WHO operational handbook on tuberculosis

Module 4: Treatment

Drug-resistant tuberculosis treatment

2022 update

World Health Organization

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https://apps.who.int/iris/bitstream/handle/10665/365309/9789240065352-eng.pdf

Acknowledgements

Abbreviations

aDSM	active tuberculosis drug safety monitoring and management
AIDS	acquired immunodeficiency syndrome
aOR	adjusted odds ratio
ART	antiretroviral therapy
ARV	antiretroviral
BMI	body mass index
BPaL	a regimen of bedaquiline, pretomanid and linezolid
BPaLC	a regimen of bedaquiline, pretomanid, linezolid and clofazimine
BPaLM	a regimen of bedaquiline, pretomanid, linezolid and moxifloxacin
CB	clinical breakpoint
CC	critical concentration
CI	confidence interval
CNS	central nervous system
DRS	drug-resistance surveillance
DR-TB	drug-resistant tuberculosis
DST	drug susceptibility testing
ECG	electrocardiography
FDC	fixed-dose combination (of medicines)
GDF	Global Drug Facility
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	isoniazid–rifampicin
HRZE	isoniazid–rifampicin–ethambutol–pyrazinamide
(H)RZE	(isoniazid optional)–rifampicin–ethambutol–pyrazinamide
Hr-TB	rifampicin-susceptible, isoniazid-resistant tuberculosis
IPD	individual patient data (or dataset)
IV	intravenous
LPA	line probe assay
MDR-TB	multidrug-resistant tuberculosis
MDR/RR-TB	multidrug- or rifampicin-resistant tuberculosis
MGIT	mycobacterial growth indicator tube
MIC	minimum inhibitory concentration

NAAT	nucleic acid amplification test
NTP	national tuberculosis programme
PLHIV	people living with HIV
pre-XDR-TB	pre-extensively drug-resistant tuberculosis
RCT	randomized controlled trial
rGLC	regional Green Light Committee
RR-TB	rifampicin-resistant tuberculosis
SoC	standard of care
TB	tuberculosis
TDM	therapeutic drug monitoring
WHO	World Health Organization
WHO/GTB	World Health Organization Global Tuberculosis Programme
XDR-TB	extensively drug-resistant tuberculosis

TB medicines

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

1. Introduction

The World Health Organization (WHO) has produced this operational handbook on tuberculosis (TB) to provide practical advice to complement the latest *WHO consolidated guidelines on tuberculosis, drug-resistant tuberculosis treatment, 2022 update* (hereafter referred to as the "WHO consolidated guidelines"). This document provides information on the choice and design of regimens for the treatment of drug-resistant TB (DR-TB), including multidrug- or rifampicin-resistant TB (MDR/RR-TB), and confirmed rifampicin-susceptible, isoniazid-resistant TB (Hr-TB) *(1)*.

The strategies described in this module are mainly based on the latest WHO recommendations *(1–3)*, which were formulated by Guideline Development Groups (GDGs) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach *(4)*. However, in many cases, the recommendations lacked the level of clinical and programmatic detail needed for implementation. This module complements the guidelines with practical advice based on best practices and knowledge from fields such as pharmacokinetics, pharmacodynamics, microbiology, pharmacovigilance, and clinical and programmatic management.

The practical guidance aims to inform the development or revision of national policies and related implementation guidance (e.g. handbooks, standard operating procedures) on the management of DR-TB.

The chapters of the handbook are aligned with the WHO consolidated guidelines document. The target audience for this handbook include NTPs, other healthcare programmes in public and private sector and technical organizations supporting national programmes.

2. Commonly used terms and key definitions in DR-TB treatment

This section briefly describes some of the main terms that are used in this module and elsewhere.

Bacteriologically confirmed: when a biological specimen is positive by smear microscopy, culture or a rapid diagnostic test for TB recommended by WHO.

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

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

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

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

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

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

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

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

Operational research or **implementation research**: "the use of systematic research techniques for programme decision-making to achieve a specific outcome" *(5)*. In the context of this document, these terms are also applied to research that aims to develop the critical evidence base that informs the effective, sustained and embedded adoption of interventions within a health system, to improve health or patient outcomes. Such research deals with the knowledge gap between efficacy, effectiveness and current practice to produce the greatest gains in disease control *(6)*. Operational research also provides decision-makers with information to enable them to improve the performance of their health programmes *(7)*.

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

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

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

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

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

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

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

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

3. Key considerations in DR-TB treatment

3.1 Access to DST

The current guidelines for treatment of DR-TB stress the need for access to reliable, quality-assured drug susceptibility testing (DST), to be provided by national TB programmes (NTPs) and associated laboratories, to inform the use of the WHO-recommended regimens. Rapid molecular testing is making it increasingly feasible for NTPs to detect MDR/RR-TB and other types of resistance quickly, and to use the results to guide treatment decisions *(8, 9)*. Hence, rapid molecular testing should be made available and accessible, to ensure DST for at least rifampicin, isoniazid and fluoroquinolones, given that DST for these drugs is essential for selecting the most appropriate initial DR-TB regimen. If capacity does not exist, NTPs must promptly build rapid molecular testing capacity, and all efforts must be made to ensure universal access to all patients initiating a regimen for any form of TB, including both drug-susceptible and drug-resistant forms. While NTPs build capacity to ensure routine performance of DST for medicines used in the clinical management of all patients, building surveillance systems to determine the local prevalence of DR-TB strains will be important to guide programmatic planning. This is especially important for drugs where resistance testing is not routinely performed or when the resistance prevalence of the drug is expected to be low initially (e.g. pretomanid) and needs to be monitored over time. Drug-resistance surveillance (DRS) can be based on data from routine diagnostic DST in TB patients (i.e. continuous surveillance) or from special surveys representative of the entire TB patient population (i.e. drug-resistance surveys) *(10)*. DST for rifampicin is mandatory for all cases, and DST for fluoroquinolones is mandatory in cases of demonstrated rifampicin resistance. DST for the drugs used in the newly recommended regimens is now increasingly critical. Data from local TB DRS may provide baseline estimates of the prevalence of resistance including among relevant subgroups of recurrent and re-registered individuals with TB disease (e.g. recurrence or new episode of TB or return after loss to follow-up). It can also provide monitoring trends to inform DST algorithms and inform broader local policy decisions *(1, 11)*.

WHO recommends the use of the approved rapid molecular test as the initial test to detect TB disease as well as resistance to several anti-TB agents before the initiation of appropriate therapy for all TB patients. The increased recognition of drug resistance and improved access to rapid molecular testing have led more NTPs to test for at least rifampicin resistance at the start of TB treatment. Almost all WHO-recommended rapid tests for the initial diagnosis of TB include rifampicin-resistance testing; also, the most recent class of nucleic acid amplification tests (NAATs) include initial testing for rifampicin and isoniazid resistance. There are several other WHO-recommended molecular tests available that offer manual or automated DST for isoniazid, fluoroquinolones, pyrazinamide, ethionamide and injectable agents. The most recent recommendation of a low complexity assay for isoniazid and fluoroquinolone testing will ensure decentralized access to essential DST *(12)*. Results can be available the same day (automated tests) or within a few days (manual tests) and can thus be used to decide on the initial regimen for treatment of Hr-TB or some other forms of DR-TB. Apart from their rapidity, some of these tests can also provide information on mutation patterns, which can influence the choice of treatment. If the *inh*A mutation is the only mutation present, it is likely that isoniazid can still be effective at a high dose, whereas if the *kat*G mutation alone or both *inh*A and *kat*G are present,

isoniazid is no longer effective, even at a high dose. Some tests report "low-level" isoniazid resistance, which implies the presence of *inh*A mutations only. If rifampicin resistance is detected, rapid molecular tests for resistance to fluoroquinolones should be performed promptly, to inform the decision on which regimen to use for the treatment *(13)*. If rifampicin resistance is not detected, rapid molecular testing for resistance to isoniazid is recommended, to inform the decision on whether the regimen to treat Hr-TB needs to be used.

Rapid molecular testing for rifampicin, isoniazid and fluoroquinolones is widely available; countries have accumulated experience in using these rapid tests, and access is also supported by the main donors where necessary. No rapid molecular testing is currently available for ethambutol, bedaquiline, clofazimine, linezolid, pretomanid and delamanid. WHO is currently evaluating tests for targeted next-generation sequencing solutions, which may provide an opportunity for the rapid molecular testing for multiple anti-TB medicines. Commercially available rapid molecular methods detect 86% (manual) to 93% (automated) of fluoroquinolone-resistant strains *(12)*. Resistance to the fluoroquinolones can be inferred from the results of molecular testing for the presence of certain *gyr*A and *gyr*B mutations; however, only some of the genetic mutations are known or can be detected. Culture-based DST for fluoroquinolones should be considered when possible, especially when the prevalence of resistance to these drugs is high, or when resistance is suspected despite the molecular tests being negative. Further details on diagnostic tests recommended can be found in the relevant WHO consolidated guidelines *(12)* and operational handbook *(14)* in *Module 3: Diagnosis – rapid diagnostics for tuberculosis detection*.

Country programmes need to work towards the establishment of phenotypic DST for all TB medicines for which there are now agreed reliable and reproducible methods (e.g. bedaquiline, clofazimine, delamanid, fluoroquinolones, isoniazid, linezolid and rifampicin). The critical concentrations for various drugs were either established for the first time (bedaquiline, clofazimine, delamanid and linezolid) or revised (fluoroquinolones) in a WHO technical consultation in 2017 *(15)*. Resistance to ethionamide/prothionamide may be inferred from the results of molecular testing for isoniazid resistance (i.e. presence of mutations in the *inh*A promotor region) using either automated or manual molecular tests. However, susceptibility to ethionamide/prothionamide cannot be inferred purely based on the absence of *inh*A promotor gene mutation in commercially available NAATs, because resistance can be conferred by other mutations in the *inh*A gene and its promotor and by mutations in the *eth*A gene that are not detected by these NAATs. A standardized phenotypic DST method for pretomanid is being developed and is likely to be available soon. Phenotypic DST for cycloserine/terizidone, ethambutol, ethionamide/prothionamide, imipenem/meropenem or *p*-aminosalicylic acid is not routinely recommended because results may be unreliable *(13)*.

The inability to undertake DST routinely in all patients despite all possible efforts should not be a barrier to starting patients on a potentially life-saving MDR-TB regimen; however, treatment should always be considered in a context of the potential risk of prescribing ineffective treatment and amplifying drug resistance, with a subsequent decrease in the likelihood of treatment effectiveness. If DST for bedaquiline and linezolid is not yet available, the clinician or the TB programme manager needs to estimate the likelihood of effectiveness of the medicines used, informed by the patient's history of use of TB medicines, the drug-resistance pattern of the contact or index case, and recent representative DRS data. A reliable clinical history of exposure to bedaquiline and linezolid should thus be considered when designing a treatment regimen; however, this should be the main source of evidence to guide regimen design only in situations where phenotypic DST is not yet available. For paediatric patients, it is not always possible to obtain a DST result, owing to the difficulty of obtaining an adequate specimen or the lack of bacteriological confirmation; hence, the treatment regimen design is usually based on the drug-resistance pattern of the index case. In the absence of individual DST, relevant population surveillance data are essential to inform the choice and design of MDR-TB treatment regimens. In addition to TB DRS findings, it is important for practitioners to know which medicines have been in frequent use in each geographical setting or patient groups. If DST is not routinely available for individual patients where there is treatment failure, storage of *M. tuberculosis* isolates collected at

baseline or during treatment monitoring can be considered for performing phenotypic DST or whole genome sequencing at reference laboratories.

New regimen adoption and implementation can and should proceed while the DST capacity is being established.

Despite some of the uncertainties about DST, NTPs should strive to test for resistance to a wide set of TB drugs and offer the most appropriate treatment regimen. The patient's clinical response to treatment should always be carefully monitored. If there is a poor treatment response, undiagnosed drug-resistance or the coexistence of susceptible and resistant organisms in the same patient should be considered, as should alternative explanations for failure to respond to treatment (e.g. poor or erratic adherence to treatment, malabsorption, inadequate patient education or support, immune reconstitution inflammatory syndrome or the presence of comorbidities) *(16)*.

3.2 Safety monitoring and management, provision of patient support and management of comorbidities

All treatment offered to people with MDR/RR-TB should align with WHO-recommended standards, including patient-centred care and support, informed consent where necessary, principles of good clinical practice, active TB drug safety monitoring and management (aDSM), and regular patient monitoring to assess regimen effectiveness. Health care providers must offer careful clinical and bacteriological follow-up to assess the TB treatment response, with general laboratory support to monitor and manage adverse events and comorbidities. The provision of social support is essential to enable adherence to treatment *(17)*. Certain programmatic components (e.g. aDSM) *(17, 18)* are recommended for all patients on any MDR/RR-TB regimen (**Web Annex 3**). An appropriate schedule of laboratory tests and clinical examinations should be included in the patient's treatment chart to identify adverse events *(17)*. In settings where aDSM has not yet been fully rolled out and national guidelines have not been updated, patients should not be left to wait until all programme components are fully in place before they can receive potentially life-saving interventions. The WHO consolidated guidelines also reinforce the message that patient support is critical for good adherence and improved outcomes *(19)*.

3.3 Regimen options in the treatment of DR-TB

In patients with MDR/RR-TB, there are several regimens that can be used based on current WHO policy. The key factors that define treatment regimen choice include drug-resistance profile, prior exposure to TB medicines and patient history, drug-resistance profile of close contacts, the patient's age, extent of pulmonary TB disease and localization of extrapulmonary TB lesions.

- **BPaLM regimen (6 Bdq-Pa-Lzd-Mfx[1])**: in patients with MDR/RR-TB where fluoroquinolone susceptibility is presumed or documented. This 6-month all-oral treatment regimen comprises bedaquiline, pretomanid, linezolid and moxifloxacin. It is possible to omit moxifloxacin and continue with the BPaL regimen for MDR/RR-TB patients with confirmed fluoroquinolone resistance.
- **9-month all-oral regimen** (**4–6 Bdq$_{(6 m)}$-Lfx/Mfx-Cfz-Z-E-Hh-Eto or Lzd$_{(2 m)}$ / 5 Lfx/Mfx-Cfz-Z-E)**: in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. The 9-month all-oral regimen comprises bedaquiline (used for 6 months), in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high dose), pyrazinamide and clofazimine (for 4 months, with the possibility of extending to 6 months if the patient remains sputum smear positive at the end of 4 months); followed by treatment with levofloxacin/moxifloxacin,

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[1]   The regimen notations used throughout this document highlight the number of months for which a relevant combination of medicines is used; where certain drugs are used for a different duration this is also noted, using subscript in brackets.

clofazimine, ethambutol and pyrazinamide (for 5 months). Ethionamide can be replaced by 2 months of linezolid.

- **Longer individualized regimens**: for patients with MDR/RR-TB who are not eligible for or had no favourable treatment outcome using the above 6-month or 9-month regimens, have TB disease caused by *M. tuberculosis* strains with extensive drug resistance (e.g. extensively drug-resistant TB [XDR-TB]) or have intolerance to key components of the above-mentioned regimens. These regimens have a duration of at least 18 months and are individually designed based on a hierarchical grouping of second-line TB medicines, the drug-resistance profile and the patient's medical history.

Based on the review of the latest available evidence, the 6-month BPaLM regimen is the preferred option for most patients with MDR/RR-TB.

BPaLM is the regimen of choice for patients with MDR/RR-TB with absent or unknown fluoroquinolone resistance. In cases where resistance to fluoroquinolones is identified before or after treatment initiation, moxifloxacin can be omitted and the BPaL regimen without moxifloxacin should be initiated or continued, because there is probably no added benefit of using a drug with demonstrated resistance that may have toxicities. If resistance to bedaquiline, linezolid or pretomanid is confirmed or suspected, the BPaLM/BPaL regimen should be stopped, and patients should be referred for a longer individualized regimen.

The duration of BPaLM regimen is largely standardized for 6 months (26 weeks), whereas BPaL can be extended to a total of 9 months (39 weeks), as described in **Chapter 4**.

Patients with MDR/RR-TB who are aged below 14 years or who are pregnant or breastfeeding are not eligible for BPaLM and they will benefit from the 9-month all-oral regimens, composed of bedaquiline, levofloxacin/moxifloxacin, clofazimine, ethionamide or linezolid, ethambutol, isoniazid (high dose) and pyrazinamide. This regimen remains a treatment option for patients with MDR/RR-TB without fluoroquinolone resistance, who do not have extensive pulmonary TB disease or severe extrapulmonary TB, and patients with less than 1 month exposure to bedaquiline, fluoroquinolones, ethionamide, linezolid and clofazimine. When exposure is greater than 1 month, these patients may still receive this regimen if resistance to the specific medicines with such exposure has been ruled out.

The 9-month all-oral regimen has two variations, with either ethionamide or linezolid; however, in both variations, an initial phase comprises seven drugs (bedaquiline – given for 6 months, levofloxacin/moxifloxacin, clofazimine, ethionamide or linezolid), ethambutol, isoniazid (high dose) and pyrazinamide, followed by 5 months of treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide. The initial phase usually lasts for 4 months, with the possibility of extending to 6 months if the patient's sputum remains bacteriologically positive at the end of the fourth month. However, linezolid is used for only 2 months regardless of the duration of the first phase, whereas ethionamide should be continued until the end of the initial phase. Bedaquiline is used for the initial 6 months of the 9-month all-oral regimen but can be extended for longer under certain circumstances. Several eligibility criteria must be considered for this regimen, with additional considerations for the use of linezolid instead of ethionamide (**Chapter 5**).

The use of longer regimens is reserved for patients with MDR/RR-TB who are not eligible for the 6-month or 9-month regimen, patients in whom these regimens failed or patients with MDR/RR-TB with fluoroquinolone resistance and additional resistance to Group A medicines (XDR-TB). These patients would then receive a longer regimen designed using the WHO priority grouping of medicines recommended in the WHO consolidated guidelines (**Chapter 6**).

Decisions on appropriate regimens should be made based on likely efficacy, safety, patient preference and clinical judgement, also taking into account the results of susceptibility testing, patient treatment history, age, severity and site of the disease (**Table 3.1**).

Table 3.1. Regimen options and factors to be considered for selection of treatment regimens for patients with MDR/RR-TB

Regimen	MDR/RR-TB fluoroquinolone susceptible	Pre-XDR-TB	XDR-TB	Extensive pulmonary TB	Extrapulmonary TB	Age <14 years
6-month BPaLM/BPaL	Yes (BPaLM)	Yes (BPaL)	No	Yes	Yes – except TB involving CNS, miliary TB and osteoarticular TB	No
9-month all-oral	Yes	No	No	No	Yes – except TB meningitis, miliary TB, osteoarticular TB and pericardial TB	Yes
Longer individualized 18-month	Yes[a]/No	Yes[a]/No	Yes	Yes	Yes	Yes
Additional factors to be considered if several regimens are possible	Drug intolerance or adverse events					
	Treatment history, previous exposure to regimen component drugs or likelihood of drug effectiveness					
	Patient or family preference					
	Access to and cost of regimen component drugs					

BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; CNS: central nervous system; MDR/RR-TB: multidrug- or rifampicin-resistant TB; TB: tuberculosis; XDR-TB: extensively drug-resistant TB.

[a] When 6-month BPaLM/BPaL and 9-month regimens could not be used.

4. The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen

This section refers to the new short, 6-month (or 26-week) treatment regimen for MDR/RR-TB: the bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen. This regimen should be the initial choice for all eligible patients diagnosed with MDR/RR-TB. The recommendation in the updated 2022 WHO guidelines states:

> **Recommendation 1.1. WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than the 9-month or longer (18-month) regimens in MDR/RR-TB patients.**
> *(Conditional recommendation, very low certainty of evidence)*

Remarks

1. Drug susceptibility testing (DST) for fluoroquinolones is strongly encouraged in people with MDR/RR-TB, and although it should not delay initiation of the BPaLM, results of the test should guide the decision on whether moxifloxacin can be retained or should be dropped from the regimen – in cases of documented resistance to fluoroquinolones, BPaL without moxifloxacin would be initiated or continued.

2. This recommendation applies to:
   a. People with MDR/RR-TB or with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR-TB).
   b. People with confirmed pulmonary TB and all forms of extrapulmonary TB except for TB involving CNS, osteoarticular and disseminated (miliary) TB.
   c. Adults and adolescents aged 14 years and older.
   d. All people regardless of HIV status.
   e. Patients with less than 1-month previous exposure to bedaquiline, linezolid, pretomanid or delamanid. When exposure is greater than 1 month, these patients may still receive these regimens if resistance to the specific medicines with such exposure has been ruled out.

3. This recommendation does not apply to pregnant and breastfeeding women owing to limited evidence on the safety of pretomanid.

4. The recommended dose of linezolid is 600 mg once daily, both for the BPaLM and the BPaL regimen.[2]

The BPaL regimen was first investigated as part of the Nix-TB study. The study was conducted in South Africa from 2015 to 2017, and investigated the safety, efficacy, tolerability and pharmacokinetic properties of a 26-week treatment regimen with BPaL to treat MDR/RR-TB and MDR/RR-TB that was resistant to any fluoroquinolone and any second-line injectable drugs, or MDR-TB patients intolerant or non-responsive to the previous MDR-TB treatment. In 2019, WHO convened a GDG that

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[2] Dosages of the other drugs are in Table 4.1.

recommended the use of the BPaL regimen under operational research for the treatment of MDR-TB patients with fluoroquinolone resistance and less than 2-week exposure to bedaquiline and linezolid.

Since the publication of the guidelines, two further studies – the TB-PRACTECAL and ZeNix trials – have confirmed the efficacy and safety of BPaL and BPaL-based regimens for a wider group of DR-TB patients. As a result, in February–March 2022, WHO again convened a GDG to consider new recommendations for the treatment of MDR/RR-TB.

The Nix-TB was a single-arm uncontrolled unblinded intervention study, in South Africa, with 108 participants, which investigated the BPaL regimen with high-dose linezolid (1200 mg daily). The ZeNix study was a partially blinded randomized controlled trial (RCT) of 181 patients, conducted in Georgia, Republic of Moldova, the Russian Federation and South Africa, investigating four different arms of the 26-week BPaL regimen with different doses (1200 mg or 600 mg) and durations (9 or 26 weeks) of linezolid. Both the Nix-TB and ZeNix trials were conducted by TB Alliance. The TB-PRACTECAL was a Phase 2–3, open-label RCT of 419 patients, investigating three different 24-week regimens containing a backbone of BPaL against the locally approved standard of care (SoC) that was based on WHO recommendations at the time of the study. The trial was conducted by Médecins Sans Frontières and the London School of Tropical Medicine & Hygiene, in Belarus, South Africa and Uzbekistan.

A total of eight BPaL-based regimens were investigated by these trials:

- Nix-TB study: BPaL for 26 weeks with 1200 mg of linezolid for the entire duration;
- ZeNix trial: BPaL for 26 weeks with 1200 mg of linezolid for the entire duration;
- ZeNix trial: BPaL for 26 weeks with 1200 mg of linezolid for 9 weeks;
- ZeNix trial: BPaL for 26 weeks with 600 mg of linezolid for the entire duration;
- ZeNix trial: BPaL for 26 weeks with 600 mg of linezolid for 9 weeks;
- TB-PRACTECAL: BPaL for 24 weeks with 600 mg linezolid for 16 weeks, followed by 300 mg for 8 weeks;
- TB-PRACTECAL: BPaL with moxifloxacin (BPaLM) for 24 weeks with 600 mg linezolid for 16 weeks, followed by 300 mg for 8 weeks; and
- TB-PRACTECAL: BPaL with clofazimine (BPaLC) for 24 weeks with 600 mg linezolid for 16 weeks, followed by 300 mg for 8 weeks.

For the 2022 guidelines, the GDG considered comparisons between each of the eight regimens. Additionally, comparison was made with the TB-PRACTECAL SoC comparator, and three other cohorts treated with all-oral regimens for MDR/RR-TB:

- a 2019 South African cohort, using a bedaquiline, linezolid and fluoroquinolone containing regimen with a treatment duration of 9-months (4244 patients);
- a 2017 South African cohort, using a bedaquiline and fluoroquinolone containing regimen for 9 months (880 patients); and
- an external cohort, from different countries, of MDR/RR-TB patients treated with bedaquiline-containing regimens, with a treatment duration of 18–24 months (850 patients).

A successful treatment outcome was achieved in more than 80% of participants, at the end of treatment, for all eight investigational regimens, with 89% treatment success in the BPaLM arm of the TB-PRACTECAL. The treatment success rates were 52% in the SoC regimens in TB-PRACTECAL, 66% in the 2019 South Africa cohort, 69% in the 2017 South Africa cohort and 75% in the multicountry cohort. Based on programmatic data, 59% treatment success rates are reported globally to WHO for MDR/RR-TB *(20)*.

4.1 Eligibility

DST for fluoroquinolones is strongly encouraged in people with MDR/RR-TB, and although it should not delay initiation of the BPaLM, results of the test should guide the decision on whether moxifloxacin can be retained or should be dropped from the regimen – in cases of documented resistance to fluoroquinolones, BPaL without moxifloxacin would be initiated or continued. The BPaLM/BPaL regimen may be offered to patients with MDR/RR-TB in the following situations:

- pulmonary TB or all forms of extrapulmonary TB, except TB involving the CNS, osteoarticular TB and disseminated (miliary) TB;
- patient is aged 14 years or older;
- no known allergy to any of the BPaLM component drugs;
- no evidence of resistance to bedaquiline, linezolid, delamanid or pretomanid, or patient has not been previously exposed to any of the component drugs for 4 weeks or longer; when exposure to the component drugs is greater than 4 weeks in duration, the patient may receive the BPaLM regimens if resistance to the specific medicines with such exposure has definitively been ruled out;
- all people regardless of HIV status;
- no XDR-TB according to the 2021 WHO definitions *(21)*; and
- patient is not pregnant or breastfeeding or, if the patient is a premenopausal woman, is willing to use effective contraception.

