World Health Organization

END TB

Workshop on update of TB Guideline - *WHO perspective*

GLOBAL TB PROGRAMME

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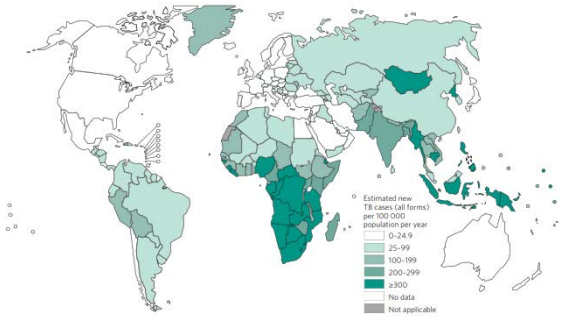
Overview

- Background
- From new drugs to new treatments
- WHO policy guidelines principles
- Assessment of evidence for policy recommendation
- Target Regimen Profiles for TB Treatment
- Summary

The Global Burden of TB, 2015



	Estimated number of cases	Estimated number of deaths
All forms of TB	**10.4** million 142 per 100,000 • 1 million children • 3.5 million women • 5.9 million men	**1.8** million* • 210,000 in children • 500,000 in women • 1,100,000 in men
HIV-associated TB	**1.2** million (11%)	**390,000**
Multidrug-resistant TB MDR/RR	**480,000** **580,000**	**190,000**

Source: WHO Global TB Report 2016

** Including deaths attributed to HIV/TB*

MDR-TB is a public health crisis

480 000

incident cases of MDR-TB in 2015
(with another 100 000 rifampicin-resistant TB cases eligible for second-line treatment)

132 000

MDR/RR-TB cases detected in 2015

125 000

patients started on MDR-TB treatment in 2015

52% 

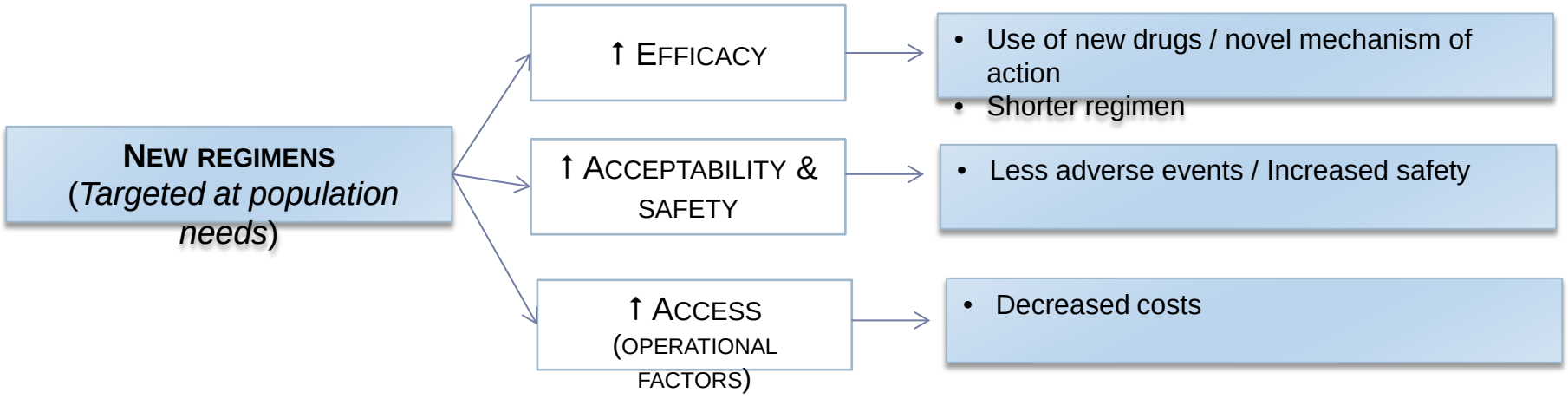
treatment success in MDR/RR-TB patients starting treatment in 2013

Treatment of TB

- Current regimens present ongoing challenges:
  - Treatment time necessary to achieve cure
  - Complexity of treatment protocols
  - Safety and toxicity issues (e.g. injectable drugs; drug-drug interactions)
  - Less efficacious and tolerable drugs to treat drug resistant TB forms
  - Cost

- Major drawbacks for drug development process:
  - Long time from pre-clinical development to the registration process

