Guidelines for the programmatic management of drug-resistant tuberculosis

2011 update

World Health Organization

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Contents

Abbreviations

ART	antiretroviral therapy
DALY	disability-adjusted life year
CDC	United States Centers for Disease Control and Prevention
DR-TB	drug-resistant tuberculosis
DST	drug susceptibility testing
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	human immunodeficiency virus
MDR-TB	multidrug-resistant tuberculosis
NTP	national tuberculosis control programme
PMDT	programmatic management of drug-resistant tuberculosis
SAE	serious adverse event
TB	tuberculosis
UNION	International Union Against Tuberculosis and Lung Disease
USAID	United States Agency for International Development
WHA	World Health Assembly
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

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Guideline Development Group (area of expertise shown in parentheses)

Jaime Bayona, Socios En Salud Sucursal, Peru (programme management, public health)

José A. Caminero, University General Hospital of Gran Canaria, Spain and The UNION, Paris, France (clinical practice)

Charles L. Daley, National Jewish Health, United States (clinical practice)

Agnes Gebhard, KNCV Tuberculosis Foundation, Netherlands (programme management)

Myriam Henkens, Médecins Sans Frontières, France (programme management)

Timothy H. Holtz, HIV/STD Research Program, United States Centers for Disease Control and Prevention–CDC, Asia Regional Office, Thailand (epidemiology, surveillance, programme evaluation)

Joël Keravec, Management Sciences for Health, Brazil (drug management)

Salmaan Keshavjee, Harvard Medical School, United States (programme management, public health)

Aamir J. Khan, Indus Hospital TB Program, Pakistan (epidemiology, programme management)

Vaira Leimane, State Infectology Center, Clinic of Tuberculosis and Lung Diseases, Latvia (programme management, clinical practice)

Andrey Mariandyshev, Northern State Medical University, Archangelsk, Russian Federation (clinical practice)

Carole D. Mitnick, Harvard Medical School, United States (epidemiology, programme support)

Gloria Nwagboniwe, Alliance for Hope, Nigeria (civil society)

Domingo Palmero, Pulmonology Division, Hospital Muñiz, Argentina (clinical practice)

Ma. Imelda Quelapio, Tropical Disease Foundation, Philippines (programme management)

Michael L. Rich, Partners In Health, United States (clinical practice)

Sarah Royce, PATH, United States (surveillance, public health)

Sabine Rüsch-Gerdes, National Reference Centre for Mycobacteria, Germany (laboratory specialist)

Archil Salakaia, Management Sciences for Health, United States (programme management)

Rohit Sarin, LRS Institute of TB and Allied Diseases, India (clinical practice)

Holger Schünemann, McMaster University, Canada (Chairman of the Guideline Development Group; epidemiology, guideline methodology)

Elena Skachkova, Federal Centre of TB Monitoring, Russian Federation (surveillance)

Francis Varaine, Médecins Sans Frontières, France (clinical and programme management)

WHO headquarters, Geneva, Switzerland (members of the Guideline Development Group shown in italics)

Stop TB Department: Léopold Blanc, *Dennis Falzon*[a], Christopher Fitzpatrick, Katherine Floyd, *Haileyesus Getahun*[a], Malgorzata Grzemska[a], Christian Gunneberg[a], *Ernesto Jaramillo*[a], *Christian Lienhardt*, *Fuad Mirzayev*, Paul Nunn, Mario C. Raviglione, *Delphine Sculier*[a], *Fraser Wares*, *Karin Weyer*, *Matteo Zignol*[a]

HIV Department: *Chris Duncombe, Marco Antonio de Avila Vitoria*[a]

[a] Member of the WHO Guideline Steering Group.

External Review Group (area of expertise shown in parentheses for non-WHO staff)

Samiha Baghdadi, WHO Regional Office for the Eastern Mediterranean, Egypt

Mercedes Becerra, Harvard Medical School, United States (academia)

Vineet Bhatia, WHO Regional Office for South-East Asia, India

Masoud Dara, WHO Regional Office for Europe, Denmark

Mirtha del Granado, WHO Regional Office for the Americas, United States

Reuben Granich, WHO HIV Department, Switzerland

Lindiwe Mvusi, Department of Health, South Africa (programme management)

Nani Nair, WHO Regional Office for South-East Asia, India

Norbert Ndjeka, Department of Health, South Africa (programme management, clinical practice)

Wilfred A.C Nkhoma, WHO Regional Office for Africa, Zimbabwe

Katsunori Osuga, WHO Regional Office for the Western Pacific, Philippines

Hendrik Simon Schaaf, Department of Paediatrics and Child Health, Stellenbosch University and Tygerberg Children's Hospital, South Africa (clinical practice, paediatric MDR-TB, surveillance)

Catharina van Weezenbeek, WHO Regional Office for the Western Pacific, Philippines

Irina Vasilyeva, Central TB Research Institute of RAMS, Russian Federation (research, clinical practice)

Wang Xie Xiu, Tianjin Centers for Disease Control and Prevention, China (surveillance)

Richard Zaleskis, WHO Regional Office for Europe, Denmark

Evidence review teams

Chunling Lu, Carole D. Mitnick–Harvard Medical School, Boston, Massachusetts, United States and Richard A. White–Harvard School of Public Health, Boston, Massachusetts, United States

Gail Kennedy, George Rutherford, Karen Steingart–University of California (San Francisco), California, United States

Matthew Arentz, David Horne, Patricia Pavlinac, Judd L. Walson–University of Washington, Seattle, Washington, United States

Melissa Bauer, Richard (Dick) Menzies, Olivia Oxlade–McGill University, Montreal, Quebec, Canada

Consultant: Patricia Whyte, Griffith University, Queensland, Australia (guideline development)

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Executive summary

This 2011 update of *Guidelines for the programmatic management of drug-resistant tuberculosis* is intended as a tool for use by public health professionals working in response to the Sixty-second World Health Assembly's resolution on prevention and control of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis. Resolution WHA62.15, adopted in 2009, calls on Member States to develop a comprehensive framework for the management and care of patients with drug-resistant TB.