In cases of possible fluoroquinolone resistance (e.g. a history of >4 weeks of fluoroquinolone use or close contact with a person infected with a fluoroquinolone-resistant strain), it is best to initiate a BPaLM regimen until DST for fluoroquinolones is available, to decide whether moxifloxacin should be continued. If the result of fluoroquinolone DST is never determined or not done, the BPaLM regimen should be used throughout. This is often done even if fluoroquinolone resistance is suspected, because the toxicity of adding moxifloxacin is low and some patients with past use of a fluoroquinolone or contact cases may still be infected with susceptible strains. If resistance is highly likely (i.e. a treatment with a fluoroquinolone failed or the patient is a close contact of a fluoroquinolone-resistant case and was unlikely to get TB from another source, or in a setting with a high prevalence of fluoroquinolone resistance and in the absence of DST) it is reasonable to omit the moxifloxacin and use the BPaL regimen for treatment.

Other considerations

Several groups of patients were excluded from the ZeNix and TB-PRACTECAL trials. Inclusion of such patients should be considered with caution because no data are available regarding the safety of BPaLM/BPaL in such populations.

Caution should be taken in patients with a known history of cardiac disease. Populations of concern include those with a baseline corrected QT interval by Fridericia (QTcF) of more than 450 ms, history of cardiac disease with syncopal episodes, significant arrythmias, personal or family history of congenital QTc prolongation, torsade de pointes (tdP), bradyarrhythmia or cardiomyopathy. Although bedaquiline and moxifloxacin can prolong QTc, reports of serious adverse events and mortality are rare.

DST for fluoroquinolones is strongly encouraged to determine whether moxifloxacin should be retained in the regimen; however, results from DST should not delay treatment initiation. For patients with confirmed MDR/RR-TB, a WHO-recommended rapid molecular test should be used as an initial rapid test, in preference to culture and phenotypic DST, to detect resistance to fluoroquinolones *(22)*. Although not readily accessible, if DST is available for bedaquiline or linezolid, it is highly desirable that this is also carried out at baseline. DST for pretomanid is being developed. Patients with strains resistant to bedaquiline, pretomanid or linezolid should commence treatment with a longer, individualized MDR-TB regimen. For patients who submit a sputum sample for culture-based second-line DST at the beginning of treatment, results may not be available until after treatment has started. If resistance to

any of the regimen component drugs (except moxifloxacin) is discovered after treatment is initiated, the regimen needs to be discontinued.

Other considerations when initiating the BPaLM/BPaL regimen include the following:

- Linezolid is associated with anaemia and thrombocytopenia, and care should be taken in patients with **anaemia**. Care should also be taken for patients who have a haemoglobin level of less than 8 g/dL or a platelet count less than 75 000/mm^3. Consideration of a linezolid-sparing 9-month or longer regimen may be a safe option.
- Patients with a very low body mass index (BMI) (<17 kg/m^2) should be monitored. Although the ZeNix-TB trial excluded those with a BMI of less than 17 kg/m^2, TB-PRACTECAL had no such exclusion criteria and 167 (40%) of those in TB-PRACTECAL had a BMI of less than 17 kg/m^2. Low BMI should not be an absolute contraindication in commencing the BPaLM/BPaL regimen, but patients should be monitored closely.
- Patients with **liver enzymes** at levels three times greater than the upper limit of normal were excluded from both the ZeNix and TB-PRACTECAL trials because bedaquiline and pretomanid are both associated with increases in liver enzymes.
- Linezolid is associated with peripheral neuropathy; therefore, those with pre-existing **peripheral neuropathy** of Grade 3–4 should be treated with caution when commencing the BPaLM/BPaL regimen. Alternatively, to decrease the risk of peripheral neuropathy exacerbation, the 9-month regimen with ethionamide (and no linezolid) could be used.
- Patients who are moribund or with advanced disease should have considerations made for symptoms control and palliative care over initiation of treatment. Decisions should be guided by clinical judgement and the patient's preferences.

Vigilance or, preferably, drug substitution should be considered when certain medications are prescribed concurrently with the BPaLM/BPaL regimen; for example:

- efavirenz may induce the metabolism of bedaquiline and alternative antiretroviral therapy (ART) should be considered for patients who are prescribed efavirenz;
- linezolid is known to be associated with serotonin syndrome; therefore, caution should be taken with other serotonergic drugs (e.g. sertraline and fluoxetine);
- concomitant drugs that prolong QTc should be avoided if possible – such drugs require extra vigilance and monitoring with electrocardiography (ECG) if prescribed with bedaquiline and moxifloxacin; for example, ondansetron, methadone, amitriptyline and clarithromycin, neuroleptics-phenothiazines (e.g. thioridazine, haloperidol, chlorpromazine, trifluoperazine, pericycline, prochlorperazine, fluphenazine, sertindole and pimozide), quinoline antimalarials (e.g. halofantrine, chloroquine, hydroxychloroquine and quinacrine) and anti-arrhythmic drugs (e.g. quinidine, procainamide, encainide, disopyramide, amiodarone, flecainide and sotalol);
- CYP3A4 inhibitors and CYP3A4 inducers can interact with bedaquiline:
  - CYP3A4 inhibitors include the azole antifungals (ketoconazole, voriconazole and itraconazole), ketolides such as telithromycin and macrolide antibiotics other than azithromycin; the azole antifungals in general can safely be used for less than 2 weeks whereas fluconazole could potentially be used for more than 2 weeks;
  - CYP3A4 inducers include phenytoin, carbamazepine, phenobarbital, St. John's wort (*Hypericum perforatum*), rifamycins and glucocorticoids; and
- drugs inducing myelosuppression should also be used with caution (e.g. azathioprine and cytotoxic agents).

In each of the above situations, if the clinician judges that the potential benefits outweigh the potential risk (also considering alternative treatment options), then treatment may proceed with caution. However, patients who are not eligible for the BPaLM/BPaL regimen can benefit from the 9-month regimen if eligible (**Chapter 5**) or the individualized longer treatment regimen (**Chapter 6**).

4.2 Composition and duration of the regimen

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

4.2.1 BPaLM regimen

The BPaLM regimen includes four components – bedaquiline, pretomanid, linezolid and moxifloxacin. Bedaquiline, linezolid and moxifloxacin are used in both the 9-month regimen and the longer regimens for MDR/RR-TB (**Chapter 5** and **Chapter 6**). when initiating the regimen, it is important to ensure that patients have not had previous exposure to bedaquiline, linezolid, pretomanid or delamanid for more than 1-month duration. When exposure is greater than 1 month, these patients may still receive these regimens if resistance to the specific medicines with such exposure has been ruled out.

The components of the BPaLM regimen all possess some bactericidal activity, making them effective anti-mycobacterial drugs when used in combination. Bedaquiline is a diarylquinoline that blocks adenosine triphosphate (ATP) synthase, pretomanid is a nitroimidazole that inhibits cell wall biosynthesis, linezolid is an oxazolidinone that inhibits protein synthesis and moxifloxacin is a fluoroquinolone that inhibits the mycobacterial topoisomerases. Further information about the mechanism of action and adverse events of each drug can be found in **Web Annex 1**.

In the BPaLM regimen, pretomanid is administered at 200 mg once daily. Bedaquiline is dosed at 400 mg once daily for 2 weeks, then 200 mg three times per week afterwards, according to the product label. However, in the ZeNix trial, bedaquiline was administered at 200 mg daily for 8 weeks followed by 100 mg daily; this is an alternative way to dose bedaquiline, which may be more convenient for patients and health care providers because it allows for daily dosing of all drugs throughout the regimen. Linezolid dosing is 600 mg once daily and moxifloxacin 400 mg once daily.

Table 4.1. Dosing of component drugs for adults and adolescents (aged ≥14 years) for BPaLM

Drug	Dose
Bedaquiline (100 mg tablet)	400 mg once daily for 2 weeks, then 200 mg 3 times per week afterwards OR 200 mg daily for 8 weeks, then 100 mg daily
Pretomanid (200 mg tablet)	200 mg once daily
Linezolid (600 mg tablet)	600 mg once daily
Moxifloxacin (400 mg tablet)	400 mg once daily

BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin.

Dose modifications for bedaquiline, moxifloxacin and pretomanid are not allowed. Given the lack of evidence for the use of other fluoroquinolones, the GDG is currently unable to recommend the substitution of moxifloxacin with levofloxacin.

It is preferred to continue linezolid at the full dose for the entire duration; however, the dose of linezolid can be reduced to 300 mg or can be discontinued (and restarted when possible) if there is significant toxicity (depending on the severity of specific adverse events or serious adverse events) associated with linezolid, including optic neuritis, peripheral neuropathy or myelosuppression. Dose modification of linezolid should be avoided if possible in the first 9 weeks of therapy. Further considerations on linezolid dosing are discussed below.

4.2.2 BPaL regimen

The BPaL regimen can be prescribed for those who have proven fluoroquinolone resistance. In cases of possible fluoroquinolone resistance (e.g. a history of >4 weeks of fluoroquinolone use or close contact with a person infected with a fluoroquinolone-resistant strain), it is best to use the BPaLM regimen until DST for fluoroquinolones is available, to decide whether or not moxifloxacin should be continued. Where DST is pending, BPaLM can be commenced, subsequently dropping moxifloxacin from the regimen once fluoroquinolone resistance is confirmed. The BPaL regimen uses the same doses for pretomanid, bedaquiline and linezolid as the BPaLM regimen.

If fluoroquinolone resistance is acquired while an individual is on the BPaLM regimen, in the absence of evidence of acquired resistance to other drugs, moxifloxacin can be omitted and BPaL should be continued, because there is no added benefit to continuing a noneffective drug that may have toxicities. If resistance to bedaquiline, linezolid or pretomanid is confirmed or suspected, the treatment is considered to have failed and individuals should be referred to the longer individualized regimen (**Chapter 6**).

4.2.3 Duration of treatment

Patients with susceptibility to fluoroquinolones can be started on the BPaLM regimen for 6 months (26 weeks). In the case of resistance to fluoroquinolones, identified after treatment initiation, moxifloxacin may be discontinued and the regimen can be continued as BPaL. When the regimen is BPaL from the start or is changed to BPaL, it can be extended to a total of 9 months (39 weeks) (continuing from the start of the therapy with BPaLM/BPaL). This extension of the BPaL regimen can occur in cases where there is a lack of culture conversion or clinical response (based on the clinical judgement of the treating physician) between months 4 and 6. Treatment interruption up to 1 month can be added to the overall treatment duration if there is a need to make up the missed doses.

Temporary cessation of the full regimen is allowed for suspected drug-related toxicity. Reintroduction of the full regimen could be considered after a cessation of no more than 14 days of consecutive treatment interruption or up to a cumulative 4 weeks of nonconsecutive treatment interruption. Missed doses need to be made up and added to the treatment duration.

Individuals who switch from BPaLM to BPaL should consider their treatment start date the same as the date BPaLM was initiated, because the patient remained on treatment with three effective drugs during the entire treatment period.

4.2.4 Linezolid dosing in the BPaLM/BPaL regimen

Linezolid is by far the most toxic drug in the BPaLM and BPaL regimens; it requires significant monitoring and at times a mitigation strategy to reduce adverse effects. Although it is preferred to continue linezolid at the full dose for the entire duration, the dose of linezolid can be reduced to

300 mg or discontinued (and restarted when possible) if there is significant toxicity. In general, action should be taken in the following manner for the common toxicities associated with linezolid:

- for optic neuritis diagnosed at any grade, permanent discontinuation of linezolid is indicated;
- for peripheral neuropathy Grade 2, reduce the dose of linezolid to 300 mg per day with a possible drug holiday for 1–2 weeks before dose reduction;
- for peripheral neuropathy Grade 3 or 4, in most cases permanent suspension of linezolid will be needed; in some cases, after a 1–2-week drug holiday and reversion to Grade 2, the linezolid can be restarted and tolerated, provided it does not revert back to a Grade 3 or 4 (caution is warranted with this approach because patients can be left with a severe painful and disabling permanent peripheral neuropathy); and
- myelosuppression (even of Grade 3 or 4) is often reversible with a short 1-to-2-week drug holiday followed by reducing the dose of linezolid to 300 mg per day; severe anaemia may need to be treated with transfusions or erythropoietin.

The adverse events were noted more frequently in regimens using high-dose linezolid (1200 mg/daily). In the ZeNix study, 18.6% (8/43) participants in the study arm using linezolid 1200 mg daily for up to 26 weeks experienced a Grade 3 or more adverse event compared with 14.0% (6/43) participants in the intervention arm using 600 mg of linezolid for 26 weeks, and 19.6% (20/102) of participants in the BPaL arm using linezolid 600 mg or 300 mg in the TB-PRACTECAL trial (1). The most common adverse events resulting in dose modifications or early interruption of linezolid in the Nix-TB study were peripheral neuropathy and myelosuppression. Although optic neuritis was infrequent, it is an important adverse event that can result in the early interruption of linezolid. In comparison, in the ZeNix and TB-PRACTECAL trials, more than 90% of participants were able to complete more than 75% of the maximal intended dose and duration of linezolid. Peripheral neuropathy and myelosuppression were noted in both trials, but were often not severe and they improved with dose reductions or cessation of linezolid. A toxicodynamic modelling study using Nix-TB data showed lower percentages of patients with severe peripheral neuropathy (median, 5% versus 19%) and severe anaemia (1% versus 15%) in patients using 600 mg compared with 1200 mg linezolid daily (23).

4.2.5 Modification of treatment

The only experience using these new regimens stems from two clinical trials; it is therefore suggested that the programmatic implementation be aligned with this experience. Safe management of adverse events may warrant dose reduction or discontinuation of the component drugs. However, the BPaLM/ 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 drugs may result in poor treatment outcomes. Although dose modification of bedaquiline and pretomanid is not recommended, dose modification of linezolid is acceptable after the first 9 weeks of treatment in cases of adverse events. Although dose modification of linezolid should be avoided in the first 9 weeks of therapy, this principle should not override the need to avoid permanent disabilities. In some circumstances, the linezolid may need to be permanently stopped and a decision made on whether to continue the other drugs to complete treatment or start a new treatment. After 9 weeks of consecutive administration of linezolid, the dose of linezolid can be reduced to 300 mg if necessary (see examples in **Box 4.1**).

Modifications of linezolid dose were made in the ZeNix and TB-PRACTECAL trials when linezolid-associated toxicity was suspected. Although no analysis was undertaken to determine whether individuals with dose reductions had poorer treatment outcomes than those who continued for the complete duration, overall treatment success was very high in all investigational arms.

Pharmacokinetic studies have suggested that dose optimization of linezolid may differ among patients (24). Therapeutic drug monitoring (TDM) is a novel approach that can be used, where available, to optimize linezolid dose and minimize adverse events, without compromising effectiveness (25).

Further research is encouraged and is ongoing, to help ascertain how to optimize TDM in the treatment of individuals with MDR/RR-TB who are prescribed linezolid.

A dosing strategy study evaluating Nix-TB study data suggested that monitoring neuropathy symptoms and haemoglobin level may help guide linezolid dosing to avoid toxicities. A decrease in haemoglobin level of 10% or more after 4 weeks of treatment may help to identify those at high risk for severe anaemia (23). However, further research on dosing strategies is needed to optimize when and how to reduce the dose of linezolid.

Regarding the cessation of any component drug of the BPaLM/BPaL regimen because of severe toxicity, the following factors should be taken into account:

- if either bedaquiline or pretomanid needs to be permanently discontinued, the entire BPaLM/BPaL regimen should also be discontinued;
- if linezolid is permanently discontinued during the initial 9 consecutive weeks of treatment, the entire regimen should be discontinued;
- if linezolid is withheld in the later weeks of the regimen, with the total remaining duration of the regimen not exceeding 8 weeks, the regimen can be considered to be completed with the remaining component drugs; and
- if moxifloxacin alone is discontinued, the regimen can be continued as the BPaL regimen.

If linezolid (or any of the drugs) is being intermittently stopped and started on the BPaLM/BPaL regimen, there may be concern for development of resistance to the other component medicines in the regimen. This may be more of a concern for patients receiving BPaL because during single drug disruption the regimen will consist of only two effective drugs.
Acquired resistance to the two remaining agents in pre-XDR-TB cases can be catastrophic to both the patient and the society.

Although there is no specific number of missed regimen dosages to automatically indicate when the BPaLM/BPaL regimen should be declared a failure and an individualized longer regimen should be used instead, this general guidance to consider clinical review and switch to an individualized longer regimen should be considered when:

- more than 2 weeks of consecutive treatment interruption of all medicines in the regimen occurs; or
- more than 4 weeks cumulative of nonconsecutive treatment interruption of all medicines in the regimen occurs.

Extension of BPaL to 9 months should be done with caution in patients with a high number of missed linezolid dosages – switching to an individualized longer regimen may be considered instead of a BPaL extension.

> **Box 4.1. Some examples of changes in linezolid dosing within the BPaLM/BPaL regimen**
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> ➤ A patient diagnosed with MDR/RR-TB (based on GeneXpert results) completes 4 weeks of treatment with BPaLM, with 600 mg of linezolid, when they experience symptoms of severe paresthesia in the feet, preventing them from completing their daily life activities. This adverse event necessitates the cessation of linezolid within the first 9 weeks of therapy. Because permanent discontinuation of linezolid was needed, the entire regimen has to be discontinued and a new regimen started.
>
> ➤ A patient completing treatment with BPaL, with 600 mg of linezolid, for MDR/RR-TB with fluoroquinolone resistance, experiences Grade 3 optic neuritis in week 20 of therapy. Linezolid must be ceased permanently; however, because there is less than 8 weeks of treatment remaining, the patient completes a further 6 weeks of therapy with bedaquiline and pretomanid and has a negative sputum culture at the end of 26 weeks, achieving a successful treatment outcome on BPaL therapy. The optic neuritis improves slowly after cessation of linezolid.

4.2.6 Discontinuation of the regimen

The BPaLM/BPaL regimen may need to be discontinued in some patients. In such cases, patients need to be evaluated and treatment switched to an individualized longer regimen, based on the WHO guidelines for regimen design using priority grouping of medicines. The most common situations in which the regimen may be discontinued are treatment failure, inability to use linezolid for enough time owing to adverse effects (discussed above) or pregnancy that occurs during treatment.

4.2.7 Pregnancy during treatment

For patients who become pregnant during treatment, it will be necessary to discontinue the BPaLM/BPaL regimen and prescribe another regimen.

4.3 Key subgroups

The following subgroup analyses were available to the GDG in considering the eligibility criteria for the BPaLM/BPaL regimen: age, smear status, smoking status, people living with HIV (PLHIV) and previous TB. The GDG also considered the eligibility criteria as stipulated by each of the trials. The resulting considerations when prescribing the BPaLM/BPaL regimen are summarized below.

4.3.1 Children

Children were excluded from the Nix-TB, ZeNix (0–13 years) and TB-PRACTECAL (0–14 years) studies; therefore, no analysis specific to this subgroup of patients could have been performed. Although bedaquiline, linezolid and fluoroquinolones have been used to treat MDR/RR-TB in children, there are no data about the use of pretomanid in children, and further study is required to expand the use of BPaLM/BPaL to children. It is recommended that children aged below 14 years with pulmonary MDR/RR-TB be given consideration for the 9-month treatment regimen. Individuals aged 14 years and older were included in all the Nix-TB, ZeNix and TB-PRACTECAL trials and can safely be started on the BPaLM/BPaL regimen.

4.3.2 PLHIV

PLHIV represented 19.5% of those enrolled in the ZeNix trial, 51% of those enrolled in the Nix-TB study and 26.7% of those enrolled in the TB-PRACTECAL trial. PLHIV were eligible to enrol in the ZeNix trial if they had a CD4 count of more than 100 cells/uL, and in TB-PRACTECAL regardless of CD4 count. Thus, patients can be enrolled in the BPaLM/BPaL regimen irrespective of the CD4 count; however, care should be taken when CD4 counts are below 100 cells/mm^{3}.

In the ZeNix trial, enrolled participants had to be taking permitted antiretroviral medications.[3] Although there was no such criterion in TB-PRACTECAL, it is important to consider drug–drug interactions when administering TB and HIV medications in combination. The antiretroviral drug efavirenz induces metabolism of bedaquiline, so its co-administration with bedaquiline may result in reduced bedaquiline exposure and loss of activity; therefore, co-administration is to be avoided. Efavirenz also reduces pretomanid exposures significantly *(26)*; therefore, an alternative antiretroviral agent (potentially dolutegravir, although there is currently insufficient evidence for this) should be used if pretomanid or the BPaLM/BPaL regimen is considered. Ritonavir may increase bedaquiline exposure, which could potentially increase the risk of bedaquiline-related adverse reactions *(27)*; however, increased risk has not been noted in studies administering both drugs concurrently *(27–29)*, including in the current ZeNix trial. Individuals who are prescribed both bedaquiline and ritonavir should be monitored closely for adverse events, including QTc prolongation. Finally, regimens including zidovudine should be avoided, if possible, because both zidovudine and linezolid may cause peripheral nerve toxicity and are known to have myelosuppression cross-toxicity.

4.3.3 Pulmonary TB

Pulmonary TB patients with radiological evidence of bilateral disease or radiological evidence of cavitation were included in the Nix-TB, ZeNix and TB-PRACTECAL studies. As such, patients with extensive pulmonary disease can be started on the BPaLM/BPaL regimen; however, close microbiological and clinical monitoring for culture conversion and clinical response should be maintained. In patients on the BPaL regimen, where there is a lack of culture conversion or clinical response between months 4 and 6, the regimen can be extended to 9 months (39 weeks) total duration.

4.3.4 Extrapulmonary TB

Patients with extrapulmonary TB were excluded from the ZeNix trial; however, in the TB-PRACTECAL trial, only those with TB involving the CNS, osteomyelitis and arthritis were excluded. WHO recommends the BPaLM/BPaL for all forms of extrapulmonary TB except TB involving the CNS, osteoarticular TB and disseminated (miliary) TB. The longer MDR-TB regimens apply to such patients. Although there is a single case study of a participant from the Nix-TB study that confirms the incidental use of BPaL in CNS TB with favourable outcome *(30)*, further studies are required to recommend the regimen for programmatic implementation in severe disseminated TB. There are few data on the CNS penetration of bedaquiline, linezolid or pretomanid (**Web Annex 1**).

4.3.5 Pregnant and breastfeeding women

Pregnant and breastfeeding women were excluded from both the ZeNix and TB-PRACTECAL trials; therefore, no analysis specific to this subgroup of patients could be performed, and safety of the BPaLM/BPaL regimen, especially of pretomanid, in pregnant and breastfeeding women has not been established. For pregnant and breastfeeding women, the longer 9-month oral regimen can be used (**Chapter 5**).

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[3] These permitted antiretroviral treatments were nevirapine in combination with tenofovir/abacavir or emtricitabine/lamivudine; lopinavir/ritonavir in combination with tenofovir/abacavir or emtricitabine/lamivudine; and integrase inhibitor in combination with tenofovir/abacavir or emtricitabine/lamivudine. For patients on efavirenz, therapy could be changed to rilpivirine with tenofovir/abacavir or emtricitabine/lamivudine.

4.4 Implementation considerations

4.4.1 DST

As detailed previously, DST for fluoroquinolones is advisable before starting therapy. Where DST is unavailable, a careful history of previous exposure to TB therapy is critical. Where the treatment history suggests there may be resistance to one of the components of the regimen (i.e. exposure to bedaquiline, pretomanid or linezolid in an inadequate regimen is greater than 1 month and DST is unavailable), the BPaLM/BPaL therapy should not be commenced, and a longer individualized regimen should be considered. Furthermore, if there is greater than 1 month exposure to fluoroquinolones that indicates probable resistance, the BPaLM regimen should be continued until resistance to fluoroquinolones is determined.

Previous exposure to delamanid may suggest cross-resistance to pretomanid (31) and exposure to clofazimine may suggest cross-resistance to bedaquiline (32). Caution should be exerted in such situations and, where possible, if DST for clofazimine, bedaquiline or delamanid is available, it should be used.

4.4.2 Treatment support

In the ZeNix trial, all medications were administered with food throughout, because the bioavailability of bedaquiline (and pretomanid) increases when taken with food. The BPaLM/BPaL regimen should be administered with food and adequate water intake. Because calcium can bind the fluoroquinolones and make them ineffective, it is recommended to avoid taking dairy products, calcium supplements or calcium-containing antacids for 2 hours before and 2 hours after taking BPaLM.

Measures to support patient adherence tailored to patient needs are important to retain patients on treatment and ensure good treatment outcomes. Support should be provided through an effective model of care and measures should include support in the community or at home, social support and digital health interventions for communication with the patient (19). Early ambulatory care was employed by the ZeNix trial and is recommended for the programmatic implementation of the BPaLM/BPaL regimen, because it complements the patient-centred approach to the management of TB.

4.4.3 Contact tracing of household contacts

Contact tracing is critical to identify further cases of MDR/RR-TB, prevent ongoing transmission and ultimately work towards the global endTB strategy. Assessment should be offered for household contacts where feasible, especially for children aged below 5 years. Measures available for screening should include symptom assessment, chest X-ray and sputum testing (preferably using WHO-recommended molecular tests) (33).

4.4.4 Infection control

Infection control is vital to both inpatient and outpatient management of MDR/RR-TB patients and for the community. Within facilities, adequate ventilation, upper-room germicidal ultraviolet light systems and appropriate respirators for staff should be considered (i.e. N95 masks). Ventilation is also important at home, and education about personal safety and practices related to cough hygiene should be provided for patients and families (34). Most TB patients are likely to become noninfectious within weeks of commencing an effective treatment (35).

4.4.5 Cost–effectiveness analysis

While there have been no cost–effectiveness studies looking at the BPaLM regimen, cost–effectiveness studies for the BPaL regimen have demonstrated lower costs, should the regimen be programmatically implemented. Owing to the substantially shorter treatment duration and reduced need for hospitalization (36, 37), the implementation of a national programme using BPaL for MDR/RR-TB was estimated to cost 57–78% less than conventional longer regimens, when including all costs (e.g. investigations, drugs and hospitalization) (36).

4.5 Treatment monitoring

4.5.1 Monitoring treatment response and outcome assignment

Response to treatment should be monitored on the basis of monthly sputum smear microscopy and culture (ideally at the same frequency). Individuals prescribed the BPaLM/BPaL regimen should be monitored to assess regimen effectiveness and safety. Given that the BPaLM/BPaL regimen is a new and shorter regimen that includes novel medications, it is also important to follow up patients after the completion of treatment, to ensure that there is no treatment relapse or unexpected adverse events.

