WHO treatment guidelines for drug-resistant tuberculosis

2016 update

THE END TB STRATEGY

World Health Organization

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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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Contents

Abbreviations & acronyms[1]

aDSM	active TB drug safety monitoring and management
aOR	adjusted odds ratio
AIDS	acquired immunodeficiency syndrome
aIPD	adult individual patient data
CDC	United States Centers for Disease Control and Prevention
CL	confidence limits
CNS	central nervous system
CPTR	Critical Path to TB Drug Regimens
DSMB	Data and Safety Monitoring Board
DST	drug susceptibility testing
EBA	early bactericidal activity
ERG	External Review Group
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	individual patient data
KNCV	KNCV Tuberculosis Foundation
LSHTM	London School of Hygiene and Tropical Medicine
LTBI	latent TB infection
MDR-TB	multidrug-resistant tuberculosis
MIC	minimum inhibitory concentration
MSF	Médecins sans Frontières
MTBDR*sl*	GenoType *Mycobacterium tuberculosis* drug-resistant second-line assay
NTM	non-tuberculous mycobacteria
OR	odds ratio
PICO	Patients, Intervention, Comparator and Outcomes
pIPD	paediatric individual patient data
RCT	randomized controlled trial
RR-TB	rifampicin-resistant TB
SAE	serious adverse event
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
TAG	Treatment Action Group
TB	tuberculosis
TB-PRACTECAL	Pragmatic Clinical Trial for a More Effective Concise and Less Toxic MDR-TB Treatment Regimen(s)
UNION	International Union Against Tuberculosis and Lung Disease
USAID	United States Agency for International Development
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

[1] See also page 23 for the abbreviations of the names of TB medicines.

Acknowledgements

The recommendations and remarks contained in this document resulted from the discussions of an *ad hoc* Guideline Development Group (GDG) convened by the Global TB Programme (GTB) of the World Health Organization (WHO) in Geneva, Switzerland from 9 to 11 November 2015 (Appendix 1). WHO gratefully acknowledges the contributions made by this Group ahead of, during and after this meeting by its members, namely Holger Schünemann (Chair and GRADE methodologist) and Charles L Daley (Co-Chair) and other experts: Farhana Amanullah, José A Caminero, Tsira Chakhaia, Daniela Cirillo, Kelly Dooley, Luis Gustavo do Valle Bastos, Michel Gasana, Agnes Gebhard, Armen Hayrapetyan, Antonia Kwiecien, Sundari Mase, Lindsay McKenna, Nguyen Viet Nhung, Maria Rodriguez, James Seddon, Tom Shinnick, Alena Skrahina, and Carlos Torres-Duque (Appendix 2). The experts on the External Review Group (ERG) who provided comments in preparation of the meeting and on the draft document before its finalization – Chen-Yuan Chiang, Dalene von Delft, Vaira Leimane, Guy Marks, Norbert Ndjeka, Lee Reichman and Rohit Sarin – are also acknowledged.

The writing of these guidelines was coordinated by Dennis Falzon and Elizabeth Harausz (Consultant), under the guidance and supervision of Ernesto Jaramillo and Karin Weyer, and the overall direction of Mario Raviglione, Director of the GTB. The authors acknowledge the contribution of other WHO staff in the production of these guidelines making up the WHO Guideline Steering Committee, namely Nathan Ford, Giuliano Gargioni, Haileyesus Getahun, Malgorzata Grzemska, Avinash Kanchar, Soleil Labelle, Christian Lienhardt, Knut Lönnroth, Fuad Mirzayev, Linh Nhat Nguyen, Marco Antonio Vitoria, Fraser Wares, Diana Weil and Matteo Zignol. The following WHO staff from the regional offices received a final draft of the guideline document for review: Masoud Dara (Europe), Mirtha del Granado (Americas), Daniel Kibuga (Africa), Hyder Khursid (South-East Asia), Mohammed Abdel Aziz (Eastern Mediterranean) and Nobuyuki Nishikiori (Western Pacific). The document was finalized following an iteration of comments in early 2016 from members of the GDG, the ERG, and the the WHO Guideline Steering Committee, ahead of submission to the WHO Guideline Review Committee (GRC) in March 2016 following the WHO internal clearance process.

The funding for the update of the guidelines was made available by the United States Agency for International Development (USAID), through the USAID–WHO Consolidated Grant No. GHA-G-00–09–00003/US-2014–735.

Declarations of interest

Guideline Development Group (GDG)

The scope of the guidelines update, and the composition of the GDG, including their biographies, were made public for comment ahead of the meeting in line with WHO's conflict of interest policy. All GDG members completed the WHO Declaration of Interest forms. The WHO Guideline Steering Committee in preparation for the update of the guidelines and the GDG meeting reviewed the completed forms.

The following GDG members *declared no interests*: Luis Gustavo do Valle Bastos, José A Caminero, Tsira Chakhaia, Michel Gasana, Armen Hayrapetyan, Antonia Kwiecien, Sundari Mase, Nguyen Viet Nhung, Maria Rodriguez, Holger Schünemann, James Seddon and Alena Skrahina.

The following GDG members *declared interests* that were judged not to be in conflict with the objectives of the meeting:

Farhana Amanullah declared having received funding for consultancies (US$500/day) and travel from WHO; and grants from the Global Fund and TB-REACH to cover her salary (10% full time equivalent).

Daniela Cirillo declared having received funding from FIND to conduct evaluation of drug susceptibility testing (DST) for new drugs (US$16 000), and from Otsuka to evaluate DST for delamanid (US$25 000). She also declared being the head of a supranational TB reference laboratory in Italy involved in country capacity building in DST technologies for second-line drugs and new diagnostics for drug-resistant TB; and being a member of the Italian national committee for the use of bedaquiline.

Charles L Daley declared having received funding from Otsuka to serve as chair of the data monitoring committee for trials of delamanid (US$47 000 over 7 years–current).

Kelly Dooley declared having received funding to provide expert advice on a trial design for TB/HIV (US$2000/year paid to the university/employer); she also declared the following activities and roles: co-chair AIDS Clinical Trials Group (ACTG) study assessing bedaquiline and delamanid; principal investigator for adjuvant paclitaxel and trastuzumab (APT) trial assessing pretomanid (PA-824); and investigator in trials assessing high-dose isoniazid for MDR-TB, rifapentine for pregnant women and children with latent TB infection (LTBI), high-dose rifampicin and levofloxacin for paediatric TB meningitis, as well as bedaquiline and delamanid for children with MDR-TB and HIV infection.

Agnes Gebhard declared that she works for the KNCV TB Foundation, which has two projects funded by the Eli Lilly and Company Foundation: (i) engaging the private sector in diagnosis and treatment of TB and MDR-TB with quality assured second-line TB drugs, and (ii) the roll-out of QuanTB (a drug forecasting tool) in countries not supported by the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) implemented by Management Sciences for Health. In addition, she declared that the KNCV TB Foundation has a collaborative project with Cepheid in two countries (Nigeria, Viet Nam) with KCNV providing services for the installation and initial training on the use of GeneXpert machines.

Carlos Torres-Duque declared having received honoraria from Janssen Pharmaceuticals for presentations on TB prevention and WHO policy on bedaquiline at a Latin American Meeting on MDR-TB held in 2014 (US$2000).

Tom Shinnick declared being an employee of the United States Centers for Disease Control and Prevention (CDC). CDC supports his travel and research related to his work on laboratory services needed for TB control. He declared having often represented CDC's position on laboratory services needed for TB diagnosis, treatment and control. As part of his official duties for CDC, he served on the Data and Safety Monitoring Board (DSMB) organized by Otsuka for the clinical trial of delamanid. He did not receive any remuneration for serving on the DSMB nor for travel expenses (CDC paid for all travel expenses related to serving on the DSMB). The DSMB has completed its work for the trial.

The following GDG members declared interests that were judged to be in conflict with some of the objectives of the meeting and were thus recused from some of the discussions:

Lindsay McKenna declared non-commercial support to Treatment Action Group (TAG), her employer, from Stop TB Partnership; Bill & Melinda Gates Foundation; the US Department of Veteran Affairs (on behalf of CDC); Janssen Therapeutics for Hepatitis C and HIV projects and the Global Alliance for TB Drug Development (a public-private entity developing new drugs and regimens for TB treatment). She was thus recused from participating in the 9 November 2015 meeting session on Patients, Intervention, Comparator and Outcomes (PICO) question 1 on MDR-TB regimen composition for adults and children.

José A Caminero stated in his biosketch that he is a staff consultant of the International Union Against Tuberculosis and Lung Disease (UNION), an agency directly involved in the implementation and evaluation of programmes using shorter MDR-TB regimens. He was therefore recused from the 10 November 2015 meeting session on PICO question 3 on shorter regimens for MDR-TB.

External Review Group (ERG)

The following ERG members declared no interest related to the objects of this meeting: Chen-Yuan Chiang, Celine Garfin, Michael Kimerling, Vaira Leimane, Gao Mengqiu, Norbert Ndjeka, Ejaz Qadeer, Lee Reichman, Rohit Sarin and Irina Vasilyeva.

The following two ERG members declared interests which were judged not to be in conflict with the objects of the guidelines development.

Guy Marks declared research support from AERAS (US$450 000) related to the evaluation of latent TB infection and the rate of recurrence of TB after initial treatment in Viet Nam. He also declared being the Vice-President (and a board member) of the UNION and Editor-in-Chief of the International Journal of Tuberculosis and Lung Disease (for which he receives an honorarium).

Dalene von Delft declared having received support from TAG, USAID, UNITAID, Janssen Pharmaceuticals, Critical Path to TB Drug Regimens (CPTR) and AERAS to cover travel costs and accommodation to give presentations/speeches on drug-resistant TB. She declared that in 2011 she received bedaquiline as part of her MDR-TB treatment through a compassionate use access programme.

Evidence reviewers

The researchers who undertook the systematic reviews of evidence for this revision were the following (Appendix 2):

McGill University, Montréal, Canada [Mayara Bastos, Gregory J Fox, Faiz Ahmad Khan, Richard (Dick) Menzies]

London School of Hygiene and Tropical Medicine (LSHTM), London, UK [Katherine Fielding, Rebecca Harris, Mishal Khan, David Moore]

Stellenbosch University, Cape Town, South Africa [Anneke Hesseling]

The evidence reviewers did not participate in the formulation of the policy recommendations.

The following reviewers declared no interest related to the objectives of this meeting: Mayara Bastos, Faiz Ahmad Khan, Richard (Dick) Menzies and Mishal Khan.

The following reviewers declared interests that were judged not to be in conflict with the objectives of the meeting:

Gregory J Fox declared having received research and non-monetary support from the UNION (sponsored by Otsuka) valued at about US$5000 to attend the 2015 International Union Conference and to receive the Young Innovator Award (he declares no work for Otsuka nor any relationship of this award with any commercial or research activities with Otsuka).

Katherine Fielding declared that her employer (LSHTM) was a recipient of an award from Médecins Sans Frontières (MSF) (GB£26 890) for the period February–December 2015 to provide statistical support for the TB-PRACTECAL study on which she is a co-investigator. The study is a Phase II-III randomized controlled trial (RCT) to evaluate the efficacy and safety of shorter MDR-TB regimens for adults.

Rebecca Harris declared she is consulting for a clinical research organization (Cromsource) working for GlaxoSmithKline (GSK) vaccines (~GB£90 000 in 2013); and on GSK vaccines not related to TB (~GB£10 000 since 2013) for Manpower Solutions.

David Moore declared receiving research support from the Wellcome Trust Research Training Fellowship Programme to supervise a PhD student to study MDR-TB in Peru (GB£ 207 056 in 2014).

Anneke Hesseling declared that her employer (Stellenbosch University) is a recipient of an award from Otsuka Pharmaceutical (~US$70 000 to date) for her work on the Phase III delamanid clinical trials in children.

Executive summary

In November 2015, the World Health Organization (WHO) convened a meeting of a Guideline Development Group (GDG) for the update of policy recommendations on the treatment of drug-resistant TB. The GDG was composed of a multidisciplinary group of tuberculosis (TB) and drug-resistant TB experts external to WHO. Before the meeting, the members of the GDG and the WHO Guideline Steering Committee had decided upon the *priority questions* in the treatment and care of patients with drug-resistant TB to be considered for the update of the guidelines. The scope of the 2016 update comprised the following:

i. The optimal combination of medicines and approach towards regimen design for TB patients (both adults and children) with isoniazid-resistant, rifampicin-resistant (RR-TB), multidrug-resistant (MDR-TB), and extensively drug-resistant (XDR-TB) forms of TB, as well as for patients with *M. bovis* disease.

ii. The effectiveness and safety of standardized regimens lasting up to 12 months for the treatment of patients with MDR-TB ("shorter regimens") when compared with longer treatment.

iii. The effect of delay in starting treatment on treatment outcomes for patients with drug-resistant TB.

iv. The effect of surgical interventions on treatment outcomes for patients with drug-resistant TB.