Improving treatment of TB



IMPACT

National level

- ✓ Policies to (early) access:
  - ✓ Diagnostic test
  - ✓ Feasible treatment regimens
  - ✓ Good quality drugs
- ↓ Costs

Implementing level

- ✓ Less burdening healthcare services
- ↓ Workload

Patient level

- ✓ Increased compliance and adherence to anti-TB regimen
- ↑ Tolerability
  ↓ Morbidity-mortality

REDUCED BOD

Global TB Drug Pipeline [1]

Discovery | **Preclinical Development** | **Clinical Development**

Lead Optimization → **Early Stage Development** → **GLP Tox.** → **Phase 1** → **Phase 2** → **Phase 3**

Lead Optimization

- Diarylquinolines
- DprE Inhibitors
- InhA Inhibitor, Ureas
- Macrolides, Azaindoles
- Mycobacterial Gyrase Inhibitors
- Pyrazinamide Analogs
- Ruthenium(II)Complexes
- Spectinamides
- Translocase-1 Inhibitors, Clp, Mmp13, Oxazolidinones, Pyrimidines DprE1, Aryl Sulfonamides, PKS13, Squaramides

Early Stage Development

- TBI-166
- CPZEN-45*
- 1599*
- SATB-082*

GLP Tox.

- BTZ-043*
- PBTZ-169*
- TBA-7371*
- GSK-070*

Phase 1

- Q203*
- PBTZ169*
- OPC-167832*

Phase 2

- Sutezolid (PNU-100480)
- Linezolid EBA
- SQ-109*
- High Dose Rifampicin for DS-TB
- Bedaquiline (TMC207)-Pretomanid (PA-824) - Pyrazinamide Regimen
- Levofloxacin with OBR for MDR-TB

Phase 3

- Rifapentine - Moxifloxacin for Drug Sensitive TB
- Delamanid (OPC-67683) with OBR for MDR-TB
- Pretomanid-Moxifloxacin-Pyrazinamide Regimen (STAND)
- Bedaquiline-Pretomanid-Linezolid NiX-TB Regimen
- Bedaquiline-STREAM MDR-TB Trial Stage 2 with oral OBR (9 mo) or OBR with injectables (6 mo)
- Bedaquiline-Linezolid with OBR for MDR-TB (NExT Trial)

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, , imidazopyridine amide. New chemical class*

[1] Details for projects listed can be found at http://www.newtbdrugs.org/pipeline.php and ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php

[2] OBR = Optimized Background Regimen

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: October 2016

The WHO Strategic Plan for rational introduction of new TB drugs and regimens in countries

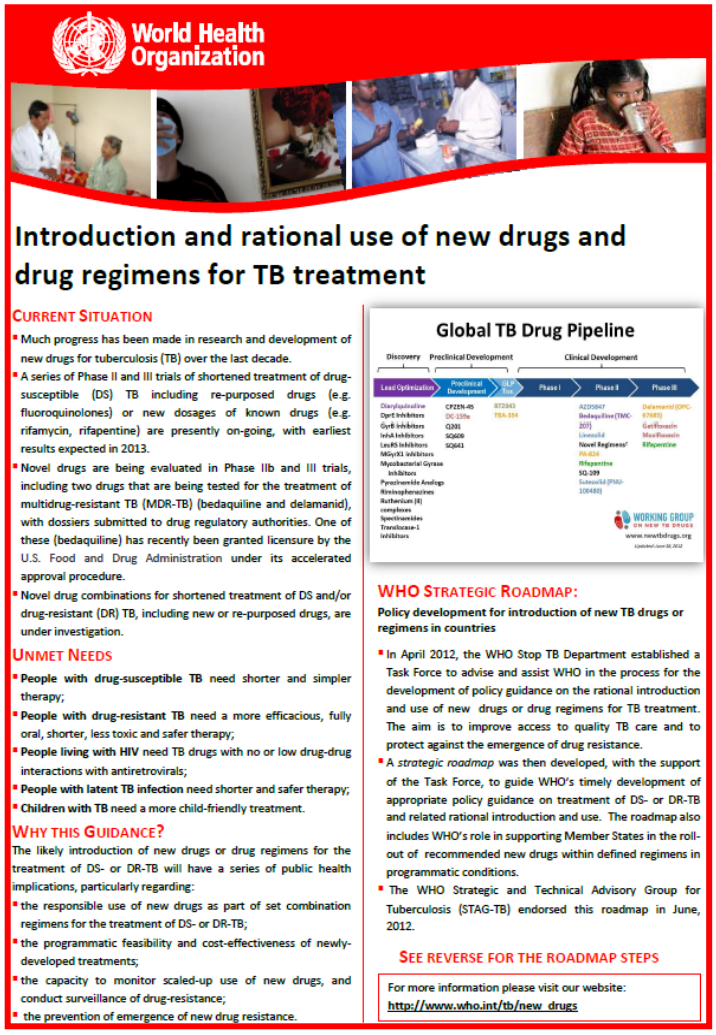
Describes key elements of a process aimed at:

