WHO consolidated guidelines on drug-resistant tuberculosis treatment

THE END TB STRATEGY

World Health Organization

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Note

These consolidated guidelines have been updated following Guideline Development Group (GDG) processes carried out between 2011 and 2018 in accordance with WHO requirements (online Annexes 3–5) *(1)*. The document replaces other WHO recommendations relating to the treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) issued since 2011 *(2–6)* (as well as recommendations in other guidelines relevant to the care of drug-resistant TB (DR-TB); *see* Box 1). The PICO (Population, Intervention, Comparator and Outcomes) questions underlying the recommendations and the revised dosage of medicines used in second-line regimens and key references are included in this document (Annexes 1 and 2 and the References section, respectively). More details on the GDG processes and participants, the main methods used to develop the recommendations, the resultant Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence summaries and decision frameworks for each recommendation, and unpublished data, data analysis plans and reports of systematic reviews are available online (online Annexes 3–9). The recommendations and other practical information to support their implementation will be reproduced in a forthcoming update of the WHO TB programmatic management handbook *(7)*.

Abbreviations and acronyms[1]

aDSM	active TB drug safety monitoring and management
aIPD	adult individual patient data
AE	adverse event
AIDS	acquired immunodeficiency syndrome
aOR	adjusted odds ratio
aRD	adjusted risk difference
ART	antiretroviral therapy
AST	aspartate aminotransferase
ATS	American Thoracic Society
CDC	(United States) Centers for Disease Control and Prevention
CL	(95%) confidence limits
CNS	central nervous system
DALY	disability-adjusted life year
DOI	WHO Declaration of Interest
DOT	directly observed treatment
DR-TB	drug-resistant tuberculosis
DST	drug susceptibility testing
ERG	External Review Group
FDC	fixed-dose combination (medicines)
GDF	Global Drug Facility
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRADEPro	online tool to create guideline materials (*see* https://gradepro.org/)
GRC	WHO Guideline Review Committee
GTB	WHO Global TB Programme
HALT	Hepatitis and Latent TB infection study
HIV	human immunodeficiency virus
(H)REZ	(isoniazid)–rifampicin–ethambutol–pyrazinamide
Hr-TB	confirmed rifampicin-susceptible, isoniazid-resistant TB
IPD	individual patient data
IPD-MA	individual patient data meta-analysis
IQR	interquartile range
ITT	intention to treat

[1] See abbreviations of TB agents in separate list in page 5.

KNCV	KNCV Tuberculosis Foundation
LPA	line probe assay
LTBI	latent tuberculosis infection
MDR-TB	multidrug-resistant tuberculosis
MDR/RR-TB	multidrug/rifampicin-resistant tuberculosis
MTBDR*sl*	GenoType *Mycobacterium tuberculosis* drug-resistant second-line assay
OR	odds ratio
PICO	Population, Intervention, Comparator and Outcomes
PK/PD	pharmacokinetics/pharmacodynamics
PLHIV	people living with HIV
RCT	randomized controlled trial
RR-TB	rifampicin-resistant TB
SAE	serious adverse event
SAT	self-administered treatment or unsupervised treatment
SGOT	serum glutamic oxaloacetic transaminase
SMS	short message service (mobile phone text message)
TB	tuberculosis
UNION	International Union Against Tuberculosis and Lung Disease
USAID	United States Agency for International Development
US NIH(NIAID)	United States National Institutes of Health (National Institute of Allergy and Infectious Diseases)
VOT	video-observed treatment
WHO	World Health Organization
WHO/GTB	Global TB Programme of the World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

Abbreviations of TB agents

Am	amikacin
Amx–Clv	amoxicillin–clavulanic acid
Bdq	bedaquiline
Cfz	clofazimine
Cm	capreomycin
Cs	cycloserine
Dlm	delamanid
E	ethambutol
Eto	ethionamide
Gfx	gatifloxacin
Hh	high-dose isoniazid
Imp–Cln	imipenem–cilastatin
Km	kanamycin
Lfx	levofloxacin
Lzd	linezolid
Mfx	moxifloxacin
Mpm	meropenem
PAS	*p*-aminosalicylic acid
Pto	prothionamide
R	rifampicin
S	streptomycin
T	thioacetazone
Trd	terizidone
Z	pyrazinamide

Key definitions[2]

Drug-susceptibility testing (DST) refers to in-vitro testing using either phenotypic methods to determine susceptibility or molecular techniques to detect resistance-conferring mutations to a medicine *(7,8)*.

Extent or severity of disease in patients older than 14 years is usually defined by the presence of cavities *or* bilateral disease on chest radiography *or* smear positivity (*see* online Annex 9). In children under 15 years, severe disease is usually defined by the presence of cavities *or* bilateral disease on chest radiography *or* extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) (adapted from *(9)*). In children, the occurrence of advanced malnutrition (defined by syndrome or by metrics) *or* advanced immunosuppression *or* positive tuberculosis (TB) bacteriology (smear, Xpert® MTB/RIF, culture) may also be considered when determining disease severity.

The **intensive (or injectable) phase**, as used in these guidelines and in the evidence reviews that informed the recommendations, is the initial part of a shorter or longer regimen for treating multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB). During this phase, an injectable agent – amikacin, capreomycin, kanamycin or streptomycin – is used. Regimens without an injectable agent are considered not to have an intensive phase.

Isoniazid-resistant TB (Hr-TB), refers to *Mycobacterium tuberculosis* strains in which resistance to isoniazid and susceptibility to rifampicin has been confirmed in vitro.

Longer MDR-TB regimens are those used for the treatment of MDR/RR-TB. These last 18 months or more and may be standardized or individualized. These regimens are usually designed to include a minimum number of second-line TB medicines considered to be effective based on patient history or drug-resistance patterns. The features and indications of these regimens are further elaborated in Sections 2 and 3 under Recommendations and remarks in these guidelines. The term "conventional" was previously used to refer to such regimens but was discontinued in 2016.

New case is defined as a newly registered episode of TB in a patient who has never been treated for TB or has taken anti-TB medicines for less than 1 month.

Polyresistance refers to resistance to more than one first-line anti-TB drug, other than isoniazid and rifampicin together.

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

Rifampicin-resistant TB (RR-TB) strains are considered not to be susceptible to rifampicin on the basis of DST and, as a result, are eligible for treatment with MDR-TB regimens. Rifampicin-resistant TB strains may be susceptible or resistant to isoniazid (i.e. MDR-TB), or resistant to other first-line TB medicines (polyresistant) or second-line TB medicines (e.g. extensively drug-resistant [XDR]-TB). In these guidelines and elsewhere, MDR-TB and RR-TB cases are often grouped together as MDR/RR-TB.

[2] *See also* online Annex 9 for more details on how regimens, outcomes and other parameters were defined for the 2018 analysis.

A **second-line TB medicine (or drug)** is an agent reserved for the treatment of drug-resistant TB. First-line TB medicines used to treat drug-susceptible TB – ethambutol, isoniazid and pyrazinamide – may also be used in MDR-TB regimens (streptomycin is now considered a second-line TB medicine and used only as a substitute for amikacin when amikacin is not available or there is confirmed resistance to it).

Serious adverse events (SAEs), for the purpose of the reviews conducted for the *WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update*, are those adverse events (AEs) classified as Grade 3 (severe), Grade 4 (life-threatening or disabling) or Grade 5 (death related to AE) *(10)*, or which led to the medicine being stopped permanently. SAEs are otherwise often defined as AEs that either lead to death or a life-threatening experience; to initial or prolonged hospitalization; to persistent or significant disability; or to a congenital anomaly *(11)*. The management of SAEs may require termination of the drug suspected of having caused the event.

A **shorter MDR-TB regimen** refers to a course of treatment for MDR/RR-TB lasting 9–12 months, which is largely standardized, and whose composition and duration follows closely the one for which there is documented evidence from different settings. The features and indications of this regimen are further elaborated in Section 4 under Recommendations and remarks in these guidelines.

The **treatment outcome** categories used in these guidelines and the term **relapse** were applied according to the definitions agreed for use by TB programmes, unless otherwise specified *(12,13)*.

Executive summary

Tuberculosis (TB) strains with drug resistance (DR-TB) are more difficult to treat than drug-susceptible ones, and threaten global progress towards the targets set by the End TB Strategy of the World Health Organization (WHO). There is thus a critical need for evidence-based policy recommendations on the treatment and care of patients with DR-TB, based on the most recent and comprehensive evidence available. In this regard, the *WHO consolidated guidelines on drug-resistant tuberculosis treatment* fulfil the mandate of WHO to inform health professionals in Member States on how to improve treatment and care for patients with DR-TB.

Between 2011 and 2018, WHO has developed and issued evidence-based policy recommendations on the treatment and care of patients with DR-TB. These policy recommendations have been presented in several WHO documents and their associated annexes (listed in Box 1), including the *WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update*, issued by WHO in December 2018. The policy recommendations in each of these guidelines have been developed by WHO-convened Guideline Development Groups (GDGs), using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to summarize the evidence, and formulate policy recommendations and accompanying remarks. The GDGs have been composed of multidisciplinary groups of external experts with experience in different aspects of the programmatic and clinical management of DR-TB, as well as affected individuals. The methods used to develop the recommendations complied with the requirements of WHO's Guideline Review Committee (GRC), and the GRC has overseen the development of each of these guidelines.

Box 1: WHO treatment guidelines that have been incorporated in the *WHO consolidated guidelines on drug-resistant tuberculosis treatment*

- Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Geneva: World Health Organization; 2011 (WHO/HTM/TB/2011.6).
- The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance. Geneva: World Health Organization; 2013 (WHO/HTM/TB/2013.6).
- The use of delamanid in the treatment of multidrug-resistant tuberculosis: interim policy guidance. Geneva: World Health Organization; 2014 (WHO/HTM/TB/2014.23).
- The use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents: interim policy guidance. Geneva: World Health Organization; 2016 (WHO/HTM/TB/2016.14).
- WHO treatment guidelines for drug resistant tuberculosis: 2016 update. Geneva: World Health Organization; 2016 (WHO/HTM/TB/2016.4).
- Guidelines for the treatment of drug-susceptible tuberculosis and patient care: 2017 update. Geneva: World Health Organization; 2017 (WHO/HTM/TB/2017.05).
- WHO treatment guidelines for isoniazid-resistant tuberculosis. Supplement to the WHO treatment guidelines for drug-resistant tuberculosis. Geneva: World Health Organization; 2018 (WHO/CDS/TB/2018.7).
- WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update. Geneva: World Health Organization; 2018 (WHO/CDS/TB/2018.15).

The present consolidated guidelines include a comprehensive set of WHO recommendations for the treatment and care of DR-TB, derived from these eight WHO guidelines documents, which they now replace. The consolidated guidelines include policy recommendations on treatment regimens for isoniazid-resistant TB (Hr-TB) and multidrug- and rifampicin-resistant (MDR/RR-TB), including longer and shorter regimens for MDR/RR-TB, culture monitoring of patients on treatment, the timing of antiretroviral therapy (ART) in MDR/RR-TB patients infected with the human immunodeficiency virus (HIV), use of surgery for patients receiving MDR-TB treatment, and optimal models of patient support and care.

The full list of 29 policy recommendations, grouped into eight sections, is provided below. The new guidance will be complemented with further advice on their implementation in a revised edition of WHO's "how-to" handbook for the programmatic management of TB.

Current policy recommendations on treatment and care for DR-TB

1. Regimens for isoniazid-resistant tuberculosis (Hr-TB)

- In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months.
- In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen.

2. The composition of longer MDR-TB regimens

- In MDR/RR-TB patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of the treatment after bedaquiline is stopped.[3] 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.
- Kanamycin and capreomycin are not to be included in the treatment of MDR/RR-TB patients on longer regimens.
- Levofloxacin or moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens.
- Bedaquiline should be included in longer MDR-TB regimens for patients aged 18 years or more. Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years.
- Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens.
- Clofazimine and cycloserine or terizidone may be included in the treatment of MDR/RR-TB patients on longer regimens.
- Ethambutol may be included in the treatment of MDR/RR-TB patients on longer regimens.
- Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens.
- Pyrazinamide may be included in the treatment of MDR/RR-TB patients on longer regimens.
- Imipenem–cilastatin or meropenem may be included in the treatment of MDR/RR-TB patients on longer regimens.[4]
- 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.

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[3] Group A = levofloxacin/moxifloxacin, bedaquiline, linezolid; Group B = clofazimine, cycloserine/terizidone; Group C = ethambutol, delamanid, pyrazinamide, imipenem–cilastatin, meropenem, amikacin (streptomycin), ethionamide/prothionamide, *p*-aminosalicylic acid (*see also* Table 2.1).

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

- 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.
- *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.
- Clavulanic acid should not be included in the treatment of MDR/RR-TB patients on longer regimens.[4]

3. The duration of longer MDR-TB regimens

- 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.
- 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.
- In MDR/RR-TB patients on longer regimens that contain amikacin or streptomycin, an intensive phase of 6–7 months is suggested for most patients; the duration may be modified according to the patient's response to therapy.

4. Use of the standardized, shorter MDR-TB regimen

- In MDR/RR-TB patients who have not been previously treated for more than 1 month with second-line medicines used in the shorter MDR-TB regimen or in whom resistance to fluoroquinolones and second-line injectable agents has been excluded, a shorter MDR-TB regimen of 9–12 months may be used instead of the longer regimens.

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

- In MDR/RR-TB patients on longer regimens, the performance of sputum culture in addition to sputum smear microscopy is recommended to monitor treatment response. It is desirable for sputum culture to be repeated at monthly intervals.

6. Start of antiretroviral therapy in patients on second-line antituberculosis regimens

- Antiretroviral therapy is recommended for all patients with HIV and DR-TB requiring second-line antituberculosis drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of antituberculosis treatment.

7. Surgery for patients on MDR-TB treatment

- In patients with RR-TB or MDR-TB, elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen.

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

- Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment.
- A package of treatment adherence interventions[5] may be offered to patients on TB treatment in conjunction with the selection of a suitable treatment administration option.[6]
- One or more of the following treatment adherence interventions (complementary and not mutually exclusive) may be offered to patients on TB treatment or to health-care providers:

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

[6] Treatment administration options include directly observed treatment (DOT), non-daily DOT, video-observed treatment (VOT), or unsupervised treatment.

a) tracers[7] and/or digital medication monitor;[8]
b) material support[9] to the patient;
c) psychological support[10] to the patient;
d) staff education.[11]

- The following treatment administration options may be offered to patients on TB treatment:
  a) Community- or home-based directly-observed treatment (DOT) is recommended over health facility-based DOT or unsupervised treatment.
  b) DOT administered by trained lay providers or health-care workers is recommended over DOT administered by family members or unsupervised treatment.
  c) Video-observed treatment (VOT) may replace DOT when video communication technology is available, and it can be appropriately organized and operated by health-care providers and patients.
- Patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalization.
- A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment.

[7] Tracers refer to communication with the patient, including home visits or via short message service (SMS), telephone (voice) call.

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

[9] Material support can be food or financial support: meals, food baskets, food supplements, food vouchers, transport subsidies, living allowance, housing incentives or financial bonus. This support addresses the indirect costs incurred by patients or their attendants in order to access health services and, possibly, tries to mitigate the consequences of income loss related to the disease.

[10] Psychological support can be counselling sessions or peer-group support.

[11] Staff education can be adherence education, chart or visual reminders, educational tools and desktop aids for decision-making and reminders.

Recommendations and remarks

Section 1. Regimens for isoniazid-resistant tuberculosis

Recommendations

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

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

Justification and evidence

The recommendations in this section address one PICO (Population, Intervention, Comparator and Outcomes) question (*see* Annex 1):

PICO question 1 (Hr-TB, 2018). In patients with isoniazid-resistant TB (other than MDR-TB), which treatment regimen composition and duration, when compared with 6 months or more of rifampicin–pyrazinamide–ethambutol, leads to a higher likelihood of success with least possible risk of harm?

Treatment with rifampicin, ethambutol and pyrazinamide – with or without isoniazid – has been used for the treatment of patients with Hr-TB *(14–16)*. The evidence reviewed for this guideline compared treatment regimens with isoniazid, rifampicin, ethambutol, pyrazinamide ((H)REZ) of different durations, i.e. 6-month regimens versus longer duration ones. Additionally, the evidence review focused on determining whether treatment outcomes of Hr-TB patients receiving (H)REZ treatment regimens of variable duration could be improved with the addition of a fluoroquinolone or streptomycin.

The evidence used to determine the composition and duration of regimens relied primarily on an analysis of individual patient data (IPD), comprising 33 databases with an analysable population of 5418 Hr-TB patients (*see also* Methods section in online Annex 6). All data used to develop these recommendations were derived from observational studies conducted in various settings (26% in Asia; 33% in Europe; 31% in the Americas; and 6% in Africa)[12] *(17)*. Patient treatment regimens analysed from the IPD contained rifampicin, ethambutol, pyrazinamide, streptomycin, isoniazid and fluoroquinolones. Thus, recommendations could be made only for regimens containing these anti-TB agents.

Duration of (H)REZ. The analysis comparing (H)REZ treatment regimens for 6- and >6 months demonstrated that a 6-month (H)REZ regimen had a higher likelihood of treatment success compared with a regimen of >6 months. Further analyses determined that there was no statistically significant difference in the treatment outcomes of patients receiving 6REZ and those receiving >6REZ regimens. Since data were not included on intermittent dosing of the 6-month and >6-month (H)REZ regimens, no inferences could be drawn about the use of alternating versus daily regimens. The effect of

[12] The number of patients highlighted in this section refers to the sample size of each study. However, the analysable sample size was later modified, depending on the availability of IPD for each analysable outcome (success; mortality).

length of pyrazinamide use in the (H)REZ regimen was assessed to investigate whether the use of this medicine could be minimized to the shortest possible duration. The reduction in treatment with pyrazinamide to <3 months was associated with a worse treatment outcome, even with the addition of streptomycin (adjusted odds ratio [aOR], 0.4; 95% confidence limits [CL] 0.2–0.7). In 118 patients on fluoroquinolone-containing regimens who received pyrazinamide for <4 months, the odds of treatment success were higher than in those who received 6(H)REZ, although the difference was not statistically significant.

Duration of levofloxacin use. In a subsample of 241 patients on an (H)REZ plus fluoroquinolone regimen, the median duration of fluoroquinolone use was 6.1 months (interquartile range [IQR] 3.5; 8.4) and for REZ, it was 9.0 months (IQR 7; 11). It therefore appears that treatment length was based upon the completion of 6 months of treatment with a fluoroquinolone in the observational studies that informed the IPD.

Acquisition of drug resistance. The analysis suggested that amplification of resistance to rifampicin was lower in patients receiving the 6(H)REZ regimen (0.6%) compared with those receiving >6(H)REZ (4.3%). This observation could be due to the effect of selection and allocation of patients into specific regimens. For instance, the number of patients with extensive disease (cavities, bilateral disease or persistent smear positivity) was slightly larger in those receiving longer regimens (>6(H)REZ); however, overall, the number of observations for each comparison was small and the effect was not statistically significant (aOR, 0.2; 95% CL 0.02–1.70).

Adverse events. Data on adverse events (AEs) were not evaluated because of lack of standardization (dissimilar reporting). The Guideline Development Group (GDG) also considered two reports containing data from patients from the United States in whom a detailed assessment on AEs indicated that there seemed to be a risk of excess hepatotoxicity with the 6(H)REZ combination *(18)*. Drug-induced hepatotoxicity is not uncommon with anti-TB drugs. It has also been reported in persons receiving rifampicin and pyrazinamide for 2 months for the treatment of latent TB infection (LTBI). In such individuals, a much higher occurrence of hepatotoxicity has been observed compared to persons receiving only isoniazid preventive therapy *(19)*. It is unknown whether the risk of hepatotoxicity is different between 6REZ and 6HREZ.

Addition of a fluoroquinolone. In patients with Hr-TB, treatment success rates were higher when fluoroquinolones were added to (H)REZ regimens as compared to patients treated with 6 or more months of (H)REZ without the addition of fluoroquinolones (aOR, 2.8; 95% CL 1.1–7.3). With the addition of fluoroquinolones in patients receiving (H)REZ, the number of deaths was reduced (aOR, 0.4; 95% CL 0.2–1.1). Acquisition of additional resistance with progression to MDR-TB was also reduced when fluoroquinolones were added to a ≥6(H)REZ regimen (aOR, 0.10; 95% CL 0.01–1.2), albeit the small absolute numbers, with 0.5% (1/221) of patients on ≥6(H)REZ plus fluoroquinolones acquiring resistance to rifampicin versus 3.8% (44/1160) of patients who did not receive fluoroquinolones. Residual confounding could have increased this observed effect. The directness of the evidence was therefore downgraded as it was unclear whether fluoroquinolones were used at the beginning of treatment or only once drug-susceptibility testing (DST) results were available (in the second month or later).

Addition of streptomycin. The analysis showed that the addition of streptomycin (up to 3 months) to an (H)REZ regimen with <4 months of pyrazinamide decreased the likelihood of treatment success (aOR, 0.4; 95% CL 0.2–0.7), an effect that may in part be due to confounding. Addition of streptomycin did not reduce mortality significantly (*see also* online Annexes 7 and 8). There were no data on the use of other injectable agents (i.e. kanamycin, amikacin, capreomycin) for the treatment of Hr-TB.

Treatment outcomes. When analysing the overall treatment outcomes for each one of the regimens assessed for this review, other limitations related to the characteristics of patients included in these studies were evident and could not be controlled for (namely, patient selection, allocation to treatment with specific regimens and their relationship with disease severity). Outcomes of patients with cavitary

disease, persistence of sputum smear positivity and previous history of TB treatment, who received a ≥6(H)RE regimen with an additional 3 months of pyrazinamide and 1–3 months of streptomycin appeared to be worse (*see* online Annex 7; [Hr-TB, 2018]). However, the limited number of observations made it difficult to draw definitive conclusions based on the severity of TB disease or the effect of other comorbidities on this regimen. In formulating the recommendations, the GDG assessed the overall balance between benefits and harms of an (H)REZ–levofloxacin regimen, as well as values and preferences, paying special attention to considerations of equity, acceptability and feasibility, in addition to clinical outcomes and the potential risks of increasing toxicities (*see* online Annexes 7 and 8 for more details). The conclusions of the GDG were that a regimen composed of 6 months of REZ plus fluoroquinolones was associated with higher treatment success rates (with or without the addition of isoniazid). The difference between the 6(H)REZ and longer >6(H)REZ regimens was modest, slightly favouring the 6-month regimen (not statistically significant). The GDG acknowledged that it was not possible to control for all possible confounding by indication when comparing the 6 months (H)REZ to the longer (H)REZ regimen. As an example (though data on the extent of disease were not systematically captured for all patients), it is possible that a larger number of cases with extensive disease received >6(H)REZ regimens, resulting in poor outcomes for this group of patients (given the extent of disease) and possibly favouring the 6-month regimen.

The GDG acknowledged the safety implications of (H)REZ–levofloxacin, particularly for hepatotoxicity associated with prolonged use of pyrazinamide-containing multidrug regimens. However, reducing the duration of the treatment with pyrazinamide to 3 months or less was associated with worse treatment outcomes, at least in Hr-TB regimens without a fluoroquinolone. Furthermore, the use of streptomycin in these regimens was associated with no significant added benefit. The use of streptomycin and other injectable agents has also been associated with increased serious adverse events (SAEs) *(20–22)*. On this basis, the GDG agreed that current data supported the use of the (H)REZ–levofloxacin regimen without streptomycin or any other injectable agent in Hr-TB cases, unless there is a compelling reason to do so (e.g. certain forms of polydrug resistance).

The GDG also noted that patients were likely to place a high value on a 6-month regimen, the likelihood of a relapse-free successful outcome and, especially, the implementation of a regimen without the use of injectable agents. GDG members agreed that the use of the 6(H)REZ regimen would probably increase health equity, given that the cost of the regimen components is relatively low (compared to the recommended regimens for MDR/RR-TB) as well as the increased probability of cure in a substantial number of patients. In addition, potential barriers to regimen administration are curtailed with the exclusion of streptomycin and other injectable agents.

Although patient costs were not factored in during the analysis, the GDG agreed that improving diagnostic capacity to detect isoniazid resistance would be beneficial. A modelling analysis performed for the 2011 update of the WHO *Guidelines for the programmatic management of drug-resistant tuberculosis* estimated that DST in all patients before treatment using a rapid test that detects resistance to isoniazid and rifampicin was the best strategy for averting deaths and preventing acquired MDR-TB *(23)*. This modelling work also showed that rapid testing for resistance to both isoniazid and rifampicin at the time of diagnosis was the most cost-effective testing strategy for any patient group or setting, even at very low levels of resistance among TB patients (MDR-TB in >1% and isoniazid resistance [other than MDR-TB] in >2%).

In general, the GDG considered that the use of the 6(H)REZ–levofloxacin regimen would be feasible in most DR-TB treatment settings. In addition, the use of a regimen based on medicines that are fully administered orally may increase feasibility. Altogether, based on present evidence, when discussing the balance between benefits and harms, preferences and values for patients and other end-users, the GDG reached overall agreement on the beneficial effect that the Hr-TB regimen may have, should the regimen be used in conformity with these policy recommendations. Although there was no clear evidence to suggest that the addition of isoniazid would add benefit to this regimen, the 4-drug (H)REZ fixed-dose combination (FDC) may be more convenient for the patient and the health service because it obviates the need to use single drugs.

Consistent with the overall framework for the management and care of patients diagnosed with DR-TB, careful selection of patients is a fundamental principle. Ahead of starting the (H)REZ–levofloxacin regimen, it is essential that resistance to rifampicin be excluded by WHO-recommended genotypic or phenotypic methods *(24,25)*. Preferably, resistance to fluoroquinolones, and if possible to pyrazinamide, should be similarly excluded prior to treatment in order to help avert the acquisition of additional drug resistance. (*See also* Implementation considerations in this Section.)

