WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis

2018 update

Pre-final text
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Pre-final text
These guidelines were developed in compliance with the process for evidence gathering, assessment and formulation of recommendations, as outlined in the WHO Handbook for Guideline Development (version March 2014; available at http://www.who.int/kms/handbook_2nd_ed.pdf).

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WHO/CDS/TB/2018.15
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This pre-final text is being released ahead of a fully edited version scheduled for publication in early 2019 as part of consolidated WHO treatment guidelines on drug-resistant TB tuberculosis. The new recommendations will not change.

Note

These guidelines were updated following a Guideline Development Group (GDG) process carried out throughout 2018 in accordance with WHO requirements (Annexes 1-3)(1). The document replaces other WHO recommendations relating to the treatment of MDR/RR-TB issued since 2011 (2),(3),(4),(5),(6) (see Table 1). The main methods used, the revised dosage of medicines used in second-line regimens and key references are included in this document – Annexes 5, 6 and 7 respectively - while more detail on the approach to the analysis and the GRADE evidence summaries and decision frameworks for each recommendation are available online (Annexes 8-10). The recommendations and other practical information to support their implementation are being reproduced in the latest edition of the WHO Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis(7).
Abbreviations & acronyms

aDSM  active TB drug safety monitoring and management
AE  adverse event
AFB  acid-fast bacilli
AIDS  acquired immunodeficiency syndrome
aOR  adjusted odds ratio
aRD  adjusted risk difference
ART  antiretroviral therapy
CDC  United States Centers for Disease Control and Prevention
CL  (95%) confidence limits
CNS  central nervous system
DST  drug susceptibility testing
ERG  External Review Group
FQ  fluoroquinolones
GDF  Global Drug Facility
GDG  Guideline Development Group
GRADE  Grading of Recommendations Assessment, Development and Evaluation
GRC  WHO Guideline Review Committee
GTB  WHO Global TB Programme
HIV  human immunodeficiency virus
IPD-LR  2018 individual patient data of longer regimens
IPD-MA  individual patient data meta-analysis
IPD-SR  2018 individual patient data of shorter regimens
IQR  interquartile range
LTFU  lost to follow-up
LPA  line probe assay
MDR-TB  multidrug-resistant tuberculosis
MDR/RR-TB  multidrug-/rifampicin-resistant tuberculosis
MTBDRsl  GenoType Mycobacterium tuberculosis drug-resistant second-line assay
MUHC  McGill University Health Centre
OR  odds ratio
PICO  Population, Intervention, Comparator and Outcomes
PK/PD  pharmacokinetics/pharmacodynamics
PLHIV  people living with HIV
PSM  propensity score matching
RCT  randomized controlled trial
R  rifampicin
ROBINS-I  risk of bias in non-randomized studies of interventions
RR-TB  rifampicin-resistant TB
SAE  serious adverse event
SD  standard deviation
SLD  second-line TB (drug) medicine
SLI  second-line injectable agent
TB  tuberculosis
UNION  International Union Against Tuberculosis and Lung Disease
US NIH (NIAID)  United States National Institutes of Health (National Institute of Allergy and Infectious Diseases)
WHO  World Health Organization
XDR-TB  extensively drug-resistant tuberculosis

1 See also page 17 for abbreviations of the names of TB medicines
Important definitions

**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 Annex 10). In children <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 TB bacteriology (smear, Xpert MTB/RIF, culture) may also be considered when determining disease severity.

The **intensive (or injectable) phase**, as in use in these guidelines and in the evidence reviews that informed the recommendations, is the initial part of a shorter or longer MDR-TB treatment during which an injectable agent - amikacin, capreomycin, kanamycin or streptomycin – is used. Regimens without an injectable agent are considered not to have an intensive phase.

**Longer MDR-TB regimens** are treatments for MDR/RR-TB which last 18 months or more and which 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 term “conventional” was previously used to refer to such regimens but was discontinued in 2016 when WHO first issued a recommendation for the use of a 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 to isoniazid, or resistant to isoniazid (i.e. MDR-TB), or resistant to other first-line TB medicines (poly-resistant) or second-line TB medicines (e.g. XDR-TB). In these guidelines and elsewhere the MDR-TB and RR-TB cases are often grouped together as MDR/RR-TB.

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 purposes of the reviews conducted for these guidelines, are those adverse events (AE) 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.

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 3 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 (11),(12).
**Executive summary**

Tuberculosis (TB) strains with multidrug- and rifampicin-resistance (MDR/RR-TB) are more difficult to treat than drug-susceptible TB and threaten global progress towards the targets of the End TB Strategy set by the World Health Organization (WHO). The *WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update* addresses the mandate of WHO to inform health professionals in Member States on how to improve MDR/RR-TB care.

In 2018, WHO convened a Guideline Development Group (GDG) to update its policy recommendations on the treatment of MDR/RR-TB. The GDG was composed of a multidisciplinary group of external experts with experience in different aspects of the programmatic management of MDR/RR-TB as well as affected individuals. Ahead of their meeting in July 2018 in Switzerland, the GDG defined seven priority questions for the updated guidelines to cover. Topical areas of uncertainty on the composition and duration of longer MDR-TB regimens for adults and children, on when the standardized 9-12 month shorter MDR-TB regimen may be offered and the use of culture to monitor treatment response were included in the scope. Other aspects of MDR/RR-TB care for which no new evidence has emerged since the last time WHO policy was revised, such as the timing of antiretroviral therapy in MDR/RR-TB patients with human immunodeficiency virus (PLHIV), use of surgery and different models of care, were not reviewed and previous policies thus remain valid.

Fresh evidence reviews and individual patient data meta-analyses (IPD-MA) were commissioned to inform the GDG about the most recent findings. This evidence base included data from recently completed Phase III trials of delamanid and the shorter MDR-TB regimen; IPD-MA with over 13,100 records from patients treated with longer MDR-TB regimens in 40 countries; another IPD-MA with over 2,600 records from patients treated with the 9-12 month shorter MDR-TB regimens from 15 countries, and pharmacokinetic and safety data from trials of bedaquiline and delamanid in patients under 18 years of age. The GRADE method (Grading of Recommendations, Assessment, Development and Evaluation) was used to summarize evidence and to formulate the recommendations and accompanying remarks.

The new recommendations, based on the most recent available evidence, signal an important departure from previous approaches to treat MDR/RR-TB (see Table 1). Injectable agents are no longer among the priority medicines when designing longer MDR-TB regimens, with kanamycin and capreomycin not recommended any more. Fully oral regimens should thus become the preferred option for most patients. Three medicines – fluoroquinolones (levofoxacin or moxifloxacin), bedaquiline and linezolid – are strongly recommended to use in a longer regimen, which is completed with other medicines ranked by a relative balance of benefits to harms. Most regimens would include at least four agents likely to be effective in the first 6 months and three thereafter. The proposed total duration of longer MDR-TB regimens is about 18-20 months, modified depending upon patient response. The standardised, shorter MDR-TB regimen may be offered to eligible patients who agree to a briefer treatment (9-12 months) that may be less effective than an individualized longer regimen and that requires a daily injectable agent for at least four months. Monitoring MDR-TB regimens with monthly culture rather than sputum microscopy alone offers the best option to detect a failing regimen in time for corrective action.

The recommendations on the composition, duration and monitoring of longer MDR-TB regimens apply generally to children and adults, to PLHIV and to MDR/RR-TB patients who have additional resistance to fluoroquinolones or other agents, subject to specific conditions. Bedaquiline may now be given to children aged 6 years and more and delamanid from 3 years of age. 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. Supportive measures to improve diagnostics and other programmatic components will be critical. Ahead of enrolment on MDR-TB treatment, all patients should be appropriately counselled to enable participatory decision-making. Patient-centred support for medication adherence and active TB drug safety monitoring and management (aDSM) are essential for anyone starting an MDR-TB regimen. The new guidance will be complemented with further advice on their implementation in a revised edition of WHO’s *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis*.
Table 1. Summary of changes made to the WHO evidence-based recommendations in 2018 compared with previous guidance

<table>
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<tbody>
<tr>
<td><strong>Treatment of patients with RR-TB</strong> (6)</td>
<td><strong>[Minimal change]</strong></td>
</tr>
<tr>
<td>It is recommended that any patient – child or adult – with RR-TB in whom isoniazid resistance is absent or unknown be treated with a recommended MDR-TB regimen, either a shorter MDR-TB regimen, or if this cannot be used, a longer MDR-TB regimen to which isoniazid is added.</td>
<td>It is recommended that any patient – child or adult – with RR-TB in whom isoniazid resistance is absent or unknown be treated with a recommended MDR-TB regimen, either a longer MDR-TB regimen to which isoniazid may be added or a standardised shorter MDR-TB regimen.</td>
</tr>
</tbody>
</table>

**Composition of longer MDR-TB treatment regimens**

In the treatment of patients with MDR-TB, ethionamide (or prothionamide) should be used (2).

In the treatment of patients with MDR-TB, a fluoroquinolone should be used (2).

In the treatment of patients with MDR-TB, a later-generation fluoroquinolone rather than an earlier-generation fluoroquinolone should be used (2).

**[Substantial changes]**

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 (5). 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.

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2 Strong recommendations in the 2018 guidelines are highlighted; all other recommendations are conditional. More details about the strength and conditions under which the recommendations apply, as well as the certainty in the evidence underpinning them are found elsewhere in this document or in the earlier guidelines referenced. Until future evidence reviews indicate a need for revision, previous recommendations that were not revised in 2018 continue to apply.

3 For the conditions of use of isoniazid in longer MDR-TB regimens see Section 1; for a description of the shorter MDR-TB regimen see the Main Definitions and Section 3.

4 See also text and Table 2 for prioritization of choice, optimal number of effective agents and further details on conditions of use.

5 Classification of medicines in 2018 guidelines: 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).
**EARLIER GUIDELINES (2011-2017)**

In patients with RR-TB or MDR-TB, a regimen with at least five effective TB medicines during the intensive phase is recommended, including pyrazinamide and four second-line TB medicines – one chosen from Group A, one from Group B, and at least two from Group C. If the minimum number of effective TB medicines cannot be composed as given above, an agent from Group D2 and other agents from Group D3 may be added to bring the total to five.(6)

In patients with RR-TB or MDR-TB, it is recommended that the regimen be further strengthened with high-dose isoniazid and/or ethambutol.(6)

Bedaquiline may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB.(3)

Delamanid may be added to a WHO-recommended regimen in patients with pulmonary MDR-TB older than 5 years.(4)

Delamanid may be added to the WHO-recommended longer regimen in children and adolescents (6 – 17 years) with multidrug- or rifampicin-resistant TB (MDR/RR-TB) who are not eligible for the shorter MDR-TB regimen, a under specific conditions.(5)

**NEW GUIDELINES (2018)**

Levofolexacin or moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens (strong recommendation)

Bedaquiline should be included in longer MDR-TB regimens for patients aged 18 years or more (strong recommendation). 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 (strong recommendation).

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.