- producing policy recommendations for the treatment of TB (all forms), according to progress made in the development of new drugs or combinations of drugs,

and

- assisting countries in the implementation of these recommendations

http://www.who.int/tb/new_drugs/en/index.html



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Introduction and rational use of new drugs and drug regimens for TB treatment

CURRENT SITUATION

- Much progress has been made in research and development of new drugs for tuberculosis (TB) over the last decade.
- A series of Phase II and III trials of shortened treatment of drug-susceptible (DS) TB including re-purposed drugs (e.g. fluoroquinolones) or new dosages of known drugs (e.g. rifamycin, rifapentine) are presently on-going, with earliest results expected in 2013.
- Novel drugs are being evaluated in Phase IIb and III trials, including two drugs that are being tested for the treatment of multidrug-resistant TB (MDR-TB) (bedaquiline and delamanid), with dossiers submitted to drug regulatory authorities. One of these (bedaquiline) has recently been granted licensure by the U.S. Food and Drug Administration under its accelerated approval procedure.
- Novel drug combinations for shortened treatment of DS and/or drug-resistant (DR) TB, including new or re-purposed drugs, are under investigation.

UNMET NEEDS

- **People with drug-susceptible TB** need shorter and simpler therapy;
- **People with drug-resistant TB** need a more efficacious, fully oral, shorter, less toxic and safer therapy;
- **People living with HIV** need TB drugs with no or low drug-drug interactions with antiretrovirals;
- **People with latent TB infection** need shorter and safer therapy;
- **Children with TB** need a more child-friendly treatment.

WHY THIS GUIDANCE?

The likely introduction of new drugs or drug regimens for the treatment of DS- or DR-TB will have a series of public health implications, particularly regarding:

- the responsible use of new drugs as part of set combination regimens for the treatment of DS- or DR-TB;
- the programmatic feasibility and cost-effectiveness of newly-developed treatments;
- the capacity to monitor scaled-up use of new drugs, and conduct surveillance of drug-resistance;
- the prevention of emergence of new drug resistance.

Global TB Drug Pipeline

Discovery | Preclinical Development | Clinical Development

Lead Optimization | Preclinical Development | GLP Tox | Phase I | Phase II | Phase III

WORKING GROUP ON NEW TB DRUGS www.newtbdrugs.org

WHO STRATEGIC ROADMAP:

Policy development for introduction of new TB drugs or regimens in countries

- In April 2012, the WHO Stop TB Department established a Task Force to advise and assist WHO in the process for the development of policy guidance on the rational introduction and use of new drugs or drug regimens for TB treatment. The aim is to improve access to quality TB care and to protect against the emergence of drug resistance.
- A *strategic roadmap* was then developed, with the support of the Task Force, to guide WHO's timely development of appropriate policy guidance on treatment of DS- or DR-TB and related rational introduction and use. The roadmap also includes WHO's role in supporting Member States in the roll-out of recommended new drugs within defined regimens in programmatic conditions.
- The WHO Strategic and Technical Advisory Group for Tuberculosis (STAG-TB) endorsed this roadmap in June, 2012.