The treatment outcome definitions and reporting framework for patients on the BPaLM/BPaL regimen are the same as those for patients on longer MDR-TB regimens (38). The updated definition of treatment failure includes situations where a patient's treatment regimen has been terminated or permanently changed to a new treatment regimen, due to any of the following:

- *Adverse drug reactions* – If bedaquiline or pretomanid need to be suspended permanently owing to severe toxicity, the entire regimen will need to be terminated and a longer individualized treatment regimen considered. Should moxifloxacin alone need to be suspended in the BPaLM regimen, the regimen can be continued as the BPaL regimen. If linezolid alone needs be suspended when the remaining time to complete the regimen is less than 8 weeks, the treatment should be completed with the remaining drugs in the regimen.
- *Poor bacteriological or clinical response to treatment* – If there is bacteriological evidence of persistent positive cultures or poor clinical response, a change in the treatment regimen should be considered. Bacteriological failure for BPaLM/BPaL is marked by persistent positive sputum culture (no conversion or reversion) from month 4 to the end of treatment (after 6 months for BPaLM and after 9 months for BPaL). Where an individual fails to respond to the BPaLM/BPaL regimen, the patient should be transferred to a longer individualized regimen (**Chapter 6**) and provided with adequate treatment support. In such patients, DST, where available, is important to guide the design of the next regimen.
- *Acquired drug resistance to drugs in the BPaLM/BPaL regimen* – If resistance to BPaLM/BPaL component drugs (except moxifloxacin) is acquired during treatment (i.e. baseline DST is susceptible and monitoring culture demonstrates resistance), it will be necessary to discontinue the regimen.

Finally, there is growing evidence of both bedaquiline and linezolid resistance being expressed in *M. tuberculosis* strains, especially for those who have been exposed to either medication previously (39, 40). The capacity to monitor for the emergence of resistance with DST will be instrumental in controlling, treating and preventing the emergence and spread of resistant strains of infection.

4.5.2 Monitoring safety

As with all TB programmes, active surveillance for adverse events is critical to ensure safety and minimize short-term and long-term morbidity of patients. A schedule for monitoring examinations should be established and applied to all patients receiving treatment with the BPaLM/BPaL regimen. Patients should undergo appropriate evaluation at the beginning of treatment (baseline), and during

and after treatment. Common adverse events for each drug used in the BPaLM/BPaL regimen can be found in **Web Annex 1**, and a schedule of recommended investigations at baseline and during follow-up is given in **Table 4.2**. The monitoring schedule should consider the following:

- laboratory and ECG monitoring should be continued at monthly intervals for the duration of treatment (i.e. 9 months in the case of treatment prolongation);
- in the case of electrolyte disturbances, haematologic or ECG abnormalities, more frequent monitoring may be performed; and
- more frequent monitoring may be advisable in specific situations; for example, in older people, PLHIV, those affected by hepatitis (caused by hepatitis B virus [HBV] or hepatitis C virus [HCV]), those with diabetes mellitus, those with moderate to severe hepatic or renal impairment, or those with baseline anaemia or visual disturbances (e.g. glaucoma, cataract or colour blindness).

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 (**Web Annex 3**); the framework should be applied alongside monitoring for treatment outcomes, including early monitoring for treatment failure. Additional evidence on adverse events will be important to build the evidence base on the safety of the BPaLM/BPaL regimen in varied settings. Monitoring of changes in dosing and duration of linezolid can also inform the future evidence base on the wider use of the BPaLM/BPaL regimen and the tolerability of linezolid in this regimen.

The NTP should thus actively monitor drug safety to ensure proper patient care, to report any adverse events to the responsible drug safety authority in the country, and to inform national and global policy.

Table 4.2. An example of the schedule of baseline, routine and post-treatment monitoring examinations for the BPaLM/BPaL regimen

Examination	Baseline	2 weeks	Monthly	End of treatment	6 and 12 months post-treatment
Clinical evaluation					
Clinical assessment[a]					
Psychosocial assessment[b]					
Weight/BMI					
Performance status					
Peripheral neuropathy screening					
Visual acuity and colour discrimination screening					
Assessment and follow-up of adverse events					
Outcome consultation					
Bacteriological evaluations					
Sputum smear					
Sputum culture					
Sputum DST[c]			If smear or culture positive		

Examination	Baseline	2 weeks	Monthly	End of treatment	6 and 12 months post-treatment
Other samples (smear/culture/DST)			If no documented response to treatment		
Radiology, ECG and laboratory evaluations					
Chest X-ray					
ECG					
Full blood count					
Liver function tests (AST, ALT and bilirubin)					
Serum electrolytes					
Urea, creatinine					
Pregnancy test					
HIV/HBV/HCV tests					
BSL/HbA1c					

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; BSL: blood sugar level; DST: drug susceptibility testing; ECG: electrocardiography; HbA1c: glycosylated haemoglobin; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; TB: tuberculosis; WHO: World Health Organization.

[a] Vital signs, TB symptom screen, pain, nausea, appetite and nutrition, diarrhoea and candidiasis. Clinical assessment should focus on monitoring the response to treatment and addressing common symptoms associated with TB treatment and long-term antibiotic use, with the goal of supporting adherence.

[b] Food security, housing, mental state and substance use. Psychosocial assessment should offer an opportunity to assess supportive factors for treatment adherence and should be directly linked to relevant interventions wherever possible, as per country-specific questionnaires.

[c] Ideally, the patient should at baseline have a WHO-recommended rapid molecular test (for rifampicin and fluoroquinolone resistance). Other investigations, if available, include culture-based second-line DST, next-generation sequencing and DST for the BPaLM component drugs.

5. The 9-month all-oral regimen

This section refers to a treatment regimen for MDR/RR-TB that has a duration of at least 9 months and uses oral agents. The recommendation in the updated 2022 guideline *(1)* states:

> **Recommendation 2.1. WHO suggests the use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded.**
> *(Conditional recommendation, very low certainty of evidence)*

The 9-month all-oral regimen comprises bedaquiline (used for 6 months), in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high dose), pyrazinamide and clofazimine (for 4 months, with the possibility of extending to 6 months if the patient remains sputum smear positive at the end of 4 months); followed by treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide (for 5 months). Ethionamide can be replaced by 2 months of linezolid (600 mg daily).

The last consolidated guidelines for the treatment of DR-TB were released in June 2020. In 2019, for the WHO guideline update, the South African Department of Health provided WHO with access to programmatic data on injectable-free regimens that had been used in South Africa since 2017, when most eligible patients were enrolled on a shorter regimen, with bedaquiline replacing the injectable. Since then, new data from patients receiving WHO-recommended shorter and longer MDR/RR-TB regimens have been incorporated into an individual patient dataset (IPD) in 2021; these data were presented to the GDG in 2022 to help inform the development of the updated WHO guidelines on DR-TB. In addition, routine data from the South African NTP were available to assess the modified 9-month all-oral regimen containing linezolid (600 mg daily) instead of ethionamide, for treatment of patients with fluoroquinolone-susceptible MDR/RR-TB and without previous exposure to second-line TB drugs. The South African routine dataset of patients receiving the modified 9-month all-oral regimen would also have excluded children aged below 6 years, as well as patients with extensive pulmonary TB disease and severe forms of extrapulmonary TB, because these patients were not considered eligible for this regimen under current national DR-TB guidelines *(41)*. For the updated 2022 WHO guidelines, the modified 9-month regimen used in South Africa was compared with the earlier dataset and the 2021 IPD from patients meeting the same eligibility criteria and who received the WHO-recommended 9-month all-oral regimen containing ethionamide instead of linezolid, or the longer regimens designed based on the 2020 WHO recommendations.

Following review of the data presented, the GDG judged the benefits of the 9-month regimen with linezolid to be small and the undesirable effects to be moderate compared with the 9-month regimen with ethionamide. The certainty of evidence was judged to be very low. Based on this, the GDG judged that the balance of health effects does not favour either the 9-month regimen with linezolid or the 9-month regimen with ethionamide. Therefore, WHO has updated its conditional recommendation that, in eligible patients with MDR/RR-TB, the 9-month all-oral regimen may be used, and that 2 months of linezolid can be used as an alternative to 4 months of ethionamide within this shorter regimen *(1)*.

The implementation of these two variations of the 9-month all-oral MDR/RR-TB regimen (i.e. including either linezolid for 2 months or ethionamide for 4 months) is expected to provide more flexible and effective treatment options for a wider range of patients requiring treatment for MDR/RR-TB.

This regimen still requires combined use of seven agents (some with considerable toxicity), most of which will be continued for at least 9 months. Patients will need support to overcome the hardships associated with TB and its treatment, including daily adherence challenges, adverse drug reactions, indirect costs and stigma.

5.1 Eligibility

In settings where the 6-month MDR/RR-TB regimen is not yet available, or implementation of the regimen is not yet feasible, or for patients who are not eligible, selected patients with MDR/RR-TB may benefit from a 9-month all-oral regimen. Several eligibility criteria must be considered for this regimen, with additional considerations for the use of linezolid instead of ethionamide.

The 9-month all-oral regimen (with either ethionamide or linezolid) may be offered to the following patients with MDR/RR-TB (where resistance to at least rifampicin has been confirmed and resistance to fluoroquinolones has been ruled out):

- those with no documented resistance or suspected ineffectiveness of bedaquiline, clofazimine, or ethionamide or linezolid (whichever is considered for inclusion in the regimen);
- those with no exposure to previous treatment with bedaquiline, fluoroquinolones,[4] clofazimine, or ethionamide or linezolid (whichever is considered for inclusion in the regimen) for more than 1 month – when prior drug exposure is greater than 1 month, patients may still receive this regimen if resistance to the specific medicine with such exposure has been ruled out;
- those with no extensive or severe TB disease[5] and no severe extrapulmonary TB;[6]
- all people living with or without HIV;
- women who are pregnant or breastfeeding: these patients may be considered eligible for the linezolid-containing 9-month regimen, but they should not receive the 9-month regimen containing ethionamide; and
- children and adults without bacteriological confirmation of TB or resistance patterns but who require MDR/RR-TB treatment based on clinical signs and symptoms of TB (including radiological findings) and history of contact with someone with confirmed MDR/RR-TB: these patients may be eligible for this regimen based on the drug resistance profile of the isolate obtained from the most likely index case.

Linezolid is associated with considerable toxicity, which necessitates close monitoring for signs of bone marrow suppression and neuropathies. Optic neuritis and peripheral neuropathies tend to be reported beyond 2 months of treatment with linezolid, whereas myelosuppression is significantly dose dependent and is more likely to occur during the first 2 months of exposure to the drug *(42, 43)*. Nevertheless, linezolid is far more effective than ethionamide and helps to maintain a relatively effective regimen, particularly in cases of MDR/RR-TB where phenotypic DST results are awaited to confirm fluoroquinolone susceptibility. Therefore, the 9-month all-oral regimen containing linezolid (instead of ethionamide) should be offered wherever possible to patients who fulfil the eligibility criteria above, as well as the following:

- serum haemoglobin above 8 g/dL, neutrophils above 0.75×10^9/L and platelets above 150×10^9/L at the start of treatment; and
- no evidence of severe peripheral neuropathy, or any sign or suspicion of optic neuritis, at the start of treatment.

The 9-month all-oral regimen with ethionamide instead of linezolid, or a longer regimen without linezolid, may be more appropriate options for patients with very low haemoglobin, neutrophils or platelets, severe peripheral neuropathy or concerns regarding vision. Mild or moderate peripheral

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[4] This includes exposure to fluoroquinolones as either treatment or prevention of MDR/RR-TB.

[5] See definitions in Chapter 2.

[6] See definitions in Chapter 2.

neuropathy (Grade 1 or 2) may also be sufficient reason to offer a 9-month regimen that uses ethionamide, based on the patient's preference after discussing the risks and benefits of not including linezolid. However, the ethionamide-containing regimen must be avoided in individuals who are pregnant or breastfeeding. The decision regarding which regimen offers the best option for cure in a patient may also depend on other considerations; for example, preferences of patients and clinicians, pill burden, drug formulations, regional DRS data, feasibility of monitoring for drug adverse effects, and availability of blood transfusion services or ophthalmology services, if required.

If the 9-month all-oral MDR/RR-TB regimen (with either linezolid or ethionamide) cannot be used, the patient must be reassessed for their eligibility for another appropriate regimen, either BPaLM/BPaL or a longer MDR-TB regimen.

5.1.1 Assessment of extent and severity of TB disease

The extent of a patient's TB disease is important in determining appropriate regimen options, in addition to the drug susceptibility of the *M. tuberculosis* and other considerations mentioned above. Patients with extensive disease are not eligible for the 9-month all-oral regimen with either linezolid or ethionamide.

Patients with severe extrapulmonary MDR/RR-TB are not eligible for a 9-month regimen with either linezolid or ethionamide. The 9-month regimen may also not be adequate therapy for patients with osteoarticular or pericardial MDR/RR-TB. Poor penetration of first-line TB drugs through the pericardial tissues leads to low pericardial drug concentrations compared with plasma *(44)*, and although definitive data are lacking, drug penetration remains a concern for second-line TB drugs also. Treatment outcomes among patients treated with longer regimens for osteoarticular MDR/RR-TB are encouraging *(45)*, and there is evidence that linezolid penetrates bone tissue well *(46)*. However, due to the general lack of data on the efficacy of shorter regimens for treatment of these extrapulmonary manifestations of MDR/RR-TB, it remains prudent to treat such patients with longer regimens. In children and young adolescents aged below 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without airway compression) are considered to be severe *(47)* and might not be adequately treated with the 9-month all-oral regimen.

5.1.2 DST results

The 9-month all-oral regimen is not adequate for the treatment of patients with pre-XDR-TB or XDR-TB; it is also not adequate to treat MDR/RR-TB that has both *inh*A and *kat*G mutations. It is recommended that samples be submitted for susceptibility testing to at least fluoroquinolones before the start of this regimen. In settings without access to the Xpert MTB-XDR cartridge, a line probe assay (LPA: MTBDR*plus*) can be used to detect the two most common mutations that confer resistance to isoniazid. These mutations are found in the *inh*A promoter and *kat*G regions, and they confer resistance to isoniazid at different levels. Low-level isoniazid resistance is conferred when only *inh*A mutations are present, and high-level resistance is conferred when mutations in the *kat*G gene are present. Mutations at the *inh*A promoter region are also associated with resistance to ethionamide and prothionamide. High doses of isoniazid (15–20 mg/kg) are generally considered to be effective in the presence of low-level isoniazid resistance when used as part of combination therapy, but the efficacy of high doses of isoniazid in the presence of *kat*G mutations remains unclear. Nevertheless, high-dose isoniazid is always included in the 9-month all-oral regimen if either (but not both) of the mutations is present. The presence of mutations in both regions (i.e. *inh*A promoter and *kat*G genes) suggests that neither isoniazid at a high dose nor thioamides may be effective and therefore the 9-month all-oral regimen is not appropriate in these cases. In the South African setting, the detection of both mutations in MDR-TB strains was considered a surrogate marker for more extensive drug resistance at the time that the 9-month linezolid-containing regimen was introduced. Patients in South Africa who had MDR-TB with both mutations were not considered eligible for the 9-month

regimen, and so were not included in the routine dataset presented to the GDG for review. Thus, the efficacy of the 9-month regimen in such cases is largely unknown. In the absence of information on isoniazid resistance or mutation patterns in the case of an individual patient, knowledge of the prevalence of both mutations among locally circulating RR-TB strains (e.g. from DRS in the relevant epidemiological setting) may also inform decisions as to which treatment regimen would be most appropriate. DST for pyrazinamide and ethambutol is not carried out routinely in most settings and these results do not affect eligibility for the 9-month all-oral regimen. There are no rapid methods to detect *M. tuberculosis* resistance to clofazimine, linezolid and bedaquiline; however, the critical concentrations for mycobacterial growth indicator tube (MGIT) have been established, enabling NTPs to perform phenotypic DST. If resistance to these drugs is detected in isolates obtained from patients with MDR/RR-TB, the 9-month all-oral regimen should not be offered, or the patient must switch to a longer individualized treatment regimen. In the absence of DST for bedaquiline, linezolid and clofazimine, treatment decisions will rely on the likelihood of effectiveness of these medicines, based on an individual patient's clinical history and surveillance data from the country or region. This should be considered a last resort and an interim measure until the capacity for DST for these drugs becomes available.

5.1.3 Haematological assessment

Due to the risk of myelosuppression associated with even relatively short exposures to linezolid, pretreatment assessment of haemoglobin, neutrophils and platelets is crucial in patients considering treatment with a linezolid-containing regimen. Severe anaemia in patients with TB is a significant risk factor for poor treatment outcomes *(48)*, and patients with a low baseline haemoglobin may be at risk of severe linezolid-induced haematological toxicity. The linezolid-containing 9-month regimen must not be offered to patients with a pretreatment serum haemoglobin below 8 g/dL that cannot be rapidly corrected (i.e. with a blood transfusion) before starting MDR/RR-TB treatment. Similarly, due to the morbidity associated with severe neutropenia and thrombocytopenia, the linezolid-containing 9-month regimen is not suitable in patients with neutrophils below 0.75×10^9/L or platelets below 150×10^9/L before starting treatment.

5.2 Composition and duration of the regimen

The two variations of the 9-month all-oral MDR/RR-TB regimen recommended by WHO in 2022 *(1)* are described below.

5.2.1 Ethionamide variation

The ethionamide variation involves the initiation of bedaquiline, levofloxacin/moxifloxacin, clofazimine, ethionamide, ethambutol, isoniazid (high dose) and pyrazinamide. All seven drugs are given for 4 months, with the possibility of extending to 6 months if the patient's sputum remains bacteriologically positive at the end of the fourth month on treatment. Ethionamide and high-dose isoniazid are dropped after 4 or 6 months, depending on the decision to extend treatment based on smear status at month 4 of treatment. This is followed by 5 months of treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide. Bedaquiline is usually given for 6 months but could be extended to 9 months, particularly if the initial phase is extended from 4 to 6 months due to a lack of sputum conversion at month 4.

The regimen is summarized as:

> **4–6 Bdq$_{(6\ m)}$-Lfx/Mfx-Cfz-Z-E-Hh-Eto / 5 Lfx/Mfx-Cfz-Z-E**
>
> *Initial phase*: **4–6 Bdq$_{(6\ m)}$-Lfx/Mfx-Cfz-Z-E-Hh-Eto**
>
> *Continuation phase*: **5 Lfx/Mfx-Cfz-Z-E**

5.2.2 Linezolid variation

The linezolid variation involves initiation of bedaquiline, linezolid, levofloxacin/moxifloxacin, clofazimine, ethambutol, isoniazid (high dose) and pyrazinamide. Linezolid is only given for the first 2 months of treatment. Clinical and haematological monitoring are crucial to detect early linezolid-associated adverse events, particularly haematological events (sudden or significant drop in haemoglobin, neutrophils or platelets). After the initial 2 months, the remaining six drugs are given for another 2 months (with the possibility of extending by an additional 2 months if the patient's sputum remains bacteriologically positive at the end of the fourth month on treatment). High-dose isoniazid is dropped after 4 or 6 months, depending on the decision to extend treatment based on smear status at month 4 of treatment. This is followed by 5 months of treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide. Bedaquiline is usually given for 6 months but could be extended to 9 months, particularly if the initial phase is extended from 4 to 6 months due to a positive sputum smear result at month 4.

The regimen is summarized as:

> **4–6 Bdq$_{(6\ m)}$-Lzd$_{(2\ m)}$-Lfx/Mfx-Cfz-Z-E-Hh / 5 Lfx/Mfx-Cfz-Z-E**
>
> *Initial phase*: **4–6 Bdq$_{(6\ m)}$-Lzd$_{(2\ m)}$-Lfx/Mfx-Cfz-Z-E-Hh**
>
> *Continuation phase*: **5 Lfx/Mfx-Cfz-Z-E**

5.2.3 Choice of fluoroquinolone

In terms of choice of fluoroquinolone, either levofloxacin or moxifloxacin may be used in the 9-month all-oral regimen, because they have shown similar efficacy for treating MDR/RR-TB. Although levofloxacin results in a higher pill burden, it is often preferred because moxifloxacin is associated with a higher risk of QT interval prolongation *(49)*. Clinically significant, severe QT interval prolongation is relatively uncommon among patients treated with the 9-month all-oral regimens. However, the additive effect of co-administration of other QT-prolonging drugs (i.e. bedaquiline and clofazimine) within the shorter regimen should be considered when deciding on an appropriate regimen for individual patients with other risk factors for cardiotoxicity.

5.2.4 Drug dosage and frequency

The dosages of all drugs included in both variations of the 9-month all-oral regimen are outlined in the **Annex**. Most drugs, except for bedaquiline, are administered once a day, 7 days per week. In the 9-month regimen, bedaquiline is initially administered daily, with a higher loading dose for the first 2 weeks, followed by a lower maintenance dose on 3 days a week (with at least 48 hours between doses) thereafter. If one dose of bedaquiline is missed in the 2-week loading phase, the missed dose does not have to be made up and the patient can continue on the daily dosing schedule. If a dose of bedaquiline is missed in the maintenance phase but is remembered within that 48-hour dosing

period, the dose should be administered as soon as possible, and the following dose adjusted to be taken 48 hours later, with resumption of the usual thrice-weekly dosing schedule thereafter. For example, if bedaquiline is dosed every Monday, Wednesday and Friday, then if the Wednesday dose is missed it can still be taken on Thursday, and then the following dose should be taken on Saturday, with a return to the usual dosing schedule on Monday. If bedaquiline is interrupted for more than 2 weeks (but <8 weeks) during the maintenance phase of dosing, the drug should be reloaded at the higher daily dose for 7 days before resuming the thrice-weekly dosing schedule. If bedaquiline is interrupted for less than 2 consecutive weeks during the maintenance phase, no reloading is required. If bedaquiline is interrupted for more than 8 consecutive weeks, then the patient and treatment plan should be reassessed because the patient will no longer be eligible to continue or restart the 9-month all-oral regimen.

5.2.5 Regimen modifications

The 9-month all-oral MDR/RR-TB regimen should be implemented as a standardized package. It is not advisable to change the composition of the regimen or the duration of either the initial or continuation phase, with a few exceptions, as follows:

• Bedaquiline is usually given for 6 months but may be extended to 9 months if the initial phase of the regimen is extended from 4 to 6 months because of positive sputum smears at month 4 of treatment.
• Linezolid is only given for 2 months (instead of 4–6 months of ethionamide). If occasional doses of linezolid are missed during that time, the missed doses can be added on to the end of the 2-month period if the patient is tolerating the drug well; however, once fluoroquinolone resistance has been definitively ruled out, it may not be strictly necessary to make up the missed doses. The linezolid dose should not be reduced to less than the recommended dose to reduce the severity of adverse effects. If the full dose of linezolid (600 mg in adults) is not tolerated for the first full 2 months of treatment (apart from occasionally missed doses, which can be added to the end of the 2-month period), then the patient must either switch to an ethionamide-containing 9-month regimen (provided fluoroquinolone susceptibility is confirmed and the patient is not pregnant) or to an individualized longer regimen without linezolid. In selected cases where the risk of undetected resistance to fluoroquinolones and other second-line TB drugs is very low and the patient is unable to tolerate linezolid but would greatly benefit from a shorter regimen (e.g. migrant populations and children), the treating clinician may, after weighing up the risks and benefits, choose to stop linezolid before 2 months and continue the 9-month all-oral regimen, with close monitoring for relapse or recurrence.
• Prothionamide may be used instead of ethionamide.
• Moxifloxacin may be used instead of levofloxacin, provided close ECG monitoring is feasible (should this be required).
• If, for any reason, a patient is unable to tolerate pyrazinamide or ethambutol within the 9-month regimen, then one (but only one) of these drugs may be dropped during the continuation phase without necessitating a switch to a longer regimen. If two or more of these drugs are not tolerated within the 9-month regimen, the treatment will have to switch to a longer regimen. If any of the other drugs within the 9-month regimen (bedaquiline, levofloxacin/moxifloxacin, linezolid/ethionamide or clofazimine) are stopped early because of toxicity or intolerance then the patient will also have to switch to a new regimen. Patients switching to a new regimen due to toxicity or intolerance need to be reported as "treatment failed" (**Chapter 10**).
• At the fourth month of treatment on the 9-month regimen, the decision to extend the initial phase from 4 to 6 months is based on the bacteriological sputum smear status of the patient's sputum specimen. If the specimen is smear negative at month 4 (regardless of smear status at the start of treatment), the patient may move to the continuation phase of treatment. If the specimen is smear positive at month 4, the initial phase is prolonged to 6 months. The duration of the continuation phase remains fixed at 5 months.

- At the sixth month of treatment, the culture result from the specimen taken at month 4 and possibly month 5 should be available, as well as the smear results from the specimens taken at months 5 and 6. If the culture from the 4-month specimen is positive for *M. tuberculosis*, the clinician should undertake a full work-up to assess for treatment failure – this involves a comprehensive clinical assessment, review of treatment adherence to address specific challenges, radiological assessment and collection of another respiratory sample for bacteriological assessment, as well as repeat DST of the most recent positive culture to test for emerging resistance to second-line TB drugs. Similarly, if the month 5 and 6 culture results remain persistently positive, treatment failure should be suspected, particularly if the patient has had suboptimal adherence to treatment or shows other signs of poor clinical or radiological response to treatment.

5.2.6 Switching between treatment regimens

If a patient starts the 9-month all-oral MDR/RR-TB regimen but is later found to be ineligible following detection of *M. tuberculosis* resistance to fluoroquinolones, the patient must switch to a different regimen. Such patients might be eligible for a 6-month BPaL regimen if their prior exposure to bedaquiline and linezolid was for less than 1 month and there is no demonstrated resistance to any components of the BPaL regimen. The BPaL regimen may only be considered if the patient meets the eligibility criteria and the regimen is available and feasible in the setting. In cases where an eligible patient starts the 9-month all-oral MDR/RR-TB regimen but additional resistance is detected later in treatment (after initial DST indicated susceptibility to Group A and B drugs), it can be assumed that further acquisition of resistance may have emerged during that period of drug exposure; such patients should be considered for a treatment outcome of failure and should not continue with the 9-month regimen. The 6-month BPaL regimen should not be offered to these patients because amplification may have occurred to linezolid and bedaquiline, key drugs in the BPaLM/BPaL regimen. The patient should switch to a longer individualized regimen, with repeated phenotypic DST to guide the composition of the longer regimen.

