WHO treatment guidelines for isoniazid-resistant tuberculosis

Supplement to the WHO treatment guidelines for drug-resistant tuberculosis

THE END TB STRATEGY

World Health Organization

WHO treatment guidelines for isoniazid-resistant tuberculosis

Supplement to the WHO treatment guidelines for drug-resistant tuberculosis

World Health Organization

WHO treatment guidelines for isoniazid-resistant tuberculosis: Supplement to the WHO treatment guidelines for drug-resistant tuberculosis

ISBN 978-92-4-155007-9

WHO/CDS/TB/2018.7

Contents

Abbreviations & acronyms v
Glossary vi
Acknowledgements vii
Declarations of interest ix
Executive summary 1
Introduction 4
Objectives 4
Target audience 4
Background and rationale 4
Methods 5
WHO policy recommendations 9
Research priorities 17
Publication, dissemination, implementation, evaluation and expiry 18
Annexes 22
Annex 1. Agenda of the Guideline Development Group meeting 22
Annex 2. Participants at the Guideline Development Group meeting 23
Annex 3. PICO question 26
Annex 4. Summary of unpublished data used for the recommendations 27

Annex 5. GRADE evidence summary tables
Annex 6. GRADE Evidence to decision tables

Annexes 5 and 6 are **only available online at**:
http://www.who.int/tb/publications/2018/WHO_guidelines_isoniazid_resistant_TB/en/

Abbreviations & acronyms

aOR	adjusted odds ratios
ART	antiretroviral therapy
ATS	American Thoracic Society
DOI	WHO Declaration of Interest
DR-TB	drug-resistant tuberculosis
DST	drug-susceptibility testing
E	ethambutol
ERG	External Review Group
FDC	fixed-dose combination medicines
GDF	Global Drug Facility
GDG	Guideline Development Group
Gfx	gatifloxacin
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRADEpro	online tool to create guideline materials (see http://gdt.guidelinedevelopment.org)
GRC	WHO Guideline Review Committee
GTB	WHO Global TB Programme
H	isoniazid
HALT	Hepatitis and Latent TB Infection study
HIV	human immunodeficiency virus
Hr-TB	confirmed rifampicin-susceptible, isoniazid-resistant TB
IPD	individual patient data
Km	kanamycin
KNCV	KNCV Tuberculosis Foundation
Lfx	levofloxacin
LPA	line probe assay
LTBI	latent tuberculosis infection
MDR-TB	multidrug-resistant tuberculosis
Mfx	moxifloxacin
M.tb	Mycobacterium tuberculosis
OR	odds ratio
PI	Principal Investigator
PICO	Patients, Intervention, Comparator and Outcomes
R	rifampicin
RCT	randomized controlled trial
RR-TB	rifampicin-resistant TB
S	streptomycin
SAE	serious adverse event
TB	tuberculosis
UNION	International Union Against Tuberculosis and Lung Disease
USAID	United States Agency for International Development
USD	United States dollars
WHO	World Health Organization
WHO/GTB	Global TB Programme of the World Health Organization
XDR-TB	extensively drug-resistant tuberculosis
Z	pyrazinamide

Glossary

The following definitions refer to common terms as used in these guidelines:

Isoniazid-resistant TB (Hr-TB), refers to *Mycobacterium tuberculosis* strains with resistance to isoniazid and susceptibility to rifampicin confirmed *in vitro*. Definitions and terms used herein have been described elsewhere.[1,2]

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

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. Policy guidelines on the use of phenotypic and molecular tests for the detection of resistance to isoniazid has been published by WHO.[3,4,5]

Previously treated refers to patients who have received one month or more of anti-TB medicines in the past.[1] **Previously treated cases** may have been treated with an individualized regimen including fluoroquinolones or injectable agents in addition to first-line TB medicines.[6]

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

Treatment outcome definitions used in these guidelines, and the term **relapse,** refer to those used for patients without rifampicin-resistant tuberculosis, unless otherwise specified.[1]

Serious adverse event (SAE) is defined as an adverse event which either leads to death or a life-threatening experience; to initial or prolonged hospitalization; to persistent or significant disability; or to a congenital anomaly. SAEs that do not immediately result in one of these outcomes but that require an intervention to prevent permanent impairment of a body function or damage to a body structure are included. The management of SAEs may require termination of the drug suspected of having caused the event.[7]

---

[1] Definitions and reporting framework for tuberculosis – 2013 revision (WHO/HTM/TB/2013.2). Available from: http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf. Geneva: World Health Organization. 2013.

[2] Guidelines for surveillance of drug resistance in tuberculosis - 5th ed [WHO/HTM/TB/2015.13]. Available from: http://apps.who.int/iris/bitstream/10665/174897/1/9789241549134_eng.pdf. Geneva: World Health Organization. 2015.

[3] Policy statement: Liquid media for culture and DST. The use of liquid medium for culture and DST, 2007. Available from: http://www.who.int/tb/areas-of-work/laboratory/policy_liquid_medium_for_culture_dst/en/. Geneva: World Health Organization. 2007.

[4] Policy guidance on drug-susceptibility testing (DST) of second-line antituberculosis drugs. Available from: http://www.who.int/tb/publications/2008/whohtmtb_2008_392/en/. 2008.

[5] WHO policy statement: molecular line probe assays for rapid screening of patients at risk of multidrug-resistant tuberculosis. Available from: http://www.who.int/tb/areas-of-work/laboratory/line_probe_assays/en/. Geneva: World Health Organization, 2008.

[6] Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis (WHO/HTM/TB/2014.11). Available from: http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf. Geneva: World Health Organization. 2014.

[7] Active tuberculosis drug-safety monitoring and management (aDSM): framework for implementation (WHO/HTM/TB/2015.28). Available from: http://apps.who.int/iris/bitstream/10665/204465/1/WHO_HTM_TB_2015.28_eng.pdf?ua=1. Geneva: World Health Organization. 2015.

Acknowledgements

The recommendations and remarks in this policy guideline are the result of the collaborative effort of professionals from a range of specialties and who have extensive expertise and experience in public health policy, programme management as well as in the care of patients with drug-resistant tuberculosis (DR-TB). The World Health Organization (WHO) is grateful for their time and support.

Guideline Development Group

The chairs of the *Guideline Development Group* (GDG) were Nancy Santesso (GRADE Methodology specialist; Canada) and Kelly Dooley (Clinical Pharmacologist, Infectious Diseases specialist; United States). In addition, the following experts served as members of the GDG: Farhana Amanullah (Paediatrician, clinical practice; Pakistan), Tsira Chakhaia (Patient representative and civil society representative; Georgia), Daniela Cirillo (Laboratory specialist; Italy), Luis Gustavo Do Valle Bastos (Drug management and procurement; Switzerland), Philipp du Cros (Programme manager, clinician; United Kingdom), Raquel Duarte (Programme management, public health; Portugal), Christopher Kuaban (Programme management; Cameroon), Rafael Laniado-Laborin (Clinician (private sector), public health specialist; Mexico), Gary Maartens (Pharmacology; South Africa), Andrei Maryandyshev (Clinician; Russian Federation), Ignacio Monedero-Recuero (Clinician; Spain), Maria Imelda Josefa Quelapio (Clinician, programme implementation; Netherlands), Wipa Reechaipichitkul (Clinician, public health; Thailand), Michael Rich (DR-TB expert; United States), Radojka (Rada) Savic (Pharmacokinetics/pharmacodynamics specialist; United States), Welile Sikhondze (Programme manager; Swaziland), and Armand Van Deun (Microbiologist; Belgium).

External Review Group

We thank the following members of the *External Review Group* (ERG) for reviewing the final guideline document and providing valuable inputs: Charles L. Daley (Clinical management; United States), Essam Elmoghazi (Programme management; Egypt), James Johnston (Clinical management; Canada), Enos Masini (Programme management, end-user; Kenya), Ingrid Oxley (Patient representative; South Africa), Rohit Sarin (Programme management, end-user; India), Simon Schaaf (Paediatrician; South Africa), Helen Stagg (Academic; United Kingdom), Carlos A. Torres-Duque (Technical agency , clinician; Colombia), Kitty van Weezenbeek (Technical agency, end-user; Netherlands), Irina Vasilyeva (End-user; Russian Federation), and Piret Viiklepp (Programme manager; Estonia).

Observers and external partners

Giovanni Battista Migliori (WHO Collaborating Centre for TB and Lung Diseases; Italy), YaDiul Mukadi (United States Agency for International Development; United States), Payam Nahid

(American Thoracic Society; United States) and Timothy Rodwell (FIND; Switzerland), Mohammed Yassin (Global Fund to Fight AIDS, TB and Malaria; Switzerland).

Systematic review team

We acknowledge Richard (Dick) Menzies and Federica Fregonese of McGill University, Canada, for conducting the systematic reviews, coordinating the individual-patient data (IPD) analysis, undertaking the analysis, developing GRADE evidence profiles and presenting these findings to the GDG during the discussions ahead and during the GDG meeting of 27 April 2017.

WHO Guideline Steering Committee

The following staff served as the WHO Steering Committee for the development of the current policy guideline: Dennis Falzon, Medea Gegia, Christopher Gilpin, Lice González-Angulo, Ernesto Jaramillo, Linh Nguyen, Karin Weyer and Matteo Zignol from the WHO Global TB Programme (WHO/GTB); Meg Doherty from the WHO HIV Department; Piero Olliaro from the Special Programme for Research and Training in Tropical Diseases (TDR); and Edward Kelley from the WHO Service Delivery and Safety Department.

The guideline text was drafted by Dennis Falzon and Lice González-Angulo with contributions from Alexei Korobitsyn, under the guidance and supervision of Ernesto Jaramillo and Karin Weyer, and the overall direction of Mario Raviglione, director of WHO/GTB. The document was reviewed and finalised following the input of the GDG, ERG and the WHO Guideline Steering Committee, ahead of submission to the Guideline Review Committee of WHO (GRC) in June 2017.