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(6) Classification of medicines in the 2016 guidelines: Group A=levofolexacin, moxifloxacin, gatifloxacin; Group B=amikacin, capreomycin, kanamycin, (streptomycin); Group C=ethionamide (or prothionamide), cycloserine (or terizidone), linezolid, clofazimine; Group D2=bedaquiline, delamanid; Group D3=p-aminosalicylic acid, imipenem-cilastatin, meropenem, amoxicillin-clavulanate, (thioacetazone). [Group D1 was composed of pyrazinamide, ethambutol and high-dose isoniazid](6)
<table>
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<tr>
<td>Imipenem-cilastatin or meropenem may be included in the treatment of MDR/RR-TB patients on longer regimens.(^7)</td>
<td>Imipenem-cilastatin or meropenem may be included in the treatment of MDR/RR-TB patients on longer regimens.(^7)</td>
</tr>
<tr>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Ethionamide or prothionamide may only be included in the treatment of MDR/RR-TB patients on longer regimens if bedaquiline, linezolid, clofazimine or delamanid are not used or if better options to compose a regimen are not possible.</td>
<td>Ethionamide or prothionamide may only be included in the treatment of MDR/RR-TB patients on longer regimens if bedaquiline, linezolid, clofazimine or delamanid are not used or if better options to compose a regimen are not possible.</td>
</tr>
<tr>
<td>(p)-aminosalicylic acid may only be included in the treatment of MDR/RR-TB patients on longer regimens if bedaquiline, linezolid, clofazimine or delamanid are not used or if better options to compose a regimen are not possible.</td>
<td>(p)-aminosalicylic acid may only be included in the treatment of MDR/RR-TB patients on longer regimens if bedaquiline, linezolid, clofazimine or delamanid are not used or if better options to compose a regimen are not possible.</td>
</tr>
<tr>
<td>Clavulanic acid should not be included in the treatment of MDR/RR-TB patients on longer regimens (strong recommendation).(^7)</td>
<td>Clavulanic acid should not be included in the treatment of MDR/RR-TB patients on longer regimens (strong recommendation).(^7)</td>
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</table>

\(^7\) Imipenem-cilastatin (Imp-Cln) and meropenem (Mpm) are administered with clavulanic acid, which is only available in formulations combined with amoxicillin (Amx-Clv). When included, clavulanic acid is not counted as an additional effective TB agent and should not be used without Imp-Cln or Mpm.
<table>
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<tr>
<td><strong>Duration of longer MDR-TB treatment regimens</strong>&lt;sup&gt;(2)&lt;/sup&gt;</td>
<td><strong>[Minimal changes in the duration of intensive phase and total duration; new recommendation on the length of treatment after culture conversion]</strong></td>
</tr>
<tr>
<td>In the treatment of patients with MDR-TB, an intensive phase of eight months is suggested for most patients; the duration may be modified according to the patient’s response to therapy.</td>
<td>In MDR/RR-TB patients on longer regimens containing amikacin or streptomycin, an intensive phase of 6-7 months is suggested for most patients, and the duration may be reduced or increased according to the patient’s response to therapy.</td>
</tr>
<tr>
<td>In the treatment of patients newly diagnosed with MDR-TB (i.e. not previously treated for MDR-TB), a total treatment duration of 20 months is suggested for most; the duration may be modified according to the patient’s response to therapy.</td>
<td>In MDR/RR-TB patients on longer regimens, a total treatment duration of 18-20 months is suggested for most patients, and the duration may be modified according to the patient’s response to therapy.</td>
</tr>
<tr>
<td><strong>Use of a shorter MDR-TB treatment regimen</strong>&lt;sup&gt;(6)&lt;/sup&gt;</td>
<td><strong>[Minimal change in eligibility; but the role of the shorter regimen as a treatment option changes]</strong></td>
</tr>
<tr>
<td>In patients with RR-TB or MDR-TB who were not previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents was excluded or is considered highly unlikely, a shorter MDR-TB regimen of 9–12 months may be used instead of the longer regimens.</td>
<td>In MDR/RR-TB patients who have not been previously treated for more than one month with second-line medicines used in the shorter MDR 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.</td>
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</table>
| **Start of antiretroviral therapy with MDR-TB treatment**<sup>(2)</sup>  
Antiretroviral therapy is recommended for all patients with HIV and drug-resistant TB requiring second-line anti-tuberculosis drugs, irrespective of CD4 cell-count, as early as possible (within the first eight weeks) following initiation of anti-tuberculosis treatment. | **[No change, remains valid]** |
| **Use of sputum-smear microscopy and culture to monitor response to treatment**<sup>(2)</sup>  
The use of sputum-smear microscopy and culture rather than sputum-smear microscopy alone is recommended for the monitoring of patients with MDR-TB during treatment. | **[Preference for monthly frequency included in the recommendation wording]**  
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). It is desirable for sputum culture to be repeated at monthly intervals. |
| **Use of surgery**<sup>(6)</sup>  
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. | **[No change, remains valid]** |
| **Models of MDR-TB care (ambulatory/hospitalization)**  
Patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalization.<sup>(2)</sup>  
A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment.<sup>(13)</sup> | **[No change, remain valid]** |
Section 1. The composition of longer MDR-TB regimens

Recommendations and remarks
Section 1. The composition of longer MDR-TB regimens

Recommendations

1.1 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 stopped⁸. 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).

1.2 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).

1.3 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).

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

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

1.6 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).

1.7 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).

1.8 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).

1.9 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).

1.10 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).⁹

1.11 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).

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

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

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⁸ Group A = levofloxacin/moxifloxacin, bedaquiline, linezolid; Group B = clofazimine, cycloserine/terizidone; Group C = ethambutol, delamanid, pyrazinamide, imipenem-cilastatin, meropenem, amikacin (streptomycin), ethionamide/prothionamide, p-aminoosalicylic acid (see also Table 2).

⁹ Imipenem-cilastatin (Imp-Cln) and meropenem (Mpm) are administered with clavulanic acid, which is only available in formulations combined with amoxicillin (Amx-Clv). Amx-Clv is not counted as an additional effective TB agent and should not be used without Imp-Cln or Mpm.
Section 1. The composition of longer MDR-TB regimens

1.14 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).9

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 3. The recommendations in this section address two PICO questions (see Annex 4), namely

PICO question 2. 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 guidelines10?

PICO question 3. In patients 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),(14). The recommendations in this section cover all forms of MDR/RR-TB, including also patients with strains susceptible to isoniazid, or with additional resistance to isoniazid (i.e. MDR-TB), or resistant to other medicines from the first-line group (poly-resistant) or from the second-line group (e.g. XDR-TB). WHO recommends that all TB patients – children or adult – diagnosed with strains shown to be resistant to rifampicin be placed on a MDR-TB treatment regimen (6). The conditional recommendation for the composition of longer MDR-TB treatment regimens featuring in the previous guidelines of 2016 proposed to include at least five effective medicines during the intensive phase, composed of pyrazinamide and four second-line TB medicines (see Table 1)(6). The addition of high-dose isoniazid and / or ethambutol could be considered to further strengthen the regimen. Given the release and increased use of the new medicines bedaquiline and delamanid in recent years, significant drops in the price 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/strain level factors (including severity of disease, resistance patterns and co-morbidities) as well as access to health care (e.g. regimens with sufficient effective agents, medications of good quality, attention to adverse events and 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 (15),(16),(17),(18). 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 needs. Longer regimens usually last 20 months or more; recommendations on their duration are discussed in Section 2 to follow.

Ahead of the Guideline Development Group (GDG) discussion, WHO made a public call for individual MDR/RR-TB patient data complete with results of treatment (19). 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 (15),(16),(20). 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 to 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 Annexes 5 and 10).

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

10
**Section 1. The composition of longer MDR-TB regimens**

**PICO question 2** (choice of individual medicines): Firstly, to analyse treatment success, failure, relapse and death for the individual medicines in longer regimens, the main 2018 IPD MA with 13,104 records from 53 studies in 40 countries was used. 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. Secondly, to analyse adverse events (AEs) resulting in permanent discontinuation of individual medicines in longer regimens, a subset of 5,450 records from 17 studies in the IPD was used, supplemented with additional information from 10 other studies that only reported AEs for either Bdq (N=130), Lzd (N=508) or carbapenems (N=139).

Separate from these data the GDG also assessed unpublished results from Phase III Trial 213 of delamanid(21); and safety and pharmacologic 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 Annex 10). In addition, a literature search was made for studies reporting outcomes of patients treated with medicines other than those included in the 2016 guidelines: perchlozone, interferon gamma and sutezolid.

**PICO question 3** (number of agents likely to be effective): to analyse treatment success, failure, relapse and death for the optimal number of medicines to include in longer regimens, the data were derived from a subset of 8,957 patients in 47 studies included in the IPD used for PICO question 2 above. Of these, 3,570 patients in 16 studies had information on the start and end dates for individual medicines in which drug susceptibility testing (DST) was reported and 5,387 patients in 31 studies had information on individual medicines used in both the intensive and continuation phases of treatment, as well as DST results. Given that this question focused on the number of agents in both the intensive phase and continuation phases, 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, 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: (1) If the prevalence of resistance to that medicine was <10% in the same population (from same country or study site if within one country, or overall at all sites if local data not available) then the medicine was counted as effective if DST result was missing. This applied to the following agents: cycloserine or terizidone, linezolid, clofazimine, bedaquiline, the carbapenems and delamanid. (2) If the prevalence of resistance to that medicine was >=10% in the same population (from same country or study site if within one country, or overall at all sites if local data not available) then imputed DST results were used if DST was missing to determine effectiveness. If imputed DST result was susceptible, then the medicine was counted as effective; if imputed DST result was resitant, 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 which 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 for 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 of the emergence of additional resistance while minimizing harms. The GDG was aware of the paediatric MDR-TB IPD meta-analysis on 975 clinically diagnosed or bacteriologically confirmed pulmonary or extrapulmonary TB cases that was used for the 2016 treatment recommendations(17). 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 analyse independently. No randomized controlled trials were included (or known to exist) at the time this dataset was compiled and the overall certainty of 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 (see Annexes 8 and 9 for the respective GRADE summaries of evidence for each medicine as well as the evidence to decision framework). Following a thorough assessment of relative benefits to harms, recommendations were made for each medicine and they were classified in three groups (see Tables 2-4).

- **Group A**: fluoroquinolones (levofloxacin and moxifloxacin), bedaquiline and linezolid were considered highly effective and strongly recommended to be included 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 (Km) and capreomycin (Cm), that were associated with poorer outcomes when used and are therefore no longer recommended for use in MDR-TB regimens
- Gatifloxacin (Gfx) and high-dose isoniazid (Hh) were used in very few patients and thioacetazone (T) that was not used at all. Quality-assured preparations of gatifloxacin are not currently available. 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** further down).
- Clavulanic acid should only be included in MDR/RR-TB regimens as a companion agent to the carbapenems (Imp-Cln and Mpm). 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; Annex 10) do not appear to produce 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 pharmacologic 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 Annex 10). 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) will not be available in a foreseeable future and only the adult tablet exists (50 mg), which is not bioequivalent and presents challenges to manipulate its contents without compromising its effectiveness.
### Section 1. The composition of longer MDR-TB regimens

#### Table 2. Grouping of medicines recommended for use in longer MDR-TB regimens

<table>
<thead>
<tr>
<th>GROUPS &amp; STEPS</th>
<th>MEDICINE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A:</strong></td>
<td>Levofloxacin OR Moxifloxacin</td>
<td>Lfx Mfx</td>
</tr>
<tr>
<td>Include all three medicines</td>
<td>Bedaquiline(^2,3)</td>
<td>Bdq</td>
</tr>
<tr>
<td></td>
<td>Linezolid(^4)</td>
<td>Lzd</td>
</tr>
<tr>
<td></td>
<td>Clofazimine</td>
<td>Cfz</td>
</tr>
<tr>
<td><strong>Group B:</strong></td>
<td>Cycloserine OR Terizidone</td>
<td>Cs Trd</td>
</tr>
<tr>
<td>Add one or both medicines</td>
<td>Ethambutol</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Delamanid(^3,5)</td>
<td>Dlm</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide(^6)</td>
<td>Z</td>
</tr>
<tr>
<td></td>
<td>Imipenem-cilastatin OR Meropenem(^7)</td>
<td>Ipm-Cln Mpm</td>
</tr>
<tr>
<td></td>
<td>Amikacin (OR Streptomycin)(^8)</td>
<td>Am (S)</td>
</tr>
<tr>
<td></td>
<td>Ethionamide OR Prothionamide(^9)</td>
<td>Eto Pto</td>
</tr>
<tr>
<td></td>
<td>(p)-aminosalicylic acid(^9)</td>
<td>PAS</td>
</tr>
</tbody>
</table>

---

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 3). 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 (T) and too few patients on gatifloxacin (Gfx) and high-dose isoniazid (Hh) for a meaningful analysis. No recommendation on perchlozone, interferon gamma or sutezolid was possible owing to the absence of final patient treatment outcome data from appropriate studies (see Annex 10).

2. Evidence on the safety and effectiveness of Bdq beyond 6 months and below the age of 6 years was insufficient for review. Use of Bdq beyond these limits should follow best practices in ‘off-label’ use(22).