Patients who start a 6-month BPaLM/BPaL regimen may switch to the 9-month all-oral regimen, if required, provided they meet the necessary eligibility criteria for the 9-month regimen. This may be warranted when toxicity to linezolid develops early in the BPaLM/BPaL regimen and necessitates a linezolid-sparing regimen, such as the 9-month regimen with ethionamide.

Patients who start on a longer regimen but are subsequently found to be eligible for the 9-month all-oral regimen may switch to the 9-month regimen if this is done within the first month of starting treatment. There is little experience in switching from longer to shorter regimens in this way; hence, clinical monitoring and adequate data collection are important to inform future treatment recommendations.

Patients who are lost to follow-up after starting the 9-month all-oral regimen are likely to have had more than 1 month of exposure to key drugs within the 9-month regimen. Should such patients return to care and require MDR/RR-TB treatment in future, the 9-month all-oral regimen may still be considered as a treatment option if resistance to bedaquiline, fluoroquinolones, clofazimine, and ethionamide or linezolid (whichever is considered for inclusion in the regimen) is ruled out and all other relevant eligibility criteria are met. In such cases, DST for the key drugs in this regimen is likely to take some time; therefore, patients may have to initiate a longer individualized regimen while awaiting DST results.

5.3 Key subgroups

5.3.1 PLHIV

The 9-month all-oral MDR/RR-TB regimen was evaluated in a setting with a high HIV prevalence. In the dataset analysed for the 2022 WHO guidelines, over 70% of patients starting a shorter regimen were also living with HIV, and among those, more than 90% were receiving ART. There is no reason to believe that a 9-month all-oral regimen would perform any differently in PLHIV who initiate ART early, in accordance with WHO recommendations. However, clinicians should be mindful of the overlapping, additive toxicities and potential drug–drug interactions with antiretroviral medicines and TB drugs. Co-administration of zidovudine and linezolid should be avoided because of the increased risk of myelosuppression. Boosted protease inhibitors can increase bedaquiline exposure, thereby increasing the risk of bedaquiline-related adverse drug reactions (e.g. QT interval prolongation), which may require closer monitoring. Efavirenz can reduce the concentration of bedaquiline; therefore, this antiretroviral drug should be avoided in patients receiving the 9-month all-oral regimen. There are no overlapping toxicities or drug–drug interactions with dolutegravir in patients receiving the shorter regimen with either linezolid or ethionamide. PLHIV receiving the 9-month all-oral bedaquiline-containing regimen will need prophylactic medication for opportunistic infections, support for adherence to TB and antiretroviral medication, and close monitoring of the biomarkers of immune status.

5.3.2 Children

Aside from bedaquiline, the medicines that compose the 9-month all-oral regimen have been part of MDR/RR-TB regimens for many years, in similar combinations, for both adults and children. The associated adverse drug reactions have been widely described and the drug dosages established (**Annex**). Child-friendly formulations are now available for all second-line drugs and should be provided to children whenever possible. When these are not available, practical instructions for use of adult formulations for administration are available, so lack of formulation should not be a hindrance to treating children of all ages. This must be addressed as a priority by treatment programmes that include management of children with MDR/RR-TB. Now that dosing and safety data are available for bedaquiline in children aged below 6 years, the removal of the age restriction for the use of bedaquiline means that children of all ages with MDR/RR-TB may be offered the 9-month all-oral regimen if they meet the eligibility criteria *(47)*. Extent of disease is defined slightly differently for children than for adults, and most children with TB have less severe forms of the disease than adults. The term "adults" in this chapter refers to individuals aged 15 years and older and "children" refers to those aged below 15 years; thus, the adult population includes older adolescents.

Evidence from the SHINE trial (Shorter Treatment for Minimal Tuberculosis in Children), which was the first and only large Phase 3 trial to evaluate the duration of TB treatment in children with nonsevere drug-susceptible TB (DS-TB), suggests that pulmonary TB disease should be classified as severe (which may include extensive, advanced and complicated disease) or nonsevere in children *(47)*. Despite the lack of comparable data among children with MDR/RR-TB disease specifically, the same definitions for severity of disease are likely to be appropriate when considering the use of a shorter regimen for children with MDR/RR-TB. Nonsevere disease in children is defined as peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion (without empyema or pneumothorax); or paucibacillary, noncavitary disease confined to one lobe of the lungs and without a miliary pattern (evaluated on chest X-ray) *(47)*.

Bacteriological confirmation of MDR/RR-TB disease in younger children is relatively uncommon, and the decision to treat for MDR/RR-TB may rely on clinical signs and symptoms, radiological findings and significant exposure to someone with microbiologically confirmed MDR/RR-TB. In children without microbiological confirmation of TB disease or rifampicin resistance, the choice of regimen relies partly on the drug-resistance pattern of the isolate obtained from the most likely index case. Although

only six children aged below 14 years were included in the analysis of the shorter regimen dataset from South Africa, the evidence supporting the use of this regimen in adults may be extrapolated to children, provided the implementation considerations are followed. The benefits of a shorter regimen for a child with MDR/RR-TB should be weighed against the high pill burden and the difficulties of administering each of the seven drugs in this regimen, particularly if child-friendly formulations of the drugs are not available. Bedaquiline is relatively well tolerated and easy to administer to children; adult-formulation bedaquiline tablets suspended in water have been shown to have the same bioavailability as tablets swallowed whole (**Annex**).

For most second-line TB drugs, adverse effects appear to be less frequent in children than in adults; however, close monitoring is still warranted in children, regardless of the regimen. Before a shorter regimen containing linezolid is offered to a child, the clinician must consider the feasibility of close monitoring, particularly for haematological side-effects, which requires repeated blood draws for at least the first 2 months of treatment. Visual acuity and colour vision are more difficult to monitor in younger children than in older children and adults. Ethionamide might be considered a safer alternative for children in some settings, but this should be balanced against the lower efficacy of the drug compared with linezolid, and the poor gastrointestinal tolerability and need to monitor for hypothyroidism.

5.3.3 Pregnant and breastfeeding women

Dosing and safety data to support the optimal use of second-line TB medicines during pregnancy are generally sparse. There have been case reports and observational data reporting successful treatment and pregnancy outcomes among women who received treatment (including bedaquiline-containing regimens) for MDR/RR-TB during pregnancy and postpartum, but pregnant and breastfeeding women are usually excluded from clinical drug trials and early access programmes. Even less is known about the effects of MDR/RR-TB treatment on the infant in-utero and after birth; however, in general, the benefits (to both parent and child) of providing effective MDR/RR-TB treatment to the parent far outweigh the potential risks posed to the fetus in-utero or the breastfed infant.

Ethionamide is usually contraindicated in pregnancy because animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans. The physiologic effects of pregnancy, which lead to a relatively low haemoglobin (due to the dilutional effect of increased blood volume) and a higher risk of peripheral neuropathies, may be exacerbated by the adverse effects of linezolid. Nevertheless, the 9-month all-oral regimen including linezolid instead of ethionamide may be considered for pregnant and breastfeeding patients who meet the eligibility criteria for the shorter regimen with linezolid, although closer monitoring is required.

More compelling evidence on the dosing and safety of specific anti-TB drugs among pregnant and breastfeeding women is needed to guide decision-making on the most appropriate regimen for treatment of MDR/RR-TB during pregnancy and postpartum. In addition, this population group requires considerable adherence support and monitoring of proper administration of MDR/RR-TB treatment, along with other chronic medications, to ensure successful treatment outcomes and minimal risk of TB transmission from mother to infant postpartum. Care providers must also pay particular attention to seamless continuity of care between antenatal and TB services, which are rarely integrated in most TB-endemic settings. In view of the complexities of service integration, the challenges in clinical management, and the scarcity of evidence-based recommendations for this group, The Sentinel Project on Pediatric Drug-Resistant Tuberculosis[7] brought together a group of providers and researchers with decades of experience caring for people with DR-TB who are pregnant or in the peripartum period. This group developed a "field guide" that is intended to supplement existing guidelines and constitutes a set of current best practices to improve the quality of care provided to pregnant and postpartum individuals, and their infants, who are living with DR-TB *(50)*.

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[7]   See https://sentinel-project.org/.

5.3.4 Extensive TB disease

Extensive (or advanced) TB disease in adults is defined as the presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged below 15 years, extensive (or advanced) disease is usually defined by the presence of cavities or bilateral disease on chest radiography (see above regarding severe and nonsevere TB disease in children). This highlights the importance of chest radiography as part of the diagnostic work-up for patients, along with the usual patient–clinician interaction. Patients with extensive MDR/RR-TB disease should not be treated with the 9-month all-oral regimen with either linezolid or ethionamide because of the lack of evidence on the impact of this regimen in this subgroup of patients.

5.3.5 Extrapulmonary TB

The dataset evaluated for the 2022 WHO guidelines included patients with uncomplicated extrapulmonary MDR/RR-TB disease. No evidence was available to discern the impact of the 9-month all-oral regimen with either linezolid or ethionamide in patients with severe extrapulmonary TB (defined in this document as the presence of miliary TB or TB meningitis). Although this definition does not specifically include osteoarticular or pericardial TB, a longer treatment regimen may be more suitable in these cases of extrapulmonary TB because of the relatively poor perfusion of TB drugs into the pericardial space and the lack of data on the efficacy of shorter MDR/RR-TB regimens in these cases. The 9-month all-oral regimen should not be offered to patients with severe or complicated extrapulmonary MDR/RR-TB disease. In children aged below 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without airway compression) are considered severe *(47)* and may not be adequately treated with the 9-month all-oral regimen.

5.4 Implementation considerations and treatment in special situations

5.4.1 DST results

The 9-month all-oral regimen is not adequate for the treatment of pre-XDR-TB or XDR-TB, and the efficacy of the regimen for treatment of MDR-TB where both *inh*A and *kat*G mutations are present is largely unknown. Therefore, DST is recommended at or before the start of this regimen to exclude resistance to at least fluoroquinolones and to determine the mutations conferring resistance to isoniazid. Results of DST should not delay the start of an appropriate MDR/RR-TB treatment regimen, particularly if DST relies on phenotypic methods. Although there appears to be no significant association between treatment delay and individual MDR/RR-TB treatment outcomes, delays in effective treatment initiation increase the risk of clinical deterioration and contribute to ongoing transmission of MDR/RR-TB *(51, 52)*. Provided that there is no history or evidence of exposure to fluoroquinolone-resistant MDR/RR-TB, the 9-month regimen containing linezolid (instead of ethionamide) may be started in eligible patients with TB that is resistant to at least rifampicin while awaiting fluoroquinolone DST results. If a linezolid-containing 9-month regimen cannot be offered while awaiting fluoroquinolone DST results (e.g. owing to contraindications to linezolid), then the patient may start an effective longer regimen with the option to switch to an ethionamide-containing 9-month regimen if fluoroquinolone resistance is definitively ruled out once DST results become available within the first month of treatment and all other eligibility criteria are met. Linezolid may offer some initial protection against as-yet-undetected fluoroquinolone resistance at the start of treatment, but ethionamide probably does not offer the same level of protection; therefore, the 9-month regimen containing ethionamide should only be considered if results of fluoroquinolone DST are available and indicate susceptibility to fluoroquinolones prior

to initiation of this regimen. **Box 5.1** and **Box 5.2** below provide examples of clinical scenarios and appropriate choices of regimens.

The LPA, MTBDR*plus*, is widely used to detect mutations conferring resistance to isoniazid, as well as rifampicin; however, in future this test may be replaced by the Xpert MTB-XDR assay cartridge in some settings. Using the GeneXpert® platform, this assay detects mutations associated with resistance to isoniazid, fluoroquinolones, second-line injectable drugs and ethionamide in a single test. The result for isoniazid resistance is reported as "high-level" or "low-level" on this platform, and additional laboratory expertise may be required to identify the specific mutations conferring resistance to isoniazid and ethionamide. In general, RR-TB isolates reported to have "high-level" isoniazid resistance as well as ethionamide resistance could be assumed to have both *inh*A and *kat*G mutations, and the 9-month regimen may not be appropriate for treatment in these cases. Molecular testing methods have a lower sensitivity for detecting isoniazid resistance than phenotypic methods; hence, in the presence of RR-TB, isoniazid susceptibility demonstrated on genotypic testing must be confirmed phenotypically before a normal dose of isoniazid is used within the 9-month all-oral regimen.

DST for pyrazinamide and ethambutol is not carried out routinely in most settings; therefore, this information is rarely available to guide treatment decisions at an individual patient level. Phenotypic DST for these drugs is often included in regional or nationwide drug-resistance surveys and this information might be useful when deciding whether to use the 9-month regimen including these drugs. The 9-month all-oral regimen is standardized and all seven drugs (including either ethionamide or linezolid) should be initiated from the outset. Pyrazinamide and ethambutol are inexpensive and generally well tolerated, and may still be efficacious against MDR/RR-TB in people who are eligible for this regimen. However, some health care providers and patients, particularly children and their caregivers, might find the high pill burden posed by these medicines challenging despite the shorter duration of this treatment regimen.

Ideally, phenotypic DST for clofazimine, linezolid and bedaquiline should be performed at the time of treatment initiation or with the first strain isolated from patients' samples during treatment monitoring. TB programmes must rapidly build the capacity to undertake DST, and all efforts must be made to ensure access to approved tests. If routine phenotypic DST for clofazimine, linezolid and bedaquiline is not feasible for all patients diagnosed with MDR/RR-TB, then DST for these drugs must be prioritized for patients with positive TB sputum cultures at month 4 of treatment or beyond. Delayed conversion to negative cultures, or reversion to positive cultures, after 4 months of MDR/RR-TB treatment may be an early indication that treatment is failing, and clinicians must consider the possibility of acquired drug resistance *(53)*.

Box 5.1. Regimen selection at RR-TB diagnosis – no initial linezolid contraindications

Patient presents with signs and symptoms of TB disease and no previous treatment with second-line TB drugs, no extensive or severe pulmonary disease, no severe extrapulmonary TB, and no contact with pre-XDR-TB or XDR-TB; thus, there are **no contraindications to linezolid**.

➔ Diagnosis of RR-TB only or RR-TB with isoniazid susceptibility, pending results of fluoroquinolone DST. This patient could start the 9-month regimen with linezolid (but preferably not with ethionamide) while DST results are awaited.

   • This patient has the option to switch from the linezolid-containing regimen to the ethionamide-containing regimen if preferred (and if not pregnant) once fluoroquinolone susceptibility is confirmed on DST and if no mutation was detected in the *inh*A promoter region.

➔ Diagnosis of RR-TB with isoniazid resistance conferred by mutations in the *inh*A promoter region only, and pending results of fluoroquinolone DST or susceptibility to fluoroquinolones is confirmed. This patient could start the 9-month regimen with linezolid (but not with ethionamide owing to the *inh*A mutation).

➔ Diagnosis of RR-TB with isoniazid resistance conferred by mutations in the *kat*G gene only, and pending results of fluoroquinolone DST. This patient could start the 9-month regimen with linezolid (but preferably not with ethionamide) while DST results are awaited.

   • This patient has the option to switch from the linezolid-containing regimen to the ethionamide-containing regimen if preferred (and if not pregnant) once fluoroquinolone susceptibility is confirmed.

➔ Diagnosis of RR-TB with isoniazid resistance conferred by mutations in the *kat*G gene only and confirmed susceptibility to fluoroquinolones. This patient could start the 9-month regimen with either ethionamide (if not pregnant) or linezolid.

> **Box 5.2. Regimen selection at RR-TB diagnosis – linezolid contraindications**
>
> Patient presents with signs and symptoms of TB disease and no previous treatment with second-line TB drugs, no extensive or severe pulmonary disease, no severe extrapulmonary TB, and no contact with pre-XDR-TB or XDR-TB, but **with contraindications to linezolid**.
>
> ➜ Diagnosis of RR-TB only, or RR-TB with isoniazid susceptibility, pending results of fluoroquinolone DST. This patient could start a longer regimen initially, but with the option to switch to a 9-month regimen with ethionamide (not linezolid because contraindicated) within the first month of treatment once fluoroquinolone susceptibility is confirmed on DST, no mutation is detected in the *inh*A promoter region and the patient is not pregnant.
>
> ➜ Diagnosis of RR-TB with isoniazid resistance conferred by mutations in the *inh*A promoter region only, and pending results of fluoroquinolone DST or susceptibility to fluoroquinolones is confirmed. This patient should preferably not receive the 9-month regimen with either ethionamide (owing to the *inh*A mutation) or linezolid (contraindicated) and should instead be considered for a longer regimen.
>
> ➜ Diagnosis of RR-TB with isoniazid resistance conferred by mutations in the *kat*G gene only, and pending results of fluoroquinolone DST. This patient could start a longer regimen initially while DST results are awaited, but with the option to switch to a 9-month regimen with ethionamide (not linezolid because contraindicated) if fluoroquinolone susceptibility is confirmed and the patient is not pregnant.
>
> ➜ Diagnosis of RR-TB with isoniazid resistance conferred by mutations in the *kat*G gene only and confirmed susceptibility to fluoroquinolones. This patient is eligible to start the shorter regimen with ethionamide (not linezolid) if not pregnant.

5.4.2 Patient subgroups

Older patients

TB-related morbidity and mortality tends to be higher among older people than in the younger population. Patients aged 65 years and older with MDR/RR-TB are more vulnerable to the adverse effects of TB medications owing to physiological changes of ageing (e.g. increase in QT interval and decrease in estimated glomerular filtration rate [eGFR]), other comorbidities and overlapping, additive drug toxicities (owing to a higher likelihood of polypharmacy in older people). Advanced age has also been reported as a risk factor for linezolid-induced anaemia *(54)*. Whereas the 9-month all-oral regimen may be offered to eligible patients of any age, older people may require closer monitoring for drug-related adverse events as well as closer adherence support and assistance to administer treatment daily or as prescribed.

Patients with diabetes mellitus

The 9-month all-oral regimen may be used to treat MDR/RR-TB in patients with diabetes; however, there are currently no data on safety and outcomes of this regimen in this specific group. Type 2 diabetes is associated with several liver disorders; therefore, it is prudent to monitor closely for hepatotoxicity among these patients. Blood sugar levels may be difficult to control in patients with MDR/RR-TB and diabetes, and insulin may be required to gain adequate blood sugar control during

treatment. Patients with diabetes are also at increased risk of peripheral neuropathies, which may be further exacerbated following exposure to linezolid and high doses of isoniazid. These patients must be counselled to report symptoms of peripheral neuropathies early because such symptoms may necessitate a change in regimen – either to the ethionamide-containing 9-month regimen (bearing in mind this will still include high doses of isoniazid in the initial phase), or a longer individualized regimen without linezolid.

Patients with hepatic dysfunction

The 9-month all-oral regimen may not be the most appropriate option for people with chronic liver disease because this regimen contains several potentially hepatotoxic drugs (e.g. pyrazinamide, isoniazid and ethionamide). Although this regimen may still be offered with close monitoring of liver enzymes in people with chronic stable liver dysfunction, a longer regimen with fewer hepatotoxic drugs may be preferable in some settings where closer monitoring is not feasible.

Patients with renal failure

The 9-month all-oral regimen may be used to treat MDR/RR-TB in patients with renal failure provided the dose or dosing interval of renally excreted drugs are adjusted for the patient's creatinine clearance. Levofloxacin (but not moxifloxacin), ethambutol and pyrazinamide require dose or frequency adjustment for adults with creatinine clearance of less than 30 mL/min. Treatment does not have to be extended unless indicated by lack of smear conversion at month 4 of treatment, as for patients with normal renal function.

Patients with anaemia

Patients with TB commonly have anaemia of chronic disease (55), and treatment with an effective drug regimen (even one that includes linezolid) may lead to improvement or resolution of the anaemia once the disease is properly treated. Many patients with TB also suffer with nutritional deficiencies, and low haemoglobin may also be a result of iron deficiency and low iron stores (56). This deficiency may resolve naturally once effective TB treatment (even including linezolid) leads to resolution of TB symptoms and improvement in the patient's diet and appetite. Extended use (≥2 weeks) of linezolid has been associated with reversible myelosuppression (57). Therefore, the linezolid-containing 9-month regimen must not be offered to patients with a pretreatment serum haemoglobin below 8 g/dL that cannot be rapidly corrected (i.e. with blood transfusions) before starting MDR/RR-TB treatment. Similarly, owing to the morbidity associated with severe neutropenia and thrombocytopenia, the linezolid-containing 9-month regimen is not suitable in patients with neutrophils below 0.75 × 10^9/L (or 750/mm^3) or platelets below 150 × 10^9/L (or 50 000/mm^3) before starting treatment. Some patients respond well to an initial blood transfusion that raises their haemoglobin above 8 g/dL and allows them to at least start a linezolid-containing regimen – linezolid will not necessarily cause myelosuppression in patients with baseline anaemia, although a baseline haemoglobin below 10.5 g/dL has been reported as a risk factor for linezolid-induced anaemia (54). It is not uncommon for haemoglobin to drop again shortly after blood transfusion in a person with untreated chronic TB disease, but the temporary increase in haemoglobin may allow enough time for a linezolid-containing regimen to be effective in treating the TB disease, and the patient's haemoglobin is likely to improve as the disease is brought under control.

Blood transfusions may not be a lasting solution in situations where haemoglobin drops significantly from baseline because of linezolid toxicity when linezolid is continued. Although blood transfusions may help to reverse anaemia following withdrawal of linezolid, they may not resolve linezolid-induced myelosuppression with ongoing exposure to the drug. Therefore, if linezolid toxicity leads to a drop in haemoglobin below 8 g/dL during the first 2 months of treatment, linezolid should be withdrawn and the regimen switched appropriately. More research is needed on the role of iron supplementation to treat anaemia during MDR/RR-TB treatment; however, oral supplementation of iron is often not well

tolerated and is not immediately effective at the start of treatment, at a time when the pill burden can be overwhelming and the risk of multiple drug side-effects is high.

5.5 Treatment monitoring

5.5.1 Monitoring treatment response and outcome assignment

Response to treatment is monitored by monthly sputum smear microscopy and culture. Older children who had microbiological confirmation of TB disease should also be encouraged to produce respiratory samples for monitoring whenever possible. Treatment response can also be monitored through regular clinical assessment of signs and symptoms of TB disease, and children should be monitored for changes in weight, height and BMI using age-appropriate growth charts. Repeat radiological assessment during treatment is not always necessary because some radiological abnormalities may persist throughout and beyond treatment completion but do not necessarily indicate poor response or failure of treatment. However, radiological deterioration and new abnormalities (compared with baseline) may assist in identifying poor treatment response; hence, radiological assessment should be repeated if clinically indicated. The updated definition of treatment failure includes situations where a patient's treatment regimen has been terminated or permanently changed to a new treatment regimen, owing to:

- no clinical or bacteriological response to treatment;
- adverse drug reaction; or
- evidence of additional drug resistance to medicines in the regimen.

The treatment outcome definitions and reporting framework for patients who received the 9-month all-oral MDR/RR-TB regimen is the same as for patients who received the longer regimens (**Chapter 10**) *(58)*. Bacteriological treatment failure is marked by persistent positive sputum culture from month 6 to the end of treatment. Treatment failure can be considered earlier than 6 months if it is accompanied by significant clinical decline consistent with TB disease progression. Permanent discontinuation due to adverse reactions or acquired drug resistance of one of the key medicines (bedaquiline, fluoroquinolone, ethionamide/linezolid or clofazimine, or two or more of the remaining medicines in the regimen), or high-dose isoniazid, ethambutol or pyrazinamide will lead to the treatment failure consideration.

All patients receiving shorter regimens should be followed up for clinical re-assessment (ideally over a 12-month period) beyond treatment completion, to monitor for potential relapse.

5.5.2 Monitoring safety

Although the 9-month all-oral MDR/RR-TB regimen is taken for much less time than the longer regimens, this regimen still has a high pill burden and includes medications with multiple overlapping toxicities. The most common adverse events associated with the 9-month all-oral regimen are anaemia (among patients receiving the linezolid-containing regimen), hepatotoxicity, QT prolongation, nausea and vomiting *(59)*. Treatment monitoring schedules must include relevant clinical and laboratory parameters to detect, manage and prevent common and significant adverse events in a timely manner.

Table 5.1. Example of a monitoring schedule for patients receiving the 9-month all-oral MDR/RR-TB regimen

Time on treatment	Baseline	Months 0–2	Months 3–6	Months 7–9 (or 11)
Clinical history and examination[a]	X	X (monthly)	X (monthly)	X (monthly)
Treatment literacy and adherence counselling	X	X (at every HCW interaction)	As required throughout treatment	
Substance use and mental health screen (with appropriate intervention and support)	X	X (monthly)	X (monthly)	X (monthly)
Weight / height / BMI (and nutritional support)	X	X (monthly)	X (monthly)	X (monthly)
Family planning, and pregnancy testing	X	X (monthly)	X (monthly)	X (monthly)
Respiratory sample for smear microscopy and TB culture (DST if indicated)	X	X (monthly)	X (monthly)	X (monthly)
Chest X-ray (or other radiological assessment)	X		X	
HIV testing	X		X (if previously negative, repeat every 3 months in high HIV prevalence settings, or if indicated)	X (if previously negative, repeat every 3 months in high HIV prevalence settings, or if indicated)
Fingerprick blood glucose	X	Repeat regularly if clinically indicated		
Full blood count and differential (if receiving Lzd)	X	X (at weeks 2, 4 and 8 if receiving Lzd)	Repeat if clinically indicated	
Liver function tests (at least ALT, AST and bilirubin)	X	Repeat regularly if clinically indicated: vomiting, right upper quadrant pain, jaundice or if person is unwell or has any evidence of liver injury		
Creatinine	X	Repeat regularly if clinically indicated (i.e. if person becomes unwell, or if baseline creatinine was abnormal or renal drug dosing required)		

Time on treatment	Baseline	Months 0–2	Months 3–6	Months 7–9 (or 11)
Serum electrolytes	X	Repeat regularly if clinically indicated (i.e. if person becomes unwell, is vomiting, has diarrhoea or has QTcF prolongation)		
TSH (if receiving Eto)	X	Repeat at 3 months if on Eto, or when QTcF is prolonged		
ECG (calculate QTcF)	X	X (monthly)	X (monthly)	X (monthly)
Peripheral neuropathy and visual acuity screen (if receiving Lzd)[b]	X	X (monthly)	Repeat regularly if clinically indicated	

ALT: alanine transaminase; AST: aspartate aminotransferase; BMI: body mass index; DST: drug susceptibility testing; ECG: electrocardiography; Eto: ethionamide; HCW: health care worker; HIV: human immunodeficiency virus; Lzd: linezolid; MDR/RR-TB: multidrug- or rifampicin-resistant TB; QTcF: corrected QT interval by Fridericia; TB: tuberculosis; TSH: thyroid stimulating hormone.

