WHO consolidated guidelines on drug-resistant tuberculosis treatment

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THE END TB STRATEGY

World Health Organization

WHO consolidated guidelines on drug-resistant tuberculosis treatment

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World Health
Organization

Contents

Abbreviations and acronyms

ACSM	advocacy, communication and social mobilization
ACTG	AIDS Clinical Trials Group
ATS	American Thoracic Society
CDC	United States Centers for Disease Control and Prevention
DALY	disability-adjusted life year
DoI	declaration of interest
DR-TB	drug-resistant tuberculosis
DSMB	Data and Safety Monitoring Board
DST	drug susceptibility testing
EFPIA	European Federation of Pharmaceutical Industries and Associations
ERG	Evidence Review Group
EtD	evidence to decision (framework)
EU	European Union
FDC	fixed-dose combination
FIND	Foundation for Innovative New Diagnostics
FTE	full-time equivalent
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRC	WHO Guideline Review Committee
GSK	Glaxo SmithKline
HALT	Hepatitis and Latent TB infection
HIV	human immunodeficiency virus
Hr-TB	isoniazid (H)-resistant tuberculosis
IDSA	United States Infectious Diseases Society of America
IPD	individual patient data
KNCV	KNCV Tuberculosis Foundation
LAM	lipoarabinomannan assay
LSHTM	London School of Hygiene and Tropical Medicine
LTBI	latent tuberculosis infection

MDR-TB	multidrug-resistant tuberculosis
MDR/RR-TB	multidrug-/rifampicin-resistant tuberculosis
MSF	Médecins Sans Frontières
NIAID	United States National Institutes of Allergy and Infectious Disease
NIH	United States National Institutes of Health
Opti-Q	Efficacy and safety of levofloxacin for the treatment of MDR-TB (study)
PICO	Population, Intervention, Comparator and Outcomes
PMDT	programmatic management of drug-resistant TB
PK/PD	pharmacokinetics/pharmacodynamics
TB-PRACTECAL	Pragmatic clinical trial for more effective, concise and less toxic MDR-TB treatment regimen(s)
RCT	randomized controlled trial
RECRU	Respiratory Epidemiology and Clinical Trials Unit (McGill University)
RR-TB	rifampicin-resistant TB
SAE	serious adverse event
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
STREAM	Evaluation of a standardised treatment regimen of anti-tuberculosis drugs for patients with MDR-TB (trial)
TAG	Treatment Action Group
TB	tuberculosis
TBTC	Tuberculosis Trials Consortium
UNION	International Union Against Tuberculosis and Lung Disease
UNITAID	Global investment initiative for TB, HIV, malaria and Hepatitis C
USAID	United States Agency for International Development
WHO	World Health Organization
WHO/GTB	World Health Organization Global TB Programme
XDR-TB	extensively drug-resistant tuberculosis

Annex 3: Agendas of the Guideline Development Group meetings

WHO treatment guidelines for isoniazid resistant tuberculosis, 2018

Date: 27 April 2017 | *Co-chair:* Nancy Santesso | *Co-chair:* Kelly Dooley

Time	Agenda item	Responsible
8:30–9:00	Registration	
9:00–9:30	Welcome & introductions Meeting objective and agenda Declarations of interest	Karin Weyer
9:30–10:00	WHO requirements for evidence-based guidelines, GRADE methodology	Nancy Santesso
10:00–10:30	Global surveillance of resistance to isoniazid, pyrazinamide and fluoroquinolones	Matteo Zignol
10:30–11:00	*Coffee break*	
11:00–11:45	Plenary – Presentation of IPD findings and GRADE tables from the systematic reviews of Hr-TB regimen composition and duration	Dick Menzies, Federica Fregonese, McGill University, Canada
11:45–12:10	Plenary – Discussants present their perspectives on the implications of the findings for the approach to the composition and duration of Hr-TB regimens in adults and children	Discussants: Philipp du Cros (adults) and Farhana Amanullah (children)
12:10–12:25	Key issues relating to the PK/PD of anti-TB medicines of relevance to the Hr-TB treatment guidelines	Rada Savic & Michael Rich
12:25–12:45	Key issues relating to the detection of resistance to isoniazid, pyrazinamide and fluoroquinolones (molecular/phenotypic), and its relevance to the Hr-TB treatment guidelines	Daniela Cirillo
12:45–13:45	*Lunch break*	

13:45–15:30	Plenary – Development of decision tables to formulate draft recommendation(s) based on certainty of the evidence, and other considerations (balance between desirable and undesirable effects, resources, feasibility, values and preferences, equity)	Co-chairs
15:30–16:00	*Coffee break*	
16:00–17:45	Finalization of draft recommendations and accompanying remarks	Facilitated discussion
17:45–18:00	Conclusion	Co-chairs

This information is included as Annex 1: Agenda of the Guideline Development Group meeting in the *WHO treatment guidelines for isoniazid-resistant tuberculosis*, page 22, available at: https://apps.who.int/iris/bitstream/handle/10665/260494/9789241550079-eng.pdf.

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

(All dates in 2018)

	24 April
	15 May
	30 May
Webinars (ahead of in-person meeting)	14 June
	26 June
	10 July
In-person meeting (Versoix, Switzerland)	16–20 July
	15 August
	13 September
Webinars (after in-person meeting)	18 October
	2 November
	12 November

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

Day 1: 25 October 2010

Time	Agenda item	Responsible
8:30–9:00	Registration	
9:00–9:30	Welcome, introductions, declarations of interest Meeting agenda and working methods	WHO (and Guidelines Review Committee)
9:30–9:45	Meeting objectives and expected outcomes • draft recommendations based on the quality of the evidence, health impact, resources and feasibility, patients' values, as well as judgements about trade-offs between benefits and harms • judge the strength of each recommendation • formulate a plan to implement and evaluate the recommendations • identify areas for future research	
9:45–10:00	Guidelines Group terms of reference and process	
10.00–10.45	WHO requirements for evidence-based guidelines, GRADE methodology	Dr Schünemann
10:45–11:00	*Coffee break*	
11:00–12:00	Plenary – Presentation of GRADE profiles Which drugs, how many, for how long? (Q5–7)	Dr Menzies & Melissa Bauer
12:00–13:00	Plenary – Discussants present draft recommendations based on quality of the evidence, then other considerations (balance between desirable and undesirable effects, resources, feasibility, values and preferences). (See decision grid circulated before meeting)	
13:00–14:00	*Lunch break*	
14:00–15:30	Plenary discussion on recommendation and decision grid, strength of their recommendation: strong vs conditional	
15:30–15:45	*Coffee break*	
15:45–16:45	Plenary: Q5 discussion to reach consensus on recommendation and its strength	
16:45–17:45	Plenary: Q6 discussion to reach consensus on recommendation and its strength	
17:45 –18:00	Summary of the day	

Day 2: 26 October 2010

Time	Agenda item	Responsible
8:30–9:30	Plenary: Q7 discussion to reach consensus on recommendations and their strength	
9:30–10:45	Finalize the discussion on recommendations on all three questions	
10:45–11:00	*Coffee break*	
11:00–11:30	Plenary – Presentation of GRADE profiles • Monitoring treatment with culture and/or smear (Q4) Plenary – Discussant presents draft recommendation based on quality of the evidence, then other considerations (decision grid)	
11:30–12:15	Plenary – Presentation of GRADE profiles • Choice of drugs for HIV-positive patients (Q9) Plenary – Discussant presents draft recommendation based on quality of the evidence, then other considerations (decision grid)	Dr Arentz/Dr Kennedy
12:15–13:00	Review/revise the recommendation and decision grid, then determine the strength of the recommendation: strong vs conditional	
13:00–14:00	*Lunch break*	
14:00–14:45	Review/revise the recommendation and decision grid, then determine the strength of the recommendation: strong vs conditional	
14:45–16:00	Plenary: Q4 discussion to reach consensus on recommendations for Q4 and its strength	
16:00–16:20	*Coffee break*	
16:20–17:20	Plenary: Q9 discussion to reach consensus on recommendations for Q9 and its strength	
17:20–18:00	Wrap up and summary of the day	

Day 3: 27 October 2010

Time	Agenda item	Responsible
8:00–8:45	Plenary – Presentation of GRADE profiles • At what prevalence of MDR is it warranted to perform rapid DST at start of treatment (Q2) Plenary – Discussant presents draft recommendation based on quality of the evidence, then other considerations (decision grid)	Dr Oxlade & Dr Menzies
8:45–9:30	Plenary – Presentation of GRADE profiles • Ambulatory vs inpatient treatment (Q10) Plenary – Discussant presents draft recommendation based on quality of the evidence, then other considerations (decision grid)	C. Fitzpatrick
9:30–10:15	Review/revise the recommendation and decision grid, then determine the strength of their recommendation: strong vs conditional	
10:15–10:30	*Coffee break*	
10:30–11:15	Review/revise the recommendation and decision grid, then determine the strength of their recommendation: strong vs conditional	
11:15–13:00	Plenary: Q2 discussion to reach consensus on recommendations for Q2 and its strength	
13:00–14:00	*Lunch break*	
14:00–15:00	Plenary: Q10 discussion to reach consensus on recommendations for Q10 and its strength	
15:00–16:00	Review recommendations as a whole (continued after break)	
16:00–16:20	*Coffee break*	
16:20–18:00	Review recommendations as a whole (continued) Evaluate this process Plans to implement (including Field Guide), evaluate new recommendations Next steps	

The dates of the GDG meeting are summarized in the Background and Methods section in the *Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update*, page 4, available at: https://apps.who.int/iris/bitstream/handle/10665/44597/9789241501583_eng.pdf.

