, some patients who have previously started treatment on a longer MDR/RR-TB regimen may in fact be ineligible for BPaL should they later develop fluoroquinolone resistance. This reaffirms WHO's previous statements on the need to carefully select eligible patients for longer or shorter MDR/RR-TB treatment regimens, and once patients are receiving a regimen, to ensure patient support and close monitoring and follow-up, including monitoring for treatment failure and relapse, and emerging drug resistance, with DST performed when indicated. If resistance is suspected during treatment and DST is not available, the strains should be conserved and referred to a WHO SRL for further testing. Each operational research protocol on the use of BPaL in a given setting will need to include detailed inclusion and exclusion criteria.

*Obtain signed patient informed consent* – consent should be obtained after giving detailed explanations on the novel nature of the regimen and pretomanid, including the risks and benefits of the regimen. The GDG members thought that informed consent should not be overly burdensome for patients; consent forms should be adapted, contextualized, streamlined and provided in the local language(s) so that they are easy for patients to understand; and patients should be fully informed about the regimen, given that it also includes a new compound, pretomanid. As part of the informed consent process, patients should be:

- offered sufficient information on potential adverse events including low blood cell counts (e.g. anaemia, thrombocytopenia and neutropenia), liver toxicities, and peripheral and optic neuropathy;
- advised that reproductive toxicities have been observed in animal studies, and that the potential effects on human male fertility have not been adequately evaluated at this time; and
- informed that pretomanid is excreted in breast milk, and its safety in infants and children has not been adequately evaluated (94).

A medication guide is available as part of the pretomanid product label; this guide may be used when informing patients about the BPaL regimen as part of a research study.

*Administer treatment under closely monitored conditions* – the aim is to enable optimal drug effectiveness and safety, and to monitor for the acquisition of emerging drug resistance, should it arise. Given that the regimen is a shorter regimen (i.e. it includes a new compound – pretomanid) and that its implementation is in the context of research, it may be especially important to monitor clinical progress after completion of treatment, to ensure relapse-free cure. Other design features of the Nix-TB study have implications for its implementation under operational research conditions. In the Nix-TB study, all medications were administered with food throughout and study medications were supervised according to local site practices, as a form of patient support. Preventing treatment interruption increases the likelihood of treatment success. 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

though the regimen is comparatively short (29). WHO recommendations on the care and support of patients with MDR/RR-TB are provided in [Section 8](#).

*Active pharmacovigilance and proper management of adverse drug reactions, and prevention of complications from drug–drug interactions* – the NTP should actively monitor drug safety to ensure proper patient care, to report any adverse drug reactions to the responsible drug-safety authority in the country, and to inform national and global policy.

The implementation of the BPaL regimen in the context of operational research implies that:

- a study protocol has been developed by appropriately skilled and experienced researchers, and that this research protocol has been submitted to a national ethics board or other ethical approval committee;
- prespecified inclusion and exclusion criteria are in place (noting the criteria used for the Nix-TB study);<sup>54</sup>
- an appropriate schedule of safety monitoring and reporting is in place, including aDSM – usually overseen by a data safety monitoring board or similar independent research governance committee;
- a predefined schedule of clinical and microbiological monitoring is in place, preferably including post-treatment completion follow-up;
- individual patient informed consent is obtained;
- patient support is provided; and
- standardized reporting and recording is used, including for adverse events.

Review of treatment and management protocols by an independent group of experts in clinical management and public health (e.g. the national MDR-TB advisory group) is recommended.

**DST** is an important implementation consideration that will need further enhancement in many countries, given the increasing potential use of bedaquiline and linezolid (even for longer regimens for MDR/RR-TB), and the inclusion of new medicines (e.g. pretomanid) in MDR-TB treatment regimens. Baseline DST will confirm eligibility for the BPaL regimen; hence, the establishment and strengthening of DST services will be a vital consideration for implementation.

In patients with bacteriologically confirmed MDR/RR-TB,<sup>55</sup> the MTBDRs/ assay may be used as the initial test, in preference to culture and phenotypic DST, to detect resistance to fluoroquinolones (conditional recommendation; certainty of evidence for direct testing of sputum from low to moderate (33)). In settings in which laboratory capacity for DST to fluoroquinolones is not yet available, or cannot be accessed, it will be difficult to carry out operational research on BPaL. If testing for susceptibility to bedaquiline or linezolid is available, it is highly desirable to also carry this out at baseline and in the absence of culture conversion during treatment; however, such testing need not be a prerequisite for treatment initiation. Drug susceptibility testing for pretomanid is not yet available.

Currently, there is limited capacity globally for DST for bedaquiline and linezolid; as these medicines and regimens become more widely used, laboratory capacity in this area should be strengthened. National and reference laboratories will need to have the reagents for DST available, and will need data on the MIC distribution of all *M. tuberculosis* lineages that are circulating globally. If resistance to any of the component medicines in the BPaL regimen is detected, treatment with a longer MDR-TB regimen should be started. The WHO SRL Network is available to support national TB reference laboratories in performing quality-assured DST. A WHO technical consultation in 2017 established

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<sup>54</sup> The protocol for the Nix-TB study is available at: <https://clinicaltrials.gov/ct2/show/NCT02333799>.

<sup>55</sup> MDR/RR-TB is usually confirmed by rapid molecular tests that detect resistance to rifampicin and *M. tuberculosis*. Current WHO recommendations state that Xpert MTB/RIF should be used rather than conventional microscopy, culture and DST as the initial diagnostic test in adults suspected of having MDR-TB or HIV-associated TB (strong recommendation, high-quality evidence). Xpert MTB/RIF should also be used rather than conventional microscopy, culture and DST as the initial diagnostic test in children suspected of having MDR-TB or HIV-associated TB (strong recommendation, very low quality evidence) (24). A recent WHO rapid communication reinforced the high diagnostic accuracy and improved patient outcomes of rapid molecular diagnostic tests such as Xpert MTB/RIF, Xpert MTB/RIF Ultra and TrueNat (37).

critical concentrations for DST for the fluoroquinolones, bedaquiline, delamanid, clofazimine and linezolid (58). Methods for testing pretomanid susceptibility are currently under development.