The recommendations contained in these guidelines address the most topical questions concerning the programmatic management of drug-resistant TB: case-finding, multidrug resistance, treatment regimens, monitoring the response to treatment, and selecting models of care. The guidelines primarily target staff and medical practitioners working in TB treatment and control, and partners and organizations providing technical and financial support for care of drug-resistant TB in settings where resources are limited.

The first two editions of the guidelines were published by WHO in 2006 and 2008 through writing committees of international experts. The current 2011 update was undertaken in accordance with the requirements of the Handbook for Guideline Development (2010) of WHO's Guidelines Review Committee. The process began in 2009 with an exercise to determine the scope of the Guidelines ("scoping"), followed by systematic reviews to summarize the evidence. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) method was used to review the evidence and formulate recommendations. The process involved three groups: a WHO Guidelines Steering Group of staff with technical expertise in different aspects of TB and in the development of evidence-based guidelines; a Guideline Development Group comprising a multi-disciplinary panel of external experts including clinicians; and an External Review Group of experts who peer-reviewed the process and the final draft.

The recommendations encourage the wider use of rapid drug-susceptibility testing with molecular techniques to detect TB patients with rifampicin resistance and provide adequate treatment. The use of culture remains important for the early detection of failure during treatment. The best available information at the time the reviews were conducted was used to help decide the most effective composition and duration of treatment for MDR-TB patients. Early use of antiretroviral agents is recommended for TB patients with HIV infection who also receive medication with second-line anti-tuberculosis regimens. Systems that primarily employ ambulatory models of care to manage patients with drug-resistant TB are recommended over others based mainly on hospitalization.

National TB control programmes, public health decision-makers and technical and implementing partners involved in the control of MDR-TB are encouraged to use the recommendations to guide their work, and to adapt national guidelines accordingly. These practices are expected to encourage more collection of evidence and initiate new research, particularly on the composition of regimens, and the duration of treatment for patients with extensively drug-resistant TB.

Funding and declarations of interest

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

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

The following members of the academic centres who performed the reviews of evidence from which the recommendations contained in these guidelines are derived presented their findings at the meeting: Matthew Arentz, Melissa Bauer, Richard Menzies, Carole D. Mitnick, Olivia Oxlade, Patricia Pavlinac and Judd L. Walson. They did not participate in the formulation of recommendations related to the respective reviews of evidence that they performed.

Objectives of the guidelines and target audience

Effective management of drug-resistant tuberculosis requires input from different components or units of the national TB control programme. These components include case detection, treatment, prevention, surveillance, and monitoring and evaluation of the programme's performance. Collectively, such activities are referred to as the "programmatic management of drug-resistant tuberculosis" (PMDT).

This 2011 update is intended as a tool for use by health professionals in response to the sixty-second World Health Assembly's call for Member States to develop a comprehensive framework for the management and care of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) (*1*). The recommendations aim to:

- address the most topical questions in MDR-TB control requiring guidance for which the best available evidence has been summarized through appropriate review of data;
- provide a reference for countries developing national guidelines and policies to scale up detection and treatment of MDR-TB as an integral part of their national programmes.

The target audience of the guidelines is staff and medical practitioners working in treatment and control of TB, partners implementing programmatic management of drug-resistant TB, and organizations providing technical and financial support for care of drug-resistant TB. Although primarily intended for use in resource-limited countries, the recommendations are also applicable in other settings.

Background and methods

The first two editions of these guidelines were published in 2006 (*2*) and 2008 (*3*) as a collaborative effort of many partners, most of whom were members of the Green Light Committee (*4*). This 2011 update follows WHO requirements for developing guidelines as specified in the Handbook for Guideline Development (2010), which involve an initial scoping exercise, use of systematic reviews to summarize evidence and application of the GRADE approach to develop recommendations (*5*).

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

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

The guidelines are limited to topics not covered by other WHO policy documents published recently, including treatment of drug-susceptible TB and use of antiretroviral agents, treatment of patients with isoniazid-resistant TB and TB infection control. The 2011 update was produced through a systematic process starting in early 2009. Priority areas to be included in the update had been identified from those listed as outstanding areas for future direction following publication of the emergency update (2008). The previous PMDT guidelines were evaluated via a user questionnaire (*6*). Various experts, including TB practitioners, public health professionals, national TB control programme staff, guideline methodologists, members of civil society and nongovernmental organizations providing technical support, and WHO staff, were invited to form a Guideline Development Group to inform the update process. A second group, comprising national TB control programme staff, WHO regional TB advisors, and clinical and public health experts, was appointed to serve as an External Review Group (the composition of both groups is listed in the Acknowledgements).