WHO treatment guidelines for drug-resistant tuberculosis, 2016 update

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

Day 1: 9 November 2015

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	Co-chairs

Day 2: 10 November 2015

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: Daniella Cirillo; Carlos Torres (isoniazid resistance); 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

8:30–9:30	Plenary – Presentation of draft GRADE tables **PICO 4: DELAYS IN STARTING MDR-TB 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

This information is included as Annex 1: Agenda for the Guideline Development Group meeting in the *WHO treatment guidelines for drug resistant TB, 2016 update*, 9–11 November 2015 in the *WHO treatment guidelines for drug resistant TB, 2016 update*, page 46, available at: https://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-eng.pdf

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

This information is summarized in the Methods used to update the guidelines section in the *Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update*, pages 19–24, available at: https://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf.

Annex 4: Participants at Guideline Development Group meetings

WHO treatment guidelines for isoniazid-resistant tuberculosis, 2018

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This information is included as Annex 2: Participants at the Guideline Development Group meeting in the *WHO treatment guidelines for isoniazid-resistant tuberculosis*, pages 23-25, available at: https://apps.who.int/iris/bitstream/handle/10665/260494/9789241550079-eng.pdf.

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

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

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This information is included in the Acknowledgments section in this guideline (pages 67–72), which is replicated from the Acknowledgements section of the *Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update*, pages ii–iv, available at: https://apps.who.int/iris/bitstream/handle/10665/44597/9789241501583_eng.pdf

WHO treatment guidelines for drug resistant tuberculosis, 2016 update

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This information is included as Annex 2: Experts involved in the development of the *WHO treatment guidelines for drug-resistant tuberculosis, 2016 update* in the *WHO treatment guidelines for drug-resistant tuberculosis, 2016 update*, page 49, available at: https://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-eng.pdf

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12	Dalene VON DELFT	TB Proof, South Africa	Patient representative
13	Fraser WARES	Royal Dutch Tuberculosis Foundation (KNCV), The Netherlands	Technical agency/programme implementation

This information is included as Annex 1: Experts involved in the development of the guidelines (Annex 1a: Participants in the Guideline Development Group [GDG] Meeting, Geneva, 11–13 July 2016 and Annex 1b: Members of the External Review Group) in the *Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update,* page 64, available at: https://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf.

Annex 5: Declarations of interest

WHO treatment guidelines for isoniazid-resistant tuberculosis, 2018

In conformity with the WHO guidelines for declarations of interest[1] for WHO experts issued by the WHO Compliance, Risk Management and Ethics Office, members of the Guideline Development Group (GDG), Evidence Review Group (ERG) and evidence reviewers were requested to submit completed WHO Declaration of Interest forms (DoIs) and declare in writing any competing interest (whether academic, financial or other) that could be deemed as conflicting with their role in the development of this guideline. In order to ensure the neutrality and independence of experts, an assessment of the DoI forms, curricula vitae, research interests and activities was conducted by the WHO Guideline Steering Committee. For cases in which potential conflicts were identified, the WHO Compliance, Risk Management and Ethics Office was consulted for further clarification and advice as to how to manage competing interests. If any declared interests were judged significant, individuals were not included in the GDG.

ERG members were also requested to declare interests and these were also assessed for potential conflict. As per WHO rules, the objectives of the guideline development process and the composition of the GDG, including member biographies, were made public 4 weeks ahead of the meeting (http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/gdg-meeting-izoniazid-resistant-tb/en/). This public notice was conducted to allow the public to provide comments pertinent to any competing interests that may have gone unnoticed or not reported during earlier assessments.

Guideline Development Group

The following GDG members declared no interests: Daniela CIRILLO, Kelly DOOLEY (Co-Chair), Gustavo DO VALLE BASTOS, Raquel DUARTE, Christopher KUABAN, Rafael LANIADO-LABORIN, Gary MAARTENS, Andrey MARYANDYSHEV, Ignacio MONEDERO-RECUERO, Maria Imelda Josefa QUELAPIO, Wipa REECHAIPICHITKUL, Nancy SANTESSO (Co-Chair), Welile SIKHONDZE and Armand VAN DEUN.

Five GDG members declared interests that were judged non-significant and not affecting the neutrality of the guideline development process. Therefore, no restrictions to their participation applied:

Farhana AMANULLAH: (1b) paediatric expert for WHO TB monitoring mission in Indonesia (value US$ 600/day, 14–27 January 2017); (2a) paediatric TB expert for Harvard Medical School Global Health Delivery grant (20% full-time equivalent [FTE]; June 2016–June 2018); (2b) paediatric TB expert for Global Fund grant (20% FTE; June 2016–December 2017).

Tsira CHAKHAIA: (1b) Research coordinator for TB Alliance NC-006 clinical trial (2016); community engagement project coordinator for TB Alliance (current); research coordinator for NiX-TB (from May 2017).

Philipp DU CROS: (2a) Member of the protocol writing committee and steering committee of the TB PRACTECAL Clinical Trial, which has received a grant of €6.8 million from the Dutch Postcode Lottery to Médecins Sans Frontières, Operational Centre Amsterdam (currently active).

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[1] Declarations of interest for WHO experts – forms for submission. Available at: http://www.who.int/about/declaration-of-interests/en/

Michael RICH: (1a) employed by Partners in Health to work on clinical care guidelines and in the programmatic management of DR-TB; (1a) WHO consultancies on treatment of drug-resistant TB to national TB programmes; (2a) conduct research and develop regimens for drug-resistant tuberculosis (DR-TB) as a recipient of the UNITAID's Expand new drug markets for TB [End TB] grant (all active during the development of the present recommendations).

Rada SAVIC: (1b) Member of the panel of the WHO Meeting on Target Regimen Profiles (value US$ 2500); grant reviewer for European and Developing Countries Clinical Trials Partnership (value US$ 1000); (2a) principal investigator or co-principal investigator of research grants by United States National Institutes of Health (NIH) and Gates Foundation on improving TB treatment options (all currently active).

External Review Group

The following ERG members declared no interests related to the objectives of this meeting: Essam ELMOGHAZI, James JOHNSTON, Enos MASINI, Rohit SARIN, Kitty VAN WEEZENBEEK, Irina VASILYEVA and Piret VIIKLEPP.

The below-mentioned ERG members declared interests that were judged not to be significant to the topic of the guideline. Some of the ERG members were involved in clinical trials not related to the treatment of Hr-TB and therefore no restrictions applied to their participation as expert reviewers.

Charles L. DALEY: (1b) Chair and member of data monitoring committees for delamanid studies (US$ 45 000 provided by Otsuka Pharmaceutical over 8 years; ongoing); Chair of data monitoring committee for clofazimine studies (US$ 2500 provided by Novartis; finished in 2016).

Ingrid OXLEY: (5b) at the Union Conference 2015 in Cape Town, TB Proof campaigns advocated for treatment of latent TB infection (LTBI) among health-care workers. She is a health-care worker and has had two episodes of TB. Many members of TB Proof who are health-care workers may have benefited from the WHO guidelines for the treatment of LTBI or received funding for LTBI treatment. This was not the focus of the current guideline.

Simon SCHAAF: (2a) research support to employer for pharmacokinetics work on second-line TB medicines in children from the NIH and Otsuka Pharmaceutical (approximately ZAR 5 million/year). NIH grant ceased in 2015; Otsuka Pharmaceutical grant is still active.

Helen STAGG: (1b) grant to employer for consultancy work on MDR-TB clinical pathways in eastern Europe (Otsuka Pharmaceutical: £59 925; 2013–2015); (2a) grant to employer for Hepatitis and Latent TB Infection (HALT) study (Department of Health of the United Kingdom; National Institute for Health Research, United Kingdom; £86 000 for HALT study (2014); £315 265 for fellowship, salary, research costs; 2015–2017); (2b) non-monetary support for HALT study (Sanofi provides free rifapentine to the research study participants; 2014–2017); (6d) received International Trainee Scholarship Award (US$ 1000 value) at the American Thoracic Society (ATS) conference 2016 where she presented the results of a review she conducted (1).

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Evidence reviewers

The independent experts who undertook the systematic reviews of evidence for this revision declared no interests related to the topic of the policy guideline objectives.

This information is included in the Declaration of interest section in the *WHO treatment guidelines for isoniazid-resistant tuberculosis*, pages ix–xi, available at: https://apps.who.int/iris/bitstream/handle/10665/260494/9789241550079-eng.pdf

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

Guideline Development Group (GDG)

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

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

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Susan ABDEL RAHMAN declared that a research grant (US$ 196 356) was received by her institution from the Thrasher Foundation in September 2017 for her role as Principal Investigator to study whether second-line TB medicines can be accurately quantified from dried blood spots (funding ongoing).

Daniela CIRILLO declared that a grant (US$ 26 000) was provided to her research unit by the Foundation for Innovative New Diagnostics (FIND) to evaluate new TB diagnostics (funding ongoing). In 2014, she received funding from Janssen (US$ 10 000) and Otsuka (US$ 25 000) for work on drug susceptibility testing (DST) of new drugs. In 2014, Janssen Italy funded her participation in an expert working group on the use of bedaquiline in Italy (US$ 1000).