[a] Clinical assessment of TB signs or symptoms and adverse events.

[b] It may be difficult to perform detailed assessments for peripheral neuropathy or visual acuity in young children, but the risk of these events appears to be lower in this group; therefore, this should not be a reason to withhold linezolid from young children who would otherwise benefit from this drug.

NTPs should already have established aDSM systems; aDSM involves the active and systematic clinical and laboratory assessment of patients on treatment with new TB medicines, or novel MDR/RR-TB regimens, to detect, manage and report suspected or confirmed drug toxicities *(18)*. Adverse events (particularly those that are considered serious or severe, or lead to drug withdrawal) among patients receiving the 9-month all-oral regimen must be reported to the national agency responsible for pharmacovigilance, within the framework of aDSM. The WHO global aDSM database collects a standard set of variables and comprises anonymized IPD on adverse events from people treated with new TB medicines or novel MDR/RR-TB regimens *(60)*. Countries where aDSM has been implemented are encouraged to contribute their national data to this database, to improve the collective knowledge of the safety of new TB medicines and regimens and to inform future TB treatment policies.

5.5.3 Modification or discontinuation of treatment

The South African NTP implemented the 9-month all-oral MDR/RR-TB regimen as a standardized course of treatment, with little room for variation. Some changes to the prescribed regimen were considered acceptable in the South African context and may be appropriate in other settings (as described in **Section 5.2**).

Some patients who start treatment with the 9-month all-oral regimen are unable to continue or complete the course of treatment, and may have to restart or switch to a different regimen; for example, in the following situations:

- Reliable DST results indicate resistance to key medicines (i.e. bedaquiline, levofloxacin/moxifloxacin, linezolid/ethionamide or clofazimine) in the 9-month all-oral MDR/RR-TB regimen; this may reflect the actual situation at the start of treatment (that was unknown at that time) or the acquisition of additional resistance during treatment. This situation would be considered "treatment failure" and the patient should not continue the 9-month regimen. Other regimens may be considered based on relevant eligibility criteria.
- Poor response or lack of response to treatment (e.g. no sputum smear conversion from positive to negative by 6 months, persistent positive sputum cultures from month 4 (or month 6 if extended)

and beyond, or clinical deterioration despite evidence of adherence to treatment). This situation would be considered "treatment failure" and other treatment options will need to be considered. A longer individualized regimen would be the most appropriate option to offer such patients; however, BPaLM may also be considered if all eligibility criteria are met.

• An adverse drug reaction that necessitates permanent withdrawal of any one of the key medicines (i.e. bedaquiline, levofloxacin/moxifloxacin, linezolid/ethionamide or clofazimine), or two or more of any of the remaining medicines included in the 9-month all-oral regimen. This situation would be considered "treatment failure" and the patient should not continue the 9-month regimen. Other regimens may be considered based on relevant eligibility criteria.

• Treatment interruption for at least 2 months after receiving treatment with the 9-month all-oral regimen for more than 1 month. If such patients return to care, they might still be eligible for the 9-month all-oral regimen again, or the BPaLM regimen, but it is likely that they will first have to start a longer regimen while awaiting results of DST to rule out acquired resistance to the key drugs in the respective regimens.

If the treatment interruption is for less than 2 months, it is up to the treating clinician to decide whether the 9-month all-oral MDR/RR-TB regimen may be continued from the point of interruption. This decision is based on the timing of the interruption (early or late in treatment), the reasons for interruption, the patient's clinical condition and the results of safety investigations. It is preferable for the patient to make up any missed doses of linezolid and bedaquiline, but this may or may not be necessary for the other medicines in the 9-month all-oral regimen.

5.6 Using modified all-oral shorter MDR-TB regimens under operational research

At present, there is little evidence to support modified all-oral shorter MDR-TB regimens that are designed using the hierarchy of TB medicines (**Table 6.1**). NTPs that intend to pilot such types of shorter MDR-TB regimens are advised to do so under operational research conditions. To facilitate such research, the Special Programme for Research and Training in Tropical Diseases (TDR), in close collaboration with the WHO Global TB Programme (WHO/GTB) and with technical partners, has developed ShORRT (Short, all-Oral Regimens for Rifampicin-resistant Tuberculosis[8]). ShORRT is an operational research package that is designed to assess the effectiveness, safety, feasibility, acceptability, cost and impact (including on quality of life) of the use of all-oral shorter drug regimens for patients with DR-TB *(61)*.

All-oral shorter MDR-TB regimens are usually designed as a four-drug or five-drug standardized regimen. There is some advantage to using the all-oral shorter MDR-TB regimens that are currently being tested in randomized clinical trials, because these regimens have been endorsed by scientific committees for testing, and their use under operational research conditions will contribute to the evidence base on these regimens. The ShORRT research package describes some proposed modified regimens for testing under operational research conditions *(61)*. The all-oral shorter MDR-TB regimens that contain all Group A drugs in combination with clofazimine (sometimes including Group C medicines such as pyrazinamide or delamanid) are possible combinations for countries to implement under operational research conditions.

When choosing an all-oral shorter MDR-TB regimen, an important consideration is that the programme must be able to follow patients for 1 year post-treatment for recurrent TB, to ensure that there is documentation that the all-oral shorter MDR-TB regimen is not resulting in a high relapse rate.

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[8]   See https://tdr.who.int/activities/shorrt-research-package.

5.6.1 Operational research conditions

Modified all-oral shorter MDR-TB regimens (i.e. regimens that differ from the recommended 9-month shorter regimens) should only be implemented under "operational research conditions". The main conditions are:

- a study protocol, which must include a 12-month follow-up after the end of treatment;
- a clinical treatment guide that includes a patient consent process;
- an approval by the national ethics review board or ministry of health; and
- at a minimum, an "aDSM core package"[9] (18).

The ShORRT research package provides more guidance on the development of the protocol, data collection tools and other supporting documents that facilitate operational research for modified all-oral shorter MDR-TB regimens (61).

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[9]   See Web Annex 3.

6. The longer regimens

The design of longer regimens (18–20 months) is founded on grouping of medicines recommended for use in longer regimens based on the drug-resistance profile (**Table 6.1**).

In ideal conditions, only a small proportion of MDR/RR-TB patients should opt for longer regimens, because this indication is mainly for those who cannot benefit from either BPaLM/BpaL or the 9-month all-oral regimen. Reasons for not using the shorter regimens may be related to the age of the patients, additional resistance (including fluoroquinolone resistance and other Group A medicines; i.e. XDR-TB), intolerance to key medicines used in shorter regimens, severity of disease, pregnancy, certain types of extrapulmonary TB or other complications needing an individualized approach.

Under many of these circumstances, only less potent and more toxic drugs are left to be used for treatment and lengthy regimens are therefore needed to cure without relapse. Longer regimens, especially if clinical conditions are complex (e.g. advanced disease with higher burden of bacilli and severe disease affecting critical organs) are usually associated with higher likelihood of toxicity, owing to factors such as longer drug exposure, higher intolerance, adverse effects and greater potential for drug–drug interactions in critically ill patients.

All these conditions that may lead to less patient-friendly regimens with higher pill burden and toxicity can increase the likelihood of unfavourable treatment outcomes such as treatment failure, loss to follow-up and death. All DR-TB patients need a patient-centred approach with treatment adherence support and aDSM, but in longer regimens these activities become more crucial. Patients will need support to overcome the hardships associated with TB and its treatment, including daily adherence challenges, adverse drug reactions, indirect costs and stigma.

No.	Recommendation
3.1	In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. *(Conditional recommendation, very low certainty of evidence)*

6.1 Eligibility

A longer treatment regimen should be proposed mainly when the BpaLM/BpaL or 9-month all-oral regimen cannot be used. **Chapter 4** and **Chapter 5** discuss the eligibility criteria for these shorter regimens.

A longer regimen is expected to be used in the following situations:

- severe extrapulmonary TB;
- additional resistance to key medicines of the BPaLM/BPaL regimen (except moxifloxacin) or the 9-month all-oral regimen;

- lack of response to shorter treatment regimens (e.g. treatment failure due to no bacteriological conversion, no clinical response, emerging resistance or loss to follow-up);
- drug intolerance to the component medicines of the BPaLM/BPaL regimen (except moxifloxacin) or 9 months shorter all-oral treatment regimen; and
- pregnant and lactating women who could not benefit from the 9-month shorter all-oral regimen owing to certain clinical conditions or children aged below 14 years who could not be treated with BpaLM/BpaL or who, for any reason, cannot opt for a 9-month regimen.

There is limited or no evidence of BpaLM/BpaL use in some patient groups; thus, a longer regimen could also be considered as an option for patients with low BMI (<17 kg/m^2), altered hepatic enzymes (3 times greater than the upper limit of normal), baseline anaemia (haemoglobin <8 g/dL), thrombocytopenia (platelet count <150 000/mm^3) or pre-existing peripheral neuropathy of Grade 3–4 *(62–64)*.

Any patient eligible for a longer regimen should undergo a pretreatment assessment to optimize the drug selection, reduce the chances of adverse events and thus increase the probability of the favourable treatment outcomes. The pretreatment assessment includes:

- a detailed clinical history (including all comorbidities, medications and known intolerances), a physical examination, a blood test, chest X-ray or other imaging and bacteriological tests; and
- a list of current effective TB medicines available based on a clinical history of drugs taken before this treatment episode and guided by the DST results or sequencing of the most recent sample from the patient (or the index case).

In addition to the eligibility criteria and preclinical assessment, a clinician should also consider:

- development of a personalized treatment approach (patient-centred approach) and close follow-up, including food support if needed, to increase bioavailability of drugs, improve nutritional status and facilitate adherence;
- provision of advice on contraception for women of childbearing age;
- availability of ancillary medications (e.g. corticosteroids in the case of disseminated TB or TB meningitis or pericarditis, pretreatment blood transfusion in the case of severe anaemia and nutritional support) and other interventions (e.g. intravenous [IV] medication in the case of severe malnutrition and malabsorption, insertion of peripherally inserted central catheter, or surgery in the case of restricted options and meeting criteria for intervention); and
- provision of counselling, depending on the patient's comorbidities (e.g. HIV or diabetes) or pre-existing conditions needing to be treated to optimize TB treatment outcomes.

6.2 Composition and duration of the regimens

When designing longer regimens, several basic principles need to be respected, in line with the best available evidence on composition of the regimens, as per the recommendations listed below.

No.	Recommendation
3.2	**Kanamycin and capreomycin** are not to be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.3	**Levofloxacin or moxifloxacin** should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)*

No.	Recommendation
3.4	**Bedaquiline** should be included in longer multidrug-resistant TB (MDR-TB) regimens for patients aged 18 years or more. *(Strong recommendation, moderate certainty of evidence)* **Bedaquiline** may also be included in longer MDR-TB regimens for patients aged 6–17 years. *(Conditional recommendation, very low certainty of evidence)* In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing **bedaquiline** may be used. *(Conditional recommendation, very low certainty of evidence)*
3.5	**Linezolid** should be included in the treatment of MDR/RR-TB patients on longer regimens. *(Strong recommendation, moderate certainty of evidence)*
3.6	**Clofazimine and cycloserine or terizidone** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.7	**Ethambutol** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.8	**Delamanid** may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens. *(Conditional recommendation, moderate certainty of evidence)* In children with MDR/RR-TB aged below 3 years **delamanid** may be used as part of longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.9	**Pyrazinamide** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.10	**Imipenem–cilastatin or meropenem** may be included in the treatment of MDR/RR-TB patients on longer regimens. *(Conditional recommendation, very low certainty of evidence)*
3.11	**Amikacin** may be included in the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions. *(Conditional recommendation, very low certainty of evidence)*
3.12	**Ethionamide or prothionamide** may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. *(Conditional recommendation against use, very low certainty of evidence)*
3.13	***P*-aminosalicylic acid** may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. *(Conditional recommendation against use, very low certainty of evidence)*
3.14	**Clavulanic acid** should not be included in the treatment of MDR/RR-TB patients on longer regimens.[10] *(Strong recommendation against use, low certainty of evidence)*

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[10] 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.

6.2.1 Choice of components for the longer MDR-TB regimens

A stepwise approach guides the design of longer MDR-TB regimens (**Table 6.1**).

The selection of medicines follows a priority order based on the revised classification of regimen components, and a fully oral regimen is preferred. **At least four** drugs must be selected, starting from Group A and then from Group B. Group C drugs are usually included in a longer regimen if it cannot be composed with Group A and B agents alone. The choice of drugs from Group C is usually determined by the order in which the medicines are ranked, and by the individual circumstances of the patient and the setting. A recent review of the observational data found no additional safety concerns when bedaquiline was used for longer than 6 months; however, no clear evidence was available to indicate whether longer use added efficacy *(1)*. The clinicians may therefore consider continuing bedaquiline for longer than 6 months and adding some flexibility for regimen design and the number of effective drugs.

In the case of longer treatment regimens, an individual approach is needed. Therefore, apart from the drug classification, it is crucial to optimize drug selection according to the patient's clinical condition and the drug-resistance pattern. Considerations include:

- the clinical history of drugs taken in the past by the patient or the index case, or according to local resistance epidemiology in the country or region;
- the DST results – where available, is it of utmost importance to guide the drug selection using phenotypic or genotypic DST; in patients with extensive patterns of resistance, whenever possible, it is advised to perform whole genome sequencing; and
- selecting drugs according to their special features – in addition to susceptibility, key drug features and clinical particularities of the patient that may boost survival must be considered (e.g. likelihood of effectiveness, CNS penetration, drug–drug interaction profile, tolerance and patient preference, oral absorption and bioavailability).

Most anti-TB drugs are used once daily to achieve a high peak serum concentration that increases the bactericidal and sterilizing effect and to support adherence (to avoid missed or partial doses). The doses of anti-TB drugs by weight bands are outlined in the **Annex**. The essential information about TB medicines used in MDR/RR-TB treatment is described in detail in **Web Annex 1**.

Many patients may have comorbidities and adverse events that need to be addressed separately. Hospitalization, surgery and other adjuvant treatment may be needed at certain stages of treatment. Comprehensive monitoring and treatment adherence support are important to ensure a favourable treatment experience. Access to palliative and end-of-life care services may be needed, with a patient-centred approach to relieve the suffering from the disease and its treatment *(65)*. Respiratory infection control measures at the sites where the patient is being treated, contact tracing and counselling are important accompanying measures for clinical care and public health.

Table 6.2 summarizes some common situations that a clinician may face, and the decisions that could be taken to adjust the treatment regimen accordingly. The suggested regimens may vary based on the individual clinical circumstances and the availability of medicines. **Table 6.2** is not exhaustive. Although it is recommended to use at least four effective agents initially, not all the regimens composed using this algorithm have been tested directly in either research or field conditions. Moreover, when Group C agents are included, the number of medicines in the regimen may exceed four, to reflect the uncertainty about the efficacy of some of these medicines. In such situations, the advice of a specialist is important to ensure the safest and most effective possible regimen.

6.2.2 Medicines used in longer MDR-TB treatment regimens

The classification of medicines used in MDR/RR-TB treatment regimens was revised following the evidence-informed update of the WHO guidelines on DR-TB treatment in 2018. TB medicines to

be used for treatment of MDR/RR-TB are categorized into Groups A, B and C (**Table 6.1**) *(1)*. This classification is based on drug class and level of certainty in the evidence on effectiveness and safety (i.e. balance between benefits and risk of harm). The data analysed relate mainly to adult patients who received regimens in recent years. Groups A–C feature the medicines to be used to compose longer MDR-TB regimens. **WHO considers that, under programmatic conditions, only these medicines (Groups A–C) have a role in longer MDR-TB treatment regimens**. In addition to agents from Groups A–C, the potential role for clavulanic acid and high-dose isoniazid was discussed (see "Other medicines" in this section).

The most notable differences between the classification of longer regimen components used before 2018 and the current guidelines are an upgrade in the priority of bedaquiline, linezolid, clofazimine and cycloserine/terizidone; placement of delamanid in Group C; and lowering of priority for pyrazinamide, amikacin, streptomycin, ethionamide/prothionamide and *p*-aminosalicylic acid, relative to other treatment options. Several agents that were featured previously in these groups are no longer included because they are:

- no longer recommended (e.g. ofloxacin, capreomycin and kanamycin);
- rarely used in longer regimens (e.g. high-dose isoniazid); or
- an adjunct agent that is not intended to be used alone (e.g. clavulanic acid is used only in combination with the carbapenems).

The classification facilitates design of the treatment regimen for patients with DR-TB who are not eligible for the BPaLM/BPaL or 9-month treatment regimens. **Table 6.1** summarizes the general steps to take when including agents for the longer MDR-TB regimen according to the latest WHO guidance, with more details provided for some of the most common situations and patient subgroups that clinicians and NTPs may encounter.

Table 6.1. Grouping of medicines recommended for use in longer MDR-TB regimens[a]

Groups and steps	Medicine and abbreviation	
Group A: **Include all three medicines**	Levofloxacin *or* moxifloxacin	Lfx Mfx
	Bedaquiline[b,c]	Bdq
	Linezolid[d]	Lzd
Group B: **Add one or both medicines**	Clofazimine	Cfz
	Cycloserine *or* terizidone	Cs Trd
Group C: **Add to complete the regimen, and when medicines from Groups A and B cannot be used**	Ethambutol	E
	Delamanid[c,e]	Dlm
	Pyrazinamide[f]	Z
	Imipenem–cilastatin *or* meropenem[g]	Ipm–Cln Mpm

Groups and steps	Medicine and abbreviation	
	Amikacin *or* streptomycin[h]	Am S
	Ethionamide *or* prothionamide[i]	Eto Pto
	P-aminosalicylic acid[i]	PAS

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

[a] This table is intended to guide the design of individualized, longer MDR-TB regimens. 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 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 *(1)*.

[b] Bedaquiline is usually administered 400 mg orally once daily for the first 2 weeks, followed by 200 mg orally thrice weekly for 22 weeks (total duration of 24 weeks). As a result of multiple reviews following new data gradually becoming available, the use of bedaquiline is not restricted by age of the patient. Evidence on the safety and effectiveness of bedaquiline use beyond 6 months was insufficient for review in 2018. Therefore, the use of bedaquiline beyond 6 months was implemented following best practices in "off-label" use *(66)*. 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. 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.

[c] Evidence on the concurrent use of bedaquiline and delamanid was insufficient for review in 2018. In 2019, new evidence on both the safety and effectiveness of concurrent use of bedaquiline and delamanid was made available to the GDG. In relation to safety, the GDG concluded that the data suggested no additional safety concerns regarding concurrent use of bedaquiline and delamanid. More evidence was added to that regard between 2020 and 2022 *(67)*. Both medicines may be used concurrently in patients who have limited other treatment options available to them, and if 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 in 2019, but owing to the limited evidence and potential residual confounding in the data, the GDG could not proceed with a recommendation on effectiveness *(1)*.

[d] Use of linezolid for at least 6 months was shown to increase effectiveness, although toxicity may limit its 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.

[e] Evidence on the safety and effectiveness of delamanid beyond 6 months was insufficient for review. The use of delamanid beyond these limits should follow best practices in "off-label" use *(66)*. As a result of multiple reviews following new data gradually becoming available throughout the years the use of delamanid is not restricted by age of the patient.

[f] Pyrazinamide is only counted as an effective agent when DST results confirm susceptibility.

[g] Every dose of imipenem–cilastatin or meropenem should be preceded by the oral administration of oral clavulanic acid 30–60 minutes beforehand; oral clavulanic acid is only available in formulations combined with amoxicillin. Amoxicillin–clavulanic acid is not counted as an additional effective TB agent and should not be used without imipenem–cilastatin or meropenem.

[h] Amikacin and streptomycin are only to be considered if DST results confirm susceptibility and high-quality audiology monitoring for hearing loss can be ensured. Streptomycin is to be considered only if amikacin cannot be used (unavailable or documented resistance) and if DST results confirm susceptibility (streptomycin resistance is not detectable with second-line molecular LPAs and phenotypic DST is required). Kanamycin and capreomycin are no longer recommended for use in MDR-TB regimens.

[i] These agents only showed effectiveness in regimens without bedaquiline, linezolid, clofazimine or delamanid and are thus only proposed when other options to compose a regimen are not possible.

Group A

Group A includes fluoroquinolones (levofloxacin and moxifloxacin), bedaquiline and linezolid. These medicines were found to be highly effective in improving treatment outcomes and reducing deaths in the evidence reviewed in 2018 for the WHO guidelines *(1)*, and it is strongly recommended that they be included in all longer MDR-TB regimens and used for all MDR/RR-TB patients eligible for longer regimens unless there is a toxicity issue or drug resistance.

Levofloxacin and moxifloxacin

Levofloxacin and moxifloxacin are later-generation fluoroquinolones, and their use in the meta-analysis that informed the WHO guidelines (2018 update) resulted in a significantly lower risk of treatment failure or relapse and death *(1, 11, 68, 69)*. Levofloxacin and moxifloxacin appear to be equally effective in fluoroquinolone-sensitive patients receiving longer regimens, and either of these drugs can be considered for MDR/RR-TB treatment using these regimens. Ciprofloxacin and ofloxacin are less effective in MDR-TB treatment and are no longer recommended.

Reliable rapid molecular DST is available for levofloxacin and moxifloxacin (including Xpert MTB/XDR and second-line LPA). Not all point mutations present the same resistance profile. Despite some mutations having consistently high minimum inhibitory concentrations (MICs) (i.e. *gyr*A D94N or D94Y), most mutations present a range of phenotypic resistance that may cross critical concentration (CC) and clinical breakpoint (CB) levels. Therefore, once fluoroquinolone resistance has been detected by molecular methods and treatment has started, a phenotypic method may be used as a reference test for distinguishing between high-level (>CB) and low-level (>CC and <CB) resistance mutations, possibly allowing for the use of a high-level fluoroquinolone dose. Where these mutations are detected, the composition of the longer regimen should be re-evaluated based on phenotypic DST results at the CB *(70)*.

If DST for moxifloxacin confirms high-level resistance, or if the patient's history suggests that moxifloxacin has not been effective (e.g. if used in a failing regimen for more than 15–30 days), moxifloxacin should not be used. Work is ongoing to optimize the use of moxifloxacin related to sequencing, CC in phenotypic DST and clinical correlation *(70–72)*.

Bedaquiline

In the IPD meta-analysis used as evidence for the WHO guidelines, bedaquiline use resulted in significantly fewer episodes of treatment failure, relapse and death *(1)*. There is growing experience of its use in children, adolescents and older people, patients with extrapulmonary TB disease and PLHIV *(73, 74)*. Currently, there is no age restriction for the use of bedaquiline, including in longer regimens *(47)*.

Analyses of observational study data highlighted the improved survival of patients treated with regimens containing bedaquiline *(47)* and the favourable safety profile of bedaquiline when the drug is used alongside other TB medicines, including medicines with a QT prolongation effect (e.g. moxifloxacin, clofazimine and delamanid) *(75–80)*. The recent data review for the WHO consolidated guidelines *(1)* suggested no additional safety concerns for the use of bedaquiline beyond 6 months, used concurrently with delamanid or in pregnancy *(77)*. The available data suggested that the concurrent use of bedaquiline and delamanid does not increase the risk of clinically meaningful QT prolongation *(81)*.

Some inconclusive evidence is emerging; for example, some published data on the rapid advent of bedaquiline resistance in settings where it is used may suggest a possibility of bedaquiline being a low genetic barrier drug (i.e. causing resistance to emerge rapidly) as a result of frequent natural mutations. Also worth considering is the long half-life of the drug (5.5 months), which may lead to the drug acting as monotherapy in patients lost to follow-up. Fluoroquinolone resistance testing should be performed to prevent bedaquiline resistance acquisition, and the levels of resistance should be monitored when possible. Bedaquiline presents cross-resistance with clofazimine in cases of *Rv0678* gene mutation (which lead to upregulation of efflux pumps) and *pepQ* mutations. Resistance may occur spontaneously, even without prior exposure to bedaquiline or clofazimine (4.1% in some studies) *(82, 83)*. Mutations at the *atp*-E gene may confer high-level resistance to bedaquiline.

Linezolid

Linezolid has shown anti-TB activity in vitro and in animal studies, and its effectiveness in humans was demonstrated in the meta-analysis conducted for the WHO guidelines, as well as in recent trials involving XDR-TB patients *(1, 84–88)*.

Linezolid is associated with considerable toxicity, which necessitates close monitoring for signs of bone marrow suppression and neuropathies. The 2018 IPD meta-analysis informing the WHO guidelines included information from more than 300 patients who were treated with linezolid for at least 1 month, mostly on 600 mg daily. About 30% of patients 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. This analysis also suggested that the optimal duration of use would be about 20 months, corresponding to the usual total duration of a longer MDR-TB regimen; however, the analysis did not account for survivorship bias (i.e. 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) *(1, 89)*.

The evidence from the WHO consolidated guidelines *(1)* suggests that linezolid should be used for as long as it is tolerated. There may be improved outcomes if linezolid is used for the full duration of treatment. However, it probably has its greatest added effect (including protection of other second-line drugs against acquired drug resistance) during the first months of treatment when the bacillary load is highest *(90)*. If toxicity develops, dosing of linezolid should be reduced or replaced by another bactericidal drug *(17)*.

Linezolid is not affected or metabolized by the cytochrome p450; however, it is an inhibitor of monoamine oxidase (IMAO), leading to an increase in serotonin and tyramine levels. Serotonergic syndrome, which can be serious and life threatening, can result when linezolid is given concomitantly with other IMAO drugs that are often used in clinical practice in TB patients (e.g. antidepressants, opioid pain killers such as tramadol, common cold medications or antitussives such as dextromethorphan) *(91)*.

Group B

Group B medicines include clofazimine and cycloserine or terizidone, which were found to be effective in improving treatment outcomes but limited in reducing deaths in the evidence reviewed in 2018 for the WHO guidelines *(1)*. One or both drugs can be added to ensure that a longer regimen starts with at least four effective medicines.