Empirical treatment of Hr-TB is generally not advised. In cases where a diagnosis of Hr-TB is strongly presumed (e.g. close contacts of Hr-TB cases with active TB but without laboratory confirmation of Hr-TB), (H)REZ–levofloxacin may be introduced pending laboratory confirmation of isoniazid resistance, so long as rifampicin resistance has been reliably excluded. Should DST results eventually indicate susceptibility to isoniazid, levofloxacin is stopped and the patient completes a 2HREZ/4HR regimen. For other patients, in whom Hr-TB is detected after the start of treatment with the 2HREZ/4HR regimen, the (H)REZ component drugs are continued (or pyrazinamide and ethambutol are reintroduced) and levofloxacin added once rifampicin resistance has been excluded.

The duration of an (H)REZ–levofloxacin regimen is usually determined by the need to complete 6 months of a levofloxacin-containing regimen. Thus, in cases where the diagnosis of Hr-TB is made after first-line TB treatment has already been initiated, the patient may receive more than 6 months of (H)REZ by the end of treatment. When the confirmation of isoniazid resistance arrives late into treatment with a 2HRZE/4HR regimen (e.g. 5 months after start during the continuation phase), the clinician would need to decide, based on an assessment of the patient's condition, whether a 6-month course of (H)REZ–levofloxacin needs to be started at that point or not.

The addition of levofloxacin to (H)REZ is recommended in all patients with Hr-TB, with the exception of the following: (i) in cases where resistance to rifampicin cannot be excluded; (ii) known or suspected resistance to levofloxacin; (iii) known intolerance to fluoroquinolones; (iv) known or suspected risk for prolonged QTc interval; and (v) pregnancy or during breastfeeding (not an absolute contraindication). In Hr-TB cases in whom a fluoroquinolone cannot be used, the patient may still be treated with 6(H)REZ.

When additional resistance (especially to pyrazinamide) is suspected or confirmed, appropriate treatment regimens will have to be designed individually. The data reviewed for this guideline could not provide separate evidence-based recommendations for such cases.

Where possible, isoniazid resistance testing should also include information on the specific mutations associated with resistance to isoniazid (*kat*G or *inh*A). In addition, knowledge about overall host acetylator[13] status at country or regional level will be useful, given that these may have implications for regimen design *(26)*.

High-throughput diagnostic platforms are in development (as an alternative to line probe assay [LPA]), which can simultaneously detect TB, and resistance to rifampicin and isoniazid. Evaluation studies of these diagnostics are under way.

Subgroup considerations

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

Patients with extensive disease. Although the IPD analysis did not provide evidence for duration of treatment extension, the prolongation of the 6(H)REZ–levofloxacin regimen to more than 6 months could be considered on an individual basis for patients with extensive disease, as determined by the presence of cavitary disease and persistence of bacteriologically positive sputum at or after month 3

[13] Decreased efficacy and toxicity of isoniazid has been related to its increased metabolism (acetylation) in certain individuals, as determined by mutations in the *N*-acetyltransferase type 2 (*NAT2*) gene.

(by culture or microscopy) *(27)*. Prolongation of treatment may increase the risk of AEs in some cases (*see also* Monitoring and evaluation in this Section).

HIV-positive individuals. The effect of longer-duration TB treatment among HIV-positive patients with and without antiretroviral therapy (ART) has been studied among patients with drug-susceptible TB *(28)*. In these cases, relapse has been reported to be 2.4 times higher in HIV-infected patients who were not on ART and who received 6 months of treatment as compared to patients in whom treatment was prolonged up to 9 months. In patients with drug-susceptible TB initiated on ART, no significant beneficial effect from prolonging rifampicin-containing regimens for over 6 months has been observed *(29)*. In the current analysis, only a limited number of patients received ART; nonetheless, in TB patients with HIV coinfection, the first priority is to ensure that they are started on ART within 8 weeks of TB treatment initiation (regardless of CD4 count), in accordance with WHO guidelines *(30)*. The 6-month (H)REZ–levofloxacin regimen is therefore recommended in HIV-positive patients.

Extrapulmonary disease. No data were available for patients with exclusive extrapulmonary Hr-TB. The regimen composition proposed is likely to be effective even in these patients. However, the treatment of patients with extrapulmonary TB should be designed in close consultation with appropriate specialists, such as infectious disease physicians and neurologists, to decide upon individual variations in treatment duration and supportive care as needed.

Implementation considerations

Case scenarios. The implementation of these recommendations requires that the (H)REZ–levofloxacin regimen is administered only in patients in whom resistance to isoniazid is confirmed and resistance to rifampicin has been excluded. Preferably, testing for resistance to fluoroquinolones, and if possible to pyrazinamide, is also done ahead of starting treatment. It is envisaged that the treatment regimen for Hr-TB would apply in the following situations:

Hr-TB is confirmed before TB treatment is started. Treatment with (H)REZ–levofloxacin is started immediately. If the diagnosis is strongly presumed (e.g. close contacts of a confirmed Hr-TB source case) but results of DST are still pending, the regimen may be introduced. Should the DST results taken at start eventually show susceptibility to isoniazid, then levofloxacin is stopped and the patient continues treatment in order to complete a 2HREZ/4HR regimen.

Hr-TB is confirmed after the start of treatment with the 2HREZ/4HR regimen. This includes patients who had undiagnosed isoniazid resistance at the start or who developed isoniazid resistance later while on treatment with a first-line regimen. In such cases, rapid molecular testing for rifampicin resistance must be done (or repeated). Once rifampicin resistance is excluded, a full 6-month course of (H)REZ–levofloxacin is given. The duration is driven by the need to give levofloxacin for 6 months, which usually implies that the companion first-line medicines are taken for longer than this.

If rifampicin resistance is detected, the patient needs to be started on a recommended MDR-TB treatment regimen (*see* the next sections of these guidelines).

Diagnostic capabilities. The overall aim of TB treatment is to achieve cure without relapse in all patients, interrupting *M. tuberculosis* transmission and preventing the acquisition (or amplification) of additional drug resistance. Globally, Hr-TB is more prevalent than MDR-TB. Efforts need to be made by all countries to move towards universal testing of both isoniazid and rifampicin resistance at the start of TB treatment and to ensure careful selection of patients eligible for the (H)REZ–levofloxacin regimen.[14] The minimum diagnostic capacity to appropriately implement these recommendations requires rapid molecular testing for rifampicin resistance prior to the start of treatment with the Hr-TB regimen, and preferably, that fluoroquinolone resistance is ruled out by WHO-recommended tests.

[14] The association between previous TB treatment history and Hr-TB is less strong than that of MDR-TB. As a result, previous TB treatment is less reliable as a proxy for Hr-TB and therefore, a laboratory diagnosis is important.

Rapid molecular tests such as Xpert MTB/RIF and LPAs are preferred to guide patient selection for the (H)REZ–levofloxacin regimen.

DR-TB surveillance indicates that fluoroquinolone resistance among patients with rifampicin-susceptible TB is generally low worldwide *(31)*. However, national data on the prevalence of fluoroquinolone resistance – including targeted or whole-genome sequencing to detect specific mutations associated with resistance to fluoroquinolones *(32)* – could help guide testing policies when the Hr-TB treatment recommendations are implemented in countries.

When additional resistance (e.g. to both fluoroquinolones and pyrazinamide) is suspected or confirmed, treatment regimens may have to be designed individually with other second-line TB medicines. The current review could not provide further evidence on effective regimens in patients with polyresistant disease.

Support and close monitoring of patients are needed in order to maximize treatment adherence and enable early detection of patients who are not responding to treatment (e.g. those with persistent sputum culture or smear positivity). Repeat DST for rifampicin and the fluoroquinolones, preferably with Xpert MTB/RIF or LPA, is indicated in the presence of non-response. Documented acquisition of resistance to rifampicin or a fluoroquinolone while on the Hr-TB treatment regimen should alert the clinician to reviewing the entire clinical and microbiological status of the patient and change the regimen accordingly.

Levofloxacin is proposed as the fluoroquinolone of first choice in the Hr-TB treatment regimen for a number of reasons. Firstly, this medicine has a better-characterized safety profile compared to other fluoroquinolones and was the one most frequently used in the studies reviewed for this guidance. Secondly, levofloxacin has fewer known drug interactions with other medications as compared to moxifloxacin. For example, while plasma peak concentration and exposure to moxifloxacin decrease significantly when combined with rifampicin *(33)*, the same effect has not been reported for levofloxacin, which is attributed to the property of levofloxacin to undergo limited metabolism in humans and to be excreted unchanged in the urine *(34)*. Additionally, although it may interfere with lamivudine clearance, unlike moxifloxacin, there are no contraindications for its use with other antiretroviral agents *(35)*.

The addition of levofloxacin to (H)REZ is recommended in patients with Hr-TB, with the exception of the following:

i. in cases where resistance to rifampicin cannot be excluded (i.e. unknown susceptibility to rifampicin; indeterminate/error results on Xpert MTB/RIF);
ii. known or suspected resistance to levofloxacin;
iii. known intolerance to fluoroquinolones;
iv. known or suspected risk for prolonged QT-interval;[15]
v. if possible in pregnancy or during breastfeeding (not an absolute contraindication).

When the confirmation of isoniazid resistance arrives late (e.g. 5 months into a 2HREZ/4HR regimen), a decision to start 6 months of (H)REZ–levofloxacin at that point depends upon the patient's clinical condition and microbiological status.

If levofloxacin cannot be used because of toxicity or resistance, the patient may be given 6(H)REZ as an alternative. Based on the results of the evidence review conducted in preparation of these guidelines, it is not advised to replace levofloxacin with an injectable agent. The evidence review could not inform on the effect of other second-line TB medicines on treatment effectiveness.

[15] Baseline-corrected QTc. Prolongation of the QT interval and isolated cases of *torsade de pointes* have been reported. Avoid use in patients with known prolongation, those with hypokalaemia, and with other drugs that prolong the QT interval.

Addition of isoniazid. There was no clear evidence showing that the addition of isoniazid adds benefit or harm to patients. For patient convenience and ease of administration, the 4-drug HREZ FDCs[16] may be used to deliver the Hr-TB treatment regimen alongside levofloxacin.

Although the use of high-dose isoniazid (10–15 mg/kg/day in adults) was not evaluated in this review due to insufficiency of data, the GDG discussed the effect of increasing isoniazid dosing beyond that provided in weight-banded FDCs, depending on the type of molecular mutations identified. In-vitro evidence seems to suggest that when specific *inh*A mutations are detected (and in the absence of any *kat*G mutations), increasing the dose of isoniazid is likely to be effective; thus, additional isoniazid to a maximum dose of up to 15 mg/kg per day could be considered. In the case of *kat*G mutations, which more commonly confer higher-level resistance, the use of isoniazid even at a higher dose is less likely to be effective *(36)*.[17]

Dosage. Although the IPD analysis did not provide evidence to address the frequency of dosing, intermittent or divided dosing of the 6(H)REZ–levofloxacin regimen is to be avoided *(29,37,38)*. In the absence of full information about optimal drug doses, a weight-band dosing scheme for levofloxacin is recommended.[18]

Drug–drug interactions. Levofloxacin may potentially interfere with lamivudine clearance (increasing the levels of lamivudine), but is not contraindicated with other antiretroviral agents and no drug dosing adjustments are needed *(35)*. Coadministration of levofloxacin with oral divalent cation-containing compounds (such as antacids) may impair its absorption and should be avoided *(7)*. Restriction of concomitant use of milk products is not necessary.

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

Cost. Cost–effectiveness analysis was not performed for this review. Table 1.1 presents approximate prices for a full course of medicines with the different regimens in adults based on the cost of products available from the Global Drug Facility (GDF) *(39)*. Use of FDCs, even for part of the regimen, reduces costs. Medicines needed for a 6HREZ–levofloxacin treatment regimen cost about three times as much as a 2HREZ/4HR regimen when using the HREZ FDC. The treatment of Hr-TB according to these guidelines is not expected to increase operational costs significantly.

Table 1.1. Illustrative costs of regimens used to treat Hr-TB compared to the 6-month first-line TB regimen (price of medicines alone)*

Regimen	Approximate cost of medicines alone, US$ *
2HREZ/4HR	31.9 (22.36)
6HREZ	104.4 (47.8)
6REZ–Lfx	122.26
6HREZ–Lfx	125.8 (68.7)
9HREZ–Lfx	186.8 (102.5)

HREZ: isoniazid, rifampicin, ethambutol, pyrazinamide; Lfx: levofloxacin

Note. * Data source: Global Drug Facility *(39)*. Prices as of 16 March 2018 for a 60 kg adult. Values in brackets reflect the price when the regimen is given in part or whole as an FDC.

[16] Of note, although most countries currently procure the 4-drug FDC via the Stop TB Partnership's Global Drug Facility (GDF), in settings where only the 3-drug combination FDC (HRZ) is available, ethambutol has to be administered separately.

[17] An isolated *kat*G or *inh*A mutation can correspond to variable minimum inhibitory concentration (MIC) levels. This implies that *inh*A mutations do not always indicate low-level isoniazid resistance or that *kat*G mutations are necessarily correlated with high-level isoniazid resistance. The presence of both mutations is usually an indication of high-level resistance *(36)*.

[18] Studies included in this IPD analysis involved the use of regimens containing levofloxacin (usually at a dose of 750–1000 mg/day), moxifloxacin (400 mg/day) or gatifloxacin (400 mg/day), as well as early-generation fluoroquinolones (ciprofloxacin and ofloxacin), which are no longer recommended for the treatment of DR-TB. Gatifloxacin is currently unavailable in quality-assured formulations and ciprofloxacin and ofloxacin are no longer recommended for use in DR-TB care.

Adherence. Although the IPD analysis contained limited data on treatment adherence strategies used (i.e. directly-observed treatment [DOT]; self-administered therapy [SAT]), improved treatment success rates appeared to be associated with increased patient support, including medication adherence support (for example, by means of digital technologies) or other means as recommended by WHO *(29)*. In contrast to regimens for drug-susceptible and MDR-TB, the recommended Hr-TB treatment regimen does not have an intensive and a continuation phase, which simplifies the delivery and monitoring of treatment.

Monitoring and evaluation

Patients who receive the (H)REZ–levofloxacin regimen need to be monitored during treatment using schedules of clinical and laboratory testing. The definitions to use when assigning outcomes are the same ones in use for drug-susceptible TB *(12)*. Signs of non-response or treatment failure should be followed up with DST for rifampicin resistance and, if possible, for fluoroquinolones and pyrazinamide. In order to limit the risk of acquisition of additional resistance, the addition of single TB medicines should be avoided in patients who remain smear- or culture-positive after month 2 of treatment, who do not show a favourable clinical response and in those without recent DST results.

As with any other TB medicine and regimen, safety precautions are required to ensure the rapid identification and proper management of any SAE. Close clinical monitoring is essential for all patients receiving this regimen, particularly liver function tests, given the hepatotoxic potential of prolonged pyrazinamide use. If possible, all patients should be tested each month for aspartate aminotransferase levels (AST or SGOT). If resources are not available to monitor all patients on the Hr-TB treatment regimen, monthly monitoring of patients at high risk, such as patients coinfected with viral hepatitis or with a history of heavy alcohol use, is strongly advised. Additionally, in order to prevent and manage the potential toxic effects of ethambutol in children (e.g. retrobulbar neuritis), it is necessary to adhere to the correct doses recommended for paediatric populations. Early signs of ethambutol toxicity can be tested in older children through red–green colour discrimination. Monitoring for retrobulbar neuritis can be sought early when appropriate *(40)*.

Section 2. The composition of longer MDR-TB regimens

Recommendations

2.1. In MDR/RR-TB patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of treatment after bedaquiline is stopped.[19] If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it (conditional recommendation, very low certainty in the estimates of effect).

2.2. Kanamycin and capreomycin are not to be included in the treatment of MDR/RR-TB patients on longer regimens (conditional recommendation, very low certainty in the estimates of effect).

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

2.4. Bedaquiline should be included in longer MDR-TB regimens for patients aged 18 years or more (strong recommendation, moderate certainty in the estimates of effect). Bedaquiline may also be

[19] Group A = levofloxacin/moxifloxacin, bedaquiline, linezolid; Group B = clofazimine, cycloserine/terizidone; Group C = ethambutol, delamanid, pyrazinamide, imipenem–cilastatin, meropenem, amikacin (streptomycin), ethionamide/prothionamide, *p*-aminosalicylic acid (*see also* Table 2.1).

included in longer MDR-TB regimens for patients aged 6–17 years (conditional recommendation, very low certainty in the estimates of effect).

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

2.6. Clofazimine and cycloserine or terizidone may be included in the treatment of MDR/RR-TB patients on longer regimens (conditional recommendation, very low certainty in the estimates of effect).

2.7. Ethambutol may be included in the treatment of MDR/RR-TB patients on longer regimens (conditional recommendation, very low certainty in the estimates of effect).

2.8. Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens (conditional recommendation, moderate certainty in the estimates of effect).

2.9. Pyrazinamide may be included in the treatment of MDR/RR-TB patients on longer regimens (conditional recommendation, very low certainty in the estimates of effect).

2.10. Imipenem–cilastatin or meropenem may be included in the treatment of MDR/RR-TB patients on longer regimens (conditional recommendation, very low certainty in the estimates of effect).[20]

2.11. Amikacin may be included in the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions (conditional recommendation, very low certainty in the estimates of effect).

2.12. Ethionamide or prothionamide may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used or if better options to compose a regimen are not possible (conditional recommendation against use, very low certainty in the estimates of effect).

2.13. *p*-aminosalicylic acid may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used or if better options to compose a regimen are not possible (conditional recommendation against use, very low certainty in the estimates of effect).

2.14. Clavulanic acid should not be included in the treatment of MDR/RR-TB patients on longer regimens (strong recommendation against use, low certainty in the estimates of effect).[20]

Justification and evidence

This section refers to MDR-TB treatment regimens that are of longer duration than the 9–12-month shorter MDR-TB regimen described in Section 4. The recommendations in this section address two PICO questions (*see* Annex 1).

PICO question 2 (MDR/RR-TB, 2018). In patients with MDR/RR-TB, which individual agents are more likely to improve outcomes when forming part of a longer regimen conforming to WHO guidelines?[21]

PICO question 3 (MDR/RR-TB, 2018). In patients with MDR/RR-TB on longer regimens composed in accordance with WHO guidelines, are outcomes safely improved with fewer or more than five effective medicines in the intensive phase?

Recommendations for the design of longer MDR-TB regimens have been issued by WHO for a number of years and have been implemented in many countries worldwide *(2,6,41)*. The recommendations in

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

[21] Given that very few trials or other studies have made head-to-head comparisons of MDR-TB medicines at different dosage regimens, it is not expected that guidance on dosage adjustment will depend on the systematic review findings.

this section cover all forms of MDR/RR-TB, and include treatment of patients with strains susceptible to isoniazid, or with additional resistance to isoniazid (i.e. MDR-TB), or resistance to other medicines from the first-line group (polyresistant) or from the second-line group (e.g. extensively drug-resistant [XDR]-TB). WHO recommends that all patients with TB – children or adults – diagnosed with strains shown to be resistant to rifampicin be placed on an MDR-TB treatment regimen *(6)*. The conditional recommendation for the composition of longer MDR-TB treatment regimens featured in the previous guidelines of 2016 proposed the inclusion of at least five effective medicines during the intensive phase, composed of pyrazinamide and four second-line TB medicines (*see* Table 2.1) *(6)*. The addition of high-dose isoniazid and/or ethambutol could be considered to further strengthen the regimen. Given the availability and increased use of the new medicines bedaquiline and delamanid in recent years, significant reduction in the prices of moxifloxacin and linezolid making them more accessible, and changes to the recommended composition and duration of longer regimens compared to previous years, it was deemed timely to review the regimen composition in the current update.

The likelihood of treatment success in MDR-TB patients on longer regimens depends upon patient-level/strain factors (including severity of disease, resistance patterns and comorbidities), as well as access to health care (e.g. regimens with sufficient effective agents, medications of good quality, management of AEs and other patient support). Longer MDR-TB regimens with sufficient effective agents are known to increase the likelihood of cure and lower the risk of death in adults and children *(42–45)*. The composition of longer regimens is governed by the selection of individual medicines considered to be effective and also by a need to combine sufficient medicines to maximize the likelihood of relapse-free cure without increasing toxicity. Regimens may be of standardized (fixed) composition or may be individualized to the patient's needs. Longer regimens usually last 20 months or more; recommendations on their duration are discussed in Section 3.

Ahead of the GDG discussion, WHO made a public call for individual MDR/RR-TB patient data complete with results of treatment *(46)*. Meta-analysis of individual patient data (IPD-MA) in adults and children treated with longer MDR-TB regimens allows the study of useful correlates of outcome, including the regimen composition *(42–44)*. The evidence base for the effectiveness of many of the medicines used in MDR-TB regimens relies heavily on observational studies with only a few having been studied under randomized controlled conditions. As a result, the overall certainty in the evidence is often graded low or very low. The sources of data used by the GDG to address the two PICO questions in this Section are summarized below (for more information about the methods used and analysis plans, please *see* online Annexes 6 and 9).

PICO question 2 (MDR/RR-TB, 2018) (choice of individual medicines). First, to analyse treatment success, treatment failure, relapse and death for the individual medicines in longer regimens, the main 2018 IPD-MA was used, with 13 104 records from 53 studies in 40 countries. The 2018 IPD contains new datasets from recent years in several countries, including a large dataset from South Africa with many patients treated with bedaquiline-containing regimens. Second, to analyse AEs resulting in permanent discontinuation of individual medicines in longer regimens, a subset of 5450 records from 17 studies in the IPD was used, supplemented with additional information from 10 other studies that only reported AEs for either bedaquiline (N=130), linezolid (N=508) or carbapenems (N=139).

Separate from these data, the GDG also assessed unpublished results from Phase III Trial 213 of delamanid *(47)*; and safety and pharmacological exposure data from unpublished paediatric studies of bedaquiline (Phase II TMC207-C211 and Phase I/II IMPAACT P1108) and delamanid (Phase I 242-12-245, Phase I 242-12-232, Phase II 242-07-204, Phase II 242-12-233) (*see* online Annex 9). In addition, a literature search was made for studies reporting outcomes of patients treated with agents other than those included in the 2016 guidelines: e.g. perchlozone, interferon gamma and sutezolid.

PICO question 3 (MDR/RR-TB, 2018) (number of agents likely to be effective). To analyse treatment success, failure, relapse and death for the optimal number of medicines to be included in longer regimens, the data were derived from a subset of 8957 patients in 47 studies included in the IPD used for PICO question 2 (MDR/RR-TB, 2018) above. Of these, 3570 patients in 16 studies had information

on the start and end dates for individual medicines in which DST was reported, and 5387 patients in 31 studies had information on individual medicines used in both the intensive and continuation phases of treatment, as well as DST results. As this question focused on the number of agents in the intensive phase, patients who did not receive an injectable agent or in whom an initial intensive phase was not defined were excluded (*N*=476). Patients who were designated "cured" or "treatment completed" but received less than 18 months of treatment – the minimum duration for longer regimens recommended by WHO in the past – were also excluded (*N*=346). For PICO question 3 (MDR/RR-TB, 2018), in cases where DST results were available, a medicine was considered effective if results showed susceptibility, and not counted as effective if results showed resistance. Where DST results were missing, two situations existed: (i) if the prevalence of resistance to that medicine was <10% in the same population (from the same country or study site if within one country, or overall at all sites if local data were not available) then the medicine was counted as effective. This applied to the following agents: cycloserine or terizidone, linezolid, clofazimine, bedaquiline, the carbapenems and delamanid. (ii) If the prevalence of resistance to that medicine was ≥10% in the same population (from the same country or study site if within one country, or overall at all sites if local data were not available) then imputed DST results were used if DST was missing to determine effectiveness. If the imputed DST result showed susceptibility, then the medicine was counted as effective; if the imputed DST result showed resistance, then the medicine was not counted as effective. This applied to the following agents: pyrazinamide, ethambutol, second-line injectable agents, fluoroquinolones, *p*-aminosalicylic acid, ethionamide or prothionamide. The following were not included when counting the number of medicines likely to be effective (regardless of any DST result that may have been available): isoniazid (including high-dose isoniazid), rifampicin, rifabutin, thioacetazone, amoxicillin–clavulanate or macrolide antibiotics.

When reviewing evidence and formulating the recommendations, the GDG considered the need for the guidelines to cater also to key subgroups that were not well represented in the 2018 IPD-MA, notably children. Where data on children were unavailable, evidence from adults was extrapolated to children. The best available evidence was used to construct recommendations for a regimen that has high relapse-free cure rates, reduces the likelihood of death and emergence of additional resistance while minimizing harms. The GDG was aware of the paediatric MDR-TB IPD-MA on 975 clinically diagnosed or bacteriologically confirmed pulmonary or extrapulmonary TB cases that was used for the 2016 treatment recommendations *(44)*. Children with XDR-TB were excluded from that analysis (*n*=36) as their treatment regimens were not considered to be comparable with those of other MDR-TB patients and their numbers were too low to be analysed independently. No randomized controlled trials (RCTs) were included (or known to exist) at the time this dataset was compiled and the overall certainty in the estimates of effect based on this evidence was judged to be very low.

Remarks

The GDG assessed the individual contribution to patient outcomes of medicines used in longer MDR-TB regimens using primarily the estimates of effect from the 2018 IPD-MA and Trial 213 (delamanid) for PICO question 2 (MDR/RR-TB, 2018; *see* online Annexes 7 and 8 for the respective GRADE [Grading of Recommendations Assessment, Development and Evaluation] summaries of evidence for each medicine as well as the evidence-to-decision framework). Following a thorough assessment of the relative benefits and harms, recommendations were made for each medicine and they were classified into three groups (*see* Tables 2.1–2.3).

- **Group A**: fluoroquinolones (levofloxacin and moxifloxacin), bedaquiline and linezolid were considered highly effective and strongly recommended for inclusion in all regimens unless contraindicated.
- **Group B**: clofazimine and cycloserine or terizidone were conditionally recommended as agents of second choice.
- **Group C**: included all other medicines that can be used when a regimen cannot be composed with Group A and B agents. The medicines in Group C are ranked by the relative balance of benefit to harm usually expected of each.