3. Evidence on the concurrent use of Bdq and Dlm was insufficient for review.

4. Use of Lzd for at least 6 months was shown to increase effectiveness, although toxicity may limit use. The analysis suggested that using Lzd for the whole duration of treatment would optimise its effect (about 70% of patients on Lzd 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 Lzd could be inferred from the IPD sub-analysis.

5. Evidence on the safety and effectiveness of Dlm beyond 6 months and below the age of 3 years was insufficient for review. Use of Dlm beyond these limits should follow best practices in ‘off-label’ use(22).

6. Z is only counted as an effective agent when DST results confirm susceptibility.

7. Every dose of Imp-Cln and Mpm is administered with clavulanic acid, which is only available in formulations combined with amoxicillin (Amx-Clv). Amx-Clv is not counted as an additional effective TB agent and should not be used without Imp-Cln or Mpm.

8. Am and S are only to be considered if DST results confirm susceptibility and high-quality audiology monitoring for hearing loss can be ensured. S is to be considered only if Am cannot be used (unavailable or documented resistance) and if DST results confirm susceptibility (S resistance is not detectable with 2\(^{nd}\) line molecular line probe assays and phenotypic DST is required). Kanamycin (Km) and capreomycin (Cm) are no longer recommended for use in MDR-TB regimens.

9. These agents only showed effectiveness in regimens without Bdq, Lzd, Cfz or Dlm, and are thus only proposed when other options to compose a regimen are not possible.
### Table 3. 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)\(^1\)

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Treatment failure or relapse versus treatment success</th>
<th>Death versus treatment success</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number treated</td>
<td>Adjusted Odds Ratio (95% confidence limits)</td>
</tr>
<tr>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levofoxacin OR moxifloxacin</td>
<td>3,143</td>
<td>0.3 (0.1-0.5)</td>
</tr>
<tr>
<td>Bedaquiline</td>
<td>1,391</td>
<td>0.3 (0.2-0.4)</td>
</tr>
<tr>
<td>Linezolid</td>
<td>1,216</td>
<td>0.3 (0.2-0.5)</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clofazimine</td>
<td>991</td>
<td>0.3 (0.2-0.5)</td>
</tr>
<tr>
<td>Cycloserine OR terizidone</td>
<td>5,483</td>
<td>0.6 (0.4-0.9)</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td>1,163</td>
<td>0.4 (0.1-1.0)</td>
</tr>
<tr>
<td>Delamanid</td>
<td>289</td>
<td>1.1 (0.4-2.8)(^*)</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>1,248</td>
<td>2.7 (0.7-10.9)</td>
</tr>
<tr>
<td>Imipenem-cilastatin OR meropenem</td>
<td>206</td>
<td>0.4 (0.2-0.7)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>635</td>
<td>0.3 (0.1-0.8)</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>226</td>
<td>0.5 (0.1-2.1)</td>
</tr>
<tr>
<td>Ethionamide OR prothionamide</td>
<td>2,582</td>
<td>1.6 (0.5-5.5)</td>
</tr>
<tr>
<td>p-aminosalicylic acid</td>
<td>1,564</td>
<td>3.1 (1.1-8.9)</td>
</tr>
<tr>
<td>Other medicines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kanamycin</td>
<td>2,946</td>
<td>1.9 (1.0-3.4)</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>777</td>
<td>2.0 (1.1-3.5)</td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid</td>
<td>492</td>
<td>1.7 (1.0-3.0)</td>
</tr>
</tbody>
</table>

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

Regarding PICO question 3, the analysis showed that in contemporary longer MDR-TB treatment regimens the risk for 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 with 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 with four agents in the continuation phase.

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

\(^1\) See text, Table 4 and Annexes 8-10 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.
Section 1. The composition of longer MDR-TB regimens

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 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 one month, mostly on 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 the few cases reported with optic neuropathy, known to be associated with long term use of linezolid (23), while haematological toxicity was reported regardless of duration of use.

Table 4. Serious adverse events (SAEs) in patients on longer MDR-TB regimens

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Absolute risk of AE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median %</td>
</tr>
<tr>
<td>Bedaquiline</td>
<td>2.4%</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>2.9%</td>
</tr>
<tr>
<td>Amoxicillin-Clavulanic acid</td>
<td>3.0%</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>3.6%</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>4.0%</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>4.1%</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>4.5%</td>
</tr>
<tr>
<td>Cycloserine / terizidone</td>
<td>7.8%</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>8.4%</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>8.8%</td>
</tr>
<tr>
<td>Ethionamide / prothionamide</td>
<td>9.5%</td>
</tr>
<tr>
<td>Amikacin</td>
<td>10.3%</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>10.8%</td>
</tr>
<tr>
<td>p-aminosalicylic acid</td>
<td>14.3%</td>
</tr>
<tr>
<td>Thioacetazone</td>
<td>14.6%</td>
</tr>
<tr>
<td>Linezolid</td>
<td>17.2%</td>
</tr>
</tbody>
</table>

In conclusion the GDG recommended that regimens be composed where possible 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 rest 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. If two agents from Group A are likely to be stopped before the end of treatment (e.g. bedaquiline stopped at month 6 and linezolid stopped early because of intolerance), 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.

12 From an “arm-based network” meta-analysis of a patient subset from the 2016 IPD for which adverse events resulting in permanent discontinuation of a TB medicine (27 studies) or classified as Grade 3-5 (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.
Section 1. The composition of longer MDR-TB regimens

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 are 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 the second-line injectable agents would also be useful. 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 drug susceptibility testing (DST) may require several weeks to produce a reliable result, implying that a decision to include or replace pyrazinamide could delay start of treatment by several weeks. In many settings DST for other medicines commonly used in MDR-TB treatment is not usually reliable enough to guide regimen composition. Because of this, other elements may be necessary to determine 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 made to ensure access to approved, rapid molecular tests. Until the capacity for second-line DST – including 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:** in 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 3). 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(17). In this analysis, high-dose isoniazid was associated with treatment success among children with confirmed MDR-TB (aOR 5.9, 95% CL 1.7-20.5, p=0.007).

**Children:** The 2018 IPD-LR was largely composed of adult patients, with only 181 of the 13,104 (1.4%) cases being under 15 years of age. Nonetheless, WHO recommendations on longer MDR-TB regimens apply to children as well as adults. Most medicines which compose 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 age 3 (see Remarks). 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 for the foreseeable future. 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. Bioavailability may further 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 by-products. 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 use of amikacin or streptomycin 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 disease. Treatment of MDR/RR-TB meningitis is best guided by DST of the infecting strain and by the knowledge on the properties of TB medicines to cross the blood-brain barrier. Levofloxacin and
moxifloxacin penetrate well the central nervous system (CNS) (24), as do ethionamide/prothionamide, cycloserine/terizidone, linezolid and imipenem-cilastatin (25), (26). Seizures may be more common in children with meningitis treated with imipenem-cilastatin (meropenem is preferred for meningitis cases and children). High-doseisoniazid and pyrazinamide can also reach therapeutic levels in the cerebrospinal fluid and may be useful if the strains are susceptible. PAS and ethambutol do not penetrate the CNS well and should not be counted on as effective agents for MDR-TB meningitis. Amikacin and streptomycin only penetrate the CNS 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. 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 individualised to include components with a safety profile that is better established.

**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 (27)). 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 PLHIV. HIV infection needs to be reliably excluded in the rare instances where thioacetazone is being considered as part of treatment.

**Implementation considerations**

The new recommendations signal an important departure from previous approaches to treat MDR/RR-TB. Fully oral regimens should 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 standardised and individualised MDR-TB regimens in low-, middle- and high-income countries worldwide, particularly in the last decade (14). While the current guidelines revision brings important changes to the grouping of medicines and the composition of longer MDR-TB regimens, it is not expected to present insurmountable challenges for 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 Global Drug Facility and most are also available in quality-assured, affordable generic formulations from other sources. Bedaquiline has been available via a donation programme for the last 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 Lists of Essential Medicines (2017) include 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 (28). The Task force is spearheading efforts to facilitate reforms needed for countries to adopt the new guidance, such as support on revising procurement plans and training and capacity building of doctors, nurses, laboratory workers, pharmacists and other health care workers to implement the new recommendations.

Where possible a patient’s MDR/RR-TB strain needs to be tested for susceptibility to medicines planned for inclusion in the regimen. Access to rapid diagnostic testing which could reliably identify resistance to fluoroquinolones and injectable agents would help clinicians to decide whether the patient is eligible to the shorter MDR-TB regimen and what agents to include in a longer MDR-TB regimen (the GenoType MTBDRs/l line probe assay may be used for this purpose). GenoType MTBDRs/l 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 MTBDRs/l assay are highly correlated with
Section 1. The composition of longer MDR-TB regimens

phenotypic resistance to ofloxacin and levofloxacin, the correlation with moxifloxacin (and gatifloxacin) is less clear and the inclusion of moxifloxacin in a 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 to 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 on the basis of 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 have that agent replaced. This applied 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, for a number of regimen components DST results would present uncertainties (e.g. cycloserine, streptomycin, ethambutol). “Likelihood of effectiveness” is generally assessed in the programmatic setting on the basis of one or more of (i) confirmed susceptibility in the individual patient; (ii) confirmed susceptibility in the presumed source case; (iii) no known resistance to another drug which 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 superfluous to the target number of medicines needed and clinical judgment 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 to 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; the inclusion of pyrazinamide with bedaquiline on the premise that the two agents may act synergistically based on evidence from other sources (29),(30)).

It is expected that most patients can be treated with 4 agents at start, of which one – usually bedaquiline – would be stopped at month 6. Given that the regimen needs to have at least 3 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 one13. 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 5 agents instead of 4 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. only a total of 2 of the agents from Group A and Group B are included in the regimen).

Given the conditionality of the recommendation for the use of the shorter MDR-TB regimen, the patient and health care provider may decide for a longer treatment in patients who are otherwise eligible for the shorter MDR-TB regimen based on the individual circumstances, such as uncertainty about DST results or lack of access to second-line line probe assay (LPA); unavailability of clofazimine or another component medicine; preference for an injectable-sparing regimen or the patient condition requires 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. Usually, whereas a patient started on the shorter MDR-TB regimen can later be transferred to a longer regimen should the need arise, patients who are placed on a longer regimen for at least 4 weeks normally can no longer be switched to the shorter regimen.

13 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 (11).
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 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 to enable informed and participatory decision-making. Patient information material needs to reflect the new changes so that patients are appropriately informed about their treatment options. Social support to enable adherence to treatment is very important to ensure a patient-centred approach to the delivery of care. Care should also be taken that the use of regimens that incur additional costs to the patient and the services (e.g. more expensive medicines or specialised services) do not upset health equity in favour of individuals and facilities that are better resourced at the expense of more marginalised settings and populations. Health systems should strive to guarantee access to treatment according to need and regardless of income levels.

This guideline update has concurrently revised the weight-based dosage schedules for medicines used in MDR-TB regimens in both children and adults (Annex 6). The update to the dosages has benefited from the expertise of both the GDG members as well as a very extensive consultation of other specialists in different fields and was based on the latest knowledge available for the optimal use of the medicines involved (31). 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 given that it will interfere with their bioavailability.¹⁴

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), (32). Electrocardiography may be indicated given that more regimens in future are expected to have two or three agents with QT-interval prolonging properties given concurrently. A separate recommendation on the use of culture and microscopy to monitor bacteriological response during treatment is being made in the 2018 update of the guidelines (see Section 4 regarding PICO question 7). Frameworks for the surveillance of bacteriological status, drug-resistance and outcomes have been standardized over the past decade (11), (12). The systematic monitoring of adverse events during and after the end of treatment is a relatively recent introduction in TB programmes and experience in its implementation is still developing in many countries. Its rationale is largely defined by frequent use of new and re-purposed medications in MDR-TB treatment regimens in the world, at times in combinations for which there has been very limited experience of use. Very few programmes are collecting adverse event data consistently and uniformly, in a manner that can be used to compare effects between regimens and between countries reliably. In contrast, standardized approaches to the surveillance of drug-resistance through continuous monitoring of diagnostic DST (including the use of sequencing(33)) and for the assignment of treatment outcomes in annual patient cohorts have been available in WHO normative documents since many years (34). Continued advocacy for greater access to DST to medicines to which reliable methods exist as well as the development of other methods for newer medicines, including the use of sequencing, will be an important accompaniment of the treatment recommendations in these guidelines.