Clofazimine

Clofazimine is an antileprosy medicine that has shown in vitro activity against *M. tuberculosis* and has been used as a second-line TB medicine for several years. The meta-analysis conducted for the WHO guidelines reinforced the evidence for the effectiveness and safety profile of clofazimine *(1)*. When used with drugs that prolong the QT interval (e.g. bedaquiline, fluoroquinolones and delamanid), clofazimine may cause additive QT prolongation. ECG monitoring should be implemented when bedaquiline is used or when several QT-prolonging drugs are also part of the regimen. Non-TB drugs that cause QT prolongation should be avoided if possible.

Common adverse events associated with clofazimine are brown-orange or purple-red discolouration of skin, conjunctiva, cornea and body fluids; dry skin, pruritus, rash, ichthyosis and xerosis; gastrointestinal intolerance; and photosensitivity. Patients should be well informed from the outset of the reversible skin colour changes that occur in most patients. The orange-brown skin changes are reversible within a few months (sometimes more) of the drug being stopped and are not considered dangerous. These skin changes can be quite concerning to patients and reassurance is required. Clofazimine can be used during pregnancy or breastfeeding owing to limited data and to pigmentation of the infant if the drug is used during breastfeeding. Clofazimine is partially metabolized by the liver; hence, caution or adjustment of the dose is required for patients with severe hepatic insufficiency.

Cycloserine

Cycloserine is a bacteriostatic drug that inhibits cell wall synthesis, and it has no known cross-resistance to other TB medicines. Terizidone (composed of two molecules of cycloserine) may be used instead of cycloserine, and cycloserine and terizidone are considered interchangeable. Because of difficulties in interpreting DST (there is no reliable genotypic or phenotypic DST for cycloserine or terizidone), cycloserine or terizidone should only be considered when other criteria of likelihood of effectiveness are met; for example, any reliable evidence on population levels of drug resistance, and prior use of cycloserine or terizidone based on a reliable clinical history (**Section 3.1**). Patients should be well informed of the potential adverse events of cycloserine. A major drug adverse event is CNS toxicity, including inability to concentrate, depression, behaviour change (e.g. violence and aggressiveness, and suicidal ideation), frank psychosis, seizures and lethargy.

Cycloserine may exacerbate pre-existing neurologic or psychiatric conditions. Situations of stigma, extreme poverty and social vulnerability are not infrequent among MDR/RR-TB patients, and these also affect mental health. Depression and anxiety are also highly prevalent and can lead to a worse prognosis and loss to follow-up, especially in programmes without patient-centred systems. In these situations, management of cycloserine toxicity is critical to obtain good clinical outcomes and to avoid serious adverse events.

Group C

Group C comprises both TB and repurposed medicines that are positioned at a lower priority than the Group A and B agents, either because they are less effective (ethambutol, delamanid, pyrazinamide, ethionamide/prothionamide and *p*-aminosalicylic acid) or because they are more toxic and cumbersome to administer parenterally (imipenem–cilastatin, meropenem, amikacin and streptomycin). These drugs are usually included in a longer regimen if it cannot be composed with Group A and B agents alone.

Ethambutol

Ethambutol is a TB medicine that is used in the treatment of DS-TB and may be added to longer MDR-TB regimens. At recommended dosages, the safety profile of ethambutol is good. Owing to difficulties in interpreting its DST, ethambutol should only be considered when other criteria of likelihood of effectiveness are met (e.g. evidence on a population level of low prevalence of drug resistance in circulating MDR/RR-TB strains and no prior use of ethambutol based on a reliable clinical history).

Delamanid

Based on current evidence on its effectiveness and safety, delamanid is recommended for use as a Group C agent *(1)*. Delamanid has a potent in vitro bactericidal activity and potential sterilizing activity; it is thought that nitroimidazooxazole derivatives generate reactive nitrogen species, including nitrogen oxide, which are responsible for cell poisoning in low metabolic states. There is no age restriction for use of delamanid and there are currently dispersible formulations that are preferred over crushing and dispersing adult tablets *(47, 92)*. Delamanid is strongly bound to plasma proteins, resulting in low CNS penetration; however, studies in humans and animals with CNS TB suggest that delamanid could potentially play a beneficial role when other options are not available *(93)*.

The recent data review for the WHO guidelines *(1)* suggested that there are no additional safety concerns for concurrent use of delamanid with bedaquiline. The combined QT effects, compared with bedaquiline or delamanid alone, were evaluated in an RCT of 75 patients (>3000 ECGs) *(78)*. Studies undertaken between 2020 and 2022 had shown no increased toxicity with the use of delamanid

beyond 6 months; they showed safety on the concomitant use of delamanid with bedaquiline, while increasing rates of survival of patients with restricted therapeutic options *(67, 81)*.

Animal data show no evidence of teratogenicity. Although the case series of pregnant women on delamanid are small, all children had excellent birth outcomes, suggesting that pregnant women in need should not be denied access to delamanid. It can be considered for the treatment of DR-TB in pregnant women with restricted therapeutic options *(50)*.

Pyrazinamide

Pyrazinamide has been routinely added to MDR-TB regimens except where there is a reasonable clinical contraindication for its use (e.g. hepatotoxicity), or other serious adverse event or drug resistance. However, reliable DST for pyrazinamide is not widely accessible; hence, this drug has often been used without DST or regardless of documented resistance. In the longer regimens, pyrazinamide is recommended for inclusion only when DST results confirm susceptibility (in such cases it is counted as one of the effective agents); in any other cases, if pyrazinamide is included in the regimen, it is not counted as one of the four effective drugs *(94, 95)*. There are synergies between pyrazinamide and other medicines such as bedaquiline, through complex mechanisms of action targeting dormant bacteria.

Imipenem–cilastatin and meropenem

Imipenem–cilastatin (not used in patients aged <15 years) and meropenem are the only carbapenems that have an established role in MDR-TB regimens. They are administered intravenously – a major drawback that limits their more widespread use outside hospitals, especially in resource-constrained settings *(96–100)*. Daily IV injections are not usually feasible unless there is a surgically fitted port (a port-a-cath) or a peripherally inserted central catheter connected to a major vein. Meropenem with clavulanate as part of regimens (usually also containing linezolid) for patients with MDR-TB and XDR-TB has been shown to improve culture conversion and survival *(101–103)*. Clavulanic acid (as co-amoxyclav) is not a TB medicine but is an adjunct agent that is given orally each time a carbapenem dose is administered, about 30 minutes before the IV infusion. When included in a regimen, clavulanic acid is not counted as one of the TB agents, and it should not be used without the carbapenem.

Amikacin and streptomycin

Amikacin and streptomycin are the only two aminoglycoside antibiotics that can be used when options for composition of the treatment regimen are limited. Based on the evidence reviewed in 2018, amikacin and streptomycin were associated with lower rates of treatment failure or relapse and death when used in people with *M. tuberculosis* strains susceptible to amikacin or streptomycin. However, these drugs share the disadvantages and serious toxicities (i.e. ototoxicity and nephrotoxicity) of other injectable agents that are no longer recommended (i.e. kanamycin and capreomycin). Given the high frequency of streptomycin resistance in patients with MDR/RR-TB in many settings, and its extensive historical use as part of older first-line TB regimens in many countries, streptomycin is unlikely to have much use in MDR-TB regimens.

Ethionamide and prothionamide

In WHO guidance, ethionamide and protionamide are considered interchangeable. The WHO consolidated guidelines make a conditional recommendation *against* their use in longer MDR-TB regimens, reserving them for situations where multiple, more effective agents (e.g. bedaquiline, linezolid and clofazimine) cannot be used. Apart from the low bactericidal profile, use of ethionamide and prothionamide is limited because of poor gastrointestinal tolerance, which could be potentially

linked to bad adherence. In pregnant women, these drugs are usually not recommended owing to poor tolerance, decrease in thyroid stimulating hormone (TSH) levels (which are fundamental for the development of the fetus) and concerns raised by effects in animal reproductive studies.

P-aminosalicylic acid

P-aminosalicylic acid (PAS) can be considered as the last resource for treatment of MDR/RR-TB. It is often poorly tolerated and has a modest bacteriostatic activity. The drug is recommended in the WHO consolidated guidelines only for use in the treatment of MDR/RR-TB patients on longer regimens if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. There is no indication of cross-resistance of *p*-aminosalicylic acid to other anti-TB drugs *(1)*. Use of *p*-aminosalicylic acid is limited owing to poor gastrointestinal tolerance.

Other medicines

Some medicines previously recommended as potential components of MDR-TB longer treatment regimens do not feature in Groups A–C.

High-dose isoniazid

High-dose isoniazid is not included in Groups A–C given the rarity of its use in longer regimens for adults. It is considered a relatively safe medicine, as shown recently in experience with its use at the 10 mg/kg dose, where only 0.5% of 1006 patients in a multicentric observational study of the shorter MDR-TB regimen reported Grade 3 or 4 neurotoxicity *(104)*. Other evidence suggests that high-dose isoniazid may also be useful in the longer MDR-TB regimens. First, in the systematic review and IPD meta-analysis commissioned by WHO in 2015 to describe treatment outcomes in children with MDR-TB (which included 975 children in 18 countries), the use of high-dose isoniazid was associated with treatment success among children with confirmed MDR-TB (adjusted odds ratio [aOR] 5.9, 95% confidence interval [CI]: 1.7–20.5, P=0.007) *(105, 106)*. Second, in a randomized, double-blinded, placebo-controlled clinical trial among adults with MDR-TB, participants who received high-dose isoniazid (16–18 mg/kg) (added to kanamycin, levofloxacin, prothionamide, cycloserine and *p*-aminosalicylic acid) were significantly more likely to experience culture conversion at 6 months of treatment than those receiving placebo or standard-dose isoniazid (5 mg/kg) (73.8% versus 48.8% or 45.0%, respectively), with median time to culture conversion significantly reduced in the high-dose isoniazid arm (3.4 versus 6.6 or 6.4 months, respectively) *(107)*. Third, a more recent early bactericidal activity study among patients with MDR-TB – in which the isoniazid resistance was mediated by isolated *inh*A mutations – demonstrated that doses of 10–15 mg/kg of isoniazid daily exhibited bactericidal activity similar to standard-dose isoniazid (5 mg/kg) given to patients with DS-TB *(108)*. Strains with isolated *kat*G or both *kat*G and *inh*A mutations are unlikely to respond even to high-dose isoniazid, given the typically high isoniazid MICs in those strains. In the absence of information on isoniazid mutation patterns for an individual patient, knowledge of the prevalence of both mutations among locally circulating RR-TB strains (e.g. from DRS in the relevant epidemiological setting) may also inform decisions as to which treatment regimens would be most appropriate.

6.2.3 Duration of the regimen

The total length of a long treatment regimen is 18 to 20 months.

Three evidence-based recommendations guide the duration of the longer MDR-TB regimens:

No.	Recommendation
3.15	In MDR/RR-TB patients on longer regimens, a **total treatment duration of 18–20 months** is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)*
3.16	In MDR/RR-TB patients on longer regimens, a **treatment duration of 15–17 months after culture conversion** is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)*
3.17	In MDR/RR-TB patients on longer regimens containing amikacin or streptomycin, **an intensive phase of 6–7 months** is suggested for most patients; the duration may be modified according to the patient's response to therapy. *(Conditional recommendation, very low certainty of evidence)*

The all-oral longer MDR-TB regimens have no intensive phase. The duration of use of different medicines will depend on their clinical indication, patient tolerability (e.g. linezolid used for as long as no serious adverse event emerges) and individual treatment response (e.g. culture negativity), until completion of the expected total duration of treatment or time after culture conversion.

Although the total length of treatment is expected to be about 18–20 months in most patients, it may be modified based on the patient's clinical situation and response to treatment.

The evidence assessed using the IPD[11] demonstrated that there was a marginally increased risk of treatment failure or relapse when the duration of MDR-TB treatment was 20–22 months (compared with 17.5–20.0 months), and 18–20 months was determined to be an optimal treatment duration to maximize treatment success (1). In practice, NTPs may choose a fixed duration (e.g. 18 months) for implementation purposes.

6.3 Key subgroups

6.3.1 PLHIV

Currently, there are no specific changes in using longer regimens in PLHIV. However, there can be cumulative risk factors for clinical complications, toxicities and drug–drug interactions (**Web Annex 1** and **Web Annex 2**); hence, these patients may need close follow-up and support.

6.3.2 Children

WHO recommendations on longer MDR/RR-TB regimens apply to children as well as adults. Currently, there is no age restriction on the use of bedaquiline, so children of all ages should receive it in longer regimens unless there is a specific contraindication. Most medicines in longer regimens have been part of MDR/RR-TB regimens for many years, in similar combinations, for both adults and children. Second-line TB medicines are also available in child-friendly formulations. The dosage for children is available in the **Annex**, including regular and dispersible medication. The duration of treatment using longer regimens in children depends on the site and severity of disease, and the extent of resistance. Children with nonsevere disease can usually be treated for much less than 18 months. Children with

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[11] Data used for analysis to support these recommendations were from patients who did not receive two or more Group A medicines. However, a small proportion of patients included in the analysis were on all-oral regimens, and in these patients the same optimal treatment duration was observed using identical parameters.

extensive disease may require longer treatment durations, depending on clinical progress or site of the disease.

6.3.3 Pregnant and lactating women

Dosing and safety data to support the optimal use of second-line TB medicines during pregnancy are generally sparse. There have been case reports and observational data reporting successful treatment and pregnancy outcomes among women who received treatment (including bedaquiline-containing regimens) for MDR/RR-TB during pregnancy and postpartum, but pregnant and lactating women are usually excluded from clinical drug trials and early access programmes. Even less is known about the effects of MDR/RR-TB treatment on the infant in-utero and after birth; however, in general, the benefits (to both parent and child) of providing effective MDR/RR-TB treatment to the parent far outweigh the potential risks posed to the fetus in-utero or the breastfed infant.

Ethionamide is usually contraindicated in pregnancy because animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans. The adverse effects of linezolid may be exacerbated by the physiological effects of pregnancy, which lead to a relatively low haemoglobin (due to the dilutional effect of increased blood volume) and a higher risk of peripheral neuropathies at treatment baseline compared with nonpregnant patients. Nevertheless, linezolid may be considered for pregnant and lactating patients. More compelling evidence on the dosing and safety of specific anti-TB drugs among pregnant and lactating women is needed to guide decision-making on the most appropriate regimen for treatment of MDR/RR-TB during pregnancy and postpartum. Amikacin and streptomycin are considered teratogenic and should be avoided during pregnancy. They should be considered only if there is no other option and the lives of the pregnant person and fetus are at risk.

Pregnant and breastfeeding women require considerable adherence support and monitoring of proper administration of MDR/RR-TB treatment, along with other chronic medications, to ensure successful treatment outcomes and minimal risk of TB transmission from mother to infant postpartum. Care providers must also pay particular attention to seamless continuity of care between antenatal and TB services; such services are rarely integrated in TB-endemic settings *(50)*.

Considerations on the use of TB medication during pregnancy are given in **Web Annex 1**.

6.3.4 Patients with diabetes mellitus

Currently, there are no specific changes in patients with diabetes; however, such patients may present cumulative risk factors for clinical complications, toxicities and drug–drug interactions. Good glycaemic control is considered essential while on TB treatment because such control optimizes the chance of cure and limits complications. The concomitant use of metformin at high doses and linezolid may increase the risk of lactic acidosis. Also, the long-term use of linezolid, high doses of isoniazid and cycloserine in patients with diabetes can lead to an increased risk of peripheral neuritis. Baseline optic nerve or retinopathy or maculopathy may worsen after linezolid use; hence, eye evaluation is recommended before and during treatment. Regarding potential baseline renal damage, amikacin and streptomycin should be used with caution. Patients with DR-TB and diabetes may need close follow-up and support, with quick identification of drug–drug interactions and adverse events.

6.3.5 Patients with extrapulmonary TB

The WHO recommendations on longer MDR-TB regimens also apply to patients with extrapulmonary disease. Adjustments may be required, depending on the specific location of disease. Treatment of MDR/RR-TB meningitis is best guided by DST of the infecting strain and by the ability of TB medicines to cross the blood–brain barrier. Group A fluoroquinolones (e.g. levofloxacin, moxifloxacin and linezolid) have good penetration across the blood–brain barrier (i.e. the CNS), as do ethionamide

(or prothionamide), cycloserine (or terizidone) and imipenem–cilastatin *(109–111)*. Seizures may be more common in children with meningitis treated with imipenem, and meropenem is preferred for cases of TB meningitis and in children *(112–114)*. High-dose isoniazid and pyrazinamide can also reach therapeutic levels in the cerebrospinal fluid (CSF) and may be useful if the strains are susceptible. Neither *p*-aminosalicylic acid nor ethambutol penetrate the CNS well and they should not be considered effective agents for MDR-TB meningitis. Amikacin and streptomycin only penetrate the CNS in the presence of meningeal inflammation. Data are sparse on the CNS penetration of clofazimine, bedaquiline or delamanid.

6.4 Implementation considerations and treatment in special situations

6.4.1 Extensive DR-TB disease

Extensive (or advanced) TB disease in adults is defined as the presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged below 15 years, extensive (or 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, along with bacteriological tests. Patients with extensive disease tend to have a higher bacterial burden, especially in cases of parenchymal lung destruction (e.g. lobe collapse, fibrotic tracts or atelectasis), where drug concentration might be low due to decreased tissue perfusion. These patients tend to benefit from longer regimens to decrease the chances of relapse on shorter regimens. Patterns of lung destruction tend to present a higher risk of negative outcomes such as treatment failure and clinical complication (e.g. bacterial, fungal or mycobacterial superinfections, bronchiectasis and respiratory failure). Disability after cure is frequent. Close follow-up is needed during and after TB treatment.

6.4.2 Severe extrapulmonary TB

A longer treatment regimen may be more suitable in cases of severe extrapulmonary TB, owing to the high risk of negative outcomes including relapse. All such cases have in common the dispersion of *M. tuberculosis* through blood. Severe extrapulmonary TB is associated with lesions in multiple organs, potentially leading to multiorgan failure. This is more frequently suffered by patients with frank or relative immunosuppression (PLHIV, children, pregnant people, older people, people with cancer, those with solid organ transplants, those on immunosuppressive medication and people with uncontrolled diabetes mellitus). The potential reasons for immunosuppression should be addressed and all potential complications managed. Corticosteroids should be considered case by case, but are recommended in TB meningitis and pericardial TB to reduce complications and disability.

6.4.3 DR-TB in different patient groups

DR-TB meningitis and brain tuberculomas

When TB affects the CNS it leads to several additional problems. For example, the concentrations of some drugs in the CNS can be reduced owing to low penetration through the blood–brain barrier. Therefore, drugs need to be selected on the basis of both susceptibility and specific CNS penetration. Drugs with high CNS penetration should be used.

Information on each drug's CNS penetration is given in **Web Annex 1**. Where options are limited, drug dosages can be increased to better reach the CNS, but with close monitoring of toxicity. Also, IV medication can be considered as the route of administration to optimize the drug concentration in

blood while avoiding potential malabsorption problems. Patients with TB in the CNS may present with reduced consciousness and may require hospitalization, nutritional support (e.g. nasogastric tube and use of dispersible or IV medication) and, in advanced cases, intensive care. In all TB meningitis cases, the use of corticosteroids should be considered, to prevent disability and improve survival. Usually, when there is TB in the CNS, this is by haematogenous dissemination; therefore, it is important to search for the presence of TB in other organs such as lungs (e.g. bronchogenic or miliary TB), liver, spleen and bone marrow.

DR-TB in older patients

Patients with MDR/RR-TB who are aged 65 years and older are generally frailer and more vulnerable to the adverse effects of TB medications owing to the physiological changes of ageing (e.g. increase in QT interval, and baseline renal, eye or hearing damage). Also, they are more likely to present with other comorbidities (e.g. diabetes mellitus or hypertension) and therefore to be on other medications (i.e. to have a higher likelihood of polypharmacy), meaning there is a greater potential for additive drug toxicities and interactions. In addition, TB can be a consequence of a decline in the immune system due to age (immunosenescence), meaning that older patients may present with complicated forms of extrapulmonary TB.

DR-TB patients with renal failure

Patients with renal failure may be older, have diabetes or present with other comorbidities and use of multiple medications; thus, an in-depth evaluation is needed for each case. Patients with renal failure may present a baseline anaemia (possibly a clinical complication) that may be made worse by the use of linezolid or another myelotoxic drug. For many anti-TB drugs, dosage and administration may need to be adjusted according to levels of renal function. **Web Annex 1** has detailed information on the use of each specific drug in renal failure.

DR-TB in patients with anaemia

Patients with TB often have anaemia, and treatment with an effective drug regimen may lead to improvement or resolution of the anaemia once the disease is properly treated. In the case of disseminated TB, *M. tuberculosis* itself may be suppressing bone marrow function. Malnutrition is also associated with anaemia, which often presents as low haemoglobin, iron deficiency and low iron stores. Iron and multivitamins are recommended, but may interact with the absorption of important drugs such as fluoroquinolones (requiring intake separated by >2 hours). In the case of severe anaemia, blood transfusion can be considered. Some of the drugs that are often used in patients with TB (e.g. linezolid, azidothymidine and co-trimoxazole) can also lead to bone marrow suppression and should be used with caution.

DR-TB in malnourished patients

Malnutrition is frequently found in children and adults with TB. Malnutrition can be a cause or a consequence of TB disease. A low BMI (<18 kg/m^2, and especially <14 kg/m^2) is considered a risk factor for negative outcomes. Immune system function is decreased in malnourished patients; thus, more complicated extrapulmonary TB affecting critical organs may develop. In a patient with malnutrition, many other complications and superinfections can coexist, making clinical management much more complex; such patients also then require more medication, with potential drug–drug interactions. Malnourished patients may have poor tolerance for the daily intake of medication (owing to gastrointestinal issues), with frequent nausea, vomiting and diarrhoea. In addition, malnourished patients tend to present with malabsorption; thus, even if the intake of the medication is correct, the concentrations of anti-TB medication in blood can be suboptimal. Malnourished patients require close monitoring and a nutritional approach while on TB treatment; they may even benefit from IV administration of TB medication for short periods until there is improvement (either clinical or

nutritional). Close monitoring of side-effects and an in-depth clinical evaluation is needed, to identify additive superinfections or comorbidities. Nutritional supplements could help malnourished patients to recover by strengthening their immune system and improving weight gain.

DR-TB in patients with hepatitis B or C

There are limited data on the use of the longer treatment regimen among people with viral hepatitis or undergoing treatment for hepatitis C. It may be prudent to monitor closely for drug–drug interactions and hepatotoxicity among this patient group.

DR-TB in patients with depression

Mental suffering and depression is common in DR-TB patients, because of, for example, symptomatic and life-threatening disease, side-effects, stigma and social exclusion, inability to work and family catastrophic costs. Some TB medications such as cycloserine (and to a lesser extent isoniazid and ethionamide) can trigger depression and suicidal ideation. These circumstances need to be seriously considered, especially in longer regimens, because depression and the social and emotional circumstances around it are often linked to difficulties in treatment adherence. Linezolid could potentially interact with all antidepressant drug families, increasing the risk of serotonergic syndrome (**Web Annex 1** has more detailed information on linezolid drug–drug interactions). A balance between risk from TB and depression needs to be considered.

DR-TB in patients who present with alcohol or other substances abuse

Patients with DR-TB presenting with alcohol or other substances abuse is a situation that is often associated with the depression and social vulnerability that occurs particularly with TB in big cities. In addition to the negative emotional impact of DR-TB, anti-TB medication can have a negative effect on the patient. Cycloserine is associated with mood changes and potentially with craving and overconsumption of food, and methadone and psychiatric medication may interact with linezolid. A comprehensive patient-centred approach and harm reduction models that include psychosocial support are especially needed in these patients and had been shown to improve outcomes.

6.5 Treatment monitoring

Individuals prescribed the longer treatment regimen should be monitored to assess regimen effectiveness and safety, taking into account resistance patterns and challenging clinical conditions, while using less active and more toxic medicines. The WHO framework for aDSM needs to be applied to patients on any 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.

No.	Recommendation
5.1	In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, the performance of sputum culture in addition to sputum smear microscopy is recommended to monitor treatment response. *(Strong recommendation, moderate certainty in the estimates of test accuracy)* It is desirable for sputum culture to be repeated at monthly intervals.

6.5.1 Monitoring treatment response and outcome assignment

Response to treatment is monitored on the basis of monthly sputum smear microscopy, as well as culture, ideally at the same frequency. Monthly culture increased the detection of patients with a true

positive bacteriological result when compared with sputum smear microscopy alone; also, it reduced the proportion of patients with a false negative result.

Concomitant use of sputum smear microscopy and culture test results helps to identify patients whose bacteriology remains positive or reverts to positive following initial conversion to negative. This combined testing will help clinicians to identify patients whose treatment is likely to fail, and thus to plan alternative options and institute infection control measures in a timely manner. Additional benefits would be expected from reduced transmission and development of resistance, and from appropriate changes to treatment regimens. Regular microscopy and culture of sputum or other specimens remain important to ensure that treatment failure is detected early. The frequency of these examinations is similar to the schedule used in patients on the 9-month all-oral MDR-TB regimen and the BPaLM/BPaL regimen.

The treatment outcome definitions and reporting framework for patients on longer regimens are the same as those for patients on other MDR-TB regimens *(38)*. The updated definition of treatment failure includes situations where a patient's treatment regimen has been terminated or permanently changed to a new treatment regimen, owing to:

- no clinical or bacteriological response to treatment;
- adverse drug reaction; and
- evidence of additional drug resistance to medicines in the regimen.

Bacteriological failure is considered when patients treated with a longer regimen remain positive without conversion, or revert to positive following initial conversion to negative.

Failure due to adverse drug reactions or drug resistance is considered when additional resistance emerges while the patient is on a longer regimen, or the regimen needs to be stopped because of a severe adverse event.

In children, smear and culture monitoring of the response to treatment may be challenging, for the same reasons that make it difficult to obtain a bacteriological confirmation of the diagnosis. In children with a bacteriologically confirmed diagnosis, all reasonable efforts should be taken to demonstrate bacteriological conversion. In children in whom cultures have become negative or who never had a confirmed diagnosis, repeated respiratory sampling may not be useful if the child is otherwise responding well clinically. Resolution of clinical symptoms and weight gain can be used as indicators of improvement. All children should have regular clinical follow-up, including weight and height monitoring. Drug dosages should be adjusted with weight gain, as needed *(47)*.