Other medicines that are not included in Groups A–C are:

- kanamycin and capreomycin, which were associated with poorer outcomes when used and are therefore no longer recommended for use in MDR-TB regimens;
- gatifloxacin and high-dose isoniazid were used in very few patients and thioacetazone was not used at all. Quality-assured preparations of gatifloxacin are not currently available following its withdrawal from the market due to concerns about dysglycaemias. Thioacetazone is unlikely to have a role in contemporary longer regimens and is not currently available in a quality-assured formulation. High-dose isoniazid may have a role in patients with confirmed susceptibility to isoniazid (*see* under Subgroup considerations later in this chapter);
- clavulanic acid should be included in MDR/RR-TB regimens only as a companion agent to the carbapenems (imipenem–cilastatin and meropenem). When used in this way, it should be given with every dose of carbapenem and should not be counted as an additional effective TB agent.

No recommendation on perchlozone, interferon gamma or sutezolid was possible owing to the absence of final patient treatment outcome data from appropriate patient studies.

Regarding the use of bedaquiline in patients younger than 18 years, and considering that exposure–response (efficacy) profiles can be extrapolated from adults to children, the GDG concluded that the doses evaluated in children and adolescents in two trials (Phase II trial TMC207-C211 and Phase I/II IMPAACT P1108; *see* online Annex 9) do not appear to result in exposures that would put patients aged 6–17 years at increased risk for treatment failure. The safety risk in children down to 6 years of age enrolled in the trials – who were all HIV negative and with limited exposure to other QT-interval-prolonging medications – did not appear to exceed that of adults. The variability present in the limited sample size precluded a comment on exposure–response (safety). The GDG also concluded that the risk–benefit considerations for the use of bedaquiline in patients aged 6–17 years are similar to those considered for adults but stressed the need for more data before considering an upgrade of this recommendation to a strong one.

With respect to the use of delamanid in children younger than 6 years, the GDG decided that on the basis of findings in adults and on the pharmacological and safety data reviewed, extrapolations on efficacy and safety should be restricted to children aged 3–5 years but not to children younger than 3 years (*see* online Annex 9). Exposure profiles in children 3–5 years of age were comparable to adults and no higher than in children 6 years of age and older, for whom past GDGs convened by WHO had already recommended the use of delamanid *(4,5)*. Based on the laboratory and cardiac data provided, no safety signals distinct from those reported in adults were observed in children aged 3–5 years. The GDG nonetheless had concerns about the feasibility of administering the correct dose to children aged 3–5 years, given that the special formulation used in the trial (25 mg) would not be available in the foreseeable future and only the adult tablet is available (50 mg), which is not bioequivalent and presents challenges to manipulating its contents without compromising its effectiveness.

Table 2.1. Grouping of medicines recommended for use in longer MDR-TB regimens[1]

Groups & steps	Medicine	
Group A: **Include all three medicines**	levofloxacin *OR* moxifloxacin	Lfx Mfx
	bedaquiline[2,3]	Bdq
	linezolid[4]	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[3,5]	Dlm
	pyrazinamide[6]	Z
	imipenem–cilastatin *OR* meropenem[7]	Ipm–Cln Mpm
	amikacin (*OR* streptomycin)[8]	Am (S)
	ethionamide *OR* prothionamide[9]	Eto Pto
	p-aminosalicylic acid[9]	PAS

1. This table is intended to guide the design of individualized, longer MDR-TB regimens (the composition of the recommended shorter MDR-TB regimen is largely standardized; *see* Section 4). Medicines in Group C are ranked by decreasing order of usual preference for use subject to other considerations. The 2018 IPD-MA for longer regimens included no patients on thioacetazone and too few patients on gatifloxacin and high-dose isoniazid for a meaningful analysis. No recommendation on perchlozone, interferon gamma or sutezolid was possible owing to the absence of final patient treatment outcome data from appropriate studies (*see* online Annex 9).
2. Evidence on the safety and effectiveness of bedaquiline use beyond 6 months and below the age of 6 years was insufficient for review. Use of bedaquiline beyond these limits should follow best practices in "off-label" use *(48)*.
3. Evidence on the concurrent use of bedaquiline and delamanid was insufficient for review.
4. Use of linezolid for at least 6 months was shown to increase effectiveness, although toxicity may limit use. The analysis suggested that using linezolid for the whole duration of treatment would optimize its effect (about 70% of patients on linezolid with data received it for more than 6 months and 30% for 18 months or the whole duration). No patient predictors for early cessation of linezolid could be inferred from the IPD subanalysis.
5. Evidence on the safety and effectiveness of delamanid beyond 6 months and below the age of 3 years was insufficient for review. Use of delamanid beyond these limits should follow best practices in "off-label" use *(48)*.
6. Pyrazinamide is counted as an effective agent only when DST results confirm susceptibility.
7. Every dose of imipenem–cilastatin and meropenem is administered with clavulanic acid, which is available only in formulations combined with amoxicillin. Amoxicillin–clavulanic acid is not counted as an additional effective TB agent and should not be used without imipenem–cilastatin or meropenem.
8. Amikacin and streptomycin are to be considered only if DST results confirm susceptibility and high-quality audiometry 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 (resistance to streptomycin is not detectable with second-line molecular LPAs and phenotypic DST is required). Kanamycin and capreomycin are no longer recommended for use in MDR-TB regimens.
9. These agents showed effectiveness only in regimens without bedaquiline, linezolid, clofazimine or delamanid, and are thus proposed only when other options to compose a regimen are not possible.

Table 2.2. Relative risk for (i) treatment failure or relapse and (ii) death (versus treatment success), 2018 IPD-MA for longer MDR-TB regimens and delamanid Trial 213 (intent-to-treat population)[22]

Medicine		Treatment failure or relapse versus treatment success		Death versus treatment success	
		Number treated	Adjusted odds ratio (95% confidence limits)	Number treated	Adjusted odds ratio (95% confidence limits)
A	Levofloxacin *OR* moxifloxacin	3 143	0.3 (0.1–0.5)	3 551	0.2 (0.1–0.3)
	Bedaquiline	1 391	0.3 (0.2–0.4)	1 480	0.2 (0.2–0.3)
	Linezolid	1 216	0.3 (0.2–0.5)	1 286	0.3 (0.2–0.3)
B	Clofazimine	991	0.3 (0.2–0.5)	1 096	0.4 (0.3–0.6)
	Cycloserine *OR* terizidone	5 483	0.6 (0.4–0.9)	6 160	0.6 (0.5–0.8)
C	Ethambutol	1 163	0.4 (0.1–1.0)	1 245	0.5 (0.1–1.7)
	Delamanid	289	1.1 (0.4–2.8)*	290	1.2 (0.5–3.0)*
	Pyrazinamide	1 248	2.7 (0.7–10.9)	1 272	1.2 (0.1–15.7)
	Imipenem–cilastatin *OR* meropenem	206	0.4 (0.2–0.7)	204	0.2 (0.1–0.5)
	Amikacin	635	0.3 (0.1–0.8)	727	0.7 (0.4–1.2)
	Streptomycin	226	0.5 (0.1–2.1)	238	0.1 (0.0–0.4)
	Ethionamide *OR* prothionamide	2 582	1.6 (0.5–5.5)	2 750	2.0 (0.8–5.3)
	p-aminosalicylic acid	1 564	3.1 (1.1–8.9)	1 609	1.0 (0.6–1.6)
Other medicines	Kanamycin	2 946	1.9 (1.0–3.4)	3 269	1.1 (0.5–2.1)
	Capreomycin	777	2.0 (1.1–3.5)	826	1.4 (0.7–2.8)
	Amoxicillin–clavulanic acid	492	1.7 (1.0–3.0)	534	2.2 (1.3–3.6)

Note: * The values are the unadjusted risk ratios as defined by the study investigators of Trial 213 by month 24.

Regarding PICO question 3 (MDR/RR-TB, 2018), the analysis showed that in contemporary longer MDR-TB treatment regimens, the risk of treatment failure, relapse and death was comparable when the treatment started with four, five or six medicines likely to be effective. The analysis also showed that patients who took three agents in the continuation phase – the situation expected when starting with four agents and stopping the injectable agent at the end of the intensive phase – fared no worse than those who took four agents in the continuation phase.

[22] *See also* text, Table 2.3 and online Annexes 7–9 for more detail on how the estimates were derived and the additional factors considered by the GDG when reclassifying medicines for use in longer MDR-TB regimens as shown in Table 2.1.

Given that the likelihood of adverse events, drug–drug interactions and pill burden increases with the number of agents in a regimen, it would be desirable to give patients the minimum number of medicines necessary to obtain comparable levels of relapse-free cure. When deciding upon the minimum number of agents to recommend, the GDG considered also analyses that included injectable agents in the regimens, while fully cognizant that future longer regimens are expected to be increasingly injectable-free. Moreover, it was important to provide for situations in which more than one medicine is stopped after the first months either because of its indication for use – bedaquiline and delamanid would normally be stopped 6 months after start – or else because of tolerability (particularly linezolid; Table 2.3), meaning that for most of its duration, the regimen would contain two key agents less than at the start. However, the 2018 IPD included experience from over 300 patients who were treated with linezolid for at least 1 month, mostly at a dose of 600 mg/day, with information on duration of use. About 30% only received linezolid for 1–6 months, but over 30% received it for more than 18 months and these patients had the lowest frequency of treatment failure, loss to follow up and death. A plot of linezolid duration and treatment failure suggests that the optimal duration of use would be around 20 months, corresponding to the usual total duration of a longer MDR-TB regimen (although such an analysis does not account for survivorship bias, meaning that those who complete the full length of treatment are more likely to have a successful outcome, given that deaths and losses to follow up occur earlier). No clear pattern of the type of AE with duration of use could be discerned, although a few cases were reported with optic neuropathy, known to be associated with long-term use of linezolid *(49)*, while haematological toxicity was reported regardless of duration of use.

Table 2.3. Serious adverse events (SAEs) in patients on longer MDR-TB regimens*

Medicine	Absolute risk of SAE	
	Median (%)	95% credible interval
Bedaquiline	2.4	[0.7, 7.6]
Moxifloxacin	2.9	[1.4, 5.6]
Amoxicillin–clavulanic acid	3.0	[1.5, 5.8]
Clofazimine	3.6	[1.3, 8.6]
Ethambutol	4.0	[2.4, 6.8]
Levofloxacin	4.1	[1.9, 8.8]
Streptomycin	4.5	[2.3, 8.8]
Cycloserine/terizidone	7.8	[5.8, 10.9]
Capreomycin	8.4	[5.7, 12.2]
Pyrazinamide	8.8	[5.6, 13.2]
Ethionamide/prothionamide	9.5	[6.5, 14.5]
Amikacin	10.3	[6.6, 17.0]
Kanamycin	10.8	[7.2, 16.1]
p-aminosalicylic acid	14.3	[10.1, 20.7]
Thioacetazone	14.6	[4.9, 37.6]
Linezolid	17.2	[10.1, 27.0]

* From an "arm-based network" meta-analysis of a patient subset from the 2016 IPD for which AEs resulting in permanent discontinuation of a TB medicine (27 studies) or classified as Grade 3–5 (3 studies) were reported. There were insufficient records on delamanid, imipenem–cilastatin and meropenem to estimate risks. Agents that are not in Groups A, B or C are italicized.

In conclusion, the GDG recommended that, where possible, regimens be composed of all three Group A agents and at least one Group B agent, so that treatment starts with at least four medicines likely to be effective and that at least three agents are continued for the remaining duration of treatment after bedaquiline is stopped. If only one or two Group A agents can be used, both Group B agents are included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. In patients in whom two agents from Group A are more likely to be stopped before the end of treatment (e.g. pre-existing comorbidities require that both bedaquiline and linezolid be stopped early because of health risks), then starting with five effective agents rather than four may be advisable. These provisions are expected to apply to most MDR-TB patients, including those with additional resistance to fluoroquinolones or other medicines.

Subgroup considerations

MDR/RR-TB alone or with additional resistance. A longer regimen is more likely to be effective if its composition is guided by reliable information on drug susceptibility. The design of longer regimens for MDR/RR-TB patients with additional resistance (including XDR-TB) follows a similar logic to that used for other MDR-TB patients. Ideally, all MDR-TB patients should be tested for resistance to fluoroquinolones as a minimum before starting MDR-TB treatment. If the shorter regimen or amikacin is being considered in the regimen then rapid testing for second-line injectable agents should be performed. Other tests for resistance to agents like bedaquiline, delamanid, linezolid, pyrazinamide and for mutation patterns commonly associated with resistance to isoniazid and ethionamide/prothionamide may help inform regimen choice (e.g. excluding the shorter regimen) and composition. Currently, there is no approved rapid test for pyrazinamide resistance, and phenotypic DST may require several weeks to produce a reliable result, implying that a decision to include or replace pyrazinamide could delay the start of treatment by several weeks. In many settings, DST for other medicines commonly used for MDR-TB treatment is not usually reliable enough to guide regimen composition. Because of this, other elements may be necessary to determine the likelihood of effectiveness (*see* Implementation considerations). If not already in place, the TB programme should rapidly build the capacity to undertake DST and all efforts should be made to ensure access to approved, rapid molecular tests. Until the capacity for second-line DST – including for bedaquiline, linezolid and clofazimine – becomes available, treatment decisions may need to rely upon the likelihood of resistance to medicines, based on an individual patient's clinical history and surveillance data from the country or region.

RR-TB. A patient – child or adult – in whom isoniazid resistance is absent needs to be treated with a recommended MDR-TB regimen, either a longer MDR-TB regimen to which isoniazid is added, or else a shorter MDR-TB regimen in eligible patients (*see also* Section 4). While high-dose isoniazid is not included in Groups A–C, given the rarity of its use in contemporary longer regimens for adults with MDR/RR-TB, it may still be used in patients with confirmed susceptibility or in the presence of mutations that do not usually confer complete resistance to isoniazid. High-dose isoniazid was shown to be an important component in paediatric regimens in the 2016 WHO guidelines evidence review, based on which its use in adults was extrapolated *(44)*. In this analysis, high-dose isoniazid was associated with treatment success among children with confirmed MDR-TB (aOR 5.9, 95% CL 1.7–20.5, P=0.007).

Children. The 2018 individual patient data of longer regimens was largely composed of adult patients, with only 181 of the 13 104 (1.4%) cases being below 15 years of age. Nonetheless, WHO recommendations on longer MDR-TB regimens apply to children as well as adults. Most medicines that are used in longer regimens have been part of MDR-TB regimens for many years, in similar combinations, for both adults and children. The GDG recommended the use of bedaquiline in children down to 6 years of age and delamanid down to 3 years of age (*see* Remarks earlier in this chapter). Reproducing the delamanid exposure achieved with the special 25 mg tablet tested in the trial in children aged 3–5 years is expected to be challenging, given that this formulation is not bioequivalent with the 50 mg delamanid adult tablet, the only preparation available in the foreseeable future (*see*

background documents for the 2018 guidelines update in Annex 9). There are also concerns that the adult tablet may shatter if attempts are made to split it, and its contents are exceedingly bitter and unpalatable. Further, bioavailability may be altered when the 50 mg tablet is split, crushed or dissolved. Delamanid is susceptible to oxidation and heat, and therefore retaining pill fragments for use at any time other than the time of administration will likely result in the delivery of lower-than-expected active compound and unspecified oxidation byproducts. The avoidance of an injectable-containing regimen is particularly desirable in children, especially those very young and with mild disease, as determined by the absence of malnutrition, serious forms of extrapulmonary disease, cavitation on chest radiography or HIV infection. Hearing loss can have a permanent impact on the acquisition of language and the ability to learn at school, and therefore should amikacin or streptomycin use be resorted to in children, regular audiometry will be critical (the 2018 recommendation is primarily for adults).

Extrapulmonary TB and TB meningitis. The WHO recommendations on longer MDR-TB regimens apply also to patients with extrapulmonary disease. Adjustments may be required depending upon the specific location of the disease. Treatment of MDR/RR-TB meningitis is best guided by DST of the infecting strain and by knowledge of the properties of TB medicines that cross the blood–brain barrier. Levofloxacin and moxifloxacin penetrate the central nervous system (CNS) well *(50)*, as do ethionamide/prothionamide, cycloserine/terizidone, linezolid and imipenem–cilastatin *(51,52)*. Seizures may be more common in children with meningitis treated with imipenem–cilastatin (meropenem is preferred for meningitis cases and in children). High-dose isoniazid and pyrazinamide can also reach therapeutic levels in the cerebrospinal fluid and may be useful if the strains are susceptible. *p*-aminosalicylic acid and ethambutol do not penetrate the CNS well and should not be counted on as effective agents for MDR-TB meningitis. Amikacin and streptomycin penetrate the CNS only in the presence of meningeal inflammation. There are little data on the CNS penetration of clofazimine, bedaquiline or delamanid.

Pregnancy. Amikacin, streptomycin, prothionamide and ethionamide are usually contraindicated during pregnancy. Following the changes made in the 2018 guidelines update, these agents are expected to be used less frequently in future longer regimens. Knowledge about the safety of bedaquiline and delamanid in pregnancy and while breastfeeding is sparse. It is recommended that in such cases, a longer regimen be individualized to include components with a safety profile that is better established. The outcomes of treatment and pregnancy, and postpartum surveillance for congenital anomalies should be documented to help inform future recommendations for MDR-TB treatment during pregnancy.

HIV infection. The composition of the treatment regimen for MDR-TB does not usually differ substantially for people living with HIV. A few drug–drug interactions may be avoided with careful attention (e.g. bedaquiline and efavirenz; *see also (35)*). Thioacetazone, which is no longer on the list of medicines usually recommended for use, should not be given to patients who are HIV positive or whose HIV status is unknown because of the risk of Stevens–Johnson syndrome and toxic epidermal necrolysis in people living with HIV (PLHIV). HIV infection needs to be reliably excluded in the rare instances where thioacetazone is being considered as part of the treatment.

Implementation considerations

The new recommendations signal an important departure from previous approaches to treat MDR/RR-TB. Fully oral regimens should be prioritized and become the preferred option for most patients, and injectable agents are no longer among the priority medicines to consider when designing longer MDR-TB regimens. The implementation of MDR-TB treatment on a large scale is feasible under programmatic conditions, as has been shown by the global expansion in the use of standardized and individualized MDR-TB regimens in low-, middle- and high-income countries worldwide, particularly in the past decade *(41)*. While the current revision of the guidelines brings important changes to the grouping of medicines and the composition of longer MDR-TB regimens, it is not expected to present

insurmountable challenges to the feasibility of their implementation. Changes to the regimen costs and the provision of sufficient resources to improve monitoring requirements may influence the rapidity with which the new recommendations are applied in programmes but should not stand in the way of increasing access to life-saving treatment to more patients in need. All of the agents recommended for use are available via the GDF and most are also available in quality-assured, affordable generic formulations from other sources. Bedaquiline has been available via a donation programme for the past few years (until March 2019) and a decrease in price has been negotiated with the manufacturer for low-resource settings. With the exception of the carbapenems and bedaquiline in children, the latest WHO Model List of Essential Medicines (2017) includes all agents required for longer regimens. In August 2018, WHO and other main technical and funding partners created a "Task Force to support country transition towards new recommendations for the treatment of MDR-TB", which started by developing an implementation resource in the form of answers to frequently asked questions *(53)*. The Task Force is spearheading efforts to facilitate the reforms needed for countries to adopt and implement the new guidance and recommendations, such as support for revising procurement plans, and training and capacity-building of doctors, nurses, laboratory workers, pharmacists and other health-care workers.

These guidelines stress past advice that a patient's MDR/RR-TB strain be tested for susceptibility to medicines planned for inclusion in the regimen so that effectiveness is maximized. Access to rapid diagnostic testing, which could reliably identify resistance to fluoroquinolones and amikacin, would help clinicians to decide whether the patient is eligible for the shorter MDR-TB regimen and what agents to include in a longer MDR-TB regimen (the GenoType MTBDR*sl* LPA may be used for this purpose). GenoType MTBDR*sl* can be used in both children and adults and as a direct and indirect test (for extrapulmonary samples). While resistance-conferring mutations to fluoroquinolones detected by the MTBDR*sl* assay are highly correlated with phenotypic resistance to ofloxacin and levofloxacin, the correlation with moxifloxacin (and gatifloxacin) is less clear and the inclusion of moxifloxacin in an MDR-TB regimen is best guided by phenotypic DST results. It is very important that the new recommendations on regimen design are accompanied by continued efforts to increase access to DST for medicines for which reliable methods exist, as well as for the development and roll-out of DST for the newer medicines. On the other hand, potentially life-saving treatment should not be withheld until all DST results become available and empirical treatment with a regimen likely to be effective may need to be started and adjusted based on DST results once they become available.

One of the important observations in the 2018 IPD-MA for longer regimens is that when a DST result indicates resistance to an agent, then it is better to replace that agent. This applies also to medicines for which DST or the DST method used is known to be unreliable for clinical decision-making. While DST is important to guide more effective treatment, DST results would present uncertainties for a number of regimen components (e.g. cycloserine, streptomycin, ethambutol). "Likelihood of effectiveness" is generally assessed in the programmatic setting on the basis of one or more of the following: (i) confirmed susceptibility in the individual patient; (ii) confirmed susceptibility in the presumed source case; (iii) no known resistance to another drug that has cross-resistance to the medicine; (iv) rare use of the medicine in an area (possibly supported by low drug-resistance levels from surveillance activities); and (v) no previous use of the medicine in a regimen that failed to cure that same patient. When there is uncertainty about the effectiveness of a certain agent, it may still be included in the regimen but it should be considered supernumerary to the target number of medicines needed and clinical judgement is advised to decide if the benefit from its inclusion outweighs any added toxicity, pill burden or other downsides. The design of the regimen has to take into account the relative benefits and harms to the individual patient, including drug–drug interactions (e.g. preference for levofloxacin over moxifloxacin to limit the likelihood of additive QT-interval prolongation).

It is expected that most patients can be treated with four effective agents at start, of which one – usually bedaquiline – would be stopped at month 6. Given that the regimen needs to have at least three effective agents after bedaquiline is stopped at 6 months, if another agent needs to be stopped

because of toxicity then that medicine would need to be replaced by another one.[23] The replacement medicine would be chosen either from Group B (unless both clofazimine and cycloserine/terizidone are already included) or from Group C. The choice from Group C is determined by the order in which the medicines are ranked and the individual circumstances of the patient and setting. Starting with five agents instead of four may be favoured in certain situations to avoid the need to replace a medicine after treatment has started, namely: (i) two of the four agents are likely to be stopped before the end of treatment; for instance, bedaquiline stopped at month 6 and linezolid stopped early because of toxicity; (ii) reliable DST is not available for one or more of the agents on the regimen but background resistance to the agent is known to be high; (iii) the agents included in the regimen are unlikely to cure the patient (e.g. a total of only two of the agents from Group A and Group B are included in the regimen).

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

This guideline update has concurrently revised the weight-based dosage schedules for medicines used in MDR-TB regimens for both children and adults (*see* Annex 2). The update to the dosages has benefited from the expertise of both the GDG members as well as a very extensive consultation with other specialists in different fields. It was based on the latest knowledge available for the optimal use of the medicines involved *(54)*. Adherence to the schedules is advised as far as possible. Manipulation of tablets (splitting, crushing, dissolving in water) beyond their indications is to be reduced to the minimum possible, as this will interfere with their bioavailability.[24]

Monitoring and evaluation

Patients on longer MDR-TB treatment regimens need to be monitored for response to treatment and for safety using reasonable schedules of relevant clinical and laboratory testing *(7,11)*. 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 AEs – alongside monitoring for treatment outcomes. Electrocardiography may be indicated as more regimens in future may have two or three agents that are expected to prolong the QT interval if given concurrently. Audiometry and specific biochemical tests should also be made available whenever certain agents are included in the regimens. Treatment in pregnancy with postpartum surveillance for congenital anomalies will help inform future recommendations for MDR-TB treatment during pregnancy.

A separate recommendation on the use of culture and microscopy to monitor bacteriological response during treatment is made in the 2018 update of the guidelines (*see* Section 5 regarding PICO question 7 MDR/RR-TB, 2018). Frameworks for the surveillance of bacteriological status, drug resistance and outcomes have been standardized over the past decade *(12,13)*. The systematic monitoring of AEs during and after the end of treatment is a relatively recent introduction in TB programmes, and experience in its implementation is still growing in many countries. Its rationale is largely defined by

[23] While replacement of one agent by another one because of toxicity may be acceptable, this should not be done if there are signs that the patient is not responding (e.g. persistent culture positivity or reversion to positive after culture has become negative). A need to replace two or more agents because of toxicity fulfils the definition of treatment failure *(12)*.

[24] This is particularly problematic with the delamanid tablet, the contents of which are very unpalatable (*see* summaries of unpublished data for the 2018 guidelines update in online Annex 9).

Patient support

The GDG emphasizes the importance of patient support to complete treatment as prescribed. The high level of success achieved in both arms of the Phase III trial of delamanid (*see* summary of evidence tables for the 2018 update in online Annex 7) points to the critical importance of ensuring medication adherence and retention to reduce treatment failure and death to a minimum. Ahead of enrolment on MDR-TB treatment, all patients should receive appropriate counselling and be empowered to participate in decisions being made about their care. Patient information material needs to reflect the new changes so that patients are aware of treatment options and the potential risks and benefits of each. Social support to enable adherence to treatment is very important to ensure a patient-centred approach to the delivery of care. Implementation of active TB drug safety monitoring and management (aDSM) whenever any MDR-TB treatment is given is a standard of care that is recommended to improve early management of drug-related harms, and contribute to global knowledge on drug safety. Care should also be taken to ensure that the use of regimens that incur additional costs to the patient and the services (e.g. more expensive medicines or specialized services) do not upset health equity in favour of individuals and facilities that are better resourced at the expense of more marginalized settings and populations. Health systems should strive to guarantee access to treatment according to need and regardless of income levels.

the frequent use of new and repurposed medications in MDR-TB treatment regimens worldwide, at times in combinations for which there has been very limited experience of use. Very few programmes are collecting AE data consistently and uniformly, in a manner that can be reliably used to compare effects between regimens and between countries. In contrast, standardized approaches to surveillance for drug resistance through continuous monitoring of diagnostic DST (including the use of sequencing *(55)*) and for the assignment of treatment outcomes in annual patient cohorts have been available in WHO normative documents since many years *(56)*. Continued advocacy for greater access to DST of medicines for which reliable methods exist as well as the development of other methods for newer medicines such as sequencing, will be an important accompaniment of the treatment recommendations in these guidelines.