The scope of the *WHO treatment guidelines for drug-resistant tuberculosis, 2016 update* thus differed from the one that guided the previous update of the WHO policy recommendations on the programmatic management of drug-resistant TB in 2011 *(1)*. It did not cover aspects of policy guidance on the programmatic management of drug-resistant TB that were of lesser priority or for which no new evidence has emerged since the 2011 revision. These included questions relating to the use of rapid diagnostics for RR-TB, the monitoring of response to treatment, the duration of longer ("conventional") MDR-TB regimens, the delay in starting antiretroviral therapy in MDR-TB patients with human immunodeficiency virus (HIV) and models of care. The GDG considered that the 2011 recommendations relating to these areas would continue to apply until future evidence reviews show a need for revision of current WHO policy.

In preparation for the GDG meeting, systematic reviews were conducted to answer questions formulated in PICO format (Patients, Intervention, Comparator and Outcomes) that addressed all domains of the guidelines scope. The treatment regimen recommendations for adults in the 2016 update were based in part on individual patient data meta-analysis (of 9153 patients who were mostly adults) that informed the 2011 guidance, supplemented with additional evidence published until August 2015, which was summarized in a study-level meta-analysis. Treatment regimen recommendations for children were based on a paediatric individual patient data

(pIPD) meta-analysis, which included data on 974 children in cohorts and studies published until September 2014. The data for shorter MDR-TB treatment regimens (up to 12 months) were from an analysis of individual patient data and aggregated data from observational studies conducted in Asia and Africa. Surgical recommendations for MDR-TB patients were based on individual patient data analysis and a study-level meta-analysis.

The evidence available on the treatment of isoniazid-resistant TB and on the delay in starting MDR-TB treatment could not address the respective PICO questions. There were very few published studies on the treatment of *M. bovis* and the regimens differed too much, precluding any attempt at formulating recommendations of clinical use.

The recommendations that address the other PICO questions are summarized below.

1. Shorter MDR-TB regimen for adults and children

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 (conditional recommendation, very low certainty in the evidence).

2. Longer MDR-TB regimens for adults and children

2a) 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 core second-line TB medicines – one chosen from Group A, one from Group B, and at least two from Group C[2] (conditional recommendation, very low certainty in the evidence). 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.[3]

2b) In patients with RR-TB or MDR-TB, it is recommended that the regimen be further strengthened with high-dose isoniazid and/or ethambutol (conditional recommendation, very low certainty in the evidence).

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. It could either be a shorter MDR-TB regimen, or a longer MDR-TB regimen to which isoniazid is added.

As a result of the update, the grouping of medicines used in the treatment of MDR/RR-TB has been revised from the one used in the last guidance to reflect the updated evidence on the efficacy and safety of the different agents. This reclassification of medicines has a bearing on the choice of medicines when users design longer, individualized regimens for patients with

[2] Group A=levofloxacin, moxifloxacin, gatifloxacin; Group B=amikacin, capreomycin, kanamycin, (streptomycin); Group C= ethionamide (or prothionamide), cycloserine (or terizidone), linezolid, clofazimine; in children with non-severe disease Group B medicines may be excluded (see guidelines text for how disease severity was assessed).

[3] Group D2=bedaquiline, delamanid; Group D3=*p*-aminosalicylic acid, imipenem–cilastatin, meropenem, amoxicillin clavulanate, (thioacetazone). The WHO policy on the role of D2 agents, including their potential use in children, was under review at the time of production on these guidelines

drug-resistant TB. There is no change in the recommended use of bedaquiline and delamanid from those defined by the WHO interim guidance. These two new medicines now occupy a unique subgroup within the *add-on agents* used to treat MDR/RR-TB.

3. Surgical interventions in patients with MDR-TB

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

MAIN CHANGES TO THE WHO POLICY RECOMMENDATIONS FOR THE TREATMENT OF DRUG-RESISTANT TB

These guidelines update the previous evidence-informed recommendations on the treatment of drug-resistant TB issued by the World Health Organization (WHO) in 2011. The current priorities in the management of drug-resistant TB have been reflected in the scope of the current guidance. For the 2016 update, the Guideline Development Group convened to update the guidelines proposed *priority questions* focused on the composition of treatment regimens for rifampicin-resistant (RR-TB) and multidrug-resistant TB (MDR-TB), the effectiveness and safety of shorter MDR-TB regimens, the treatment of isoniazid-resistant and *M. bovis* TB, the role of surgery, and the impact of delays in starting treatment for RR-TB. In contrast to the 2011 recommendations the current guidance did not update the policy on the use of rapid diagnostics for RR-TB, the monitoring of response to treatment, the duration of longer MDR-TB regimens, the delay in starting antiretroviral therapy in MDR-TB patients with HIV infection and models of care. For these aspects of the programmatic management of drug-resistant TB, the 2011 recommendations continue to apply until future evidence reviews conducted for the purpose of updating WHO policy show a need for revision.

The main changes in the 2016 recommendations are as follows:

- A shorter MDR-TB treatment regimen is recommended under specific conditions.
- Medicines used in the design of longer MDR-TB treatment regimens are now regrouped differently based upon current evidence on their effectiveness and safety. Clofazimine and linezolid are now recommended as core second-line medicines in the MDR-TB regimen while *p*-aminosalicylic acid is an *add-on agent.*
- MDR-TB treatment is recommended for all patients with RR-TB, regardless of confirmation of isoniazid resistance.
- Specific recommendations are made on the treatment of children with RR-TB or MDR-TB.
- Clarithromycin and other macrolides are no longer included among the medicines to be used for the treatment of MDR/RR-TB.
- Evidence-informed recommendations on the role of surgery are now included.

There is no change in the role of new drugs – bedaquiline and delamanid – which have now been assigned to a specific subgroup of *add-on agents.*

Introduction

The *WHO treatment guidelines for drug-resistant tuberculosis, 2016 update* aims to support health professionals worldwide to respond to the continued challenge posed by multidrug-resistant and extensively drug-resistant tuberculosis in the post-2015 period of the End TB Strategy *(2)*. It includes important policy changes made following a review of the latest available evidence on the medical and surgical treatment of both adults and children. This revision updates several of the evidence-informed recommendations released by WHO in 2011 *(1)*. Until such time as future evidence reviews conducted for the purpose of updating WHO policy guidance show a need for further revision, the previous recommendations which were not revised in the 2016 update continue to apply (see also **Table 1**).

Methods

Preparation for revision

The WHO Guideline Steering Committee met regularly from November 2014 through November 2015 to draft the scope and the corresponding PICO (Patients, Intervention, Comparator and Outcomes) questions, and to follow up the development of the guidelines. An application for the revision of the guidelines was submitted to the WHO Guideline Review Committee (GRC) in August 2015 that received final approval in September 2015.

Seven webinars (using WebEx) were held between May and November 2015 (on May 20, July 17, August 7, August 28, September 16, October 6, and November 5) to discuss with the GDG members the scoping, the PICO questions, the scoring of the outcomes, and progress with the evidence reviews ahead of the meeting. For certain sessions, the groups assessing the evidence were invited to these discussions in their capacity as resource persons. In between the webinars, discussions were continued via email. Two WebEx discussions were also held in 2015 with the External Review Group (ERG) members (on 7 September and 29 October), during which they were briefed about their roles and expectations as peer-reviewers.

Table 1. Summary of changes in the evidence based recommendations between the 2011*(1) and 2016 guidelines*[a]

2011 GUIDELINES *(1)*	2016 GUIDELINES
Use of rapid diagnostics for rifampicin resistance Rapid drug susceptibility testing (DST) of isoniazid and rifampicin or of rifampicin alone is recommended over conventional testing or no testing at the time of TB diagnosis, subject to available resources (conditional recommendation, very low quality evidence).	UPDATED [from *(3)*] Rapid DST of at least rifampicin is recommended in adults and children over conventional testing or no testing at the time of TB diagnosis (strong recommendation, high certainty in the evidence).
Use of sputum-smear microscopy and culture to monitor response to treatment 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 (conditional recommendation, very low quality evidence).	REMAINS VALID[b]
Use of a shorter MDR-TB treatment regimen NO SPECIFIC RECOMMENDATION	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 (conditional recommendation, very low certainty in the evidence).[c]
Composition of longer MDR-TB treatment regimens In the treatment of patients with MDR-TB, a fluoroquinolone should be used (strong recommendation, very low quality evidence). In the treatment of patients with MDR-TB, a later-generation fluoroquinolone rather than an earlier-generation fluoroquinolone should be used (conditional recommendation, very low quality evidence). In the treatment of patients with MDR-TB, ethionamide (or prothionamide) should be used (strong recommendation, very low quality evidence). In the treatment of patients with MDR-TB, regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and either cycloserine or *p*-aminosalicylic acid (PAS) if cycloserine cannot be used (conditional recommendation, very low quality evidence). In the treatment of patients with MDR-TB, four second-line anti-tuberculosis drugs likely to be effective (including a parenteral agent), as well as pyrazinamide, should be included in the intensive phase (conditional recommendation, very low quality evidence).	UPDATED[d] 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 core second-line TB medicines – one chosen from Group A, one from Group B, and at least two from Group C[e] (conditional recommendation, very low certainty in the evidence). 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.[f] In patients with RR-TB or MDR-TB, it is recommended that the regimen be further strengthened with high-dose isoniazid and/or ethambutol (conditional recommendation, very low certainty in the evidence).

2011 GUIDELINES *(1)*	2016 GUIDELINES
Treatment of patients with RR-TB NO SPECIFIC RECOMMENDATION	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.
Duration of longer MDR-TB treatment regimens 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 (conditional recommendation, very low quality evidence). 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 (conditional recommendation, very low quality evidence).	REMAINS VALID[b]
Start of antiretroviral therapy with MDR-TB treatment 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 (strong recommendation, very low quality evidence).	REMAINS VALID[b]
Use of surgery as part of MDR-TB treatment NO SPECIFIC RECOMMENDATION	In patients with RR-TB or MDR-TB, elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen (conditional recommendation, very low certainty in the evidence).
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 (conditional recommendation, very low quality evidence).	REMAINS VALID[b]

[a] These recommendations need to be read along with the accompanying remarks in the relevant sections of this document, which are critical to their proper implementation.

[b] This recommendation continues to apply. It will be revised if a future evidence review conducted for the purpose of updating WHO policy guidance shows such a need.

[c] See text for the definition of the shorter MDR-TB treatment regimen, and for other conditions that apply when implementing this recommendation.

[d] No changes to the WHO interim policies on the use of bedaquiline and delamanid have been made in this update *(4,5)*. The WHO policy on the role of D2 agents, including their potential use in children, was under review at the time of production of these guidelines

[e] Group A=levofloxacin, moxifloxacin, gatifloxacin; Group B=amikacin, capreomycin, kanamycin, (streptomycin); Group C=ethionamide (or prothionamide), cycloserine (or terizidone), linezolid, clofazimine; in children with non-severe disease Group B medicines may be excluded (see guidelines text for how disease severity was assessed).

[f] Group D2=bedaquiline, delamanid; Group D3=*p*-aminosalicylic acid, imipenem–cilastatin, meropenem, amoxicillin–clavulanate, (thioacetazone).

Scope

The 2016 update of the *WHO treatment guidelines for drug-resistant tuberculosis, 2016 update* aimed to revise the previous evidence-informed policy recommendations from 2011 *(1)*. The scope of the current guidelines differed from that of the 2011 guidance in a number of ways. In 2011, the scope of the guidelines was broader and included programmatic aspects, such as rapid diagnostics for RR-TB, patient monitoring with culture and sputum microscopy during treatment, length of the intensive phase and total duration of treatment in longer ("conventional") regimens, use of antiretroviral therapy and ambulatory/inpatient models of care. In deciding the scope of the 2016 update, the GDG and the WHO Guideline Steering Committee considered priority questions at the time of the update (2014–2015). The scope did not cover other aspects of policy guidance on the programmatic management of drug-resistant TB for which no new evidence has been published since the 2011 revision.