**Dosing of linezolid.** The linezolid dosage used in the Nix-TB study was 1200 mg per day. Initially, all study participants received 600 mg of linezolid BID, because that was the approved dose used to treat bacterial infections for up to 28 days at the time the study commenced. However, in May 2018, the protocol was changed to dosing of 1200 mg QD. According to the protocol, dose reduction to 600 mg daily, and further to 300 mg daily or temporary cessation of linezolid, was permitted for up to 35 consecutive days for any known linezolid adverse reactions of myelosuppression, peripheral neuropathy and optic neuropathy. If toxicity prohibited further treatment with linezolid, patients could remain on bedaquiline and pretomanid, provided that they had received the 1200 mg per day dose for at least the first 4 consecutive weeks, were sputum smear negative, and were responding to treatment based on clinical monitoring and follow-up. Missed doses of linezolid were not made up during the Nix-TB study, and dose modifications for bedaquiline and pretomanid were not allowed. Overall, 18 patients (17.3%) in the Nix-TB study completed a full course of linezolid at the 1200 mg dose, 38 (36.5%) completed with a 600 mg dose, 16 (15.4%) completed with a 300 mg dose and 32 (30.7%) stopped linezolid early due to an adverse event. The experience of the Nix-TB study suggests that it may be necessary to modify the dose of linezolid during treatment based on adverse events, highlighting the importance of close monitoring and patient follow-up, and aDSM. Additional studies such as the ZeNix study (TB Alliance) are underway to assess the optimal dosing and duration of linezolid for the treatment of drug-resistant TB; however, the results of these studies are not yet available for review.

To date, the BPaL regimen has been studied as a standardized course of treatment. Modification of the regimen through early discontinuation or replacement of any of the component medicines may result in poor treatment outcomes. The pretomanid product label recommends that if either bedaquiline or pretomanid tablets are discontinued, the entire BPaL regimen should also be discontinued. If linezolid is permanently discontinued during the initial 4 consecutive weeks of treatment, bedaquiline and pretomanid should also be discontinued. If linezolid is discontinued after the initial 4 weeks of consecutive treatment, clinicians should continue administering bedaquiline and pretomanid, consistent with the Nix-TB study protocol. In the Nix-TB study, it was necessary for patients to complete 6 months of the regimen (i.e. 26 weeks of prescribed doses) within 8 months; for those in whom treatment was extended, it was necessary for patients to complete 9 months of treatment (i.e. 39 weeks of prescribed doses) within 12 months. Patients who remained culture positive or who reverted to being culture positive between months 4 and 6, and whose clinical condition suggested they may have ongoing TB infection, had their treatment extended to a total of 9 months.

## 4.6 Monitoring and evaluation

Patients who receive BPaL (or any shorter regimen for the treatment of MDR/RR-TB) need to be tested at baseline and then monitored during treatment using schedules of relevant clinical and laboratory testing. According to the product label of pretomanid, baseline assessments before initiation of the BPaL regimen include assessments for symptoms and signs of liver disease (e.g. fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness and hepatomegaly) and the conduct of laboratory tests such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase and bilirubin, complete blood count and serum potassium, calcium and magnesium (which should be corrected if abnormal). Treating clinicians should also obtain an ECG before initiation of treatment. The baseline monitoring schedule of the Nix-TB study was much more comprehensive than this; it included a thorough baseline clinical assessment, then a schedule of weekly patient monitoring until week 20, followed by 4–6 weekly monitoring, partly dependent on whether the patient had treatment for 6 months in total or 9 months in total.

Given that the BPaL regimen is new and is being implemented under operational research conditions, it is also important to follow up patients after the completion of treatment for possible relapse. In

the Nix-TB study, monitoring after the completion of treatment was carried out monthly for months 1–3, and 3-monthly thereafter. Follow-up after treatment completion was for a total of 24 months; however, at the time of data analysis, about half of the patients had been followed up for this period. The analysis of the Nix-TB study data indicated that treatment failure or recurrence occurred in three patients (2.8% of patients overall), taking into account the period of post-treatment completion follow-up.

Detailed schedules of baseline and follow-up monitoring, including post-treatment completion, should be developed for any BPaL operational research protocol, with standardized measures for recording adverse events. A suggested schedule of monitoring is provided in the upcoming operational handbook on TB. The WHO framework for aDSM needs to be applied to patients on any type of MDR-TB regimen, to ensure appropriate action and an acceptable level of monitoring for and prompt response to adverse events – alongside monitoring for treatment outcomes, including early monitoring for treatment failure. Additional evidence generated on adverse events will be important to build the evidence base on the safety of the BPaL regimen in varied settings.

Monitoring of changes in dosing and duration of linezolid in particular (when needed) will also be important, to inform the future evidence base on the wider use of the BPaL regimen and the tolerability of linezolid in this regimen.

## Section 5. Monitoring patient response to MDR-TB treatment using culture

### 5.1 Recommendation

No.	Recommendation
5.1	<b>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</b> ( <i>strong recommendation, moderate certainty in the estimates of test accuracy</i> ). <b>It is desirable for sputum culture to be repeated at monthly intervals.</b>

### 5.2 Justification and evidence

The recommendation in this section addresses the following PICO question:

**PICO question 11** (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 (7, 95, 96). 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 (7). 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 and drug-resistant 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). While 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 loss to follow-up; 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 (of which 1.8% were children <15 years

of age) 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 HIV-positive. 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 under Implementation considerations and Table 5.1). The data could not address the outcome on acquisition (amplification) of additional drug resistance, and it could not assess directly whether the frequency of culture/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-MA compared (i) the performance of the two methods in terms of sensitivity/specificity, and (ii) culture testing once a month versus once every 2 months to assess the minimum frequency of testing needed in order 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 versus 0.51) but slightly lower specificity (0.97 versus 0.99). Likewise, the sensitivity of culture done every month is much higher than once every 2 months (0.93 versus 0.73) but has a slightly lower specificity (0.97 versus 0.98). Monthly culture increases the number of patients detected with a true positive bacteriological result by 13 per 1000 patients and reduces false-negative results by 13 per 1000 patients when compared with sputum smear microscopy alone. In contrast, monthly culture is 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, which could 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% CIs) of treatment failure in MDR/RR-TB patients without sputum conversion by the end of successive months of treatment compared with patients who converted, by testing method used, IPD-MA 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
<b>Culture</b>	<b>3.6</b>	<b>4.1</b>	<b>5.2</b>	<b>7.4</b>	<b>10.3</b>	<b>16.4</b>	<b>24.7</b>	<b>44.5</b>
	(2.11, 5.97)	(2.76, 6.09)	(3.55, 7.55)	(5.00, 10.8)	(6.88, 15.38)	(10.72, 25)	(15.53, 39.20)	(26.53, 74.46)
<b>Smear microscopy</b>	<b>1.9</b>	<b>2.7</b>	<b>3.2</b>	<b>4.2</b>	<b>6.8</b>	<b>10.4</b>	<b>16.5</b>	<b>28.9</b>
	(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)

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 very similar clinical characteristics to the 22 760 individuals excluded, although they were slightly less likely to be HIV coinfecting, have a history of previous treatment or have second-line drug resistance. On the other hand, the rate of failure in those included in the analysis was only 3% compared to 12.7% of those excluded from the analysis.