Section 3. The duration of longer MDR-TB regimens

Recommendations

3.1. In MDR/RR-TB patients on longer regimens, a total treatment duration of 18–20 months is suggested for most patients; the duration may be modified according to the patient's response to therapy (conditional recommendation, very low certainty in the estimates of effect).

3.2. In MDR/RR-TB patients on longer regimens, a treatment duration of 15–17 months after culture conversion is suggested for most patients; the duration may be modified according to the patient's response to therapy (conditional recommendation, very low certainty in the estimates of effect).

3.3. In MDR/RR-TB patients on longer regimens containing amikacin or streptomycin, an intensive phase of 6–7 months is suggested for most patients; the duration may be modified according to the patient's response to therapy (conditional recommendation, very low certainty in the estimates of effect).

Justification and evidence

This section refers to MDR-TB treatment regimens that are of longer duration than the 9–12-month shorter MDR-TB regimen described in Section 4. The recommendations in this section address three PICO questions (*see* Annex 1):

- *PICO question 5 (MDR/RR-TB, 2018).* In patients with MDR/RR-TB on longer regimens composed in accordance with WHO guidelines, are outcomes safely improved with a total duration shorter or longer than 20 months?
- *PICO question 6 (MDR/RR-TB, 2018).* In patients with MDR/RR-TB on longer regimens composed in accordance with WHO guidelines, what is the minimum duration of treatment after culture conversion that is most likely to improve outcomes?
- *PICO question 4 (MDR/RR-TB, 2018).* In patients with MDR/RR-TB on longer regimens composed in accordance with WHO guidelines, are outcomes safely improved with an intensive phase shorter or longer than 8 months?

These recommendations update the ones made in the 2011 WHO guidelines *(2)* (*see* Key definitions for an explanation of the intensive phase). In 2011, an intensive phase of 8 months was recommended for most MDR-TB patients and a total treatment duration of 20 months in patients who had not been previously treated, conditional and modifiable according to the patient's response to therapy.

Subsets of the main 2018 IPD-MA with 13 104 patients overall from 53 studies in 40 countries were analysed for the risk of treatment failure and relapse versus success associated with different durations in these three recommendations (*see* online Annexes 7 and 8 for the GRADE Tables and online Annex 9 for the analysis plan). Patients followed up for relapse and the number reported with relapse were relatively small. The three IPD subsets were as follows:

The evidence to inform *PICO question 5 (MDR/RR-TB, 2018)* was derived from a subset of 6356 patients from 51 observational studies for the primary analysis. Of 6356 patients, 5352 were treated with an individualized MDR-TB regimen and 1004 were treated with a standardized MDR-TB regimen. Of the 13 104 records in the main IPD, 6748 records were excluded for the following reasons – lost to follow up: *n*=2261; died: *n*=2043; treatment duration not available: *n*=230; number of effective drugs less than five or less than four plus pyrazinamide: *n*=2072; treatment duration less than 6 months: *n*=52; treatment duration ≥36 months: *n*=90).

The analysis to address *PICO question 6 (MDR/RR-TB, 2018)* was derived from a subset of 4175 patients from 39 observational studies. All but 3 of the 4175 patients were on individualized regimens. The reasons for exclusion of 8929 records from the main dataset were as follows – lost to follow up: *n*=2261; died: *n*=2043; treatment duration not reported: *n*=230; culture information not reported: *n*=1945; baseline culture negative: *n*=754, patient never culture converted: *n*=426; number of effective drugs less than five or less than four plus pyrazinamide: *n*=1215; treatment duration less than 6 months: *n*=4; treatment duration ≥36 months: *n*=49; culture converted post treatment: *n*=2.

The analysis for *PICO question 4 (MDR/RR-TB, 2018)* looked for different durations of the intensive phase. For the primary analysis, it used a subset of records from 3750 patients from 42 observational studies, of whom 2720 were treated with an individualized MDR-TB regimen and 1030 were treated with standardized MDR-TB regimens. Of the 13 104 records in the main IPD, 9354 records were excluded for the following reasons – lost to follow up: *n*=2261; died: *n*=2043; did not receive an injectable: *n*=1094; no information on duration of injectable: *n*=2341; number of medicines likely to be effective less than five or less than four plus pyrazinamide: *n*=1450; duration of injectable longer than 20 months: *n*=165.

Subgroup considerations

MDR/RR-TB alone or with additional resistance. The analysis for the three PICO questions in this section did not show any differences overall in treatment failure or relapse when comparing patients with MDR-TB with or without additional second-line drug resistance, including XDR-TB. In patients with resistance to amikacin and streptomycin, recommendation 3.3 does not apply. The duration of treatment may need to be longer than 20 months overall in MDR/RR-TB cases with additional resistance, subject to the clinical response to treatment.

Patients on regimens without amikacin/streptomycin. In patients on regimens that do not contain injectable agents in the intensive phase, recommendation 3.3 does not apply and the length of treatment is determined by recommendations on total duration and on time after culture conversion (i.e. recommendations 3.1 and 3.2). This is expected to apply to an increasing proportion of patients in future who are treated with oral-only regimens. If bedaquiline or other agents (e.g. linezolid, delamanid) are given only for the initial part of a regimen, this period does not equate with an "intensive phase" unless an injectable agent is used concurrently, as premised by the meta-analysis that informed recommendation 3.3.

Persons with extensive TB disease. The duration of treatment post culture conversion may be modified according to the patient's response to therapy (e.g. culture conversion before 2 months of treatment) and other risk factors for treatment failure or relapse. This should be considered in patients with extensive TB disease.

Children. These recommendations apply also to children. Use of amikacin or streptomycin in children should be resorted to only when other options are not possible, when testing confirms susceptibility and the possibility to monitor for ototoxicity and nephrotoxicity is present. Given that many patients in the paediatric age group may only be clinically diagnosed or have extrapulmonary disease, it is expected that treatment duration will largely be guided by recommendation 3.1, subject to response to treatment. Shortening the total treatment duration to less than 18 months may be considered in the case of children without severe disease (*see* Key definitions on page 6).

Pregnant women. Due to the potential for teratogenic effects, injectable agents are usually contraindicated in pregnancy and therefore recommendation 3.3 will be of very limited relevance in this subgroup.

Extrapulmonary TB and culture-negative TB. Extrapulmonary MDR/RR-TB is generally treatable with the same combination of medicines and duration of use as pulmonary disease (*see also* Section 2 regarding specific medicines for cerebral disease). Other durations of treatment may be appropriate for persons with culture-negative TB and recommendation 3.2 does not apply. In such cases, a total duration of 18–20 months of treatment is advised and the response should be monitored by clinical parameters other than specimen bacteriology. A negative culture result may reflect poor laboratory performance rather than true sputum negativity, which underscores the importance of quality assurance in the laboratory.

Implementation considerations

In patients taking amikacin or streptomycin who are culture positive at the start of treatment, all three recommendations apply. For patients on an all-oral MDR-TB regimen, the length of treatment is determined by the recommendations on total duration and time after culture conversion (recommendations 3.1 and 3.2, respectively). In patients with bacteriologically negative TB or most forms of extrapulmonary disease, recommendation 3.1 on total duration is the only one applicable.

National TB programmes may find it more practical and straightforward to apply a fixed duration of the intensive phase (e.g. 6 months), total duration (e.g. 20 months) or time after conversion (e.g. 16 months) to facilitate implementation throughout its sites. The clinician may find it necessary to

prolong the intensive phase if there are grounds for doing so (e.g. prolonged positivity of sputum), within the terms of a conditional recommendation. In case there is emergence of toxicity associated with the injectable agent, a change of regimen becomes necessary and the continuation phase should be started with the revised treatment. Regimens that vary substantially from the recommended composition and duration can be explored under operational research conditions (e.g. 9-month regimen composed of all Group A and B agents; *see also* Section 4).

The 6-month duration of use of bedaquiline and delamanid generally recommended in these guidelines reflects how these medicines have been used in most patient data reviewed, which is aligned to the prescribing recommendations that their manufacturers filed with regulatory authorities (e.g. *(57–59)*). Use beyond this duration needs to be decided by the programme on a case-by-case basis and represents "off-label" use *(48)*. It is important to keep in mind that, in contrast to bedaquiline and delamanid, several of the other medicines included in MDR-TB regimens (e.g. fluoroquinolones, clofazimine) are used beyond their primary indication, and the recommended duration of use in MDR-TB regimens is often much longer than the one proposed for their original purpose. Other medicines may need to be used for shorter durations because of toxicity associated with their long-term administration (particularly linezolid).

Some countries experience difficulties with the implementation and quality assurance of sputum culture, which impacts upon this recommendation as it is dependent on access to culture. The yield of smear microscopy and culture also depends on the quality of the sputum produced, so care should be taken to obtain adequate specimens and transport them to the laboratory according to standard procedures to maintain the viability of the bacilli to get a valid culture result.

Preventing treatment interruption is important to increase the likelihood of treatment success. Measures to support patient adherence, either by facilitating patient visits to health-care facilities or home visits by health-care staff or by using digital technologies for daily communication, may be important to increase retention *(29)*. Patients on injectable agents require the intervention of a skilled health-care worker every day or even hospitalization for the first months to administer the intramuscular injections.

Monitoring and evaluation

Patients on longer MDR-TB treatment regimens need to be monitored for treatment response or failure and safety, using reasonable schedules of relevant clinical and laboratory testing *(7,11)*. Response to treatment and toxicity is monitored through regular history-taking, physical examination, chest radiography, special tests such as audiometry, visual acuity tests, electrocardiography and laboratory monitoring. Using smear microscopy or culture to assess conversion of bacteriological status is an important means of assessing response and most patients are usually expected to have converted to a sputum-negative status within the first few months of starting treatment. Persistence of culture positivity beyond that point, or close to the expected end of the intensive phase when injectable agents are in use, is a trigger for a review of the regimen and performance of DST.

Frameworks for the surveillance of bacteriological status, drug resistance and assignment of outcomes have been fairly standardized in past years *(12)*. In contrast, systematic monitoring of AEs during and after the end of treatment needs to be strengthened in most TB programmes, given the relative novelty of active pharmacovigilance within national TB programmes. In the case of this recommendation, it is important to monitor for hearing loss and kidney function, especially with the use of the aminoglycosides. The rationale for aDSM is largely supported by the increasing use worldwide of combinations of new and repurposed medications in MDR-TB treatment regimens. The toxicity of certain agents may increase with the duration of use (such as nerve damage with linezolid) and may limit their continued use in a patient, and at times, result in complete cessation of treatment. The prospective collection of accurate data for key variables at the case-based level using an electronic register is strongly advised in the best interests of the individual patient, and to inform local and global policy revisions *(60)*.

Section 4. Use of the standardized shorter MDR-TB regimen

Recommendation

4.1. In MDR/RR-TB patients who have not been previously treated for more than 1 month with second-line medicines used in the shorter MDR-TB regimen or in whom resistance to fluoroquinolones and second-line injectable agents has been excluded, a shorter MDR-TB regimen of 9–12 months may be used instead of the longer regimens (conditional recommendation, low certainty in the estimates of effect).

Justification and evidence

The recommendation in this section addresses one PICO question (*see* Annex 1), *PICO question 1 (MDR/RR-TB, 2018)*. In patients with MDR/RR-TB, is a shorter treatment regimen (9–12 months) more or less likely to safely improve outcomes than longer regimens conforming to WHO guidelines?[25]

The interest in reducing the duration of treatment for MDR-TB has motivated a number of initiatives in recent years to treat patients with shorter regimens under programmatic as well as trial conditions *(61–66)*. When used in carefully selected MDR-TB patients who have not been previously exposed or have strains resistant to second-line medicines, these regimens have been reported to achieve relapse-free cure in over 85% of cases even under programmatic conditions. In 2016, on the basis of data from observational studies of the shorter regimens in different Asian and African countries, WHO recommended a standardized shorter MDR-TB regimen based on the ones under study for eligible patients *(6)*. At that time, the GDG that assessed the evidence and formulated the recommendation using the GRADE method proposed a conditional recommendation based on very low certainty in the estimates of effect. By the end of 2017, 62 countries reported that they had introduced the shorter MDR-TB regimen and about 10 000 patients were reported to have been started on shorter regimens that year alone *(41)*.

In October 2017, the principal investigators of the STREAM trial presented the preliminary findings of the study during the 48th Union World Conference on Lung Health *(62)*. STREAM Stage 1 was a phase III, multicentre, international, parallel-group, open-label RCT of a standardized MDR-TB treatment regimen lasting 9–11 months versus a longer regimen designed according to the 2011 WHO recommendations using a non-inferiority design.[26] The trial enrolled patients between July 2012 and June 2015 in Ethiopia, Mongolia, South Africa and Viet Nam (intention-to-treat [ITT] population n=424 [n=282 in study arm; n=142 control arm]; modified ITT (mITT) population n=369 [n=245 in study arm; n=124 control arm]). Treatment allocation was not blinded to the participants, caregivers or data managers. All local and reference laboratory assessments, including microbiological tests, involved in the assignment of patient outcome, were conducted blind. Audiometry was available only at one site. When the preliminary data were presented, the findings led to public debate and queries regarding the implications for continued use of the regimen under programmatic conditions, particularly among PLHIV in whom deaths were higher in the study arm than in the control arm. On the basis of the preliminary results, WHO issued a position statement, recommending the continued use of the shorter MDR-TB regimen until a full update of the MDR-TB treatment guidelines was completed later in the year *(67)*. The final outcomes of the STREAM trial were much awaited because they provided additional information on the efficacy and safety of the shorter regimen and the data were expected to improve the certainty of the estimates (i.e. quality of evidence). In July 2018, the final results of the STREAM trial were made available to WHO. In the analyses of these data, the main

[25] The characteristics of previous longer ("conventional") regimens are described in the WHO treatment guidelines for drug-resistant tuberculosis, 2011 and 2016 *(2,6)*.

[26] Elsewhere, these guidelines refer to 9–12-month regimens, given that some patients required slightly more than 11 months to complete a shorter regimen owing to brief interruptions.

observation was that both the shorter and the control regimens obtained a high level of success, even if favourable outcomes were slightly higher in the control regimen (78.8% vs 79.8% in the mITT population). The upper limit of the confidence interval did not reach 10% upon adjustment, thus showing non-inferiority of the shorter regimen as defined in the trial protocol (*see also* GRADE tables in online Annex 7 that have been updated with the final trial results).

A public call for data launched by WHO in February 2018 invited national authorities and technical agencies to submit IPD for both shorter and longer MDR-TB regimen cohorts to inform the 2018 guidelines update *(46)*. As a result of this call, pooled IPD were compiled from MDR/RR-TB patients enrolled on standardized shorter regimens between 2005 and 2017 in observational studies or under programmatic conditions in 15 countries (Bangladesh, Benin, Burkina Faso, Burundi, Cameroon, Côte d'Ivoire, Central African Republic, Democratic Republic of Congo, Eswatini, Kyrgyzstan, Niger, Rwanda, Tajikistan, South Africa and Uzbekistan). The main analysis included a maximum of 2625 records from the shorter regimen studies and 2717 records from 39 studies of patients on the longer MDR-TB regimens from the separate IPD used to answer PICO questions 2–7 (MDR/RR-TB, 2018) (a description of this IPD is provided in the respective evidence-to-decision frameworks in online Annex 8). This overall analysis gave an aOR of 2.0 for treatment failure or relapse in the shorter regimen when compared with the longer regimen and an aOR of 1.2 for death. These effects were largely reproduced in all the main subgroup analyses done: when the longer regimen included bedaquiline, linezolid or delamanid (OR fail/relapse 9.1; OR death 1.4); patients who were PLHIV (2.1; 1.0); pyrazinamide-resistant/fluoroquinolone-susceptible patients (10.7; 0.3); ethionamide-resistant/fluoroquinolone-susceptible patients (3.9; 1.5); those with extensive disease (1.2; 1.0). Adherence was better with the shorter regimen than the longer regimen (statistically significant) in all subgroups, presumably a direct consequence of its briefer duration. Direct comparison of the shorter regimen with an all-oral longer regimen remains limited because up to now the longer regimen composed primarily of Group A and B agents would have been reserved for patients who would not have been eligible for the shorter regimen. No data from variants of the shorter regimen in which the injectable agent was replaced by bedaquiline were reported to WHO while the 2018 guideline update was being prepared.

Subgroup considerations

When WHO first issued its recommendations on the shorter MDR-TB regimen in 2016, they were accompanied by inclusion criteria *(6)*. Previous treatment with second-line drugs for more than 1 month, resistance to medicines in the regimen, extrapulmonary disease and pregnancy were exclusion criteria. The recommendation was made subject to patients having been tested for in-vitro resistance to at least the fluoroquinolones and the injectable agent used in the regimen before starting treatment. In some settings, patients without laboratory confirmation of susceptibility but who were highly unlikely to be infected with resistant strains based on clinical or recent representative surveillance data, were also eligible for the shorter MDR-TB regimen.

In the evidence reviewed for the 2018 guidelines, treatment outcomes were poorer in patients with laboratory-confirmed resistance to pyrazinamide and ethionamide/prothionamide than in those without additional resistance. The 2018 recommendation thus reinforces the importance of excluding resistance to the fluoroquinolones and second-line injectable agents before the shorter MDR-TB regimen is considered. Other testing, such as DST for pyrazinamide and genotyping studies of isoniazid resistance – are also considered important and should be performed if possible.

Decisions to start newly diagnosed patients who do not have any of the following conditions on the standardized shorter MDR-TB regimen should be made according to patient preference and clinical judgement (*see also* Fig. 4.1):

1. resistance to or suspected ineffectiveness of a medicine in the shorter MDR-TB regimen (except isoniazid resistance);

2. exposure to one or more second-line medicines in the regimen for >1 month (unless susceptibility to these second-line medicines is confirmed);
3. intolerance to any medicine in the shorter MDR-TB regimen or risk of toxicity from a medicine in the shorter regimen (e.g. drug–drug interactions);
4. pregnancy;
5. disseminated, meningeal or CNS TB;
6. any extrapulmonary disease in HIV patients.

Considerations for specific subgroups are provided below, based on the review of the current evidence by the GDG.

People living with HIV. One third of the STREAM trial participants were HIV positive and participation was not restricted by CD4 count. Nineteen of the 24 deaths among the 151 participants with HIV occurred in two sites in South Africa. The reason for the higher mortality observed in the study arm among PLHIV remains unclear but may be a clinically relevant signal. A detailed assessment of the causes of death by the expert panel in the 33 study subjects (nine of whom were HIV negative) who died during treatment or on follow up did not provide any indication that the shorter regimen was associated with additional harms in PLHIV due to excessive pill burden, poor adherence, or drug–drug interactions with ART. In the IPD-MA for the shorter regimen among PLHIV (90% on ART), the likelihood of treatment failure and death was similar to that in HIV-negative patients. The shorter regimen may be used in PLHIV alongside timely initiation of ART in accordance with WHO guidelines, and careful monitoring of the effectiveness of ART and adverse reactions to it. PLHIV receiving the shorter regimen may also need prophylactic medication for opportunistic infections, as well as support for medication adherence, and close monitoring and follow up as part of routine HIV care.

RR-TB without MDR-TB. Only 5.8% of STREAM trial participants in the study arm were isoniazid susceptible. All patients – children or adults – with RR-TB in whom isoniazid resistance is not confirmed may be treated with the shorter MDR-TB treatment regimen, subject to the other conditions for eligibility.

Resistance in addition to isoniazid and rifampicin. The STREAM trial demonstrated the effectiveness of the regimen in patients *without* resistance to fluoroquinolones and second-line injectable agents. STREAM trial data showed a higher unadjusted relative risk of culture reversion, relapse or lack of culture conversion for patients with baseline resistance to pyrazinamide and ethionamide (albeit not statistically significant and with wide confidence limits). The IPD-MA also showed a higher risk of treatment failure and relapse in patients with strains resistant to pyrazinamide and ethionamide/prothionamide when compared to those with susceptible strains. In patients infected with strains that have laboratory-confirmed resistance to components in the shorter MDR-TB regimen, or there is solid ground to believe that they are ineffective (e.g. contact with a patient with documented resistance), the shorter regimen should not be used. In the absence of reliable test results for regimen components in an individual patient, representative data on the background prevalence of resistance may help to decide if the shorter regimen may be used or not. It is also recommended that alternative regimens be used in areas with a high prevalence of pyrazinamide or ethionamide resistance. Such uncertainty is one of the reasons that the recommendation for the shorter regimen remains conditional. The studies reviewed showed a higher risk of treatment interruption with the longer regimen than with the shorter regimen, stressing the importance of supporting patients to complete longer regimens as recommended for them to benefit from increased likelihood of relapse-free cure (*see* Sections 2 and 3).

Children. Children were excluded from the STREAM trial. However, 78 patients aged 18 years or less were included in the 2018 IPD- MA for the shorter regimen. The effect of the shorter regimen on treatment outcomes in children and adolescents has been difficult to determine due to the small numbers for each outcome. Whereas there is no plausible biological reason to believe that these

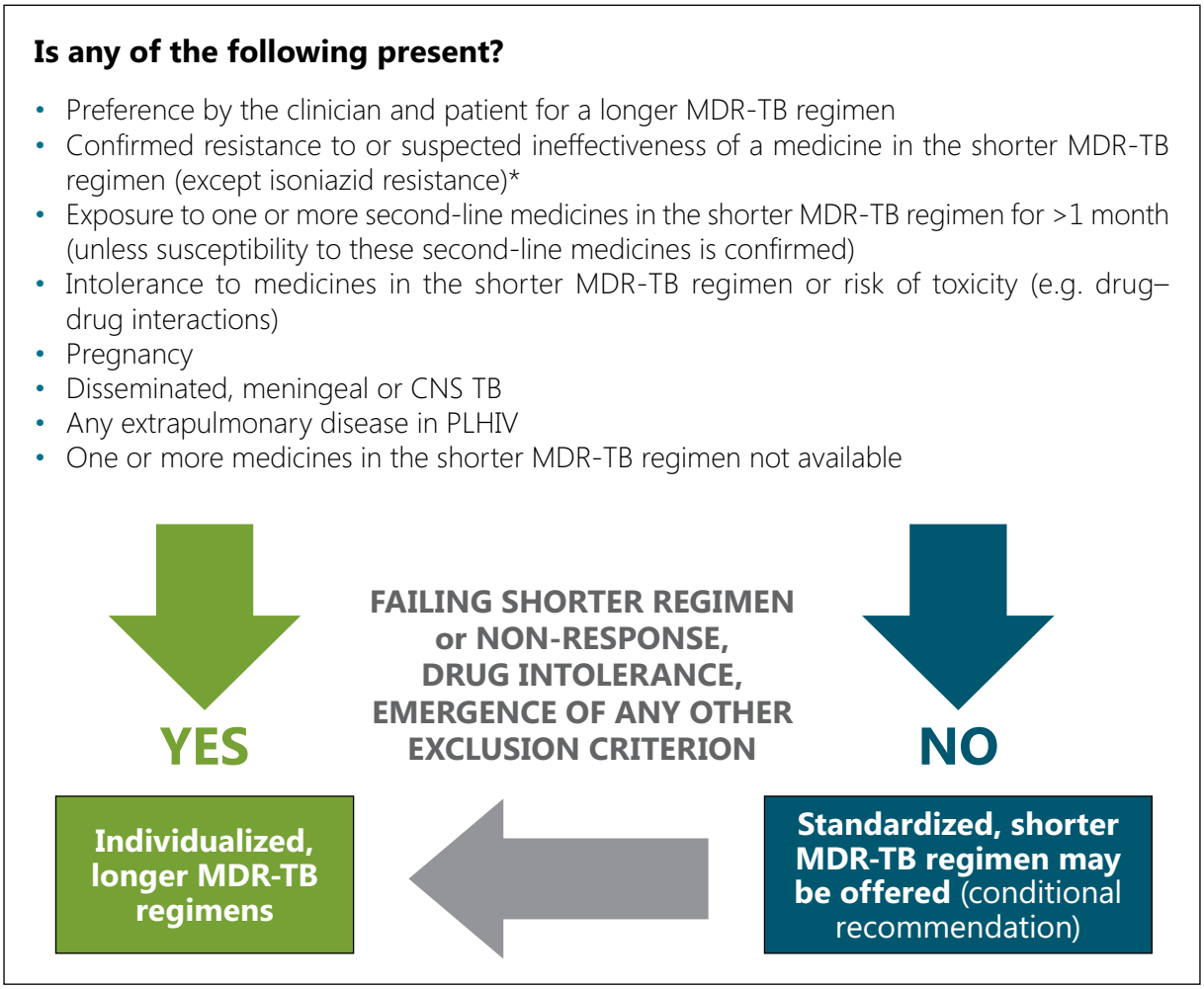
regimens are less effective or less tolerable in children than in adults, it is acknowledged that additional data on its use in children would be useful. The avoidance of an injectable-containing regimen is particularly desirable in children, especially those very young, given the negative impact that hearing loss can have on development. The use of injectable agents in children has to be accompanied with regular audiometry. It is recommended that children with pulmonary MDR/RR-TB be otherwise given the same consideration for treatment with a shorter MDR-TB treatment regimen as adults.

Pregnant women. Pregnancy was an exclusion criterion for the STREAM trial. Two of the components of the shorter MDR-TB regimens – the injectable agent and ethionamide (or prothionamide) – are usually contraindicated in pregnancy. Withholding these medicines from the shorter MDR-TB treatment regimen could seriously compromise its effectiveness. In the case of pregnant women, it is therefore recommended that an individualized, longer regimen be used, which can allow the selection of four or more effective medicines with a lower teratogenic risk.