The GDG agreed to limit the scope of these guidelines to the following priority areas within the current debates on the treatment and care of patients with drug-resistant TB:

i. The optimal combination of medicines and approach towards regimen design for TB patients with isoniazid-resistant, rifampicin-resistant (RR-TB), multidrug-resistant (MDR-TB), and extensively drug-resistant (XDR-TB) forms of TB as well as for patients with *M. bovis* disease.

ii. The effectiveness and safety of standardized regimens lasting up to 12 months for the treatment of patients with MDR-TB ("shorter regimens") when compared with longer treatment.

iii. The effect of delay in starting treatment on treatment outcomes for patients with drug-resistant TB.

iv. The effect of surgical interventions on treatment outcomes for patients with drug-resistant TB.

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.

Key questions

The PICO questions were grouped into four sets (see full versions in Appendix 3). PICO questions 1 and 2 were devoted to the first area of the guidelines scope (see i above). PICO question 3 was devoted entirely to the second area (see ii above) and PICO question 4 covered both the third and fourth areas (see iii and iv above).

The outcomes were defined and scored by the GDG (Table 2). The mean scores for the nine responses received were all in the "Critical" range (7–9 points).

Table 2. Scoring of outcomes considered relevant by the GDG for evidence reviews related to the *WHO treatment guidelines for drug-resistant TB 2016 update*[a]

OUTCOMES	MEAN SCORE
Adherence to TB treatment (treatment interruption due to non-adherence)	6.8
Avoiding adverse reactions from TB medicines	7.0
Avoiding the acquisition or amplification of drug resistance	7.9
Cure or successful completion by the end of treatment	9.0
Culture conversion by month six	7.4
Death (survival) by the end of projected treatment	8.1
Treatment failure	8.7
Relapse	7.7

[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.

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. The GDG also made a statement about research priorities within the different dimensions covered by each of the PICO questions (see Section E below).

The certainty of evidence is categorized into four levels (Table 3). 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 Appendix 4). A number of factors may increase or decrease the certainty of evidence (see Figure 9.1 of *(6)*). 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.

Table 3. Certainty of evidence and definitions *(7)*

CERTAINTY OF EVIDENCE	DEFINITION
High (⊕⊕⊕⊕)	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate (⊕⊕⊕◯)	Further research is likely to have an important impact on our confidence in the effect and may change the estimate.
Low (⊕⊕◯◯)	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low (⊕◯◯◯)	Any estimate of effect is very uncertain.

A recommendation may be strong or conditional. Apart from the quality of evidence, the strength of a recommendation is determined by the balance between desirable and undesirable effects, values and preferences, and costs or resource allocation (online Appendix 5; *(7)*). For strong recommendations, the GDG is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects. For conditional recommendations, the GDG considers that desirable effects probably outweigh the undesirable effects. The strength of a recommendation has different implications for the individuals affected by these guidelines (Table 4).

Table 4. Implications of the strength of a recommendation for different users (adapted from *(7)*)

PERSPECTIVE	STRONG RECOMMENDATION	CONDITIONAL RECOMMENDATION
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guidelines could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients, and that patients must be helped to arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
For policy-makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

Definitions

Rifampicin-resistant TB (RR-TB) refers to TB strains that are considered eligible for treatment with MDR-TB regimens *(8)*. Rifampicin-resistant TB strains may be susceptible to isoniazid, or resistant to isoniazid (i.e. MDR-TB), or resistant to other medicines from the first-line group (poly-resistant) or from the second-line medicine group (e.g. XDR-TB) *(9)*.

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 particular medicine. New policy guidance on the use of line probe assay for the detection of resistance to second-line anti-TB drugs are now available *(10)*.

A **second-line TB medicine (drug or agent)** is used to treat drug-resistant TB (see also Section B under WHO policy recommendations in these guidelines). For the treatment of RR-TB and MDR-TB, streptomycin is included as a substitute for second-line injectable agents when aminoglycosides or capreomycin cannot be used and susceptibility is highly likely. The **core second-line TB medicines (or agents)** refer to those in Groups A, B or C.

A **shorter MDR-TB regimen** refers to a course of treatment for RR-TB or MDR-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 *(11–13)*. The features and indications of this regimen are further elaborated in Section A under WHO policy recommendations in these guidelines.

Longer MDR-TB regimens are treatments for RR-TB or MDR-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 *(1,8)*. These regimens were previously qualified as "conventional", having been the mainstay of MDR-TB treatment before the 2016 update. The features and indications of longer regimens are further elaborated in Section B of the current document.

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 *(9,14)*.

For the purposes of the reviews conducted for these guidelines, a **serious adverse event (SAE)** is defined as one which was classified as Grade 3 (severe) or Grade 4 (life-threatening or disabling) *(15)*, or which led to the medicine being stopped permanently.

Assessment of evidence and its grading

Teams of experts were commissioned to assess the evidence for the PICO questions and their outcomes through systematic literature reviews following a standard methodology *(16)*. Evidence reviewers are listed in Appendix 2; more details on the methods used in unpublished studies are presented in Appendix 6 (online) and in published studies referenced under the respective sections. Titles, abstracts and full text of potentially relevant literature were screened using key subject words and text words. Authors in the field and members of the GDG were

contacted to identify missing studies or studies in progress. Individual patient-level data were used to address PICO 1 (adults *(17)* and children; see also Section B), for PICO 3 (shorter MDR-TB regimens; see Section A) and PICO 4 (use of surgery *(18)*; see Section D).

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. More details are provided in the notes on the GRADE evidence profiles that were used to summarize the results of systematic reviews done for each question (online Appendix 4). The evidence profiles were prepared using GRADEPro software – an online tool to create guideline materials (see http://gdt.guidelinedevelopment.org). 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 *(6)*.

The GDG membership represented a broad cross-section of future users of the guidelines as well as affected persons (including the patient). Ahead of the GDG meeting held at the WHO headquarters in Geneva, Switzerland, between 9 and 11 November 2015, one or more discussants were identified from among the GDG members to assess the evidence for each of the PICO questions and to present his or her perspective on the implications of the findings during the meeting. Drafts of the review reports were shared with the GDG members ahead of the meeting (Appendices 4 and 6). During the days of the meeting and in the following weeks additional analyses were shared with the group upon their demand. The GRADE evidence profiles were discussed by the GDG ahead of formulating the recommendations. The group used the "Evidence to Decision" tables via the GRADEPro interface to capture the content of the discussions, make judgements, annotate the different considerations, develop the wording and strength of the recommendations, and add the remarks that accompany each recommendation (online Appendix 5).

Apart from the quality of evidence, the strength of a recommendation was determined by assessing the balance between desirable and undesirable effects, values and preferences, considerations on equity, resource use and feasibility. 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 particular attention 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 not assessed by means of formal cost-effectiveness studies, and the GDG assessed it from the perspective of the patient and the health services, in terms of feasibility and opportunity cost. 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 the recommendation on surgery (part of PICO 4), the final wording was agreed through voting. None of the recommendations for these guidelines were strong and all the certainty in the evidence was rated as very low.

External review

The ERG commented on the questions during their formulation (in mid-2015) and on a draft text of the guidelines, including the recommendations, following comments from the GDG (in February 2016). Six reviewers provided substantive comments on the draft of the guidelines.

Publication, implementation, evaluation and expiry

These guidelines were published 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 freely downloadable pdf files from 13 May 2016. The main text of the guidelines (without Appendices 4, 5 and 6) will also be made available in print version in late 2016. The evidence reviews as well as the recommendations are also 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 the WHO implementation handbook for programmatic management of drug-resistant TB planned later in 2016 *(8)*.

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 (e.g. on bedaquiline and delamanid use). These changes will also be reflected in a forthcoming revision of the implementation handbook *(8)*.

WHO policy recommendations

A. The effectiveness and safety of standardized regimens lasting up to 12 months for the treatment of patients with MDR-TB when compared with longer treatment

Recommendation

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 (conditional recommendation, very low certainty in the evidence).

Justification

The interest in reducing the duration of treatment for MDR-TB has motivated a number of initiatives to treat patients with shorter regimens under programmatic as well as trial conditions. Experience and data on the effect of shorter MDR-TB regimens was limited until recently and before the 2016 update of the guidelines WHO advised that shorter regimens were to be used only under operational research conditions and with close monitoring for effectiveness and safety during and after the end of treatment. In the past few years, results from three studies of MDR-TB patients on shorter regimens have been published and other observational studies as well as a randomized controlled trial in different settings have begun *(11–13, 19)*. Early results from observational studies in Bangladesh, Cameroon and Niger using regimens lasting 12 months or less have shown much higher likelihood of treatment success compared with longer regimens when treating patients with specific inclusion criteria (such as lack of previous exposure to second-line anti-TB medications). Given the published data and potential impact of shorter regimens on treatment cost and affordability, WHO proceeded with the evidence assessment. A PICO question was developed to assess the effectiveness of the shorter MDR-TB treatment regimens lasting up to 12 months and to inform a possible policy change with respect to their use and application (Appendix 3; Question 3).

The evidence reviewed for this question compared the treatment outcomes for confirmed RR-TB or MDR-TB patients treated with these regimens with those of patients treated with longer regimens (online Appendix 4; Section I). The shorter MDR-TB treatment regimens were standardized in content and duration and split into two distinct parts. The first was an intensive phase of four months (extended up to a maximum of six months in case of lack of sputum smear conversion) and included the following drugs: gatifloxacin (or moxifloxacin), kanamycin, prothionamide, clofazimine, high-dose isoniazid, pyrazinamide and ethambutol. This was followed by a continuation phase of five months with the following medicines:

gatifloxacin (or moxifloxacin), clofazimine, pyrazinamide and ethambutol (prothionamide was kept in the continuation phase in earlier studies). In the studies, patients were placed on these regimens based on a set of criteria, and individuals who had prior exposure to second-line TB drugs were excluded from the analysis. No modifications were made to the shorter MDR-TB regimen if previously unknown drug resistance was detected after start of treatment. The recommendation made on the shorter MDR-TB regimen applies only to a regimen profile with similar characteristics of the ones studied. This is because the substitution or exclusion of one or more of the medicines of this regimen may affect its overall performance which is not possible to predict given the lack of evidence of the impact of such modifications (see "Implementation considerations" below).

All data used to assess the shorter MDR-TB treatment regimens were derived from observational studies (see online Appendix 6 for background, methods and summary of findings). Individual patient data from Bangladesh (n=493; supported by the Damien Foundation), Uzbekistan (n=65; supported by Médecins sans Frontières (MSF)) and Swaziland (n=24; MSF) as well as aggregated data from Cameroon (n=150) *(12)*, Niger (n=65) *(13)* and seven sub-Saharan African countries (n=408; supported by the International Union Against Tuberculosis and Lung Disease (UNION)) were included in the analysis (total number of observations=1205, of whom 89 cases were lost to follow-up and were therefore excluded in certain analyses). These were compared with the outcomes of patients without previous exposure to second-line TB drugs who were included in the adult individual patient data (aIPD) analysis (n=7665) *(17)* (see also Section B below for more details on the aIPD). The standard outcomes used in the intervention and comparator arms largely complied with the standardized outcomes used by TB programmes *(9,14,20)*.

The analyses performed for the evidence assessment showed that patients who met specific inclusion criteria for receiving the shorter MDR-TB treatment regimens had a statistically significant higher likelihood of treatment success than those who received longer regimens – 90% versus 78% when success was compared with treatment failure/relapse/death (Table 5) and 84% versus 62% when compared with treatment failure/relapse/death/loss to follow-up (see also online Appendix 4). The number of relapses was very low, although this may be due to the relatively small number of patients followed up. As expected, treatment success was lower among patients with additional resistance to pyrazinamide and/or fluoroquinolones on shorter MDR-TB regimens, even if in general it remained high and exceeded that in the patients on longer regimens (although the differences were not statistically significant).

Table 5. Treatment success in patients treated with a shorter MDR-TB regimen vs longer MDR-TB regimens[a]

RESISTANCE PATTERN	SHORTER MDR-TB REGIMEN		LONGER MDR-TB REGIMEN	
	N	% (95% CL)	N	% (95% CL)
All cases regardless of pyrazinamide and fluoroquinolone susceptibility	1008/1116	*90.3% (87.8%– 92.4%)*	4033/5850	*78.3% (71.2%–84%)*
Pyrazinamide resistant; fluoroquinolone resistant	19/28	67.9% (47.6%–84.1%)	81/137	59.1% (50.6%–67.1%)
Pyrazinamide resistant; fluoroquinolone susceptible	90/100	88.8% (47.3%–98.6%)	840/1075	81.4% (71.6%–88.4%)
Pyrazinamide susceptible; fluoroquinolone resistant	12/15	80.0% (50.0%–94.1%)	72/120	64.4% (49.6%–76.9%)
Pyrazinamide susceptible; fluoroquinolone susceptible	121/125	96.8% (77.3%–99.6%)	890/1119	83.5% (75.7%–89.2%)

[a] Treatment success (cured or treatment completed *(9,14))* versus treatment failure/relapse/death in patients not previously treated with second-line TB medications; percentages shown have been adjusted where possible (see also online Appendix 4; Section I for more details).