### 5.3 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 <15 years of age** with MDR/RR-TB comprised less than 2% of the IPD-MA 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 means to detect viable TB bacilli even if very few organisms are present in the sputum or other samples, 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** is commonly paucibacillary and biological specimens may therefore contain few or no bacilli. In such a situation, 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** with TB typically have higher bacterial counts in the sputum and a greater likelihood of detection with smear microscopy. In such a situation, one may expect that the difference in test sensitivity between smear and culture would be less extreme, as 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** 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/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. While the current analysis did not include patients treated with shorter regimens, the GDG proposes that programmes that implement this regimen 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.

## 5.4 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 (97). Some countries experience difficulties with the implementation and quality assurance of sputum culture, which impacts upon this recommendation as 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 to get 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 (98, 99).

The implementation of more frequent culture testing would require appropriate resources to be made available, both for the laboratories undertaking the tests as well as 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.

## 5.5 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 (41). Sometimes these registers may exist as part of an electronic laboratory or patient information system, which facilitates greatly the access of data in real time by multiple users and can also help 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 improve the quality of care, such as 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.

## Section 6. Starting antiretroviral therapy in patients on second-line antituberculosis regimens

### 6.1 Recommendation

No.	Recommendation
6.1	<b>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.</b> <i>(Strong recommendation, very low quality evidence)</i>

### 6.2 Justification and evidence

The recommendation in this section addresses one PICO question:

**PICO question 12 (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?*<sup>56</sup>

Evidence was reviewed from 10 studies (100–109) to assess patient treatment outcomes when ART and second-line antituberculosis drugs were used together. None of the data were from RCTs. Individual patient data were available for 217 drug-resistant TB patients in total, of whom 127 received ART. The level of evidence in individual observational studies varied from a low to a very low quality.

### 6.3 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 quality evidence for other outcomes that were considered critical or important for decision-making (for example, 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 a number of 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 cost and improving population access to appropriate care.

### 6.4 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

<sup>56</sup> 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 drug-resistant 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 drug-resistant TB, 12. Prevention or interruption of transmission of drug-resistant 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.

ART is not employed (110) particularly in highly immunocompromised patients (CD4 cell count <50 cells/mm<sup>3</sup>) (111, 112). 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 the HIV-positive drug-susceptible TB patient. 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 (110, 113). However, for HIV-positive TB patients with profound immunosuppression (e.g. CD4 counts less than 50 cells/mm<sup>3</sup>), they should receive ART within the first 2 weeks of initiating TB treatment (30).

## 6.5 Risks

The successful implementation of this recommendation will depend upon 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 likely be needed. The need for increased integration of HIV and TB care for effective patient management, prompt evaluation of AEs and case-holding throughout treatment will necessitate more resources. For the benefit of the user, a table of AEs for which both an antiretroviral agent and an antituberculosis medicine have been implicated and could conceivably interact was included when these guidelines were published. Updated information on drug–drug interactions between antiretroviral and antituberculosis medicines is now available online (36).

## 6.6 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.

## Section 7. Surgery for patients on MDR-TB treatment

### 7.1 Recommendation

No.	Recommendation
7.1	<b>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.</b> <i>(Conditional recommendation, very low certainty in the evidence)</i>

### 7.2 Justification and evidence

The recommendation in this section addresses one PICO question:

**PICO question 13** (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?*<sup>57</sup>

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 MDR/XDR-TB, and the risk of serious sequelae, the role of pulmonary surgery is being re-evaluated as a means to reduce the amount of lung tissue with intractable pathology, reduce bacterial load and thus improve prognosis. The review for this question was based on both an IPD-MA to evaluate the effectiveness of different forms of elective surgery as an adjunct to combination medical therapy for MDR-TB (114), as well as a systematic review and study-level meta-analysis (115) (web Annex 6[DR-TB, 2016]). Demographic, clinical, bacteriological, surgical and outcome data of MDR-TB patients on treatment were obtained from the authors of 26 cohort studies participating in the adult individual patient data (aIPD) (61). 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 loss to follow-up. Two sets of such tables were prepared for (i) partial pulmonary resection, and (ii) 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 versus patients who did not undergo surgery, those who underwent partial lung resection had statistically significantly higher rates of treatment success. Those patients who underwent pneumonectomy did not have better outcomes than those who did not undergo surgery. Prognosis appeared to be better when partial lung resection was performed after culture conversion. This effect was not observed in patients who underwent pneumonectomy. There are several important caveats to these data. Substantial bias is likely to be present, as only patients judged to be fit for surgery would have been operated upon. No patient with HIV coinfection in the aIPD underwent lung resection surgery. Therefore, the effects of surgery among HIV-infected patients with MDR-TB could not be evaluated. Rates of death did not differ significantly between those who underwent surgery versus those who received medical treatment

<sup>57</sup> 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).

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 upon.

### 7.3 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 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, which could not be adjusted for.

### 7.4 Implementation considerations

Partial lung resection for patients with MDR-TB is to be considered only under conditions of good surgical facilities, trained and experienced surgeons, and with careful selection of candidates.

### 7.5 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 AEs, 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.



## Section 8. Care and support for patients with MDR/RR-TB

### 8.1 Recommendations

No.	Recommendation
8.1	<b>Health education and counselling on the disease and treatment adherence should be provided to patients on tuberculosis (TB) treatment.</b> <i>(Strong recommendation, moderate certainty in the evidence)</i>
8.2	<b>A package of treatment adherence interventions<sup>58</sup> may be offered to patients on TB treatment in conjunction with the selection of a suitable treatment administration option.<sup>59</sup></b> <i>(Conditional recommendation, low certainty in the evidence)</i>
8.3	<b>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:</b> a. tracers <sup>60</sup> and/or digital medication monitor <sup>61</sup> <i>(conditional recommendation, very low certainty in the evidence);</i> b. material support <sup>62</sup> to the patient <i>(conditional recommendation, moderate certainty in the evidence);</i> c. psychological support <sup>63</sup> to the patient <i>(conditional recommendation, low certainty in the evidence);</i> d. staff education <sup>64</sup> <i>(conditional recommendation, low certainty in the evidence).</i>
8.4	<b>The following treatment administration options may be offered to patients on TB treatment:</b> a. Community- or home-based directly observed treatment (DOT) is recommended over health facility-based DOT or unsupervised treatment <i>(conditional recommendation, moderate certainty in the evidence).</i> b. DOT administered by trained lay providers or health care workers is recommended over DOT administered by family members or unsupervised treatment <i>(conditional recommendation, very low certainty in the evidence).</i> c. Video-observed treatment (VOT) may replace DOT when the video communication technology is available, and it can be appropriately organized and operated by health care providers and patients. <i>(conditional recommendation, very low certainty in the evidence)</i>

<sup>58</sup> Treatment adherence interventions include social support such as material support (e.g. food, financial incentives or transport fees), psychological support, tracers such as home visits or digital health communications (e.g. SMS or telephone calls), medication monitor and staff education. The interventions should be selected based on the assessment of the individual patient's needs, the provider's resources and conditions for implementation.