Geraint (Gerry) Rhys DAVIES declared that he was until November 2017 the academic coordinator of the PreDiCT-TB consortium, a public–private partnership funded by the European Union Innovative Medicines Initiative and the European Federation of Pharmaceutical Industries and Associations (EFPIA). Although this role involved engagement with industrial partners (GSK, Sanofi, Janssen) in pre-competitive areas of research into TB drug development, these activities were fully supported by public funding from the European Union (EU) and neither he nor his research institution have received any funding from EFPIA or from the individual industrial partners. He has been asked and intends to provide advice to the STREAM study team on possible PK studies, which may be carried out in future using existing or further prospectively collected samples (no payment or research support has been offered for this activity). In 2017, he was paid fees by WHO for expert consultancies (US$ 5000). He is a member of a steering group convened by Critical Path to TB Regimens to advise on development of the lipoarabinomannan (LAM) biomarker developed by Otsuka in the context of adaptive clinical trials (receives no payment for this activity).

Bernard FOURIE declares receiving US$ 16 000 per year (ongoing) to act as a non-executive director and member of the Board of the National Bioproducts Institute in South Africa, which is exclusively involved in the production and marketing of blood- and plasma-derived products.

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

Carrie TUDOR declares that her employer receives funding from the Eli Lilly Foundation (~US$ 1 000 000 for 2013–2017; ongoing at US$ 243 000 in 2018) to run the International Council of Nurses' TB/MDR-TB project. The project focuses on building the capacity of nurses and allied professionals on TB and DR-TB care through training and currently operates in China, Eswatini, Ethiopia, Lesotho, Malawi, the Russian Federation, Uganda and Zambia. She also received US$ 20 000 from the KwaZulu Natal Research Institute for TB & HIV (South Africa) and Fogarty/NIH (US) for her dissertation and post-doctoral research on TB until 2014.

Zarir UDWADIA declares that he has supported about 40 patients to access bedaquiline and three patients to access delamanid through the compassionate use programmes of Janssen and Otsuka, respectively. He declares that he did not charge fees to the patients involved and there were no financial transactions with the manufacturers.

Andrew VERNON declares that he heads a clinical research group at US CDC (Tuberculosis Trials Consortium [TBTC]) doing TB trials. TBTC often collaborates with pharmaceutical companies, which may provide modest support, e.g. drug supplies, funding for PK sub-studies. Sanofi Aventis awarded ~US$ 2.8 million in six unrestricted grants to CDC Foundation in 2007–2015 to facilitate or support TBTC work on rifapentine (e.g. PK studies, staff contracts, travel for invited speakers, preparation of data to support regulatory filings). These funds have not otherwise benefited the research group. TBTC has studies under way with rifapentine (TBTC Study 31) and levofloxacin (Opti-Q, TBTC Study 32). He declares that his branch has supported studies of drug-susceptible TB that have included moxifloxacin (TBTC Study 27, Study 28 and Study 31). His branch has also supported enrolment at two of the three sites involved in the Opti-Q Study. This study evaluates different doses of levofloxacin in the treatment of DR-TB and has no comparator arm. There is no involvement with drug procurement. The principal investigator and management of the study, including data handling, analysis and drug procurement, are at Boston University. The Opti-Q outcomes are not yet known and the final analysis has yet to start. The majority of the study was funded by the US NIH (National Institutes of Allergy and Infectious Diseases [NIAID]).

The following GDG member declared an *interest that was judged to conflict* with the objectives of the guidelines (funding for new medicines for use in MDR-TB regimens). He therefore withdrew from the GDG panel and participated as a technical resource. Gary MAARTENS declared that his laboratory will receive US$ 2 184 608 from the US NIH (NIAID) to undertake drug assays for a trial on the safety, tolerability and PK of bedaquiline and delamanid, alone and in combination, among patients on MDR-TB treatment (AIDS Clinical Trials Group study A5343). He will receive no salary support.

External Review Group (ERG)

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

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

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

Evidence reviewers

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

The following evidence reviewer declared interests that were judged *not to be in conflict* with the objectives of the guidelines: Faiz Ahmad KHAN declared payment by WHO to collect data and carry out a meta-analysis on the shorter MDR-TB regimens for the 2016 guidelines (CAD4080) and travel fees to present these findings at a GDG meeting in 2015. He also declares undertaking an update of the same analysis in 2016–2018 for the ATS guidelines for which he receives no remuneration.

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

Funding for the meetings and reviews involved in the updating of the guidelines came entirely from the United States Agency for International Development (USAID). The experts on the Guideline Development Group (GDG) and the institutions where they work contributed time for the various discussions and other activities involved in the update process.

The Declaration of interest forms were completed by all non-WHO members of the GDG and the External Review Group, as well as the members of the academic centres who were involved in the reviews. Four members of the GDG declared interests that were judged to represent a potential conflict and were excused from the sessions of the meeting on 25–27 October 2010 during which recommendations relating to the drug regimens were discussed. Jaime BAYONA was a consultant for the development of clinical trial design for studies of an antituberculosis drug manufactured by Otsuka Pharmaceutical Co. Ltd (OPC-67683). Charles L. DALEY was chairperson of drug safety monitoring for two trials conducted by Otsuka Pharmaceutical Co. Ltd. Carole D. MITNICK served as a member of the Scientific Advisory Board of Otsuka Pharmaceutical Co. Ltd and had an advisory role on drug OPC-67683. Ma. Imelda QUELAPIO received support (monetary and non-monetary) for research from Otsuka Pharmaceutical Co. Ltd.

The following members of the academic centres, who performed the reviews of evidence from which the recommendations contained in these guidelines are derived, presented their findings at the meeting: Matthew ARENTZ, Melissa BAUER, Richard MENZIES, Carole D. MITNICK, Olivia OXLADE, Patricia PAVLINAC and Judd L. WALSON. They did not participate in the formulation of recommendations related to the respective reviews of evidence that they performed.

This information is included in the *Funding and declarations of interest* section in the *Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update*, page 2, available at: https://apps.who.int/iris/bitstream/handle/10665/44597/9789241501583_eng.pdf

WHO treatment guidelines for drug-resistant tuberculosis, 2016 update

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 conflicting 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/HI (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 objectives 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 objectives of the guidelines. 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 (online Annex 4):

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, Mishal KHAN and Richard (Dick) MENZIES.

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 or 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) (£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 Glaxo SmithKline (GSK) vaccines (~£90 000 in 2013); and on GSK vaccines not related to TB (~£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 (£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.

This information is included in the Declaration of interest section in the *WHO treatment guidelines for drug-resistant tuberculosis, 2016 update,* pages 2–5, available at: https://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-eng.pdf

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

The scope for the update of the *Guidelines for treatment of drug-susceptible tuberculosis and patient care* and the composition of the Guideline Development Group (GDG), as well as the External Review Group, were established in line with WHO's policy on conflict of interest. All contributors completed a WHO Declaration of Interest form. All stated declarations of interest were evaluated by three members of the steering group for the existence of any possible financial or intellectual conflict of interest. In some cases there was possible conflict of interest justifying the exclusion from membership of the GDG, and the Director of the WHO Global TB Programme, the WHO Guideline Review Committee and the WHO Legal Office were consulted on this and a decision was made. Diversity and broad representation in the GDG were sought in an effort to address and overcome any potential intellectual conflicts of interest. The GDG was composed of representatives of technical partners and academia, a GRADE methodologist, national TB programme managers from different WHO regions, representatives of civil society organizations, experts from WHO collaborating centres, professional organizations and a representative from the International Organization for Migration (*see* Annex 1). The biographies of the GDG members were made public ahead of the meeting, and the WHO Guidelines Steering Committee, which was formed in preparation for the update of the guidelines, reviewed the completed forms at the beginning of the meeting with everyone present.

I. Guideline Development Group (GDG)

The following members declared no interests: Si Thu AUNG; Frank BONSU; Jeremiah CHAKAYA; Lucy CHESIRE; Daniela CIRILLO; Poonam DHAVAN; Kathy FIEKERT; Andrei MARYANDYSHEV; Nguyen Viet NHUNG; Ejaz QADEER; Abdul Hamid SALIM; Holger SCHÜNEMANN; Pedro SUAREZ; Justin Wong Yun YAW.

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

Kelly DOOLEY declared that she did not receive any salary support from drug companies for her work in the following roles and activities: Co-chair of the AIDS Clinical Trials Group (ACTG) study assessing bedaquiline and delamanid for MDR-TB; principal investigator, assessing pretomanid for tuberculosis trial, assessing pretomanid (PA-824, investigational drug) for treatment of drug-sensitive TB; investigator on trials assessing rifapentine for pregnant women with latent TB infection, rifapentine for treatment shortening in patients with pulmonary TB, high-dose rifampicin and levofloxacin for paediatric TB meningitis, high-dose isoniazid for MDR-TB, and delamanid for MDR-TB in children with and without HIV. *Mike FRICK* declared that his organization received non-commercial support (1) to track investment made in TB research and development; (2) to host a symposium at the UNION meeting; (3) advocate for increased funding for TB research and development, research and access to evidence-based interventions; and (4) management of community research advisors group. *Simon SCHAAF* declared receiving grants for pharmacokinetic drug studies in children of second-line drugs and for studying preventive therapy in MDR-TB. *Carrie TUDOR* declared that her organization receives funding from Eli Lilly Foundation for activities related to TB and MDR-TB projects.