Exclusive extrapulmonary disease. The findings from the STREAM trial were limited to patients who had pulmonary localization and they cannot be extrapolated directly to all different forms of extrapulmonary disease. It is suggested that the shorter regimen be avoided in patients with disseminated or CNS TB, as well as in all PLHIV who have extrapulmonary disease.

Persons with diabetes mellitus. There are no data on the use of the shorter regimen among people with diabetes mellitus. It is recommended that patients with diabetes be given the same consideration for treatment with a shorter MDR-TB treatment regimen as for all other patients.

Fig. 4.1. Criteria to decide when the shorter MDR-TB regimen may be offered



* Strains from MDR/RR-TB patients should ideally be tested for resistance to fluoroquinolones and other regimen components regardless of the type of MDR-TB treatment regimen offered.

Implementation considerations

The shorter MDR-TB regimen has become well known in the TB community. Attempts to gradually reduce the duration of the regimen in Bangladesh started two decades ago and stabilized in recent years to a 9-month regimen with seven agents in a 4-month intensive phase and four agents in a 5-month continuation phase *(63)*. This regimen, with some variations, was subsequently adopted in other low-resource settings, mostly in Africa, but also in high MDR-TB settings (e.g. Kyrgyzstan, Tajikistan, Uzbekistan). The same regimen – 4–6Km–Mfx–Cfz–Eto–Z–E–Hh/5Mfx–Cfz–Z–E[27] – was tested in the STREAM Stage 1 trial, which enrolled patients between 2012 and 2015. In 2016, WHO recommended the use of the shorter MDR-TB regimen subject to specific inclusion/exclusion criteria; since then, several countries have introduced the regimen. Given its largely standardized composition and duration, the regimen has been relatively easy to implement.

In order to reproduce the high cure rates achieved in the STREAM trial, all efforts need to be made to prevent the acquisition of additional resistance through careful selection of patients to be enrolled, and effective patient support to enable full adherence to treatment. It is important that patients be tested for susceptibility or resistance to fluoroquinolones and to the second-line injectable agent used in the regimen before being started on a shorter MDR-TB regimen. Patients with strains resistant to any of the two groups of medicines should be transferred to treatment with a longer MDR-TB regimen. If testing is available for susceptibility or resistance to pyrazinamide or other medicines used in the regimen, it is highly desirable that this is also carried out at baseline.

The availability of reliable and rapid tests to identify resistance to isoniazid, fluoroquinolones and injectable agents helps programmes to decide within a few days which patients would be eligible for shorter MDR-TB regimens – or what modifications to longer MDR-TB regimens would be necessary based on the resistance detected. In patients with confirmed MDR/RR-TB, the MTBDR*sl* assay may be used as the initial test, over culture and phenotypic DST, to detect resistance to fluoroquinolones and to the second-line injectable drugs (conditional recommendations; certainty of evidence for direct testing of sputum from low to moderate *(32)*). This applies to testing in both children and adults. While resistance-conferring mutations to fluoroquinolones detected by the MTBDR*sl* assay are highly correlated with phenotypic resistance to ofloxacin and levofloxacin, the correlation with moxifloxacin and gatifloxacin is less clear and the inclusion of moxifloxacin in an MDR-TB regimen is best guided by phenotypic DST results (likewise for gatifloxacin, should a quality-assured preparation become available in future). In settings in which laboratory capacity for DST to fluoroquinolones and injectable agents is not yet available, the clinician and the TB programme manager would need to decide on the basis of the likelihood of resistance to these medicines, informed by the patient's clinical history and recent representative surveillance data. The MTBDR*plus* rapid assay can determine whether both the *inh*A and *kat*G mutations are present, in which case both isoniazid and ethionamide are likely to be ineffective and therefore the shorter regimen is not indicated.[28] As rapid DST is not available for all medicines used in the shorter regimen (for example, pyrazinamide, which relies on phenotypic testing), the shorter regimen may be started while waiting for these results and, if needed, the patient can be transferred to a longer regimen if additional resistance is detected.

The evidence for the effectiveness and safety of the shorter MDR-TB regimen now derives from both trial sites and observational studies where this treatment was administered under fairly standardized conditions, with relatively little variation in the content and duration. The recommendation on the use of the shorter MDR-TB regimen is made under the premise that it is implemented as per the composition and duration used in the studies. This may make it difficult to implement in countries where one or more of the regimen components cannot be procured. Replacement of medicines and prolongation/shortening of the duration would be permissible only within the parameters applied in these studies (e.g. gatifloxacin replaced by moxifloxacin; prothionamide replaced by ethionamide;

[27] Km: kanamycin; Mfx: moxifloxacin; Cfz: clofazimine; Eto: ethionamide; E: ethambutol; Z: pyrazinamide; Hh: high-dose isoniazid.

[28] In the absence of information on mutation patterns for an individual patient, knowledge about the frequency of concurrent occurrence of both mutations may inform about the likelihood of effectiveness of the shorter regimen in a given epidemiological setting.

intensive phase prolonged up to 6 months in case sputum conversion does not occur). No data from variants of the shorter regimen, in which the injectable agent was replaced by bedaquiline, were reported to WHO while the 2018 guideline update was in process. Regimens that vary substantially from the recommended composition and duration (e.g. a standardized 9–12-month shorter MDR-TB regimen in which the injectable is replaced by bedaquiline) can be explored under operational research conditions.

At the present time, there are no quality-assured formulations of gatifloxacin available. Two staples of the regimen – clofazimine and single-dose isoniazid – may be difficult to procure in some countries. Moreover, available formulations of clofazimine are not satisfactory for younger children and dividing the capsule into smaller doses is impossible, making dosing in children uncertain. The new scored tablets of 50 mg and 100 mg clofazimine should make dosing easier in both adults and children (*see* Annex 2). Given the global shortage in the supply of quality-assured gatifloxacin in recent years, the STREAM trial, observational studies and programmes have had to substitute this agent with high-dose moxifloxacin. This has led to an increase in the overall price of the regimen, with moxifloxacin typically accounting for about one half of overall drug costs, even though its cost has recently come down as a result of the availability of more generic preparations. The implementation of these guidelines at the national level needs to ensure that sufficient quantities of these medicines are available to meet the demand and that no stock-outs occur. The dosing of all medicines in the shorter regimen remains as per the recommendations of the STREAM trial *(61)*. The GDG also revised the dosage schedules for adults and children alongside the 2018 guidelines update (*see* Annex 2).

DOT was carried out during the STREAM trial by clinic staff or family members or other members of the community, depending on the local circumstances. Among trial participants who died, there is an indication that adherence was worse than among other study participants. It is proposed that DOT with patient support be implemented to help patients complete the shorter MDR-TB regimen. In this context, the use of patient-centred approaches *(29)*, including digital technologies to support adherence (e.g. video-supported therapy) could have a role, as evidence of the effectiveness of this kind of support becomes stronger *(29)*. In addition, aDSM needs to be established and used in countries implementing the shorter regimen to detect, manage and report suspected or confirmed AEs or drug toxicities *(7,11)*. WHO has published a framework for aDSM, which provides information on the implementation of aDSM. Among the elements monitored in aDSM for patients on the shorter MDR-TB regimen, audiometry services are important to establish the level of hearing and any auditory deficits already present at baseline, and to monitor for hearing loss over time.

If the shorter regimen is used, the GDG recommended that:

1. there be shared decision-making between the clinician and patient when choosing between a shorter and a longer regimen;
2. before the start of treatment, emphasis be placed on DST for fluoroquinolones and second-line injectable agents, as well as other regimen components where possible (e.g. pyrazinamide, mutations associated with isoniazid and ethionamide resistance);
3. kanamycin be replaced by amikacin (based on evidence from the comparative effectiveness of these two injectable agents – *see* PICO question 2 (MDR/RR-TB, 2018) in Section 2);
4. other exclusion criteria be observed.

The shorter length of the 9–12-month regimen is the main advantage to the patient and increases the likelihood of completion of treatment and an earlier return of the patient to work and social activity. The reduced cost of the shorter regimen to patients and the health services is expected to favour equity by releasing more resources to cover the care of more patients. These benefits need to be balanced with the disadvantages of this injectable-containing regimen compared to newer treatment approaches.

Monitoring and evaluation

Patients who receive a shorter MDR-TB treatment regimen need to be monitored during treatment using schedules of relevant clinical and laboratory testing, which have been successfully applied in the studies under field conditions. If feasible, it is important to follow up patients after the completion of treatment for possible relapse. The STREAM trial (interim) results indicated that relapse occurred in 3.3% in the study arm, which is higher than was inferred from observational studies. However, the final results of the STREAM trial did not demonstrate a statistically significant higher rate of reversion, relapse or lack of conversion in patients using the shorter regimen.

The WHO framework for aDSM needs to be applied to ensure appropriate action and prompt response to AEs, and an acceptable level of monitoring for them, alongside monitoring for treatment outcomes. The use of electrocardiography is still recommended, particularly for patients receiving the 800 mg/day dose of moxifloxacin. Audiometry should also be available.

Resistant mutations to fluoroquinolones and second-line injectable agents detected using MDRTBs*l* should be considered a contraindication for the shorter regimen. Likewise, the presence of both *inh*A and *kat*G mutations is a contraindication for the use of the shorter regimen. Resistance to pyrazinamide (or any other component of the shorter regimen), when determined using reliable DST, is also considered an exclusion criterion. However, there is currently no approved rapid test for pyrazinamide susceptibility. As it may require several weeks to obtain a phenotypic DST result where this is available, this test is not imposed as a prerequisite ahead of treatment initiation. Patients may be started on the shorter regimen until pyrazinamide DST results become available. If a test result eventually shows resistance into treatment with the shorter MDR-TB regimen, the clinician needs to decide whether to switch to a longer MDR-TB regimen based on the patient's response to treatment and other considerations.

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

Recommendation

5.1. In MDR/RR-TB patients on longer regimens, the performance of sputum culture in addition to sputum smear microscopy is recommended to monitor treatment response (strong recommendation, moderate certainty in the estimates of test accuracy). It is desirable for sputum culture to be repeated at monthly intervals.

Justification and evidence

The recommendation in this section addresses the following PICO question (*see* Annex 1):

PICO question 7 (MDR/RR-TB, 2018). In patients with MDR/RR-TB treated with longer or shorter regimens composed in accordance with WHO guidelines, is monitoring using monthly cultures, in addition to smear microscopy, more likely to detect non-response to treatment?

Previous studies have indicated that monthly culture is the optimum strategy to detect non-response as early as possible and was conditionally recommended by WHO in 2011 as the preferred approach *(2,68,69)*. The findings of the evidence review and analysis performed for this question are expected to influence the continued validity, in its present form, of the 2011 WHO recommendation *(2)*. Since then, significant changes in MDR-TB treatment practices have taken place on a large scale globally, such as the wider use of later-generation fluoroquinolones, bedaquiline and linezolid; a tendency towards an intensive phase of longer duration; and the widespread use of the shorter regimen, which could influence the speed and durability of culture conversion during the continuation phase, when this PICO question is of greatest relevance.

Achieving sustained bacteriological conversion from positive to negative is widely used to assess response to treatment in both drug-susceptible and drug-resistant TB. Culture is a more sensitive test for bacteriological confirmation of TB than direct microscopy of sputum and other biological specimens. Culture also facilitates phenotypic testing for DST, a critical consideration in TB diagnostics. However, performing culture requires considerable logistical organization and a well-equipped laboratory to limit cross-contamination, ensure proper bacterial growth and match other quality standards. Apart from the resource requirements, culture results become available after a significant delay of weeks or months, contrasting markedly with the relative immediacy of the result of direct microscopy (although microscopy cannot confirm mycobacterial viability). While molecular techniques can now provide a rapid and reliable diagnosis, they cannot replace culture or microscopy for the monitoring of bacteriological status during treatment.

The evidence used to explore the added value of culture over sputum smear microscopy alone, and the optimal frequency of monitoring, was obtained from a subset of the IPD reported to WHO by South Africa for the 2018 update. The South African dataset comprised 26 522 patients overall. Of these, 22 760 records were excluded from the dataset for the following reasons: 11 236 had a treatment outcome of death or loss to follow up; 698 had a successful treatment outcome but had received less than 17.5 months of treatment; 1357 had fewer than six culture samples recorded; 1632 had no baseline culture recorded; 2502 were baseline culture negative; 2920 were smear negative at baseline or had a missing smear at baseline and 2415 had insufficient smear data to match the culture data. This left 3762 MDR/RR-TB patients (of which 1.8% were children <15 years of age) treated with longer MDR-TB regimens between 2010 and 2015, who had both monthly smear and culture data throughout treatment to address PICO question 7 (MDR/RR-TB, 2018). About 60% of these patients were HIV positive. The analysis focused on whether monthly culture versus monthly smear microscopy or culture every 2 months is needed to not miss treatment failure in MDR/RR-TB patients on treatment. The odds of treatment failure in patients who do not convert at 6 months or later was also discussed (*see* under Implementation considerations and Table 5.1). The data could not address the outcome on acquisition (amplification) of additional drug resistance, and it could not assess directly whether the frequency of culture/smear microscopy had an identical effect on failure in patients on the 9–12-month shorter MDR-TB regimen as envisaged in the original PICO question 7 (MDR/RR-TB, 2018).

The IPD-MA compared (i) the performance of the two methods in terms of sensitivity/specificity, and (ii) culture testing once a month versus once every 2 months to assess the minimum frequency of testing needed in order to not unnecessarily delay any revision of the treatment. The focus of the analysis was to compare how the two tests performed in terms of predicting treatment failure or relapse.

The main findings of the analysis were that monthly culture had a higher sensitivity than monthly smear microscopy (0.93 vs 0.51) but slightly lower specificity (0.97 vs 0.99). Likewise, the sensitivity of culture done every month is much higher than once every 2 months (0.93 vs 0.73) but has a slightly lower specificity (0.97 vs 0.98). Monthly culture increases the number of patients detected with a true positive bacteriological result by 13 per 1000 patients and reduces false-negative results by 13 per 1000 patients when compared with sputum smear microscopy alone. In contrast, monthly culture is estimated to lead to 17 per 1000 fewer true-negative results and 17 per 1000 more false-positive results for treatment failure, implying that treatment may be prolonged in the case of false positivity or missed true negativity. The added inconvenience to the patient and programme is considered relatively small, given that taking sputum and many other biological specimens is usually non-invasive and routine practice in many programmes. In a setting where testing is repeated at monthly intervals, a single false-positive test result is unlikely to prove harmful to the patient because treatment decisions usually rely upon at least two consecutive positive results (to denote prolonged positivity or reversion) and the effect of one spurious result would last only until the test repeated 1 month later is reported.

The crude odds of treatment failure increased steadily with each additional month without bacteriological conversion, from 3.6 at the end of the first month to 45 at the eighth month when

using culture (Table 5.1). However, no discrete cut-off point, which could serve as a reliable marker of a failing regimen, could be discerned at which the odds of failure increased sharply when monitoring with either sputum smear microscopy or culture. The threshold for when to change treatment thus depends on the clinician's desire to minimize the risk of failure and, in particular, to limit the risk of prolonging a failing regimen.

Table 5.1. Crude odds ratios (95% CLs) of treatment failure in MDR/RR-TB patients without sputum conversion by the end of successive months of treatment compared with patients who converted, by testing method used, IPD-MA for PICO question 7 MDR/RR-TB, 2018 (South Africa, N=3762)

Crude odds ratios according to	Month							
	1	2	3	4	5	6	7	8
Culture	**3.6**	**4.1**	**5.2**	**7.4**	**10.3**	**16.4**	**24.7**	**44.5**
	(2.11, 5.97)	(2.76, 6.09)	(3.55, 7.55)	(5.00, 10.8)	(6.88, 15.38)	(10.72, 25)	(15.53, 39.20)	(26.53, 74.46)
Smear microscopy	**1.9**	**2.7**	**3.2**	**4.2**	**6.8**	**10.4**	**16.5**	**28.9**
	(1.27, 2.73)	(1.82, 3.88)	(2.11, 4.73)	(2.69, 6.48)	(4.19, 10.97)	(6.00, 17.92)	(9.15, 29.77)	(14.87, 56.14)

There was moderate certainty in the estimates of test accuracy and the GDG considered that, under normal conditions, culture would always be a more sensitive test of positive bacterial status than sputum smear microscopy. However, the overall quality of the evidence was judged to be low. The effects observed may vary in patients or populations with a profile markedly different from the one included in the analysis, such as low HIV-prevalence settings, children, patients with extrapulmonary forms of disease or those treated with the shorter MDR-TB regimen. The 3762 patients included in the analysis had very similar clinical characteristics to the 22 760 individuals excluded, although they were slightly less likely to be HIV coinfected, have a history of previous treatment or have second-line drug resistance. On the other hand, the rate of failure in those included in the analysis was only 3% compared to 12.7% of those excluded from the analysis.

Subgroup considerations

The recommendation would apply to any longer regimen, regardless of the number of Group A, B or C agents used and whether an injectable (intensive) phase was used or not. The GDG considered that the findings may apply to other key patient subgroups.

Patients <15 years of age with MDR/RR-TB comprised less than 2% of the IPD-MA analysed for PICO question 7 (MDR/RR-TB, 2018). Younger children usually cannot produce sufficient sputum spontaneously to allow a bacteriological diagnosis (many are typically sputum smear-microscopy negative). In these patients, culture may be a more sensitive means to detect viable TB bacilli even if very few organisms are present in the sputum or other samples, below the detection threshold of direct microscopy. However, in children who are unable to expectorate, gastric aspirates or induced sputa may be possible but the repetition of such tests at monthly frequency may not be acceptable.

Extrapulmonary disease is commonly paucibacillary and biological specimens may therefore contain few or no bacilli. In such a situation, detection of persistent disease is more likely with culture, although collection of samples often poses problems. Direct microscopy should still be attempted because it may determine positivity much faster than culture.

HIV-negative individuals with TB typically have higher bacterial counts in the sputum and a greater likelihood of detection with smear microscopy. In such a situation, one may expect that the difference in test sensitivity between smear and culture would be less extreme, as fewer patients would have subthreshold bacterial counts. However, past studies on datasets from multiple sites in which HIV positivity was low reported findings that led to the WHO recommendation even in 2011 for joint use of both microscopy and culture, preferably every month.

Patients on the shorter MDR-TB regimen have a much shorter duration of intensive phase and total treatment. They receive 7 drugs in the initial phase and, if fully compliant with the inclusion/exclusion criteria, usually have a more favourable prognostic outlook than other MDR-TB patients. Programmes may thus consider that patients on a shorter MDR-TB regimen may need less frequent or no culture to monitor treatment. While the current analysis did not include patients treated with shorter regimens, the GDG proposes that programmes that implement this regimen aim for more frequent culture testing, especially after the intensive phase, to confirm bacteriological cure in patients who complete treatment without signs of failure. Any sign of recurrence after termination of treatment should also be investigated using sputum smear microscopy, culture and DST.

Implementation considerations

Good-quality sputum specimens are necessary to ensure that laboratories can diagnose TB properly. In addition, laboratories should have sufficient space to ensure the quality, safety and efficiency of the services provided to clients whose samples are tested, and to ensure the safety of laboratory personnel, patients and visitors *(70)*. Some countries experience difficulties with the implementation and quality assurance of sputum culture, which impacts upon this recommendation as it is dependent on access to quality-assured laboratories that can offer TB culture. Sputum smear and culture examinations are also dependent on the quality of the sputum produced, so care should be taken to obtain adequate specimens and transport them to the laboratory according to standard procedures to maintain the viability of the bacilli to get a valid culture result.

In programmatic settings, the practitioner treating MDR-TB patients is typically guided not only by bacteriological tests but also by markers of response to treatment or of disease progression, such as the patient's general condition, weight gain over time, resolution of disease manifestations, blood indices and results of imaging (e.g. chest radiography). The potential use of Xpert MTB/RIF assay in monitoring treatment response has yet to be determined *(71,72)*.

The implementation of more frequent culture testing would require appropriate resources to be made available, both for the laboratories undertaking the tests as well as the patient who may have to spend more time visiting the facilities and, at times, pay for the testing. Patient values and preferences need to be considered to ensure a more acceptable service and patient-centred delivery of care. Increased monitoring should not be done at the expense of overburdening the laboratory services or upsetting health equity by displacing resources from other essential components of the programme.

Monitoring and evaluation

Culture and microscopy results for tests performed in patients on MDR-TB treatment should be captured in the second-line TB treatment register as well as the respective laboratory registers *(12)*. Sometimes these registers may exist as part of an electronic laboratory or patient information system, which facilitates greatly the access of data in real time by multiple users and can also help limit errors. It is important for the programme manager to assess the records in the second-line TB treatment register for completeness of testing using both culture and sputum smear microscopy, any discordance between the two modalities, and whether decisions on regimen changes or assignment of outcome are coherent (e.g. does a case have sufficient negative culture test results available to be classified as *Cured*?). Performance indicators help improve the quality of care, such as contamination rates, turnaround times and proportion of culture tests done without results being recorded in the patient information system. In the case of repeated positive cultures, repeat testing for drug susceptibility or resistance is important.

Section 6. Start of antiretroviral therapy in patients on second-line antituberculosis regimens

Recommendation

6.1. Antiretroviral therapy is recommended for all patients with HIV and DR-TB requiring second-line antituberculosis drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of antituberculosis treatment (strong recommendation, very low quality evidence).

Justification and evidence

The recommendation in this section addresses one PICO question (*see* Annex 1):

PICO question 6 (DR-TB, 2011). In patients with HIV infection and drug-resistant TB receiving antiretroviral therapy, is the use of drugs with overlapping and potentially additive toxicities, compared with their avoidance, more or less likely to lead to cure or other outcomes?[29]

Evidence was reviewed from 10 studies *(73–82)* to assess patient treatment outcomes when ART and second-line antituberculosis drugs were used together. None of the data were from RCTs. Individual patient data were available for 217 drug-resistant TB patients in total, of whom 127 received ART. The level of evidence in individual observational studies varied from a low to a very low quality.

Summary of findings

The pooled IPD from longitudinal cohort studies showed a lower risk of death and a higher likelihood of cure and resolution of TB signs and symptoms in patients using ART compared with those not using ART (low-quality evidence). There is very low-quality evidence for other outcomes that were considered critical or important for decision-making (for example, SAEs from second-line drugs for DR-TB, occurrence of sputum smear or culture conversion, interactions of ART with antituberculosis drugs and default from treatment). Available data did not allow assessment for a number of other outcomes of interest, namely, avoiding the acquisition of additional drug resistance, preventing TB transmission, sustaining relapse-free cure, establishing the optimal duration of MDR-TB treatment, avoiding unnecessary MDR-TB treatment, reducing cost and improving population access to appropriate care.

Benefits

The strong recommendation for the use of ART is based in part on indirect evidence from its use in any patient with active TB, which shows large beneficial effects and a very high mortality when ART is not employed *(83)*, particularly in highly immunocompromised patients (CD4 cell count <50 cells/mm^3) *(84,85)*. In the absence of other data specific to patients with DR-TB receiving second-line antituberculosis medication, the decision on when to start ART should be no different from the approach to the HIV-positive drug-susceptible TB patient. ART should thus be initiated regardless of CD4 cell count and as soon as antituberculosis treatment is tolerated, ideally as early as 2 weeks and no later than 8 weeks after initiation of antituberculosis treatment *(83,86)*.

[29] The outcomes considered for this question comprised: 1. Cure (treatment failure), 2. Prompt initiation of appropriate treatment, 3. Avoiding the acquisition or amplification of drug resistance, 4. Survival (death from TB), 5. Staying disease-free after treatment; sustaining a cure (relapse), 6. Case-holding so the TB patient remains adherent to treatment (default or treatment interruption due to non-adherence), 7. Population coverage or access to appropriate treatment of drug-resistant TB, 8. Smear or culture conversion during treatment, 9. Accelerated detection of drug resistance, 10. Avoidance of unnecessary MDR-TB treatment, 11. Population coverage or access to diagnosis of drug-resistant TB, 12. Prevention or interruption of transmission of drug-resistant TB to other people, including other patients and health-care workers, 13. Shortest possible duration of treatment, 14. Avoiding toxicity and adverse reactions from antituberculosis drugs, 15. Cost to the patient, including direct medical costs and other costs such as transportation and lost wages due to disability, 16. Resolution of TB signs and symptoms; ability to resume usual life activities, 17. Interaction of antituberculosis drugs with non-TB medications, and 18. Cost to the TB control programme (*see also* Annex 1).

Risks

The successful implementation of this recommendation will depend upon the availability of more providers trained specifically in the care of HIV and DR-TB, and drug–drug interactions. A substantial increase in the availability of and patient's access to treatment, and additional support for ensuring adherence would likely be needed. The need for increased integration of HIV and TB care for effective patient management, prompt evaluation of AEs and case-holding throughout treatment will necessitate more resources. For the benefit of the user, a table of AEs for which both an antiretroviral agent and an antituberculosis medicine have been implicated and could conceivably interact was included when these guidelines were published. Updated information on drug–drug interactions between antiretroviral and antituberculosis medicines is now available online *(35)*.

Values and preferences

A high value was placed on outcomes such as prevention of early death and TB transmission, and a lower value was placed on the resources required to make ART available to all MDR-TB patients infected with HIV.

Section 7. Surgery for patients on MDR-TB treatment

Recommendation

7.1. In patients with RR-TB or MDR-TB, elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen (conditional recommendation, very low certainty in the evidence).