¹⁴ This is particularly problematic with the delamanid tablet, the contents of which are very unpalatable (see Annex 10).
Section 2. The duration of longer MDR-TB regimens

Recommendations

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

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

2.3 In MDR/RR-TB patients on longer regimens, a treatment duration of 15 to 17 months after culture conversion is suggested for most patients, and 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 3. The recommendations in this section address three PICO questions (see Annex 4), namely

PICO question 4. 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 eight months?

PICO question 5. 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 twenty months?

PICO question 6. 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 more likely to improve outcomes?

These recommendations update the ones made in the 2011 WHO guidelines(2). In 2011, an intensive phase of eight 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 subject 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 risk of treatment failure and relapse versus success associated with different durations in these three recommendations (see Annexes 7 and 8 for the GRADE Tables and Annex 9 for the analysis plan). Patients followed up for relapse and number reported with relapse was relatively small. The three IPD subsets were as follows:

The analysis for PICO question 4 looked for different durations of the intensive phase. For the primary analysis it used a subset of records from 3,750 patients, from 42 observational studies, of whom 2,720 were treated with an individualized MDR-TB regimen and 1,030 were treated with standardized MDR-TB regimens. Of the 13,104 records in the main IPD, 9,354 records were excluded for the following reasons – lost to follow up: n=2,261; died: n=2,043; did not receive an injectable: n=1,094; no information on duration of injectable: n=2,341; number of medicines likely to be effective less than five or less than four plus pyrazinamide: n=1,450; duration of injectable greater than 20 months: n=165.

The evidence to inform PICO question 5 was derived from a subset of 6,356 patients from 51 observational studies for the primary analysis. Of 6,356 patients, 5,352 were treated with an individualized MDR-TB regimen and 1,004 were treated with a standardized MDR-TB regimen. Of the 13,104 records in the main IPD, 6,748 records were excluded for the following reasons – lost to follow up: n=2,261; died: n=2,043; treatment duration not available: n=230; number of effective drugs less than five or less than four plus pyrazinamide: n=2,072; treatment duration less than six months: n=52; treatment duration greater than or equal to 36 months: n=90).
Section 2. The duration of longer MDR-TB regimens

The analysis to address PICO question 6 was derived from a subset of 4,175 patients from 39 observational studies. All but 3 of the 4,175 patients were on individualized regimens. The reasons for exclusion of 8,929 records from the main dataset were as follows – lost to follow up: 2,261; died: 2,043; treatment duration not reported: 230; culture information not reported: 1,945; baseline culture negative: 754, patient never culture converted: 426; number of effective drugs less than five or less than four plus pyrazinamide: 1,215; treatment duration less than six months: 4; treatment duration greater than or equal to 36 months: 49; culture converted post treatment: n=2.

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. XDR-TB patients could benefit from an intensive phase of 5-6 months although the number of cases was small and the potential contribution of injectable agents when the strain is resistant is doubtful. 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 the treatment.

Patients on regimens without amikacin/streptomycin: in patients on regimens without an intensive phase containing injectable agents, recommendation 2.1 does not apply and the treatment duration is determined by total duration and time after culture conversion (i.e. recommendations 2.2 and 2.3). 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 only given 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 2.1.

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 to both children and adults. However, use of amikacin or streptomycin in children should only be resorted to when other options are not possible, when testing confirms susceptibility and the possibility to monitor for ototoxicity and nephrotoxicity is present. Given that many paediatric patients may only be clinically diagnosed or have extrapulmonary disease it is expected that treatment duration will largely be guided by achieving 18-20 months of regimen subject to response to treatment. Shortening total treatment duration to less than 18 months may be considered in the case of children without severe disease (see Main definitions on page 6).

Pregnant women: due to the potential for teratogenic effects, injectable agents are usually contraindicated in pregnancy and therefore recommendation 2.1 will be of very limited relevance.

Extrapulmonary TB and culture-negative TB: extrapulmonary MDR/RR-TB is generally treatable with the same combination of medicines and duration as pulmonary disease and recommendation 2.3 does not apply in these cases (see also Section 1 regarding specific medicines for cerebral disease). Other durations of treatment may be appropriate for persons with pulmonary or extrapulmonary culture negative TB. In such cases a total duration of treatment of 18-20 months 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 negativity of sputum, 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 2.2 and 2.3.
Section 2. The duration of longer MDR-TB regimens

respectively). In patients with bacteriologically negative or most extrapulmonary disease the recommendation on total duration is the only applicable one.

National TB programmes may find it more practical and straightforward to apply a fixed duration of intensive phase (e.g. 6 months), of total duration (e.g. 20 months) or of time after conversion (e.g. 16 months) to facilitate implementation throughout its sites. 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 3).

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 the case of the emergence of toxicity associated with the injectable agent a change of the regimen becomes necessary and the continuation phase started with the revised treatment. Apart from injectable agents given in the intensive phase, the duration of use of bedaquiline and delamanid has been determined by the manufacturer’s instruction on use, as reflected in their marketing authorisation. Use beyond this duration needs to be decided by the programme on a case-by-case basis and represents “off-label use”(22). Other medicines may need to be used for shorter durations because of toxicity associated with 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 depend on the quality of the sputum produced, so care should be taken to obtain adequate specimens and transporting them to the laboratory according to standard procedures to maintain viability of the bacilli to get a valid culture result.

Prevention of treatment interruption is an important factor to increase the likelihood of treatment success. Measures to support patient adherence, either by facilitating patients to visit health care facilities or by home visits of health care staff or by using digital technologies for daily communication, may be important to increase retention(13). 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 monitoring for treatment response or failure and for safety using reasonable schedules of relevant clinical and laboratory testing (7),(32). Monitoring response to treatment and toxicity is done through regular history taking, physical examination, chest radiography, special tests such as audiometry, visual acuity tests, and electrocardiography and laboratory monitoring. Conversion of bacteriological status using smear microscopy or culture is an important means of assessing response and most patients are usually expected to have converted to negative 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 the performance of DST.

Frameworks for the surveillance of bacteriological status, drug-resistance and the assignment of outcomes have been fairly standardized in past years (11). In contrast, the systematic monitoring of adverse events 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 given the use of the injectable agent. The rationale for aDSM is largely supported by the increasing use worldwide of combinations of new and re-purposed 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 employment in a patient, and at times the complete cessation of treatment. The prospective collection of accurate data for key variables at 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 (35).
Section 3. The use of the standardized shorter MDR-TB regimen

Recommendation
In MDR/RR-TB patients who have not been previously treated for more than one month with second-line medicines used in the shorter MDR 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 3), namely PICO question 1. 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\(^\text{15}\)?

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 (36,37,38,39,40,41). When used in carefully selected MDR-TB patients not previously exposed or having 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 Guideline Development Group assessing the evidence and formulating 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 having introduced the shorter MDR-TB regimen and about 10,000 patients were reported to have been started on shorter regimens that year alone\(^14\).

In October 2017, the STREAM trial principal investigators presented the preliminary findings of the study during the 48\(^{th}\) Union World Conference on Lung Health\(^37\). STREAM Stage 1 was a phase III, multi-centre, international, parallel group, open-label, randomized controlled trial of a standardized MDR-TB treatment regimen lasting 9-11 months versus a longer regimen using a non-inferiority design. The trial enrolled patients between July 2012 and June 2015 in Ethiopia, Mongolia, South Africa and Viet Nam (intention to treat (ITT) population = 424 [282 in study arm; 142 control arm]; modified ITT (Mitt) population = 369 [245 in study arm; 124 control arm]). Treatment allocation was not blinded to the participants, care givers or data managers. All local and reference laboratory assessments, including microbiological tests involved in the assignment of patient outcome, were conducted blind. When the preliminary data were presented, the findings led to public debate and queries regarding their 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 is completed later in the year\(^42\). The final outcomes of the STREAM trial have been much awaited because they will provide additional information on the efficacy and safety of the shorter regimen and the data are 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 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 Annex 8 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 regimen cohorts to inform the 2018 guidelines update\(^19\). As a result of this call, pooled IPD from MDR/RR-TB patients enrolled on standardized shorter regimens between 2005 and 2017 in observational studies or under programmatic conditions in 15

\(^{15}\) The characteristics of previous longer (“conventional”) regimens are described in the WHO treatment guidelines for drug-resistant tuberculosis of 2011 and 2016\(^2\),\(^6\).
countries were compiled (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 2,625 records from the shorter regimen studies and 2,717 records from 39 studies of patients on the longer MDR-TB regimens from the separate IPD used to answer PICO questions 2-7 (a description of this IPD is provided in the respective evidence to decision frameworks). 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 one 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 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 in patients with laboratory confirmed resistance to pyrazinamide and ethionamide/prothionamide were poorer than in those without additional resistance. The 2018 recommendation thus reinforces the importance of excluding resistance to fluoroquinolones and second-line injectable agents before the shorter MDR-TB regimen is considered. Other testing, such as DST to pyrazinamide and genotyping studies of isoniazid resistance – are also considered important and should be performed if possible.

Decisions to start newly diagnosed patients on the standardized shorter MDR-TB regimen should be made according to patient preference and clinical judgement, for patients who do not have any of the following conditions (see also Figure 1):  
1. Resistance to or suspected ineffectiveness to 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 central nervous system TB;  
6. Any extrapulmonary disease in HIV patients.

Considerations for specific sub-groups 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. The majority of deaths among PLHIV occurred in two sites in South Africa (19/24 deaths among 151 total participants). The reason for the excess deaths observed in the study arm among PLHIV remains unclear but may be a clinically-relevant signal. A detailed assessment by the expert panel of the cause of death in the 33 study subjects (9 of whom were HIV negative) who died during treatment or on follow-up did not reveal any signals that the shorter regimen was associated with additional harms in PLHIV due to excessive pill burden, poor adherence, or drug-drug interactions with antiretroviral therapy (ART). Among PLHIV in the IPD-MA for the shorter regimen (90% on ART) the likelihood of treatment failure and death were similar to 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 ART effectiveness and adverse reactions. 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 adult – with rifampicin-resistant 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 additional 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 resistance to pyrazinamide and ethionamide/prothionamide demonstrated among patients with resistance, when compared to those who were susceptible. In patients having strains with laboratory-confirmed resistance to components in the shorter MDR-TB regimen, or solid grounds 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 decide if the shorter regimen may be used or not. It is also recommended that in areas with a high prevalence of pyrazinamide or ethionamide resistance that alternative regimens be used. 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 for patients to be supported to complete longer regimens as recommended for them to benefit from increased likelihood of relapse-free cure (see Sections 1 and 2 above).

**Children:** Children were excluded from the STREAM trial. However, there were 78 children and adolescents who received the shorter regimen in the 2018 IPD SR MA. The effect of the shorter regimen on treatment outcomes for 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 females it is therefore recommended that an individualised, longer regimen be used which can allow the selection of four or more effective medicines with lower teratogenic risk.

**Exclusive extra-pulmonary disease:** The findings from STREAM trial were limited to patients who had pulmonary localisation and they cannot be extrapolated directly to all different forms of extrapulmonary disease. It is proposed that the shorter regimen be avoided in patients with disseminated TB or TB of the central nervous system, as well as in all PLHIV who have extra-pulmonary 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 as for all other patients.
Section 3. The use of the standardized shorter MDR-TB regimen

Figure 1. Criteria to decide when the shorter MDR-TB regimen may be offered

<table>
<thead>
<tr>
<th>YES</th>
<th>Failing shorter regimen or non-response, drug intolerance, emergence of any other exclusion criterion</th>
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<tbody>
<tr>
<td></td>
<td>Individualized, longer MDR-TB regimens</td>
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| NO  | Standardized, shorter MDR-TB regimen may be offered (conditional recommendation) |

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 stabilised latterly to a 9 month regimen with 7 agents in a 4-month intensive phase and 4 agents in a 5-month continuation phase (38). 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 – was tested out 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 standardised 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 and patients with strains resistant to any of the two groups of medicines transferred to treatment with a longer MDR-TB regimen. If testing for susceptibility or resistance to pyrazinamide or other medicines used in the regimen is available it is highly desirable that this is also carried out at baseline.