Funding

The United States Agency for International Development (USAID) is acknowledged for its financial support to the guideline development process (GDG meeting; systematic reviews; WHO salary support administration; and guideline production) through the WHO-USAID grant (Grant number GHA-G-00-09-00003/US-2014-827). The consolidation of the database comprising individual level data on patients with isoniazid-resistant TB (Hr-TB) was coordinated by McGill University simultaneously with an update of the IPD analysis on rifampicin-resistant/multidrug-resistant TB (RR-/MDR-TB) outcomes[8] which was funded by the American Thoracic Society (ATS), the Infectious Diseases Society of America (IDSA) and the United States Centers for Disease Control and Prevention (U.S. CDC). ATS/CDC/IDSA and WHO/GTB agreed to the mutual exchange of results of the two analyses to inform the revision of their respective TB guidelines.

[8] Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, Becerra MC, Benedetti A, Burgos M, Centis R, Chan ED. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012 Aug 28;9(8):e1001300.

Declarations of interest

In conformity with WHO guidelines for declaration of interests[9] for WHO experts issued by the *WHO Compliance and Risk Management and Ethics* Office, members of the GDG, 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) which 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 four 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 USD600/day, Jan 14-27 2017); (2a) paediatric TB expert for Harvard Medical School Global Health Delivery grant (20% FTE; Jun 2016-June 2018); (2b) paediatric TB expert for Global Fund grant (20% FTE; Jun 2016-Dec 2017).

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

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 EUR 6.8 million from Dutch Postcode Lottery to *Médecins Sans Frontières, Operational Centre Amsterdam* (currently active).

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 DR-TB as recipient of the UNITAID's Expand new drug markets for TB [endTB] grant (all active during the development of present recommendations).

Rada Savic: (1b) Member of the panel of the WHO Meeting on Target Regimen Profiles (value USD2500); grant reviewer for *European and Developing Countries Clinical Trials Partnership* (value USD1000); (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 objects 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 which 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 to their participation as expert reviewers applied.

Charles L. Daley: (1b) Chair and member of data monitoring committees for delamanid studies (USD45,000 provided by Otsuka Pharmaceutical over 8 years; ongoing); Chair of data monitoring committee for clofazimine studies (USD2,500 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 healthcare workers. She is a healthcare worker and has had two episodes of TB. Many members of TB Proof who are healthcare workers may have benefited from the WHO guidelines for the treatment of latent TB 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 (approx. 5 million ZAR/year). NIH grant ceased in 2015; Otsuka Pharmaceutical grant still active.

Helen Stagg: (1b) Grant to employer for consultancy work on MDR-TB clinical pathways in eastern Europe (Otsuka Pharmaceutical; GBP59,925; 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; GBP86,000 for HALT study (2014); GBP315,265 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 (USD1000 value) at the ATS conference 2016 where she presented the results of a review she conducted (2).

Carlos A. Torres-Duque: (5a) & (5b) as member of the National Advisory Committee for Tuberculosis (Ministry of Health of Colombia) participates in the updates of national TB treatment guidelines. His expert opinion is based upon evidence and local/international experience and does not generate any profits to him.

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.

Executive summary

Isoniazid (H) is one of the most important first-line medicines for the treatment of active tuberculosis (TB) and latent TB infection (LTBI), with high bactericidal activity and a good safety profile. The emergence of TB strains resistant to isoniazid threaten to reduce the effectiveness of TB treatment *(1)*. About 8% of TB patients worldwide are estimated to have rifampicin-susceptible, isoniazid-resistant TB (Hr-TB).

In April 2017, the World Health Organization (WHO) convened a *Guideline Development Group* (GDG) meeting to develop policy guidelines on the treatment of Hr-TB. The development of these policy guidelines was conducted in accordance with procedures established by the WHO Guideline Review Committee *(2)*. This was the first time that Hr-TB treatment recommendations were developed following the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) to review the evidence and formulate the recommendations *(3)*. This method included an assessment of the quality of the evidence, a consideration of the overall balance of benefits and harms (at individual and population levels), health equity, resource use, acceptability and feasibility of interventions across a variety of settings, including those where access to drug-susceptibility testing (DST) is limited.

The new recommendations for the treatment of Hr-TB complement the 2016 update of the WHO treatment guidelines for DR-TB *(4)*[10]. The recommendations will also feature in a chapter of the forthcoming update of the *Companion Handbook to the WHO guidelines for the programmatic management of drug-resistant TB* and replace previous recommendations for the treatment of Hr-TB based on expert opinion *(5-7)*.

Following an assessment of available evidence for the treatment of Hr-TB, including the evaluation of results from an analysis of individual patient data (IPD), and advice from members of the GDG, WHO made the following recommendations:

***In patients with <u>confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis</u>, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months* [*Conditional recommendation, very low certainty in the estimates of effects* ⨁◯◯◯]**

Notes.— The 4-drug "HREZ" fixed-dose combination (FDC) with *isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide (Z)* – may be used (as there is no approved REZ FDC available), to limit the need for using single drugs. Drug susceptibility to fluoroquinolones should preferably be confirmed ahead of start of treatment (*See text below for other important remarks*).

♦♦♦

***In patients with <u>confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis</u>, it <u>is not recommended</u> to add streptomycin or other injectable agents to the treatment regimen* [*Conditional recommendation, very low certainty in the estimates of effects* ⨁◯◯◯]**

[10] Concurrent with the release of the Hr-TB treatment guidelines, and ahead of the update of this handbook, practical implementation issues are being provided in the document "Frequently asked questions on the WHO treatment guidelines for isoniazid-resistant tuberculosis", available on the same website as the new guidelines.

Remarks[11]

- Although there was no clear evidence to suggest that the addition of isoniazid would add benefit to this regimen, the 4-drug HREZ FDC may be more convenient for the patient and the health service because it obviates the need to use single drugs.
- Consistent with the overall framework for the management and care of patients diagnosed with DR-TB, careful selection of patients is a fundamental principle. Ahead of starting the *(isoniazid)-rifampicin-ethambutol-pyrazinamide* plus *levofloxacin (Lfx)* regimen (henceforth abbreviated as *(H)REZ-Lfx)*, it is essential that resistance to rifampicin be excluded by WHO-recommended genotypic or phenotypic methods *(8, 9)*. Preferably, *resistance to fluoroquinolones*, and if possible to pyrazinamide, is similarly be excluded prior to treatment in order to help avert the acquisition of additional drug resistance. (See "*Implementation considerations*" in pg. 9).
- Empirical treatment of Hr-TB is not generally advised. In cases where Hr-TB diagnosis is strongly presumed (e.g. close contacts of Hr-TB cases with active TB but without laboratory confirmation of Hr-TB), *(H)REZ-Lfx* may be introduced pending laboratory confirmation of isoniazid resistance, so long as rifampicin resistance has been reliably excluded. Should DST results eventually indicate susceptibility to isoniazid, levofloxacin is stopped and the patient completes a 2HRZE/4HR regimen. For other patients, in whom Hr-TB is detected after the start of treatment with the 2HRZE/4HR regimen, the (H)REZ component drugs are continued (or pyrazinamide and ethambutol are re-introduced) and levofloxacin added once rifampicin resistance has been excluded.
- The *(H)REZ-Lfx* regimen is given for as long as it is necessary for the patient to receive levofloxacin for six months. Thus, in cases where the diagnosis of Hr-TB is made after first-line TB treatment has already been initiated, the patient may receive more than six months of *(H)REZ* by the end of treatment. When the confirmation of isoniazid resistance arrives late into treatment with a 2HRZE/**4**HR regimen (e.g. 5 months after start during the continuation phase), the clinician would need to decide, based on an assessment of patient condition and laboratory tests, whether a 6 months course of *(H)REZ-Lfx* needs to be started at that point or not.
- The addition of levofloxacin to *(H)REZ* is recommended in all patients with Hr-TB, with exception of the following: **(i)** in cases where resistance to rifampicin cannot be excluded; **(ii)** known or suspected resistance to levofloxacin; **(iii)** known intolerance to fluoroquinolones; **(iv)** known or suspected risk for prolonged QTc interval; and **(v)** pregnancy or during breastfeeding (not an absolute contraindication). In Hr-TB cases in whom a fluoroquinolone cannot be used, the patient may still be treated with 6(H)REZ.
- When additional resistance (especially to pyrazinamide) is suspected or confirmed, appropriate treatment regimens will have to be designed individually. The data reviewed for this guideline could not provide separate evidence-based recommendations for such cases.

[11] See **Implementation Considerations** section (***page 9***) for more detailed information.

- Where possible, isoniazid resistance testing should also include information on the specific mutations associated with resistance to isoniazid (*kat*G or *inh*A). In addition, knowledge about overall *host acetylator*[12] status) at country or regional level will be useful given that these may have implications for regimen design *(10)*.
- High throughput diagnostic platforms are in development (as an alternative to LPA) that can simultaneously detect tuberculosis, and resistance to rifampicin and isoniazid. Evaluation studies of these diagnostics are underway and it is expected that WHO will review their operational and performance characteristics later in 2018.

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

Introduction

This policy guideline anticipates the most common situations under which these recommendations will be applied, in order to provide the end-user with practical options when deciding upon clinical management, such as what to do while awaiting DST results, making best use of FDCs available to the programme, or principles to prevent the acquisition of additional resistance. It also addresses considerations for implementation, monitoring and adaptation in different subgroups (e.g. children; HIV-infected individuals) and other situations[13].

The production of these guidelines has highlighted a number of gaps in knowledge about the treatment of Hr-TB, and further studies and operational research are strongly recommended.

Objectives

The objective of this guideline is to provide recommendations on the composition and duration of suitable treatment regimens for the treatment of Hr-TB, based on a review of the best available evidence. These recommendations complement existing WHO guidelines for treatment of DR-TB cases.

Target audience

These guidelines are primarily targeted at policy-makers in ministries of health or managers of national TB programmes (NTPs) who formulate country-specific TB treatment guidelines or who are involved in the planning of TB treatment programmes. In addition, health professionals, including doctors, nurses and educators working in governmental and non-governmental organizations, as well as technical agencies involved in treating patients and organizing treatment services are expected to use these guidelines.