6.5.2 Monitoring safety

The safety profile of some medicines used concomitantly in a long treatment regimen may present its own concerns. aDSM should be performed, as well as proper management of adverse events and prevention of complications from drug–drug interactions. The NTP should actively monitor drug safety to ensure proper patient care, to report any adverse events to the responsible drug safety authority in the country, and to inform national and global policy.

The medicines included in the selected regimen determine which monitoring tests are needed. Therefore, the monitoring schedule should consider:

- clinical assessments to identify optic and peripheral neuropathy and psychiatric disturbances;
- clinical and biochemical assessments (especially when linezolid is used for a longer period) to identify pancytopenia, lactic acidosis and peripheral neuritis including frequent eye or visual assessment and any potential drug–drug interaction (e.g. serotoninergic syndrome) and
- ECG and monitoring of electrolytes, particularly when the regimen contains multiple QT interval prolonging agents (e.g. bedaquiline, delamanid, moxifloxacin and clofazimine) – in the case of electrolyte disturbances or ECG abnormalities, more frequent monitoring should be performed.

More frequent monitoring may be advisable in specific situations; for example, in older people, PLHIV, those affected by hepatitis (caused by HBV or HCV) or diabetes, or people with moderate to severe hepatic or renal impairment.

Any adverse events during treatment should be managed immediately to relieve suffering, minimize the risk of treatment interruptions, and prevent morbidity and mortality. Details on monitoring and management of adverse events are provided in **Web Annex 2** and **Web Annex 3**.

Table 6.2. Summary algorithm for longer MDR-TB regimen composition in commonplace situations of resistance pattern or contraindication[a]

Medicines to which there is resistance or contraindication of use	Consider adding medicines likely or confirmed to be effective			Examples of regimens
	Group A	**Group B**	**Group C[b]**	
1 Two Group A medicines	Remaining medicine	Both medicines	At least 1 medicine	18 Bdq$_{(6 m\ or\ longer)}$-Cfz-Cs-Dlm$_{(6 m\ or\ longer)}$-(Z or E) 18 Lzd-Cfz-Cs-Dlm$_{(6 m\ or\ longer)}$-(Z or E) 18 Lfx-Cfz-Cs-Dlm$_{(6 m\ or\ longer)}$-(Z or E) If there is a suspected resistance to E or Z, replace with Group C drugs
2 One Group B medicine	All 3 medicines	Remaining medicine	May not be needed	18 Bdq$_{(6 m\ or\ longer)}$-(Lfx or Mfx)-Lzd-(Cfz or Cs)
3 Both Group B medicines	All 3 medicines	None	1 or 2 medicines	18 Bdq$_{(6 m\ or\ longer)}$-(Lfx or Mfx)-Lzd – Dlm$_{(6 m\ or\ longer)}$-(Z or E) If there is a suspected resistance to E or Z, replace with Group C drugs
4 One Group A and both Group B medicines	Remaining 2 medicines	None	At least 3 medicines	18 Bdq$_{(6 m\ or\ longer)}$-(Lfx or Mfx)-Dlm$_{(6 m\ or\ longer)}$-Z-E _____ 18 (Lfx or Mfx)-Lzd-Dlm$_{(6 m\ or\ longer)}$-Z-E _____ 18 Bdq$_{(6 m\ or\ longer)}$-Lzd-Dlm$_{(6 m\ or\ longer)}$-Z-E If there is a suspected resistance to E or Z, replace with Group C drugs
5 All Group A medicines	None[c]	Both	3 or more medicines	18–20 Cfz-Cs-Dlm-Z-E or other combinations of Group C drugs, depending on known or suspected resistance

Bdq: bedaquiline; CB: clinical breakpoint; Cfz: clofazimine; Cs: cycloserine; Dlm: delamanid; E: ethambutol; Lfx: levofloxacin; Lzd: linezolid; m: months; MDR-TB: multidrug-resistant TB; MDR/RR-TB: multidrug- or rifampicin-resistant TB; Mfx: moxifloxacin; MIC: minimum inhibitory concentration; TB: tuberculosis; WHO: World Health Organization; Z: pyrazinamide.

[a] The situations shown are not exhaustive. Other factors may influence choice, such as patient risk for poor outcome or drug–drug interactions, clinician and patient preference and availability of a medicine. More medicines may be added than the recommended minimum if there is limited confidence in the effectiveness of regimen components, or if the patient was exposed in a setting where second-line TB drug resistance is frequent and longer MDR-TB regimens perform poorly despite good programmatic management of MDR/RR-TB. For MDR-TB with confirmed fluoroquinolone resistance, no fluoroquinolone is used and, if Group C agents are needed, the recommended WHO grouping will be followed based on benefit versus risk and individual circumstances.

[b] The choice and number of Group C medicines to include depends on the confidence in the effectiveness of medicines in this group and the other components of the regimen, thus:

- if 4 Group A and B agents are included and there is confidence in all of them, then Group C agents are not needed;

- if 3 Group A and B agents are included and there is confidence in all of them, then at least one Group C agent is added; and

- if 2 Group A and B agents are included and there is confidence in all of them, then at least three Group C agents are added.

[c] Moxifloxacin, a later-generation fluoroquinolone, may still be effective at a high dose when the fluoroquinolone MIC is below the CB. If the MIC is elevated, then fluoroquinolones are not used, and additional Group C agents will be needed.

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7. Regimen for rifampicin-susceptible and isoniazid-resistant TB

This section refers to an Hr-TB treatment regimen that has a duration of 6 months and uses oral agents.

WHO released its first evidence-based guidance for the treatment of Hr-TB using the GRADE approach in 2018 *(1)*. The guidance is based on these two recommendations:

> **Recommendation 4.1. In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months.**
> *(Conditional recommendation, very low certainty in the estimates of effect)*

> **Recommendation 4.2. In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen.**
> *(Conditional recommendation, very low certainty in the estimates of effect)*

The recommendations made were conditional *(4)* and had very low certainty of evidence.

The basic regimen can be summarized as:

Hr-TB regimen: 6(H)RZE-Lfx

All medicines in this regimen are to be used daily for 6 months. When fixed-dose combination (FDC) formulations are used, isoniazid is included but it is not obligatory for the regimen. If levofloxacin cannot be used because there is fluoroquinolone resistance or intolerance or other contraindications to the use of fluoroquinolone, then 6(H)RZE may be prescribed daily for 6 months.

7.1 Eligibility

The Hr-TB regimen is recommended once isoniazid resistance has been confirmed and rifampicin resistance excluded. Rifampicin resistance needs to be excluded using rapid molecular tests (e.g. Xpert MTB/RIF) before levofloxacin is used, to avoid the inadvertent treatment of MDR/RR-TB with an inadequate regimen. Ideally, rapid DST for fluoroquinolones and pyrazinamide is also performed.

It is not advisable to give a regimen for Hr-TB unless isoniazid resistance is confirmed or highly suspected (e.g. confirmed TB patient who is the close contact of a documented Hr-TB case). This will avert the unnecessary use of levofloxacin and prolonged pyrazinamide exposure in TB patients who may be cured with 2HRZE/4HR. Once the Hr-TB regimen has been started, if the results of initial DST reveal isoniazid susceptibility, the regimen may be modified so that the patient effectively completes a course of first-line TB treatment.

The recommendations apply to both adults and children, including PLHIV. Thus, HIV testing and treatment of PLHIV with ART is important, and the aim is to start ART within 8 weeks of TB treatment initiation (regardless of CD4 count), or within the first 2 weeks in patients with profound immunosuppression (e.g. CD4 counts <50 cells/mm^3) *(115)*. The regimen is also likely to be effective in patients with extrapulmonary Hr-TB; however, consultation with appropriate specialists is advised.

Hr-TB treatment is expected to be started if either of the following circumstances apply:

- Hr-TB is confirmed and rifampicin resistance is ruled out before TB treatment is started – in such cases, the 6(H)RZE-Lfx regimen is started immediately. If the diagnosis is strongly presumed (e.g. close contact of a confirmed Hr-TB source case) but results of DST are still pending, the regimen may be introduced. Should DST results taken at the start eventually show susceptibility to isoniazid, then levofloxacin is stopped and the patient continues treatment to complete a 2HRZE/4HR regimen.
- Hr-TB is discovered after the start of treatment with the 2HRZE/4HR regimen (this includes patients who had undiagnosed isoniazid resistance at the start or who developed isoniazid resistance while on first-line treatment) – in such cases, rapid molecular testing for rifampicin resistance must be undertaken (or repeated). Once rifampicin resistance has been excluded, a full 6-month course of (H)RZE-Lfx 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 6 months. A report of resistance during treatment presents the clinician with a challenge, because the results may no longer reflect the drug susceptibility of the current bacterial population, given that an inadequate regimen – at times a functional monotherapy – may have favoured the acquisition of additional resistance in the interval. The unexpected discovery of resistance to one agent should prompt the clinician to repeat DST for other agents in the regimen. The example in **Box 7.1** illustrates a typical situation that could arise.

7.2 Composition and duration of the regimen

The duration of Hr-TB treatment is driven by the need to complete 6 months of a fluoroquinolone-containing regimen. This implies that, when Hr-TB is diagnosed *after* the start of the regimen for treatment of DS-TB, the companion medicines (HRZE) would end up being given for more than 6 months.

In patients with cavitary disease and with persistent positivity on sputum smear and culture, prolongation of (H)RZE-Lfx beyond 6 months could be considered on a case-by-case basis. Prolongation of treatment increases the risk of toxicity, particularly from pyrazinamide and ethambutol, which are usually only given for 2 months in the first-line TB regimen. The evidence reviewed for the WHO guidance on Hr-TB precluded a recommendation to limit the pyrazinamide duration to less than 4 months when a fluoroquinolone is given.

Levofloxacin is the preferred fluoroquinolone for Hr-TB regimens. The exposure to moxifloxacin decreases markedly when it is combined with rifampicin *(116)*. This effect has not been reported in the case of levofloxacin; also, levofloxacin appears to cause less QT interval prolongation than moxifloxacin *(49, 117, 118)*.

Levofloxacin is included in Hr-TB regimens except in the following instances: when rifampicin resistance cannot be tested for, when there is documented resistance or known intolerance to fluoroquinolones, and when there is pre-existing prolongation of the QT interval and pregnancy. If a fluoroquinolone cannot be used, a patient with Hr-TB can still be treated with 6(H)RZE; streptomycin is not required in such cases.

For patient convenience and ease of administration, the HRZE FDC may be used to treat Hr-TB (given that no RZE FDC is currently available). The dosage of other TB medicines in the Hr-TB regimen is the same as in the standardized DS-TB 2HRZE/4HR regimen. The inclusion of isoniazid in the regimen has not been shown to lead to substantial benefit or harm to patients; however, isoniazid may increase the hepatotoxicity of pyrazinamide *(119, 120)*. High-dose isoniazid (10–15 mg/kg per day) may still be effective when used in combination regimens in the presence of isolated *inh*A mutations linked to low MIC, even in "fast acetylators" (i.e. individuals who metabolize isoniazid rapidly) *(121)*. In the presence of both *inh*A and *kat*G mutations, addition of isoniazid (even at a high dose) is unlikely to add value to the regimen.

Box 7.1. Evaluation of a typical scenario – a delayed DST result in a patient on a first-line regimen

Before starting the 2HRZE/4HR regimen, a patient with rifampicin-susceptible TB confirmed by Xpert MTB/RIF has a sputum sample sent to a regional laboratory for phenotypic DST. The results are returned to the treating physician 3 months later; they show resistance to isoniazid. The patient has meanwhile adhered to their treatment regimen, gained weight and been symptom free for 2 months.

What does the clinician need to think about and do?

➔ Given that the DST results are 3 months old, the initial resistance pattern may no longer be indicative of the current situation, because the bacteria may have acquired additional resistance.

➔ Since the beginning of the third month, the patient should have been in the continuation phase with isoniazid and rifampicin (usually in FDC); however, the patient is effectively on rifampicin monotherapy. Resistance to rifampicin may have developed and needs to be checked, even if the clinical progress suggests that the regimen is working. Xpert MTB/RIF needs to be repeated.

➔ If rifampicin resistance is detected, the patient should be started on MDR-TB treatment (as detailed in **Chapter 5**, **Chapter 6** and **Chapter 7**).

➔ If rifampicin resistance is not detected, the patient should be switched to the (H)RZE-Lfx regimen for 6 months. Ideally, DST for fluoroquinolones should be performed.

Patients with Hr-TB may have a higher risk of acquiring additional resistance and MDR-TB, which may manifest during the same treatment episode or in a subsequent relapse. The effect of additional resistance to ethambutol and pyrazinamide on the treatment of Hr-TB is unclear.

7.3 Considerations for implementation

The regimens recommended for treatment of Hr-TB is not divided into an intensive and a continuation phase – this simplifies the delivery and monitoring of treatment. Treatment is given daily, and intermittent treatment should be avoided. Relevant measures to support adherence, social support and the use of digital technologies should be considered to ensure favourable treatment outcomes *(19)*.

The cost of medicines to compose a full 6(H)RZE regimen with levofloxacin is slightly higher than the cost of a 2HRZE/4HR regimen used for DS-TB *(122)*. Nonetheless, the 6(H)RZE regimen is an affordable and feasible intervention, even in low-income settings. Use of FDCs simplifies treatment and lowers

costs, and the use of dispersible formulations of HRZ, ethambutol and levofloxacin is preferred in children. As with the treatment of other forms of TB, the expenses associated with the proper delivery of care (e.g. DST, adherence support and clinical monitoring) far exceed the cost of medicines.

A new diagnostic platform has been approved for the detection of Hr-TB – the new Xpert MTB/XDR cartridge, which can detect isoniazid resistance in less than 90 minutes, matching the rapidity and convenience of Xpert MTB/RIF for rifampicin resistance. First-line LPA can also detect isoniazid resistance, and the infrastructure required is typically available in a provincial or central level facility. Typical processing time for an LPA specimen is about 2–3 days, owing to batching. DST based on liquid culture (or MGIT) could also detect Hr-TB at the level of a reference laboratory, but this means a processing delay of at least 10 days. Testing on solid media is also an option, but it takes several months to obtain results; hence, this approach is of limited use for baseline testing and monitoring of treatment response.

Current epidemiological data indicate that more than three quarters of the global burden of Hr-TB occurs among previously untreated ("new") TB cases. Previous TB treatment is thus not a strong indicator of risk of Hr-TB – the correlation with previous TB treatment is weaker than it is with MDR-TB. Reserving isoniazid DST to such patients is therefore unlikely to yield many Hr-TB cases. There are various concerns about empirical Hr-TB treatment of previously treated TB cases, without prior DST. First, such treatment will lead to unnecessary overtreatment with fluoroquinolones and prolongation of pyrazinamide use in many patients. Most recurrent cases will not have Hr-TB and can be cured with a 2HRZE/4HR regimen. Second, unless rifampicin resistance is excluded at the baseline, patients with MDR/RR-TB would be exposed to an inadequate regimen, with the risk of acquiring additional resistance, including fluoroquinolones. Third, this policy would deflect the focus of the programme from testing new TB patients, who usually harbour the main burden of Hr-TB. Finally, this approach would risk creating once again a "re-treatment regimen", similar to the situation that prevailed in many settings until recently with the indiscriminate use of the streptomycin-containing 8-month "Category 2" regimen in all previously treated TB patients.

In a situation where access to DST is good, a logical diagnostic algorithm would start with Xpert MTB/RIF as the initial test for all patients evaluated for TB. Cases in whom TB is confirmed and rifampicin resistance is not detected would be further tested with Xpert MTB/XDR or LPA. Liquid culture may replace LPA, but the additional delay in obtaining results is a disadvantage.

7.4 Treatment monitoring

The clinical monitoring of patients on Hr-TB treatment follows similar principles to those that apply to other first-line TB regimens. Bacteriological monitoring of sputum generally follows the same schedule as DS-TB, with direct microscopy at months 2, 5 and 6. It is desirable, however, to perform a culture together with smear microscopy (or at least in the last month of treatment) to check for any emergent resistance, especially to rifampicin. Non-response to treatment should be investigated with DST.

Liver and kidney function and other blood tests may be necessary, based on clinical manifestations and medications in use. ECG for patients on 6(H)RZE-Lfx is not usually required unless there are other risks for QT interval prolongation. The first-line TB agents may cause adverse drug reactions, which are mostly mild, not serious and self-limiting or manageable with basic measures. TB practitioners are likely to be more familiar with the use of these medicines than with levofloxacin, which has a fairly good safety profile in both adults and children when used at the dose recommended in the **Annex**, even when taken for longer than 6 months. Dosage adjustment, in consultation with a specialist, is recommended if creatinine clearance is below 30 mL/min *(17)*. Adverse drug reactions should be reported to the spontaneous pharmacovigilance systems required by national regulations, as for other drug-related harms. In patients on regimens for Hr-TB, aDSM is not mandatory.

As with all other notifiable TB cases, patients with Hr-TB should be registered in the TB register, regardless of whether treatment has started, or whether a regimen containing second-line TB medicines is being given *(100)*. The case may be retained in the TB register for the purposes of monitoring the treatment response and the interim or final outcomes. Cases without Hr-TB may be enumerated with the main DS-TB cases for the purposes of treatment outcome reporting. Hr-TB cases given fluoroquinolones or other second-line agents in addition to 6(H)RZE may also be registered in the second-line TB register if the programme wishes to monitor how many patients are being given regimens containing second-line medicines *(17)*. If this is done, it is important that cases without RR-TB are not enumerated with the MDR/RR-TB cohort for treatment outcome monitoring purposes.

It will be helpful to monitor efforts to improve testing coverage, detection, enrolment and outcomes for Hr-TB separately from other TB or MDR/RR-TB cases. The indicators for MDR/RR-TB may be adapted for this purpose; outcome definitions are the same as for non-MDR/RR-TB *(100)*. Reporting can be at the same frequency as that recommended for standard monitoring of other TB cohorts.

Combining data for patients with different resistance patterns into a single cohort may complicate comparison of performance between centres and determination of trends over time, given that these patients may have different risks for treatment failure. However, treatment of TB patients who do not have rifampicin resistance with regimens discussed in this section should lead to a successful outcome in most patients, and maximizing the likelihood of success should be the end objective of TB programmes. The use of electronic case-based databases facilitates the grouping of patients by comparable resistance patterns or treatment episodes to undertake more advanced analyses, allowing adjustment for at least some covariates. Programmes are encouraged to follow good practices when collecting these data, and to participate in collaborative initiatives to share individual patient records for pooled reviews of global patient series *(123–126)*. Such data could be useful to guide future policy on the optimization of regimens for the treatment of DR-TB.

8. Adjuncts to MDR-TB treatment

8.1 Surgery in the treatment of MDR/XDR-TB

Surgery has been employed in the treatment of TB since before the advent of chemotherapy. With the challenging prospect that more cases of MDR/XDR-TB are virtually untreatable with all available drugs or risk having serious sequelae, there has been re-evaluation of the role of pulmonary surgery as a way to reduce the amount of lung tissue with intractable pathology and to reduce the bacterial load. Large case series have reported that resection surgery may be safe and an effective adjunct when skilled thoracic surgeons and excellent postoperative care are available *(127, 128)*.

The updated WHO consolidated guidelines include a conditional recommendation for elective partial lung resection (lobectomy or wedge resection) as an adjunct to the chemotherapy of MDR/RR-TB patients with resistance to additional medicines. The recommendation does not apply to radical pneumonectomy, which had no statistically significant effect *(127)*. The recommendation was based on evidence from an IPD meta-analysis to evaluate the effectiveness of different forms of elective surgery as an adjunct to combination medical therapy for MDR-TB *(127)*, and a systematic review and study-level meta-analysis *(129)*.

The relative benefits of surgery are expected to depend substantially on the population subgroups that are targeted. The reviews for the guideline update in 2016 *(11)* could not provide a refined differentiation of the type of patient who would be best suited to an intervention, or the type of intervention that would carry 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 MDR/RR-TB and resistance to fluoroquinolones and injectable agents were significantly lower when they underwent surgery compared with other patients (aOR: 0.4, 95% CI: 0.2–0.9) *(127)*. This finding is likely to be biased, given that patients who underwent surgery would have had other factors predisposing them to poor outcomes – factors that could not be adjusted for. Programmes with limited access to surgery may target patients who remain sputum smear positive, who have resistance to many drugs and who have localized pulmonary disease. Computerized tomography, pulmonary function testing and quantitative lung perfusion or ventilation may have a role in the preoperative work-up.

Resection surgery should be timed to give the patient the best possible chance of cure with the least risk of harm. Thus, the timing of surgery may be earlier in the course of the disease when the patient's risk of morbidity and mortality are lower (e.g. when the disease is still localized to one lung or one lung lobe). Generally, at least 2 months of therapy should be given before resection surgery, to decrease the bacterial infection in the surrounding lung tissue. Prognosis appears to be better when partial lung resection is performed after culture conversion. Even with successful resection, the total duration of treatment and the duration of treatment after culture conversion should be guided by the recommendations in **Section 5**, **Section 6** and **Section 7**.

Partial lung resection for patients with MDR/RR-TB is only to be considered when good surgical facilities, staffed by trained and experienced surgeons, are available. Many programmes will have limited access to surgical interventions. In programmes with suboptimal surgical facilities and with

no trained thoracic surgeons, resection surgery may increase morbidity or mortality. Specialized surgical facilities should include stringent infection control measures (given that infectious material and aerosols are generated in large quantities during surgery), mechanical ventilation and postoperative pulmonary hygiene manoeuvres. After resection, direct laboratory testing of the resection material (lung lesion) will be useful. If the results of laboratory testing differ between the resected material and other clinical specimens, the treating clinician may need to adjust treatment based on the results obtained from the resected material or other clinical specimens.

There are still many uncertainties about the role of surgery in MDR-TB treatment. All data available for the 2016 recommendations were from observational data from case series, which may be biased. For instance, it is likely that in choosing patients to be operated on there would have been systematic exclusion of patients deemed unfit for surgery and anaesthesia, such as older patients and those who were very sick with comorbidities (e.g. no patient with HIV in the dataset had undergone surgery) or extensive disease. There were not enough data on adverse events, surgical complications or long-term sequelae – some of which may be fatal – to allow for a meaningful analysis. Conversely, the effectiveness of surgery may have been underplayed in the analysis because of the lack of a suitable control group.

8.2 Use of corticosteroids

Corticosteroids have been used to support the treatment of serious and severe consequences of TB, such as miliary TB, respiratory insufficiency, CNS involvement and pericarditis.

The WHO *Guidelines for treatment of drug-susceptible TB and patient care, 2017 update* made the following recommendations *(2, 130)*:

- **In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks should be used.** *(Strong recommendation, moderate certainty in the evidence)*
- **In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used.** *(Conditional recommendation, very low certainty in the evidence)*

The recommendations are limited to these two forms of extrapulmonary TB. In patients with TB meningitis, evidence from RCTs *(131–135)* showed lower rates of death, severe disability and relapse when patients received steroids with TB treatment. The mortality benefit increased with increasing severity of TB meningitis. Adverse events and severe adverse events, including severe hepatitis, were lower in patients receiving steroids. In patients with TB pericarditis, studies showed a benefit to steroid treatment in relation to death, constrictive pericarditis and treatment adherence *(136–143)*.

Although the evidence and the recommendations primarily relate to non-MDR-TB, these recommendations could also apply to patients with MDR/RR-TB, on the condition that the patient is still receiving the TB treatment regimen. Corticosteroids are immunosuppressive and therefore can weaken the body's response to fight TB; hence, they should only be used if clearly indicated and if the patient is on an adequate effective regimen. If corticosteroids are used in an inadequate regimen, this could accelerate the patient's deterioration. Oral treatment can be given, but when a more immediate response is needed, injectable corticosteroids are often used initially.

8.3 Treatment of MDR/RR-TB patients with HIV

With regard to **HIV infection**, a specific recommendation was made in 2011 on the use of ART in all patients with HIV and DR-TB *(68, 115)*:

> **6.1. ART is recommended for all patients with HIV and drug-resistant TB requiring second-line anti-tuberculosis drugs irrespective of CD4 cell count, as early as possible**

(within the first 8 weeks) following initiation of anti-tuberculosis treatment
(Strong recommendation, very low quality of evidence)

Delaying ART increases the risk of dying among TB patients living with HIV; therefore, ART should be started in all TB patients living with HIV, regardless of their CD4 cell count. The therapy should be initiated as soon as possible within the first 8 weeks of TB treatment, or within the first 2 weeks in patients with profound immunosuppression (e.g. CD4 counts <50 cells/mm^3). In children with HIV and active TB, ART should be initiated as soon as possible and within 8 weeks following the initiation of anti-TB treatment, regardless of the CD4 cell count and clinical stage *(144)*.

There may be a potential for overlapping, additive toxicities or drug–drug interactions between some antiretroviral medicines and the injectable agents, moxifloxacin and clofazimine; however, there are usually no grounds to warrant modifications of the MDR-TB or the ART regimens. It is not recommended to use bedaquiline and efavirenz in combination (**Web Annex 2**). **Web Annex 1** provides information on individual medicines used to treat MDR/RR-TB and their drug interactions. In addition, information on HIV drug interactions is available on the HIV drug interactions webpage *(145)*. Antiretroviral treatment regimens need to be optimized, and should be initiated early, in accordance with WHO recommendations *(17, 68)*. Close monitoring for response and toxicity is advised for patients on both TB and HIV treatment. Other comorbidities (e.g. diabetes and mental health disorders) should be managed accordingly *(17)*.

9. Programmatic implementation of MDR-TB regimens

Introducing the longer and shorter MDR-TB regimens entails a series of steps that are the same as those necessary when an NTP introduces a new MDR-TB treatment component. This chapter summarizes some key considerations for those steps.

9.1 Policy and operational documents

Policy and operational documents that govern the main components of the programme will need to be revised. Such documents include the national strategic plan for TB, treatment guidelines and algorithms, diagnostic algorithms, the essential medicines list, regulations (e.g. importation of clofazimine and pretomanid), drug orders and training material. Ideally, the type of regimen used by the patient would be indicated in the register and could be summarized for reporting. The TB treatment card may be changed to allow the tabulation of results of periodic testing for treatment response and adverse reactions (this may have already been done for the purposes of aDSM) *(18)*. Any changes should also cover the use of the regimen in private practice.