The availability of reliable and rapid tests 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 resistance detected. In

Is any of the following present?

- Preference by the clinician and patient for a longer MDR-TB regimen
- Confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance)
- Exposure to one or more 2nd line medicines in the shorter MDR-TB regimen for >1 month (unless susceptibility to these 2nd line medicines is confirmed)
- Intolerance to medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)
- Pregnancy
- Disseminated, meningeal or central nervous system TB
- Any extrapulmonary disease in PLHIV
- One or more medicines in the shorter MDR-TB regimen not available
patients with confirmed MDR/RR-TB, the MTBDRsl 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 \((43)\)). This applies to testing in both children and adults. While resistance-conferring mutations to fluoroquinolones detected by the MTBDRsl 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 a 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 MTBDRplus rapid assay can determine whether both \(\text{inhA}\) and \(\text{katG}\) mutations are present, in which case both isoniazid and ethionamide are likely to be ineffective and therefore the shorter regimen is not indicated\(^{18}\). As rapid DST is not available for all medicines used in the shorter regimen (for example, pyrazinamide, which relies on phenotypic testing) then the short 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 standardised 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 only be permissible within the parameters applied in these studies (e.g. gatifloxacin replaced by moxifloxacin; prothionamide replaced by ethionamide; intensive phase prolonged up to 6 months in case of no sputum conversion). 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. 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 if its cost has recently come down as a result of the availability of more generic preparations. The implementation of these guidelines at 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 remain as per the recommendations in the STREAM trial \(^{36}\). The GDG also revised the dosage schedules for adults and children alongside the 2018 guidelines update (see Annex 6).

Direct observation of treatment (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 \(^{13}\), including digital technologies to support adherence (e.g. video-supported therapy) could have a role as evidence of the effectiveness of this

\(^{18}\) 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
Section 3. The use of the standardized shorter MDR-TB regimen

kind of support becomes stronger (13). In addition, active TB drug-safety monitoring and management (aDSM) needs to be established and used in countries implementing the shorter regimen, to detect, manage and report suspected or confirmed adverse events or drug toxicities (7),(32). WHO has published an implementation framework for aDSM which provides additional information on implementation considerations for 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. Shared decision making between the clinician and patient is important when choosing between a shorter and longer regimen
2. Drug susceptibility testing for fluoroquinolones and second-line injectable agents before start of treatment is emphasised, as well as other regimen components where possible (e.g. pyrazinamide, mutations associated with isoniazid and ethionamide resistance)
3. Kanamycin should be replaced by amikacin (based on evidence from the comparative effectiveness of these two injectable agents – see PICO question 2 in Section 1)
4. Other exclusion criteria be observed

The shorter duration of the 9-12 month regimen is a clear advantage to the patient and increases the likelihood that the treatment is completed and an earlier return of the patient to work and social activity. The reduced cost to patients and the services of the shorter regimen is expected to favour equity by releasing more resources to cover the care of more patients.

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 significantly higher rate of reversion, relapse or lack of conversion for patients using the shorter regimen.

The WHO framework for aDSM needs to be applied to ensure appropriate action to respond promptly to adverse events and an acceptable level of monitoring for them – alongside the 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/ should be considered a contraindication for the shorter regimen. The presence of both inhA and katG mutations likewise contraindicates 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; given that it may require several weeks to obtain a phenotypic DST result when this is available this test is not imposed as a prerequisite ahead of treatment start. 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 4. Monitoring patient response to MDR-TB treating using culture

Recommendation
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 3):

PICO question 7. 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),(44),(45). 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 been applied at large scale globally, such as the broader 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 tuberculosis. Culture is a more sensitive test for bacteriological confirmation of tuberculosis than direct microscopy of sputum and other biological specimens. Culture also facilitates phenotypic testing for drug-susceptibility testing, a critical consideration in tuberculosis diagnostics. However, performing culture requires a substantive logistical organization and a better equipped laboratory to limit cross contamination, ensure proper bacterial growth and match other quality standards. Apart from the resource requirements culture results entail 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 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 treatment outcome of success but had less than 17.5 months of treatment; 1,357 had fewer than six culture samples recorded; 1,632 had no baseline culture recorded; 2,502 were baseline culture negative; 2,920 were smear negative at baseline or had a missing smear at baseline and 2,415 had insufficient smear data to match the culture data. This left 3,762 MDR/RR-TB patients (of which 1.8% were children <15 years), treated on longer MDR-TB regimens between 2010 and 2015, who had both monthly smear and culture data throughout treatment to address PICO question 7. About 60% of these patients were HIV positive. The analysis focused on whether monthly culture vs. monthly smear microscopy or culture every two months is needed not to 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 4). The data could not address the outcome on acquisition (amplification) of drug resistance, and it could not assess directly whether the effect on failure would be identical in patients on the 9-12 month shorter MDR-TB regimen as envisaged in the original PICO 7.
Section 4. Monitoring patient response to MDR-TB treating using culture

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 two months to assess the minimum frequency of testing needed in order not to delay unnecessarily 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 two months (0.93 vs. 0.73) but has a slightly lower specificity (0.97 vs. 0.98). Monthly culture increases the detection of patients with a true positive bacteriological result by 13 per 1,000 patients and reduces false negatives by 13 per 1,000 patients when compared with sputum smear microscopy alone. In contrast monthly culture is estimated to lead to 17 per 1,000 fewer true negatives and 17 per 1,000 more false positives for treatment failure, implying that treatment may be prolonged in the case of false positivity or missed true negativity. The added inconvenience on 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 only last until the test repeated one 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). However, no discrete cut-off point could be discerned at which the odds of failure increased sharply when monitoring with either sputum smear microscopy or culture that could serve as a reliable marker of a failing regimen. The threshold on which to make a treatment change thus needs to rely on the clinicians’ desire to minimize risk of failure and, in particular, to minimize the risk of continuing a failing regimen.

Table 5. Crude odds (95% CLs) of treatment failure in MDR/RR-TB patients without sputum conversion by the end of successive months of treatment compared with patients converting, by testing used, IPD-MA for PICO question 7 (South Africa, N=3,762).

<table>
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<tr>
<td>Culture</td>
<td>3.6</td>
<td>4.1</td>
<td>5.2</td>
<td>7.4</td>
<td>10.3</td>
<td>16.4</td>
<td>24.7</td>
<td>44.5</td>
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<td></td>
<td>(2.11, 5.97)</td>
<td>(2.76, 6.09)</td>
<td>(3.55, 7.55)</td>
<td>(5.00, 10.8)</td>
<td>(6.88, 15.38)</td>
<td>(10.72, 25)</td>
<td>(15.53, 39.20)</td>
<td>(26.53, 74.46)</td>
</tr>
<tr>
<td>Smear microscopy</td>
<td>1.9</td>
<td>2.7</td>
<td>3.2</td>
<td>4.2</td>
<td>6.8</td>
<td>10.4</td>
<td>16.5</td>
<td>28.9</td>
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<tr>
<td></td>
<td>(1.27, 2.73)</td>
<td>(1.82, 4.73)</td>
<td>(2.11, 4.48)</td>
<td>(2.69, 10.97)</td>
<td>(4.19, 17.92)</td>
<td>(6.00, 29.77)</td>
<td>(9.15, 56.14)</td>
<td>(14.87, 56.14)</td>
</tr>
</tbody>
</table>

There was moderate certainty in the estimates of test accuracy and the GDG considered that under normal conditions culture will always be a more sensitive test of bacterial positive 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 3,762 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 co-infected, have a history of previous treatment or to 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 existed or not. The GDG considered that the findings may apply to other key patient subgroups.

Patients <15 years of age younger children with MDR/RR-TB represented less than 2% of the IPD-MA analysed for PICO question 7. Younger children commonly 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 sputum or other samples, below the detection threshold of direct microscopy. However, in children 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 culture stands a better chance of detecting persistent disease 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 sputum and a greater likelihood to be detectable with smear microscopy. In such a situation one may expect that the difference in test sensitivity between smear and culture would be less extreme given that fewer patients would have sub-threshold 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, receive 7 drugs in the initial phase and, given a number of inclusion/exclusion criteria, usually have a more favourable prognostic outlook than the average MDR-TB treatment. The current analysis did not include patients treated with these regimens. It may thus be argued that in patients on the shorter MDR-TB regimen there are less grounds to support a recommendation for the use of monthly culture to monitor treatment. The GDG however 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 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 the clients whose samples are tested and to ensure the safety of laboratory personnel, patients and visitors (46). 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 transporting them to the laboratory according to standard procedures to maintain 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 the results of imaging (e.g. chest radiography). The potential use of Xpert MTB/RIF assay in monitoring treatment response has yet to be determined (47),(48).

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 to visit the facilities and, at times, to pay for the testing. The patient values and preferences need to be
considered to ensure a more acceptable and patient-centred delivery of care service. 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 on the *Second-line TB treatment register* as well as the respective laboratory registers (11). 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 on 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 such as contamination rates, turnaround times and proportion of culture tests done without results recorded in the patient information systems help improve quality of care. In the case of repeated positive culture repeat testing for drug-susceptibility or resistance is important.
Research priorities

In addition to summarizing the available evidence, the reviews undertaken for this update revealed several gaps in current knowledge about critical areas in MDR/RR-TB treatment. The estimates of effect for patient studies were commonly assigned a low or very low certainty rating, being 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 serious adverse events, resulting in GDG members having to express their own judgement on behalf of the people addressed by these guidelines. 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 drug-resistant tuberculosis.

The research priorities have been divided by the respective sections of the guidelines although a number of them are interlinked.

Section 1. The composition of longer MDR-TB regimens
- The optimal combination of medicines and approach towards regimen-design for adults and children with MDR/RR-TB with or without additional resistance to key agents
- Randomized controlled trials, especially involving the 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 endpoints chosen for these studies, requiring at times additional, off protocol analysis of data to explore potential added value of the experimental interventions.
- Inclusion and separate reporting of outcomes for key subgroups, especially children and HIV-positive individuals on treatment, in randomized controlled studies.
- Studies of pharmacokinetics and safety to determine optimal drug dosing (especially in pregnancy) and the effect of extemporaneous manipulation of existing dosing forms.
- Complete recording of adverse events and standardized data recording on organ class, seriousness, severity, and certainty of association, to allow meaningful comparison of the association between adverse events and exposure to different medicines between studies, patient subgroups, and different regimens.
- Determination of the minimum number of drugs and treatment duration (especially in patients previously treated for MDR-TB).
- Improved diagnostics and drug-susceptibility testing 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 that would be particularly helpful for the following agents:
  - **Levofloxacin**: optimization of the dose (the Opti-Q study will provide new information on this shortly(49))
  - **Bedaquiline**: use in children, to determine optimal pharmacokinetic properties; revised cost effectiveness analyses based on the IPD meta-analysis
  - **Linezolid**: optimization of the dose and duration in both adults and children; patient predictors for adverse reactions
  - **Clofazimine**: optimization of dose especially in children; any added value in use of 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 (PK/PD), PLHIV and pregnant women; mechanisms of development of drug resistance
  - **Pyrazinamide**: molecular testing for resistance (pursuing either line probe assay 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 Mpm and Imp-Cln
Research priorities

- **Amikacin:** the safety and effectiveness of three-times weekly administration at a higher dose (about 25mg/kg/day) (31)

Section 2. 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 3. The 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.
- The effectiveness of these variants of the shorter regimen would be helpful to compare in:
  - Patient subgroups which have often been systematically excluded from studies or country programme cohorts, such as children, patients with additional resistance, 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 4. Monitoring patient response to MDR-TB treating using culture
- Future analysis on 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 and reduce time needed to make decisions:
  - Patients <15 years of age.
  - Extrapulmonary disease (different forms).
  - Patients on shorter MDR-TB regimens (standardised 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 monitor also treatment response.
- Evaluation of engineering challenges to implement more affordable liquid culture systems.
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<tr>
<td>In-person meeting (Versoix, Switzerland)</td>
<td>16-20 July</td>
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<td>Webinars (after in-person meeting)</td>
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</tr>
</tbody>
</table>
Annex 2. Experts involved in the production of the WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update

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Andreas A REIS

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Tereza KASAЕVA

WHO Regions
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SEAR: Vineet BHATIA
Annex 3. Declarations of interest

Guideline Development Group (GDG)

The scope of the guidelines update, and the composition of the GDG, including the biographies of the members, were made public for comment ahead of the meeting in line with WHO requirements (http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/gdg-meeting-mdr-rr-tb-treatment-2018-update/en/). All GDG members completed the WHO Declaration of Interest form and agreed to the confidentiality undertaking. The WHO Guideline Steering Committee reviewed the completed forms.