Background and rationale

TB remains a threat to global public health and is the leading cause of death by a single infectious agent globally *(1)*. In 2016, an estimated 10.4 million people developed TB and 1.7 million died from the disease. In the same year an estimated 600 000 TB patients developed rifampicin-resistant (RR-TB) or multidrug-resistant TB (MDR-TB, resistance to rifampicin and isoniazid); about 240 000 patients with MDR/RR-TB were estimated to have died. Patients with MDR/RR-TB roughly account for 4.1% of all new and 19% of retreatment TB cases globally, although wide regional and country differences occur. About 8% of TB cases worldwide are estimated to have Hr-TB, ranging from 5 to 11% between the WHO regions *(1)*. In a recent systematic review, the comparison of treatment outcomes between Hr-TB cases and patients with drug-susceptible TB receiving the WHO standard regimen for new patients, suggested that

[13] Concurrent with the release of the new guidelines, and ahead of the update of the *Companion handbook*, practical implementation issues are being provided in the document "Frequently asked questions on the WHO treatment guidelines for isoniazid-resistant tuberculosis", available on the same website as the new guidelines.

patients with confirmed isoniazid resistance had worse outcomes – i.e., higher treatment failure (11% vs 1%); relapse (10% vs 5%); as well as higher rates of acquired drug resistance (8% vs 0.3%) *(11)*.

A Guideline Development Group (GDG) convened by WHO in 2015 to revise policy guidelines on treatment of DR-TB also evaluated available evidence on the treatment of Hr-TB *(4)*. The evidence reviewed could not locate cohort studies or randomized-controlled trials (RCTs) which included fluoroquinolones as part of standardized TB regimens designed primarily for Hr-TB. Three RCTs aimed at investigating whether the use of fluoroquinolones could shorten drug-susceptible TB regimens did not show an advantage when fluoroquinolones were included in the regimens of a limited number of patients who were ultimately diagnosed with Hr-TB *(12-14)*. A study-level analysis based on these patients could not inform the composition of suitable regimens to treat Hr-TB. The GDG thus concluded that no policy recommendation on the treatment of Hr-TB could be formulated and suggested that an analysis of individual-patient data (IPD) from studies of subjects treated for Hr-TB using different regimens be done. An IPD analysis covering patients treated between January 2000 and April 2016 was subsequently commissioned by WHO in order to address major questions related to Hr-TB management.

Methods

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 recommendations

In preparation for the in-person meeting of the GDG on 27 April 2017 (Annex 1), a WHO Guideline Steering Committee was formed to draft the initial scoping and planning documents (Annex 2). A proposal was submitted to the WHO 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 finalise the scoping, establish the PICO (*Patients, Intervention, Comparator* and *Outcomes*) questions, the scoring of the outcomes, and the results of the evidence reviews.

PICO question

The PICO questions, inclusive of sub-populations, treatment regimen composition and duration and outcomes, were agreed upon by the GDG members (Annex 3). The questions were framed to capture the effect of different treatment regimen compositions and duration, when compared with six or more months of treatment with rifampicin-pyrazinamide-ethambutol combination therapy (Annex 3).

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**).

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 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 (Annex 4). All studies identified were observational; no cohort studies or RCTs which 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 co-infection, sputum microscopy positivity, cavitation identified in 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 *(15)*.

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*(16, 17)*. 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 summarised in the GRADE tables annexed to these guidelines (see Online **Error! Reference source not found.**). 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) *(17)*.

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 (⨁⨁⨁◯)	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.

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 to implement the intervention *(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).

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.	Recognise 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.

Note.—Adapted from *(17)*.

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 *(18)*. IPD analyses also allow the investigation of whether an intervention is more or less effective for different sub-populations *(19)*. 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 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 only be done using variable and limited subsets of the IPD due to limitations in comparability and incompleteness of the data (see Online **Error! Reference source not found.**). 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 Annexes 5 & 6 online).

External review

A draft of the guidelines document complete with the recommendations, accompanying remarks and GRADE tables was circulated to the External Review Group for their comments. Feedback provided was incorporated into the subsequent version of the guidelines.

WHO policy recommendations

***In patients with <u>confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis</u>, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months* [*Conditional recommendation, very low certainty in the estimates of effects* ⨁◯◯◯]**

Notes.— The 4-drug "HREZ" fixed-dose combination (FDC) with *isoniazid (H) - rifampicin (R) – ethambutol (E) – pyrazinamide (Z)* -may be used (as there is no approved REZ FDC available), to limit the need of using single drugs. Drug susceptibility to fluoroquinolones should preferably be confirmed ahead of start of treatment (*See text below for other important remarks*).

♦♦♦

***In patients with <u>confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis</u>, it <u>is not recommended</u> to add streptomycin or other injectable agents to the treatment regimen* [*Conditional recommendation, very low certainty in the estimates of effects* ⨁◯◯◯]**

Implementation considerations

- *Case scenarios:* The implementation of these recommendations requires that the *(H)REZ-Lfx* regimen is administered only in patients in whom resistance to isoniazid is confirmed and resistance to rifampicin has been excluded. Preferably, testing for resistance to fluoroquinolones, and if possible to pyrazinamide, is also done ahead of start of treatment. It is envisaged that the Hr-TB treatment regimen would apply in the following situations:
  - <u>Hr-TB is confirmed before TB treatment is started:</u> treatment with the *(H)REZ-Lfx* is started immediately. If the diagnosis is strongly presumed (e.g. close contacts of a confirmed Hr-TB source case) but results of drug susceptibility testing are still pending the regimen may be introduced. Should drug susceptibility test results taken at start eventually show susceptibility to isoniazid, then levofloxacin is stopped and the patient continues treatment in order to complete a 2HREZ/4HR regimen.
  - <u>Hr-TB is confirmed after the start of treatment with 2HREZ/4HR regimen</u>: This includes patients who had undiagnosed isoniazid resistance at the start or who developed isoniazid resistance later while on first-line regimen treatment. In such cases, rapid molecular testing for rifampicin resistance must be done (or repeated). Once rifampicin resistance is excluded, a full 6-month course of (H)REZ-Lfx is given. The duration is driven by the need to give levofloxacin for 6 months, which usually implies that the companion first-line medicines are taken for longer than this.

If rifampicin resistance is detected, the patient needs to be started on a recommended MDR-TB treatment regimen *(4)*.

- *Diagnostic capabilities:* The overall aim of TB treatment is to achieve cure without relapse in all patients, interrupting *M. tuberculosis* transmission and preventing the acquisition (or amplification) of additional drug resistance. Globally, Hr-TB is more prevalent than MDR-TB. Efforts need to be made by all countries to move towards universal testing of both isoniazid and rifampicin at the start of TB treatment and to ensure the careful selection of patients eligible for the *(H)RZE-Lfx* regimen[14]. The minimum diagnostic capacity to appropriately implement these recommendations requires rapid molecular rifampicin testing prior to the start of treatment with the Hr-TB regimen, and preferably, that fluoroquinolone resistance is ruled-out by WHO-recommended tests. Rapid molecular tests such as Xpert MTB/RIF and line probe assays (LPA) are preferred to guide patient selection for the *(H)RZE-Lfx* regimen.
- DR-TB surveillance indicates that fluoroquinolone resistance among patients with rifampicin-susceptible TB is generally low worldwide *(20)*; however national data on the prevalence of fluoroquinolone resistance - including targeted or whole genome sequencing to detect specific mutations associated with resistance to fluoroquinolones *(21)* - could help guide testing policies when the Hr-TB treatment recommendations are implemented in countries.
- When additional resistance (especially to fluoroquinolones or pyrazinamide) is suspected or confirmed, treatment regimens may have to be designed individually with other second-line TB medicines. The current review could not provide further evidence on effective regimens in patients with poly-resistant disease.
- Support and close monitoring of patients are needed in order to maximise treatment adherence and enable early detection of patients who are not responding to treatment (e.g. those with persistent sputum culture or smear positivity). Repeat DST to rifampicin and the fluoroquinolones, preferably with Xpert MTB/RIF or LPA, is indicated in the presence of non-response. Documented acquisition of resistance to rifampicin or a fluoroquinolone while on the Hr-TB regimen should alert the clinician to reviewing the entire clinical and microbiological status of the patient and change the regimen accordingly.
- Levofloxacin is proposed as the fluoroquinolone of first choice in the Hr-TB regimen for a number of reasons. Firstly, this medicine has a better-characterized safety profile compared to other fluoroquinolones and was the one most frequently used in the studies reviewed for this guidance. Secondly, levofloxacin has fewer known drug interactions with other medications as compared to moxifloxacin. For example, while plasma peak concentration and exposure to moxifloxacin decrease significantly when combined with rifampicin, *(22)* the same effect has not been reported for levofloxacin, attributed to the property of levofloxacin to undergo limited metabolism in humans and to be excreted unchanged in the urine *(23)*. Additionally, although it may interfere with lamivudine clearance, unlike moxifloxacin there are no contraindications for its use with other antiretroviral agents *(24)*.

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

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

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

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

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

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

  Although the use of high-dose isoniazid (10-15mg/kg/day) was not evaluated in this review due to insufficiency of data, the GDG discussed the effect of increasing isoniazid dosing beyond that which is provided in weight-banded FDCs, depending on the type of molecular mutations identified. *In vitro* evidence seems to suggest that when specific *inhA* mutations are detected (and in the absence of any *katG* mutations), increasing the dose of isoniazid is likely to be effective; thus, additional isoniazid to a maximum dose of up to 15mg/kg per day could be considered. In the case of *katG* mutations, which more commonly confer higher-level resistance, the use of isoniazid even at higher-dose is less likely to be effective[17]. WHO plans to systematically review evidence related to phenotypic DST correlated with genotypic mutations associated with isoniazid resistance in late 2018 *(25)*.

- *Dosage*: Although the IPD analysis did not provide evidence to address the frequency of dosing, intermittent or divided dosing of the *6(H)REZ-Lfx* regimen is to be avoided *(26, 27)*.