Until more evidence is available, WHO recommends that the shorter MDR-TB regimen not be used in patients who have been previously treated with second-line drugs for more than one month or who have documented or are likely to have strains resistant to medicines in the regimen. Preferably, resistance to at least fluoroquinolones and the injectable agent used in the regimen is excluded before starting treatment by in vitro testing. In the absence of such testing, patients who are highly unlikely to be infected with resistant strains based on history of exposure, use of second-line medicines at country level or recent representative surveillance data may also be eligible for the shorter MDR-TB regimen (see "Implementation considerations" below).

Subgroup considerations

Rifampicin-resistant TB (RR-TB) without MDR-TB. All patients – children or adult – with RR-TB in whom isoniazid resistance is not confirmed may be treated with the shorter MDR-TB treatment regimen.

Resistance additional to MDR-TB. For patients infected with strains known or strongly suspected of being resistant to one or more drugs in the shorter MDR-TB treatment regimen (e.g. pyrazinamide) it is recommended not to use the shorter regimen until more evidence becomes available about its performance in such a situation.

People living with HIV need to be given the same consideration for treatment with the shorter MDR-TB treatment regimen as people who are HIV seronegative.

Children were generally excluded from studies of shorter MDR-TB treatment regimens. However, given that the same medicines have been in use in paediatric MDR-TB regimens for many years, there is no plausible biological reason to believe that these regimens are less effective or safe in children than in adults. As a result, it is recommended that children with confirmed RR-TB or MDR-TB be given the same consideration for treatment with a shorter MDR-TB treatment regimen as adults.

Pregnancy was an exclusion criterion for the shorter MDR-TB treatment regimen studies. Two of the core components of the shorter MDR-TB regimens – the injectable agent and ethionamide (or prothionamide) – are usually contraindicated in pregnancy *(8)*. Withholding these medicines from the shorter MDR-TB treatment regimen could seriously compromise its effectiveness. Thus for pregnant women, it is recommended that a longer individualized regimen be used which can allow the inclusion of four or more effective second-line TB medicines with no known teratogenic properties (see Section B below).

Extrapulmonary disease. The findings from studies of shorter MDR-TB regimen were limited to patients with pulmonary disease, and they cannot be extrapolated directly to extrapulmonary TB cases. No recommendation is thus possible at this stage to use the shorter regimen in patients with extrapulmonary MDR-TB.

Implementation considerations

In order to reproduce the high cure rates achieved by the studies included in the reviews for this guidance, all efforts need to be made to avoid the acquisition of additional resistance, by ensuring careful selection of patients to be enrolled, and effective patient support to enable full adherence to treatment. It is recommended that patients be tested for susceptibility or resistance to fluoroquinolones and to second-line injectable agents used in the regimen before being started on a shorter MDR-TB regimen. Patients with strains resistant to any of the two groups of medicines are to be transferred to a longer MDR-TB regimen (see Section B below).

The availability of reliable and rapid tests would be valuable in deciding (within a few days) which patients would be eligible for the shorter MDR-TB regimen, and what modifications to longer, individualized MDR-TB regimens are necessary based on the resistance detected. In patients with confirmed RR-TB or MDR-TB, WHO now recommends that the GenoType *M. tuberculosis* drug-resistant second-line assay (MTBDR*sl)* be used as an initial direct test, instead of phenotypic culture-based DST, to detect resistance to fluoroquinolones and second-line injectable drugs (conditional recommendation; certainty of evidence low to moderate *(10),(21)*). This applies to testing in both children and adults. While resistance-conferring mutations to fluoroquinolones detected by the MTBDR*sl* assay are highly correlated with phenotypic resistance to ofloxacin and levofloxacin, the correlation with moxifloxacin and gatifloxacin is less clear and the inclusion of moxifloxacin or gatifloxacin in a MDR-TB regimen is best guided by phenotypic DST results.

In settings in which laboratory capacity for DST to fluoroquinolones and injectable agents is not yet available, treatment decisions would need to be guided by the likelihood of resistance to these medicines, informed by the patient's clinical history and recent representative surveillance data.

The evidence for the effectiveness and safety of the shorter MDR-TB regimen derives from studies where treatment was administered under fairly standardized conditions with relatively little variation in the content and duration, and with close monitoring. Thus, the recommendation for the shorter MDR-TB regimen is premised on the use of a regimen similar in composition and duration to those used in observational studies. Any replacement of medicines or any changes to the duration are only to be considered within the parameters applied in these studies (e.g. gatifloxacin replaced by moxifloxacin; prothionamide replaced by ethionamide; intensive phase is prolonged up to six months in case of no sputum conversion).

Two staples of the regimen, clofazimine and high-dose isoniazid may be difficult to procure in some countries. Moreover, there are no good paediatric formulations of clofazimine and dividing the capsule into smaller doses is almost impossible, making dosing in children uncertain. Given the global shortage in the supply of quality-assured gatifloxacin in recent years, the sites where observational studies have been conducted have had to substitute this agent with moxifloxacin. This led to an increase in the overall price of the regimen, although the costs for quality-assured moxifloxacin have since declined. The implementation of these guidelines at the national level needs to ensure that sufficient quantities of these medicines are available to meet the demand and that no stock-outs occur.

Monitoring and evaluation

Patients who receive a shorter MDR-TB treatment regimen need to be monitored during treatment and after completion of treatment using schedules of relevant clinical and laboratory testing which have been successfully applied in the studies under field conditions. The WHO framework for active TB drug-safety monitoring and management (aDSM) needs to be applied to ensure appropriate action to monitor and respond promptly to adverse events *(22,23)*. This could be conducted alongside the routine programme monitoring for patient response and for treatment outcomes that has been conducted worldwide for many years *(9,24)*.

Continued efforts to reduce MDR-TB treatment duration, both under observational and trial conditions, is ongoing and is expected to increase the knowledge base for the effectiveness/efficacy and safety of the regimens under different field conditions, patient subgroups and composition – including new medicines.

B. The optimal combination of medicines and approach towards regimen design for TB patients with RR-TB and MDR-TB

As part of the GDG discussion on the design of MDR-TB regimens for adults and children, a regrouping of TB medicines from that being formerly used is proposed *(1,8)*. These include medicines used in first-line TB treatment that may also have a role in strengthening MDR-TB

regimens (Table 6). When reclassifying these medicines, the GDG assessed the available evidence and the associated level of certainty, as well as other considerations relating to the balance between anticipated desirable and undesirable effects, and feasibility of implementation. **WHO considers that currently only the medicines shown in Table 6 have a role in MDR-TB treatment under programmatic conditions.**[4]

Table 6. Medicines recommended for the treatment of RR-TB and MDR-TB[a]

Group A. Fluoroquinolones[b]		Levofloxacin	Lfx
		Moxifloxacin	Mfx
		Gatifloxacin	Gfx
Group B. Second-line injectable agents		Amikacin	Am
		Capreomycin	Cm
		Kanamycin	Km
		(Streptomycin)[c]	(S)
Group C. Other core second-line agents[b]		Ethionamide / prothionamide	Eto / Pto
		Cycloserine / terizidone	Cs / Trd
		Linezolid	Lzd
		Clofazimine	Cfz
Group D. Add-on agents (not part of the core MDR-TB regimen)	**D1**	Pyrazinamide	Z
		Ethambutol	E
		High-dose isoniazid	H[h]
	D2	Bedaquiline	Bdq
		Delamanid	Dlm
	D3	*p*-aminosalicylic acid	PAS
		Imipenem–cilastatin[d]	Ipm
		Meropenem[d]	Mpm
		Amoxicillin-clavulanate[d]	Amx-Clv
		(Thioacetazone)[e]	(T)

[a] This regrouping is intended to guide the design of longer regimens; the composition of the recommended shorter MDR-TB regimen is standardized (see Section A).

[b] Medicines in Groups A and C are shown by decreasing order of usual preference for use (subject to other considerations; see text).

[c] Refer to the text for the conditions under which streptomycin may substitute other injectable agents. Resistance to streptomycin alone does not qualify for the definition of XDR-TB *(25)*.

[d] Carbapenems and clavulanate are meant to be used together; clavulanate is only available in formulations combined with amoxicillin.

[e] HIV-status must be confirmed to be negative before thioacetazone is started.

[4] Other medicines than those in Table 6 are currently being investigated for use in TB (see Figure 8.3 of reference *(24)*).

B1. Longer treatment regimens for RR-TB

The recommendations in this section cover all forms of 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) (online Appendix 4; Section II).

Recommendations[5]

- 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 core second-line TB medicines – one chosen from Group A, one from Group B, and at least two from Group C[6] (conditional recommendation, very low certainty in the evidence). 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.[7]
- In patients with RR-TB or MDR-TB, it is recommended that the regimen be further strengthened with high-dose isoniazid and/or ethambutol (conditional recommendation, very low certainty in the evidence).

Justification

Treatment of MDR-TB in adults and children with longer second-line regimens has been known to increase the likelihood of cure and lower the risk of chronicity and death *(17,26)*. This section refers to MDR-TB treatment regimens that are of longer duration than the shorter MDR-TB regimen described in Section A. The composition and duration of longer regimens are based on a number of factors, including the combination of sufficient agents considered to be effective, the balance of expected benefits to harms, and the response or reactions to treatment in the individual patient. Recommendations for the design of these regimens have been issued for a number of years and have been implemented in many countries worldwide.

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 quality of the evidence is graded as low or very low.

Adults. The evidence that informed the adult treatment recommendations is based on two main sources (see GRADE tables in online Appendix 4; Section II): (i) an IPD meta-analysis including data on 9153 mostly adult patients (only 76 were under <15 years) from studies that incorporated three systematic reviews of MDR-TB treatment outcomes published until 2010 *(17)*; and (ii) additional evidence published until August 2015 that summarized a study-level meta-analysis conducted expressly for the revision of the current guidelines (see online Appendix 6 for background, methods and summary of findings). All studies included had to

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[5] No changes to the WHO interim policies on the use of bedaquiline and delamanid have been made in this update *(4,5)*.

[6] Group A=levofloxacin, moxifloxacin, gatifloxacin; Group B=amikacin, capreomycin, kanamycin, (streptomycin); Group C=ethionamide (or prothionamide), cycloserine (or terizidone), linezolid, clofazimine; in children with non-severe disease Group B medicines may be excluded.

[7] Group D2=bedaquiline, delamanid; Group D3=*p*-aminosalicylic acid, imipenem-cilastatin, meropenem, amoxicillin-clavulanate, (thioacetazone). The WHO policy on the role of D2 agents, including their potential use in children, was under review at the time of production on these guidelines.

report treatment outcomes, have less than 10% extrapulmonary cases (unless pulmonary and extrapulmonary cases were reported separately), and include at least 25 adult patients with bacteriologically confirmed MDR-TB.

The best available evidence has been used to construct recommendations for a regimen that has high relapse-free cure rates, reduced likelihood of death and low emergence of additional resistance while minimizing SAEs. In the case of high-dose isoniazid, the results from a separate, paediatric individual patient data (pIPD) meta-analysis were extrapolated to adults.

Children. These treatment regimen recommendations are based on the pIPD meta-analysis that included both published and unpublished data on 974 children up until September 30, 2014 (see GRADE tables in online Appendix 4 Section III; and online Appendix 6, Section 3 for background, methods and summary of findings). Datasets were eligible if they included a minimum of three children (aged <15 years) within a defined treatment cohort who were treated for clinically diagnosed or bacteriologically confirmed pulmonary or extrapulmonary MDR-TB, and for whom treatment outcomes were reported, using standard WHO TB case definitions. Eligible study designs included controlled and uncontrolled retrospective and prospective studies and case series. No randomized control trials were included (or known to exist) and as a result the overall certainty of the evidence is very low.