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

Questions and outcomes

Table 1 lists the seven priority questions identified by the Guideline Development Group, worded in the PICO (Population, Intervention, Comparator, Outcome) or similar format.

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

1.	At what prevalence of MDR-TB in any group of TB patients is rapid drug-susceptibility testing warranted to detect resistance to rifampicin and isoniazid or rifampicin alone on all patients in the group at the time of TB diagnosis, in order to prescribe appropriate treatment at the outset?
2.	Among patients with MDR-TB receiving appropriate treatment in settings with reliable direct microscopy, is monitoring using sputum smear microscopy alone rather than sputum smear and culture, more or less likely to lead to the outcomes listed in Table 2 below?
3.	When designing regimens for patients with MDR-TB, is the inclusion of specific drugs (with or without documented susceptibility) more or less likely to lead to the outcomes listed in Table 2?
4.	When designing regimens for patients with MDR-TB, is the inclusion of fewer drugs in the regimen (depending on the drug used, the patient's history of its use and isolate susceptibility) more or less likely to lead to the outcomes listed in Table 2?
5.	In patients with MDR-TB, is shorter treatment, compared with the duration currently recommended by WHO, more or less likely to lead to the outcomes listed in Table 2?
6.	In patients with HIV infection and drug-resistant TB receiving antiretroviral therapy, is the use of drugs with overlapping and potentially additive toxicities, compared with their avoidance, more or less likely to lead to the outcomes listed in Table 2?
7.	Among patients with MDR-TB, is ambulatory therapy, compared with inpatient treatment, more or less likely to lead to the outcomes listed in Table 2?

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

1–3 points Not important for making recommendations on choice of testing and treatment strategies for drug-resistant TB*
4–6 points Important but not critical for making recommendations on choice of testing and treatment strategies
7–9 points Critical for making recommendations on choice of testing and treatment strategies

* None of the outcomes was scored in this category.

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

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

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

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

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

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

Assessment of evidence and its grading

The evidence review teams assessed the evidence for the questions and their outcomes through a series of systematic literature reviews following an approved methodology that was documented (Annex 1). Titles, abstracts and full text of potentially relevant literature were screened using key subject words and text words. The search was not limited by study type or time period. Authors in the field and members of the Guideline Development Group were contacted to identify missing studies or studies in progress. Case-based data

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

were collected from authors of published studies to analyse the effects relating to the questions dealing with bacteriology and treatment regimen (questions 2–6 in Table 1). Modelling work was done in the context of questions 1 and 2. The question on models of care (question 7) was addressed by a review of published and unpublished studies containing a full economic evaluation of patients on MDR-TB treatment.

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

GRADE evidence profiles based on the results of the systematic reviews were prepared for each question using a standard approach. These summaries present the effect of the intervention on each outcome (for example, the number of patients with MDR-TB), as well as the quality of the evidence for each outcome. The quality of evidence was assessed using the following criteria: study design, limitations in the studies (risk of bias), imprecision, inconsistency, indirectness, publication bias, magnitude of effect, dose–effect relations and residual confounding. Quality of evidence was categorized into four levels (Table 4).

Table 4. Quality of evidence and definitions *(8)*

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

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

At the meeting, the GRADE evidence profiles were assessed by the members of the Guideline Development Group when preparing the recommendations. The group used standard decision tables to move from evidence to recommendations. One table was prepared for each recommendation to record decisions and ensure that the group uniformly considered the quality of the evidence, the certainty about the balance of benefits versus harms, the similarity in values and the costs of an intervention compared with the alternative. The profiles allowed members to base their judgments when making recommendations on evidence summarized in a concise and uniform manner. Agreement on the recommendations was reached following discussions. In their deliberations, members of the group assessed the level of evidence and judged the strength of the recommendations according to the criteria shown in Table 5 (see web Annex 2 for a glossary of GRADE terms).

Table 5. Assessment of the strength of a recommendation

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

Apart from the quality of evidence, the strength of a recommendation was determined by the balance between desirable and undesirable effects, values and preferences, and costs or resource allocation (*5*). The higher the quality of evidence, the more likely that it leads to a strong recommendation. However, a strong recommendation may be made in the presence of very low quality evidence given variability in values and preferences between the experts, the balance between desirable and undesirable consequences of an intervention, and resource implications. For instance, evidence from observational studies without randomization is always of low quality, but if the studies are methodologically sound (not downgraded for concerns about the validity)

and the estimates of effect are consistent, a strong recommendation may still be possible. It is important to note that when making a conditional recommendation, the group considered its application only to a specific group, population or setting, or that new evidence might change the balance of risk to benefit or that the benefits might not warrant the cost or resource requirements in all settings (see also Table 6).

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

Table 6. Implications of the strength of a recommendation for different users (5)

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

External review

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

Publication, implementation, evaluation and expiry

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

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

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

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

1. Rapid drug susceptibility testing for early start of appropriate treatment

Recommendation

Rapid drug susceptibility testing (DST) of isoniazid and rifampicin or of rifampicin alone is recommended over conventional testing or no testing at the time of diagnosis of TB, subject to available resources (conditional recommendation, ⊕◯◯◯/very low quality evidence).

Evidence

The evidence used to determine the optimal timing of DST and the method of testing to be used relied on simulations from modelling work (*9*). There are inherent limitations when using models, which are linked to the underlying assumptions. Sensitivity analyses, however, showed fairly consistent results when epidemiological conditions and costs were varied.