<sup>59</sup> Treatment administration options include DOT, non-daily DOT, VOT or unsupervised treatment.

<sup>60</sup> "Tracers" refer to the communication with the patient, including home visits or via SMS or telephone (voice) call.

<sup>61</sup> A digital medication monitor is a device that can measure the time between openings of the pill box. The medication monitor can have audio reminders or send an SMS to remind the patient to take medications, along with recording when the pill box is opened.

<sup>62</sup> 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 the indirect costs incurred by patients or their attendants in order to access health services, and may try to mitigate the consequences of income loss related to the disease.

<sup>63</sup> Psychological support can be counselling sessions or peer-group support.

<sup>64</sup> Staff education can be adherence education, chart or visual reminders, educational tools and desktop aids for decision-making and reminders.

No.	Recommendation
8.5	<b>Patients with multidrug-resistant TB (MDR-TB) should be treated using mainly ambulatory care rather than models of care based principally on hospitalization.</b> (Conditional recommendation, very low quality evidence)
8.6	<b>A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment.</b> (Conditional recommendation, very low certainty in the evidence)

## 8.2 Justification and evidence

The recommendations in this section address three PICO questions.

**PICO question 14** (DS-TB, 2017): *In patients with TB, are any interventions to promote adherence to TB treatment more or less likely to lead to the outcomes listed below?*<sup>65</sup>

**PICO question 15** (DR-TB, 2011): *Among patients with MDR-TB, is ambulatory therapy, compared with inpatient treatment, more or less likely to lead to the outcomes listed below?*<sup>66</sup>

**PICO question 16** (DS-TB, 2017): *Is decentralized treatment and care for MDR-TB patients more or less likely to lead to the outcomes listed below?*<sup>67</sup>

**Treatment supervision.** Currently, WHO defines DOT as any person observing the patient taking medications in real time. The treatment observer 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 supervisor or supporter. Observed treatment may also be achieved with real-time video observation and video recording. However, in this document, DOT refers to treatment administered under direct observation by another person. Adherence definitions varied across the studies. However, in general, adherence was defined as taking >90% of medications under conditions of direct observation by another person.

The systematic review conducted in support of this guideline was based on synthesis of data from RCTs (116–123) and from observational studies (124–137), with preference given to the results of RCTs. Outcomes of DOT and SAT given under standard TB practice and without any additional support were compared. DOT could be administered by a health care worker, a family member or a community member and either at home, in the patient's community or at a clinic. DOT was generally administered daily. The GDG focused preferentially on RCT data from the systematic review. When the data from RCTs were limited or not available, observational study data were examined, and their results presented. Interpretation of the associations, however, needs caution due to limitations of the observational data when the associations are confounded by different factors. In uncontrolled

<sup>65</sup> The outcomes comprise: 1. Adherence to treatment (or treatment interruption due to non-adherence), 2. Conventional TB treatment outcomes: cure or treatment completion, failure, relapse, survival/death, 3. Adverse reactions from TB drugs (severity, type, organ class), 4. Cost to the patient (including direct medical costs as well as others such as transportation, lost wages due to disability, and 5. Cost to the health services.

<sup>66</sup> The outcomes comprise: 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 drug-resistant TB, 8. Smear or culture conversion during treatment, 9. Accelerated detection of drug resistance, 10. Avoiding unnecessary MDR-TB treatment, 11. Population coverage or access to diagnosis of drug-resistant TB, 12. Prevention or interruption of transmission of drug-resistant 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.

<sup>67</sup> The outcomes comprise: 1. Adherence to treatment (or treatment interruption due to non-adherence), 2. Conventional TB treatment outcomes: cure or treatment completion, failure, relapse, survival/death, 3. Adverse reactions from TB drugs (severity, type, organ class), 4. Acquisition (amplification) of drug resistance, 5. Cost to the patient (including direct medical costs as well as others such as transportation, lost wages due to disability, and 6. Cost to the health services.

observational studies, for instance, patients with more severe disease or higher risk of non-adherence are likely to be assigned DOT and patients who are less sick or less likely to be non-compliant are assigned SAT. The same may apply to the selection of DOT location, DOT provider or other interventions in cohort studies. 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 moderate, depending on the outcome being assessed and type of study.

When DOT alone was compared with SAT, patients who were on DOT 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 DOT had a slightly higher relapse rate. The GDG considered that, overall, the evidence was inconsistent in showing a clear advantage of DOT 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 more from DOT than other patients; or specific types of DOT delivery (e.g. locations of DOT or DOT 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, tracer and use of medication monitor) in conjunction with DOT or SAT, treatment outcomes were significantly improved compared to DOT or SAT alone (*see below*). Only cohort studies were available to examine DOT and SAT in HIV-positive TB patients (138–154), and many of these studies were conducted in the pre-ART era or shortly after the introduction of early ART for HIV-positive TB patients (150–153). As above, DOT could have been administered by a variety of people in a variety of settings, including homes and clinics, and occasionally, during the initial intensive phase of treatment, it was hospital-based. A few studies provided incentives and enablers or provided DOT 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 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 DOT than general TB patients 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 DOT to offer a significant advantage over SAT. DOT and SAT in MDR-TB patients were also examined in the systematic review. However, very limited data were available from a cohort study (141). 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 DOT, although the differences were not significant.

**DOT provider.** RCTs (118, 120–122) and observational studies (126, 129, 131, 136, 139, 144, 146, 147, 149, 150, 154, 155) were available for examination of the effect of DOT providers versus SAT. Providers were grouped as health care workers, lay providers and 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. DOT by lay providers had higher rates of treatment success and cure, and a slightly lower rate of loss to follow-up compared with SAT. Patients receiving DOT from a family member had higher rates of treatment success and lower rates of loss to follow-up compared with patients using SAT. When DOT 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 health care worker DOT. The effect that different types of DOT provider had on outcomes was also examined. DOT provided by health care workers and DOT provided by lay persons were compared. Only observational studies were available in the literature (126, 129, 146, 156–160). Slightly higher rates of success, and lower rates of mortality, failure and loss to follow-up were observed among patients who had DOT administered by a lay provider versus a health care worker, although the difference was not statistically significant. 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 high depending on the outcome being assessed and type of study.

When provision of DOT by a family member was compared to provision of DOT by a health care worker, 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 DOT administered by family members. Therefore, although DOT 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 DOT and a family member is the least preferred DOT provider.