Children with XDR-TB were excluded from the 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. For analysis, children were split in two different cohorts: (i) those who were bacteriologically confirmed as having MDR-TB, and (ii) those who were clinically diagnosed with MDR-TB. When making treatment recommendations, preference was given to the results in the bacteriologically confirmed cohort, as this group had a higher certainty of diagnosis. The children with bacteriologically confirmed MDR-TB were more likely to have severe disease; they had statistically significant higher levels of malnutrition, severe disease on chest radiography, severe extrapulmonary disease and were more likely to be HIV positive. Children without these features were considered to have milder forms of disease.

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 SAEs.

Remarks

Based on the evidence reviews, it is recommended that the MDR-TB regimen be composed of at least five drugs that are likely to be effective, i.e. four core second-line drugs plus pyrazinamide. If a minimum of four core second-line TB medicines cannot be reached by using agents from Groups A to C alone, drugs from Group D2 (in adults) or, if not possible, from Group D3 are added. Pyrazinamide is added routinely unless there is confirmed resistance from reliable DST, or well-founded reasons to believe that the strain is resistant, or there is risk of significant toxicity. If pyrazinamide is compromised or cannot be used, the regimen may also be strengthened with an additional agent from Groups C or D (preferably D2, or if not

possible, from D3). Other agents from Group D1 are included if they are considered to add benefit (e.g. high-dose isoniazid in patients without high-level isoniazid resistance). The total number of TB medicines to include in the regimen needs to balance expected benefit with risk of harms and non-adherence when the pill-burden is high.

The recommendations for children are mostly identical to those of adults. However, in children with mild forms of disease, the harms associated with Group B medications (second-line injectable agents) outweigh potential benefits and therefore Group B medications may be excluded in this group of children. The GDG based this decision on the observation that treatment success in children with clinically diagnosed disease (which was associated with less severe clinical or radiological manifestations) was high and not significantly different in patients treated with and without a Group B medication (93.5% versus 98.1%; n=219; see online Appendix 4). No new data were analysed for the use of bedaquiline and delamanid for the update of these guidelines and the WHO policy on the role of D2 agents – including their potential use in children – was under review at the time of release of these guidelines.

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. In such cases, isoniazid is added alongside the rest of the MDR-TB regimen until susceptibility results are confirmed. If isoniazid susceptibility cannot be tested, isoniazid may still be added to the regimen unless there are well-founded grounds to consider the drug ineffective.

Desirable and undesirable effects

Group A. Fluoroquinolones

Based on the evidence reviews, the GDG concluded that treatment with later-generation fluoroquinolones (defined for these guidelines as high-dose levofloxacin,[8] moxifloxacin, and gatifloxacin) significantly improves treatment outcomes in adults with RR-TB and MDR-TB. This group of medicines is considered to be the most important component of the core MDR-TB regimen and the benefits from their use outweigh potential risks. They should therefore always be included unless there is evidence for absolute contraindication for their use. The order of preference for the inclusion of later-generation fluoroquinolones in longer MDR-TB regimens is: high-dose levofloxacin, moxifloxacin and gatifloxacin. It is recommended that ofloxacin be phased out from MDR-TB regimens and ciprofloxacin never used due to the limited evidence of their effectiveness. Although the pIPD had high levels of confounding and insufficient numbers to discern the treatment effect of high-dose levofloxacin, moxifloxacin and gatifloxacin, data from adults with MDR-TB show a treatment benefit. Therefore these recommendations have been extrapolated to children.

Fluoroquinolones in general have a good safety profile and considering the seriousness of RR-TB and MDR-TB, the potential for drug-related harms is offset by the benefits from their use. Although adverse events were poorly recorded, in the study-level meta-analysis the frequency of SAEs attributed to fluoroquinolones was low (1.2%–2.8%; Table 7). Moxifloxacin

[8] For levofloxacin, high-dose is usually defined as 750 mg/day or more. The definition of high-dose will be the subject of discussion of another WHO consultation planned in early 2017.

and other fluoroquinolones carry a risk of QT prolongation, which is a cause for concern when used in combination with medications that have a similar effect, such as bedaquiline, delamanid and clofazimine.

Table 7. Serious adverse events (SAEs) in patients on MDR-TB treatment regimens

MEDICINE	COHORTS USING THE DRUG AND REPORTING SAEs (N)	PATIENTS RECEIVING MEDICINE (N)	SAEs ATTRIBUTED TO INDIVIDUAL MEDICINE	
			N PATIENTS	% (95%CL)[a]
Pyrazinamide	19	2023	56	2.8% (2.1%–3.7%)
Ethambutol	16	1325	6	0.5% (0.2%–1.1%)
Second-line injectable agent	19	2538	184	7.3% (6.2%–8.4%)
Ofloxacin or ciprofloxacin	9	1408	40	2.8% (1.9%–4.1%)
Other fluoroquinolones	13	827	10	1.2% (0.6%–2.4%)
Ethionamide/ prothionamide	17	2106	173	8.2% (7.0%–9.6%)
Cycloserine	16	2140	96	4.5% (3.6%–5.5%)
p-aminosalicylic acid	16	1706	208	12.2% (10.6%–13.9%)
Linezolid	8	190	28	14.7% (10.0%–20.6%)

[a] values from fixed effects meta-analysis.

Source: study-level meta-analysis (Bastos M, Lan Z, Menzies R. An updated systematic review and meta-analysis for treatment of multidrug-resistant tuberculosis, 2016. [under review, 25 July 2016]); 43/73 studies reported adverse events, but only 5/43 studies reported Grade 3–4 adverse events, and 28/43 studies reported TB drugs being stopped due to adverse events; for linezolid estimate is based on an aggregated analysis of eight observational studies *(27–34)* (see also online Appendix 4 Section II for the respective GRADE tables).

Concerns about dysglycaemia reported in 2006 in patients treated with gatifloxacin for conditions other than TB led the parent company to stop manufacturing the medicine *(35)*, and a global shortage in quality-assured formulations of this drug ensued. A trial of a four-month standardized regimen for drug-susceptible TB which included gatifloxacin (400 mg once daily) published in 2014 reported no significant risk of hyperglycaemia associated with exposure to gatifloxacin *(36)*. Although in general adverse events were poorly recorded in the studies assessed for this review, the data showed that there was a lower risk of SAEs in patients taking gatifloxacin than in those who did not, including those receiving no fluoroquinolones (3.6% vs 8%, not statistically significant; see online Appendix 4 Section II). The frequency of SAEs associated with gatifloxacin was thus comparable to the one associated with fluoroquinolones in the study-level meta-analysis (Table 7).

Group B. Second-line injectable agents

Based on the available evidence, second-line injectable agents were associated with an increased likelihood of treatment success when included in a longer MDR-TB treatment regimen (the small size of the population not receiving an injectable agent in the aIPD limited the power to quantify the impact of this class of agents). It is therefore recommended that adults with RR-TB or MDR-TB always receive a second-line injectable agent as part of their regimen unless there is an important contraindication. In children with mild forms of disease, however, the harms associated with this group of medications may outweigh potential benefits and therefore injectable agents may be excluded for children. The GDG based this decision upon the observation that in children with clinically-diagnosed disease – which was associated with less severe clinical manifestations – treatment success was in general high and did not differ significantly between patients who received Group B medication and those who did not (see above and online Appendix 4 Section III). For children with additional resistance to fluoroquinolones, Group B medications are best retained.

The choice from among amikacin, capreomycin or kanamycin would be determined by the likelihood of effectiveness and implementation considerations. While streptomycin is not usually included with the second-line drugs it can be used as the injectable agent of the core MDR-TB regimen if none of the other three agents can be used and if the strain is unlikely to be resistant to it. Streptomycin resistance by itself does not qualify to define XDR-TB *(25)* and DST methods for it are not considered accurate or reproducible *(37)*.

Adverse events need to be carefully monitored while using second-line injectable agents. Hearing loss and nephrotoxicity are the most frequent and serious adverse reactions. However, skin rash, hypersensitivity and peripheral nephropathy may also occur. The risk of adverse reactions increases with the total cumulative dose of second-line injectable agents, so particular caution should be given to people who have previously received these medications, including streptomycin as part of a regimen for drug-susceptible TB. In children especially, hearing loss can have a profound impact on their quality of life, affecting acquisition of language and the ability to learn at school.

Although adverse events are poorly reported, the data for this review found that 7.3% of adult patients (10.1% in children) had SAEs attributed to second-line injectable agents (Table 7). In a study focused on hearing loss in children with TB (30% of the children were HIV-infected), 24% of children treated for MDR-TB with an injectable agent had hearing loss and 64% of children had progression of hearing loss after completing the treatment *(38)*.

Group C. Other core second-line agents

When designing the core MDR-TB treatment regimen, two or more of the following four medicines are to be included: ethionamide (or prothionamide), cycloserine (or terizidone), linezolid and clofazimine, usually in this order of preference, unless the balance of benefits-to-harms for the individual patient demands otherwise. Group C agents are included to bring the total number of effective second-line TB medicines in the core regimen to at least four during the intensive phase. If pyrazinamide cannot be included or counted upon, another agent is added. Ethionamide can be used interchangeably with prothionamide, and terizidone can be used instead of cycloserine.

Given the lack of reliable DST for drugs in Group C, the choice of which ones to include is determined by the balance of desirable to undesirable effects and implementation considerations. The aIPD and pIPD meta-analyses showed an increase in the likelihood of treatment success when MDR-TB treatment regimens included cycloserine (marginally statistically significant) and ethionamide/prothionamide (statistically significant only in adults). In the pIPD, the vast majority of children received ethionamide or prothionamide and significance testing was therefore not always possible for want of sufficient number of controls. In contrast to cycloserine/terizidone and ethionamide/prothionamide, RCT data from a few recent studies are now available for clofazimine and linezolid *(31,39,40)*. Linezolid has shown a statistically significant treatment benefit in both RCT and in cohort studies in adult patients, with this benefit being most pronounced in patients with additional resistance to fluoroquinolones and with XDR-TB *(40)*. Both the aIPD and pIPD showed no significant increase in treatment success associated with the use of clofazimine, while linezolid was used too sparingly in the cohorts included to allow a conclusive analysis *(17)*.

Ethionamide and prothionamide cause gastrointestinal disturbance, in particular vomiting, which can limit tolerability. Hypothyroidism may occur, especially in combination with PAS, but is reversible upon cessation of drugs. This review found that 8.2% of patients had SAEs due to ethionamide or prothionamide, although adverse events were poorly reported across the individual studies (Table 7).

Cycloserine has a well-established association with neuropsychiatric adverse reactions. However, the aIPD meta-analysis in adults revealed low levels of SAEs (4.5% in the study-level meta-analysis conducted for this update). A meta-analysis published in 2013 comparing the adverse effects of cycloserine with terizidone found that terizidone had no to little benefit over cycloserine with regard to adverse reactions *(41)*.

Adverse reactions of linezolid include lactic acidosis, thrombocytopenia and anaemia. These can be severe and life threatening, although they are reversible with cessation of the drug or on some occasions by lowering its dose (usually from 600 mg daily to 300 mg daily) *(8)*. Haematologic toxicities are less common with current strategies of once-daily dosing. Peripheral neuropathy may or may not improve with cessation of the drug. Optic neuropathy should be treated as a medical emergency. Given the potential seriousness of the adverse reactions associated with linezolid the decision to use it must balance its risks and benefits, and the availability of other TB medicines. Its use needs to be accompanied by close monitoring for adverse events. Where this is not possible, linezolid would best be reserved for MDR-TB patients who have additional drug resistance, or XDR-TB patients, or those who are intolerant to other components of the core regimen.

Clofazimine probably contributes to the sterilizing function of MDR-TB regimens where pyrazinamide is not effective. Although the single published for clofazimine use in MDR-TB had serious methodological concerns, it showed a statistically significant treatment benefit associated with clofazimine use *(39)*. However, much of the evidence for the effect of clofazimine in MDR-TB is based upon observational studies, which showed conflicting or inconclusive findings *(42)*. One of the main adverse effects of clofazimine is skin discoloration/darkening, which may be distressing to patients. In the RCT, the adverse events reported were

mostly limited to skin conditions and discoloration, and did not lead to discontinuation in the use of the drug. Overall, small rates of adverse events were noted in the observational studies and SAEs appear to be relatively uncommon. Clofazimine may prolong the QT interval, so caution is advised when using this medication in combination with other drugs also known to have the same effect.

Group D. Add-on agents

This group of medicines includes drugs that do not form part of the core second-line agents. It is split into three subgroups:

Group D1 consists of pyrazinamide, ethambutol and high-dose isoniazid. These agents are usually added to core second-line medications, unless confirmed resistance, pill burden, intolerance or drug–drug interaction outweigh their potential benefits.