For the purposes of the recommendation, the group considered a rapid test as one providing a diagnosis of resistance to isoniazid and rifampicin or rifampicin alone within two days of specimen testing. Only molecular tests can detect resistance so fast, of which two technologies – line probe assay and Xpert MTB/RIF – are currently recommended for use by WHO. Conventional DST of cultured mycobacteria typically provides results within 1–3 months.

Outcomes of interest were reduced mortality, increased likelihood of cure, decreased development of additional resistance, and reduced likelihood of failure and relapse, expressed as the cost per DALY averted. The model did not take into consideration ongoing transmission that may occur if diagnosis of resistance is delayed.

Summary of findings

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. 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%). For previously untreated patients, DST at the start of treatment was a better strategy than waiting to

test only those patients who remained sputum-smear positive later in the course of their first-line treatment.

Rapid DST of rifampicin alone did not have the same benefit as rapid testing of both isoniazid and rifampicin resistance. This is because DST of rifampicin alone could not prevent the acquisition of additional resistance in patients resistant to isoniazid only.

Benefits

A short time to diagnosis may influence the composition of a patient's initial treatment and increase the likelihood of starting appropriate treatment early. The likely benefits of rapid DST therefore include increased cure rates, decreased mortality, reduced development of additional drug resistance, and a reduced likelihood of failure and relapse.

The detection of rifampicin resistance by Xpert MTB/RIF usually suffices to start a patient on a second-line TB regimen (*10*), subject to confirmatory testing in situations with low rifampicin resistance (see also under Risks).

Use of rapid tests to detect resistance to both rifampicin and isoniazid would have better outcomes than tests to detect resistance to rifampicin alone. The detection of patients with isoniazid resistance alone may provide an opportunity to initiate effective treatment before additional acquisition of resistance to rifampicin develops. The model assumptions included appropriate treatment for non-MDR-TB isoniazid-resistant TB. The optimal regimen for the treatment of isoniazid-resistant strains has not been determined, and benefits may be less if suboptimal regimens are used.

The influence on secondary transmission of resistant strains was not included in the model and therefore estimates of reduction in mortality and morbidity from early detection and treatment are likely to be conservative. The increased costs of using the diagnostic test may be offset by a reduction in the requirement of conventional TB laboratory capacity which may be substantial.

Risks

The harms of rapid DST include false-positive results leading to wasted resources, and increased toxicity to the patient from unnecessary administration of second-line medications. Awareness of these potential harms is particularly important in patient groups in which rifampicin resistance is rare. Rifampicin resistance detected by Xpert MTB/RIF in such a situation will have a low predictive value and results need to be confirmed by phenotypic DST or line probe assay (*10*). Another potential harm from placing all rifampicin-resistant patients on an MDR-TB regimen is the exclusion of isoniazid from their treatment, thus depriving them of a safe and useful bactericidal drug.

Values and preferences

A high value was placed on outcomes such as preventing death and transmission of MDR-TB as a result of delayed diagnosis, as well as lowered costs. Such costs to the TB control programme were considered important but not critical. The recommendation is conditional, in part because of the resources required for its implementation. Programmes that cannot adhere to the recommendation for rapid testing at the time of TB diagnosis in all patient groups according to the thresholds mentioned above may still decide to perform rapid testing in previously treated patients (*11*) and other groups at higher risk of MDR-TB ideally based on surveillance data.

2. Monitoring the response to MDR-TB treatment

Recommendation

The use of sputum smear microscopy and culture rather than sputum smear microscopy alone is recommended for the monitoring of patients with MDR-TB during treatment (conditional recommendation, ⊕◯◯◯/very low quality evidence).

Evidence

The evidence used to assess how best to monitor treatment in MDR-TB patients using sputum smear microscopy and culture in settings with reliable direct microscopy was based on data pooled from 10 published observational studies (*12–19*). Monthly monitoring by culture was used as the reference in all the analyses. Random-effects Cox proportional hazards models were used to estimate the hazard ratio of failure, comparing monthly culture to alternative monitoring strategies.

Summary of findings

Performing monthly sputum smear microscopy and culture was the best strategy in identifying failures earlier. Sputum smear microscopy alone resulted in delayed detection of failure: when done at monthly rather than two monthly intervals it increased the detection of failure slightly (not significantly). In patients who were smear-negative at the start of treatment, monthly smear monitoring (compared with culture) resulted in a statistically significantly greater risk of delayed detection of failure compared with smear-positive patients. Stratified estimates by HIV serostatus, body mass index, and extent of disease on chest radiograph, were not significantly different (P>0.05).

The related end-points of drug resistance, initiation of appropriate treatment and the acquisition of resistance were not measured. There was no information about reversion or reinfection and no data were available to assess the quality of culture and smear testing. Other methods of evaluating response to treatment such as clinical indicators or chest radiography were not evaluated.

Benefits

Concomitant use of sputum smear microscopy and culture test results helps identify patients whose bacteriology remains positive or reverts to positive following initial

conversion to negative. This is of use to clinicians in identifying patients likely to fail their treatment and instituting infection control measures in a timely manner. There was overall certainty about the risk of missing or delaying the detection of failure if smear alone was used instead of culture. Additional benefits would be expected from reduced transmission and development of resistance as well as appropriate changes to treatment regimens, but these were not explicitly addressed by the analysis.