II. External Review Group

The following External Review Group members declared no interest related to the objectives of this meeting: Riitta DLODLO, Celine GARFIN, Lee REICHMAN, Vaira LEIMANE, Rohit SARIN, Dalene VON DELFT and Fraser WARES. The following WHO staff from the regional offices reviewed the final draft of the guideline document: Masoud DARA (Europe), Mirtha DEL GRANADO (Americas), Daniel KIBUGA (Africa), Hyder KHURSHID (South-East Asia), Mohamed AZIZ (Eastern Mediterranean), and Nobuyuki NISHIKIORI (Western Pacific).

III. Evidence reviewers

The researchers who undertook the systematic reviews of evidence for this revision were the following:

- Narges ALIPANAH, Cecily MILLER, Payam NAHID (team leader for PICO 1, 2 & 7–10), University of California, San Francisco, United States of America; and Lelia CHAISSON, Johns Hopkins Bloomberg School of Public Health, Baltimore, United States of America.
- Richard MENZIES, McGill University, Montreal, Canada (team leader for PICO 3, 4 & 6); and James JOHNSTON, University of British Columbia, Vancouver, Canada.
- Gregory FOX (team leader for PICO 11) and Jennifer HO, University of Sydney, Sydney, Australia.

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

The following reviewers declared no interest related to the objectives of and their attendance at the meeting: Narges ALIPANAH, Jennifer HO and James JOHNSTON. The following reviewer declared interests that were judged not to be in conflict with the policy of WHO, or the objectives of the meeting: *Payam NAHID* declared that his research unit received support from the United States Centers for Disease Control and Prevention through a federal contract to support clinical trial units in San Francisco, USA, and in Hanoi, Viet Nam.

This information is included in the *Declaration and management of conflict of interest* section in the *Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update*, pages 6–7, available at: https://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf

Annex 6: Main methods

WHO treatment guidelines for isoniazid-resistant tuberculosis, 2018

These WHO guidelines were developed following the recommendations for standard guidelines as described in the *WHO Handbook for guideline development, 2014 (2)*. The GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) was used to rate the certainty in the estimate of effect (quality of evidence) as high, moderate, low or very low, and to determine the strength of the recommendations (as strong or conditional) *(2)*.

Preparation for evidence assessment and formulation of the recommendations

In preparation for the in-person meeting of the GDG on 27 April 2017 (online Annex 3), a WHO Guideline Steering Committee was formed to draft the initial scoping and planning documents (online Annex 4). A proposal was submitted to the WHO Guideline Review Committee (GRC) in February 2017 and was approved in March 2017. In preparation for the GDG meeting, two webinars (via WebEx) were held with GDG members to finalize the scoping, establish the PICO (Patients, Intervention, Comparator and Outcomes) questions, scoring of the outcomes, and results of the evidence reviews.

PICO question

The PICO questions, inclusive of subpopulations, treatment regimen composition and duration, and outcomes, were agreed upon by the GDG members (Annex 1). The questions were framed to capture the effect of different treatment regimen compositions and durations, when compared with 6 or more months of treatment with rifampicin–pyrazinamide–ethambutol combination therapy (Annex 1).

GDG members were invited to score the outcomes and the mean scores for the 14 responses received were all in the "critical" or "important" range (Table 1 in this Section).

Table 1. Scoring of outcomes considered relevant by the GDG for the evidence review related to the WHO treatment guidelines for Hr-TB

Outcomes	Mean score
Cured by the end of treatment/treatment completed	8
Treatment failure ± relapse	9
Survival (or death)	8
Adverse reactions from anti-TB medicines (severity, type, organ class)	7
Acquisition (amplification) of additional drug resistance	8

Note. Relative importance was rated on an incremental scale: *1–3 points*: not important for making recommendations on choice of treatment strategies for Hr-TB; *4–6 points*: important but not critical for making recommendations on choice of treatment strategies for Hr-TB; and *7–9 points*: critical for making recommendations on choice of treatment strategies for Hr-TB.

Evidence gathering and analysis

McGill University coordinated the consolidation of an individual patient data (IPD) database for Hr-TB during 2016. By November 2016, data on 5418 Hr-TB patients from 33 global datasets were identified and retained for the analysis *(3)*. All studies identified were observational; no cohort studies or RCTs that included fluoroquinolones as part of standardized TB regimens designed for Hr-TB were identified. Estimates of effect for each outcome were adjusted for age, sex, HIV coinfection, sputum microscopy positivity, cavitation identified on chest radiography, history of TB treatment and resistance to first-line medicines other than isoniazid. Propensity score matching (caliper method with difference of 0.02 allowed, with replacement) was used to estimate the adjusted odds ratios of outcome and their 95% confidence intervals *(4)*.

Decision-making during the Guideline Development Group meeting

Decision-making was based on unanimous agreement among all GDG members or by reaching consensus. No recourse to voting was required during the GDG process.

Certainty of evidence and strength of recommendations

In assessing the quality of evidence, a number of factors can increase or decrease the quality of evidence *(5,6)*. The highest-quality rating is usually assigned to evidence gathered from RCTs while evidence from observational studies is usually assigned a low or very low-quality value. The higher the quality of evidence, the more likely a strong recommendation can be made. The criteria used by the GDG to determine the quality of available evidence are summarized in the GRADE (Grading of Recommendations Assessment, Development and Evaluation) tables annexed to these guidelines (*see* online Annexes 7 and 8). The certainty in the estimates of effect (quality of evidence) was assessed and either rated down or up based on: risk of bias; inconsistency or heterogeneity; indirectness; imprecision; and other considerations (Table 2 in this Section) *(6)*.

Table 2. Classification of the certainty in the evidence

Certainty in the evidence	Definition
High (⊕⊕⊕⊕)	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate (⊕⊕⊕O)	Further research is likely to have an important impact on our confidence in the effect and may change the estimate.
Low (⊕⊕OO)	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 (⊕OOO)	Any estimate of effect is very uncertain.

Through the GRADE system, the **strength of a recommendation** is classified as "strong" or "conditional". The strength of a recommendation is determined by the balance between desirable and undesirable effects, values and preferences, resource use, equity considerations, acceptability and feasibility of implementing the intervention *(6)*. 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 3 in this Section).

Table 3. Implications of the strength of a recommendation for different users

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 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.

Note: Adapted from *(6)*.

Assessment of the quality of the evidence

One of the advantages of IPD analyses is that they allow the examination of patient-level characteristics, outcome harmonization, and exploration of variability in effectiveness *(7)*. IPD analyses also allow the evaluation of whether an intervention is more or less effective for different subpopulations *(8)*. Additionally, between-study heterogeneity can be reduced by IPD analysis, given that results for specific subgroups of participants can be obtained across studies and the differential (treatment) effects can be assessed across individuals.

The isoniazid-resistant TB (Hr-TB) IPD was composed of observational studies, and despite the adjustment done for potential confounding using propensity score matching, bias in exposure–effect estimates could still occur due to residual or unmeasured confounding. Residual confounding could also have arisen from unknown factors, associated both with the exposure and the outcome, for which data were not collected. Specific analyses could be done only using variable and limited subsets of the IPD due to limitations in comparability and incompleteness of the data (*see* online Annexes 7 and 8). This led to serious imprecision for most of the estimates of effect. The GDG concluded that, overall, the studies included posed serious risk of bias attributed to residual confounding. In view of these factors, the certainty in the estimates of effect was judged to be "low" or "very low". This influenced the GDG's decision in favour of *conditional* rather than *strong* recommendations for the proposed treatment options (*see* online Annexes 7 and 8).

External review

A draft of the guidelines document complete with the recommendations, accompanying remarks and GRADE tables, was circulated to the External Review Group (ERG) for their comments. The feedback provided was incorporated in the subsequent version of the guidelines.

This information is included in the Methods section in the *WHO treatment guidelines for isoniazid-resistant tuberculosis*, pages 5–8, available at: https://apps.who.int/iris/bitstream/handle/10665/260494/9789241550079-eng.pdf

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

Preparation for the revision

The WHO Guideline Steering Committee met regularly from January to July 2018 to draft the scope of the new guidelines, the evidence reviews and prepare for the webinars and physical meeting of the GDG. An application for the revision of the guidelines was submitted to the WHO GRC in February 2018 and received final approval after revisions in April 2018. Six webinars (using WebEx) were held between April and July 2018 for the GDG members, the systematic reviewers and the WHO Guideline Steering Committee to discuss the scoping, PICO questions (Annex 1), scoring of the outcomes (Table 1 in this Section), collection of data and analysis plans for the data from the trials (delamanid and shorter regimen), and the individual patient database (IPD) from the shorter and longer regimens. Discussions were also held alongside with the GDG on updates to the dosing schedules for children and adults (Annex 2). In between the webinars, discussions continued via email. After the July meeting, the GDG and systematic reviewers met three more times over webinar until mid-October to finalize the decisions.

Rationale, scope and objectives

The latest evidence-based guidance for the treatment of MDR/RR-TB was published by WHO in October 2016 in accordance with the requirements of the GRC, using the GRADE methodology *(2)*. Since these guidelines were released, there have been some relevant developments that necessitate a revision in order to ensure that TB programme managers, policy-makers as well as medical practitioners in a variety of geographical, economic and social settings receive the best possible advice, and multidrug-resistant/rifampicin-resistant (MDR/RR)-TB patients receive treatment in accordance with the best evidence and medication available. These include the following:

1. Additional data from observational studies evaluating longer MDR-TB regimens for the treatment of MDR/RR-TB have been assembled to supplement an earlier meta-analysis of pooled, multicountry IPD *(9)*.