[15] Baseline-corrected QTc. Prolongation of the QT interval and isolated cases of *torsade de pointes* have been reported. Avoid use in patients with known prolongation, those with hypokalaemia, and with other drugs that prolong the QT interval.
[16] Of note, although most countries currently procure the 4-drug FDC via the Stop TB Partnership's Global Drug Facility (GDF), in settings where only the 3-drug combination FDC (HRZ) is available, ethambutol has to be administered separately.
[17] Emerging data indicate that an isolated *kat*G or *inh*A mutation can indicate variable MIC levels, and that *inh*A mutations do not always indicate very low level resistance or that *kat*G mutations not necessarily very high.

In the absence of full information about optimal drug doses, a weight-band dosing scheme for levofloxacin is recommended.[18]

- *Drug-drug interactions:* levofloxacin may potentially interfere with lamivudine clearance (increasing levels of lamivudine), but is not contraindicated with other antiretroviral agents and no drug dosing adjustments are needed *(24)*. Co-administration of levofloxacin with oral divalent cation-containing compounds (such as antacids) may impair its absorption and should be avoided *(7)*. Restriction of concomitant use of milk products is not necessary.
- *Treatment prolongation beyond 6 months:* may be considered for patients with extensive cavitary disease or in patients slow to convert to negative smear/culture. In the latter, acquisition of additional resistance to rifampicin must be ruled-out, as well as resistance to fluoroquinolones and pyrazinamide if possible. Such patients require careful monitoring and follow-up.
- *Cost:* Cost-effectiveness analysis was not performed for this review. Table 4 presents approximate prices for a full course of medicines for the different regimens in adults based on the cost of products available from the Global Drug Facility *(28)*. Use of FDCs, even for part of the regimen, reduces costs. Medicines needed for a 6HREZ-Lfx treatment cost about three times as much as a 2HREZ/4HR when using the HREZ FDC. The impact of treating Hr-TB according to these guidelines is not expected to increase operational costs significantly.

Table 4. Illustrative costs of regimens used to treat Hr-TB compared to the 6-month first-line TB regimen (price of medicines alone)*

Regimen	Approximate cost of medicines alone, USD *
2HREZ/4HR	31.9 (22.36 - kit)
6HREZ	104.4 (47.8)
6REZLfx	122.26
6HREZLfx	125.8 (68.7)
9HREZLfx	186.8 (102.5)

Note.—* Data source : Global Drug Facility *(28)*. Prices as of 16 March 2018 for a 60kg adult. Values in brackets reflect the price when the regimen is given in part or whole as a FDC.

- *Adherence:* Although the IPD analysis contained limited data on treatment adherence strategies used (i.e. directly observed therapy, DOT; self-administered therapy), improved treatment success rates appeared to be associated with increased patient support, including medication adherence support (for example, by means of digital technologies) or other means as recommended by WHO *(26)*. In contrast to regimens for drug-susceptible and MDR-TB, the recommended Hr-TB treatment regimen does not have an intensive and a continuation phase, which simplifies the delivery and monitoring of treatment.

[18] Studies included in this IPD analysis involved the use of regimens containing levofloxacin (usually at a dose of 750-1000 mg/day), moxifloxacin (400mg/day) or gatifloxacin (400mg/day), as well as early-generation fluoroquinolones (ciprofloxacin and ofloxacin) which are no longer recommended in the treatment of DR-TB. For further information on dosing regimens see the "Frequently asked questions on the WHO treatment guidelines for isoniazid-resistant tuberculosis", available on the same website as these guidelines

- *Monitoring and evaluation:* Patients who receive the *(H)REZ-Lfx* regimen need to be monitored during treatment using schedules of clinical and laboratory testing. The definitions to use when assigning outcomes are the same ones in use for drug-susceptible TB *(29)*. Signs of non-response or treatment failure should be followed up with DST to rifampicin and, if possible, to fluoroquinolones and pyrazinamide. In order to limit the risk of acquisition of additional resistance, the addition of single TB medicines should be avoided in patients who remain smear- or culture-positive after month 2 of treatment, who do not show a favourable clinical response and in those without recent DST results.

  As with any other TB medicine and regimen, safety precautions to ensure the rapid identification and proper management of any serious adverse event (SAE) are required. Close clinical monitoring is essential for all patients receiving this regimen, particularly, liver function tests, given the hepatotoxic potential of prolonged pyrazinamide use. If possible, all patients should be tested each month for aspartate aminotransferase levels (AST or SGOT). If resources are not available to monitor all patients on the Hr-TB regimen, monthly monitoring of patients at high risk, such as patients co-infected with viral hepatitis or with a history of heavy alcohol use, is strongly advised. Additionally, in order to prevent and manage the potential toxic effects of ethambutol in children (e.g. retrobulbar neuritis), it is necessary to adhere to correct doses recommended for paediatric populations. Early signs of ethambutol toxicity can be tested in older children through red-green colour discrimination. Monitoring for retrobulbar neuritis can be sought early when appropriate *(30)*.

Subgroup considerations

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

Patients with extensive disease: Although the IPD analysis did not provide evidence for duration of treatment extension, the prolongation of the 6*(H)REZ-Lfx* to more than six months could be considered on an individual basis for patients with extensive disease, as determined by cavitary disease and persistence of bacteriologically positive sputum at or after month 3 (by culture or microscopy) *(31)*. Prolongation of treatment may increase the risk of adverse events in some cases (See "*Monitoring and Evaluation*" above).

HIV-positive individuals: The effect of longer TB treatment duration among HIV-positive patients with and without antiretroviral therapy (ART) has been studied among patients with drug-susceptible TB *(32)*. In these cases, relapse has been reported to be 2.4 times higher in HIV-infected patients who were not on ART and who received 6 months of treatment as compared to patients in whom treatment was prolonged up to nine months. In patients with drug-susceptible TB initiated on ART, no significant beneficial effect from prolonging rifampicin-containing regimens for over 6 months has been observed *(26)*. In the current analysis, only a limited

number of patients received ART; nonetheless, in TB patients with HIV co-infection, the first priority is to ensure that they are started on ART within 8 weeks of TB treatment initiation (regardless of CD4 count), in accordance with WHO guidelines *(33)*. The 6-month *(H)REZ-Lfx* regimen is therefore recommended in HIV-positive patients.

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

Justification

Treatment with rifampicin, ethambutol and pyrazinamide - with or without isoniazid - has been used in the last few years for the treatment of patients with Hr-TB *(34-36)*. The evidence reviewed for this guideline compared treatment regimens with *(H)REZ* of different durations, i.e. six-month regimens *versus* longer duration. Additionally, the evidence review focused on determining whether treatment outcomes of Hr-TB patients receiving (*H)REZ* treatment regimens of variable duration could be improved with the addition of a fluoroquinolone or with the addition of streptomycin.

The evidence used to determine the composition and duration of regimens relied primarily on an IPD analysis, comprising 33 databases with an analysable population of 5418 Hr-TB patients (See also "*Methods*" above). All data used to develop these recommendations derived from observational studies conducted in various settings (26% in Asia; 33% in Europe; 31% in the Americas; and 6% in Africa) (Annex 4).[19] Patient regimens analysed in the IPD contained rifampicin, ethambutol, pyrazinamide, streptomycin, isoniazid and fluoroquinolones. Thus, recommendations could only be made for regimens containing these anti-TB agents.

Duration of (H)REZ: The analysis comparing *(H)REZ* for 6- and >6-month treatment demonstrated that a 6-month *(H)REZ* regimen had a higher likelihood of treatment success compared with a regimen of >6 months. Further analyses determined that there was no statistically significant difference in treatment outcomes of patients receiving *6REZ* and those receiving >*6REZ* regimens. Since data on intermittent dosing of the 6 months and >6 months *(H)REZ* regimens were not included, no inferences could be drawn about the use of alternating dosing versus daily regimens. The effect of length of pyrazinamide use in the *(H)REZ* regimen was assessed to investigate whether the use of this medicine could be minimised to the shortest possible duration. The reduction in treatment with pyrazinamide to less than 3 months was associated with worse treatment success, even with the addition of streptomycin (aOR, 0.4; 95%CI 0.2-0.7). In 118 patients on fluoroquinolone-containing regimens who received

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

pyrazinamide for less than 4 months the odds of treatment success was higher than in those who received 6(H)REZ, although the difference was not statistically significant.

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

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

Adverse events: Data on adverse events were not evaluated because of lack of standardization (dissimilar reporting). The GDG also considered two reports containing data from patients from the United States in whom a detailed assessment on adverse events indicated that there seemed to be a risk of excess hepatotoxicity with the *6(H)REZ* combination *(37)*. Drug-induced hepatotoxicity is not uncommon with anti-TB drugs. It has also been reported in persons receiving rifampicin and pyrazinamide during two months for LTBI treatment. In such individuals, a much higher occurrence of hepatotoxicity has been observed compared to persons receiving only isoniazid preventive therapy *(38)*. It is unknown whether the risk of hepatotoxicity is different between *6REZ* and *6HREZ*.

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

Addition of streptomycin: the analysis showed that the addition of streptomycin (up to 3 months) to a HREZ regimen with <4 months of pyrazinamide decreased the likelihood of treatment success (aOR, 0.4; 95%CI 0.2-0.7), an effect that may in part be due to confounding. Addition of streptomycin did not reduce mortality significantly (see also Online Annexes 5 and 6). There were no data on the use of other injectable agents (i.e. kanamycin, amikacin, capreomycin) for treatment of Hr-TB.

Treatment outcomes: When analysing the overall treatment outcomes for each one of the regimens assessed for this review, other limitations, related to the characteristics of patients included in these studies, were evident and could not be controlled for (namely, patient selection, allocation to treatment with specific regimens and their relationship with disease severity). Outcomes of patients with cavitary disease, persistence of sputum smear positivity and past history of TB treatment who received ≥*6(H)RE* with an additional three months of pyrazinamide and one to three months of streptomycin appeared to result in worse outcomes when patients received this regimen (see Online **Annex 5**, GRADE table 5-3); however, the limited number of observations made it difficult to draw definitive conclusions based on severity of TB disease or the effect of other comorbidities on this regimen.