Risks

Delayed detection of failure is expected to increase transmission and increase the probability of acquisition of resistance. Up to now, a minimum of monthly sputum smear microscopy and culture examination prior to culture conversion to negative[2] and quarterly culture with monthly smear examination after conversion has been recommended for the monitoring of patients on treatment for MDR-TB (*3*).

Even if monthly culture performed throughout treatment showed the highest benefit to detect failures, resource implications are important. Cost for sputum smear testing alone ranged between one-fourth to a half of the combined cost of culture and smear testing (based on information from nine studies reviewed for these guidelines) (*20–26*). It is likely that this difference may be higher where culture diagnosis is not readily available. More laboratory resources (staff, equipment, utilities) are required to perform culture, and fewer culture laboratories exist in the low-resource conditions of most high-burden countries. In settings where the risk of failure is low, selected patients can be prioritized for monthly culture.

The quality of culture performance differs importantly. False-positive cultures could lead to changes in regimen that may entail more potentially toxic medication. A false-negative culture result may influence a treatment decision based on clinical and direct microscopy findings.

Values and preferences

A high value was placed on outcomes such as preventing death, decreasing the transmission of MDR-TB that could result from its delayed diagnosis, and avoiding increased use of resources. The recommendation is conditional in part because of the resources required for implementing it.

As direct microscopy of sputum smear can identify the most infectious cases within a very short time, it has added value alongside culture for infection control purposes.

[2] Defined as two consecutive sets of negative results of sputum smear microscopy and culture from samples collected at least 30 days apart.

3. Composition of second-line anti-tuberculosis regimens

Recommendations

3.1 In the treatment of patients with MDR-TB, a fluoroquinolone should be used (strong recommendation, ⊕◯◯◯/very low quality evidence).

3.2 In the treatment of patients with MDR-TB, a later-generation fluoroquinolone rather than an earlier-generation fluoroquinolone should be used (conditional recommendation, ⊕◯◯◯/very low quality evidence).

3.3 In the treatment of patients with MDR-TB, ethionamide (or prothionamide) should be used (strong recommendation, ⊕◯◯◯/very low quality evidence).

3.4 In the treatment of patients with MDR-TB, four second-line anti-tuberculosis drugs likely to be effective (including a parenteral agent), as well as pyrazinamide, should be included in the intensive phase[3] (conditional recommendation,⊕◯◯◯/very low quality evidence).

3.5 In the treatment of patients with MDR-TB, regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and either cycloserine or PAS (*p*-aminosalicylic acid) if cycloserine cannot be used (conditional recommendation, ⊕◯◯◯/very low quality evidence).

Evidence

The evidence used to address the questions on which drugs to include (with or without information on their DST patterns) and the number of drugs to be used in regimens for MDR-TB patients was based on studies published in three major systematic reviews (*27–29*). All three reviews searched EMBASE and MEDLINE databases as well as the Cochrane Library and the ISI Web of Science. Studies published before 1970 and those including only XDR-TB cases were excluded. The reviewers then pooled individual patient data from studies which had featured in the systematic reviews for a meta-analysis.

The meta-analysis included 32 studies with more than 9000 treatment episodes for which the authors could be contacted and were willing to share their data (*30*). Patients

[3] The intensive phase is the initial part of a course of treatment during which a parenteral (injectable) agent is used.

with XDR-TB (N=410) were excluded, as their treatment regimens were considered not to be comparable with those of other MDR-TB patients. Cohorts included had to have had at least 25 subjects treated for MDR-TB, and one or more of the treatment outcomes meeting the standard definitions (*31*). Missing values for age, sex, past TB, extent of disease, HIV infection and DST were imputed (>50% of cohort members having an observed value for these variables), but not those for treatment modality or outcome. None of the cohorts was part of randomized controlled trials and thus the quality of evidence was judged to be low or very low. While the odds ratios in the analysis were adjusted for age, sex, HIV-serostatus, past TB treatment, past MDR-TB treatment and extent of disease, there remains a risk of substantial bias (certain drugs may have only been used for sicker patients). Other limitations included incomplete ascertainment of relapse, the under-representation of certain geographical regions, and missing data for some of the variables examined.

Findings from this analysis may not necessarily be generalizeable to all populations in settings with high or low prevalences of drug resistance or different levels of resources. Nonetheless, the results of this analysis represented the best available evidence to date for the group to make recommendations on the composition of treatment regimens.

Summary of findings

Use of drugs to which the strain was reportedly susceptible showed a marginal benefit when compared with their use regardless of susceptibility patterns. Choice of drug would thus depend on the DST of the strain isolated from the patient or close contacts with MDR-TB, previous use of the drug in the patient, and the frequency of its use or documented background drug resistance in the setting. In applying this observation to clinical practice, it is important to underline the uncertainties around the reproducibility and reliability of DST of pyrazinamide (and ethambutol) (*32*), as well as the second-line drugs other than the parenteral agents and the fluoroquinolones (*33*).

The analysis showed that in the intensive phase, a regimen with at least four drugs likely to be effective, when adjusted for clinical covariates, all other drugs used concomitantly as well as the total number of susceptible drugs used throughout treatment, was associated with a statistically significant peak in cure with a plateau thereafter.

Data from this analysis did not reveal any second-line parenteral agent – kanamycin, amikacin or capreomycin – to be superior in effect to any other. Given its lower cost, kanamycin would be preferred. Amikacin can be used instead of kanamycin. In an analysis comparing patients who were cured or completed treatment with those who failed or relapsed, capreomycin was shown to be effective if the case was resistant to kanamycin. The use of streptomycin in MDR-TB patients is not recommended.