The following GDG members declared no interests conflicting with the objectives of the guidelines development:

Eden ABADIANO MARIANO, Sarabjit S CHADHA, Fernanda DOCKHORN COSTA JOHANSEN, Edwin HERRERA-FLORES, Ayuko HIRAI, Alexander KAY, Rafael LANIADO-LABORIN, Lawrence MBUAGBAW, Austin Arinze OBIEFUNA, Cristina POPA, Wipa REECHAI PICHITKUL, Maria RODRIGUEZ, Holger SCHÜNEMANN, Adman Skirry SHABANGU and Sabira TAHSEEN.

The following GDG members declared interests which were judged not to be in conflict with the objectives of the guidelines development:

Susan ABDEL RAHMAN declared that a research grant (USD196,356) was received by her institution from the Thrasher Foundation in September 2017 for her role as Principal Investigator to study whether second-line TB medicines can be accurately quantified from dried blood spots (funding ongoing).

Daniela CIRILLO declared that a grant (USD26,000) was provided to her research unit by FIND to evaluate new TB diagnostics (funding ongoing). In 2014 she received funding from Janssen (USD10,000) and Otsuka (USD25,000) for work on new drug DST. In 2014, Janssen Italy funded her participation in an expert working group for use of bedaquiline in Italy (USD1000).

Geraint (Rhys) DAVIES declared that he was until November 2017 the academic co-ordinator of the PreDiCT-TB consortium, a public-private partnership funded by the European Union Innovative Medicines Initiative and the European Federation of Pharmaceutical Industries and Associations. Although this role involved engagement with industrial partners (GSK, Sanofi, Janssen) in pre-competitive areas of research into TB drug development, these activities were fully supported by public funding from the EU and neither he nor his research institution have received any funding from EFPIA or from the individual industrial partners. He has been asked and intends to provide advice to the STREAM study team on possible PK studies which may be carried out in future using existing or further prospectively collected samples (no payment or research support has been offered for this activity). In 2017 he was paid fees by WHO for expert consultancies (USD5000). He is a member of a steering group convened by Critical Path to TB Regimens to advise on development of the LAM biomarker developed by Otsuka in the context of adaptive clinical trials (receives no payment for this activity).

Bernard FOURIE declares receiving USD16,000 per year (ongoing) to act as a non-executive Director and member of the Board of the National Bioproducts Institute in S Africa, which is exclusively involved in the production and marketing of blood- and plasma-derived products.

Payam NAHID declares an ongoing Federal US CDC contract to the University of California San Francisco to support clinical trial units in San Francisco and Viet Nam (total amount not specified).

Carrie TUDOR declares that her employer receives funding from the Eli Lilly Foundation (~USD1,000,000 for 2013-2017; ongoing at USD243,000 in 2018) to run the International Council of Nurses’ TB/MDR-TB project. The project focuses on building the capacity of nurses and allied professions on TB and DR-TB care through training and currently operates in China, Eswatini, Ethiopia, Lesotho, Malawi, the Russian Federation, Uganda and Zambia. She also received USD20,000 from the KwaZulu Natal Research Institute for TB & HIV (S Africa) and Fogarty/NIH (US) for her dissertation and post-doc research on TB until 2014.
Zarir UDWADIA declares that he has supported about 40 patients access bedaquiline and 3 patients to access delamanid through the compassionate use programmes of Janssen and Otsuka respectively. He declares that he did not charge fees to the patients involved and there were no financial transactions with the manufacturers.

Andrew VERNON declares that he heads a clinical research group at US CDC (TBTC) doing TB trials. TBTC often collaborates with pharmaceutical companies, which may provide modest support, e.g. drug supplies, funding for PK sub-studies. Sanofi Aventis awarded ~USD2.8million in six unrestricted grants to CDC Foundation in 2007-2015 to facilitate or support TBTC work on rifapentine (e.g. PK studies, staff contracts, travel for invited speakers, preparation of data to support regulatory filings). These funds have not otherwise benefited research group. TBTC has studies underway with rifapentine (TBTC Study 31) and levofloxacin (Opti-Q, TBTC Study 32). He declares that his branch has supported studies of drug-susceptible TB that have included moxifloxacin (TBTC Study 27, Study 28, and Study 31). His branch has also supported enrolment at 2 of the 3 sites involved in the Opti-Q Study. This study evaluates different doses of levofloxacin in the treatment of drug-resistant TB and has no comparator arm. There is no involvement with drug procurement. The principal investigator and management of the study, including data handling, analysis, and drug procurement is at Boston University. The Opti-Q outcomes are not yet known and the final analysis has yet to start. The majority of the study was funded by US NIH (NIAID).

The following GDG member declared an interest that was judged to conflict with the objectives of the guidelines development (funding for new medicines for use in MDR-TB regimens). He therefore withdrew from the GDG panel and participated as a technical resource.

Gary MAARTENS declared that his laboratory will receive USD2,184,608 from US NIH (NIAID) to undertake drug assays for a trial of the safety, tolerability and pharmacokinetics of bedaquiline and delamanid, alone and in combination, among patients on MDR-TB treatment (AIDS Clinical Trials Group study A5343). He will receive no salary support.

External Review Group (ERG)
The following ERG members declared no interest conflicting with the objectives of the guidelines revision: Essam ELMOGHAZI, Mildred FERNANDO-PANCHO, Anna Marie Celina GARFIN, Barend (Ben) MARAIS, Andrei MARYANDYSHEV, Alberto MATTEELLI, Giovanni Battista MIGLIORI, Nguyen Viet NHUNG, Rohit SARIN, Welile SIKHONDZE, Ivan SOLOVIC, Pedro SUAREZ and Carlos TORRES.

The following ERG member declared interests which were judged not to be in conflict with the objectives of the guidelines development:

Thato MOSIDI declares that she represents people affected by and living with TB on the Global Fund Country Coordinating Mechanism in South Africa. She is also an active member of TB Proof, a not-for-profit organization which advocates for patient access to TB medicines.

Evidence reviewers
The following evidence reviewers from McGill University, Montréal, Canada – Syed ABIDI, Jonathon CAMPBELL, Zhiyi LAN and Dick MENZIES – declared no interest conflicting with the objectives of the guidelines revision.

The following evidence reviewer declared interests which were judged not to be in conflict with the objectives of the guidelines development:

Faiz Ahmad KHAN declared payment by WHO to collect data and carry out a meta-analysis on the shorter MDR-TB regimens for the 2016 guidelines (CAD4,080) and travel fees to present the same findings at a Guideline Development Group in 2015. He also declares undertaking an update of the same analysis in 2016-2018 for the American Thoracic Society guidelines for which he receives no remuneration.
Annex 4. PICO questions

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? 

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| MDR/RR-TB patients | - 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) | - Use of at least 4 effective SLDs 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 end of treatment  
• Adherence to treatment (or treatment interruption due to non-adherence)  
• Treatment failure or relapse  
• Survival (or death)  
• Adverse reactions from anti-TB medicines  
• Acquisition (amplification) of drug resistance |
| a. previously treated with 2nd 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 (0-14y) / adults (adolescents 10-19y if available)  
f. persons with HIV (+/- ARVs)  
g. pregnant women  
h. people with diabetes  
i. extrapulmonary disease  
j. malnutrition | | |

17 The characteristics of current longer and shorter regimens are 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?

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. MDR/RR-TB without resistance or severe intolerance to the second line drugs</td>
<td>A 2nd line regimen as per WHO guidelines that INCLUDES 19</td>
<td>- fluorquinolones (Mfx/Lfx/Gfx) - no fluorquinolones or a FQ or different generation (Ofx/Mfx/Lfx/Gfx)</td>
<td>• Culture conversion by 6 months • Successful completion of treatment (or lack of successful completion) • Bacteriological cure by end of treatment • Adherence to treatment (or treatment interruption due to non-adherence) • Treatment failure or relapse • Survival (or death) • Adverse reactions from anti-TB medicines • Acquisition (amplification) of drug resistance</td>
</tr>
<tr>
<td>b. MDR/RR-TB with resistance or severe intolerance to</td>
<td></td>
<td>- injectable agents (Km/Am/Cm) 20 - no injectable agent or different one (Km/Am/Cm)</td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones, incl. Ofx and Cpx (by mutation pattern)</td>
<td></td>
<td>- prothionamide or ethionamide - no prothionamide or ethionamide</td>
<td></td>
</tr>
<tr>
<td>2nd line injectable agents, both classes</td>
<td></td>
<td>- cycloserine or terizidone - no cycloserine or terizidone</td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones + 2nd line injectable agents (i.e. XDR-TB +/- other resistance)</td>
<td></td>
<td>- linezolid - no linezolid</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td></td>
<td>- clofazimine - no clofazimine</td>
<td></td>
</tr>
<tr>
<td>Group C agents (ethionamide, prothionamide, cycloserine, terizidone, linezolid and clofazimine)</td>
<td></td>
<td>- pyrazinamide - no pyrazinamide</td>
<td></td>
</tr>
<tr>
<td>c. children (0-14y) / adults (adolescents 10-19y if available)</td>
<td></td>
<td>- high-dose isoniazid - no high-dose isoniazid</td>
<td></td>
</tr>
<tr>
<td>d. persons with HIV (+/- ARVs)</td>
<td></td>
<td>- ethambutol - no ethambutol</td>
<td></td>
</tr>
<tr>
<td>e. pregnant women</td>
<td></td>
<td>- bedaquiline - no bedaquiline</td>
<td></td>
</tr>
<tr>
<td>f. people with diabetes</td>
<td></td>
<td>- delamanid - no delamanid</td>
<td></td>
</tr>
<tr>
<td>g. extrapulmonary disease</td>
<td></td>
<td>- individual Group D3 agent 21 - individual Group D3 agent 21 absent</td>
<td></td>
</tr>
<tr>
<td>h. malnutrition</td>
<td></td>
<td>- sutezolid 22 - no sutezolid</td>
<td></td>
</tr>
<tr>
<td>i. interferon G 22 - no interferon G</td>
<td></td>
<td>- perchlozone 22 - no perchlozone</td>
<td></td>
</tr>
</tbody>
</table>

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

19 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.

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

21 **Group D3 agents**: p-aminosalicylic acid (PAS), imipenem-clastatin, meropenem, amoxicillin-clavulanate (used alone or with carbapenems), thiaacetazone.

22 as yet unauthorized by US FDA, 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 23?

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

23 See Implementation considerations under Section 1 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 eight months?

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDR/RR-TB patients</td>
<td>- duration of intensive phase 8 months or more (in different brackets)</td>
<td>- duration of intensive phase &lt;8 months (in different brackets)</td>
<td>• Culture conversion by 6 months</td>
</tr>
<tr>
<td>a. previously treated with a 1st line regimen (for new or retreatment)</td>
<td>Matching by:</td>
<td></td>
<td>• Successful completion of treatment (or lack of successful completion)</td>
</tr>
<tr>
<td>b. previously treated for MDR-TB</td>
<td>- number of likely effective agents</td>
<td></td>
<td>• Bacteriological cure by end of treatment</td>
</tr>
<tr>
<td>c. with XDR-TB vs. no XDR-TB</td>
<td></td>
<td></td>
<td>• Adherence to treatment (or treatment interruption due to non-adherence)</td>
</tr>
<tr>
<td>d. surrogate of advanced disease (cavitary disease on radiography or SS+)</td>
<td></td>
<td></td>
<td>• Treatment failure or relapse</td>
</tr>
<tr>
<td>e. use of bedaquiline, delamanid and other individual medicines beyond 6 months</td>
<td></td>
<td></td>
<td>• Survival (or death)</td>
</tr>
<tr>
<td>f. children (0-14y) / adults (adolescents 10-19y if available)</td>
<td></td>
<td></td>
<td>• Adverse reactions from anti-TB medicines</td>
</tr>
<tr>
<td>g. persons with HIV (+/- ARVs)</td>
<td></td>
<td></td>
<td>• Acquisition (amplification) of drug resistance</td>
</tr>
<tr>
<td>h. extrapulmonary disease</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 twenty months?