In formulating the recommendations, the GDG assessed the overall *balance between benefits and harms* of *(H)REZ-Lfx* regimen, as well as values and preferences, paying special attention to considerations of equity, acceptability and feasibility in addition to clinical outcomes and the potential risks of increasing toxicities (See Online **Annexes 5** and **6** for more details). The conclusions of the GDG were that a regimen composed of 6 months of *REZ* plus fluoroquinolones was associated with higher treatment success rates (with or without the addition of isoniazid). The difference between *6(H)REZ* and longer *>6(H)REZ* duration was modest, slightly favouring the 6-month regimen (not statistically significant). The GDG acknowledged that it was not possible to control for all possible confounding by indication when comparing the 6 months *(H)REZ* to the longer *(H)REZ* duration; as an example, though data on the extent of disease were not systematically captured for all patients, it is possible that a higher number of cases with extensive disease received >6*(H)REZ* regimens, resulting in poor outcomes for this group of patients (given the extent of disease) and possibly favouring the 6-month regimen.

The GDG acknowledged the safety implications of *(H)REZ-Lfx*, particularly for hepatotoxicity associated with prolonged use of pyrazinamide-containing multidrug regimens. However, reducing the duration of the treatment with pyrazinamide to three months or less was associated with worse treatment outcomes, at least in Hr-TB regimens without a fluoroquinolone. Furthermore, the use of streptomycin in these regimens was associated with no significant added benefit. The use of streptomycin and other injectable agents has also been associated with increased SAE *(39-41)*. On this basis, the GDG agreed that current data supported the use of the *(H)REZ-Lfx* regimen without streptomycin or any other injectable agent in Hr-TB cases, unless there is a compelling reasons to do so (e.g. certain forms of polydrug resistance).

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

Although patient costs were not factored in during the analysis, the GDG agreed that improving diagnostic capacity to detect isoniazid resistance would be beneficial. According to a modelling analysis performed for the *WHO guidelines for the programmatic management of drug-resistant tuberculosis (2011 update)*, performing DST in all patients before treatment using a rapid test that detects resistance to isoniazid and rifampicin was the best strategy for averting deaths and preventing acquired MDR-TB *(42)*. The modelling work showed that rapid testing of both isoniazid and rifampicin at the time of diagnosis was the most cost-effective testing strategy for any patient group or setting, even at very low levels of resistance among TB patients (MDR- TB in >1% and isoniazid resistance (other than MDR-TB) in >2%).

In general, the GDG considered that the use of *6(H)REZ-Lfx* regimen would be feasible in most DR-TB treatment settings. In addition, the use of a regimen based on medicines that are fully administered orally may increase feasibility. Altogether, based on present evidence, when discussing the balance between benefits and harms, preferences and values for patients and for other end-users, the GDG reached overall agreement on the beneficial effect that the Hr-TB regimen may have, should the regimen be used in conformity with these policy recommendations.

Research priorities

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

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

- The need for randomized trials evaluating the efficacy, safety and tolerability of regimens for Hr-TB, and for cases with additional resistance to other medicines such as ethambutol or pyrazinamide (e.g. polydrug resistance);
- Research to clarify the potential benefits and risks of treatment with high-dose isoniazid;
- High-quality studies on the optimization of the regimen composition (e.g. reducing duration of pyrazinamide) and duration in children and adults, particularly the role of high-dose isoniazid, fluoroquinolones, and other second-line medicines;
- Modelling studies measuring the *number-needed-to-treat* for empirical use of an Hr-TB regimen, balancing risk to benefit;
- High-quality studies on treatment prolongation among HIV-positive individuals;

- High-quality studies evaluating regimens in which especial emphasis is placed on extrapulmonary or disseminated TB;
- Feasibility of developing FDCs for REZ alone (with or without integrating levofloxacin);
- Monitoring of patient response, by isoniazid resistance genotype (e.g. *katG* vs. *inhA* mutations), either in an individual-patient or distribution of genotypes in a population;
- Cost-effectiveness of different approaches to DST, including the rapid testing of all TB patients for both isoniazid and rifampicin resistance before start of treatment;
- Participatory action research within communities and other stakeholders (e.g. field practitioners, community workers) to explore and implement socio-cultural factors that can facilitate treatment adherence and influence outcomes;
- Effect of underlying fluoroquinolones/isoniazid polydrug resistance on treatment outcomes;
- Diagnostic accuracy of second-line line probe assays in rifampicin-sensitive patients.

Publication, dissemination, implementation, evaluation and expiry

The recommendations contained in this policy guideline are published as a supplement to the 2016 WHO treatment guidelines for DR-TB *(4)*, and made accessible on the WHO website (http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/en/). "Frequently asked questions on the WHO treatment guidelines for isoniazid-resistant tuberculosis" are being released concurrently with the guidelines on the same website. The changes to the policy guideline will also be reflected in the *Compendium of WHO guidelines and associated standards: ensuring optimum delivery of the cascade of care for patients with tuberculosis (44)* and, in a forthcoming, revision of the *Companion Handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis (7)*. The evidence reviews on Hr-TB as well as the specific recommendations for its management will be published in peer-reviewed journals and shared with key TB stakeholders and partners through various list serves to improve dissemination of the main messages.

WHO will work closely with its Regional and Country Offices, as well as with technical and funding agencies and partners, to ensure wide dissemination and translation of these recommendations through technical meetings and training activities. Implementation and impact of these guidelines will be assessed and monitored through the annual WHO *Global TB Surveillance & Monitoring System* as well as through technical assistance missions and National TB Programme Reviews.

WHO/GTB will review and update these policy recommendations within 4-5 years after their release, or earlier if new evidence becomes available.

References

1 Global tuberculosis report 2017 [WHO/HTM/TB/2017.23] Available from: http://apps.who.int/iris/bitstream/10665/259366/1/9789241565516-eng.pdf?ua=1 World Health Organization: Geneva. 2017.

2 WHO handbook for guideline development – 2nd ed. Available from: http://apps.who.int/iris/bitstream/10665/145714/1/9789241548960_eng.pdf. World Health Organization: Geneva. 2014.

3 Schünemann H, Brożek J, Gordon Guyatt G, Andrew Oxman A. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach [Internet]. 2013 [Updated October 2013] Available from: https://gdt.gradepro.org/app/handbook/handbook.html. 2013.

4 WHO treatment guidelines for drug-resistant tuberculosis, 2016 update. October 2016 revision [WHO/HTM/TB/2016.04]. Available from: http://apps.who.int/iris/bitstream/10665/250125/1/9789241549639-eng.pdf. World Health Organization: Geneva. 2016.

5 Guidelines for the programmatic management of drug-resistant tuberculosis [WHO/HTM/TB/2006.361]. Available from: http://apps.who.int/iris/bitstream/10665/246249/2/9789241546959-eng.pdf. World Health Organization: Geneva. 2006.

6 Guidelines for the programmatic management of drug-resistant tuberculosis - Emergency update [WHO/HTM/TB/2008.402]. Available from: http://apps.who.int/iris/bitstream/10665/43965/1/9789241547581_eng.pdf. World Health Organization: Geneva. 2008.

7 Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis [WHO/HTM/TB/2014.11]. Available from: http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf. World Health Organization: Geneva. 2014.

8 Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children [WHO/HTM/TB/2013.16]. Available from: http://apps.who.int/iris/bitstream/10665/112472/1/9789241506335_eng.pdf?ua=1. World Health Organization: Geneva. 2013.

9 The use of molecular line probe assays for the detection of resistance to isoniazid and rifampicin [WHO/HTM/TB/2016.12]. Available from: http://apps.who.int/iris/bitstream/10665/250586/1/9789241511261-eng.pdf?ua=1. World Health Organization: Geneva. 2016.

10 Bollela VR, Namburete EI, Feliciano CS, Macheque D, Harrison LH, Caminero J. Detection of katG and inhA mutations to guide isoniazid and ethionamide use for drug-resistant tuberculosis. The International Journal of Tuberculosis and Lung Disease. 2016;20(8):1099-1104.

11 Gegia M, Winters N, Benedetti A, van Soolingen D, Menzies D. Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis. The Lancet Infectious Diseases. 2017;17(2):223-234.

12 Jawahar MS, Banurekha VV, Paramasivan CN, Rahman F, Ramachandran R, Venkatesan P et al. Randomized clinical trial of thrice-weekly 4-month moxifloxacin or gatifloxacin containing regimens in the treatment of new sputum positive pulmonary tuberculosis patients. PLoS One. 2013;8(7):e67030.

13 Merle CS, Fielding K, Sow OB, Gninafon M, Lo MB, Mthiyane T et al. A four-month gatifloxacin-containing regimen for treating tuberculosis. New England Journal of Medicine. 2014;371(17):1588-1598.

14 Gillespie SH, Crook AM, McHugh TD, Mendel CM, Meredith SK, Murray SR et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. New England Journal of Medicine. 2014;371(17):1577-1587.

15 Fox GJ, Benedetti A, Mitnick CD, Pai M, Menzies D, Collaborative Group for Meta-Analysis of Individual Patient Data in M-T. Propensity Score-Based Approaches to Confounding by Indication in Individual Patient Data Meta-Analysis: Non-Standardized Treatment for Multidrug Resistant Tuberculosis. PLoS One. 2016;11(3):e0151724 (https://www.ncbi.nlm.nih.gov/pubmed/27022741, accessed.

16 The Cochrane collaboration. Cochrane handbook for systematic reviews of interventions Version 5.1.0. [updated March 2011]. Available from: http://handbook-5-1.cochrane.org/. John Wiley & Sons. 2011.

17 Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A et al. Rating quality of evidence and strength of recommendations: Going from evidence to recommendations. BMJ: British Medical Journal. 2008;336(7652):1049.