2. Final results from a phase III randomized controlled trial (RCT) of the new MDR-TB medicine delamanid were released in October 2017 *(10)*.

3. Preliminary results from the first-ever RCT of a 9-month shorter MDR-TB regimen were released in October 2017 (including interim results of a study of the health economic impact) *(11)*.

4. Final results from a multicentric study of a 9-month shorter MDR-TB regimen in African settings were published in December 2017 *(12)*.

5. New data from the programmatic use of bedaquiline, delamanid and novel regimens also became available to WHO following a public call for these data in February 2018 *(13)*.

The aim of the 2018 update is to review all previous evidence-informed policy recommendations made by WHO to date on the treatment of MDR/RR-TB with both the old and the new medicines. In deciding the scope of the 2018 update, the GDG considered priority debates on the treatment and care of MDR/RR-TB patients in mid-2018. The GDG members were sensitive to the growing dissatisfaction of patients and caregivers to the continued inclusion of injectable agents as priority medicines in MDR-TB regimens. Injectable agents require special conditions; they have to be administered by skilled workers, they cause pain and often lead to serious adverse reactions such as hearing loss and kidney

dysfunction. In addition, the GDG was keenly aware of the importance of adherence to treatment and the problems with patient retention on treatment regimens lasting 2 years or more, particularly when multiple agents that can cause serious toxicities are administered concurrently.

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

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

1. *The composition of longer MDR-TB regimens*: optimal combination of medicines and approach towards regimen design for patients with MDR/RR-TB and extensively drug-resistant (XDR)-TB
2. *The duration of longer MDR-TB regimens*: identifying the best range for the total length of treatment, duration of the intensive phase and time after culture conversion
3. *Use of the shorter MDR-TB regimen*: the role of the standardized 9–12-month regimen recommended by WHO since 2016
4. *Monitoring patient response to MDR-TB treatment using culture*: the added value of culture over sputum smear microscopy alone and the preferred frequency of testing to detect a failing regimen.

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

Key questions

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

The 2018 revision addressed key questions of topical debate on which TB authorities in Member States and other implementers demand guidance from WHO. The scope of the new guidelines covered key questions included in the 2011 and 2016 editions of the DR-TB treatment guidance *(14,15)*, as well as other emerging topical areas relating to newer medicines. Questions worded in PICO format (**P**opulation, **I**ntervention, **C**omparator, **O**utcome) were finalized by the GDG as below (for a disaggregation of each element of the PICO questions, *see* Annex 1).

Q1. In patients with rifampicin-resistant or multidrug-resistant TB (MDR/RR-TB) is a shorter treatment regimen (9–12 months) more or less likely to safely improve outcomes than longer regimens conforming to WHO guidelines?[2]

Q2. In patients with rifampicin-resistant or multidrug-resistant TB (MDR/RR-TB), which individual agents are more likely to improve outcomes when forming part of a longer regimen conforming to WHO guidelines?[3]

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

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

Table 1. Scoring of outcomes considered relevant by the GDG for evidence reviews related to the WHO treatment guidelines for MDR/RR-TB tuberculosis, 2018 update[a]

PICO	Outcomes							
	Culture conversion by 6 months	Successful completion of treatment	Cure	Adherence to treatment	Failure or relapse	Death	Adverse reactions from TB medicines	Acquisition of drug resistance
1 shorter regimen	7	7	8	7	8	9	7	7
2 longer regimen, medicines to use	7	7	8	6	8	8	7	7
3 longer regimen, number of medicines to use	7	7	8	7	8	8	7	7
4 length of intensive phase	7	7	8	7	8	8	7	7
5 total length	6	8	8	8	8	9	7	7
6 length after conversion	6	7	8	8	9	8	7	7
7-monthly culture	7				9			8

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

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

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

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

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

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

The GDG members listed and scored the most relevant outcomes on an incremental scale of importance from 1 to 9 *(2)*. The outcomes proposed by the GDG for scoring were similar to those used in the past, namely:

- culture conversion by 6 months
- successful completion of treatment (or lack of successful completion)
- bacteriological cure by end of treatment
- adherence to treatment (or treatment interruption due to non-adherence)
- treatment failure or relapse
- death (or survival)
- adverse reactions from anti-TB medicines
- acquisition (amplification) of drug resistance.

The outcomes were defined and scored by each GDG member anonymously. Outcomes assigned by each member were considered "Critical" if scoring between 7 and 9, "Important" if between 4 and 6 and "Not important" if lower. Scores were averaged across all voting members (using the arithmetic mean). Mean scores for the nine responses received were all in the "Critical" range (7–9 points; *see* Table 1 in this Section).

Certainty of evidence and strength of recommendations

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

The certainty of evidence is categorized into four levels (Table 2 in this Section). The criteria used by the evidence reviewers to qualify the quality of available evidence are summarized in the GRADE tables annexed to these guidelines (online Annex 7). A number of factors may increase or decrease the certainty of evidence (*see* Fig. 9.1 of *(2)*). The highest rating is usually assigned to data from RCTs while evidence from observational studies is usually assigned a low or very low-quality value at the start.

Table 2. Certainty of evidence and definitions *(16)*

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 and direction of a recommendation is determined by the balance between desirable and undesirable effects, values, equity, resource use, acceptability and feasibility *(17)*. 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 3 in this Section).

Table 3. Implications of the strength of a recommendation for different users (adapted from *(16)*)

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

Assessment of evidence and its grading

Two teams of experts (listed in online Annex 4) were commissioned to assess the evidence for the seven PICO questions and their outcomes. Meta-analysis of the IPD from studies and trials of longer and shorter MDR-TB treatment regimens was used to inform all PICO questions. The studies were traced through a systematic literature review of published papers following a standard methodology *(5)*, supplemented by other unpublished data reported to WHO following a public call for data issued in February 2018 *(13)*. Members of the GDG were contacted to identify missing studies or studies in progress.

Relative effects (relative risks or odds ratios of an event) were calculated from pooled data in individual or aggregated formats from the included studies. Absolute effects and risk differences were used to express the magnitude of an effect or difference between the intervention and comparator groups. Where possible, adjustments were made to reduce the risk of bias and confounding (including propensity score matching). More details on the methods used in unpublished studies are presented in online Annex 9 and in published studies of earlier versions of these IPD meta-analysis (9,18,19).

The summary-of-evidence profiles were prepared using the GRADEPro software, an online tool to create guideline materials (20). 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 (2).

The GDG membership represented a broad cross-section of future users of the guidelines as well as affected persons (including patients). Biographies of experts proposed for the GDG were published on a WHO website in June 2018 (http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/gdg-meeting-mdr-rr-tb-treatment-2018-update/en/). Six webinars were held between April and July 2018, ahead of the GDG meeting held between 16 and 20 July 2016 in Versoix, Switzerland. The webinars were chaired by the GDG chair and co-chair, and served to brief the members about the methods used to analyse the data and produce the guidelines according to the GRADE approach. Evidence from some of the analysis was also shared and discussed during the webinars ahead of the physical meeting. Drafts of the review reports and GRADE summary of evidence profiles were shared with the GDG members ahead of the meeting (online Annexes 7 and 8). During the days of the meeting and in the following weeks, additional analyses were shared with the group upon their demand. The discussions on culture monitoring (PICO 7) and on the use of delamanid (part of PICO 2) – inclusive of an analysis of the individual data of Trial 213 provided by Otsuka – were finalized in webinars lasting until 12 November 2018 (online Annex 3). The GRADE summary-of-evidence profiles were discussed by the GDG ahead of formulating the recommendations. Apart from the quality of evidence, the wording, direction and strength of the recommendations were decided upon considerations of the relative magnitude of the desirable and undesirable effects, overall certainty in the evidence of effects, values and preferences, resource implications, incremental costs, impact on health equity, acceptability and feasibility. The group used "evidence-to-decision" (EtD) frameworks via the GRADEPro interface to capture the content of the discussions, make judgements, vote (using at times the PanelVoice function), annotate the different considerations, and develop and add the remarks accompanying each recommendation on justification, implementation, subgroups, monitoring and evaluation, and research gaps (online Annex 8).

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

External review

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

Publication, implementation, evaluation and expiry

These guidelines were 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 21 December 2018. The main text of the guidelines (without online Annexes 3–9) will also be made available in print version in early 2019 and translated into all the WHO official languages. The evidence reviews as well as the recommendations are being published separately in peer-reviewed journals to disseminate further the main messages. The changes to the policy guidance will also be reflected in a forthcoming revision of WHO's implementation manual – the *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis* – planned for early 2019 *(21)*.

WHO/GTB 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 continue to scan for any new evidence that has a bearing on the continued validity of its recommendations. Significant results from new studies, trials or other valid data are expected to become available from mid-2019, in which case WHO will pursue the GDG process to decide if or which revisions are necessary.

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

The first two editions of these guidelines were published in 2006 *(22)* and 2008 *(23)* as a collaborative effort of many partners, most of whom were members of the Green Light Committee *(24)*. This 2011 update follows WHO requirements for developing guidelines, as specified in the *Handbook for guideline development* (2010), which involve an initial scoping exercise, use of systematic reviews to summarize evidence, and application of the GRADE approach to develop recommendations *(6)*.

The updated guidelines focus on the detection and treatment of drug-resistant TB in settings where resources are limited. Priority topics identified by WHO in this field and by its external experts were:

- case-finding (use of rapid molecular tests; investigation of contacts and other high-risk groups);
- regimens for MDR-TB and their duration in HIV-positive and HIV-negative patients;
- monitoring during treatment;
- models of care.