Justification and evidence

The recommendation in this section addresses one PICO question (*see* Annex 1):

PICO question 4 (DR-TB, 2016). Among patients on MDR-TB treatment, are the following two interventions (delay in start of treatment and elective surgery) likely to lead to cure and other outcomes?[30]

Surgery has been employed in treating TB patients since before the advent of chemotherapy. In many countries, it remains one of the treatment options for TB. With the challenging prospect in many settings of inadequate regimens to treat MDR/XDR-TB, and the risk of serious sequelae, the role of pulmonary surgery is being re-evaluated as a means to reduce the amount of lung tissue with intractable pathology, reduce bacterial load and thus improve prognosis. The review for this question was based on both an IPD-MA to evaluate the effectiveness of different forms of elective surgery as an adjunct to combination medical therapy for MDR-TB *(87)*, as well as a systematic review and study-level meta-analysis *(88)* (online Annex 7; [DR-TB, 2016]). Demographic, clinical, bacteriological, surgical and outcome data of MDR-TB patients on treatment were obtained from the authors of 26 cohort studies participating in the adult individual patient data (aIPD) *(42)*. The analyses summarized in the GRADE tables consist of three strata comparing treatment success (e.g. cure and completion) with different combinations of treatment failure, relapse, death and loss to follow up. Two sets of such tables were prepared for (i) partial pulmonary resection, and (ii) pneumonectomy.

In the study-level meta-analysis that examined all forms of surgery together, there was a statistically significant improvement in cure and successful treatment outcomes among patients who received surgery. However, when the aIPD meta-analysis examined patients who underwent partial lung

[30] The outcomes are listed in Annex 1. They comprise: 1. Cured/completed by end of treatment, 2. Culture conversion by 6 months, 3. Failure, 4. Relapse, 5. Survival (or death), 6. Adverse reactions (severity, type, organ class), and 7. Adherence to treatment (or treatment interruption due to non-adherence).

resection and those who had a more radical pneumonectomy versus patients who did not undergo surgery, those who underwent partial lung resection had statistically significantly higher rates of treatment success. Those patients who underwent pneumonectomy did not have better outcomes than those who did not undergo surgery. Prognosis appeared to be better when partial lung resection was performed after culture conversion. This effect was not observed in patients who underwent pneumonectomy. There are several important caveats to these data. Substantial bias is likely to be present, as only patients judged to be fit for surgery would have been operated upon. No patient with HIV coinfection in the aIPD underwent lung resection surgery. Therefore, the effects of surgery among HIV-infected patients with MDR-TB could not be evaluated. Rates of death did not differ significantly between those who underwent surgery versus those who received medical treatment only. However, the outcomes could be biased because the risk of death could have been much higher among patients in whom surgery was prescribed had they not been operated upon.

Subgroup considerations

The relative benefits of surgery are expected to depend substantially on the population subgroups that are targeted. The analysis could not provide a refined differentiation of the type of patient who would be best suited to benefit from the intervention or the type of intervention that would have the most benefit. The effect is expected to be moderate in the average patient considered appropriate for surgery. The odds of success for patients with XDR-TB were statistically significantly lower when they underwent surgery compared with other patients (aOR 0.4, 95% CL: 0.2–0.9). This effect is likely to be biased, given that patients who underwent surgery would have had other factors predisposing to poor outcomes, which could not be adjusted for.

Implementation considerations

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

Monitoring and evaluation

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

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

Recommendations

8.1. Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment (strong recommendation, moderate certainty in the evidence).

8.2. A package of treatment adherence interventions[31] may be offered to patients on TB treatment in conjunction with the selection of a suitable treatment administration option[32] (conditional recommendation, low certainty in the evidence).

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

[32] Treatment administration options include DOT, non-daily DOT, VOT or unsupervised treatment.

8.3. One or more of the following treatment adherence interventions (complementary and not mutually exclusive) may be offered to patients on TB treatment or to health-care providers:

a) tracers[33] and/or digital medication monitor[34] (conditional recommendation, very low certainty in the evidence);

b) material support[35] to the patient (conditional recommendation, moderate certainty in the evidence);

c) psychological support[36] to the patient (conditional recommendation, low certainty in the evidence);

d) staff education[37] (conditional recommendation, low certainty in the evidence).

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

a Community- or home-based DOT is recommended over health facility-based DOT or unsupervised treatment (conditional recommendation, moderate certainty in the evidence).

b) DOT administered by trained lay providers or health-care workers is recommended over DOT administered by family members or unsupervised treatment (conditional recommendation, very low certainty in the evidence).

c) Video-observed treatment (VOT) may replace DOT when the video communication technology is available, and it can be appropriately organized and operated by health-care providers and patients (conditional recommendation, very low certainty in the evidence).

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

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

Justification and evidence

The recommendations in this section address three PICO questions (*see* Annex 1).

PICO question 10 (DS-TB, 2017). In patients with TB, are any interventions to promote adherence to TB treatment more or less likely to lead to the outcomes listed below?[38]

PICO question 7 (DR-TB, 2011). Among patients with MDR-TB, is ambulatory therapy, compared with inpatient treatment, more or less likely to lead to the outcomes listed below?[39]

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[33] Tracers refer to the communication with the patient, including home visits or via SMS, telephone (voice) call.

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

[35] Material support can be food or financial support: meals, food baskets, food supplements, food vouchers, transport subsidies, living allowance, housing incentives, or financial bonus. This support addresses the indirect costs incurred by patients or their attendants in order to access health services and, possibly, tries to mitigate the consequences of income loss related to the disease.

[36] Psychological support can be counselling sessions or peer-group support.

[37] Staff education can be adherence education, chart or visual reminders, educational tools and desktop aids for decision-making and reminders.

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

[39] The outcomes are listed in Annex 1. They comprise: 1. Cure (treatment failure). 2. Prompt initiation of appropriate treatment. 3. Avoiding the acquisition or amplification of drug resistance. 4. Survival (death from TB). 5. Staying disease-free after treatment; sustaining a cure (relapse). 6. Case holding so the TB patient remains adherent to treatment (default or treatment interruption due to non-adherence). 7. Population coverage or access to appropriate treatment of drug-resistant TB. 8. Smear or culture conversion during treatment. 9. Accelerated detection of drug resistance. 10. Avoiding unnecessary MDR-TB treatment. 11. Population coverage or access to diagnosis of drug-resistant TB. 12. Prevention or interruption of transmission of drug-resistant TB to other people, including other patients and health-care workers. 13. Shortest possible duration of treatment. 14. Avoiding toxicity and adverse reactions from antituberculosis drugs. 15. Cost to the patient, including direct medical costs and other costs such as transportation and lost wages due to disability. 16. Resolution of TB signs and symptoms; ability to resume usual life activities. 17. Interaction of antituberculosis drugs with non-TB medications. 18. Cost to the TB control programme.

PICO question 11 (DS-TB, 2017). Is decentralized treatment and care for MDR-TB patients more or less likely to lead to the outcomes listed below?[40]

Treatment supervision. Currently, WHO defines DOT as any person observing the patient taking medications in real time. The treatment observer does not need to be a health-care worker, but could be a friend, a relative or a lay person who works as a treatment supervisor or supporter. Observed treatment may also be achieved with real-time video observation and video recording. However, in this document, DOT refers to treatment administered under direct observation by another person. Adherence definitions varied across the studies. However, in general, adherence was defined as taking >90% of medications under conditions of direct observation by another person.

The systematic review conducted in support of this guideline was based on synthesis of data from RCTs *(89–96)* and from observational studies *(97–110)*, with preference given to the results of RCTs. Outcomes of DOT and SAT given under standard TB practice and without any additional support were compared. DOT could be administered by a health-care worker, a family member or a community member and either at home, in the patient's community or at a clinic. DOT was generally administered daily. The GDG focused preferentially on RCT data from the systematic review. When the data from RCTs were limited or not available, observational study data were examined and their results presented. Interpretation of the associations, however, needs caution due to limitations of the observational data when the associations are confounded by different factors. In uncontrolled observational studies, for instance, patients with more severe disease or higher risk of non-adherence are likely to be assigned DOT and patients who are less sick or less likely to be non-compliant are assigned SAT. The same may apply to the selection of DOT location, DOT provider or other interventions in cohort studies.

When DOT alone was compared with SAT, patients who were on DOT had better rates of treatment success, adherence and 2-month sputum conversion; and also had slightly lower rates of loss to follow up and acquired drug resistance. However, patients on DOT had a slightly higher relapse rate. The GDG considered that, overall, the evidence was inconsistent in showing a clear advantage of DOT alone over SAT or vice versa. However, the evidence showed that some subgroups of patients (e.g. TB patients living with HIV) with factors affecting treatment adherence are likely to benefit more from DOT than other patients; or specific types of DOT delivery (e.g. locations of DOT or DOT providers) are likely to work better than others. The evidence also showed that when patients received treatment adherence interventions (e.g. different combinations of patient education, staff education, material support, psychological support, tracer and use of medication monitor) in conjunction with DOT or SAT, treatment outcomes were significantly improved compared to DOT or SAT alone (*see below*). Only cohort studies were available to examine DOT and SAT in HIV-positive TB patients *(111–127)*, and many of these studies were conducted in the pre-ART era or shortly after the introduction of early ART for HIV-positive TB patients *(123–126)*. As above, DOT could have been administered by a variety of people in a variety of settings, including homes and clinics, and occasionally, during the initial intensive phase of treatment, it was hospital-based. A few studies provided incentives and enablers or provided DOT only for persons considered to be at higher risk of loss to follow up. HIV-positive TB patients on SAT had lower rates of treatment success, treatment completion and cure. They had higher rates of mortality, treatment failure and loss to follow up. The evidence showed that HIV-positive TB patients, as a subgroup, benefit more from DOT than general TB patients do, and that SAT alone is not advisable in HIV-positive TB patients. Reasons such as increased rates of drug–drug interactions and more severe disease in this cohort may cause DOT to offer a significant advantage over SAT. DOT and SAT in MDR-TB patients were also examined in the systematic review. However, very limited data were available from a cohort study *(114)*. There were higher rates of mortality and non-adherence and lower rates of treatment completion in MDR-TB patients on SAT compared with those on DOT, although the differences were not significant.

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

DOT provider. RCTs *(91,93–95)* and observational studies *(98,99,102,104,109,112,117,119,120,122,123,127)* were available for examination of the effect of DOT providers versus SAT. Providers were grouped as health-care workers, lay providers and family members. The health-care worker group was varied and included personnel working at different levels of health-care systems and who had received health training. Health-care workers could be nurses, physicians or trained community health workers. Lay providers were also varied and could include teachers, community volunteers or traditional healers. DOT by lay providers had higher rates of treatment success and cure, and a slightly lower rate of loss to follow up compared with SAT. Patients receiving DOT from a family member had higher rates of treatment success and lower rates of loss to follow up compared with patients using SAT. When DOT provided by a health-care worker was compared to SAT, there were higher rates of cure and adherence, and lower rates of relapse and acquisition of drug resistance with health-care worker DOT. The effect that different types of DOT provider had on outcomes was also examined. DOT provided by health-care workers and DOT provided by lay persons were compared. Only observational studies were available in the literature *(99,102,119,128–132)*. Slightly higher rates of success, and lower rates of mortality, failure and loss to follow up were observed among patients who had DOT administered by a lay provider versus a health-care worker, although the difference was not statistically significant.

When provision of DOT by a family member was compared to provision of DOT by a health-care worker, there were higher rates of mortality, loss to follow up and failure, and lower rates of successful treatment, cure and treatment adherence among patients who had DOT administered by family members. Therefore, although DOT by a health-care worker, trained lay provider and family member showed advantages compared to SAT, provision by trained lay providers and health-care workers are the preferred options for DOT and a family member is the least preferred DOT provider.

DOT location. RCTs and observational studies examined how DOT location affected treatment outcome. Locations were grouped by community- or home-based DOT, and health facility-based DOT *(91,93,95,97,104,109,117,119,122,123,133–170)*. Community- or home-based DOT was defined as DOT delivered in the community close to the patient's home or workplace. In general, community- or home-based DOT was provided close to the patients. Health facility-based DOT was defined as DOT delivered at a health centre, clinic or hospital. There were some instances of community- or home-based DOT being provided by health-care workers. When comparing DOT locations, community- or home-based DOT had higher rates of treatment success, cure, treatment completion and 2-month sputum conversion. Community- or home-based DOT also had lower rates of mortality and lower rates of unfavourable outcomes compared with health facility-based DOT. When comparing community-/home-based DOT or health facility-based DOT with SAT, there were no significant differences across the outcomes in RCTs. However, cohort studies showed higher rates of treatment success and adherence, and a lower rate of loss to follow up with community-/home-based DOT compared with SAT. Observational data from cohort studies also showed lower rates of treatment completion, and slightly higher rates of failure and loss to follow up in health-facility DOT compared to SAT. Therefore, community- or home-based DOT is the preferred option rather than health facility-based DOT and SAT. Combining the evidence on DOT provider and DOT location, DOT should preferably be delivered at home or in the community and by a health-care worker or trained lay provider. DOT delivered at a health facility, DOT provided by a family member and unsupervised treatment are not preferred options.

Video-observed treatment (VOT). For VOT there were only two cohort studies from high-income countries and no data from low- and middle-income countries *(171,172)*. These studies compared in-person DOT with VOT done in real time. Patients who were provided with VOT had no statistically significant difference in treatment completion and mortality compared to patients who had in-person DOT. Although there is some concern as to the indirectness of evidence for VOT, as the studies were conducted in high-income countries and the uncertainty of evidence surrounding the use of VOT, the results from the two cohort studies showed that in-person DOT was not better than VOT. DOT has been the standard of care that many programmes aim for, even if in practice they have to resort to SAT in many patients because of lack of resources. The advantages of using VOT are its potential to observe adherence to treatment from a distance – and even when people travel and cannot visit

or be visited by a DOT provider. VOT is also more flexible to people's schedules by offering virtual observation at different times of the day. VOT could help achieve better levels of patient interaction at a much lower cost and less inconvenience when compared with in-person DOT. VOT can be used as an addition to, or interchangeable with, in-person DOT or other treatment administration options. For instance, it is not expected that a patient receives VOT as the sole option of supervision during the whole duration of treatment. Furthermore, the technology required for VOT (broadband Internet and smartphone availability) is becoming increasingly available in resource-constrained settings. Moreover, VOT delivery options are evolving (e.g. enhanced possibility for real-time communication in addition to recorded video), and therefore evidence and best practices are likely to develop further in the coming years, especially from ongoing RCTs. The benefits of VOT may become more apparent as programmes are able to choose forms of VOT that best meet their needs. In fact, VOT may be particularly useful for easing the burden on the health-care system in low- and middle-income countries.

Package of combined treatment adherence interventions. Both RCTs and observational studies examining the effects of combined treatment adherence interventions were reviewed *(137–143,172–178)*. When patients receiving combined treatment adherence interventions along with DOT or SAT were compared to those receiving DOT or SAT alone, patients who received combined treatment adherence interventions had higher rates of treatment success, treatment completion, cure and adherence, and lower rates of mortality and loss to follow up. The mixture of types of adherence interventions was varied (Table 8.1). These included different combinations of patient education, staff education, material support (e.g. food, financial incentives, transport fees, bonuses for reaching treatment goals), psychological support and counselling. The treatment adherence interventions also included tracers such as home visits, use of digital health communication (e.g. SMS, telephone calls) or a medication monitor. The interventions should be selected on the basis of assessment of the individual patient's needs, providers' resources and conditions for implementation.

Table 8.1. Treatment adherence interventions

Treatment adherence intervention	Description
Patient education	Health education and counselling.
Staff education	Education, chart or visual reminder, educational tool and desktop aid for decision-making and reminder.
Material support	Food or financial support such as meals, food baskets, food supplements, food vouchers, transport subsidies, living allowance, housing incentives or financial bonus. This support addresses indirect costs incurred by patients or their attendants in accessing health services and, possibly, tries to mitigate the consequences of income loss related to the disease.
Psychological support	Counselling sessions or peer-group support.
Tracer	Communication with the patient, including home visit or via mobile telephone communication such as SMS or telephone (voice) call.
Digital medication monitor	A digital medication monitor is a device that can measure the time between openings of the pill box. The medication monitor can give audio reminders or send an SMS to remind the patient to take medications, along with recording when the pill box is opened.

Tracers and digital health interventions rather than VOT. Varied tracers were included in RCTs and observational studies *(171,172,179–191)*. These interventions could include SMS, telephone calls or automated telephone reminders. Patients who missed appointments or failed to collect their medication received reminder letters or home visits by health-care workers. Medication monitors or computer systems in the clinic were also used to aid health-care workers in tracing patients. Medication monitors can measure the time between openings of the pill box, give audio reminders, record when the pill box is opened or send SMS reminders to take medications. There were higher rates of treatment success, treatment adherence and 2-month sputum conversion, and lower rates of mortality, loss to follow up and drug resistance acquisition with tracers, either through home visits or mobile telephone communication (SMS or telephone call). When mobile telephone interventions (SMS or telephone call) were examined separately, there were higher rates of treatment success, cure and 2-month sputum conversion, and lower rates of treatment failure, loss to follow up, poor adherence and unfavourable outcomes with mobile telephone reminders as opposed to no intervention. Medication monitors had better rates of adherence and favourable outcomes, and combined interventions of SMS and medication monitors also showed better adherence compared to no intervention. It should be noted, however, that only a small number of studies were available for all digital health interventions. With all the digital interventions and tracers, including VOT, patient support and the ability of the patient to interact with health-care workers should be preserved. In fact, these interventions should be considered as tools to enable better communication with the health-care provider rather than as replacements for other adherence interventions. In practice, it is expected that SMS, telephone calls and VOT may replace in-person DOT for periods of time rather than for the entire duration and that they promote patient-centred approaches to care. Mobile telephone interventions, tracers and VOT may also increase health equity if the need to travel to a health clinic or to a patient's home is reduced. However, the ability of patients to participate in these programmes depends on the patients living in an area with a good telecommunication infrastructure.

Material support for patients. The effects of material support were examined both with RCTs *(150–153)* and observational studies *(159,192–199)*. The interventions included giving meals with DOT, monthly food vouchers, food baskets, food supplements and vitamins. Food support for patients and family members is an important incentive for TB patients and it also helps protect patients from the catastrophic costs associated with TB. Food may be an incentive, but it may also improve outcome biologically due to reduction in malnutrition and consequent improvement in immune function. Other material support could be financial support in the form of financial incentives, transport subsidies, living allowance, housing incentives or financial bonuses after reaching treatment targets. There were higher rates of treatment success, completion and sputum conversion in patients who received material support, and lower rates of treatment failure and loss to follow up in patients who did not receive material support. It is of note that all of these studies were in low- and middle-income countries, so presumably these incentives were of significant value to the patients in these settings. However, material support would be of significant value to TB patients even in higher-income countries, especially in countries that do not have a good social welfare system, as TB is a disease of poverty. The studies in this review found that material support was usually given to the most vulnerable groups, and therefore health equity was presumably improved by this intervention. However, if these incentives are not applied equitably, health disparities may be increased. The distribution of material support is likely to depend on the country context and may have different effects within and between countries.

Patient education or educational counselling. Analysis of the benefit of patient education included RCTs *(145–148)* and an observational study *(156)*. Patients who received education or educational counselling had better rates of treatment success, treatment completion, cure and treatment adherence, and had lower rates of loss to follow up. It should be noted in this case that "counselling" refers to educational counselling and not psychological counselling. Patient education could include oral or written education via health-care workers or pharmacists. The education could be one-time at discharge from the intensive phase of therapy or at each presentation for follow-up care. The educational session might include only the health-care worker or it might involve the patients' social network and family members. It is important to make sure that education and counselling are

done in a culturally appropriate manner. Additionally, specific marginalized populations may require special educational efforts.

Staff education. Staff education may include peer training, visual aids to help initiate conversations with patients, other tools to aid in decision-making and as reminders, and the education of laboratory staff. This intervention was examined in both RCTs and observational studies *(149,150,199,200)*. There were higher rates of treatment success and slightly lower rates of mortality and loss to follow up with staff education. With better staff education, treatment for patients is likely to improve and any stigma that health-care workers may hold towards patients would decrease, as health-care workers better understand TB disease and TB treatment.

Psychological support. Psychological support was varied and could include self-help groups, alcohol cessation counselling and TB clubs *(137,155,201)*. Patients who had access to psychological support had higher rates of treatment completion and cure, as well as lower rates of treatment failure and loss to follow up. However, the GDG had concerns about confounding in these studies due to the severity of illness in the groups receiving support. Additionally, allocation of patients to the support groups was not always randomized. When considering these data, it should also be noted that psychological support types are very broad and may not be adequately represented in this review. To maximize health equity, psychological support should be targeted at the most marginalized populations.

Ambulatory care. Outcomes from models of MDR-TB care based mainly on clinic-based ambulatory treatment were compared with those using mainly hospital-based inpatient treatment. The data used came from cost–effectiveness studies in four countries (Estonia and the Russian Federation [Tomsk oblast] *(202)*, Peru *(203)* and the Philippines *(204)*).The design of these observational studies did not allow direct comparison of effects between models of care. Given that none of the studies were RCTs, the evidence was considered of very low quality. Cost–effectiveness was modelled for all possible WHO Member States in a probabilistic analysis of the data from the four countries *(205)*.

A high value was placed on conserving resources and on patient outcomes such as preventing death and transmission of MDR-TB as a result of delayed diagnosis and inpatient treatment. There should always be provision for a back-up facility to manage patients who need inpatient treatment. This may be necessary in certain patient groups at particular risk, such as children during the intensive phase, among whom close monitoring may be required for a certain period of time.

Decentralized care. As the use of Xpert MTB/RIF expands, more patients will be diagnosed and enrolled on MDR-TB treatment. Having treatment and care provided in decentralized health-care facilities is a practical approach to scaling up treatment and care for patients who are eligible for MDR-TB treatment. Therefore, a systematic review of the treatment and care of bacteriologically confirmed or clinically diagnosed MDR-TB patients in decentralized versus centralized systems was conducted to gather evidence on whether the quality of treatment and care is likely to be compromised with a decentralized approach. Data from both RCTs and observational studies were analysed, the majority being from low- and middle-income countries *(201,206–213)*. The review provided additional value to the recommendation in the previous guidelines *(2)* on ambulatory over hospitalized models of care for MDR-TB patients, where the evidence was examined only for treatment and care of patients outside or inside hospitals. In the review, decentralized care was defined as care provided in the local community where the patient lives, by non-specialized or peripheral health centres, by community health workers or nurses, non-specialized doctors, community volunteers or treatment supporters.

Care could occur at local venues or at the patient's home or workplace. Treatment and care included DOT and patient support, in addition to injections during the intensive phase. In this group, a brief phase of hospitalization of less than 1 month was accepted for patients who were in need in the initial phase of treatment or when they had any treatment complications. Centralized care was defined as inpatient treatment and care provided solely by specialized DR-TB centres or teams for the duration of the intensive phase of therapy or until culture or smear conversion. Afterwards, patients could receive decentralized care. Centralized care was usually delivered by specialist doctors or nurses and could

include centralized outpatient clinics (outpatient facilities located at or near the site of the centralized hospital). Analysis of the data showed that treatment success and loss to follow up improved with decentralized care compared to centralized care. The risks of death and treatment failure showed minimal differences between patients undergoing decentralized care and centralized care.

There were limited data on adverse reactions, adherence, acquired drug resistance and cost. Both HIV-negative and HIV-positive persons were included in the reviewed studies; however, the studies did not stratify patients according to HIV status. There was some discussion regarding the quality of the data. The GDG expressed concerns that health-care workers may have selected for the centralized care groups those patients who they thought might have a worse prognosis. None of the studies controlled for this risk of bias.

Subgroup considerations

Treatment administration. Although the reviewed evidence did not allow for conclusions about the advantages of DOT over SAT or vice versa for TB patients, in a subgroup analysis of TB patients living with HIV, DOT showed a clear benefit with significantly improved treatment outcomes. It is likely that DOT may be not beneficial for all patients but is likely to have more benefit in certain subgroups of TB patients. Apart from HIV-positive TB patients, other factors or groups of patients that were more or less likely to result in treatment adherence and therefore require DOT were not within the scope of the systematic review.

Decentralized care. Decentralized care may not be appropriate for patients with severe TB disease, extremely infectious forms of the disease, serious comorbidities or those for whom treatment adherence is a concern. Measures to protect the safety of patients on MDR-TB regimens, especially those containing new or novel medicines, need to be maintained in outpatient settings. These recommendations for decentralized care should not preclude hospitalization if appropriate. This review did not include patients requiring surgical care.

Implementation considerations

Treatment adherence interventions. As treatment supervision alone is not likely to be sufficient to ensure good TB treatment outcomes, additional treatment adherence interventions need to be provided. Patient education should be provided to all patients on TB treatment. A package of the other treatment adherence interventions also needs to be offered to patients on TB treatment. The interventions should be selected on the basis of an assessment of the individual patient's needs, provider's resources and conditions for implementation. With regard to telephone or video-assisted interventions, there may be reluctance to use new technology, making implementation more difficult. There may be privacy concerns surrounding security of telephone data, so encryption and other measures to safeguard privacy will need to be considered. The feasibility of implementing these types of interventions depends on telecommunication infrastructure, telephone availability and connection costs. Multiple organizations have initiated programmes such as these, so TB programmes may find it helpful to collaborate and communicate with other medical service delivery programmes that have already set up infrastructure. There may be reluctance on the part of implementers (e.g. national or local governments, health partners) to pay for incentives. Implementers may be more willing to pay for material support for smaller subgroups with particularly high risk (e.g. patients with MDR-TB). However, one of the components of the End TB Strategy *(206)* is to provide "social protection and poverty alleviation" for patients with TB. This publication specifically calls for measures to "alleviate the burden of income loss and non-medical costs of seeking and staying in care". Included in these suggested protections are social welfare payments, vouchers and food packages. The benefit of material support found in this review supports these components of the End TB Strategy *(206)*. In order to distribute the material support, government and/or nongovernment organization (NGO) infrastructure would need to be in place, including anti-fraud mechanisms (e.g. reliable unique personal identifiers) and

appropriate accounting to ensure that incentives are distributed equitably and to the people who need them most. Countries should choose incentives that are the most appropriate for their situation.