SEE REVERSE FOR THE ROADMAP STEPS

For more information please visit our website: http://www.who.int/tb/new_drugs

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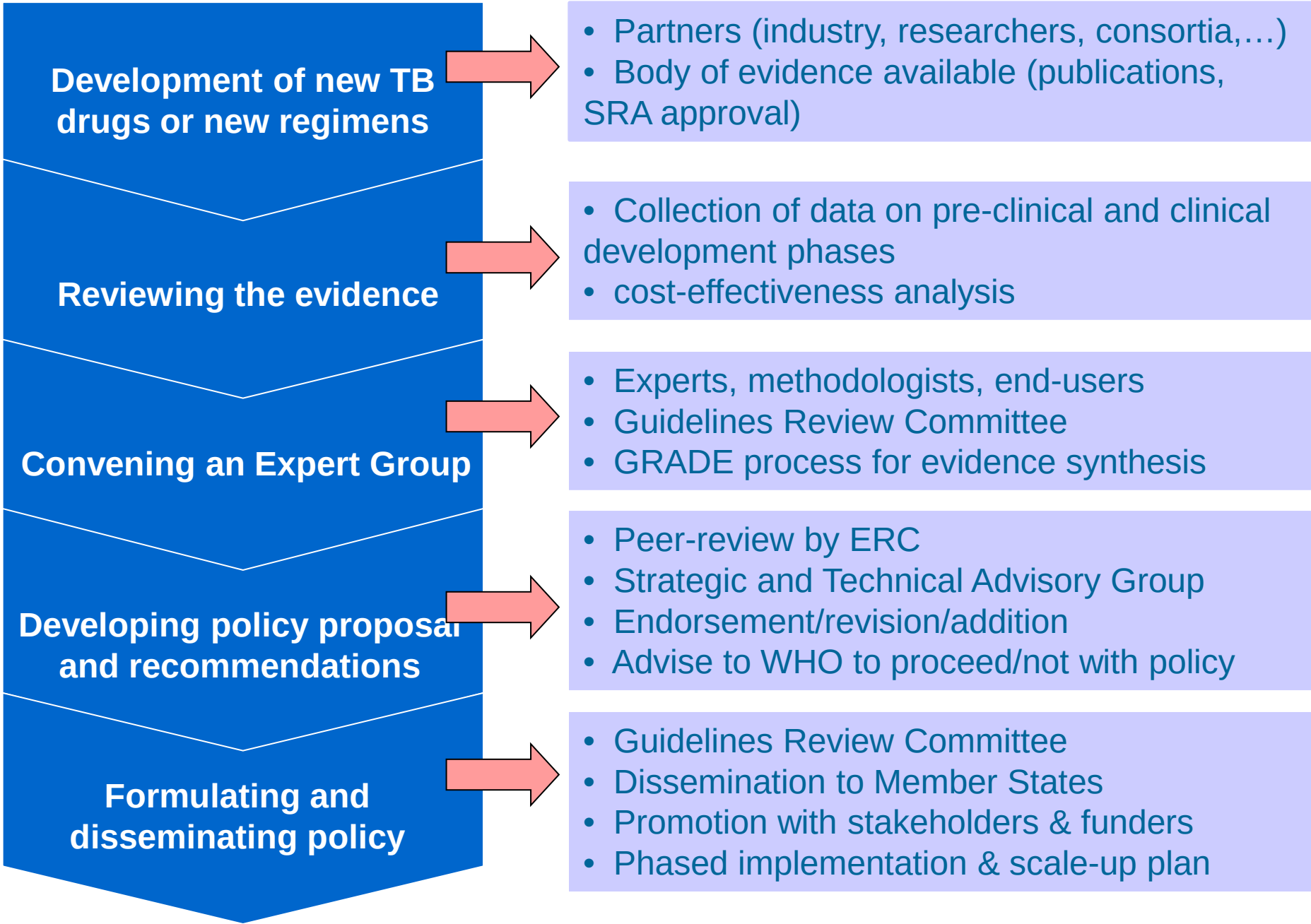
WHO Policy Development Framework