Fluoroquinolones were significantly associated with cure and this effect was more pronounced in later-generation fluoroquinolones (see Background and methodology for definition). It was highest when used against strains known to be susceptible.

Fluoroquinolones should therefore always be used unless there is an important contraindication. Ciprofloxacin, even if it may have some anti-tuberculosis activity, should not be used (*34*).

Among the oral bacteriostatic drugs, the association with cure was higher with ethionamide than with cycloserine, which was higher than with PAS. Ethionamide or prothionamide should therefore always be included in a regimen unless there is a particular contraindication. Ethionamide showed little effect in patients who had taken prior treatment for MDR-TB. PAS performed the worst, showing no significant effectiveness in the main analysis. Its use would thus be recommended only if an additional drug is needed to achieve a five-drug regimen or if ethionamide or cycloserine cannot be used or are unlikely to be effective. The data did not allow comparison of outcomes between once daily PAS and divided doses, or the formulation of PAS: decisions on how to administer PAS should thus rely on a balance between its tolerance in the patient and the resources available to observe doses.

Patients on Group 5 drugs were observed to have worse outcomes, an effect largely attributed to confounding. When the individual effect of amoxicillin/clavulanate, clofazimine, macrolides[4] and thioacetazone was analysed, no significant association with cure could be discerned. No separate analysis was possible for linezolid and high-dose isoniazid given the small number of cases treated with these agents.

Pyrazinamide showed a slightly added benefit in one of the analyses in which adjustment was made for other medication used concomitantly. Ethambutol was associated with a marginal but statistically significant reduction in likelihood of cure among patients not previously treated for MDR-TB. As in the case of Group 5 drugs this effect was attributed to confounding rather than a detrimental effect of ethambutol.

The analysis of data from this review bore inconclusive results about the contribution of ethambutol and Group 5 drugs in the treatment of MDR-TB patients and as a result they have not been included among the drugs making up the recommended standard MDR-TB regimen.

The principle of using additional drugs for extensive disease could not be supported by the data used for this review.

As patients with XDR-TB were excluded from the analysis, the current recommendations do not necessarily apply to this subgroup of patients. Until better evidence is available to determine the optimal regimens for treatment of these patients, the same principles used to design MDR-TB regimens should be used, based where possible on the DST pattern of the individual patient, particularly for later-generation fluoroquinolones and second-line parenteral agents. All MDR-TB patients should thus be tested for susceptibility to these two classes of drugs.

[4] Azithromycin, clarithromycin and roxithromycin were included in this analysis.

The recommended composition of second-line regimens for MDR-TB patients has changed from those in the 2008 emergency update (*3*) (Table 7). The previous guidelines had likewise recommended designing regimens based on known drug resistance patterns in the country or patient, the history of previous treatment by the patient, and the drugs commonly used in the country. The inclusion of at least four drugs with either certain, or almost certain, effectiveness was previously recommended. The previous recommended regimen was composed of pyrazinamide and/or ethambutol, one fluoroquinolone, one parenteral agent and second-line oral bacteriostatic drugs. Resort to antibiotics from Group 5 was only recommended if additional drugs were needed to bring the total to four. More drugs were recommended in the case of extensive disease or uncertain effectiveness.

Table 7. Changes to the recommendations on regimen composition between the 2008 and 2011 updates of the guidelines

2008 emergency update (*3*)	2011 update
Include at least four anti-tuberculosis drugs with either certain, or almost certain, effectiveness during the intensive phase of treatment.	Include at least four second-line anti-tuberculosis drugs likely to be effective as well as pyrazinamide during the intensive phase of treatment.
Consider adding more drugs in patients with extensive disease or uncertain effectiveness.	No evidence found to support the use of more than four second-line anti-tuberculosis drugs in patients with extensive disease. Increasing the number of second-line drugs in a regimen is permissible if the effectiveness of some of the drugs is uncertain.
The regimen should include pyrazinamide and/or ethambutol, one fluoroquinolone, one parenteral agent and second-line oral bacteriostatic anti-tuberculosis drugs (no preference of oral bacteriostatic second-line anti-tuberculosis drug was made).	The regimen should include pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and cycloserine, or else PAS if cycloserine cannot be used.
Ethambutol may be considered effective and included in the regimen if DST shows susceptibility.	Ethambutol may be used but is not included among the drugs making up the standard regimen.
Treatment with Group 5 drugs is recommended only if additional drugs are needed to bring the total to four.	Group 5 drugs may be used but are not included among the drugs making up the standard regimen.

Benefits

The recommendations contained in this section aim to increase the likelihood of cure and reduce the risk of failure, relapse and death. The decision to recommend an additional drug to the regimen during the intensive phase of treatment – from the minimum of four inferred from the analysis – was based on expert opinion. It is intended

to safeguard against the acquisition of additional resistance, particularly in the case of undetected primary resistance to the four drugs considered to be effective given the unreliable nature of DST for drugs other than parenteral agents and fluoroquinolones. Estimates of effects for fluoroquinolones were probably conservative given that patients treated with ciprofloxacin were included in the control group. Studies of the *inhA* promoter region mutation, although not assessed in this review, may guide treatment by identifying strains that are resistant to ethionamide (*35*) although the additional costs need to be considered.