Treatment administration. Community-based or home-based DOT has more advantages than health facility-based DOT, though family members should not be the first or only option for administering DOT. DOT is better provided at home or in the community and by trained lay providers or health-care workers. There may be challenges in providing community- or home-based DOT by health-care workers because of the increased number of health-care workers required and the increased costs of staff time and daily travel to the community or patient's home. DOT provision in the community or at home by trained local lay persons is more feasible. A combination of lay provider and health-care worker for provision of community- or home-based DOT is also an option. Community-based or home-based DOT is more likely to be acceptable and accessible to patients than other forms of DOT. However, stigma may continue to be an issue with community- or home-based DOT. Having a health-care worker coming regularly to a patient's house may be stigmatizing and the feeling of being "watched over" may be disempowering for patients. Other forms of DOT (e.g. administered by an emotionally supportive relative or close friend) may be more acceptable but may still be stigmatizing. Given complex family social dynamics, family members may not always be the best people to supervise treatment, and the suitability of such treatment adherence supervisors needs to be carefully analysed in each national or local context. If family members are providing DOT, careful identification and training of those persons is required. Additional supervision of local supporters or health-care workers is still needed, as family members cannot be depended on as the only option for care. Patients will continue to need social support, even if family members are providing DOT. Assessment of potential risk factors for poor adherence must be taken into account by health-care workers at the start of treatment in order to decide which treatment administration option should be selected for the patient. Some groups of patients who are less likely to adhere to treatment may benefit more from DOT than others. Another factor to consider when selecting treatment administration options is that some patients with inflexible work or family responsibilities may not be able to do DOT. Any option of treatment administration offered to a patient must be provided in conjunction with proper medical care, including regular pick-up of TB drugs, consultations with a physician or other health-care workers when necessary, TB treatment that is free of charge, and provision to the patient of essential information on TB treatment.

Ambulatory care. Cost varied widely across the modelled settings. The cost per disability-adjusted life year (DALY) averted by an ambulatory model in one setting was sometimes higher than the cost per DALY averted by a hospitalization model in another setting. However, cost per DALY averted was lower under outpatient-based care than under inpatient-based care in the vast majority (at least 90%) of settings for which cost–effectiveness was modelled. The variation in cost–effectiveness among settings correlated most strongly with the variation in the cost of general health-care services and other non-drug costs. Despite the limitations in the data available, there was no evidence that was in conflict with the recommendation and which indicated that treatment in a hospital-based model of care leads to a more favourable treatment outcome.

The overall cost–effectiveness of care for a patient receiving treatment for MDR-TB can be improved with an ambulatory model. The benefits include reduced resource use, and at least as many deaths avoided among primary and secondary cases compared with hospitalization models. This result is based on clinic-based ambulatory treatment (patients attend a health-care facility); in some settings, home-based ambulatory treatment (provided by a worker in the community) might improve cost–effectiveness even further. The benefit of reduced transmission can be expected only if proper infection control measures are in place in both the home and the clinic. Potential exposure to people who are infectious can be minimized by reducing or avoiding hospitalization where possible, reducing the number of outpatient visits, avoiding overcrowding in wards and waiting areas, and prioritizing community-care approaches for TB management *(214)*. The regimen used in one of the studies on ambulatory care was from a time when the combinations of medicines were not yet optimized, so outcomes achieved were probably inferior to those that can be obtained with the regimens in use

today. Admission to hospitals for patients who do not warrant it may also have important social and psychological consequences that need to be taken into account.

There may be some important barriers to accessing clinic-based ambulatory care, including distance to travel and other costs to individual patients. Shifting costs from the service provider to the patient has to be avoided, and implementation may need to be accompanied by appropriate enablers. While placing patients on adequate therapy would be expected to decrease the bacterial load and transmission of DR-TB, infection control measures for home-based and clinic-based measures will need to be part of an ambulatory model of care to decrease the risk of transmission in households, the community and clinics. TB control programmes will have to consider whether they are capable of reallocating resources from hospital to ambulatory care support in order to undertake the necessary changes in patient management. The choice between these options will affect the feasibility of implementing the recommendation in a particular programme.

Decentralized care. National TB programmes should have standardized guidelines regarding which patients are eligible for decentralized care. Patient preference should be given a high value when choosing centralized or decentralized care.

Decentralized care for MDR-TB patients requires appropriate treatment supervision, patient education and social support, staff training, infection control practices and quality assurance. The optimal treatment supervision options and treatment adherence interventions recommended in this section should be considered for MDR-TB patients on decentralized care.

Several of the studies in the review addressed treatment costs. However, the cost estimates were found to vary widely and no concrete recommendations could be made on the basis of cost. Resource requirements are likely to vary because TB treatment programmes are highly variable, so costs for these programmes vary across different countries. The GDG raised several issues for TB programmes to consider. Although hospitalization is generally thought to be more expensive than outpatient care, the costs of good outpatient programmes can also be significant. Additionally, outpatient costs may vary significantly according to the services provided. A cost-saving measure to consider in decentralized care is that patients may be able to receive treatment faster. The financial benefits of decentralized care would include finding patients before they are very ill and require more medical care, while treating people before TB can be transmitted to contacts would be a public health benefit.

If a patient is living with a person from a high-risk group, such as a PLHIV or a young child, there may be complications in sending the patient home for treatment. However, the risk posed to these high-risk groups varies significantly, depending on whether the TB programme gives preventive treatment to high-risk persons. Studies involving preventive therapy for MDR-TB therapy are ongoing.

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

Research priorities

In addition to summarizing the available evidence, the reviews undertaken for these consolidated guidelines revealed several gaps in current knowledge about critical areas in DR-TB treatment and care. The estimates of effect for patient studies were commonly assigned a low or very low certainty rating, which is one of the main reasons why most of the recommendations in these guidelines are conditional. Some gaps persist from the ones identified in previous TB treatment guidelines *(6)*. When completing the GRADE evidence-to-decision frameworks, there was a lack of studies about how patients, caregivers and other stakeholders value different treatment options and outcomes, such as time to sputum conversion, cure, treatment failure and relapse, death and SAEs. Implementation research, studies of resource use, incremental cost, acceptability, feasibility, equity, values and preferences of patients and health-care workers, and the inclusion of indicators of quality of life would be relevant to many priority questions in the programmatic management of DR-TB.

The research priorities that were identified by the successive GDGs are grouped by the respective sections of these guidelines, although a number of them are interlinked.

Section 1. Regimens for isoniazid-resistant tuberculosis

The development of the current recommendations was made possible by the availability of a global Hr-TB IPD. As in other IPD analyses conducted to inform WHO treatment guidelines in recent years, the Hr-TB IPD analysis facilitated the comparison of different patient groups, some adjustment for covariates and better interpretation of the results *(43)*. It is important for researchers and national programmes to continue contributing patient records to the Hr-TB IPD to increase its value as a source of information for future treatment policy.

It should be noted that all recommendations were conditional and were based on very low certainty in the estimates of effect. Thus, further research is needed to inform the refinement of policies to optimize the treatment of Hr-TB. The GDG identified various research priorities, including the following:

- The need for RCTs evaluating the efficacy, safety and tolerability of regimens for Hr-TB, and for cases with additional resistance to other medicines such as ethambutol or pyrazinamide (e.g. polydrug resistance);
- Research to clarify the potential benefits and risks of treatment with high-dose isoniazid;
- High-quality studies on optimizing the composition and duration of regimens in children and adults, particularly of high-dose isoniazid, fluoroquinolones, and other second-line medicines and reducing the duration of pyrazinamide;
- Modelling studies to estimate the number-needed-to-treat for empirical use of an Hr-TB regimen, balancing risks to benefits;
- High-quality studies on treatment prolongation among HIV-positive individuals;
- High-quality studies evaluating regimens for extrapulmonary or disseminated TB;
- Feasibility of developing FDCs for REZ alone (with or without integrating levofloxacin);
- Monitoring patient response by isoniazid resistance genotype (e.g. *kat*G vs. *inh*A mutations), either in an individual patient or distribution of genotypes in a population;
- Cost–effectiveness of different approaches to DST, including rapid testing of all TB patients for both isoniazid and rifampicin resistance before the start of treatment;

- Participatory action research within communities and with other stakeholders (e.g. field practitioners, community workers) to explore sociocultural factors that can facilitate treatment adherence and influence outcomes;
- Effect of underlying fluoroquinolones/isoniazid polydrug resistance on treatment outcomes;
- Diagnostic accuracy of second-line LPAs in rifampicin-sensitive patients.

Section 2. The composition of longer MDR-TB regimens

- The optimal combination of medicines and approach to regimen design for adults and children with MDR/RR-TB with or without additional resistance to key agents;
- RCTs, especially involving new drugs and regimens, remain rare. The release of results from the first Phase III trials for MDR-TB has led to substantial debate about the clinical relevance of the design and end-points chosen for these studies, requiring at times additional, off-protocol analysis of data to explore the potential added value of the experimental interventions.
- Inclusion and separate reporting of outcomes for key subgroups in RCTs, especially children, pregnant and breastfeeding women, and HIV-positive individuals on treatment;
- Studies of pharmacokinetics and safety to determine optimal drug dosing (especially in pregnancy) and the effect of extemporaneous manipulation of existing dosing forms;
- Complete recording of AEs and standardized data on organ class, seriousness, severity and certainty of association to allow meaningful comparison of the association between AEs and exposure to different medicines between studies, patient subgroups and different regimens;
- Determination of the minimum number of drugs and treatment duration (especially in patients previously treated for MDR-TB);
- Improved diagnostics and DST methods (e.g. which test for pyrazinamide, especially for medicines for which no rapid molecular methods are currently available in the field);
- Further research and developments would be particularly helpful for the following agents:
  - *Levofloxacin:* optimization of the dose (the Opti-Q study will provide new information on this shortly *(215)*);
  - *Bedaquiline:* use in children to determine optimal pharmacokinetic properties; revised cost–effectiveness analyses based on the IPD-MA; optimization of the duration in both adults and children;
  - *Linezolid:* optimization of the dose and duration in both adults and children; patient predictors for adverse reactions;
  - *Clofazimine:* optimization of the dose especially in children; any added value in using a loading dose; availability of DST methods;
  - *Cycloserine/terizidone:* differences in efficacy between the two medicines; approaches to test for susceptibility to them; best practices in psychiatric care for persons on these medicines;
  - *Delamanid:* better understanding of its role in MDR-TB regimens, including in children (pharmacokinetics/pharmacodynamics [PK/PD]), PLHIV and pregnant women; mechanisms of development of drug resistance; optimization of the duration in both adults and children;
  - *Pyrazinamide:* molecular testing for resistance (pursuing either LPA or other approach);
  - *Carbapenems:* given their effectiveness in the evidence reviews, further research on their role in MDR-TB regimens is important, including the potential role and cost–effectiveness of ertapenem (that can be given intramuscularly) as a substitute for meropenem and imipenem–cilastatin;
  - *Amikacin:* the safety and effectiveness of thrice-weekly administration at a higher dose (about 25 mg/kg/day) *(54)*.

Section 3. The duration of longer MDR-TB regimens

- Identification of factors that determine the optimal duration of treatment (e.g. previous treatment history, baseline resistance patterns, site of disease, age);

- Exploration of strategies to optimize the balance of benefits versus harms of regimen duration through risk-stratification approaches.

Section 4. Use of the standardized shorter MDR-TB regimen

- The effectiveness/safety of variants of the shorter MDR-TB treatment regimen in which the injectable agent is replaced by an oral agent (e.g. bedaquiline) and the total duration reduced to 6 months or less;
- Comparison of the effectiveness of these variants of the shorter regimen would be helpful in
  - patient subgroups that have often been systematically excluded from studies or country programme cohorts, such as children, patients with additional resistance, those with extrapulmonary TB, pregnant/breastfeeding women;
  - settings where background resistance to drugs other than fluoroquinolones and second-line injectable agents is high (e.g. pyrazinamide or high-level isoniazid resistance).

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

- Future analysis on the predictors and biomarkers of treatment failure (related to strain, regimen and host), in addition to bacteriological response, in the following important subgroups would be helpful to identify more resource-saving options and reduce the time needed to make decisions:
  - patients <15 years of age
  - patients with extrapulmonary disease (different forms)
  - patients on shorter MDR-TB regimens (standardized or all-oral variants);
- It will also be helpful to keep assessing the potential role of future-generation rapid molecular testing beyond diagnostic testing to also monitor treatment response;
- Engineering challenges to implementing more affordable liquid culture systems should be evaluated.

Section 7. Surgery for patients on MDR-TB treatment

- The role of surgery (i.e. decisions about when to operate and the type of surgical intervention, drug-resistance patterns) needs to be better defined;
- Improved collection, reporting, standardization of data on surgery, including long-term survival post-surgery.

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

- Patient support and treatment supervision interventions that are best suited to particular populations;
- Patient support interventions that are most effective in low- and middle-income countries;
- Analysis of the cost–effectiveness of different types of incentives;
- Research into the effectiveness of VOT in low- and middle-income countries, as the available data are from high-income countries;
- Which types of psychological support are most appropriate;
- Evaluation of the risk of TB transmission in different settings, i.e. does treatment centred on hospital care or outpatient clinics pose a higher risk of transmission?
- Additional cost–effectiveness studies of decentralized versus centralized care;
- Systematic collection and publication of data on decentralized care. Many programmes provide decentralized care, but very few have published the data.

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WHO treatment guidelines for isoniazid-resistant tuberculosis, 2018

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WHO Guideline Steering Committee

The following staff served as the WHO Steering Committee for the development of the current policy guideline: Dennis FALZON, Medea GEGIA, Christopher GILPIN, Licé GONZÁLEZ-ANGULO, Ernesto JARAMILLO, Linh NGUYEN, Karin WEYER and Matteo ZIGNOL from the WHO Global TB Programme (WHO/GTB); Meg DOHERTY from the WHO HIV Department; Piero OLLIARO from the Special Programme for Research and Training in Tropical Diseases (TDR); and Edward KELLEY from the WHO Service Delivery and Safety Department. The guideline text was drafted by Dennis FALZON and Licé GONZÁLEZ-ANGULO with contributions from Alexei KOROBITSYN, under the guidance and supervision of Ernesto JARAMILLO and Karin WEYER, and the overall direction of Mario RAVIGLIONE, director of WHO/GTB. The document was reviewed and finalized following the input of the GDG, ERG and the WHO Guideline Steering Committee, ahead of submission to the Guideline Review Committee of WHO (GRC) in June 2017.

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

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[41] Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012;9(8):e1001300.

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

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WHO treatment guidelines for drug-resistant tuberculosis, 2016 update

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Guidelines for the treatment of drug-susceptible tuberculosis and patient care, 2017 update

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[42] WHO/GTB staff members were also invited to be part of the development of the ATS/CDC/IDSA guideline.

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Annex 1: PICO questions

1a. PICO question from the *WHO treatment guidelines for isoniazid resistant tuberculosis, 2018*

Q1. *In patients with isoniazid-resistant tuberculosis (other than MDR-TB), which treatment regimen composition and duration, when compared with 6 or more months of rifampicin–pyrazinamide–ethambutol, leads to a higher likelihood of success with least possible risk of harm?*

Population	Intervention	Comparator	Outcomes
Isoniazid-resistant TB cases: with/out *kat*G mutation and use of normal dose/high-dose isoniazid; with/out *inh*A promoter mutation and use of normal dose/ high-dose isoniazid; in whom ethambutol, pyrazinamide or injectable agents are unlikely to work; previously treated for TB; with extensive disease; with HIV; with HIV on antiretroviral therapy; children (0–14 years); and with diabetes	6REZ	>6REZ	• Treatment completed or bacteriological cure by end of treatment; • Treatment failure ± relapse; • Survival (or death); • Adverse reactions from anti-TB medicines (severity, type, organ class); and • Acquisition (amplification) of drug resistance
	6+RE + 2Z + fluoroquinolone	6+REZ	
	6+REZ + fluoroquinolone	6+REZ	
	6+REZ + injectable agent	6+REZ	

E: ethambutol; H: isoniazid; R: rifampicin; Z: pyrazinamide

1b. PICO questions from the *WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update*

Q1. *In patients with rifampicin-resistant or multidrug-resistant TB (MDR/RR-TB) is a shorter treatment regimen (9–12 months) more or less likely to safely improve outcomes than longer regimens conforming to WHO guidelines?*[43]

Population	Intervention	Comparator	Outcomes
MDR/RR-TB patients a. previously treated with second-line drugs or not b. with severe disease (cavities on radiography) c. with additional drug resistance patterns (for first-line and second-line agents; specificity on mutation H, Z, ETO, fluoroquinolone, injectable agent, etc.); d. with history of patient use ethambutol, ethionamide or pyrazinamide e. children (0–14 years)/adults (adolescents 10–19 years if available); f. persons with HIV (± ARVs); g. pregnant women; h. people with diabetes; i. persons with extrapulmonary disease j. persons with malnutrition	– duration of 9–12 months – injectable agent for 4–6 months – combination of drugs (usually 7 in the intensive phase and 4–5 in the continuation phase)	– Use of at least 4 effective second-line drugs plus pyrazinamide – Injectable agent given for about 8 months, at least 4 months after culture conversion – Total treatment for about 20 months, and at least 18 months past the date of culture conversion to negative – Injectable agent given until smear conversion and total treatment for at least 12 months after smear conversion	• Culture conversion by 6 months • Successful completion of treatment (or lack of successful completion) • Bacteriological cure by the end of treatment • Adherence to treatment (or treatment interruption due to non-adherence) • Treatment failure or relapse • Survival (or death) • Adverse reactions to anti-TB medicines • Acquisition (amplification) of drug resistance

ARV: antiretroviral (drug); Eto: ethionamide; H: isoniazid; MDR/RR-TB: multidrug-resistant/rifampicin-resistant TB; TB: tuberculosis; Z: pyrazinamide

[43] At the time this PICO was formulated, the characteristics of longer and shorter regimens were as described in the *WHO treatment guidelines for drug-resistant tuberculosis, 2016 update* (apps.who.int/iris/bitstream/10665/250125/1/9789241549639-eng.pdf). The previous WHO recommendation for a longer regimen can be found in the 2011 edition of the guidelines (whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf). WHO-recommended longer regimens referred to in this Annex have a duration of 18 months or more.

Q2. *In patients with rifampicin-resistant or multidrug-resistant TB (MDR/RR-TB), which individual agents are more likely to improve outcomes when forming part of a longer regimen conforming to WHO guidelines?*[44]

Population	Intervention	Comparator	Outcomes
a. MDR/RR-TB **without** resistance **or** severe intolerance to the second-line drugs b. MDR/RR-TB **with** resistance **or** severe intolerance to • Fluoroquinolones, including Ofx and Cpx (by mutation pattern) • Second-line injectable agents, both classes • Fluoroquinolones + second-line injectable agents (i.e. XDR-TB ± other resistance) • Pyrazinamide • Group C agents (ethionamide, prothionamide, cycloserine, terizidone, linezolid and clofazimine) c. children (0–14 years) / adults (adolescents 10–19 years if available) d. persons with HIV (± ARVs) e. pregnant women f. people with diabetes g. persons with extrapulmonary disease h. persons with malnutrition	A second-line regimen as per WHO guidelines that INCLUDES:[45]		• Culture conversion by 6 months • Successful completion of treatment (or lack of successful completion) • Bacteriological cure by the end of treatment • Adherence to treatment (or treatment interruption due to non-adherence) • Treatment failure or relapse • Survival (or death) • Adverse reactions to anti-TB medicines • Acquisition (amplification) of drug resistance
	– fluoroquinolones (Mfx/Lfx/Gfx)	– no fluoroquinolones or a fluoroquinolone of a different generation (Ofx/Mfx/Lfx/Gfx)	
	– injectable agents (Km/Am/Cm)[46]	– no injectable agent or a different one (Km/Am/Cm)	
	– prothionamide or ethionamide	– no prothionamide or ethionamide	
	– cycloserine or terizidone	– no cycloserine or terizidone	
	– linezolid	– no linezolid	
	– clofazimine	– no clofazimine	
	– pyrazinamide	– no pyrazinamide	
	– high-dose isoniazid	– no high-dose isoniazid	
	– ethambutol	– no ethambutol	
	– bedaquiline	– no bedaquiline	
	– delamanid	– no delamanid	
	– individual Group D3 agent[47]	– individual Group D3 agent[46] absent	
	– sutezolid[48]	– no sutezolid	
	– interferon G[48]	– no interferon gamma	
	– perchlozone[48]	– no perchlozone	

Am: amikacin; ARV: antiretroviral (drug); Cm: capreomycin; Cpx: ciprofloxacin; Eto: ethionamide; H: isoniazid; Gfx: gatifloxacin; Km: kanamycin; Lfx: levofloxacin; MDR/RR-TB: multidrug-resistant/rifampicin-resistant TB; Mfx: moxifloxacin; Ofx; ofloxacin; TB: tuberculosis; XDR-TB: extensively-drug resistant TB; Z: pyrazinamide

[44] The evidence for this PICO question will be used to review the currently recommended cascade for a longer regimen design (*see* Table 6 of *(6)*). Among others, the best use of bedaquiline and delamanid and their combined use will be examined.

[45] Very few studies are known to have made head-to-head comparisons of MDR-TB medicines at different dosages. If such information is available it will be used to guide the systematic review and presentation of effects.

[46] Additional detail on the effectiveness and safety of injectable agents used three times weekly (at 15 mg or 25 mg/kg/day) vs daily would be of interest.

[47] Group D3 agents: *p*-aminosalicylic acid (PAS), imipenem–cilastatin, meropenem, amoxicillin–clavulanate (used alone or with carbapenems), thioacetazone.

[48] As yet unauthorized by US Food and Drug Administration (FDA), European Medicines Agency (EMA) or other stringent regulatory authorities.

Q3. *In patients with rifampicin-resistant or multidrug-resistant TB (MDR/RR-TB) on longer regimens composed in accordance with WHO guidelines, are outcomes safely improved with fewer or more than five effective medicines in the intensive phase?*[49]

Population	Intervention[44]	Comparator *(current WHO recommendation)*	Outcomes
MDR/RR-TB patients a. XDR-TB vs no XDR-TB b. surrogate of advanced disease (cavitary disease on radiography or SS+) c. use of bedaquiline, delamanid and other dividual medicines beyond 6 months d. children (0–14 years)/adults (adolescents 10–19 years if available) e. persons with HIV (± ARVs) f. pregnant women g. people with diabetes h. persons with extrapulmonary disease i. persons with malnutrition	– **More agents**: intensive phase with >5 TB medicines likely to be effective; continuation phase with 4 or more medicines likely to be effective – **Fewer agents**: intensive phase with 4 medicines; continuation phase with 3 medicines Specify the grouping to which the medicines belong (A, B, C, D1, D2, D3) and their likely effectiveness	Intensive phase with 5 agents likely to be effective; continuation phase with 4 agents likely to be effective	• Culture conversion by 6 months • Successful completion of treatment (or lack of successful completion) • Bacteriological cure by the end of treatment • Adherence to treatment (or treatment interruption due to non-adherence) • Treatment failure or relapse • Survival (or death) • Adverse reactions to anti-TB medicines • Acquisition (amplification) of drug resistance

ARV: antiretroviral (drug); MDR/RR-TB: multidrug-resistant/rifampicin-resistant TB; SS+: sputum smear positive; XDR-TB: extensively drug-resistant TB

A agents: levofloxacin, moxifloxacin, gatifloxacin

B agents: amikacin, capreomycin, kanamycin, (streptomycin)

C agents: ethionamide/ prothionamide, cycloserine/terizidone, linezolid, clofazimine

D1 agents: pyrazinamide, ethambutol, high-dose isoniazid

D2 agents: bedaquiline, delamanid

D3 agents: *p*-aminosalicylic acid, imipenem–cilastatin, meropenem, amoxicillin–clavulanate, (thioacetazone)

[49] *See* Implementation considerations under Section 2 for the definition of "effective agents". The evidence for this PICO question will be used to review the currently recommended cascade for longer regimen design (*see* Table 6 of *(6)*).

Q4. *In patients with rifampicin-resistant or multidrug-resistant TB (MDR/RR-TB) on longer regimens composed in accordance with WHO guidelines, are outcomes safely improved with an intensive phase shorter or longer than 8 months?*

Population	Intervention	Comparator	Outcomes
MDR/RR-TB patients a. previously treated with a first-line regimen (for new or retreatment cases) b. previously treated for MDR-TB c. with XDR-TB vs no XDR-TB d. surrogate of advanced disease (cavitary disease on radiography or SS+) e. use of bedaquiline, delamanid and other individual medicines beyond 6 months f. children (0–14 years)/adults (adolescents 10–19 years if available) g. persons with HIV (± ARVs) h. persons with extrapulmonary disease	– duration of intensive phase 8 months or more (in different brackets) Matching by : – number of likely effective agents	– duration of intensive phase <8 months (in different monthly groupings)	• Culture conversion by 6 months • Successful completion of treatment (or lack of successful completion) • Bacteriological cure by the end of treatment • Adherence to treatment (or treatment interruption due to non-adherence) • Treatment failure or relapse • Survival (or death) • Adverse reactions to anti-TB medicines • Acquisition (amplification) of drug resistance

ARV: antiretroviral (drug); MDR/RR-TB: multidrug-resistant/rifampicin-resistant TB; SS+: sputum smear positive; XDR-TB: extensively drug-resistant TB

Q5. ***In patients with rifampicin-resistant or multidrug-resistant TB (MDR/RR-TB) on longer regimens composed in accordance with WHO guidelines, are outcomes safely improved with a total duration shorter or longer than 20 months?***

Population	Intervention	Comparator	Outcomes
MDR/RR-TB patients a. previously treated with a first-line regimen (for new or retreatment cases) b. previously treated for MDR-TB c. with XDR-TB vs no XDR-TB d. surrogate of advanced disease (cavitary disease on radiography or SS+) e. use of bedaquiline, delamanid and other individual medicines beyond 6 months f. children (0–14 years)/adults (adolescents 10–19 years if available) g. persons with HIV (± ARVs) h. persons with extrapulmonary disease	– total duration of treatment lasting up to 20 months Matching by: – number of likely effective agents	– total duration of treatment lasting more than 20 months (in different monthly groupings)	• Culture conversion by 6 months • Successful completion of treatment (or lack of successful completion) • Bacteriological cure by the end of treatment • Adherence to treatment (or treatment interruption due to non-adherence) • Treatment failure or relapse • Survival (or death) • Adverse reactions to anti-TB medicines • Acquisition (amplification) of drug resistance

ARV: antiretroviral (drug); MDR/RR-TB: multidrug-resistant/rifampicin-resistant TB; SS+: sputum smear positive; XDR-TB: extensively drug-resistant TB

Q6. *In patients with rifampicin-resistant or multidrug-resistant TB (MDR/RR-TB) on longer regimens composed in accordance with WHO guidelines, what is the minimum duration of treatment after culture conversion that is most likely to improve outcomes?*

Population	Intervention	Comparator	Outcomes
MDR/RR-TB patients a. who by month 6 convert sputum culture vs who do not convert b. previously treated with a first-line regimen (for new or retreatment cases) c. previously treated for MDR-TB d. with XDR-TB vs no XDR-TB e. surrogate of advanced disease (cavitary disease on radiography or SS+) f. use of bedaquiline, delamanid and other individual medicines beyond 6 months g. children (0–14 years)/adults (adolescents 10–19 years if available) h. persons with HIV (± ARVs) i. persons with extrapulmonary disease	the duration of treatment after culture conversion up to 12 months (in different brackets) Matching by: – duration of intensive phase – number of likely effective agents	the duration of treatment after culture conversion >12 months (in different monthly groupings)	• Culture conversion by 6 months • Successful completion of treatment (or lack of successful completion) • Bacteriological cure by the end of treatment • Adherence to treatment (or treatment interruption due to non-adherence) • Treatment failure or relapse • Survival (or death) • Adverse reactions to anti-TB medicines • Acquisition (amplification) of drug resistance

ARV: antiretroviral (drug); MDR/RR-TB: multidrug-resistant/rifampicin-resistant TB; SS+: sputum smear positive; XDR-TB: extensively drug-resistant TB

Q7. In patients with rifampicin-resistant or multidrug-resistant TB (MDR/RR-TB) treated with longer or shorter regimens composed in accordance with WHO guidelines, is monitoring using monthly cultures, in addition to smear microscopy, more likely to detect non-response to treatment?