Rational introduction of new drugs against MDR-TB

Key questions for recommendation of new regimens for TB treatment

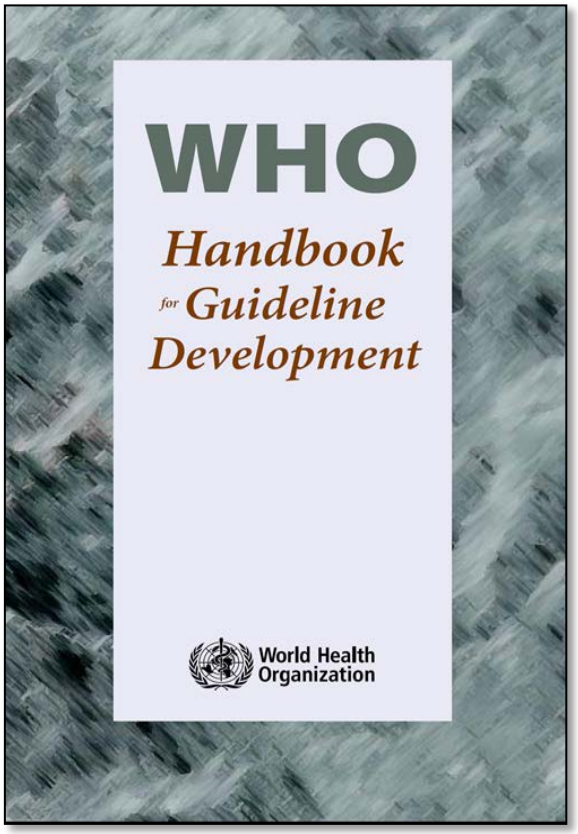
1. *What would be the added value and best impact of the new regimen(s) considering its characteristics and the variability of national contexts?*
   - Efficacy, safety, harms *vs*. benefits, patients' values, feasibility

2. *What population would benefit most of the new regimen(s)?*
   - DS-TB treatment: all patients regardless of susceptibility to other drugs ? If need to assess other resistance, practical implications (e.g. FQ resistance)
   - MDR-TB treatment: all MDR-TB patients ? only those with additional FQ and/or INJ resistance ?
   - consider high-risk groups (HIV infected patients; children)

3. *How to ensure optimal deployment of new regimens in countries?*
   - operationalization (eligibility requirements, feasibility, affordability, pharmacovigilance)
   - risk of irrational use (off-label, inadequate combinations, inadequate doses or duration, etc.)
   - risk of resistance development

WHO Guidelines

- Must meet the highest quality standards for evidence-based guidelines
- Evidence-informed policy, based on high-quality systematic reviews and meta-analysis
- Use GRADE, which provides an explicit approach to:
  - assess the *quality of evidence* across studies and outcomes
  - translate evidence to recommendations
- Processes to minimize bias and optimize usability
- Transparency in all judgments and decision making
- Expert panels with broad constituency



Source: WHO, 2014

GRADE: Grades of Recommendation Assessment, Development and Evaluation

Involves two fundamental determinations:

- Quality of evidence: reflects the extent to which confidence in an estimate of the effect is adequate to support recommendations.

- Strength of recommendation: reflects the extent to which we can, across the range of patients for whom the recommendations are intended, be confident that the desirable effects of an intervention outweigh the undesirable effects.

GRADE working group

http://gradeworkinggroup.org/

Determinants of quality of evidence

- **RCTs ⊕⊕⊕⊕**
- **observational studies ⊕⊕◯◯**
- **5 factors that can lower quality**
  1. limitations in detailed study design and execution *(risk of bias criteria)*
  2. Inconsistency *(or heterogeneity)*
  3. Indirectness *(PICO and applicability)*
  4. Imprecision
  5. Publication bias
- **3 factors can increase quality**
  1. large magnitude of effect
  2. opposing plausible residual bias or confounding
  3. dose-response gradient

Adapted from H. Schünemann, Nov 2015

Strength of a recommendation

"The strength of a recommendation reflects the extent to which we can, across the range of patients for whom the recommendations are intended, be confident that desirable effects of a management strategy outweigh undesirable effects."

- Strong or conditional

Assessment of evidence for recommendation of new TB treatment regimens

Objective:

- To describe the type of evidence required by WHO to develop or update policy recommendations on treatment of TB, based on outputs of studies and/or clinical trials investigating new regimens, and following the policy development process in use at WHO.
- Evidence arising from:
  - Pre-clinical studies
  - PK/PD and DDI studies
  - Phase I
  - Phase II
  - Phase III trials

Assessment of evidence for recommendation of new TB treatment regimens

Principles:

- All studies/trials must imperatively comply with ICH-GCP and GLP recommendations;
- The rationale for the choice of drugs and the composition of regimen(s) needs to be clearly described;
- Data should support the selection of the regimen(s) to be advanced into clinical development and describe the contribution of individual agents;
- Clear description of selected design as well as related issues (margins of non-inferiority; selection of controls; use of Bayesian adaptive design, etc.) and potential pitfalls.