Risks

A slight incremental trend in serious adverse events (SAE) was discerned as the number of drugs in the continuation phase increased from two to five. About 14% of patients on oral bacteriostatic drugs had SAE, while for the other drugs evaluated this was much lower (1–6%). An association between the total number of drugs used and the risk of SAE was observed. This association was not observed during the intensive phase.

The risk of additional acquisition of resistance is a concern in cases of unrecognized resistance to some of the drugs used. The long-term potential for SAE, particularly in children and for the later-generation fluoroquinolones, remains unknown. However, a Cochrane review assessing fluoroquinolones as additional or substitute drugs in regimens for drug-sensitive and drug-resistant patients found that substituting or adding fluoroquinolones to a regimen had no demonstrable effect on the occurrence of SAE (*34*).

Values and preferences

A high value was placed on preventing death and transmission of MDR-TB and a lower value on the potential for SAE resulting from long-term treatment. As a result, the long-term use of fluoroquinolones was considered to outweigh the higher cost and any possible long-term SAE. The recommendation is thus strong. While the use of later-generation fluoroquinolones is generally preferred, a separate recommendation on their use was graded conditional rather than strong because there is uncertainty about the risk of SAE from the long-term use of these agents.

4. Duration of second-line anti-tuberculosis regimens

Recommendations

4.1 In the treatment of patients with MDR-TB, an intensive phase of at least 8 months' duration is recommended (conditional recommendation, ⊕◯◯◯/ very low quality evidence).

4.2 In the treatment of patients with MDR-TB, a total treatment duration of at least 20 months is recommended in patients without any previous MDR-TB treatment (conditional recommendation, ⊕◯◯◯/very low quality evidence).

Evidence

The evidence used to derive recommendations on the duration of treatment was based on an analysis of the same individual patient data collected and described in Section 3 above. All data were from observational studies, and the quality of evidence was classified as very low. Attempts to control for selection bias and confounding in this review are unlikely to have adjusted for all important factors, and patients who receive longer therapy may be those who are more sick. Patients with XDR-TB were also excluded from the analysis. The findings may not be generalizable to all populations in settings with high or low prevalence of drug resistance or with different levels of resources.

Summary of findings

The analysis provided evidence for an association between treatment success and the total length of treatment and the length of the intensive phase. The trend in relative risk for cure over successive months of treatment was studied to determine the optimal minimum duration for both total treatment and the intensive phase. The adjusted relative risk for cure peaked at an intensive phase lasting between 7.1 and 8.5 months (see also Table 8 and Annex 2). For total treatment duration, the peak occurred between 18.6 and 21.5 months for patients who had no previous MDR-TB treatment. The peak occurred later in patients who had been treated for MDR-TB (27.6–30.5 months), but no clear incremental trend was observed in these patients and the number of observations was far fewer than for those who had no previous MDR-TB treatment.

Table 8. Odds ratios of treatment success by duration of intensive phase and total treatment

Duration of intensive phase of treatment			Total duration of treatment[a]		
Duration (months)	Observations	Adjusted[b] odds ratio (95% CLs)	Duration (months)	Observations	Adjusted[b] odds ratio (95% CLs)
1–2.5	308	1.0 (ref)	6.0–12.5	743	1.0 (ref)
2.6–4.0	1406	1.2 (0.5–2.9)	12.6–15.5	384	2.4 (1.5–3.6)
4.1–5.5	481	2.4 (1.3–4.3)	15.6–18.5	1646	4.6 (2.0–10.4)
5.6–7.0	377	3.7 (1.9–7.1)	18.6–21.5	612	9.3 (5.8–15.0)
7.1–8.5	172	5.1 (2.1–12.7)	21.6–24.5	435	6.8 (4.2–11.1)
8.6–20	792	2.2 (1.2–3.9)	24.6–27.5	207	8.2 (4.2–15.9)
			27.6–30.5	106	2.4 (1.2–5.0)
			30.6–36	48	1.3 (0.6–2.7)

[a] Only in patients with no previous treatment for MDR-TB.

[b] Adjusted for age, sex, HIV status, previous TB treatment, previous MDR-TB treatment and extent of disease.

CLs = Confidence Limits

Most patients may be expected to receive this length of treatment but in some it may have to be modified depending on their bacteriological status and other indicators of treatment progress.

The recommendations have thus changed from those contained in the 2008 emergency update, which recommended a duration of treatment for MDR-TB patients based on the use of a parenteral agent for a minimum of 6 months and at least 4 months past culture conversion, and a minimum total length of treatment of 18 months after culture conversion. The new recommended duration of intensive phase is 2 months longer than the minimum previously recommended. There is, however, no substantial difference in the total length of treatment being recommended because conversion typically takes a few months to occur. The data used for this analysis could not inform whether a minimum duration of the intensive phase after conversion was a determinant of outcome.

Benefits

When selecting the duration of treatment, the analysis allowed a choice to be made within a narrow margin of a few consecutive months, thus reducing the likelihood of prolonging treatment unnecessarily. While shorter regimens would confer clear benefits and be preferred, evidence for the effectiveness of a 9-month regimen for MDR-TB patients has up to now been limited to data from one setting (included in this review) (*16*). The Guideline Development Group supports further investigation of

the safety and effectiveness of shorter regimens using the randomized controlled trial design in order to strengthen evidence for their potential use for the treatment of drug-resistant TB.