9.2 National MDR-TB expert committee or technical working group

A national MDR-TB expert committee or technical working group (the consilium or its equivalent structure within the NTP) will assist health care providers as early as possible to:

- coordinate policy changes and activities related to the introduction of the revised MDR-TB regimens in both the public and private sectors (e.g. training, communication and establishing patient eligibility for the different MDR-TB regimens);
- train staff in the clinical aspects of aDSM;
- provide patient support; and
- provide technical and clinical advice.

Additional support may be provided by other experts at national and international levels, and at regional level through, for example, the regional Green Light Committee (rGLC). In making use of such support, it is important to consider any phased implementation process, such as the initial introduction in one or a few centres before full scale-up, or whether implementation is also occurring in the private sector.

9.3 Electronic recording and reporting

There is a need to improve the quality of patient data using standardized variables, such as data on DST patterns, prescribed treatment, treatment outcomes and adverse drug reactions. The collection and utility of these data are important for future evidence-based recommendations, especially given the lack of RCTs on the management of DR-TB *(126)*. If digital patient records do not already exist, it

is important that the programme managers consider their introduction, at least for surveillance and possibly also for case management *(146)*. If patient records are already digital, changes may be needed in the electronic recording and reporting system to allow individuals belonging to MDR-TB regimen cohorts of interest (e.g. shorter regimen, bedaquiline-containing regimens and operational research subgroups) to be identifiable, and for certain options to be included in the monitoring framework (e.g. addition of clofazimine and registration of ECG findings). It is crucial for programmes to maintain such data diligently and prospectively, so that they can contribute to programme evaluation and to global policy-making (e.g. the development of the WHO consolidated guidelines benefited hugely from the experience of patient treatment within programmes) *(123, 124)*. The treatment outcome cohort reports for MDR/RR-TB do not need to change (for the digital and paper version). Moreover, electronic tools can enhance the quantification of consumables; for example, volumes of medicine can be calculated automatically using QuanTB, an application (app) that is available for download free of charge.[12] It is important to ensure that digital records can accommodate key measures in children that may differ from those for adults.

9.4 Estimates (epidemiological and logistics)

Estimates are needed by the NTP and other health care providers, to determine the number of MDR/RR-TB patients eligible for the longer and shorter MDR-TB regimens, to revise the budget accordingly, and to submit the corresponding requests for drug orders, taking into account the existing stock of medicines. These estimates of MDR/RR-TB patients likely to be enrolled are based on current notification trends and an expected increase in line with national and subnational plans. The programme first establishes the number of MDR-TB enrolments expected in the coming years, depending on the future increase in programme capacity (e.g. as part of a project supported by a grant from the Global Fund to Fight AIDS, Tuberculosis and Malaria). Then, based on knowledge from surveillance, eligibility and estimated rate of scale-up, the programme defines different patient groups; for example, those expected to receive different variants of the longer MDR-TB regimens and those likely to receive a shorter MDR-TB regimen. When estimating the caseload to put on treatment, it is necessary to factor in not just eligibility, but also what would be feasible to achieve within a given time, to ensure that all elements are in place for starting and maintaining patients on treatment (e.g. training and provision of an adequate framework for patient monitoring and support). Associated programme and patient costs other than the medicines themselves usually dominate the total cost for both longer and shorter MDR-TB regimens (e.g. treatment of adverse events, hospitalization, diagnostic consumables, other clinical care and social support); however, total costs are expected to be lower for shorter regimens, given the shorter duration of treatment.

9.5 Management of the supply chain and storage conditions for pharmaceuticals

Management of the supply chain and storage conditions for pharmaceuticals should be reviewed to ensure that TB drug orders are made in good time and are correctly quantified to avoid overstocking or shortages. The NTP must ensure an uninterrupted supply of TB medicines through proper quantification, supply planning and rigorous quarterly monitoring, with a functional early warning system to avoid stock-outs and subsequent treatment interruptions. Similarly, other consumables (e.g. medicines for symptomatic relief and adverse reactions, syringes, diagnostic kits, medication for management of adverse effects, masks and N95 respirators) will be needed to ensure that the intervention is delivered as per internationally recommended standards *(147)*. The principles for the quantification of medicines needed for the longer and shorter MDR-TB regimens are similar. The health care provider needs to have some basic details about how many patients will be treated and when they will start; the expected increment in caseload over successive years; the average body weight

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[12] Available at https://siapsprogram.org/tools-and-guidance/quantb/.

of the patients; whether children will also be enrolled; the expected losses (from interruptions, deaths and transfers to another regimen); and current stock on hand, including expiry dates and orders of medicines already in the pipeline and not yet delivered. It is best to split an order of medicines, the first part being for the patients expected to be started within 6 months, and the second part adjusted based on the actual enrolments. Technical assistance to strengthen the procurement and supply and to establish an early warning system for stock-outs can be accessed via the secretariats of the Global Drug Facility (GDF) and rGLC (which are housed in WHO regional offices) or via the WHO country offices. GDF provides support to many NTPs on the procurement and supply chain aspects of phase-in and phase-out plans of products or regimens and can procure child-friendly formulations. Child-friendly formulations allow more accurate paediatric dosing and are more acceptable to children and parents; they should be provided as the SoC wherever possible.

9.6 Preparation for the introduction of new treatment regimens

Given the increased use of newer and repurposed medicines in combination MDR-TB regimens, aDSM is particularly important. aDSM defines the active and systematic clinical and laboratory assessment of patients on MDR-TB treatment to detect, manage and report suspected or confirmed drug toxicities *(18)*. It applies the principles of active pharmacovigilance to the specific needs and context of NTPs, and is embedded within the routine patient monitoring function (e.g. treatment outcome cohort monitoring) of NTPs. The management of patient safety is an inherent part of aDSM, inseparable from its monitoring component. The recording and reporting activities of aDSM primarily target serious adverse events as a priority requirement, but any adverse event during treatment administration (whether or not it is related to drug toxicity) needs to be managed to limit harms to patients. MDR-TB treatment sites may also monitor nonserious adverse events that are of clinical significance or of special interest to the programme, as part of more comprehensive aDSM. In aDSM, in addition to the spontaneously reported reactions, adverse events are elicited as part of a patient monitoring plan that comprises a set of questions and often an array of laboratory or clinical tests at defined periods of time, before, during and after treatment (**Web Annex 3**).

When planning important changes for the national TB treatment policy to align with the latest WHO recommendations, the programme needs to balance the will to provide the best possible options for patients according to the latest evidence against the programmatic circumstances and the implications of such changes (e.g. the need to re-train staff or obtain funds for reprogramming). **Table 9.1** presents a checklist for considerations by the programme manager when implementing the MDR-TB regimens that are currently recommended. The programme must balance the need to provide access to new medicines for which the evidence is still incomplete with the need to protect patients from avoidable toxicity, the emergence of resistance to the new agents and observance of proper ethical conduct and respect for patient rights.

Table 9.1. Checklist to assess programme readiness for introduction of novel regimens

Parameter		
Access to new medicines is a priority as per national TB programme guidelines?	Yes	No
Well-functioning MDR-TB programme component is in place?	Yes	No
MDR-TB expert committee or committees are available to oversee use and support policy development or clinical decision-making?	Yes	No
Staff training is up to date with the latest developments?	Yes	No

Parameter		
Diagnostic capacity for WHO-recommended second-line DST is available?	Yes	No
Clinical monitoring capacity (especially ECG, full blood counts, liver function, audiometry and electrolytes) is available?	Yes	No
Key components of aDSM are in place?	Yes	No
Drug registration or other provision to allow importation of the new and repurposed medicines is in place?	Yes	No
Quantification and drug procurement procedures are in place?	Yes	No
Mechanism for patient informed consent is in place?	Yes	No
Electronic recording and reporting system is in place or has been updated?	Yes	No

10. Treatment outcome definitions

TB is largely curable with treatment that is affordable and widely accessible. If a TB treatment regimen is not administered correctly, it may fail to deliver a relapse-free cure, thus increasing transmission and accelerating the emergence of drug resistance. Monitoring the effectiveness of TB treatment is thus critically important in both clinical practice and surveillance, to maximize the quality of individual patient care and the effectiveness of public health action. Hence, standardized TB treatment outcome definitions have been a feature of WHO policies and national TB surveillance systems for many years, as a cornerstone of effective TB strategies. This standardization has allowed the monitoring of TB treatment outcomes over time at national and global levels.

Standardized treatment outcome definitions for DS-TB have been in widespread use for more than 3 decades, and outcome definitions for DR-TB were first proposed in 2005 *(148)*. The development of DR-TB treatment outcome definitions was based on the outcome definitions for DS-TB in use at the time. The DR-TB treatment outcome definitions were adopted by WHO soon after and remained largely unchanged until 2013, when WHO updated its TB definitions and reporting framework *(149)*. As treatment regimens for DR-TB have significantly changed in composition and duration, an update of the treatment outcome definitions and monitoring parameters was necessary.

10.1 Treatment outcome definitions

In November 2020, WHO/GTB convened an online consultation and released new definitions of TB treatment outcomes, which were the same for DS-TB and DR-TB *(150, 151)*.

The principles guiding the update of the definitions were:

- applicability to treatment regimens of different duration;
- a lessening of the traditional division between the intensive and continuation phases;
- identification of appropriate criteria for bacteriological conversion (or reversion) in relation to the definitions of "treatment failed", "cured" and "treatment completed" that are grounded in knowledge from microbiology;
- consideration of the use of appropriate diagnostics for treatment monitoring;
- setting of clear parameters for defining treatment failure, based on reliable evidence of non-response or other reasons that lead to a decision to change or stop treatment; and
- aiming for practical clinical and programmatic monitoring, and feasible implementation.

A new optional definition, "sustained treatment success", was also proposed for use in operational research only. Post-treatment follow-up may be useful, when or if it is feasible (e.g. for patients suffering from post-treatment sequelae) *(152)*.

The new treatment outcome definitions are summarized in **Table 10.1**.

The 2020 treatment outcome definitions allow all patients with either DS-TB or DR-TB to have a treatment outcome assigned when completing treatment (cure or treatment success) or when unfavourable events occur (e.g. loss to follow-up, failure or death).

Although the definitions of treatment outcomes have been harmonized, minor differences remain between those for DS-TB and DR-TB (e.g. treatment monitoring by sputum culture for DR-TB and by sputum smear microscopy for DS-TB).

Despite some distinct treatment phases remaining in current regimens, the overall trend is towards monophasic regimens. Thus, it is best to avoid linking definitions to treatment phases; hence, the time thresholds for declaring cure or treatment failure have been revised.

Although the role of new bacteriological tests was considered, treatment monitoring will continue to rely on the available tools (i.e. sputum culture for DR-TB and sputum microscopy for DS-TB), despite their limitations.

10.2 Considerations for implementation

It is both important and feasible for NTPs to ascertain cure at the end of treatment. The notion of relapse-free cure or sustained treatment success after the end of treatment is critical; however, it is beyond the means of routine programmatic monitoring and is feasible only under operational research conditions (e.g. in special cohorts, in patients undergoing rehabilitation and during follow-up for post-TB lung disease). Therefore, the specific operational definition "sustained treatment success" was proposed (**Table 10.1**), with the possibility of assessing numbers of patients alive and free of TB at 6 months (for DS-TB and DR-TB) and at 12 months (for DR-TB only) after successful TB treatment.

Table 10.1. New definitions of TB treatment outcomes for both DS-TB and DR-TB

Outcome	Definition
Treatment failed	A patient whose treatment regimen needed to be terminated or permanently changed[a] to a new regimen or treatment strategy.
Cured	A patient with pulmonary TB with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy, with evidence of bacteriological response[b] and no evidence of failure.
Treatment completed	A patient who completed treatment as recommended by the national policy but whose outcome does not meet the definition for cure or treatment failure.
Died	A patient who died[c] before starting treatment or during the course of treatment.
Lost to follow-up	A patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A patient for whom no treatment outcome was assigned.[d]
Treatment success	The sum of all patients cured and treatment completed.
An optional definition was also proposed for use in operational research only	
Sustained treatment success	An individual assessed at 6 months (for DS-TB and DR-TB) and at 12 months (for DR-TB only) after successful TB treatment, who is alive and free of TB.

DR-TB: drug-resistant TB; DS-TB: drug-susceptible TB; TB: tuberculosis.

[a] Reasons for the change include:

  • no clinical response or no bacteriological response, or both (see note 'b');

  • adverse drug reaction; or

  • evidence of additional drug-resistance to medicines in the regimen.

[b] "Bacteriological response" refers to bacteriological conversion with no reversion:

  • "bacteriological conversion" describes a situation in a patient with bacteriologically confirmed TB where at least two consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only) taken on different occasions at least 7 days apart are negative; and

  • "bacteriological reversion" describes a situation where at least two consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only) taken on different occasions at least 7 days apart are positive either after the bacteriological conversion or in patients without bacteriological confirmation of TB.

[c] Patient died for any reason.

[d] This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown; however, it excludes those lost to follow-up.

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Annex: Weight-based dosing of medicines used in multidrug-resistant TB regimens, adults and children[a]

Group A medicines	Formulation (tablets, diluted in 10 mL of water, as applicable)	3–<5 kg	5–<7 kg	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
Levofloxacin (Lfx)	100 mg dt (10 mg/mL)	5 mL (0.5 dt)	1	1.5	2	3	–	–					
	250 mg tab (25 mg/mL)	2 mL[b]	5 mL (0.5 tab)[b]		1	1.5	2	3		4			
	500 mg tab	–					1	1.5		2			
	750 mg tab	–							1		1.5		
Moxifloxacin (Mfx)	100 mg dt (10 mg/mL)	4 mL	8 mL	1.5	2	3	4	4	–				
	400 mg tab (40 mg/mL) Standard dose	1 mL[b]	2 mL[b]	3 mL[b]	5 mL (0.5 tab)[b]	7.5 mL (0.75 tab)[b]	1	1					
	400 mg tab high dose[c]	–	–	–	–	–		1 or 1.5	1.5	1.5 or 2	2		

Group A medicines	Formulation (tablets, diluted in 10 mL of water, as applicable)	3–<5 kg	5–<7 kg	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
Bedaquiline (Bdq)	20 mg dt	0 to <3 months: 1.5 od (2 weeks); then 0.5 od M/W/F (22 weeks) ≥ 3 months: 3 od for 2 weeks; then 1 od M/W/F for 22 weeks		0 to <3 months: 1.5 od for 2 weeks; then 0.5 od M/W/F 3 to <6 months: 3 od for 2 weeks; then 1 od M/W/F ≥6 months: 4 od for 2 weeks; then 2 od M/W/F	3 to <6 months: 3 od for 2 weeks; then 1 od M/W/F ≥ 6 months: 6 od for 2 weeks; then 3 od M/W/F	10 od for 2 weeks; then 5 od M/W/F		20 od for 2 weeks; then 10 od M/W/F		–			
	100 mg tab (10 mg/mL)[d]	0 to <3 months: 3 mL od for 2 weeks; then 1 mL od M/W/F[b] ≥ 3 months: 6 mL od for 2 weeks; then 2 mL od M/W/F[b]		0 to <3 months: 3 mL od for 2 weeks; then 1 mL od M/W/F[b] 3 to <6 months: 6 mL od for 2 weeks; then 2 mL od M/W/F[b] ≥ 6 months: 8 mL od for 2 weeks; then 4 mL od M/W/F[b]	3 to <6 months: 6 mL od for 2 weeks; then 2 mL od M/W/F[b] ≥ 6 months: 12 mL od for 2 weeks; then 6 mL od M/W/F[b]	2 od for 2 weeks; then 1 od M/W/F	4 od for 2 weeks; then 2 od M/W/F						
	100 mg tab (10 mg/mL)	–								200 mg daily (od) for 8 weeks; then 100 mg dose daily (od)			Dosing scheme is for BPaLM/BPaL regimen (>14 years).

Group A medicines	Formulation (tablets, diluted in 10 mL of water, as applicable)	3–<5 kg	5–<7 kg	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
Linezolid (Lzd)	20 mg /mL susp	2 mL	4 mL	6 mL	8 mL	11 mL	14 mL	15 mL	20 mL	–			
	150 mg dt (15 mg/mL)	2.5 mL	5 mL (0.5 dt)	1		2[e]		2	3	–			
	600 mg tab (60 mg/mL)	–	1.25 mL[b]	2.5 mL[b]		5 mL (0.5 tab)[b, e]		5 mL (0.5 tab)[b]	7.5 mL (0.75 tab)[b]	1	1		

Group B medicines	Formulation	3–<5 kg	5–<7 kg	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
Clofazimine (Cfz)	50 mg cap or tab[f]	1 M/F	1 M/W/F		1		2	2					For children <24 kg, the use of the 50 mg tab is preferred.
	100 mg cap or tab[f]	–	1 M/F		1 M/W/F		1	1					
Cycloserine or terizidone (Cs/Tz)	125 mg mini cap (Cs) (12.5 mg/mL)	2 mL[b, g]	4 mL[b]	1	2	3	4	4		–			
	250 mg cap (25 mg/mL)	1 mL[b, g]	2 mL[b]	5 mL[b]	1	2	2	2		3			

Group C medicines	Formulation	3–<5 kg[a]	5–<7 kg[a]	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
Ethambutol (E or EMB)	100 mg dt (10 mg/mL)	5 mL (0.5 dt)	1	2	3	4	–			–			–
	400 mg tab (40 mg/mL)	1.5 mL[b]	3 mL[b]	4 mL[b]	6 mL	1	1.5	2		3		4	
Delamanid (Dlm)	25 mg dt	1 od	<3 months: 1 od / ≥3 months: 1 bd		1 bd	2 morning / 1 evening		2 bd		–			
	50 mg tab[h] (5 mg/mL)	5 mL (0.5 tab) od[b]	<3 months: 5 mL (0.5 tab) od[b] / ≥3 months: 5 mL (0.5 tab) bd[b]		5 mL (0.5 tab) bd[b]	10 mL (1 tab) morning / 5 mL (0.5 tab) evening		1 bd		2 bd			

Group C medicines	Formulation	3–<5 kg[a]	5–<7 kg[a]	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
Pyrazinamide (Z or PZA)	150 mg dt (15 mg/mL)	5 mL (0.5 dt)	1	2	3	5	–	–					–
	400 mg tab (40 mg/mL)	2.5 mL[b]	5 mL (0.5 tab)[b]	7.5 mL (0.75 tab)[b]	1	2	2.5	3	4			5	
	500 mg tab (50 mg/mL)	2 mL[b]	5 mL (5 mL)[b]		1	1.5	2	2.5	3			4	
Imipenem–cilastatin (Ipm/**Cln**)	500 mg + 500 mg powder for injection, vial (10 mL)	Not used in patients aged <15 years (use meropenem)						2 vials (1 g + 1 g) bd					Only to be used with clavulanic acid.
Meropenem (Mpm)	1 g powder for injection, vial (20 mL)	1 mL tid	2 mL tid	4 mL tid	6 mL tid	9 mL tid	11 mL tid	1 vial tid or 2 vials bd					Only to be used with clavulanic acid.
Amikacin (Am)	500 mg/2 mL solution for injection, ampoule	–[i]								3–4 mL	4 mL	4 mL	Recommended only in adults aged >18 years.
Streptomycin (**Sm**)	1 g powder for injection, vial	–[i]								Calculate according to the dilution used			Recommended only in adults aged >18 years.
Ethionamide or Prothion-amide (Eto/Pto)	125 mg dt (Eto) (12.5 mg/mL)	3 mL[b]	7 mL[b]	1	2	3	4	4	–				Although once daily dose advised, two divided doses can be also given to improve tolerance.
	250 mg tab (25 mg/mL)	–	3 mL[b]	5 mL (0.5 tab)[b]	1	2		2		3		4	
_P_-aminosal-icylic acid (PAS)	PAS sodium salt (equivalent to 4 g PAS acid) sachet	0.3 g bd	0.75 g bd	1 g bd	2 g bd	3 g bd	3.5 g bd	4 g bd				4–6 g bd	Usually given in divided doses.

Other medicines	Formulation	3–<5 kg	5–<7 kg	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
Isoniazid[j] (INH or H) (high dose)	50 mg/5 mL soln	5 mL	9 mL	15 mL	20 mL	–	–	–					Pyridoxine is always given with high-dose isoniazid in children (1–2 mg/kg) and in people at risk of side-effects (e.g. those with HIV or malnutrition). In infants, pyridoxine may be given as part of a multi-vitamin syrup.
	100 mg dt or tab (10 mg/mL)	5 mL (0.5 dt)	1	1.5	2	3	4	4	4.5	–			
	300 mg tab	–				1	1.5	1.5		2			
Clavulanic acid[j] (as amoxicillin/ clavulanate) (Amx/clav)	62.5 mg clavulanic acid as amoxicillin/clavulanate (250/62.5 mg), powder for oral solution, 5 mL	1.5 mL tid	2 mL tid	3 mL tid	5 mL tid	8 mL tid	10 mL tid	10 mL bd or tid		–			Only available in combination with amoxicillin. To be given with each dose of imipenem/cilastatin (bd) or meropenem (tid).
	125 mg clavulanic acid as amoxicillin/clavulanate (500/125 mg) tab	–					1 tid	1 bd or tid					
Pretomanid (Pa)	200 mg tab	–						1					Currently only used as part of the BPaLM/BPaL regimens.

bd: two times a day; BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; cap: capsule; DR-TB: drug-resistant TB; dt: dispersible tablet; g: gram; GDG: Guideline Development Group; HIV: human immunodeficiency virus; kg: kilogram; MDR-TB: multidrug-resistant TB; MDR/RR-TB: multidrug- or rifampicin-resistant TB; mg: milligram; mL: millilitre; M/F: Monday and Friday; M/W/F: Monday, Wednesday and Friday; od: once daily; soln: solution; susp: suspension; tab: tablet; TB: tuberculosis; tid: three times a day; WHO: World Health Organization.

[a] Dosing guidance is based on currently available data and may be revised once additional data are available. Dosages were established by the GDGs for the WHO guidelines on DR-TB treatment (2018 and 2020 updates), the WHO Global Task Force on the Pharmacokinetics and Pharmacodynamics (PK/PD) of TB medicines and the expert consultation on dosing convened by WHO in October 2021, following the GDG meeting on child and adolescent TB in June 2021.

Doses for children and young adolescents weighing <46 kg were revised according to Annex 6 of the 2022 *WHO operational handbook on tuberculosis – Module 5: Management of tuberculosis in children and adolescents (153)*, which was informed by an expert consultation on dosing convened by WHO in October 2021 *(154)*. They are based on the most recent reviews and best practices in the treatment of (paediatric) MDR/RR-TB. For certain medicines the dosages were informed by pharmacokinetic modelling results based on the principle of allometric scaling and maturation *(155)*. Due to the pharmacokinetic properties of certain medicines the doses proposed may exceed the mg/kg/day ranges shown here in order to achieve blood concentrations similar to target levels in an average adult patient. The guidance for the 3–<5 kg weight band and for bedaquiline and delamanid is based on currently available data and may be revised when new data become available.

[b] Dissolving of crushed adult tablets or capsule content in 10 mL of water is required for administering this dose. The number of mL in the table reflects the dose to provide. This avoids fractioning solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (use of dispersible tablets is preferred).

[c] The higher dose may be used except when there is risk of toxicity; levels are expected to be lowered because of pharmacokinetic interactions, malabsorption or other reasons; or the strain has low-level drug resistance.

[d] Bedaquiline adult tablets (100 mg) crushed and suspended in water have been shown to be bioequivalent to tablets swallowed whole. Vigorous stirring/shaking is needed prior to administering the 100 mg tablet crushed and suspended in water.

[e] When using the 600 mg tab and the 150 mg dt to dose children weighing 16 to <24 kg, the dose in mg/kg will exceed 10–12 mg/kg and clinicians may opt to administer 1.5 dt or 4 mL of the 600 mg tab dispersed in 10 mL water.

[f] Clofazimine tablets are technically not dispersible but they do slowly (this takes approximately 5 minutes) dissolve in water (5 mL and 10 mL for the 50 mg and 100 mg tablets, respectively). The suspension should be stirred prior to administration. The 100 mg soft gel capsule is difficult to swallow for young children and therefore countries are strongly encouraged to make the 50 mg tablet formulation available.

[g] In children weighing 3 to <7 kg doses are lower than previously recommended. This is because of relatively high exposures associated with risk of neuropsychiatric adverse events, which is especially concerning when co-administering cycloserine with delamanid.

[h] Delamanid adult tablets (50 mg) crushed and suspended in water have been shown to be bioequivalent to tablets swallowed whole.

[i] Amikacin and streptomycin may be used in adults aged 18 years or more, in situations where an effective regimen cannot otherwise be designed using oral agents, when susceptibility is demonstrated and when adequate measures are in place to monitor for adverse events. Given the profound impact that hearing loss can have on the acquisition of language and the ability to learn at school, the use of injectable agents in children should be exceptional and limited to salvage therapy, and the treatment needs to be provided under strict monitoring to ensure early detection of ototoxicity. If used, the weight-based daily dose for amikacin is 15–20 mg/kg and for streptomycin it is 20–40 mg/kg for children aged 2 years and older. To determine the dosing for infants and children aged below 2 years, a paediatric DR-TB expert should be consulted and a lower mg/kg dose used to compensate for immature clearance. Co-administration with lidocaine is advised to reduce pain at the injection site (156).

[j] These medicines are only recommended as a companion agent (amoxicillin/clavulanic acid) or are not included in Groups A, B and C, because of a lack of data from the latest analysis on longer MDR-TB regimens in adults (isoniazid).

Specific comments on dosing children with medicines used in second-line MDR-TB regimens:

• For dosing of premature and low birth weight infants weighing <3 kg, advice should be sought from a paediatric DR-TB expert.

• For dosing of infants weighing 3 to <5 kg, a paediatric DR-TB expert should be consulted whenever possible.

• The use of child-friendly, dispersible tablets in infants and young children is preferred over manipulating adult tablets or administering or manipulating capsules. Where applicable, the dosing provided is based on dissolving the dispersible formulation in 10 mL of water and administering the number of mL (aliquots). The number of mL in the table reflects the dose to provide. The dissolved solution should be used immediately and the remainder of the 10 mL should be discarded.

• For some weight bands, dosing is indicated with both child-friendly, dispersible formulations and adult formulations. If adult formulations are used, the table provides the dose using aliquots in mL and tablet fractions where applicable (if the fraction is 0.5 or more). Aliquots refer to the volume to administer after crushing and dissolving the tablet in 10 mL of water.

See the detailed description of individual TB medicines in Web Annex 1.

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