Assessment of evidence for recommendation of new TB treatment regimens

Trial documentation:

1. Full protocol(s) with detailed description of - and justification for - the trial design, treatment regimens, drug dosages, efficacy and safety endpoints, study power, sample size, including justification for chosen non-inferiority margin, duration of follow up.
2. If and when appropriate, clear definition of the surrogate endpoints of treatment efficacy used (based on bacteriological outcome data)
3. Statistical analysis plan incl. planned interim analyses
4. Approval by IRBs/Ethics Committees
5. Data Safety and Monitoring Report (DSMB) reports
6. Laboratory methods – incl. standardization, specimen collection, culture media, specimen processing, determination and interpretation of results
7. Complete raw data for the primary efficacy and safety objectives

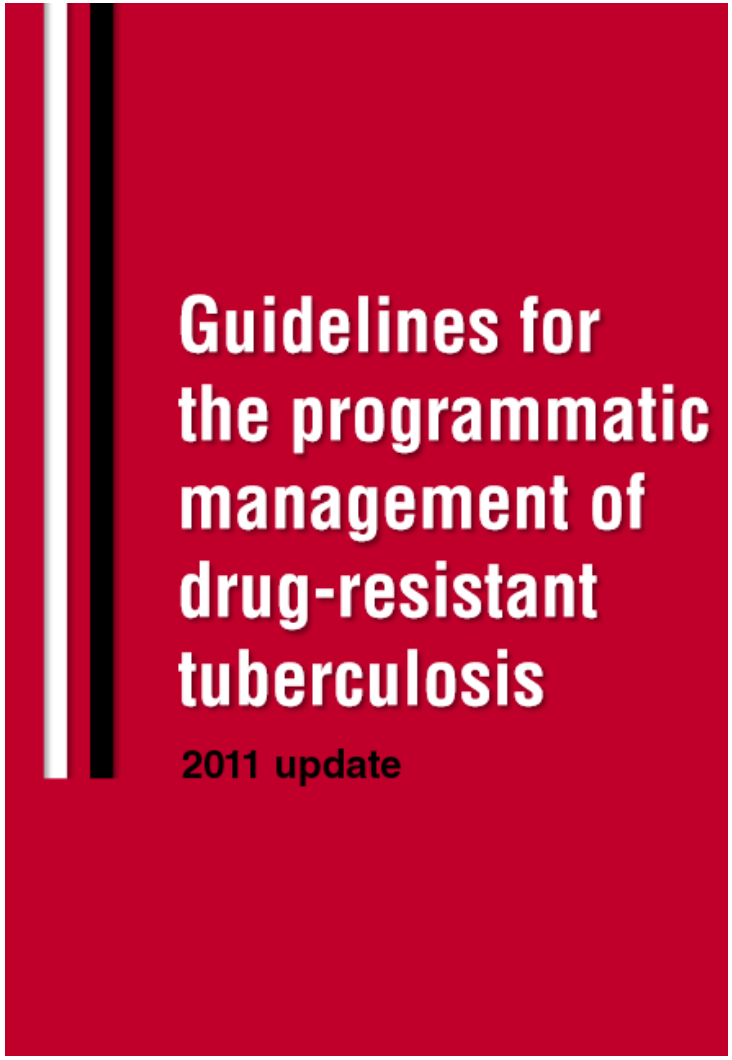
Comparator

- GRADE: randomized controlled trials constitute highest quality evidence
- PICO question (Population, Intervention, Comparator, Outcome) insists on the need for comparison
- Key to describe and justify the choice of controls
    - Concurrent control, external controls, historical controls
    - External or historical controls have more potential for bias than concurrent controls (potential problems with covariate adjustment, placebo effect, and regression to the mean
- Non-randomized comparative designs provide low-quality evidence.