18 Tugwell P, Knottnerus JA. Advantages of individual patient data analysis in systematic reviews. Journal of clinical epidemiology. 2010;63(3):233-234.

19 Stewart LA, Tierney JF, Clarke M. Reviews of individual patient data. In: Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series 2008 Sep 22. John Wiley & Sons, Ltd, Chichester, UK, John Wiley & Sons, Ltd, Chichester, UK. 2008.
20 Zignol M, Dean AS, Alikhanova N, Andres S, Cabibbe AM, Cirillo DM et al. Population-based resistance of Mycobacterium tuberculosis isolates to pyrazinamide and fluoroquinolones: results from a multicountry surveillance project. The Lancet Infectious Diseases. 2016;16(10):1185-1192.
21 The use of molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs: policy guidance [WHO/HTM/TB/2016.07]. Available from: http://apps.who.int/iris/bitstream/10665/246131/1/9789241510561-eng.pdf?ua=1. World Health Organization: Geneva. 2016.
22 Ramachandran G, Kumar AH, Srinivasan R, Geetharani A, Sugirda P, Nandhakumar B et al. Effect of rifampicin & isoniazid on the steady state pharmacokinetics of moxifloxacin. The Indian journal of medical research. 2012;136(6):979.
23 Fish DN, Chow AT. The clinical pharmacokinetics of levofloxacin. Clin Pharmacokinet. 1997;32(2):101-119 (https://www.ncbi.nlm.nih.gov/pubmed/9068926, accessed.
24 University of Liverpool. HIV drug interaction checker [Updated December 2017]. Available from: https://www.hiv-druginteractions.org/checker.
25 Lempens P, Meehan CJ, Vandelannoote K, Fissette K, de Rijk P, Van Deun A et al. Isoniazid resistance levels of Mycobacterium tuberculosis can largely be predicted by high-confidence resistance-conferring mutations. Scientific Reports. 2018;8(1):3246.
26 Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update [WHO/HTM/TB/2017.05]. Available from: http://apps.who.int/iris/bitstream/10665/255052/1/9789241550000-eng.pdf?ua=1. World Health Organization: Geneva. 2017.
27 Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A et al. Official American Thoracic Society/centers for disease control and prevention/infectious diseases society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. Clinical Infectious Diseases. 2016;63(7):e147-e195.
28 Global Drug Facility (GDF) catalogueProducts List. Available from: http://www.stoptb.org/gdf/drugsupply/drugs_available.asp. Stop TB Partnership: Geneva.
29 Definitions and reporting framework for tuberculosis – 2013 revision (updated December 2014) [WHO/HTM/TB/2013.2]. Available from: http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf. . World Health Organization: Geneva. 2013.
30 Guidance for national tuberculosis programmes on the management of tuberculosis in children [WHO/HTM/TB/2014.03]. Available from: http://apps.who.int/iris/bitstream/10665/112360/1/9789241548748_eng.pdf?ua=1. Geneva: World Health Organization. 2014.
31 Blumberg H, Burman WJ, Chaisson RE, Daley CL, Etkind SC, Friedman LN et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. American journal of respiratory and critical care medicine. 2003;167(4):603.
32 Ahmad Khan F, Minion J, Al-Motairi A, Benedetti A, Harries AD, Menzies D. An updated systematic review and meta-analysis on the treatment of active tuberculosis in patients with HIV infection. Clinical Infectious Diseases. 2012;55(8):1154-1163.
33 Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach, 2nd ed. Available from: http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf?ua=1. World Health Organization: Geneva. 2016.
34 Escalante P, Graviss EA, Griffith DE, Musser JM, Awe RJ. Treatment of isoniazid-resistant tuberculosis in southeastern Texas. CHEST Journal. 2001;119(6):1730-1736.
35 Nolan C, Goldberg S. Treatment of isoniazid-resistant tuberculosis with isoniazid, rifampin, ethambutol, and pyrazinamide for 6 months. The International Journal of Tuberculosis and Lung Disease. 2002;6(11):952-958.
36 Kim YH, Suh GY, Chung MP, Kim H, Kwon OJ, Lim SY et al. Treatment of isoniazid-resistant pulmonary tuberculosis. BMC infectious diseases. 2008;8(1):6.
37 Andrade RJ, Tulkens PM. Hepatic safety of antibiotics used in primary care. Journal of Antimicrobial Chemotherapy. 2011;66(7):1431-1446.
38 Centers for Disease Control and Prevention (Atlanta). Update: Fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC recommendations--United States, 2001. MMWR. Morbidity and mortality weekly report. 2001;50(34):733.
39 Voogt G, Schoeman H. Ototoxicity of aminoglycoside drugs in tuberculosis treatment. The South African journal of communication disorders= Die Suid-Afrikaanse tydskrif vir Kommunikasieafwykings. 1996;43:3-6.

40 Gülbay BE, Gürkan ÖU, Yıldız ÖA, Önen ZP, Erkekol FÖ, Baççıoğlu A et al. Side effects due to primary antituberculosis drugs during the initial phase of therapy in 1149 hospitalized patients for tuberculosis. Respiratory medicine. 2006;100(10):1834-1842.

41 Bloss E, Kukša L, Holtz T, Riekstina V, Skripčonoka V, Kammerer S et al. Adverse events related to multidrug-resistant tuberculosis treatment, Latvia, 2000–2004. The International Journal of Tuberculosis and Lung Disease. 2010;14(3):275-281.

42 Oxlade O, Falzon D, Menzies D. The impact and cost-effectiveness of strategies to detect drug-resistant tuberculosis. European Respiratory Journal. 2012;39(3):626-634.

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

44 Compendium of WHO guidelines and associated standards: ensuring optimum delivery of the cascade of care for patients with tuberculosis [WHO/HTM/TB/2017.13]. Available from: http://apps.who.int/iris/bitstream/10665/259180/1/9789241512572-eng.pdf. World Health Organization: Geneva. 2017.

Annexes

Annex 1. Agenda of the Guideline Development Group meeting

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	Finalisation of draft recommendations and accompanying remarks	Facilitated discussion
17:45 – 18:00	Conclusion	Co-chairs

Annex 2. Participants at the Guideline Development Group meeting

Guideline Development Group members

1. **Dr AMANULLAH, Farhana**
   Consultant Paediatrician
   Director Paediatric TB Program
   The Indus Hospital, Korangi Crossing,
   Karachi
   PAKISTAN

2. **Dr CHAKHAIA, Tsira (via webinar)**
   ACSM Advisor, Civil Society Georgia
   USAID Georgia TB Prevention Project
   University Research Co., LLC
   57 Shartava Street
   0178 – Tbilisi
   GEORGIA

3. **Dr CIRILLO, Daniela Maria**
   Head
   Emerging Bacterial Pathogens Unit
   Fondazione Centro San Raffaele
   Via Olgettina, 60
   20132 – Milano
   ITALY

4. **Dr DOOLEY, Kelly (Co-chair)**
   Associate Professor of Medicine
   Pharmacology & Molecular Science
   Divisions of Clinical Pharmacology &
   Infectious Diseases
   Johns Hopkins University School of
   Medicine, Center for Tuberculosis Research
   600 N. Wolfe Street, Osler 527
   21287 - Baltimore, MD
   UNITED STATES

5. **Dr DO VALLE BASTOS, Luis Gustavo**
   Capacity Building Team Leader
   Stop TB Partnership's Global Drug
   Facility (GDF)
   Chemin de Blandonnet 2
   1214 – Geneva
   SWITZERLAND

6. **Dr DU CROS, Philipp**
   Research Advisor
   Médecins Sans Frontières
   67-74 Saffron Hill
   EC1N 8QX – London
   UNITED KINGDOM

7. **Prof DUARTE, Raquel**
   TB consultant
   National HIV/AIDS/TB Programme
   Hospital Centre of Vila Nova de
   Gaia/Espinho,
   Medical School, Porto University
   Institute of Public Health, Porto University
   Porto
   PORTUGAL

8. **Professor KUABAN, Christopher**
   Dean, Faculty of Health Sciences
   University of Bamenda, Cameroon
   Bamenda, North West Region
   CAMEROON

9. **Dr LANIADO-LABORIN, Rafael**
   Head, TB Clinic, Hospital
   General de Tijuana
   Instituto Estatal de Salud de Baja California
   Tijuana
   MEXICO

10. **Professor MAARTENS, Gary**
    Faculty of Health Sciences
    Division of Clinical Pharmacology
    Department of Medicine
    University of Cape Town
    7925 - Observatory
    SOUTH AFRICA

11. **Professor MARYANDYSHEV, Andrei**
    Head of Phthisiopulmonary Department
    Northern State Medical University
    Troitsky 51, 163061 - Arkhangelsk
    RUSSIAN FEDERATION

12. **Dr MONEDERO-RECUERO, Ignacio**
    MDR-TB and TB-HIV Consultant
    International Union of TB and Lung
    Disease (The Union)
    68, boulevard Saint-Michel
    F-75006 Paris
    FRANCE

13. **Dr QUELAPIO, Maria Imelda Josefa**
Senior Consultant
KNCV TB Foundation
P.O. Box 146
Van Bylandt Huis
Benoordenhoutsweg 46
2596 BC – The Hague
NETHERLANDS

14. **Dr REECHAIPITKUL, Wipa**
Professor
Department of Medicine
Faculty of Medicine
Khon Kaen University
123 Mittraparb Rd., A. Muang
40002 - Khon Kaen
THAILAND

15. **Dr RICH, Michael**
Global Health Physician
Partners in Health
Harvard Medical School
641 Huntington Avenue
02115 - Boston, MA
UNITED STATES

16. **Dr SANTESSO, Nancy (Co-chair)**
Assistant Professor
Department of Health Research Methods, Evidence, and Impact
Deputy Director, Cochrane Canada
Health Sciences Centre, Rm 2C, McMaster University
1280 Main Street West
Hamilton ON L8S 4L8
CANADA

17. **Dr SAVIC, Rada**
Associate Professor
Department of Bioengineering and Therapeutic Sciences
Division of Pulmonary and Critical Care Medicine
Schools of Pharmacy and Medicine
University of California San Francisco
1700 4th Street, Box 2552
San Francisco, CA 94158
UNITED STATES