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDR/RR-TB patients</td>
<td>- total duration of treatment lasting up to 20 months</td>
<td>- total duration of treatment lasting more than 20 months (in different brackets)</td>
<td>- Culture conversion by 6 months</td>
</tr>
<tr>
<td>a. previously treated with a 1st line regimen (for new or retreatment)</td>
<td>Matching by: - number of likely effective agents</td>
<td></td>
<td>- Successful completion of treatment (or lack of successful completion)</td>
</tr>
<tr>
<td>b. previously treated for MDR-TB</td>
<td></td>
<td></td>
<td>- Bacteriological cure by end of treatment</td>
</tr>
<tr>
<td>c. with XDR-TB vs. no XDR-TB</td>
<td></td>
<td></td>
<td>- Adherence to treatment (or treatment interruption due to non-adherence)</td>
</tr>
<tr>
<td>d. surrogate of advanced disease (cavitary disease on radiography or SS+)</td>
<td></td>
<td></td>
<td>- Treatment failure or relapse</td>
</tr>
<tr>
<td>e. use of bedaquiline, delamanid and other individual medicines beyond 6 months</td>
<td></td>
<td></td>
<td>- Survival (or death)</td>
</tr>
<tr>
<td>f. children (0-14y) / adults (adolescents 10-19y if available)</td>
<td></td>
<td></td>
<td>- Adverse reactions from anti-TB medicines</td>
</tr>
<tr>
<td>g. persons with HIV (+/- ARVs)</td>
<td></td>
<td></td>
<td>- Acquisition (amplification) of drug resistance</td>
</tr>
<tr>
<td>h. extrapulmonary disease</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 more likely to improve outcomes?

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| MDR/RR-TB patients | the duration of treatment after culture conversion up to 12 months (in different brackets) | the duration of treatment after culture conversion > 12 months (in different brackets) | • Culture conversion by 6 months  
• Successful completion of treatment (or lack of successful completion)  
• Bacteriological cure by end of treatment  
• Adherence to treatment (or treatment interruption due to non-adherence)  
• Treatment failure or relapse  
• Survival (or death)  
• Adverse reactions from anti-TB medicines  
• Acquisition (amplification) of drug resistance |
| a. who by month 6 convert sputum culture vs. do not convert  
b. previously treated with a 1st 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. use of bedaquiline, delamanid and other individual medicines beyond 6 months  
g. children (0-14y) / adults (adolescents 10-19y if available)  
h. persons with HIV (+/- ARVs)  
i. extrapulmonary disease | Matching by:  
- duration of intensive phase  
- number of likely effective agents |
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?

<table>
<thead>
<tr>
<th>Population</th>
<th>MDR/RR-TB patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. on longer regimens vs. shorter regimen</td>
<td></td>
</tr>
<tr>
<td>b. previously treated with a 1st line regimen (for new or retreatment)</td>
<td></td>
</tr>
<tr>
<td>c. previously treated for MDR-TB</td>
<td></td>
</tr>
<tr>
<td>d. with XDR-TB vs. no XDR-TB</td>
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<td></td>
</tr>
<tr>
<td>g. persons with HIV (+/- ARVs)</td>
<td></td>
</tr>
</tbody>
</table>

| Intervention |
| 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) |

| Comparator (current WHO recommendations) |
| Monthly sputum smear and culture²⁴ |

| Outcomes |
| Culture conversion by 6 months |
| Treatment failure or relapse |
| Acquisition (amplification) of drug resistance |

²⁴ 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 (45). 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.
Annex 5. Main methods

Preparation for the revision

The WHO Guideline Steering Committee met regularly from January to July 2018 to draft the scope of the new guidelines, the evidence reviews and the preparations for the webinars and the physical meeting of the GDG. An application for the revision of the guidelines was submitted to the WHO Guideline Review Committee (GRC) in February 2018 and received final approval after revisions in April 2018. Six webinars (using WebEx) were held between April and July 2018 for the GDG members, the systematic reviewers and the WHO Guideline Steering Committee to discuss the scoping, the PICO (Population, Intervention, Comparator and Outcomes) questions (Annex 3), the scoring of the outcomes (Annex 5, Table 1), the collection of data and the analysis plans for the data from the trials (delamanid and shorter regimen), and the individual patient data from the shorter and longer regimens. Discussions were also held alongside with the GDG on updates to the dosing schedules for children and adults (Annex 6). In between the webinars, discussions continued via email. After the July meeting, the GDG and systematic reviewers met three more times over webinar until mid-October to finalise the decisions.

Rationale, scope and objectives

The latest evidence-based guidance for the treatment of MDR/RR-TB was published by WHO in October 2016 in accordance with the requirements of the GRC, using GRADE (1). Since these guidelines were released there have been some relevant developments that motivate a revision in order to ensure that TB programme managers, policy makers as well as medical practitioners in a variety of geographical, economic and social settings receive the best possible advice and MDR/RR-TB patients receive treatment in accordance with the best evidence and medication available. These include

1) additional data from observational studies evaluating longer MDR-TB regimens for the treatment of MDR/RR-TB have been assembled to supplement an earlier meta-analysis of pooled, multi-country individual-patient data (16);
2) final results from a phase III RCT of the new MDR-TB medicine delamanid were also released in October 2017 (50);
3) preliminary results from the first-ever randomized controlled trial (RCT) of a 9-month shorter MDR-TB regimen were released in October 2017 (including interim results of a study of health economic impact) (37);
4) final results from a multi-centric study of a 9-month shorter MDR-TB regimen in African settings were published in December 2017 (41); and
5) new data from the programmatic use of bedaquiline, delamanid and novel regimens are also expected to be made available to WHO by April 2018 following a public call for these data in February 2018 (19).

The aim for the 2018 update is to review all previous evidence-informed policy recommendations made by WHO to date on the treatment of MDR/RR-TB with both the old and new medicines. In deciding the scope of the 2018 update, the GDG considered priority debates on the treatment and care of MDR/RR-TB patients in mid-2018. The GDG members were sensitive to the growing dissatisfaction of patients and caregivers to the continued inclusion of injectable agents as priority medicines in MDR-TB regimens. Injectable agents require special conditions to administer by skilled workers, they cause pain and often lead to serious adverse reactions like hearing loss and kidney dysfunction. In addition, the GDG was keenly aware of the importance of adherence to treatment and the problems with patient retention on treatment regimens lasting two years or more, particularly when multiple agents that can cause serious toxicities are administered concurrently.

The scope did not cover aspects of the programmatic management of drug-resistant TB for which no new evidence has become available that was likely to challenge the validity of the latest WHO recommendations. These included recommendations on rapid diagnostics, timing to start of antiretroviral agents in PLHIV, models of care and treatment delivery, use of surgery, time to start of
treatment and treatment of isoniazid-resistant TB. For these areas the GDG considered that the existing recommendations remain valid and is reproducing them in the current update (Table 1).

The scope of the 2018 update of the guidelines was focused on the following four priority areas:

2. *The duration of longer MDR-TB regimens*: identifying the best range for the total length of treatment, duration of the intensive phase and time after culture conversion
3. *The use of the shorter MDR-TB regimen*: the role of the standardized 9-12 month regimen recommended by WHO since 2016
4. *Monitoring patient response to MDR-TB treating using culture*: the added value of culture over sputum smear microscopy alone and the preferred frequency of testing to detect a failing regimen

As far as possible, and where evidence exists, the guidelines also aimed to formulate recommendations which would be relevant to patients of all ages as well as individuals with key comorbidities (e.g. HIV, diabetes).

The target audience of the guidelines includes staff and medical practitioners working in prevention and care of TB, managers implementing the programmatic management of drug-resistant TB within their centres and national programmes, and organizations providing technical and financial support for drug-resistant TB. Although primarily intended for use in resource-limited countries, the recommendations are also applicable in other settings. It is expected that once the recommendations are published they will serve as an authoritative policy grounded in the best available evidence on the use of contemporary regimens both under trial and programmatic conditions. Programmes adhering to the new guidelines would thus increase the impact that treatment with longer and shorter regimens could have while focusing on common challenges such as procurement of the most effective regimen components and increasing medication adherence and acceptability of treatment.

**Key questions**

Seven PICO questions were formulated to address the four priority areas that defined the scope of the guidelines (see above). PICO questions 2 and 3 were devoted to the first area of the guidelines scope (see above); PICO questions 4, 5 and 6 related to the second area; PICO question 1 covered the third area and PICO questions 7 the fourth area.

The 2018 revision addressed key questions of topical debate on which TB authorities in Member States and other implementers demand guidance from WHO. The scope of the new guidelines covered key questions included in the 2011 and 2016 editions of the drug-resistant TB treatment guidance(2), (6), as well as other emerging topical areas relating to newer medicines. Questions worded in PICO format (Population, Intervention, Comparator, Outcome) were finalised by the GDG as below (for a disaggregation of each element of the PICO questions see Annex 3).

**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?25

**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?26

---

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

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

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 eight months?

Annex 5. Table 1. Scoring of outcomes considered relevant by the GDG for evidence reviews related to the WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update

<table>
<thead>
<tr>
<th>PICO</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Culture conversion by 6 months</td>
</tr>
<tr>
<td></td>
<td>Successful completion of treatment</td>
</tr>
<tr>
<td></td>
<td>Bacteriological cure</td>
</tr>
<tr>
<td></td>
<td>Adherence to treatment</td>
</tr>
<tr>
<td></td>
<td>Failure or relapse</td>
</tr>
<tr>
<td></td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>Adverse reactions from TB medicines</td>
</tr>
<tr>
<td></td>
<td>Acquisition of drug resistance</td>
</tr>
<tr>
<td>1 Shorter regimen</td>
<td>7</td>
</tr>
<tr>
<td>2 Longer regimen, which medicines to use</td>
<td>7</td>
</tr>
<tr>
<td>3 Longer regimen, number of medicines to use</td>
<td>7</td>
</tr>
<tr>
<td>4 Length of intensive phase</td>
<td>7</td>
</tr>
<tr>
<td>5 Total treatment duration</td>
<td>6</td>
</tr>
<tr>
<td>6 Length of treatment after conversion</td>
<td>6</td>
</tr>
<tr>
<td>7 Monitoring using culture</td>
<td>7</td>
</tr>
</tbody>
</table>

a. Relative importance was rated on an incremental scale:
   1–3 points: Not important for making recommendations on the treatment of drug-resistant TB.
   4–6 points: Important but not critical for making recommendations on the treatment of drug-resistant TB.
   7–9 points: Critical for making recommendations on the treatment of 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 twenty months?

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 more likely to improve outcomes?

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?

The GDG members listed and scored the most relevant outcomes on an incremental scale of importance going from 1 to 9 (1). The outcomes proposed by the GDG for scoring were similar to those used in the past, namely:

- Culture conversion by 6 months
- Successful completion of treatment (or lack of successful completion)
- Bacteriological cure by end of treatment
- Adherence to treatment (or treatment interruption due to non-adherence)
- Treatment failure or relapse
- Death (or survival)
- Adverse reactions from anti-TB medicines
- Acquisition (amplification) of drug resistance
The outcomes were defined and scored by each GDG member anonymously. Outcomes assigned by each member were considered “Critical” if scoring between 7 and 9, “Important” if between 4 and 6 and “Not important” if lower. Scores were averaged across all voting members (using the arithmetic mean). Mean scores for the nine responses received were all in the “Critical” range (7–9 points; see Annex 5. Table 1).