The aIPD showed improved likelihood of success (versus treatment failure, relapse or death combined) in patients who had pyrazinamide included in their regimens. This effect was significant both statistically and in absolute terms. The pIPD did not show a significant treatment effect with use of pyrazinamide. In many settings, RR-TB strains frequently have additional resistance to pyrazinamide. While it would be desirable to avoid giving pyrazinamide to patients whose strains are resistant to the drug, it is acknowledged that reliable DST for pyrazinamide is very often unavailable in resource-constrained settings. Although adverse events were poorly reported, data from the study-level meta-analysis showed that 2.8% of patients who received pyrazinamide had SAEs (Table 7). The balance of desirable to undesirable effects favours the addition of pyrazinamide to the core second-line MDR-TB regimen by default, unless there is confirmed resistance from reliable DST, or well-founded reasons to believe that the strain is resistant, or there are other contraindications for its use, particularly risk of significant toxicity. As for the drugs from the core regimen, if pyrazinamide is compromised or cannot be used, more agents from Group C and subsequently Group D are added until at least five effective medicines are available in the intensive phase.

The recommendation for the inclusion of isoniazid[9] in adult MDR-TB regimens is largely based on evidence from the analysis of pIPD. This analysis showed a statistically significant increased likelihood of treatment success (versus treatment failure, relapse or death combined) in children with bacteriologically confirmed MDR-TB, even after adjustment for age, HIV status, sex, TB disease severity and treatment centre (treatment with high-dose isoniazid was almost exclusively done in South African sites). An RCT of high-dose isoniazid therapy for MDR-TB in adults found no increased risk of hepatotoxicity *(43)*. Additionally, high-dose isoniazid was very well tolerated in children with drug susceptible tuberculous meningitis in a large cohort study from the Western Cape *(44)*.

Isoniazid is recommended alongside a full MDR-TB regimen in patients with rifampicin-resistant strains confirmed or suspected to be susceptible to isoniazid. High-dose isoniazid is one of the core components of the shorter MDR-TB treatment regimen (see Section A above).

[9] For isoniazid, the definition of high-dose will be the subject of discussion of another WHO consultation planned in early 2017.

Strains bearing mutations in the promoter region of the inhA gene may have a minimum inhibitory concentration (MIC) to isoniazid that is low enough to be overcome by high-dose isoniazid. In such settings the drug may still add benefit *(45)*. However, this mutation has been associated with high-level ethionamide resistance *(46)* and therefore, if present, ethionamide (or prothionamide) may have to be replaced in the regimen. In settings with elevated prevalence of high-level isoniazid resistance associated with katG mutations, high-dose isoniazid may be less effective and therefore its routine use may not be warranted. In such a situation the susceptibility to ethionamide (or prothionamide) is not affected and it can be used in combination with high-dose isoniazid.

The aIPD did not show any statistically significant association between the use of ethambutol and likelihood of treatment success. Ethambutol may cause ocular toxicity, which can be difficult to diagnose in young children, although this risk is reduced if the dose does not exceed recommended limits. SAEs were reportedly associated in 0.5% of cases in the meta-analysis conducted for this review although the reporting of adverse events data was incomplete (Table 7). Special care is needed when renal function is compromised. RR-TB and MDR-TB strains may also be resistant to ethambutol, particularly in those patients who have been treated with this drug previously. However, DST for this drug is not considered reliable and reproducible *(37)*. The potential benefit that ethambutol may add to a core MDR-TB regimen needs to be balanced carefully with the inconvenience of adding another medicine to the regimen and the risks of associated harms.

Group D2 is made up of two new drugs released in recent years – bedaquiline and delamanid. WHO issued an interim policy on the use of these medicines in 2013 and 2014 *(4,5)*. The current guidelines make no change to the previous recommendations on how bedaquiline and delamanid may be added to a core MDR-TB regimen in adults, and no recommendation for their use in children is yet possible. When the results from ongoing studies and the Phase III trials become available the evidence for the effectiveness of these two new drugs will be re-evaluated with respect to the other medicines making up the MDR-TB regimen.

Group D3 consists of *p*-aminosalicylic acid (PAS), imipenem–cilastatin, meropenem, clavulanate and thioacetazone. These drugs are only to be used when a MDR-TB regimen with at least five effective drugs in the intensive phase (i.e. four core second-line medicines plus pyrazinamide) cannot be otherwise composed.

The aIPD *(17)*, as well as the study-level meta-analysis conducted for the current guidelines revision, found no significant effect of PAS on treatment success. PAS use is associated with a high frequency of adverse reactions (12.2% SAEs in the meta-analysis undertaken for this study) and is thus reserved for situations when there is no option to use other drugs.

Carbapenems (imipenem–cilastin or meropenem) appear to be hydrolyzed more slowly by *M. tuberculosis* when combined with clavulanic acid *(47,48)*. Amoxicillin-clavulanate has shown poor results in in vitro studies and in early bactericidal activity (EBA) studies *(49–51)*. The aIPD showed that patients treated with amoxicillin- clavulanate were more likely to have poor treatment outcomes, although this may be due to confounding by the higher likelihood that patients receiving this drug tended to have more severe disease (not all confounding could

be adjusted for in the analysis). WHO recommends that whenever amoxicillin-clavulanate and carbapenems are included in regimens they are always to be used together. Clavulanate is only available as a combination preparation containing amoxicillin. The spectrum of adverse reactions associated with amoxicillin-clavulanate and carbapenems is to a large extent identical to that associated with penicillins *(52)*.

Thioacetazone has been used extensively in the past as part of first-line combination therapy for TB, based on RCT evidence of effectiveness *(53)*. Use of the drug in TB treatment has however been restricted since the early 1990s due to the severe skin reactions it causes (including Stevens–Johnson syndrome and toxic epidermal necrolysis that can lead to death, especially in people living with HIV *(54)*), as well as the widespread availability of safer, affordable alternatives for combination TB regimens. If thioacetazone is being considered as part of a MDR-TB treatment regimen, close monitoring for severe skin reactions is required and it is imperative that the patient be tested for HIV, and the drug not used if the patient is HIV seropositive.

M. tuberculosis is intrinsically resistant to the macrolide class of antibiotics *(55)*. The evidence reviews for the current guidelines did not show any effectiveness of drugs of this class (clarithromycin, azithromycin) *(56)*, which have at times been included in MDR-TB regimens in both adults and children. In addition, the aIPD showed an increased risk – although not statistically significant – for poor outcomes in patients receiving macrolides although macrolides appeared to be safe during prolonged use. Macrolides are associated with QT prolongation *(57)*, which would be of particular concern if patients are receiving other TB drugs with a similar risk, such as moxifloxacin, clofazimine, bedaquiline or delamanid. WHO therefore no longer recommends the use of clarithromycin or azithromycin as part of regimens for the treatment of MDR/RR-TB.

Adverse reactions linked to PAS include gastrointestinal disturbance and hypothyroidism (in particular when given in combination with ethionamide/prothionamide). Hypothyroidism is reversible upon cessation of drugs. Although adverse events were poorly reported in studies assessed, the data for this review found that 12.2% of patients had SAEs attributed to PAS (Table 7). The pIPD showed the possibility of harm associated with the use of PAS (not statistically significant). However, PAS is frequently given to children when few other treatment options remain, and therefore this effect may be due to confounding by indication (sites that had poorer outcomes with PAS also had significantly higher rates of children who were HIV seropositive and malnourished, as well as with severe pulmonary disease, and additional resistance to fluoroquinolones and second-line injectable medicines).

Subgroup considerations

Rifampicin-resistant TB/MDR-TB with additional resistance to fluoroquinolones, second-line injectable agents and XDR-TB. In patients with RR-TB and MDR-TB, if there is confirmed or well-founded belief of resistance to medications from Group A (fluoroquinolones) or Group B (second-line injectable agents), the medicines in the regimen that belong to these classes are substituted as detailed in the beginning of section B1. If any of the components of the regimen – the four core second-line medicines and pyrazinamide – is not considered to be effective, additional agents from Groups D2 or D3 are added. This is almost always necessary when

resistance to both Groups A and B drugs (i.e. XDR-TB) is present. Analysis of additional individual patient data collected for the update of the WHO drug-resistant TB treatment guidelines of 2011 concluded that regimens containing more drugs were associated with the highest odds of success for MDR-TB patients who had additional resistance to fluoroquinolones and/or second-line injectable agents *(58)*. The current WHO advice continues to apply when designing regimens for patients with resistance to fluoroquinolones and second-line injectable medications, as well as those with XDR-TB *(8)*.

Access to rapid diagnostic testing, which could reliably identify resistance to Group A or Group B agents, would help clinicians decide on how to modify longer MDR-TB regimens. The Genotype MTBDR*sl* line probe assay *(21)* may now be used as an initial test, over phenotypic culture-based DST, to detect resistance to fluoroquinolones and to the second-line injectable drugs among patients with MDR/RR-TB (conditional recommendation; certainty of evidence low to moderate for direct testing *(11)*). Genotype MTBDR*sl* can be used in both children and adults and as a direct and indirect test (it could thus be used on extrapulmonary samples). While resistance-conferring mutations to fluoroquinolones detected by the MTBDR*sl* assay are highly correlated with phenotypic resistance to ofloxacin and levofloxacin, the correlation with moxifloxacin and gatifloxacin is less clear and the inclusion of moxifloxacin or gatifloxacin in a MDR-TB regimen is best guided by phenotypic DST results.

TB of the central nervous system. The treatment of tuberculous meningitis related to rifampicin-resistant or MDR strains is best guided by drug susceptibility results and the known properties of TB drugs to penetrate the central nervous system (CNS) *(8)*. In patients with MDR/RR-TB meningitis, it is recommended that medications selected for the regimen have good CNS penetration properties.

The fluoroquinolones recommended by these guidelines have good CNS penetration *(59)*, as do ethionamide (or prothionamide), cycloserine (or terizidone) and linezolid *(60,61)*. Pyrazinamide has good CNS penetration, although caution should be exercised, as a large percentage of MDR-TB strains may be resistant. Isoniazid penetrates the CNS very well, with higher doses reaching adequate MICs in the cerebrospinal fluid. Due to its good CNS penetration, high-dose isoniazid is recommended as part of the treatment regimen unless high-level resistance is known to exist.

PAS and ethambutol do not penetrate the CNS well and should not be counted on as effective drugs to treat MDR-TB meningitis. Kanamycin, amikacin and streptomycin only penetrate the cerebrospinal fluid in the presence of meningeal inflammation. There are little data on the CNS penetration of capreomycin, clofazimine, bedaquiline or delamanid.

People living with HIV. The composition of the treatment regimen for MDR-TB does not differ for people living with HIV. However, thioacetazone should not be given to patients who are HIV positive. If it is being considered as part of a treatment regimen, then HIV infection needs to be reliably excluded in the patient.

Implementation considerations

The implementation of MDR-TB chemotherapy is feasible under programmatic conditions, as has been amply shown by the global expansion in the use of MDR-TB regimens worldwide, particularly in the past decade *(24,62)*. Changes made by the current revision to the grouping of medicines and composition of longer MDR-TB regimens are not expected to have a major impact on their continued use. Most of the fluoroquinolones and injectable agents are readily available as are the majority of the Group C and Group D agents. The latest WHO Model Lists of Essential Medicines (August 2015) include most of the agents in Table 6 except for gatifloxacin and thioacetazone *(63,64)*. However, clofazimine, meropenem, imipenem–cilastatin and amoxicillin-clavulanate are listed for indications other than TB, while bedaquiline and delamanid are only included in the adult list. Other specific factors important for implementation are discussed in the respective sections below.

Where possible a patient's rifampicin-resistant or MDR-TB strain needs to be tested for susceptibility to medicines planned for inclusion in the regimen. The availability of reliable, rapid tests for susceptibility to fluoroquinolones and second-line injectable drugs which would give results within a few days is valuable to ensure that longer MDR-TB regimens are strengthened as necessary *(10,37)*. Where reliable DST is not an option, proof of the effectiveness of a medicine needs to be based on careful clinical history of the patient's previous exposure to the medicine, of significant contact with another MDR/RR-TB patient whose antibiogramme is documented, and knowledge of the prevalent resistance patterns based on representative drug-resistance surveillance. Both the DST and the individual clinical history should be considered when constructing a treatment regimen. The only reliable laboratory tests for TB drug susceptibility (or resistance) which are widely used today are those for isoniazid, rifampicin, fluoroquinolones and second-line injectable agents.