**DOT location.** RCTs and observational studies examined how DOT location affected treatment outcome. Locations were grouped by community- or home-based DOT, and health facility-based DOT (118, 120, 121, 124, 131, 136, 144, 146, 149, 150, 161–198). Community- or home-based DOT was defined as DOT delivered in the community close to the patient's home or workplace. In general, community- or home-based DOT was provided close to the patients. Health facility-based DOT was defined as DOT delivered at a health centre, clinic or hospital. There were some instances of community- or home-based DOT being provided by health care workers. 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 high, depending on the outcome being assessed and type of study. When comparing DOT locations, community- or home-based DOT had higher rates of treatment success, cure, treatment completion and 2-month sputum conversion. Community- or home-based DOT also had lower rates of mortality and lower rates of unfavourable outcomes compared with health facility-based DOT. When comparing community-/ home-based DOT or health facility-based DOT with SAT, there were no significant differences across the outcomes in RCTs. However, cohort studies showed higher rates of treatment success and adherence, and a lower rate of loss to follow-up with community-/home-based DOT 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 DOT compared to SAT. Therefore, community- or home-based DOT is the preferred option rather than health facility-based DOT and SAT. Combining the evidence on DOT provider and DOT location, DOT should preferably be delivered at home or in the community and by a health care worker or trained lay provider. DOT delivered at a health facility, DOT provided by a family member and unsupervised treatment are not preferred options.

**Video-observed treatment (VOT).** For VOT there were only two cohort studies from high-income countries and no data from low- and middle-income countries (199, 200). These studies compared in-person DOT with VOT done in real time. Patients who were provided with VOT had no statistically significant difference in treatment completion and mortality compared to patients who had in-person DOT. 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. Although there is some concern as to the indirectness of evidence for VOT, as the studies were conducted in high-income countries and the uncertainty of evidence surrounding the use of VOT, the results from the two cohort studies showed that in-person DOT was not better than VOT. DOT has been the standard of care that many programmes aim for, even if in practice they have to resort to SAT in many patients because of lack of resources. The advantages of using VOT are its potential to observe adherence to treatment from a distance – and even when people travel and cannot visit or be visited by a DOT provider. VOT is also more flexible to people's schedules by offering virtual observation at different times of the day. VOT could help achieve better levels of patient interaction at a much lower cost and less inconvenience when compared with in-person DOT. VOT can be used as an addition to, or interchangeable with, in-person DOT or other treatment administration options. For instance, it is not expected that a patient receives VOT as the sole option of supervision during the whole duration of treatment. Furthermore, the technology required for VOT (broadband Internet and smartphone availability) is becoming increasingly available in resource-constrained settings. Moreover, VOT 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 ongoing RCTs. The benefits of VOT may become more apparent as programmes are able to choose forms of VOT that best meet their needs. In fact, VOT may be particularly useful for easing the burden on the health care system in low- and middle-income countries.

**Package of combined treatment adherence interventions.** Both RCTs and observational studies examining the effects of combined treatment adherence interventions were reviewed (165–171, 200–206). 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 moderate depending on the outcome being assessed and type of study. When patients receiving combined treatment adherence interventions along with DOT or SAT were compared to those receiving DOT or SAT alone, patients who received 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 interventions was varied (Table 8.1). 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. The interventions should be selected on the basis of assessment of the individual patient’s needs, providers’ resources and conditions for implementation.

**Table 8.1. 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	<p>Food or financial support such as meals, food baskets, food supplements, food vouchers, transport subsidies, living allowance, housing incentives or financial bonus.</p> <p>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.</p>
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 VOT.** Varied tracers were included in RCTs and observational studies (199, 200, 207–219). These interventions could include 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. 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. 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 (SMS or telephone call) 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. With all the digital interventions and tracers, including VOT, patient support and the ability of the patient to interact with health care workers should be preserved. In fact, these 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 VOT may replace in-person DOT for periods of time rather than for the entire duration and that they promote patient-centred approaches to care. Mobile telephone interventions, tracers and VOT 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 patients living in an area with a good telecommunication infrastructure.

**Material support for patients.** The effects of material support were examined both with RCTs (178–181) and observational studies (187, 220–227). The interventions included giving meals with DOT, monthly food vouchers, food baskets, food supplements and vitamins. Food support for patients and family members is an important incentive for TB patients and it also helps protect patients from the catastrophic costs associated with TB. Food may be an incentive, but it may also improve outcome biologically due to reduction in malnutrition and consequent improvement in immune function. Other material support could be financial support in the form of financial incentives, transport subsidies, living allowance, housing incentives or financial bonuses after reaching treatment targets. 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 high, depending on the outcome being assessed and type of study. 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 in patients who did not receive material support. It is of note that all of these studies were in low- and middle-income countries, so presumably these incentives were of significant value to the patients in these settings. However, material support would be of significant value to TB patients even in higher-income countries, especially in countries that do not have a good social welfare system, as 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 within and between countries.

**Patient education or educational counselling.** Analysis of the benefit of patient education included RCTs (173–176) and an observational study (184). 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 moderate depending on the outcome being assessed and type of study. 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 one-time 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 or it might 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, and the education of laboratory staff. This intervention was examined in both RCTs and observational studies (177, 178, 227, 228). 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 moderate, depending on the outcome being assessed and type of study. There were higher rates of treatment success and slightly lower rates of mortality and loss to follow-up with staff education. With better staff education, treatment for patients is likely to improve and any stigma that health care workers may hold towards patients would decrease, as 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 examined in both RCTs and observational studies (165, 183, 229). 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 high, depending on the outcome being assessed and type of study. 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 had 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 psychological support types 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.

**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 (Estonia and the Russian Federation [Tomsk oblast] (230), Peru (231) and the Philippines (232)). The design of these observational studies did not allow direct comparison of effects between models of care. Given that none of the studies were RCTs, the evidence was considered 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 (233).

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 patient groups 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.** 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 to scaling up treatment and care for patients who are eligible for MDR-TB treatment. Therefore, a systematic review of the treatment and care of bacteriologically confirmed or clinically diagnosed MDR-TB patients in decentralized versus centralized systems was conducted to gather evidence on whether the quality of treatment and care is likely to be compromised with a decentralized approach. Data from both RCTs and observational studies were analysed, the majority being from low- and middle-income countries (229, 234–241). The review provided additional value to the recommendation in the previous guidelines (7) on ambulatory over hospitalized models of care for MDR-TB patients, where the evidence was examined only for treatment and care of patients outside or inside hospitals. In the review, decentralized care was defined as care provided in the local community where the patient lives, by non-specialized or peripheral health centres, by community health workers or nurses, non-specialized doctors, community volunteers or treatment supporters. The evidence was considered of very low to low quality, depending on the outcome being assessed and type of study.