The guidelines are limited to topics not covered by other WHO policy documents published recently, including treatment of drug-susceptible TB and use of antiretroviral agents, treatment of patients with isoniazid-resistant TB and TB infection control. The 2011 update was produced through a systematic process starting in early 2009. Priority areas to be included in the update had been identified from those listed as outstanding areas for future direction following publication of the emergency update (2008). The previous programmatic management of drug-resistant TB (PMDT) guidelines were evaluated via a user questionnaire *(25)*. Various experts, including TB practitioners, public health professionals, national TB control programme staff, guideline methodologists, members of civil society and nongovernmental organizations providing technical support, and WHO staff were invited to form a Guideline Development Group (GDG) to inform the update process. A second group, comprising national TB control programme staff, WHO regional TB advisors, and clinical and public health experts, was appointed to serve as an External Review Group (the composition of both groups is listed in the Acknowledgements).

The GDG provided input on the selection of questions to address outstanding topics of controversy or areas where changes in policy or practice were warranted. It also selected and scored outcomes to determine those that were critical or important for making decisions on recommendations and to identify the data which were to be sought during retrieval and synthesis of evidence. By September 2009, the scope of the guidelines had been agreed, the questions formulated, and the selection and scoring of the main outcomes had been completed. Between October 2009 and May 2010, teams from leading academic centres were commissioned to review and compile the evidence. The early results of the reviews were made available to members of the GDG before and during a meeting to develop the recommendations held at WHO headquarters in Geneva, Switzerland on 25–27 October 2010.

Questions and outcomes

Table 1 in this Section lists the seven priority questions identified by the GDG, worded in the PICO (Population, Intervention, Comparator, Outcome) or similar format.

Table 1. PICO questions for the 2011 update of the guidelines

1. At what prevalence of MDR-TB in any group of TB patients is rapid drug-susceptibility testing warranted to detect resistance to rifampicin and isoniazid or rifampicin alone on all patients in the group at the time of TB diagnosis, in order to prescribe appropriate treatment at the outset?

2. Among patients with MDR-TB receiving appropriate treatment in settings with reliable direct microscopy, is monitoring using sputum smear microscopy alone rather than sputum smear and culture, more or less likely to lead to the outcomes listed in Table 2 below?

3. When designing regimens for patients with MDR-TB, is the inclusion of specific drugs (with or without documented susceptibility) more or less likely to lead to the outcomes listed in Table 2?

4. When designing regimens for patients with MDR-TB, is the inclusion of fewer drugs in the regimen (depending on the drug used, the patient's history of its use and isolate susceptibility) more or less likely to lead to the outcomes listed in Table 2?

5. In patients with MDR-TB, is shorter treatment, compared with the duration currently recommended by WHO, more or less likely to lead to the outcomes listed in Table 2?

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

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

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

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

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

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

* None of the outcomes was scored in this category.

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

Outcomes (text in parentheses shows the same outcome phrased in the negative)	Average score	Relative importance
1. Cure (treatment failure)	8.7	Critical
2. Prompt initiation of appropriate treatment	8.3	Critical
3. Avoiding the acquisition or amplification of drug resistance	8.1	Critical
4. Survival (death from TB)	7.9	Critical
5. Staying disease-free after treatment; sustaining a cure (relapse)	7.6	Critical
6. Case-holding so the TB patient remains adherent to treatment (default or treatment interruption due to non-adherence)	7.6	Critical
7. Population coverage or access to appropriate treatment of drug-resistant TB	7.5	Critical
8. Smear or culture conversion during treatment	7.4	Critical
9. Accelerated detection of drug resistance	7.4	Critical
10. Avoiding unnecessary MDR-TB treatment	7.2	Critical
11. Population coverage or access to diagnosis of drug-resistant TB	7.1	Critical
12. Prevention or interruption of transmission of drug-resistant TB to other people, including other patients and health-care workers	6.9	Important but not critical
13. Shortest possible duration of treatment	6.7	Important but not critical
14. Avoiding toxicity and adverse reactions from anti-tuberculosis drugs	6.5	Important but not critical
15. Cost to patient, including direct medical costs and other costs such as transportation and lost wages due to disability	6.4	Important but not critical
16. Resolution of TB signs and symptoms; ability to resume usual life activities	6.3	Important but not critical
17. Interaction of anti-tuberculosis drugs with non-TB medications	5.6	Important but not critical
18. Cost to the TB control programme	5.4	Important but not critical

For the scope of the discussion leading to the recommendations on question 1 (Table 1 in this Section), the term *rapid tests* refers to those providing a diagnosis within two days of specimen testing, thereby including only tests using molecular techniques (line probe assay and Xpert MDR/RIF[4]). The different groups of drugs referred to in the text are composed of the agents shown in Table 3 in this Section. In the analyses of data for questions 3–5, streptomycin was found to be used but it is generally considered a first-line drug. Later-generation fluoroquinolones included levofloxacin (750 mg/day or more), moxifloxacin, gatifloxacin and sparfloxacin. Ciprofloxacin, ofloxacin and levofloxacin (up to 600 mg/ day) were considered earlier-generation fluoroquinolones for this analysis.

Table 3. Groups of second-line anti-tuberculosis agents referred to in these guidelines

Group name	Anti-tuberculosis agent	Abbreviation
Second-line parenteral agent (injectable anti-tuberculosis drugs)	kanamycin	Km
	amikacin	Am
	capreomycin	Cm
Fluoroquinolones	levofloxacin	Lfx
	moxifloxacin	Mfx
	gatifloxacin	Gfx
	ofloxacin	Ofx
Oral bacteriostatic second-line anti-tuberculosis drugs	ethionamide	Eto
	prothionamide	Pto
	cycloserine	Cs
	terizidone	Trd
	p-aminosalicylic acid	PAS
Group 5 drugs	clofazimine	Cfz
	linezolid	Lzd
	amoxicillin/clavulanate	Amx/Clv
	thioacetazone	Thz
	clarithromycin	Clr
	imipenem	Ipm

NB. Other drugs not generally considered as second-line anti-tuberculosis agents were also used to treat drug-resistant TB in some of the cohorts included in this analysis. These included the parenteral agent *viomycin*, the fluoroquinolones *ciprofloxacin* and *sparfloxacin*, as well as *azithromycin*, *roxithromycin*, *high-dose isoniazid* and *thioridazine*, which were included under the Group 5.

Assessment of evidence and its grading

The evidence review teams assessed the evidence for the questions and their outcomes through a series of systematic literature reviews following an approved methodology that was documented (Annex 6). Titles, abstracts and full text of potentially relevant literature were screened using key subject words and text words. The search was not limited by study type or time period. Authors in the field and members of the GDG were contacted to identify missing studies or studies in progress. Case-based data were collected from authors of published studies to analyse the effects relating to the questions dealing with bacteriology and treatment regimen (questions 2–6 in Table 1 in this Section). Modelling work was done in the context of questions 1 and 2. The question on models of

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[4]   Xpert MTB/RIF refers to the currently available methodology that employs an automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance.

care (question 7) was addressed by a review of published and unpublished studies containing a full economic evaluation of patients on MDR-TB treatment.

Where possible, relative effects (hazard ratios, relative risks or odds ratios of an event) were calculated from pooled data of included studies. In two of the analyses, outcome was expressed as the cost per disability-adjusted life year (DALY) averted. The DALY is a summary indicator that expresses the burden of mortality and morbidity into a single value: perfect health is valued at 1 and death at 0 (a year with TB disease is valued at 0.729) *(26)*. For the modelling of rapid drug-susceptibility testing (DST), estimated cost outcomes included total costs for each DST strategy, cost per MDR-TB case prevented, cost per TB-related death avoided and cost per DALY averted. Transmission of resistant strains and subsequent secondary cases were not estimated. For the analysis of models of care (question 7), costs considered for inclusion could be from any of the following perspectives: cost from the health service provider's perspective, cost from the patient's perspective (including direct medical costs as well as indirect costs related to transportation) and total societal cost. Whenever possible, the following outcomes were included in the outcome: proportion of treatment success, default or long-term deaths (including secondary, default and relapse cases) and case reproduction rate (transmission from primary cases).

GRADE evidence profiles based on the results of the systematic reviews were prepared for each question using a standard approach. These summaries present the effect of the intervention on each outcome (for example, the number of patients with MDR-TB), as well as the quality of the evidence for each outcome. The quality of 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. Quality of evidence was categorized into four levels (Table 4 in this Section).

Table 4. Quality of evidence and definitions *(6)*

Quality of evidence	Definition
High (⊕⊕⊕⊕)	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate (⊕⊕⊕O)	Further research is likely to have an important impact on our confidence in the effect and may change the estimate.
Low (⊕⊕OO)	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 (⊕OOO)	Any estimate of effect is very uncertain.

The GDG held teleconferences to discuss the available evidence, the presentation of the results and their impact on making recommendations. One discussant was chosen from among the GDG's members to assess the evidence for each of the questions and to complement the presentation of the evidence by the evidence review teams. A preparatory meeting was held in September 2010 to review the interim results of the work relating to the questions on treatment regimens and duration and use of rapid DST. The GDG met at WHO headquarters in Geneva, Switzerland, between 25 and 27 October to develop the revised recommendations. A week before the meeting, members were able to review the evidence profiles for each question via a password-protected electronic website (EZ Collab site). During the meeting and in the following months, additional files and successive versions of the guidelines were shared with the GDG on the same site.