Risks

The risk of serious adverse events (SAE) was observed to increase beyond the first 12 months of treatment but was not correlated with the length of the intensive phase beyond the first 2 months. These trends should be interpreted with caution as they may be confounded by the number of drugs used (independently correlated with SAE) as well as features of the illness process not accounted for in the measure of extent of disease used in this analysis.

Values and preferences

A high value was placed on outcomes such as preventing death and transmission of MDR-TB as a result of failed treatment as well as avoiding harms and minimizing use of resources. The group placed a lower value on reducing the duration of treatment, while acknowledging that many patients may place a higher value on avoiding a long treatment course due to burden and inconvenience.

5. Use of antiretrovirals in patients on second-line anti-tuberculosis regimens

Recommendation

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

Evidence

Evidence was reviewed from 10 studies (*36–45*) to assess patient treatment outcomes when antiretroviral therapy (ART) and second-line anti-tuberculosis drugs were used together. None of the data were from randomized controlled trials. Individual patient data were available for 217 drug-resistant TB patients in total, of whom 127 received ART. The level of evidence in individual observational studies varied from low to very low quality.

Summary of findings

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

Benefits

The strong recommendation for use of ART is based in part on indirect evidence from its use in any patient with active TB, which shows large beneficial effects and a very high mortality when ART is not employed (*46)*, particularly in very immunocompromised patients (CD4 cell-count <50 cells/mm^3) (*47*, *48*). In the absence of other data specific to patients with drug-resistant TB receiving second-line anti-tuberculosis medication, the decision on when to start ART should be no different from the approach to the HIV-positive drug-susceptible TB patient. ART should thus be initiated regardless of CD4 cell-count and as soon as anti-tuberculosis treatment is tolerated, ideally as early as 2 weeks and no later than 8 weeks after initiation of anti-tuberculosis treatment (*46*, *49*).

Risks

The successful implemention of this recommendation will depend upon the availability of more providers trained specifically in the care of HIV and drug-resistant TB and drug–drug interactions. A substantial increase in the availability of and patient's access to treatment and additional support for ensuring adherence would likely be needed. The need for increased integration of HIV and TB care for effective patient management, prompt evaluation of adverse events and case-holding throughout treatment will necessitate more resources. For the benefit of the user, a table of adverse events for which both an antiretroviral agent and an anti-tuberculosis medicine have been implicated and could conceivably interact is included online (Annex 3).

Values and preferences

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

6. Models of care for managing MDR-TB

Recommendation

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

Evidence

Outcomes from models of MDR-TB care based mainly on clinic-based ambulatory treatment were compared with those using mainly hospital-based inpatient treatment. The data used came from published and unpublished cost-effectiveness studies in four countries (Estonia, Peru (*17*), the Philippines (*18*) and the Russian Federation [Tomsk oblast]). The design of these observational studies did not allow direct comparison of effects between models of care. Given that none of the studies were randomized controlled trials the evidence was considered very low. Cost-effectiveness was modelled for all possible WHO Member States in a probabilistic analysis of the data from the four countries (50).

Summary of findings

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

Benefits

The overall cost-effectiveness of care for a patient receiving treatment for MDR-TB can be improved with an ambulatory model. The benefits include reduced resource use, and at least as many deaths avoided among primary and secondary cases, compared

with hospitalization models. This result is based on clinic-based ambulatory treatment (patients attend a health-care facility); in some settings, home-based ambulatory treatment (provided by a worker in the community) might improve cost-effectiveness even further. The benefit of reduced transmission can only be expected if proper infection control measures are in place in both the home and the clinic. Potential exposure to people who are infectious can be minimized by reducing or avoiding hospitalization where possible, reducing the number of outpatient visits, avoiding overcrowding in wards and waiting areas and prioritizing community-care approaches for TB management (*51*). The regimen used in one of the studies of ambulatory care was from a time when the combinations of medicines were not yet optimized, so outcomes achieved were probably inferior to those which can be accomplished with the regimens in use today. Admission to hospitals for patients who do not warrant it may also have important social and psychological consequences which need to be taken into account.

Risks

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

Values and preferences

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

Research gaps

The process of developing these guidelines revealed some important gaps in knowledge that are important to address in future research, particularly in the context of large-scale expansion of treatment for patients with drug-resistant TB. These include:

- lack of moderate or high quality evidence from randomized controlled trials for optimizing treatment regimens in patients with MDR-TB, including the best combination of drugs and treatment duration;
- lack of evidence for the best drug regimens for treating patients with isoniazid resistance, with XDR-TB and with non-MDR-TB polydrug-resistance;
- very limited information about treatment of paediatric MDR-TB;
- identification of the most effective chemoprophylaxis for contacts of MDR-TB cases;
- the therapy for symptomatic relief from adverse reactions linked to second-line anti-tuberculosis drugs.

A number of the gaps listed above had been identified in a review published in 2008 (*52*). It is expected that the current update of the guidelines will stimulate more support for studies on treatment and other aspects of programmatic management of patients with drug-resistant TB.

Available at www.who.int/tb/challenges/mdr/programmatic_guidelines_for_mdrtb/

Annex 1. Methods for evidence reviews and modelling

WHO/HTM/TB/2011.6a

Annex 2. GRADE glossary and summary of evidence tables

WHO/HTM/TB/2011.6b

Annex 3. Potentially overlapping toxicities of antiretrovirals and anti-tuberculosis agents (including first-line TB drugs)

WHO/HTM/TB/2011.6c

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