Care could occur at local venues or at the patient's home or workplace. Treatment and care included DOT and patient support, in addition to injections during the intensive phase. In this group, a brief phase of hospitalization of less than 1 month was accepted for patients who were in need in the initial

phase of treatment or when they had any treatment complications. Centralized care was defined as inpatient treatment and care provided solely by specialized DR-TB centres or teams for the duration of the intensive phase of therapy or until culture or smear conversion. Afterwards, patients could receive decentralized care. Centralized care was usually delivered by specialist doctors or nurses and could include centralized outpatient clinics (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 compared to centralized care. The risks of death and treatment failure showed minimal differences between patients undergoing decentralized care and 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; however, the studies did not stratify patients according to 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.

### 8.3 Subgroup considerations

**Treatment administration.** Although the reviewed evidence did not allow for conclusions about the advantages of DOT over SAT or vice versa for TB patients, in a subgroup analysis of TB patients living with HIV, DOT showed a clear benefit with significantly improved treatment outcomes. It is likely that DOT may be not beneficial for all patients but 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 DOT were not within the scope of the systematic review.

**Decentralized care.** Decentralized care may not be appropriate for patients with extensive TB disease, extremely infectious forms of the disease, serious comorbidities or those 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.

### 8.4 Implementation considerations

**Treatment adherence interventions.** As treatment supervision alone is not likely to be sufficient to ensure good TB treatment outcomes, additional treatment adherence interventions 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 TB treatment. The interventions should be selected on the basis of an assessment of the individual patient's needs, provider's 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 surrounding 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 telecommunication 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 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 with particularly high risk (e.g. patients with MDR-TB). However, one of the components of the End TB Strategy (234) is to provide "social protection and poverty alleviation" for patients with TB. This publication specifically calls for measures to "alleviate the burden of income loss and non-medical costs of seeking and staying in care". Included in these suggested

protections 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 (234). In order to distribute the material support, government and/or nongovernment 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 DOT has more advantages than health facility-based DOT, though family members should not be the first or only option for administering DOT. DOT is better provided at home or in the community and by trained lay providers or health care workers. There may be challenges in providing community- or home-based DOT by health care workers because of the increased number of health care workers required and the increased costs of staff time and daily travel to the community or patient's home. DOT provision 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 DOT is also an option. Community-based or home-based DOT is more likely to be acceptable and accessible to patients than other forms of DOT. However, stigma may continue to be an issue with community- or home-based DOT. 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 for patients. Other forms of DOT (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, and the suitability of such treatment adherence supervisors needs to be carefully analysed in each national or local context. If family members are providing DOT, 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 DOT. Assessment of potential risk factors for poor adherence must be taken into account by health care workers at the start of treatment in order to decide which treatment administration option should be selected for the patient. Some groups of patients who are less likely to adhere to treatment may benefit more from DOT than others. Another factor to consider when selecting treatment administration options is that some patients with inflexible work or family responsibilities may not be able to do DOT. Any option of treatment administration offered to a patient must 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.

**Ambulatory care.** 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 was in conflict with the recommendation and 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 resource use, and at least as many deaths avoided among primary and secondary cases compared with hospitalization models. This result is based on clinic-based ambulatory treatment (patients attend a health care facility); in some settings, home-based ambulatory treatment (provided by a 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 (274). The regimen used in one of the studies on ambulatory care was from a time when the combinations of medicines were not yet optimized, so outcomes achieved were probably inferior to those that can be obtained with the regimens in use today. Admission to hospitals 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 to travel and other costs to individual patients. Shifting costs from the service provider to the patient has to 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 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 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.

**Decentralized care.** NTPs should have standardized guidelines regarding which patients are eligible for decentralized care. Patient preference should be given a high value when choosing 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 this section should be considered for MDR-TB patients on decentralized care.

Several of the studies in the review addressed treatment costs. However, the cost estimates were found to vary widely and no concrete recommendations could be made on the basis of cost. Resource requirements are likely to vary because TB treatment programmes are highly variable, so costs for these programmes 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. A 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 are 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, such as a PLHIV or a young child, there may be complications in sending the patient home for treatment. However, the risk posed to these 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 therapy are ongoing.

An additional implementation issue to consider is that it may be illegal in some settings to treat MDR-TB patients in a decentralized setting, especially when the treatment involves injections. Such legal concerns need to be addressed.

# 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 drug-resistant 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 persist from the ones identified in previous TB treatment guidelines (10, 11). When completing the GRADE evidence-to-decision frameworks, there was a lack of studies of how patients, caregivers and other stakeholders value different treatment options and outcomes (e.g. time to sputum conversion, cure, treatment failure and relapse, death and serious adverse events). Areas that would be relevant to many priority questions in the programmatic management of drug-resistant TB include implementation research, studies of resource use, incremental cost, acceptability, feasibility, 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 the successive GDGs are grouped by the respective sections of these guidelines, although some are interlinked.

## Section 1. Regimens for isoniazid-resistant 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 (63). 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 pyrazinamide (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, fluoroquinolones and other second-line medicines, and of reducing the duration of pyrazinamide;
- 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 HIV-positive individuals;
- 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* versus *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;
- effect of underlying fluoroquinolones/isoniazid polydrug resistance on treatment outcomes; and
- diagnostic accuracy of second-line LPAs in rifampicin-sensitive patients.

## Section 2. Shorter all-oral bedaquiline-containing 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 would be helpful 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 fluoroquinolones and second-line injectable agents is high (e.g. pyrazinamide or high-level isoniazid resistance);
- additional RCTs and odds ratio on all-oral shorter MDR-TB treatment regimens, also allowing comparison of all-oral shorter regimens to all-oral longer regimens;
- programmatic data from countries other than South Africa;
- data from children, pregnant women, elderly, 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 likely 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.

## Section 3. Longer regimens for MDR /RR-TB

Further research is needed in the following areas:

- the optimal combination of medicines and approach to regimen design for adults and children with MDR/RR-TB, with or without additional resistance to key agents;
- RCTs, which there is a lack of, especially those involving new drugs and regimens – the release of results from the first Phase III trials for MDR-TB has led to debate about the clinical relevance of the design and end-points 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 HIV-positive individuals on treatment;
- studies of pharmacokinetics and safety to determine optimal drug dosing (especially in pregnancy), and the effect of extemporaneous manipulation of existing dosing forms;
- complete recording of adverse events and standardized data on organ class, seriousness, severity and certainty of association to allow meaningful comparison of the association between adverse events 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 pyrazinamide) 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 (242);
  - *bedaquiline*: use in children to determine optimal pharmacokinetic properties, revised cost–effectiveness analyses based on the IPD meta-analysis, 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/pharmacodynamics), PLHIV and pregnant women; mechanisms of development of drug resistance; and optimization of the duration in both adults and children;
  - *pyrazinamide*: 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) (84);
- 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.