18. **Dr SIKHONDZE, Welile**
National Tuberculosis Control Programme
Advisor and Research Coordinator
Mbabane
SWAZILAND

19. **Dr VAN DEUN, Armand**
Bacteriology Consultant
Department of Biomedical Sciences
Mycobacteriology Unit
Prince Leopold Institute of Tropical Medicine
Nationalestraat 155
B-2000 – Antwerpen
BELGIUM

Observers

20. **Professor MIGLIORI, Giovanni Battista**
Director, WHO Collaborating Centre for TB and Lung Diseases
Fondazione S. Maugeri, Care and Research Institute
21049 - Tradate
ITALY

21. **Dr MUKADI, Ya Diul**
Medical Officer
Tuberculosis Division/Infectious Disease Office
Global Health Bureau
USAID – CP3 #10094A
1300 Pennsylvania Avenue NW
Washington, DC 20523
UNITED STATES

22. **Dr NAHID, Payam**
Professor of Medicine
Division of Pulmonary and Critical Care Medicine
University of California
San Francisco General Hospital
1001 Potrero Ave, 5K1
94110 – San Francisco CA
UNITED STATES

23. **Dr RODWELL, Timothy**
Foundation for Innovative New Diagnostics (FIND)
Avenue de Budé 16
1202 - Geneva
SWITZERLAND

24. **Dr YASSIN, Mohammed**
Senior Advisor
The Global Fund
Chemin de Blandonnet 8
1214 Vernier – Geneva
SWITZERLAND

Evidence Reviewers

25. **Dr MENZIES, Dick**
    Director, Respiratory Division
    MUHC and McGill University,
    Room K1.24
    Montréal Chest Institute
    3650 St. Urbain
    H2X 2P4 – Montréal, PQ
    CANADA

26. **Dr FREGONESE, Federica**
    McGill University Health Centre
    Montréal, Quebec,
    CANADA

WHO/HQ Secretariat

27. **Dr WEYER, Karin**, Coordinator, HQ/HTM/GTB/LDR
28. **Dr FALZON, Dennis**, Medical Officer, HQ/HTM/GTB/LDR
29. **Mr GAO Xu,** Intern, HQ/HTM/GTB/RTE
30. **Mr van GEMERT, Wayne,** Technical Officer, HQ/HTM/GTB/LDR
31. **Dr GILPIN, Christopher,** Scientist, HQ/HTM/GTB/LDR
32. **Ms GONZÁLEZ-ANGULO, Licé**, Technical Officer, HQ/HTM/GTB/RTE
33. **Dr JARAMILLO, Ernesto,** Medical Officer, HQ/HTM/GTB/LDR
34. **Dr KOROBITSYN, Alexei**, Technical Officer, HQ/HTM/GTB/LDR
35. **Dr MIRYAZEV, Fuad,** Medical Officer, HQ/HTM/GTB/LDR
36. **Dr OLLIARO, Piero**, Unit Leader, Intervention Research, HQ/HTM/TDR/IIR
37. **Dr ZIGNOL, Matteo**, Scientist, HQ/HTM/GTB/TME

Annex 3. PICO question

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

<table>
<tr><th>Population</th><th>Intervention[1]</th><th>Comparator[1]</th><th>Outcomes</th></tr>
<tr><td rowspan="4">Isoniazid-resistant TB cases:
with/out katG mutation and use of normal dose /high-dose isoniazid;
with/out inhA promoter mutation and use of normal dose /high-dose isoniazid;
in whom ethambutol, pyrazinamide or injectable agents are unlikely to work;
previously treated for TB;
with extensive disease;
with HIV;
with HIV on antiretroviral therapy;
children (0-14y); and
with diabetes.</td><td>6REZ</td><td>>6REZ</td><td rowspan="4">• Treatment completed or bacteriological cure by end of treatment;
• Treatment Failure +/- relapse;
• Survival (or death);
• Adverse reactions from anti-TB medicines (severity, type, organ class); and
• Acquisition (amplification) of drug resistance.</td></tr>
<tr><td>6+RE + 2Z + fluoroquinolone</td><td>6+REZ</td></tr>
<tr><td>6+REZ + fluoroquinolone</td><td>6+REZ</td></tr>
<tr><td>6+REZ + injectable agent</td><td>6+REZ</td></tr>
</table>

[1] E=ethambutol; H=isoniazid; R=rifampicin; Z=pyrazinamide

Analysis of Individual-patient Data of Patients on treatment for isoniazid-resistant tuberculosis

- UNDER REVIEW FOR PUBLICATION -

Authors of summary report: Federica Fregonese and Dick Menzies, on behalf of the IPD in INHR Group.

Members of the IPD in INHR Group: Ahuja S, Akkerman OW, Baghaei P, Bang D, BanuRekha VV, Bastos M, Benedetti A, Bonnet M, Cattamanchi A, Cegielski P, Chien J-Y, Cox H, Dedicoat M, Elliott A, Erkens C, Escalante P, Falzon D, Fregonese F, Garcia-Prats A, Gegia MCT, Glynn JR, Goldberg S, Hesseling A, Huyen MNC, Jacobson KR, Johnston J, Jones-Lopez E, Khan A, Kim YHS, Koh W, Kritski A, Lan Z, Lee H, Lee JH, Levin J, Li PZ, Maciel EL, Menzies D, Merle CSC, Munang M, Nahid P, Narendran G, Ohkado AA, Park JS, Phillips PPJ, Ponnuraja C, Quy H, Romanowski K, Schaaf S, Seaworth B, Seung KJ, Skrahina A, Sundari M, Swaminathan S, Tabarsi P, Trajman A, Trieu L, Viet Nhung N, Vikklepp P, Wang J-Y, Yoshiyama T.

Background and rationale: One of the major challenges impeding global tuberculosis (TB) control is drug-resistant TB (DR-TB). The World Health Organization (WHO) has estimated that approximately 10% of all TB cases have isoniazid-resistant TB without resistance to rifampicin (Hr-TB) *(1)*. The impact of Hr-TB on treatment outcomes is not as serious as MDR-TB but combined failure and relapse in randomized trials of first-line therapy are around 12-13%. In a recent systematic review *(2)*, failure and relapses were significantly higher in patients with Hr-TB than with drug-susceptible TB. Building upon this systematic review, and the experience that the McGill group acquired with the individual-patient data (IPD) analysis for MDR-TB treatment *(3)*, we realised an IPD meta-analysis for treatment outcome of patients with Hr-TB in whom resistance to rifampicin had been excluded.

Methods: The Hr-TB treatment IPD was used to inform the WHO treatment policy for the treatment of this form of TB.[1] Ahead of the WHO Guideline Development Group discussions on Hr-TB treatment, the expert panel involved developed a series of PICO[2] questions to guide the evidence review (Annex 3). The outcomes of interest were: 1) Cured or completed ("success") by end of treatment; 2) Failure and/or relapse; 3) Death from any cause during treatment; 4) Adverse reactions from anti-TB medicines (severity, type, organ class); and 5) Acquisition (amplification) of drug resistance for rifampicin. Relapse was defined as any recurrence of disease within two years after successful treatment completion. Studies of Hr-TB treatment were primarily identified from the 2016 systematic review *(2)*. The search was done using PubMed,

[1] [Public notice - Guideline Development Group (GDG) meeting - 27 April 2017] WHO treatment guidelines for isoniazid-resistant tuberculosis. Available at: http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/gdg-meeting-izoniazid-resistant-tb/en/

[2] PICO is an acronym for **P**opulation, **I**ntervention, **C**omparator, **O**utcome.

with no language restrictions, looking for publications since 1994 which reported treatment outcomes in patients with Hr-TB, either cohorts (with at least 20 Hr-TB subjects) or RCT. The review was updated until February 2016. Authors were invited to submit a set of standardized variables for patient-level data.

Outcomes were compared in patients on regimens grouped by the major elements of their composition (isoniazid [H], rifampicin [R], ethambutol [E], pyrazinamide [Z], fluoroquinolone [FQ], streptomycin [S]) and duration (6 months or >6 months). Relapse was combined with treatment failure for all analyses and "success" was compared with this composite outcome. Death was reported in all studies, but could not be analysed as a function of regimen length because in many studies treatment was individualized and thus the impact of death on its duration could not be reliably calculated from the information available. Mortality and success analysis were done in different populations, as deaths and loss to follow-up were removed from the population utilised in success analysis. The "actual" duration of treatment was used whenever this was reported by the authors; otherwise the "planned" duration was used. Pooled analysis of adverse events was not done owing to the different ways in which this was recorded in the datasets.

We used propensity score matching (caliper method with difference of 0.02 allowed, with replacement) to estimate the adjusted odds ratios of outcome and their 95% confidence intervals. Patients were considered clustered within studies; hence intercepts and slopes of the main exposure variables were allowed to vary across studies. This is to account for otherwise unmeasured inter-study differences in patient populations, as well as centre-specific differences in data ascertainment, measurement and other factors. This analysis method provides very good matching of covariates. Risk differences were calculated with fixed effects generalized linear mixed effects models. Results were summarised in GRADE tables (see Online Annex 5).

Estimates of effect of each treatment parameter for each dataset were adjusted for the following covariates: age, gender, HIV co-infection, AFB smear positivity, cavitation on chest identified in radiography, past history of TB treatment and resistance to other first-line medicines beside isoniazid (if drug is used).

All analysis was performed using SAS, version 9.4 (SAS Institute, Cary, N.C.).

This project was approved by the Research Ethics Board of the Montréal Chest Institute, McGill University Health Centre, and also (if deemed necessary) by local ethics boards of originally approved studies.

Results: Data on 5537 patients from 33 databases were combined and 5418 patients with adequate information were included in the analysis (Figure a; Table a).

Only 2% were children (0-14 years); a specific analysis on children was therefore not possible. Study characteristics are summarised in Table 3.