At the meeting, the GRADE evidence profiles were assessed by the members of the GDG when preparing the recommendations. The GDG used standard decision tables to move from evidence to recommendations. One table was prepared for each recommendation to record decisions and ensure that the group uniformly considered the quality of the evidence, the certainty about the balance of benefits versus harms, the similarity in values and the costs of an intervention compared with the alternative. The profiles allowed members to base their judgments when making recommendations on evidence summarized in a concise and uniform manner. Agreement on the recommendations was reached following discussions. In their deliberations, members of the GDG assessed the level of evidence and judged the strength of the recommendations according to the criteria shown in Table 5 (*see* online Annex 7 for a glossary of GRADE terms).

Table 5. Assessment of the strength of a recommendation *(6)*

Strength	Definition
Strong	The Guideline Development Group is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects.
Conditional	The Guideline Development Group concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects.

Apart from the quality of evidence, the strength of a recommendation was determined by the balance between desirable and undesirable effects, values and preferences, and costs or resource allocation *(6)*. The higher the quality of evidence, the more likely that it would lead to a strong recommendation. However, a strong recommendation may be made in the presence of very low-quality evidence, given the variability in values and preferences between the experts, the balance between desirable and undesirable consequences of an intervention, and resource implications. For instance, evidence from observational studies without randomization is always of low quality, but if the studies are methodologically sound (not downgraded for concerns about the validity) and the estimates of effect are consistent, a strong recommendation may still be possible. It is important to note that when making a conditional recommendation, the GDG considered its application only to a specific group, population or setting, or that new evidence might change the balance of risk to benefit or that the benefits might not warrant the cost or resource requirements in all settings (*see also* Table 6 in this Section).

The recommendations in these guidelines are to be read along with the accompanying remarks on available evidence, which are relevant to their proper interpretation and implementation.

Table 6. Implications of the strength of a recommendation for different users (adapted from *(6)*)

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 adapted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

External review

The External Review Group commented on the questions during their formulation (in mid-2009) and on a draft text of the guidelines, including recommendations, following comments from the GDG (in early 2011). For the initial discussion, eight of the peer reviewers submitted comments that were used for the revised set of priority questions submitted to the evidence review centres for the systematic reviews. Six reviewers made comments on the draft guidelines in early 2011.

Publication, implementation, evaluation and expiry

The guidelines will be published in English on the WHO website as well as in a peer-reviewed publication. WHO's Stop TB Department will work closely with regional and country offices, the Stop TB Partnership and other implementing partners to ensure their wide dissemination in electronic and paper formats.

A companion manual is planned for 2011 to provide practical information on implementing programmatic management of drug-resistant TB. The manual will update previous guidance on this subject.

An evaluation of how users have implemented the guidelines will be developed to measure different dimensions of uptake of the recommendations, including the time until adaptation (if any) and barriers to effective implementation.

It is expected that the Stop TB Department, in collaboration with its partners, will review and update these guidelines about four years after their publication or earlier if new evidence, regimens or diagnostic tests become available.

This information is included in the Background and Methods section in the *Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update*, pages 3–10, available at: https://apps.who.int/iris/bitstream/handle/10665/44597/9789241501583_eng.pdf. Additional information on the methods used for these guidelines is also available in Annex 1: Methods for evidence reviews and modelling (question 7), available online at: https://apps.who.int/iris/bitstream/handle/10665/70676/WHO_HTM_TB_2011.6a_eng.pdf

WHO treatment guidelines for drug resistant tuberculosis, 2016 update

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, which received final approval in September 2015.

Seven webinars (using WebEx) were held between May and November 2015 (on 20 May, 17 July, 7 August, 28 August, 16 September, 6 October, and 5 November) to discuss with the Guideline Development Group (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.

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 *(14)*. 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 that 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 the 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 Annex 1. 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 1 in this Section). The mean scores for the nine responses received were all in the "Critical" range (7–9 points).

Table 1. 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 6	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.

The certainty of evidence is categorized into four levels (Table 2 in this Section). The criteria used by the evidence reviewers to qualify the quality of available evidence are summarized in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tables annexed to these guidelines (online Annex 7). A number of factors may increase or decrease the certainty of evidence (*see* Fig. 9.1 of *(2)*). The highest rating is usually assigned to data from randomized controlled trials (RCTs) while evidence from observational studies is usually assigned a low or very low-quality value at the start.

Table 2. Certainty of evidence and definitions *(6)*

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 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 Annex 8; *(6)*). 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 the desirable effects probably outweigh the undesirable effects. The strength of a recommendation has different implications for the individuals affected by these guidelines (Table 3 in this Section).

Table 3. Implications of the strength of a recommendation for different users (adapted from *(6)*)

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 *(27)*. RR-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) *(28)*.

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 *(29)*.

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 *(30–32)*. 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 *(14,27)*. 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 *(28,33)*.

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) *(34)*, 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 *(5)*. Evidence reviewers are listed in online Annex 4; more details on the methods used in unpublished studies are presented in online Annex 6 of the *WHO treatment guidelines for drug-resistant tuberculosis, 2016 update*, available at: https://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-eng. pdf 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 *(18)* and children), PICO 3 (shorter MDR-TB regimens) and PICO 4 (use of surgery *(35)*).

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 the 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 Annex 7). 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 *(2)*.

The GDG membership represented a broad cross-section of future users of the guidelines as well as affected persons (including patients). 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 (online Annex 7 and online Annex 6 of the *WHO treatment guidelines for drug-resistant tuberculosis, 2016 update*, available at: https://apps.who. int/iris/bitstream/handle/10665/250125/9789241549639-eng.pdf). 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 Annex 8).

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 original online Annexes 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 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 (27).

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 (27).

This information is available in the Methods section of the *WHO treatment guidelines for drug-resistant tuberculosis, 2016 update*, pages 9–17, available at: https://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-eng.pdf

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

Scope of the guideline update

The scope of the 2017 update of the drug-susceptible TB treatment guideline is to update the previous evidence-based policy recommendations in the *Guidelines for treatment of tuberculosis* released in 2010 (36). The 2017 guideline update is broader than the 2010 guidelines as it includes additional evidence-based policy recommendations on cross-cutting issues relevant to patient care and support for patients with drug-susceptible TB or drug-resistant TB. In the context of patient care for this guideline update, the decentralized model of care for drug-resistant TB patients, which had never previously been addressed by any WHO TB guidelines, was also included for assessment of the available evidence. This is part of the plan of WHO's Global TB Programme to produce consolidated guidelines that will include all the recommendations on management of both drug-susceptible TB and drug-resistant TB.

The WHO Guidelines Steering Group and the Guideline Development Group (GDG) considered priority questions for the update by focusing on important areas of drug-susceptible TB treatment and care that had not been addressed by previous guidelines and for which evidence was likely to be available by the time of the guideline update. A further priority was those areas that were already addressed by previous guidelines but for which new evidence had emerged that was likely to lead to a change in the existing recommendation. The WHO Guidelines Steering Group and the GDG agreed to limit the scope of the *Guidelines for treatment of drug-susceptible tuberculosis and patient care* to the following priority areas:

1. Treatment of drug-susceptible TB

1.1 Effectiveness of TB treatment with the use of 4-month fluoroquinolone-containing regimens

1.2 Effectiveness of fixed-dose combination (FDC) formulations for treatment of new TB patients

1.3 Frequency of dosing in the intensive and continuation phases for treatment of new patients with pulmonary TB

1.4 Initiation of antiretroviral therapy in TB patients living with HIV

1.5 Duration of TB treatment for HIV-coinfected patients with drug-susceptible pulmonary TB

1.6 Effectiveness of adjuvant corticosteroids in patients with tuberculous pericarditis and tuberculous meningitis

1.7 Treatment regimen and management of patients with a previous history of TB treatment (i.e. treatment interruption or recurrence of disease) who require retreatment.

2. Patient care and support

2.1 Effectiveness of treatment supervision (e.g. directly observed treatment [DOT], video-observed treatment [VOT]) and other treatment adherence interventions

2.2 Effectiveness of a decentralized model of care for MDR-TB.

The 2017 update of the guidelines does not cover the aspects of policy guidance on treatment of drug-susceptible TB for which no new evidence has been published since the 2010 revision *(36)*. However, in the updated guidelines, there is a section referring to existing WHO policy recommendations on the treatment of drug-susceptible TB and patient care for which no new evidence has emerged since they were released and which are therefore still valid. These existing recommendations will be included in the guidelines with clear reference to the previous guidelines where GRADE assessments and summaries of evidence were presented.

The key audience for these guidelines is policy-makers in ministries of health or managers of national TB programmes who formulate country-specific TB treatment guidelines or who plan TB treatment programmes. In addition, health professionals – including doctors, nurses and educators working both in government services and in nongovernmental organizations, such as technical agencies that are treating patients and organizing treatment services – are expected to use these guidelines. The guidelines include GRADE-assessed recommendations while aiming at a wide variety of health workers and other audiences who may have widely different needs that are unlikely to be met with the same guidance. Separate "how to" guidance, which will be developed subsequently, will include additional information on how to implement the recommendations. As noted, WHO's Global TB Programme also aims to consolidate the essential guidance on management of drug-susceptible and drug-resistant TB into a single guideline.