Superiority *vs.* non-inferiority

- The choice of **delta** must be justified on statistical AND clinical grounds
  - *Would the possibility of an increase in failure/relapse of X % be acceptable to physicians in high-burden countries ?*
  - *Need to weigh in advantages in reducing the duration of chemotherapy vs. possible increase in relapse rates of up to X%...*
- Risk of potential for erosion of the efficacy of the control regimen (**bio-creep**).
  - *occurs when a less effective regimen declared to be non-inferior then becomes the SOC in the next non-inferiority trial;*
  - *as time goes on what is regarded as an acceptable response could slip further away from the original standard;*
  - *non-inferiority trials should use as their control the best known SOC (World Medical Association; WHO).*

2011 WHO MDR-TB guidelines



"… evidence for the effectiveness of a 9-month regimen for MDR-TB patients has up to now been limited to data from one setting … 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."

whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf

Shorter regimens for MDR-TB

WHO advice to countries (since 2012):

1. approval of the project by a national ethics review committee, ahead of patient enrolment,
2. delivery of treatment under operational research conditions following international standards (including Good Clinical Practice and safety monitoring), with the objective of assessing the effectiveness and safety of these regimens (active pharmacovigilance),
3. monitoring of the MDR-TB component of the TB programme, and its corresponding research project, by an independent monitoring board set up by and reporting to WHO.

Prioritize problems

⇩

Establish review team and/or guideline panel

⇩

Define questions to be addressed

⇩

Find and critically appraise systematic review(s)[a]
and/or
Prepare protocol(s) for systematic review(s)
and
Prepare systematic review(s)
(searches, selection of studies, data collection and analysis)[a]

⇩

(Re)assess the relative importance of outcomes

⇩

Prepare an evidence profile
including
An assessment of the quality of evidence for each outcome
and
A summary of the findings

⇩

If developing guidelines:
Assess the overall quality of evidence
and
Decide on the direction (which alternative) and strength of the recommendation

⇩

Draft the systematic review or guideline

⇩

Consult with stakeholders and/or external peer reviewers

⇩

Disseminate the review or guideline

⇩

Update review or guideline when needed

⇩

Adapt guideline, if needed

⇩

Prioritize recommendations for implementation

⇩

Implement or support implementation of the guideline

⇩

Evaluate the impact of the guideline and implementation strategies

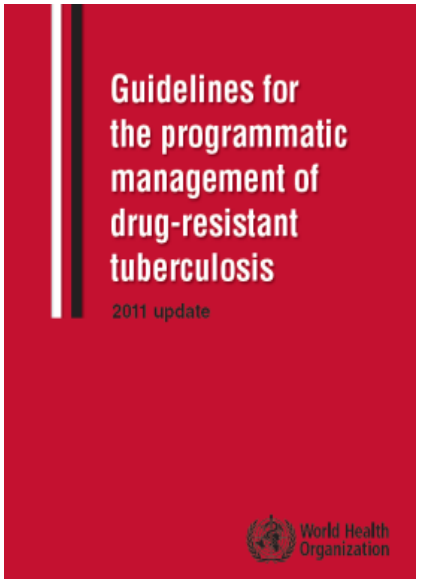
⇩

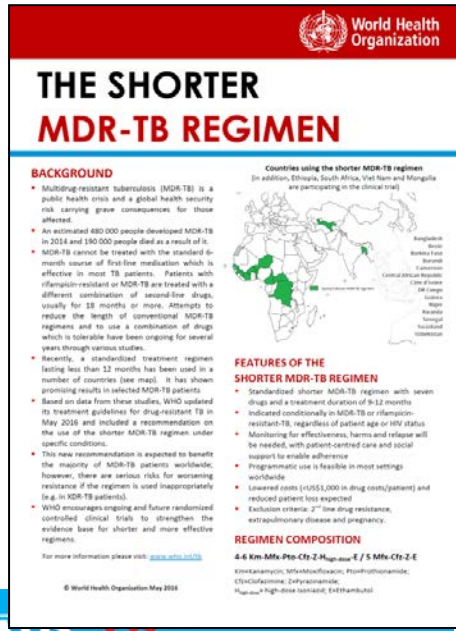
Update the systematic review and guideline

GRADE

November 2014

May 2016





Journal of Clinical Epidemiology 2011 64, 383-394DOI: (10.1016/j.jclinepi.2010.04.026)

Developing TPPs for TB Treatment: *starting with the goal in mind…*

We need new TB treatment regimens that are:

- ☑ Shorter
- ☑ Less toxic
- ☑ Less expensive
- ☑ Less burdening
- ☑ Operationally feasible

- **Objective**

To align the targets and specifications that developers should meet for the performance of new TB treatment regimens with the needs of end-users.

- **Target audience**

Pharmaceutical industry, research institutions, product development partnerships, donors, NGOs and CSOs.