Population	Intervention	Comparator *(current WHO recommendations)*	Outcomes
MDR/RR-TB patients a. on longer regimens vs shorter regimen b. previously treated with a first-line regimen (for new or retreatment) c. previously treated for MDR-TB d. with XDR-TB vs no XDR-TB e. surrogate of advanced disease (cavitary disease on radiography or SS+) f. number of likely effective agents g. persons with HIV (± ARVs)	Vary the – timing of culture conversion/ number of months with negative cultures – composite of culture conversion + other indicators of response to treatment (e.g. radiography changes, need to change regimen)	Monthly sputum smear and culture[51]	• Culture conversion by 6 months • Treatment failure or relapse • Acquisition (amplification) of drug resistance

ARV: antiretroviral (drug); MDR/RR-TB: multidrug-resistant/rifampicin-resistant TB; SS+: sputum smear positive; XDR-TB: extensively drug-resistant TB

[50] This recommendation was made in the 2011 WHO treatment guidelines and was based on modelling of data from patients on longer regimens, which showed increased risk of treatment failure as frequency of culture testing diminished in the continuation phase *(69)*.

1c. PICO questions from the Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update

Q6. In patients with HIV infection and drug-resistant TB receiving antiretroviral therapy, is the use of drugs with overlapping and potentially additive toxicities, compared with their avoidance, more or less likely to lead to the outcomes listed in Table 2?

Q7. Among patients with MDR-TB, is ambulatory therapy, compared with inpatient treatment, more or less likely to lead to the outcomes listed in Table 2?

Table 2: Most important possible outcomes when making decisions on choice of testing and treatment strategies for drug-resistant-TB

Outcomes (text in parentheses shows the same outcome phrased in the negative)	Average score	Relative importance
1. Cure (treatment failure)	8.7	Critical
2. Prompt initiation of appropriate treatment	8.3	Critical
3. Avoiding the acquisition or amplification of drug resistance	8.1	Critical
4. Survival (death from TB)	7.9	Critical
5. Staying disease-free after treatment; sustaining a cure (relapse)	7.6	Critical
6. Case-holding so the TB patient remains adherent to treatment (default or treatment interruption due to non-adherence)	7.6	Critical
7. Population coverage or access to appropriate treatment of drug-resistant TB	7.5	Critical
8. Smear or culture conversion during treatment	7.4	Critical
9. Accelerated detection of drug resistance	7.4	Critical
10. Avoiding unnecessary MDR-TB treatment	7.2	Critical

Outcomes (text in parentheses shows the same outcome phrased in the negative)	Average score	Relative importance
11. Population coverage or access to diagnosis of drug-resistant TB	7.1	Critical
12. Prevention or interruption of transmission of drug-resistant TB to other people, including other patients and health-care workers	6.9	Important but not critical
13. Shortest possible duration of treatment	6.7	Important but not critical
14. Avoiding toxicity and adverse reactions from antituberculosis drugs	6.5	Important but not critical
15. Cost to the patient, including direct medical costs and other costs such as transportation and lost wages due to disability	6.4	Important but not critical
16. Resolution of TB signs and symptoms; ability to resume usual life activities	6.3	Important but not critical
17. Interaction of antituberculosis drugs with non-TB medications	5.6	Important but not critical
18. Cost to the TB control programme	5.4	Important but not critical

MDR-TB: multidrug-resistant TB

Table 2 summarizes the scored outcomes that were selected by the Guideline Development Group. Fourteen members submitted scores for outcomes they considered to be the most critical when making decisions on choice of testing and treatment strategies. Members were asked to take a societal perspective in rating the outcomes. Relative importance was rated on an incremental scale:

1–3 points: Not important for making recommendations on choice of testing and treatment strategies for drug-resistant TB.*

4–6 points: Important but not critical for making recommendations on choice of testing and treatment strategies.

7–9 points: Critical for making recommendations on choice of testing and treatment strategies.

* None of the outcomes was scored in this category.

1d. PICO question from the *WHO treatment guidelines for drug-resistant tuberculosis, 2016 update*

Q4. *Among patients on MDR-TB treatment, are the following two interventions (delay in start of treatment and elective surgery) likely to lead to the outcomes listed below?*[51]

Population[52]	Intervention	Comparator	Outcomes
• Patients on MDR-TB treatment • Patients on XDR-TB treatment • Children (0–14 years) vs adults • Persons with HIV (on antiretrovirals) • Pregnant women and people with diabetes	Start of adequate treatment within 4 weeks of diagnosis (or strong presumption)	Treatment started beyond 4 weeks of diagnosis (or strong presumption)	• Cured/completed by the end of treatment • Culture conversion by 6 months • Failure • Relapse • Survival (or death) • Adverse reactions (severity, type, organ class) • Adherence to treatment (or treatment interruption due to non-adherence)
	Elective surgery (different types/ stages of disease)	No elective surgery	

MDR-TB: multidrug-vresistant TB; XDR-TB: extensively drug-resistant TB

[51] The populations are expected to differ for the two subquestions: patients who are surgically operated are more likely to have XDR-TB and persons with HIV who are on antiretrovirals would be particularly important for the first subquestion.

1e. PICO questions from the *Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update*

Q10. *In patients with TB, are any interventions to promote adherence to TB treatment more or less likely to lead to the outcomes listed below?*

Population	Intervention	Comparator	Outcomes
• Patients on treatment for drug-susceptible TB • Patients on treatment for MDR-TB • Children (0–14 years) and adults • HIV-infected and HIV-uninfected persons • TB patients	Any intervention to promote treatment adherence • Supervision of treatment (DOT, virtual (video)-observed therapy) • Measures to improve treatment adherence (e.g. medication monitors and/or SMS or telephone call reminders) • Social support (educational, psychological, material) • Combinations of the above interventions	Routine practice[52]	• Adherence to treatment (or treatment interruption due to non-adherence) • Conventional TB treatment outcomes: cure or treatment completion, failure, relapse, survival/death • Adverse reactions to TB drugs (severity, type, organ class) • Cost to the patient (including direct medical costs as well as others such as transportation, lost wages due to disability) • Cost to the health services

DOT: directly observed treatment; MDR-TB: multidrug-resistant TB

[52] Routine practice: regular TB drugs pick-up and consultations with physician or other health-care workers are available when necessary; TB treatment is free of charge; essential information/health education in relation to TB treatment is provided.

Q11. *Is decentralized treatment and care for MDR-TB patients more or less likely to lead to the outcomes listed below?*

Population	Intervention	Comparator	Outcomes
Patients on treatment for MDR-TB	Decentralized treatment and care (provided by non-specialized or peripheral health centres; by community health workers, community volunteers or treatment supporters) • DOT and patient support • Injection during the intensive phase • Specialist care for comorbidities (e.g. HIV, diabetes, chronic lung diseases, or other conditions such as auditory function, renal function, liver function, neurology, ophthalmology)	Treatment and care provided solely by specialized drug-resistant TB centres or teams	• Adherence to treatment (or treatment interruption due to non-adherence) • Conventional TB treatment outcomes: cure or treatment completion, failure, relapse, survival/death • Adverse reactions to TB drugs (severity, type, organ class) • Acquisition (amplification) of drug resistance • Cost to the patient (including direct medical costs as well as others such as transportation, lost wages due to disability) • Cost to the health services

DOT: directly observed treatment; MDR-TB: multidrug-resistant TB

Annex 2: Dosage by weight band for medicines used in MDR-TB regimens, adults and children

Dosing of medicines used in second-line MDR-TB regimens by weight band in patients older than 14 years

Group	Medicine	Weight-based daily dose	Formulation	Weight bands for patients older than 14 years[a]					Usual upper daily dose[b]	Comments
				30–35 kg	36–45 kg	46–55 kg	56–70 kg	>70 kg		
A	*Fluoroquinolones*									
	Levofloxacin	-[c]	250 mg tab	3	3	4	4	4	1.5 g	
			500 mg tab	1.5	1.5	2	2	2		
			750 mg tab	1	1	1.5	1.5	1.5		
	Moxifloxacin	standard dose[c,d]	400 mg tab	1	1	1	1	1	400 mg	
		high dose[c,d]	400 mg tab	1 or 1.5	1.5	1.5 or 2	2	2	800 mg	as used in the standardized shorter MDR-TB regimen
	Bedaquiline	-[c]	100 mg tab	4 tabs od for first 2 weeks; then 2 tabs od M/W/F for 22 weeks					400 mg	
	Linezolid	-[c]	600 mg tab	(<15 y)	(<15 y)	1	1	1	1.2 g	
B	Clofazimine	-[c]	50 mg cap or tab	2	2	2	2	2	100 mg	
			100 mg cap or tab	1	1	1	1	1	100 mg	
	Cycloserine or terizidone	10–15 mg/kg	250 mg cap	2	2	3	3	3	1 g	

Group	Medicine	Weight-based daily dose	Formulation	Weight bands for patients older than 14 years[a]					Usual upper daily dose[b]	Comments
				30–35 kg	36–45 kg	46–55 kg	56–70 kg	>70 kg		
C	Ethambutol	15–25 mg/kg	400 mg tab	2	2	3	3	3	–	
	Delamanid	–[c]	50 mg tab	2 bd	2 bd	2 bd	2 bd	2 bd	200 mg	
	Pyrazinamide	20–30 mg/kg	400 mg tab	3	4	4	4	5	-	
			500 mg tab	2	3	3	3	4		
	Imipenem-cilastatin	–[c]	0.5 g + 0.5 g vial	2 vials (1 g + 1 g) bd					–	To be used with clavulanic acid
	Meropenem	–[c]	1 g vial (20 ml)	1 vial 3 times per day or 2 vials bd					–	To be used with clavulanic acid
	Amikacin	15–20 mg/kg	500 mg/2 ml vial[e]	2.5 ml	3 ml	3 to 4 ml	4 ml	4 ml	1 g	
	Streptomycin	12–18 mg/kg	1 g vial[e]	Calculate according to the dilution used					1 g	
	Ethionamide or prothionamide	15–20 mg/kg	250 mg tablet	2	2	3	3	4	1 g	Once daily dose advised but can start with 2 divided doses until tolerance improves
	p-aminosalicylic acid	8–12 g/day in 2–3 divided doses	PAS sodium salt (4 g) sachet	1 bd	1 bd	1 bd	1 bd	1 to 1.5 bd	12 g	
			PAS acid (4 g) sachet	1 bd	1 bd	1 bd	1 bd	1 to 1.5 bd		
Other medicines[f]	Isoniazid	4–6 mg/kg (standard dose)[d]	300 mg tab	2/3	1	1	1	1	-	100 mg isoniazid tablet can facilitate the administration of certain dosages Pyridoxine given with isoniazid in patients at risk (such as those with HIV, malnutrition)
		10–15 mg/kg (high dose)[d]	300 mg tablet	1.5	1.5	2	2	2		
	Clavulanic acid[g]	–[c]	125 mg tab[g]	1 bd	1 bd	1 bd	1 bd	1 bd	–	Only to be used with carbapenems

Group	Medicine	Weight-based daily dose	Formulation	Weight bands for patients older than 14 years[a]					Usual upper daily dose[b]	Comments
				30–35 kg	36–45 kg	46–55 kg	56–70 kg	>70 kg		
Other medicines[f]	Kanamycin	15–20 mg/kg	500 mg/2 ml vial[e]	2 to 2.5 ml	2.5 to 3 ml	3 to 4 ml	4 ml	4 ml	1 g	M/W/F dosing of aminoglycosides at 25 mg/kg/day may limit toxicity and inconvenience when the injectable agents are used in longer MDR-TB regimens
	Capreomycin	15–20 mg/kg	500 mg/2 ml vial[e]	2.5 ml	3ml	3 to 4 ml	4 ml	4 ml	1 g	
	Gatifloxacin	–[c]	400 mg tab	2	2	2	2	2	800 mg	Not used in <18 year olds (no quality assured product currently available)
	Thioacetazone	–[c]	150 mg tab	1	1	1	1	1	–	Not used in <18 year olds (no quality assured product currently available)

(<15 y) = follow the separate dose schedule for patients younger than 15 years of age; bd = two times a day; cap = capsule; g = gram; im = intramuscular; iv = intravenous; kg = kilogram; ml = millilitre; mg = milligram; M/W/F = Monday, Wednesday, Friday; soln = solution; susp = suspension; tab = tablet

[a] Dosages were established by the Guideline Development Group for the *WHO treatment guidelines for rifampicin- and multidrug-resistant tuberculosis, 2018 update* and the WHO Global task force on the pharmacokinetics and pharmacodynamics (PK/PD) of TB medicines and other experts. They are based on the most recent reviews and best practices in the treatment of MDR/RR-TB. For certain agents the dosages were informed by pharmacokinetic modelling results based on the principle of allometric scaling (Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol 2008;48:303–32). 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. In patients <30 kg follow the schedule for <15 year olds unless otherwise indicated. If multiple dose options are given for one weight band select the lower or higher option depending on whether the patient is at the lower or higher limit of the body weight range. Dosing more closely to the target mg/kg/day should be aimed for, and is more feasible with oral or parenteral fluids and when solid forms of different dosages are available. Fractioning of tablets into halves or less should be avoided, if possible. Therapeutic drug monitoring is advised when the dose is at the upper and lower ends of the range to minimize the adverse therapeutic consequences of over- and under-exposure, respectively (especially for injectable agents, linezolid and fluoroquinolones).

[b] Clinicians may decide to exceed these values in particular cases to improve therapeutic effect.

[c] No weight-based dosing is proposed.

[d] Unless there is risk of toxicity, the high dose may be used if antimicrobial levels may be lowered because of pharmacokinetic interactions, malabsorption or other metabolic reasons or if the strain has low-level drug resistance.

[e] Weight-based daily dose is for 6 or 7 days/week administration (M/W/F scheduling may permit higher dosing). Volumes shown may differ by preparation. Streptomycin may be diluted in three different ways. For iv use, the volume may be increased.

[f] In the 2018 WHO treatment guidelines, these agents are either no longer recommended (kanamycin, capreomycin), only recommended as a companion agent (amoxicillin/clavulanic acid) or not included because of lack of data from the latest analysis on longer MDR-TB regimens in adults (gatifloxacin, isoniazid and thioacetazone).

[g] Only available in combination with amoxicillin as co-amoxyclav (e.g. 500 mg amoxicillin/125 mg clavulanic acid fixed dose combination). It is given with each dose of carbapenem, either as 125 mg bd or 125 mg 3 times daily.

See the text of the guidelines for more details on the use of medicines.

Dosing of medicines used in second-line MDR-TB regimens by weight band in patients under 15 years[a]

Group	Medicine	Weight-based daily dose[b]	Formulation	Weight bands among patients not yet 15 years old[a]							Usual upper daily dose[b]	Comments
				5–6 kg	7–9 kg	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg		
A	*Fluoroquinolones*											
	Levofloxacin	15–20 mg/kg	100 mg dt	1	1.5	2 or 3	3 or 4	(>14 y)	(>14 y)	(>14 y)	1.5 g	
			250 mg tab	0.5	0.5	1 or 1.5	1.5 or 2	2	3	(>14 y)	1.5 g	
	Moxifloxacin	10–15 mg/kg	100 mg dt[c]	0.8	1.5	2	3	4	(>14 y)	(>14 y)	400 mg	
			400 mg tab[c]	2 ml[c]	3 ml[c]	5 ml[c]	0.5 or 0.75	1	(>14 y)	(>14 y)	400 mg	Use 10 mg/kg in <6 months
	Bedaquiline	–	100 mg tab	–	–	-	2 tabs od for two weeks; then 1 tab od M/W/F for 22 weeks		4 tabs od for 2 weeks; then 2 tabs od M/W/F for 22 weeks		–	Only in patients >5 years old (lower dose from 15–29 kg; higher dose from >29 kg)
	Linezolid	15 mg/kg od in <16 kg 10–12 mg/kg od in >15 kg	20 mg /ml susp	4 ml	6 ml	8 ml	11 ml	14 ml	15 ml	20 ml[d]	600 mg	
			600 mg tab[c]	0.25	0.25	0.25	0.5	0.5	0.5	0.75[d]		
B	Clofazimine	2–5 mg/kg	50 mg cap or tab	1 alt days	1 alt days	1 alt days	1	2	2	(>14 y)	100 mg	Give on alternate days if dose in mg/kg/day is too high
			100 mg cap or tab	M/W/F	M/W/F	1 alt days	1 alt days	1	(>14 y)	(>14 y)	100 mg	
	Cycloserine or terizidone	15–20 mg/kg	125 mg mini capsule (cycloserine)[c]	1	1	2	3	4	(>14 y)	(>14 y)	1 g	
			250 mg cap[c]	4–5 ml[c]	5–6 ml[c]	7–10 ml[c]	2	2	2	(>14 y)	1 g	
C	Ethambutol	15–25 mg/kg	100 mg dt	1	2	3	4	-	-	(>14 y)	–	
			400 mg tab[c]	3 ml[c]	4 ml[c]	6 ml[c]	1	1 or 1.5	2	(>14 y)		

Group	Medicine	Weight-based daily dose[b]	Formulation	Weight bands among patients not yet 15 years old[a]							Usual upper daily dose[b]	Comments
				5–6 kg	7–9 kg	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg		
C	Delamanid	–	50 mg tab	–	–[e]	–[e]	–[e]	1 bd	1 bd	2 bd	200 mg	Only in patients >2 years old (25 mg bd in 3–5 years; 50 mg bd in 6–11 years; 100 mg bd in 12–17 years)
	Pyrazinamide	30–40 mg/kg	150 mg dt	1	2	3	4 or 5	-	-	(>14 y)	–	
			400 mg tab	0.5	0.75	1	1.5 or 2	2.5	3	(>14 y)		
			500 mg tab	0.5	0.5	0.75 or 1	1.5	2	2.5	(>14 y)		
	Imipenem-cilastatin	–	0.5 g + 0.5 g vial	–	–	–	–	–	–	–	–	Not used in patients <15 years (use meropenem)
	Meropenem	20–40 mg/kg iv every 8 hours	1 g vial (20 ml)	2 ml	4 ml	6 ml	8-9 ml	11 ml	(>14 y)	(>14 y)	–	To be used with clavulanic acid
	Amikacin	15–20 mg/kg	500 mg/2 ml vial[f]	0.4 ml	0.6 ml	0.8 - 1.0 ml	1.2 - 1.5 ml	2.0 ml	(>14 y)	(>14 y)	1 g	
	Streptomycin	20–40 mg/kg	1 g vial[f]	Calculate according to the dilution used					(>14 y)	(>14 y)	1 g	
	Ethionamide or prothionamide	15–20 mg/kg	125 mg dt (ethionamide)	1	1	2	3	4	4	(>14 y)	1 g	
			250 mg tab	0.5	0.5	1	2	2	2	(>14 y)	1 g	
	p-aminosalicylic acid	200–300 mg/kg in 2 divided doses	PAS acid (4 g) sachet	0.5–0.75 g bd	0.75–1 g bd	1–2 g bd	2–3 g bd	3–3.5 g bd	(>14 y)	(>14 y)	–	Full dose can be given once daily if tolerated
			PAS sodium salt (4 g) sachet	0.5–0.75 g bd	0.75–1 g bd	1–2 g bd	2–3 g bd	3–3.5 g bd	(>14 y)	(>14 y)		
			PAS sodium salt 60% (9.2 g) sachet	1.5 g bd	2–3 g bd	3–4 g bd	4 or 6 g bd	6 or 8 g bd	8–12 g bd	8–12 g bd	–	

Group	Medicine	Weight-based daily dose[b]	Formulation	Weight bands among patients not yet 15 years old[a]							Usual upper daily dose[b]	Comments
				5–6 kg	7–9 kg	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg		
Other medicines[g]	Isoniazid	15–20 mg/kg (high dose)	50 mg/5 ml soln	8–10 ml	15 ml	20 ml	–	–	–	–		300 mg isoniazid tablet can be used in patients >20 kg Pyridoxine is always given with high-dose isoniazid in children (12.5 mg od in <5 y olds and 25 mg od in >4 y olds)
			100 mg tab	1	1.5	2	3	4	4	(>14 y)		
	Clavulanic acid[h]	–	250 mg amoxicillin/62.5 mg clavulanic acid/5 ml susp[h]	2 ml bd[h]	3 ml bd[h]	5 ml bd[h]	8 ml bd[h]	10 ml bd[h]	(>14 y)	(>14 y)		Only to be used with carbapenems
	Kanamycin	15–20 mg/kg	500 mg/2 ml vial[f]	0.4 ml	0.6 ml	0.8–1.0 ml	1.2–1.5 ml	2.0 ml	(>14 y)	(>14 y)	1 g	1 g vials (3 ml) also available
	Capreomycin	15–20 mg/kg	500 mg/2 ml vial[f]	0.4 ml	0.6 ml	0.8–1.0 ml	1.2–1.5 ml	2.0 ml	(>14 y)	(>14 y)	1 g	1 g vials (2 ml) also available
	Gatifloxacin	–	400 mg tab	–	–	–	–	–	–	–	–	Not used in <18 y olds (no quality assured product currently available)
	Thioacetazone	–	–	–	–	–	–	–	–	–	–	Not used in <18 y olds (no quality assured product currently available)

(>14 y) = follow the separate dose schedule for patients older than 14 years of age; alt = alternate; bd = two times a day; cap = capsule; dt = dispersible tablet; g = gram; im = intramuscular; iv = intravenous; kg = kilogram; ml = millilitre; mg = milligram; M/W/F = Monday, Wednesday, Friday; soln = solution; susp = suspension; tab = tablet

[a] Dosages were established by the Guideline Development Group for the *WHO treatment guidelines for rifampicin- and multidrug-resistant tuberculosis, 2018 update* and the WHO Global task force on the pharmacokinetics and pharmacodynamics (PK/PD) of TB medicines and other experts. They are based on the most recent reviews and best practices in the treatment of MDR/RR-TB. For certain agents the dosages were informed by pharmacokinetic modelling results based on the principle of allometric scaling (Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu

Rev Pharmacol Toxicol 2008;48:303–32). 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. In patients >30 kg follow the schedule for >14 year olds unless otherwise indicated. If multiple dose options are given for one weight band select the lower or higher option depending on whether the patient is at the lower or higher limit of the body weight range. Dosing more closely to the target mg/kg/day should be aimed for, and is more feasible with oral or parenteral fluids and when solid forms of different dosage are available. Fractioning of tablets into halves or less should be avoided if possible. Therapeutic drug monitoring is advised when the dose is at the upper and lower ends of the range to minimize the adverse therapeutic consequences of over- and under-exposure respectively (especially for injectable agents, linezolid and fluoroquinolones).

[b] Clinicians may decide to exceed these values in particular cases to improve therapeutic effect.

[c] Dissolving in 10 ml of water may facilitate administration in patients in lower weight-bands and avoids fractioning solid formulations, although bioavailability is uncertain (use of dispersible tablets is preferred if available).

[d] In individuals >44 kg a dose of 600 mg od is proposed.

[e] May be used in children 3–5 years of age. Giving half a 50 mg adult tablet in these children does not result in the same blood levels observed in trials using the special 25 mg paediatric tablet. Bioavailability may further be altered when the 50 mg tablet is split, crushed or dissolved.

[f] Weight-based daily dose is for 6 or 7 days/week administration (M/W/F scheduling may permit higher dosing). Volumes shown may differ by preparation. Streptomycin may be diluted in three different ways. Dosing closer to the upper limit of the mg/kg/day is more desirable. For iv use, the volume may be increased.

[g] In the 2018 WHO treatment guidelines, these agents are either no longer recommended (kanamycin, capreomycin), only recommended as a companion agent (amoxicillin/clavulanic acid) or not included because of lack of data from the latest analysis on longer MDR-TB regimens in adults (gatifloxacin, isoniazid and thioacetazone).

[h] Only available in combination with amoxicillin as co-amoxyclav. Only to be used with carbapenems, in which case they are given together, e.g. 125 mg bd or 125 mg 3 times daily in the 24–30 kg weight band.

See the text of the guidelines for more details on the use of medicines.

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THE END TB STRATEGY

World Health Organization