Key questions

The PICO questions were grouped into two sets – drug-susceptible TB treatment and patient care. There were nine PICO questions devoted to the treatment of drug-susceptible TB and two PICO questions on patient care and support (*see* Scope of the guideline update, above, and Annex 1 for the full version of all PICO questions).

Certainty of evidence and strength of recommendations

The recommendations in these guidelines qualify both their strength and the certainty in the evidence on which they are based. The certainty (quality) of the evidence is categorized into four levels (Table 1 in this Section). The criteria used by the evidence reviewers to qualify the quality of evidence are summarized in the GRADE tables annexed to these guidelines (online Annex 7). A number of factors may increase or decrease the quality of evidence (*see* Tables 12.2b and 12.2c in the *WHO handbook for guideline development (2)*). The highest-quality rating is usually assigned to evidence from randomized controlled trials, while evidence from observational studies is usually assigned a low or very low-quality value at the start.

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. 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 2 in this Section).

Table 1. Certainty in the evidence

Certainty in the 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.

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 to the implementation of the policy.

Assessment of evidence and its grading

The development of these guidelines required a substantial evidence review and assessment using the GRADE process, as stipulated by the WHO Guideline Review Committee *(2)*. The systematic reviews focused primarily on the randomized controlled trials with direct comparison between the intervention and comparator. However, data on the outcomes from the observational cohort studies were also

summarized and assessed by the GDG, especially when limited or no evidence from randomized controlled trials was available. The systematic reviews were commissioned by independent reviewers. The evidence reviewers are listed in online Annex 4. Contributors to this work were not members of the GDG so that the latter can provide independent oversight of recommendations based on evidence assessment. The WHO Steering Group and methodologists supervised the contractors' performance of the reviews, including assessing and providing feedback on the protocol for each systematic review and the evidence tables. Teams of experts were commissioned to assess the evidence for the PICO questions and their outcomes through systematic literature reviews following a standard methodology. Titles, abstracts and full text of potentially relevant literature were screened using key subject words and text words. Authors or experts in the field were contacted to identify missing studies or studies in progress.

For the systematic reviews that were conducted for the updated ATS/CDC/IDSA TB treatment guidelines, the same groups of reviewers who conducted the reviews also prepared GRADE evidence profiles and presented them to the GDG for the WHO guidelines for assessment prior to and during the GDG meeting. The GDG revised the quality of the evidence assigned by the evidence reviewers on the standard criteria (e.g. directness, precision) using the automated function on the GRADEpro platform.

Table 2. Implications of the strength of a recommendation for different users (adapted from (6))

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.

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 the 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 Annex 3). The evidence profiles were prepared

using the GRADEpro software – an online tool to create guideline materials.[5] 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.

The GDG membership represented a broad cross-section of future users of the guidelines as well as affected persons (including patients). Ahead of the GDG meeting held at the WHO headquarters in Geneva, Switzerland, 11–13 July 2016, 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. Evidence profiles and drafts of the review reports (online Annexes 7 and 9) were shared with the GDG members ahead of the meeting. During the meeting and in the following weeks, additional analyses were shared with the group upon demand. The GRADE evidence profiles were discussed by the GDG ahead of formulating the recommendations.

The GDG used the "Evidence-to-Decision" tables via the GRADEpro interface to capture the content of the discussions (online Annex 8). During the meeting on 11–13 July 2016, GDG members formulated the first draft of the recommendations on the basis of their assessment of

evidence. The GDG discussed the proposed wording of the recommendations and the rating of strength (strong or conditional) considering not only the nature and quality of evidence but also assessing the balance between benefits and harms, as well as patients' values and preferences, resource implications, equity and human rights, acceptability and feasibility. In the case of the question on use of the category II regimen for treatment of previously treated TB, the available evidence generated by the GRADE approach was insufficient for the GDG to make a decision on a recommendation. A good practice statement approach was considered more appropriate in this case and was therefore used in formulating the recommendation.

All decisions on the recommendations were reached by discussion and consensus, including the strength of the recommendations and, where appropriate, the conditions to be attached to the recommendations. The Chair facilitated the discussions in order to reach consensus during the meeting; consequently, there was no need to vote on any of the recommendations. An additional analysis was conducted by the reviewers after the GDG meeting, addressing a gap in information that was identified in PICO question 10 on treatment adherence interventions. The additional evidence led to a slight revision of two recommendations on treatment supervision options. All evidence provided, and the revised recommendations, were shared with all GDG members for review and endorsement.

External review

The process of peer review involved the External Review Group, which was composed of experts and end-users from national programmes, technical agencies and WHO regional offices. These persons provided their review and inputs on the completed draft guidelines after all comments by GDG members were incorporated.

Publication, dissemination, implementation, evaluation and expiry

These guidelines are published on the WHO Global TB Programme (WHO/GTB) website and are freely downloadable (as pdf and in other electronic formats). The main text of the guidelines will be made available in a print version in early 2017 and will be widely distributed to WHO regional and country offices as well as to national TB programmes. This document will appear in six languages: Arabic, Chinese, English, French, Russian and Spanish. It is also expected that the evidence reviews and recommendations will be published in peer-reviewed journals to improve dissemination of the main messages. The updates of policy guidance will also be reflected in the implementation guidance

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[5]   *See*: https://gradepro.org/

on TB management and the revision of the WHO implementation handbook on programmatic management of drug-resistant TB *(27)*.

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 at different levels will work with technical partners to support national TB programmes in adopting the new recommendations in national TB policies and guidelines. The evaluation of implementation of the recommendations by countries or end-users will be conducted by WHO/GTB and partners several years following publication. WHO/GTB will also review and update the guidelines some 4–5 years after their publication, or earlier if new evidence becomes available, and these changes will be reflected in the implementation guidance documents.

This information is included in the Methods used to update the guidelines section in the *Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update*, pages 19–24, available at: https://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf.

Annex 7: GRADE evidence summary tables

WHO treatment guidelines for isoniazid-resistant tuberculosis, 2018

Refer to Annex 5: GRADE evidence summary tables in the *WHO treatment guidelines for isoniazid-resistant tuberculosis* (https://www.who.int/tb/publications/2018/WHO_treatment_guidelines_isoniazid_resistant_TB_Online_GRADE_tables_Annexes.pdf, accessed 2 March 2019).

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

Refer to Annex 8: GRADE evidence summary tables in the *WHO treatment guidelines for multidrug-and rifampicin-resistant tuberculosis, 2018 update* (https://www.who.int/tb/areas-of-work/drug-resistant-tb/Annexes_8-10.pdf, accessed 2 March 2019).

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

Refer to Annex 2: GRADE glossary and summary of evidence tables (questions 6 and 7) in the *Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update* (https://apps.who.int/iris/bitstream/handle/10665/70677/WHO_HTM_TB_2011.6b_eng.pdf, accessed 2 March 2019).

WHO treatment guidelines for drug-resistant tuberculosis, 2016 update

Refer to Annex 4: GRADE tables (question 4) in the *WHO treatment guidelines for drug-resistant tuberculosis, 2016 update* (https://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/resources/en/, accessed 2 March 2019).

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

Refer to Annex 3: GRADE evidence profiles (questions 10 and 11) in the *Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update* (https://www.who.int/tb/publications/2017/dstb_guidance_2017/en/, accessed 2 March 2019).

Annex 8: GRADE evidence-to-decision tables

WHO treatment guidelines for isoniazid-resistant tuberculosis, 2018

Refer to Annex 6: GRADE evidence-to-decision tables in the *WHO treatment guidelines for isoniazid-resistant tuberculosis* (https://www.who.int/tb/publications/2018/WHO_treatment_guidelines_ isoniazid_resistant_TB_Online_GRADE_tables_Annexes.pdf, accessed 2 March 2019).

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

Refer to Annex 9: GRADE evidence-to-decision tables in the *WHO treatment guidelines for multidrug-and rifampicin-resistant tuberculosis, 2018 update* (https://www.who.int/tb/areas-of-work/ drug-resistant-tb/Annexes_8-10.pdf, accessed 2 March 2019).

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

Refer to Annex 2: GRADE glossary and summary of evidence tables (questions 6 and 7) in the *Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update* (https:// apps.who.int/iris/bitstream/handle/10665/70677/WHO_HTM_TB_2011.6b_eng.pdf, accessed 2 March 2019), where the content of the evidence-to-decision process was summarized in the remarks relating to each recommendation.

WHO treatment guidelines for drug-resistant tuberculosis, 2016 update

Refer to Annex 5: Evidence-to-decision tables (question 4) in the *WHO treatment guidelines for drug-resistant tuberculosis, 2016 update* (https://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/ resources/en/, accessed 2 March 2019).

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

Refer to Annex 4: Evidence-to-decision tables (questions 10 and 11) in the *Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update* (https://www.who.int/tb/publications/2017/ dstb_guidance_2017/en/, accessed 2 March 2019).

Annex 9: Summaries of unpublished data, analysis plans and reports of systematic reviews

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

Refer to Annex 10: Summaries of unpublished data and analysis plans used for the recommendations in the *WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update* (https://www.who.int/tb/areas-of-work/drug-resistant-tb/Annexes_8-10.pdf, accessed 2 March 2019).

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

Refer to Annex 5: Reports of the systematic reviews (reports on systematic reviews for: adherence interventions in tuberculosis treatment and decentralized treatment and care for multidrug-resistant tuberculosis patients) in the *Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update* (https://www.who.int/tb/publications/2017/dstb_guidance_2017/en/, accessed 2 March 2019). The systematic reviews have subsequently been published *(37,38)*.

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