The recommendations made by the current guidelines envisage a more widespread application of the shorter MDR-TB regimen among MDR/RR-TB patients. This implies that a larger proportion of the patients to whom longer MDR-TB regimens will be given would have additional resistance to core second-line medications than is the case today. For this reason additional care will need to be taken to ensure that regimens are adequately strengthened to ensure the best possible outcomes for these patients.

The current revision of the guidelines did not re-analyse the optimal duration of treatment (intensive and continuation phases). Thus the recommendations from the 2011 guidelines which were based on the aIPD meta-analysis continue to apply *(1,17)*. The 2011 guidelines conditionally recommended an intensive phase of eight months for most MDR-TB patients and total treatment duration of 20 months in patients who had not been previously treated. The duration may need to be modified according to the patient's response to therapy *(8)*. The association between treatment success and the total length of treatment was less clear in patients who had been previously treated compared with those who had not, although the likelihood of treatment success appeared to peak between 27.6 and 30.5 months. The number of observations was also far fewer than for those who had no previous MDR-TB treatment. As a result no recommendation on total duration was made in the 2011 revision for previously-treated patients. Many of the MDR/RR-TB patients who will be ineligible for the shorter

MDR-TB regimen and referred for treatment with longer regimens would have been treated with second-line medication in the past. In these patients, uncertainties will remain on the optimal duration of treatment and therefore the duration of therapy would need to be guided primarily by their response to therapy.

Group A. Fluoroquinolones. Both levofloxacin and moxifloxacin are commonly used to treat MDR-TB. Levofloxacin is more widely available than moxifloxacin, which is more expensive although a reduction in its price is expected in the coming years.

Gatifloxacin is an affordable drug that was commonly used by TB treatment programmes until the concerns about its dysglycaemic effects led to a global shortage in its supplies. If manufacture of quality-assured formulations of the drug restarts, it could provide more options for regimen design and could lower the costs of regimens by substituting more expensive fluoroquinolones.

Moxifloxacin is relatively easy to administer to older children. However, the tablet must be split to accommodate dosing in younger children and it is highly unpalatable once split or crushed. Levofloxacin is available as a suspension.

Group B. Second-line injectable agents. These agents present problems to administer intramuscularly or intravenously on a daily basis for several months, often necessitating hospitalization. Giving injections to children and underweight adults is particularly unpleasant and unwelcome.

Group C. Other core second-line agents. Ethionamide and prothionamide are inexpensive, readily available worldwide and easily administered.

Cycloserine has been one of the standard inexpensive drugs for the treatment of MDR-TB for several years and therefore experience in its use is widespread. Terizidone is less widely used but is available on the Global Drug Facility (GDF) Products List.

Clofazimine is relatively inexpensive but it can be difficult to procure. The implementation of the recommendation on the shorter MDR-TB regimen, of which this medicine is an irreplaceable core component, needs to ensure that sufficient quantities of this medicine are available to meet the demand and that no stock-outs occur.

When linezolid is used, there needs to be close monitoring for adverse effects, particularly anaemia, thrombocytopenia, lactic acidosis, peripheral neuropathy and optic neuropathy, as these can be severe and life threatening. Historically linezolid has been very expensive, however, it has recently come off patent and the availability of generic products has hugely reduced its market price and it may become even more affordable in future.

Group D. Add-on agents. Pyrazinamide is inexpensive, readily available and easy to administer. Isoniazid is inexpensive. It is important to consider the epidemiology of high-level versus low-level isoniazid resistance in a population before standard treatment regimens including high-dose isoniazid are recommended. Ethambutol is inexpensive and readily available. All of these three medicines are core components of first-line regimens for drug-susceptible TB.

PAS may be difficult to obtain although it is available through the GDF. Otherwise it is relatively inexpensive and easy to administer.

Amoxicillin-clavulanate is inexpensive and easily obtainable. However, the carbapenems are expensive and are difficult to administer as they must be given two or three times per day via an intravenous line.

Thioacetazone is inexpensive but it has limited availability and is not currently available through the GDF.

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 *(8,23)*. Frameworks for the surveillance of bacteriological status, drug-resistance and outcomes have been fairly standardized over the past decade. The systematic monitoring of adverse events during and after the end of treatment is a recent introduction in TB programmes and experience in their 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.

B2. Treatment regimens for isoniazid-resistant TB and *M. bovis*

In the review for isoniazid-resistant TB, no cohorts or RCTs were found which included fluoroquinolones as part of standardized combination TB regimens intended primarily for isoniazid-resistant TB. Fluoroquinolones, when used, were individualized and introduced at varying points in a patient's regimen. These studies thus did not allow meaningful pooling. In three recent RCTs that investigated the potential for fluoroquinolones to shorten first-line TB regimens *(36,65,66)* over 240 patients with non-MDR, isoniazid-resistant strains were placed on fluoroquinolone-containing regimens. Data for 66 of these patients enrolled in one of these RCTs showed similar levels of unfavourable outcome (treatment failure/relapse/death/loss to follow-up) in patients on fluoroquinolone-containing four-month regimens (20.7%) compared with the standard 2HRZE/4HR[10] regimen (21.6%) *(36)* (personal communication, Merle C). In a second trial, success rates in patients treated with four-month fluoroquinolone-containing regimens were similar in subgroups with isoniazid-resistant strains and those with fully susceptible strains *(65)* (personal communication, Gillespie SH). In conclusion, the evidence reviews of published studies on isoniazid-resistant TB could not address the PICO question.

Only eight studies identified by the literature search provided information on treatment and treatment outcomes of patients with confirmed *M. bovis* disease. Of these only three studies included 20 or more subjects – a minimum criterion for the review. In the three case series retained, treatment regimens were very different and tended to be individualized. It was thus impossible to group the different case series for pooled analysis.

[10] 2HRZE/4HR = two months of isoniazid, rifampicin, pyrazinamide and ethambutol followed with four months of rifampicin and isoniazid.

Owing to the lack of data to address the questions directly, no clinically useful recommendations could be made for these two forms of TB.

C. The effect of delay in starting treatment on treatment outcomes for patients with drug-resistant TB

Global monitoring of the response to MDR/RR-TB shows that several countries have successfully expanded diagnostic services for RR-TB without matching it with complementary capacity to enrol patients on adequate treatment *(62,68)*. This has led to patients with confirmed drug-resistant TB waiting for months or even years to initiate treatment. It is widely held, based largely upon findings from TB patients without drug-resistant disease, that prolonging the time to initiate treatment in TB patients is undesirable and predisposes to unfavourable clinical and public health consequences, such as increased disease progression with higher bacillary load in sputum, more lung damage and continued transmission. A PICO question was thus developed to inform any policy recommendation to be made in support of earlier start of treatment (see Appendix 3, PICO 4). Evidence was reviewed to assess whether starting an adequate treatment regimen within four weeks of diagnosis, or a strong presumption of MDR/RR-TB, was associated with positive outcome, and to quantify any such effect.

An initial search of the literature yielded 1978 references of which 64 underwent full text review *(69)*. None of these articles fulfilled the inclusion criteria. A supplementary full text review of the 64 references was undertaken with the explicit aim of determining whether any articles described treatment outcomes in MDR-TB patients stratified by delay to initiation of treatment. The original parameters were subsequently broadened from those in the PICO question to allow for the use of other time delay categorizations and to look for other relevant outcomes such as culture conversion. Sixteen articles were identified from which scant data could be abstracted. None of these articles addressed the independent effect of delay in start of treatment upon treatment outcomes with a meaningful comparator group.

A major obstacle to finding published evidence to support the assumption that shorter delays lead to better outcomes is the lack of studies reporting outcome in which treatment delay could be analysed as a dependent variable in groups which were otherwise comparable or in which other covariates could be adjusted for.

Differences in time to treatment initiation rarely occur in isolation. Programmatic changes related to delivery of care and modifications in drug regimen are common in the literature reviewed. Attribution of variations in delay to treatment outcomes is thus a significant challenge. Even if such data were available, an additional constraint is that the interval from RR-TB or MDR-TB diagnosis to start of treatment does not account for any delay in diagnosis, the magnitude of which may dominate overall delay and overshadow any benefits that could accrue from reducing the time to start treatment once the disease is diagnosed.

Despite the absence of a discrete evidence base, it is reasonable to advise national programmes to adhere to the general standard of TB care which promotes an early start of appropriate therapy when MDR/RR-TB are diagnosed or strongly suspected *(70)*. Studies to address this

question are not a priority and intentionally withholding or delaying treatment presents ethical concerns. Nonetheless, this should not preclude from attempts to quantify the effect of delay using data from studies – observational or otherwise – mounted to answer other questions.

D. The effect of surgical interventions on treatment outcomes for patients with drug-resistant TB

Recommendation

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

Justification

Surgery has been employed in treating TB patients since before the advent of chemotherapy. In many countries it remains one of the treatment options for TB. With the challenging prospect in many settings of inadequate regimens to treat MDR-/XDR-TB, and the risk for serious sequelae, the role of pulmonary surgery is being re-evaluated as a means to reduce the amount of lung tissue with intractable pathology, to reduce bacterial load and thus improve prognosis.

The review for this question was based on both an individual patient-level meta-analysis to evaluate the effectiveness of different forms of elective surgery as an adjunct to combination medical therapy for MDR-TB *(18)*, as well as a systematic review and study-level meta-analysis *(71)* (online Appendix 4 Section IV). Demographic, clinical, bacteriological, surgical and outcome data of MDR-TB patients on treatment were obtained from the authors of 26 cohort studies participating in the aIPD *(17)*. The analyses summarized in the GRADE tables consist of three strata comparing treatment success (cure and completion) with different combinations of treatment failure, relapse, death and loss to follow-up. Two sets of such tables were prepared for (i) partial pulmonary resection, and (ii) pneumonectomy.

In the study-level meta-analysis that examined all forms of surgery together, there was a statistically significant improvement in cure and successful treatment outcomes among patients who received surgery. However, when the aIPD meta-analysis examined patients who underwent partial lung resection and those who had a more radical pneumonectomy, versus patients who did not undergo surgery, those who underwent partial lung resection had statistically significantly higher rates of treatment success. Those patients who underwent pneumonectomy did not have better outcomes than those who did not undergo surgery. Prognosis appeared to be better when partial lung resection was performed after culture conversion. This effect was not observed in patients who underwent pneumonectomy.

There are several important caveats to these data. Substantial bias is likely to be present given that only patients judged to be fit for surgery would have been operated upon. No patient with HIV co-infection in the aIPD underwent lung resection surgery. Therefore the effects of surgery among HIV-infected patients with MDR-TB could not be evaluated.

Rates of death did not differ significantly between those who underwent surgery versus those who received medical treatment only. However, the outcomes could be biased because the risk of death could have been much higher among patients in whom surgery was prescribed had they not been operated upon.

Subgroup consideration

The relative benefits of surgery are expected to depend substantially on the population subgroups that are targeted. The analysis could not provide a refined differentiation of the type of patient who would be best suited to benefit from the intervention or the type of intervention that would bear most benefit. The effect is expected to be moderate in the average patient considered appropriate for surgery.

The odds of success for patients with XDR-TB were statistically significantly lower when they underwent surgery compared with other patients (adjusted OR 0.4, 0.2–0.9). This effect is likely to be biased given that patients who underwent surgery would have had other factors predisposing to poor outcomes, which could not be adjusted for.

Implementation considerations

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

Monitoring and evaluation

The rates of death in the IPD for surgical outcomes did not differ significantly between patients who underwent surgery and those who received medical treatment only.

There were not enough data on adverse events, surgical complications or long term sequelae – some of which may be fatal – to allow a meaningful analysis.

Despite the unknown magnitude of perioperative complications the GDG assumed that overall there is a net benefit from surgery.

E. Research priorities

In addition to summarizing the available evidence, the reviews undertaken for this update revealed a number of gaps in current knowledge about critical areas for the treatment for MDR/RR-TB. Where evidence was available it was usually assigned a very low quality rating. This was one of the main reasons why all the recommendations made in this guidelines revision are conditional.

The GDG discussed research priorities and highlighted a number of them. They identified some problem areas which had already been singled out by earlier efforts to define research priorities for MDR-TB treatment, such as preventive therapy for MDR-TB and improving evidence on reduction of regimen duration *(1,72,73)*.

The optimal combination of medicines and approach towards regimen-design for patients (both adults and children) with isoniazid-resistant TB, RR-TB, MDR-TB and XDR-TB, as well as for patients with M. bovis disease.