Target Regimen Profiles for TB Treatment

- Target regimen profiles seek to guide the development process toward *essential regimen characteristics*.
- *Minimum* and *optimal* characteristics of the regimen(s) to be developed
  - minimum criteria are the characteristics to achieve the minimally acceptable level of global health impact
  - optimal criteria are the characteristics of an ideal product for which the global health impact should be broader, deeper, quicker and sustainable.
- Criteria *quantitative* in nature – measurable
- The rationale on the thinking and data or references that support the targets clearly described.
- Indications on the respective attributes to be considered at the *developmental* level.

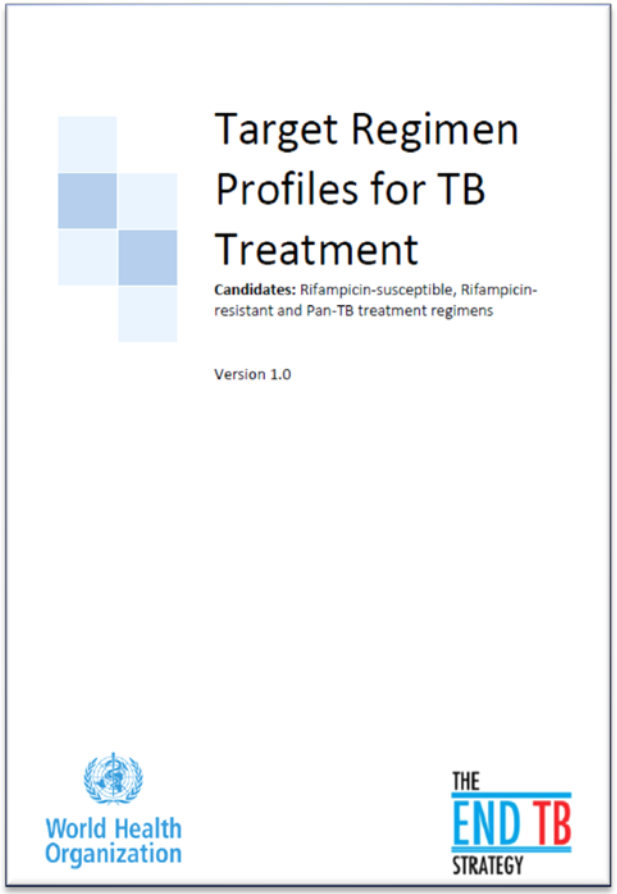
Target Regimen Profiles for TB Treatment

All Target Regimen Profiles explicitly describe:

- *clinical indication* of the treatment (e.g. DS-TB; DR-TB; all forms of TB)
- *critical endpoints* to be obtained and their measurement (e.g. non relapsing cure within 2/4/6/9 months of starting treatment)
- *target population* (children, adults, PLHIV, …)
- *treatment characteristics*: e.g.. expected duration; frequency and route of administration (e.g. daily, fully oral); formulation (dispersible tabs; FDCs) etc.;
- likely set of users.

Target Regimen Profiles for TB Treatment

- **Three Target Regimen Profiles:**
  - rifampicin-susceptible;
  - rifampicin-resistant;
  - pan-TB regimen.
- **Description:**
  - medical need
  - critical assumptions
  - summary tables: detail of the various priority and desirable attributes of the regimens with relevant appropriate targets
- **Cross-cutting issues**
  - background antimicrobial resistance – DSTs
  - accessibility and affordability
  - public financing for research and innovation



http://www.who.int/tb/areas-of-work/treatment/new_drugs/en/

Summary

- General principles:
  - WHO guidelines based on best available evidence
  - GRADE approach for evidence assessment across questions and outcomes
  - Criteria for moving from evidence to recommendations
- Main aspect : what is the best available evidence that can be brought about that ultimately benefits patients ?
- Need for clearly and rationally justified approaches (choice of drug combination, design, conduct, end-points, analyses);
- Based on the premise that TB drug R&D focus is shifting towards developing and testing *TB regimens* (rather than individual drugs), a set of targets is proposed;
- These targets are based on prioritized characteristics, encompassing the needs of end-users, care providers and policy-makers to have shorter, less toxic, and operationally feasible regimens;
- Targets are given for three types of indications: RS-TB, RR-TB and Pan-TB

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Thank you for your attention !

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