## Section 4. The BPaL regimen for MDR-TB with additional fluoroquinolone resistance

Further research is needed in the following areas:

- the efficacy, safety and tolerability of BPaL compared with other all-oral regimens;
- data from other regions and countries (beyond South Africa);
- description of the mechanism and molecular markers of pretomanid resistance, and surveillance for the development of resistance with adequate consideration paid to the impact of selected mutations;
- documenting the full adverse event profile of pretomanid, and the frequency of relevant adverse events, with a focus on hepatotoxicity and reproductive toxicity in humans (the reproductive toxicities of pretomanid have been signalled in animal studies, but the potential effects of this medicine on human fertility have not been adequately evaluated);
- exploring the relative efficacy (and added value in multidrug regimens) of pretomanid and delamanid; and
- optimal dose and duration of linezolid use in drug-resistant TB regimens (ZeNix study).

## Section 5. Monitoring patient response to MDR-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 under 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.

## Section 6: Starting antiretroviral therapy in patients on second-line antituberculosis regimens

- No gaps identified

## Section 7. Surgery for patients on MDR-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, and drug-resistance patterns; and
- improved collection, reporting and standardization of data on surgery, including long-term survival post-surgery.

## Section 8. Care and support for patients with MDR-TB

Further research is needed in the following areas:

- patient support and treatment supervision interventions that are best suited to particular populations;
- patient support interventions that are most effective in low- and middle-income countries;
- analysis of the cost-effectiveness of different types of incentives;
- research into the effectiveness of VOT in low- and middle-income countries, given that the available data are from high-income countries;
- which types of psychological support are most appropriate;
- evaluation of the risk of TB transmission in different settings (i.e. which poses a higher risk of transmission, treatment centred on hospital care or on outpatient clinics?);
- additional cost-effectiveness studies of decentralized versus centralized care; and
- systematic collection and publication of data on decentralized care – many programmes provide decentralized care, but few have published the data.

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# Supplementary Table

## Summary of changes to the WHO MDR/RR-TB treatment recommendations between 2019 and current updates

Note: The WHO consolidated guidelines on drug-resistant tuberculosis treatment were a compilation of existing and new recommendations on the treatment and management of MDR/RR-TB and as such they included new recommendations published in 2019 and existing recommendations that had been previously published. In the current update (2020), there are two new recommendations (Recommendations 2.1 and 4.1) and a minor change to the wording of a pre-existing recommendation (Recommendation 3.1). Recommendation 2.1 is an update to a previous recommendation on shorter regimens for MDR/RR-TB while recommendation 4.1 was based on a new PICO question concerning the BPaL regimen. Recommendations on the duration of longer regimens for MDR/RR-TB (Recommendations 3.15, 3.16 and 3.17) were combined into the section on the composition of longer regimens for MDR/RR-TB (Recommendations 3.1 to 3.14), however the wording of the recommendations on duration remained unchanged. All other recommendations remain unchanged.

Recommendations in the 2019 update	Recommendations in the current update
<b>Section 1: Regimens for isoniazid-resistant tuberculosis</b>	<b>Section 1: Regimen for rifampicin-susceptible and isoniazid-resistant tuberculosis</b>
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 ( <i>conditional recommendation, very low certainty in the estimates of effect</i> ).	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. ( <i>Conditional recommendation, very low certainty in the estimates of effect</i> ). <b>(no change)</b>
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 ( <i>conditional recommendation, very low certainty in the estimates of effect</i> ).	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. ( <i>Conditional recommendation, very low certainty in the estimates of effect</i> ). <b>(no change)</b>



Recommendations in the 2019 update	Recommendations in the current update
<p><b>Section 2: The composition of longer MDR-TB regimens</b></p> <p>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.<sup>68</sup> 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 (<i>conditional recommendation, very low certainty in the estimates of effect</i>).</p> <p>Kanamycin and capreomycin are not to be included in the treatment of MDR/RR-TB patients on longer regimens (<i>conditional recommendation, very low certainty in the estimates of effect</i>).</p> <p>Levofloxacin or moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens (<i>strong recommendation, moderate certainty in the estimates of effect</i>).</p> <p>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 (<i>conditional recommendation, very low certainty in the estimates of effect</i>).</p>	<p><b>Section 3: Longer regimens for multidrug-/ rifampicin-resistant tuberculosis</b></p> <p>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. (<i>Conditional recommendation, very low certainty in the estimates of effect</i>). (<b>editing of the word “after” to “if” with reference to stopping bedaquiline</b>)</p> <p>3.2 Kanamycin and capreomycin are not to be included in the treatment of MDR/RR-TB patients on longer regimens. (<i>Conditional recommendation, very low certainty in the estimates of effect</i>). (<b>no change</b>)</p> <p>3.3 Levofloxacin or moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens. (<i>Strong recommendation, moderate certainty in the estimates of effect</i>). (<b>no change</b>)</p> <p>3.4 Bedaquiline should be included in longer multidrug-resistant TB (MDR-TB) regimens for patients aged 18 years or more. (<i>Strong recommendation, moderate certainty in the estimates of effect</i>) Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years. (<i>Conditional recommendation, very low certainty in the estimates of effect</i>). (<b>no change</b>)</p>

<sup>68</sup> 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

Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens (*strong recommendation, moderate certainty in the estimates of effect*).

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*).

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*).

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*).

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*).

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*).

### Recommendations in the current update

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)*)

3.6 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)*)

3.7 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)*)

3.8 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)*)

3.9 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)*)

3.10 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. (no change)*)

<sup>69</sup> 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

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*).

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*).

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*).

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*).<sup>70</sup>

### Recommendations in the current update

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**)

3.12 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**)

3.13 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**)

3.14 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*). (**no change**)

<sup>70</sup> 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 current update
<p><b>Section 3: The duration of longer MDR-TB regimens</b></p> <p>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 (<i>conditional recommendation, very low certainty in the estimates of effect</i>).</p> <p>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 (<i>conditional recommendation, very low certainty in the estimates of effect</i>).</p> <p>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 (<i>conditional recommendation, very low certainty in the estimates of effect</i>).</p>	<p><b>Section 3: Longer regimens for multidrug- / rifampicin-resistant tuberculosis</b></p> <p>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. (<i>Conditional recommendation, very low certainty in the estimates of effect</i>). <b>(no change to wording but combined with section above called: Section 3: Recommendations on the use of longer regimens for multidrug/ rifampicin resistant tuberculosis)</b></p> <p>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. (<i>Conditional recommendation, very low certainty in the estimates of effect</i>). <b>(no change to wording but combined with section above called: Section 3: Recommendations on the use of longer regimens for multidrug/ rifampicin resistant tuberculosis)</b></p>
<p>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 (<i>conditional recommendation, very low certainty in the estimates of effect</i>).</p>	<p>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. (<i>Conditional recommendation, very low certainty in the estimates of effect</i>). <b>(no change to wording but combined with section above called: Section 2.2: Recommendations on the use of longer regimens for multidrug/ rifampicin resistant tuberculosis)</b></p>
<p><b>Section 4: Use of the standardized shorter MDR-TB regimen</b></p> <p>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 (<i>conditional recommendation, low certainty in the estimates of effect</i>).</p>	<p><b>Section 2: Shorter, all-oral, bedaquiline-containing regimen for multidrug- / rifampicin-resistant tuberculosis</b></p> <p>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. (<i>Conditional recommendation, very low certainty in the evidence</i>). <b>(updated recommendation)</b></p>