Certainty of evidence and strength of recommendations

The recommendations in these guidelines qualify their strength as well as the certainty of evidence on which they are based. The text of the recommendation itself should be read along with the accompanying remarks that summarize the evidence upon which the recommendation was made, the anticipated desirable and undesirable effects of the interventions to assess the balance of expected benefits to risks, and other considerations which are important for the implementation of the policy and monitoring its effect. The GDG also made a statement about Research Priorities within the different dimensions covered by each of the PICO questions.

The certainty of evidence is categorized into four levels (Annex 5. Table 2). The criteria used by the evidence reviewers to qualify the quality of available evidence are summarized in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tables annexed to these guidelines (online Annex 8). A number of factors may increase or decrease the certainty of evidence (see Figure 9.1 of (1)). The highest rating is usually assigned to data from randomized controlled trials (RCT) while evidence from observational studies is usually assigned a low or very low quality value at the start.

Annex 5. Table 2. Certainty of evidence and definitions (51)

<table>
<thead>
<tr>
<th>CERTAINTY OF EVIDENCE</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Further research is very unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Further research is likely to have an important impact on our confidence in the effect and may change the estimate.</td>
</tr>
<tr>
<td>Low</td>
<td>Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</td>
</tr>
<tr>
<td>Very low</td>
<td>Any estimate of effect is very uncertain.</td>
</tr>
</tbody>
</table>

A recommendation may be strong or conditional. Apart from the quality of evidence, the strength and direction of a recommendation is determined by the balance between desirable and undesirable effects, values, equity, resource use, acceptability and feasibility(52). For strong recommendations, the GDG is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects. For conditional recommendations, the GDG considers that desirable effects probably outweigh the undesirable effects. The strength of a recommendation has different implications for the individuals affected by these guidelines (Annex 5. Table 3).

Annex 5. Table 3. Implications of the strength of a recommendation for different users (adapted from (51))

<table>
<thead>
<tr>
<th>Target audience</th>
<th>Strong recommendation</th>
<th>Conditional recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Most would want the intervention; only a small proportion would not and decision aides not likely to be necessary</td>
<td>Most would want the intervention, but many would not;</td>
</tr>
<tr>
<td>Clinicians</td>
<td>Most individuals should receive the intervention</td>
<td>Different choices will be appropriate for individual patients; decision aids are likely to be necessary</td>
</tr>
<tr>
<td>Policy-makers</td>
<td>The recommendation can be adopted as policy in most situations</td>
<td>Policy-making will require substantial debate and involvement of various stakeholders</td>
</tr>
</tbody>
</table>
Assessment of evidence and its grading

Two teams of experts (listed in Annex 2) were commissioned to assess the evidence for the 7 PICO questions and their outcomes. Meta-analysis of individual patient data from studies and trials of longer and shorter MDR-TB treatment regimens were used to inform all PICO questions. The studies were traced through a systematic literature review of published papers following a standard methodology(53), supplemented by other unpublished data reported to WHO following a public call for data issued in February 2018(19). Members of the GDG were contacted to identify missing studies or studies in progress.

Relative effects (relative risks or odds ratios of an event) were calculated from pooled data in individual or aggregated formats from the included studies. Absolute effects and risk differences were used to express the magnitude of an effect or difference between the intervention and comparator groups. Where possible, adjustments were made to reduce risk of bias and confounding (including propensity score matching). More details on the methods used in unpublished studies are presented in Annex 10 (online) and in published studies of earlier versions of these IPD meta-analysis(15),(16),(54).

The summary of evidence profiles were prepared using GRADEPro software, an online tool to create guideline materials(55). The certainty of the evidence was assessed using the following criteria: study design, limitations in the studies (risk of bias), imprecision, inconsistency, indirectness, publication bias, magnitude of effect, dose–effect relations and residual confounding(I).

The GDG membership represented a broad cross-section of future users of the guidelines as well as affected persons (including the patient). Biographies of experts proposed for the GDG were published on a WHO website in June 2018 (http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/gdg-meeting-mdr-rr-tb-treatment-2018-update/en/). Six webinars were held between April and July 2018, ahead of the GDG meeting held between 16 and 20 July 2016 in Versoix, Switzerland. The webinars were chaired by the GDG chair and co-chair and served to brief the members about the methods used to analyse the data and to produce the guidelines according to the GRADE approach. Evidence from some of the analysis was also shared and discussed during the webinars ahead of the physical meeting. Drafts of the review reports and GRADE summary of evidence profiles were shared with the GDG members ahead of the meeting (Annexes 8 and 9). During the days of the meeting and in the following weeks additional analyses were shared with the group upon their demand. The discussions on culture monitoring (PICO 7) and on the use of delamanid (part of PICO 2) – inclusive of an analysis of the individual data of Trial 213 provided by Otsuka - were finalised in webinars lasting until 12 November 2018 (Annex 1). The GRADE summary of evidence profiles were discussed by the GDG ahead of formulating the recommendations. Apart from the quality of evidence, the wording, direction and strength of the recommendations were decided upon considerations of relative magnitude of the desirable and undesirable effects, overall certainty in the evidence of effects, values and preferences, resource implications, incremental costs, impact on health equity, acceptability and feasibility. The group used “evidence to decision” (EtD) frameworks via the GRADEPro interface to capture the content of the discussions, make judgements, vote (using at times the PanelVoice function), annotate the different considerations, and develop, and add the remarks accompanying each recommendation on justification, implementation, subgroups, monitoring and evaluation and research gaps (Annex 9).

In the preparation of PICO questions and outcomes, and in the discussions of the evidence before, during and after the meeting, the GDG members paid attention in particular to the spectrum of values and preferences attached to the recommendations by the different users. One important factor that lowered the strength of all recommendations made in these guidelines was the variability in values and preferences of those affected by these policies as perceived by the GDG members. Resource use was at times informed by unit cost of medicines from the Global Drug Facility (for PICOs 1, 2 and 3) and from interim data from one study (PICO 1: STREAM Stage 1 trial). Otherwise no formal studies on incremental costs, impact on health equity, acceptability and feasibility were assessed by the GDG. Decisions on the certainty of evidence and on the wording of a recommendation and of its strength were
largely made through moderated discussion. Any disagreements were resolved by a group decision on an acceptable position. For a minority of judgements, final wording and strength of a recommendation the decision was taken by voting.

**External review**

The ERG commented on a draft text of the guidelines, including the recommendations, following comments from the GDG up to early November 2018.

**Publication, implementation, evaluation and expiry**

These guidelines were first published as a prefinal version on the World Health Organization Global TB Programme (WHO/GTB) website (http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/ resources/en/) as downloadable pdf files on 21 December 2018. The main text of the guidelines (without Annexes 8-10) will also be made available in print version in early 2019 and translated into all WHO official languages. The evidence reviews as well as the recommendations are being published separately in peer-reviewed journals to improve the dissemination of the main messages. The changes to the policy guidance will also be reflected in a forthcoming revision of WHO’s implementation manual - the *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis* - planned for early 2019 (7).

WHO will work closely with its regional and country offices, as well as technical and funding agencies and partners, to ensure wide communication of the updated guidance in technical meetings and training activities. WHO/GTB will review and update these guidelines within four to five years after their publication, or earlier if new evidence becomes available.
## Annex 6: Dosage by weight band for medicines used in MDR-TB regimens, adults and children

<table>
<thead>
<tr>
<th>Group</th>
<th>Medicine</th>
<th>Weight-based daily dose</th>
<th>Formulation</th>
<th>50-55 kg</th>
<th>56-65 kg</th>
<th>66-75 kg</th>
<th>&gt;75 kg</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Ethambutol</td>
<td>15 mg/kg</td>
<td>600 mg tab</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Isoniazid</td>
<td>30 mg/kg</td>
<td>900 mg tab</td>
<td>1.5</td>
<td>1.5</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Rifampicin</td>
<td>15 mg/kg</td>
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<td>1</td>
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<td>1</td>
</tr>
</tbody>
</table>

### Notes

- Dosages were established by the Global TB Guidelines Group for second-line MDR-TB regimens and in combination with other antituberculosis drugs. The recommended doses are based on the pharmacokinetic and pharmacodynamic profiles of MDR-TB drugs.
- Dosages are provided for adults and children. Dosing for children is usually lower than for adults, and the doses are adjusted based on body weight.

### Additional Notes

- For children, lower dosages are typically used, and the dosages are adjusted based on body weight.
- The dosages provided are examples and may vary depending on the specific MDR-TB regimen and the patient's individual needs.

### References


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

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<th>Medicine</th>
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<td>900 mg tab</td>
<td>1.5</td>
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<tr>
<td></td>
<td>Rifampicin</td>
<td>15 mg/kg</td>
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<td>1</td>
<td>1</td>
<td>1</td>
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</tr>
</tbody>
</table>

### Notes

- Dosages were established by the Global TB Guidelines Group for second-line MDR-TB regimens and in combination with other antituberculosis drugs. The recommended doses are based on the pharmacokinetic and pharmacodynamic profiles of MDR-TB drugs.
- Dosages are provided for adults and children. Dosing for children is usually lower than for adults, and the doses are adjusted based on body weight.

### Additional Notes

- For children, lower dosages are typically used, and the dosages are adjusted based on body weight.
- The dosages provided are examples and may vary depending on the specific MDR-TB regimen and the patient's individual needs.

### References


---

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Medicine</th>
<th>Weight-based daily dose</th>
<th>Formulation</th>
<th>50-55 kg</th>
<th>56-65 kg</th>
<th>66-75 kg</th>
<th>&gt;75 kg</th>
<th>Comments</th>
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<tbody>
<tr>
<td>A</td>
<td>Ethambutol</td>
<td>15 mg/kg</td>
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<td>5</td>
<td>3</td>
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<tr>
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<td>Isoniazid</td>
<td>30 mg/kg</td>
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<td>1.5</td>
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<td>2</td>
<td>2</td>
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<tr>
<td></td>
<td>Rifampicin</td>
<td>15 mg/kg</td>
<td>450 mg tab</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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</tr>
</tbody>
</table>

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<th>66-75 kg</th>
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<th>Comments</th>
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<tbody>
<tr>
<td>A</td>
<td>Ethambutol</td>
<td>15 mg/kg</td>
<td>600 mg tab</td>
<td>5</td>
<td>3</td>
<td>4</td>
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<td>Isoniazid</td>
<td>30 mg/kg</td>
<td>900 mg tab</td>
<td>1.5</td>
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<td>Rifampicin</td>
<td>15 mg/kg</td>
<td>450 mg tab</td>
<td>1</td>
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</tbody>
</table>

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### References

<table>
<thead>
<tr>
<th>Group</th>
<th>Medicine</th>
<th>Weight-based (daily dose)</th>
<th>Formulation</th>
<th>Weight bands among patients not over 55 years old*</th>
<th>Usual upper daily dose*</th>
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<td>2-3 mg</td>
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<td>(10 mg)</td>
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<td>B</td>
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<td>Captopril</td>
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<td>4</td>
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<td>C</td>
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<td>3 mg</td>
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<td>4 mg</td>
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<td>2 mg</td>
<td>3 mg</td>
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<tr>
<td></td>
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<td>3 mg</td>
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<td>Lisinopril</td>
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<td>&gt;60 mg/kg</td>
<td>2 mg</td>
<td>3 mg</td>
<td>4</td>
<td>(10 mg)</td>
</tr>
</tbody>
</table>

* Administered as immediate-release formulations. Do not give to patients with eGFR > 90 ml/min/1.73 m² or with a serum potassium concentration > 5.0 mmol/L. Do not exceed the maximum recommended daily dose in patients with renal impairment. The maximum recommended daily dose of Candesartan is 16 mg, Losartan is 50 mg, Ramipril is 5 mg, Lisinopril is 40 mg, and Captopril is 25 mg. The maximum recommended daily dose of Enalapril is 20 mg, Benazepril is 25 mg, and Quinapril is 20 mg.
Annex 7. References


27. University of Liverpool. HIV Drug Interactions [Internet]. Available from: https://www.hiv-druginteractions.org/checker
49. Efficacy and Safety of Levofloxacin for the Treatment of MDR-TB (Opti-Q) [Internet]. Available from: https://clinicaltrials.gov/show/NCT01918397