- More randomized controlled trials, especially involving the new drugs and regimens, but also for patients with isoniazid-resistant forms of TB who are placed on fluoroquinolone-containing regimens.
- Inclusion and separate reporting of outcomes for key subgroups, especially children and HIV-positive individuals on treatment, in randomized controlled studies.
- Complete recording of adverse events and standardized data recording on organ class, seriousness, severity, and certainty of association, to allow reliable comparison of the association between adverse events and exposure to different medicines.
- Identification of factors that determine the optimal duration of treatment (e.g. previous treatment history, baseline resistance patterns, site of disease, child/adult).
- Determination of the minimum number of drugs and treatment duration (especially in patients previously treated for MDR-TB).
- Determination of conditions under which injectable-sparing regimens can be used in both children and adults (e.g. surrogates for severity / extent of disease, alternative medication).
- Pharmacokinetic studies to determine optimal drug dosing and safety (especially in pregnancy).
- Improved diagnostics and drug-susceptibility testing methods (e.g. which test for pyrazinamide).
- Randomized controlled trials to define the benefits and harms of chemoprophylaxis for child and adult contacts of MDR/RR-TB (with and without additional resistance patterns) *(8,74)*. The composition, dosages and duration of the latent TB infection (LTBI) regimen for MDR-TB needs to be optimized and the potential role of newer drugs with good sterilization properties investigated. Studies are needed to examine the adverse reactions of the long-term use of fluoroquinolones in preventive treatment.
- Palliative and end-of-life care in patients with very advanced resistance patterns.

The effectiveness and safety of standardized regimens lasting up to 12 months for the treatment of patients with MDR-TB ("shorter regimens") when compared with longer treatment

- Future research needs to include the effectiveness/safety of the shorter MDR-TB treatment regimen in subgroups which have been systematically excluded from study protocols (e.g. children, patients with different forms of extrapulmonary TB) and in settings where background resistance to drugs other than fluoroquinolones and second-line injectable agents is high (e.g. pyrazinamide or high-level isoniazid resistance).
- Implementation research on the introduction of the shorter MDR-TB regimen.
- More studies on cost effectiveness and health-related quality of life.

The effect of surgical interventions on treatment outcomes for patients with drug-resistant TB

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

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Appendix 1. Agenda for the Guidelines Development Group meeting on the *WHO treatment guidelines for drug-resistant TB 2016 update*, 9–11 November 2015

Chair: Holger Schünemann | *Co-chair:* Charles L Daley

Day 1

8:30–9:00	Registration	
9:00–9:15	Welcome and introductions	Karin Weyer
9:15–9:30	Meeting objectives and expected outcomes, agenda and working methods Declarations of interest	Ernesto Jaramillo Dennis Falzon
9:30–10:00	WHO requirements for evidence-based guidelines, GRADE methodology	Holger Schünemann
10:00–10:45	Plenary – Presentation of draft GRADE tables **PICO 1: MDR-TB REGIMEN COMPOSITION – SYSTEMATIC REVIEWS OF INDIVIDUAL DRUGS**	Dick Menzies, Mayara Bastos
10:45–11:00	*Coffee break*	
11:00–11:30	Plenary – Presentation of draft GRADE tables **PICO 1: MDR-TB REGIMEN COMPOSITION – PAEDIATRIC IPD**	Anneke Hesseling
11:30–11:40	Plenary – Discussants present their perspectives on the implications of the findings for the approach to the composition and duration of MDR-TB regimens in adults and children.	Discussants: Charles L Daley (adults), Farhana Amanullah (children)
11:40–13:00	Plenary – Development of decision tables to formulate draft recommendations based on quality of the evidence, and other considerations (balance between desirable and undesirable effects, resources, feasibility, values and preferences).	Facilitated discussion
13:00–14:00	*Lunch break*	
14:00–15:30	Continued – Development of decision tables to formulate draft recommendations based on quality of the evidence, and other considerations (balance between desirable and undesirable effects, resources, feasibility, values and preferences).	Facilitated discussion
15:30–15:45	*Coffee break*	
15:45–17:45	Continued – Finalization of draft recommendations	Facilitated discussion
17:45–18:00	Summary of the day	Chair

Day 2

8:30–9:15	Plenary – Presentation of draft GRADE tables **PICO 2: REGIMENS FOR ISONIAZID RESISTANCE and *M. bovis***	Dick Menzies, Mayara Bastos
9:15–9:30	Plenary – Discussants present their perspectives on the implications of the findings for the approach to the composition and duration of regimens in adults and children.	Discussants: Daniela Cirillo; Carlos Torres (isoniazid-resistant); Jose Caminero; Agnes Gebhard (*M.bovis*)
9:30–10:45	Plenary – Development of decision tables to formulate draft recommendations based on quality of the evidence, and other considerations (balance between desirable and undesirable effects, resources, feasibility, values and preferences).	Facilitated discussion
10:45–11:00	*Coffee break*	
11:00–13:00	Continued – Finalization of draft recommendations	Facilitated discussion
13:00–14:00	*Lunch break*	
14:00–14:45	Plenary – Presentation of GRADE tables **PICO 3: SHORTER REGIMENS FOR MDR-TB**	Dick Menzies, Faiz A Khan
14:45–15:00	Plenary – Discussants present their perspectives on the implications of the findings for the treatment of MDR-TB using shorter regimens.	Discussants: Sundari Mase, Tsira Chakhaia, Michel Gasana
15:00–16:00	Plenary – Development of decision tables to formulate draft recommendations based on quality of the evidence, and other considerations (balance between desirable and undesirable effects, resources, feasibility, values and preferences).	Facilitated discussion
16:00–16:15	*Coffee break*	
16:15–17:00	Continued – Finalization of draft recommendations	Facilitated discussion
17:00–17:45	Implications of the findings from reviews of PICO 1 and PICO 3 for the approach to the composition and duration of MDR-TB regimens.	Facilitated discussion
17:45–18:00	Wrap-up and summary of the day	Chair

Day 3

8:30–9:30	Plenary – Presentation of draft GRADE tables **PICO 4: DELAYS IN STARTING MDR TREATMENT, THE ROLE OF SURGERY**	Mishal Khan, Rebecca Harris, Greg Fox
9:30–9:40	Plenary – Discussant presents perspectives on the implications of the findings for the approach to the management of MDR-TB.	Discussant : Armen Hayrapetyan (role of surgery)
9:40–10:45	Plenary – Development of decision tables to formulate draft recommendations based on quality of the evidence, and other considerations (balance between desirable and undesirable effects, resources, feasibility, values and preferences).	Facilitated discussion
10:45–11:00	*Coffee break*	
11.00–11.30	Levels of resistance to pyrazinamide and fluoroquinolones	Matteo Zignol
11:30–13:00	Review of the recommendations for the four PICOs combined (continued)	Facilitated discussion
13:00–14:00	*Lunch break*	
14:00–15:00	Research priorities on treatment of drug-resistant TB	Dick Menzies Christian Lienhardt
15:00–15:30	Next steps and closure	Chair & Karin Weyer

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Appendix 3.
PICO questions[a]

Q1. In patients with RR-TB or MDR-TB, what individual drugs in the regimens are likely to lead to the outcomes listed below?

POPULATION	INTERVENTION	COMPARATOR	OUTCOMES
Rifampicin-resistant TB only MDR-TB *without* resistance *or* severe intolerance to the second-line drugs MDR-TB *with* resistance *or* severe intolerance to a. Fluoroquinolones b. Second-line injectable drugs, both classes c. Pyrazinamide d. 2 or 3 Group 4 drugs[b] e. Fluoroquinolones + second-line injectables (i.e. XDR-TB +/- other resistance) Children (0–4, 5–14 years), persons with HIV, pregnant women, persons with diabetes	A second-line regimen[c] which INCLUDES:		• Cured/completed by end of treatment • Culture conversion by six months • Failure • Relapse • Survival (or death) • Adverse reactions (severity, type, organ class)
	– pyrazinamide	– no pyrazinamide	
	– injectable agents (kanamycin/ amikacin/capreomycin)	– no injectable agents (kanamycin/ amikacin/capreomycin)	
	– prothionamide/ethionamide	– no prothionamide/ethionamide	
	– cycloserine or terizidone	– no cycloserine or terizidone	
	– PAS	– no PAS	
	– later-generation fluoroquinolone[d]	– no later-generation fluoroquinolone[d]	
	– high-dose isoniazid	– no high-dose isoniazid	
	– clofazimine	– no clofazimine	
	– linezolid	– no linezolid	
	– bedaquiline	– no bedaquiline	
	– delamanid	– no delamanid	
	– other individual Group 5[b] drugs	– no other individual Group 5[b] drugs	

[a] PICO = *P*opulation, *I*ntervention, *C*omparator, *O*utcomes

[b] Group 4 drugs refer to: ethionamide, prothionamide, cycloserine, terizidone, PAS. Group 5 drugs refer to: amoxicillin-clavulanate, bedaquiline, clarithromycin, clofazimine, delamanid, high-dose isoniazid, imipenem–cilastatin, linezolid, meropenem, thioacetazone. For bedaquiline and delamanid, definitive recommendations on their role in treatment will only be possible once the results of the Phase III trials become available.

[c] Data from regimens lasting up to 12 months will not be included in this question but in Question 3.

[d] Moxifloxacin or gatifloxacin; high-dose levofloxacin may be included but results to be made available separately.

Q2. In TB patients with drug-resistance patterns other than with rifampicin resisitance or multidrug resistance, what drug regimen composition and duration is likely to lead to the outcomes listed below?

POPULATION[a]	INTERVENTION[b]	COMPARATOR	OUTCOMES
Resistance to isoniazid[c]	RZE + FQ[d] for 6–9 months	– HRZE for 6–9 months – RZE for 6–9 months – 8-month first-line drug retreatment regimen (“Category 2”) – 6-month first-line drug treatment regimen (“Category 1 or 3”) – other	• Cured/completed by end of treatment • Culture conversion by 6 months • Failure • Relapse • Survival (or death) • Adverse reactions (severity, type, organ class) • Acquisition (amplification) of additional drug resistance
	RZ + FQ[d] for 9–12 months	– 8-month first-line drug retreatment regimen (“Category 2”) – 6-month first-line drug initial treatment regimen (“Category 1 or 3”) – other	
	Second-line injectable/R/Eto/FQ[d] for 3 months + R/Eto/FQ[d] for 15 months	– 8-month first-line drug retreatment regimen (“Category 2”) – 6-month first-line drug initial treatment regimen (“Category 1 or 3”) – other	
M. bovis	6- or 8-month first-line drug treatment regimens (“Category 1, 2 or 3”)	– other – 2HRE/7HR	

[a] If data are available the effects will be stratified by key subpopulations: children (0–4, 5–14 years), persons with HIV, pregnant women, and people with diabetes.

[b] The treatment modalities described in the MDR-TB treatment handbook *(8)*.

[c] Including cases with or without additional resistance to ethambutol and pyrazinamide. The assessment of evidence and recommendations on these resistance patterns will be conditioned by the fact that DST for ethambutol and pyrazinamide is often unreliable (although reliable DST to pyrazinamide may be available in some settings), but which nonetheless may bring about the use of fluoroquinolones, and that the evidence may be based on experience from patients who may have been switched to fluoroquinolone-containing regimens after a period of time on first-line regimens.

[d] If data are available the effects will be stratified by the type of fluoroquinolone (early versus later generation).

R = rifampicin Z = pyrazinamide E = ethambutol; FQ = fluoroquinolone; Eto = ethionamide; H = isoniazid.

Q3. In MDR-TB patients, are treatment regimens lasting up to 12 months likely to lead to the outcomes listed below when compared with those recommended in the WHO guidelines of 2011?

POPULATION	INTERVENTION[a]	COMPARATOR[a]	OUTCOMES
MDR-TB patients Previously treated with second-line drugs or not Severity of disease (mild/extensive radiographic lesions) Drug resistance patterns (for first-line drugs and second-line drugs) History of patient use of ethambutol or pyrazinamide Children (0–14 years) vs adults Persons with HIV, pregnant women, and people with diabetes	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 second-line drugs plus pyrazinamide Injectable agent given for about 8 months, at least 4 months after culture conversion Total treatment for 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	• Cured/completed by end of treatment • Culture conversion by 6 months • Failure • Relapse • Survival (or death) • Adverse reactions (severity, type, organ class) • Acquisition (amplification) of additional drug resistance • Adherence to treatment (or treatment interruption due to non-adherence)

[a] Regimens lasting >12 and <18 months will not be included in the intervention or comparator.

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

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

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

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