Recommendations in the 2019 update	Recommendations in the current update
<p><i>Not included in 2019 guidelines</i></p>	<p><b>Section 4: The bedaquiline, pretomanid and linezolid (BPaL) regimen for MDR-TB with additional fluoroquinolone resistance</b></p>
<p><i>Not included in 2019 guidelines</i></p>	<p>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. (<i>Conditional recommendation, very low certainty in the estimates of effect.</i>) <b>(new recommendation)</b></p>
<p><b>Section 5: Monitoring patient response to MDR-TB treatment using culture</b></p> <p>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 (<i>strong recommendation, moderate certainty in the estimates of test accuracy</i>).</p>	<p><b>Section 5: Monitoring patient response to MDR-TB treatment using culture</b></p> <p>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 (<i>strong recommendation, moderate certainty in the estimates of test accuracy</i>). It is desirable for sputum culture to be repeated at monthly intervals. <b>(no change)</b></p>
<p><b>Section 6: Start of antiretroviral therapy in patients on second-line antituberculosis regimens</b></p> <p>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 (<i>strong recommendation, very low-quality evidence</i>).</p>	<p><b>Section 6: Start of antiretroviral therapy in patients on second-line antituberculosis regimens</b></p> <p>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. (<i>Strong recommendation, very low quality evidence.</i>) <b>(no change)</b></p>

Recommendations in the 2019 update	Recommendations in the current update
<p><b>Section 7: Surgery for patients on MDR-TB treatment</b></p> <p>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 (<i>conditional recommendation, very low certainty in the evidence</i>).</p>	<p><b>Section 7: Surgery for patients on MDR-TB treatment</b></p> <p>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. (<i>Conditional recommendation, very low certainty in the evidence</i>). <b>(no change)</b></p>
<p><b>Section 8: Care and support for patients with MDR/RR-TB</b></p> <p>Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment (<i>strong recommendation, moderate certainty in the evidence</i>).</p> <p>A package of treatment adherence interventions<sup>71</sup> may be offered to patients on TB treatment in conjunction with the selection of a suitable treatment administration option (<i>conditional recommendation, low certainty in the evidence</i>).<sup>72</sup></p>	<p><b>Section 8: Care and support for patients with MDR/RR-TB</b></p> <p>8.1 Health education and counselling on the disease and treatment adherence should be provided to patients on tuberculosis (TB) treatment. (<i>Strong recommendation, moderate certainty in the evidence</i>) <b>(no change)</b></p> <p>8.2 A package of treatment adherence interventions<sup>71</sup> may be offered to patients on TB treatment in conjunction with the selection of a suitable treatment administration option.<sup>72</sup> <b>(no change)</b></p>

<sup>71</sup> Treatment adherence interventions include social support such as 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 an assessment of the individual patient's needs, provider's resources and conditions for implementation.

<sup>72</sup> Treatment administration options include directly observed treatment (DOT), non-daily DOT, video-observed treatment (VOT), or unsupervised treatment.



## Recommendations in the 2019 update

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<sup>73</sup> and/or digital medication monitor<sup>74</sup> (*conditional recommendation, very low certainty in the evidence*);
- b. material support<sup>75</sup> to the patient (*conditional recommendation, moderate certainty in the evidence*);
- c. psychological support<sup>76</sup> to the patient (*conditional recommendation, low certainty in the evidence*);
- d. staff education (*conditional recommendation, low certainty in the evidence*).<sup>77</sup>

## Recommendations in the current update

8.3 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<sup>73</sup> and/or digital medication monitor<sup>74</sup> (*conditional recommendation, very low certainty in the evidence*);
- b. material support<sup>75</sup> to the patient (*conditional recommendation, moderate certainty in the evidence*);
- c. psychological support<sup>76</sup> to the patient (*conditional recommendation, low certainty in the evidence*);
- d. staff education<sup>77</sup> (*conditional recommendation, low certainty in the evidence*).  
**(no change)**

<sup>73</sup> Tracers refer to communication with the patient, including home visits or via short message service (SMS), telephone (voice) call.

<sup>74</sup> A digital medication monitor is a device that can measure the time between openings of the pill box. The medication monitor can have audio reminders or send an SMS to remind the patient to take medications, along with recording when the pill box is opened.

<sup>75</sup> 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 the indirect costs incurred by patients or their attendants in order to access health services and, possibly, tries to mitigate the consequences of income loss related to the disease.

<sup>76</sup> Psychological support can be counselling sessions or peer-group support.

<sup>77</sup> Staff education can be adherence education, chart or visual reminders, educational tools and desktop aids for decision-making and reminders.



### Recommendations in the 2019 update

The following treatment administration options may be offered to patients on TB treatment:

- a. Community- or home-based directly-observed treatment (DOT) is recommended over health facility-based DOT or unsupervised treatment (*conditional recommendation, moderate certainty in the evidence*).
- b. DOT administered by trained lay providers or health-care workers is recommended over DOT administered by family members or unsupervised treatment (*conditional recommendation, very low certainty in the evidence*).
- c. Video-observed treatment (VOT) may replace DOT when video communication technology is available, and it can be appropriately organized and operated by health-care providers and patients (*conditional recommendation, very low certainty in the evidence*).

### Recommendations in the current update

8.4 The following treatment administration options may be offered to patients on TB treatment:

- a. Community- or home-based directly observed treatment (DOT) is recommended over health facility-based DOT or unsupervised treatment (*conditional recommendation, moderate certainty in the evidence*).
- b. DOT administered by trained lay providers or health care workers is recommended over DOT administered by family members or unsupervised treatment (*conditional recommendation, very low certainty in the evidence*).
- c. Video-observed treatment (VOT) may replace DOT 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 in the evidence*)  
**(no change)**

Patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalization (*conditional recommendation, very low-quality evidence*).

A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment (*conditional recommendation, very low certainty in the evidence*).

8.5 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 quality evidence*)  
**(no change)**

8.6 A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment. (*Conditional recommendation, very low certainty in the evidence*)  
**(no change)**







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