PICO 1: 6(H)REZ vs >6(H)REZ

6REZ was associated with a marginally statistically significant higher likelihood of treatment success when compared with 7-9 months of REZ (the effect was no longer statistically significant when a single large study was excluded). No added benefit from adding H to the regimen could be shown. Duration was not associated with a statistically significant difference in the acquisition of rifampicin resistance in Hr-TB patients.

PICO 2: 6 months or more (H)RE plus <4 months Z plus FQ vs 6 months or more (H)REZ

Use of FQ was associated with higher odds of treatment success when Z was given for less than 4 months, although not significant: a small number of patients received this regimen (*n*=118; 105 of whom received levofloxacin, moxifloxacin or gatifloxacin) and the comparator group also had a high level of success (crude success rates were 99% in FQ group and 93% in comparator group) (*Data not shown in GRADE tables*).

PICO 3: 6 months or more (H)REZ plus FQ vs 6 months or more (H)REZ

The addition of FQ to 6 months or more of (H)REZ is moderately associated with an improvement in success rates (97.6% vs 92.8%; aOR=2.8 95%CI 1.1-7.3), an effect which remains statistically significant even in the absence of H. Given the high success rate of the comparator regimen, it was unclear if FQ added benefit when Z was given for the full duration (See also PICO 2 above). Use of FQ was associated with lower odds of dying (in patients without H) and of acquired resistance to rifampicin.

PICO 4: 6 months or more (H)RE plus <4 months Z plus 3 months S vs 6 months or more (H)REZ

Treatment with 3 months or less of Z was consistently associated with worse outcomes, even when S was added. The WHO retreatment regimen ("Category 2"; 2SHREZ/1HREZ/5HRE) had significantly and substantially worse treatment success compared to 6REZ (83.4% vs 92.8%; aOR=0.4 95%CI 0.2-0.7). The odds of dying were lower for patients on S-containing regimens, although this effect was not statistically significant when the analysis was restricted to the studies included for the analysis of treatment success. Stratified analysis did not show differences in the odds of dying by S resistance, regardless of the inclusion of S in the regimens.

Conclusions: In summary, it appears that 6 REZ can result in high levels of treatment success in Hr-TB patients. The addition of FQ to these regimens appears to lower the risk of death and acquisition of rifampicin resistance; it may increase the likelihood of success even when Z is used for <4 months, which could thus reduce the risk of hepatotoxicity associated with this medicine. In contrast, the use of S was not associated with improved outcomes. The data could not identify which patient subgroups (e.g. extensive disease, polydrug resistance) could benefit most from prolonging the treatment beyond 6 months or by adding H or FQ or S to REZ.

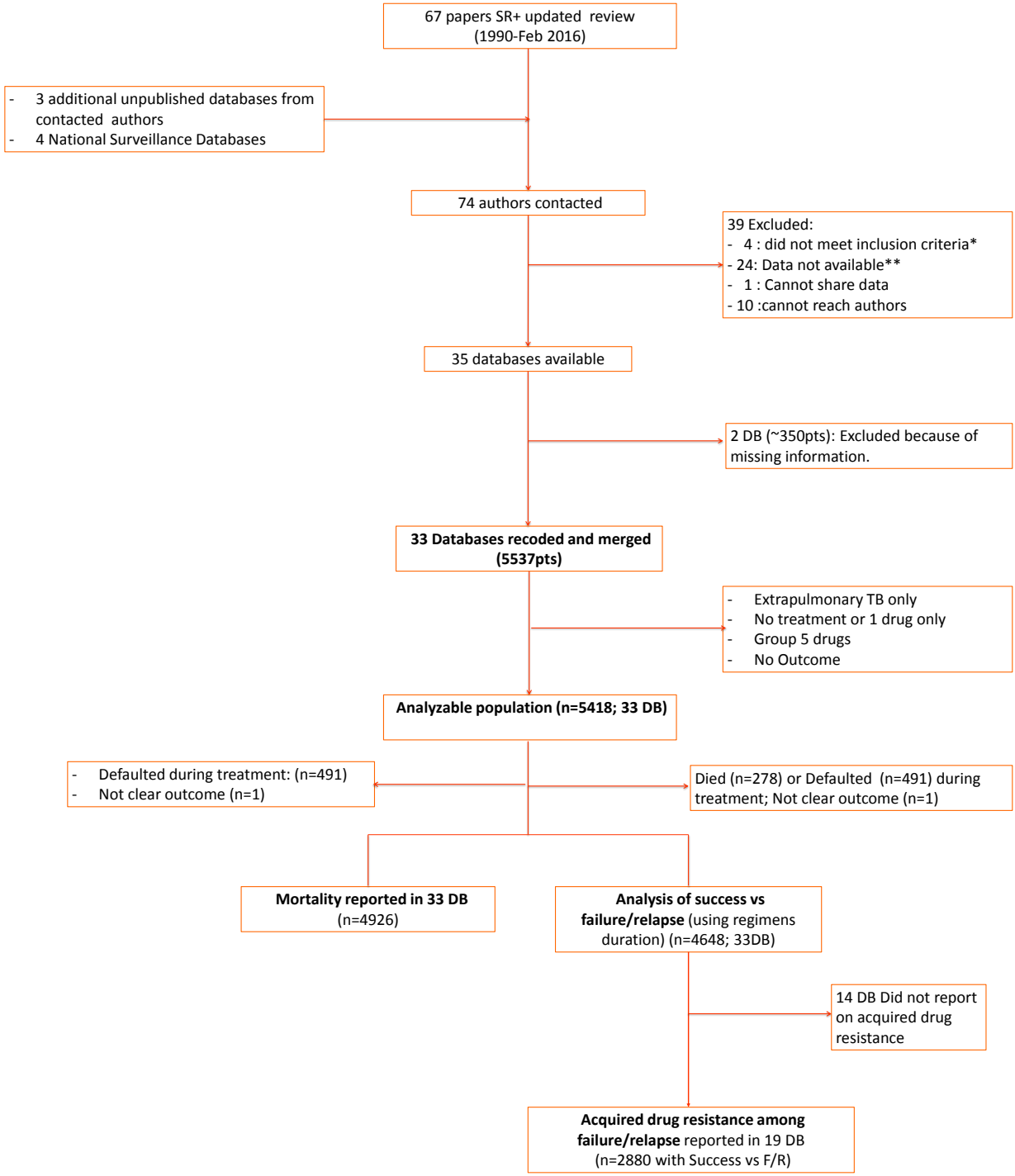
References

1) Global tuberculosis report 2014 (WHO/HTM/TB/2014.08). Geneva, World Health Organization. 2014. Available from: http://www.who.int/tb/publications/global_report/gtbr14_main_text.pdf

2) Gegia M, Winters N, Benedetti A et al. Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis. Lancet Infect Dis. 2017 Feb;17(2):223-234. doi: 10.1016/S1473-3099(16)30407-8.

3) Ahuja SD, *et al* for the Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012;9(8):e1001300

Figure a. Study selection flowchart



Notes.—* No treatment information; or sample size <20 patients. ** Data unavailable as studies done in the 1990s, authors have changed institutions; data inaccessible (damaged in storage etc).

Table a. Analysable data in included databases

First author	Setting	Years	Type of regimen	Type of regimen duration used in analysis	Number of patients		
					All	Analyzable for treatment success outcome	Analyzable for mortality outcome
Bang	Denmark	2002-2007	Individualized	Actual	75	66	68
Bonnet	Georgia	2003-2013	Individualized	Actual	59	48	50
Brazilian NTB	Brazil	2012-2014	Standardized	Actual	187	151	158
Cattamanchi	US-California	1992-2005	Standardized	Actual	119	47	110
CDC S24	US and Canada	1999-2004	Standardized	Actual	60	108	47
Cegielski	US-Texas	1984-2007	Individualized	Actual	43	35	38
Chien (Wang)	Taiwan	2004-2012	Individualized	Actual	380	336	380
Cox	Uzbekistan	2001-2002	Standardized	Planned	56	45	47
Escalante	US-Texas	1990-1997	Individualized	Actual	51	48	49
Estonia National TB	Estonia	2008-2015	Individualized	Actual	108	89	100
Garcia-Prats, Hesseling and Schaaf	South Africa	2006-2012	Individualized	Actual	51	48	48
Gegia	Georgia	2007-2009	Standardized	Planned	864	686	716
Glynn	Malawi	1983-2015	Standardized	Actual	138	104	126
Huyen (Cobelens)	Vietnam	2005-2007	Standardized	Planned	204	191	201
Jacobson	South Africa	2001-2009	Individualized	Actual	59	45	45
Johston	Canada-BC	2002-2014	Individualized	Actual	143	119	124
Jones-Lopez	Uganda	2005	Standardized	Planned	34	26	32
Kim (Koh)	Korea	2003	Standardized	Planned	39	39	39
Lee (Koh)	Korea	2008	Standardized	Actual	140	140	140
Munang	UK	1999-2010	Individualized	Actual	46	40	40
Netherland TB	Netherlands	1993-2015	Individualized	Actual/planned	551	474	490
NITR-XXA	India	2004-2006	Standardized	Planned	25	21	23
NITR-XXII	India	2004-2006	Standardized	Planned	30	30	30
NITR-XXIII	India	2006-2008	Standardized	Planned	5	4	5
NYC TB	US-NYC	1994-2014	Individualized	Actual	1123	976	1062
OFLOTUB	Africa (Multicountry)	2007	Standardized	Planned	68	66	67
Ohkado	Philippines	2000	Standardized	Actual	33	29	30
Park (Lee)	Korea	2005-2013	Individualized	Actual	17	16	16
Quy (Cobelens)	Vietnam	1998-2000	Standardized	Planned	419	379	393
REMOX	Multicountry	2013	Standardized	Planned	127	121	122
Skrahina	Belarus	2012-2016	Individualized	Actual	21	17	18
Tabarsi&Baghaei	Iran	2003-2015	Individualized	Actual	123	88	95
Yoshiyama	Nepal	2003-2005	Standardized	Planned	20	17	17


9 789241 550079