Introduction of new drugs for the treatment of DR-TB at the country level

Overview of the presentation

- Background and the WHO Strategic Plan for rational introduction of new TB drugs and regimens in countries
- The WHO Policy Implementation Package for introduction of new TB drugs/regimens in countries
- A working example: the case of bedaquiline
- Lessons learnt

Public health challenges of introduction of new TB drugs in countries

Implications for TB control programmes:

- to determine optimal regimens for treatment of DS- and DR-TB under programmatic conditions;
- to evaluate requirements for patients' eligibility;
- to assess programmatic feasibility;
- to evaluate effectiveness and cost-effectiveness;
- to ensure proper safety monitoring – especially in case of accelerated/conditional approval;
- to ensure responsible use (appropriate indication, doses, drug combination(s), and treatment duration); and
- to prevent emergence of resistance.

WHO's Strategic Plan for rational introduction of new TB drugs and regimens in countries (1)

Key Principles:

- Need for combination regimen(s);
- Adaptation to largely variable country settings (health and NTP infrastructure, geography, demography, TB epidemiology, level of preparedness, etc.);
- Ensure equitable access to safe and quality-assured new drugs for all patients in needs;
- Link with measures to prevent misuse of the drugs; and
- Multistage and pluri-partner process.

WHO's Strategic Plan for rational introduction of new TB drugs and regimens in countries (2)

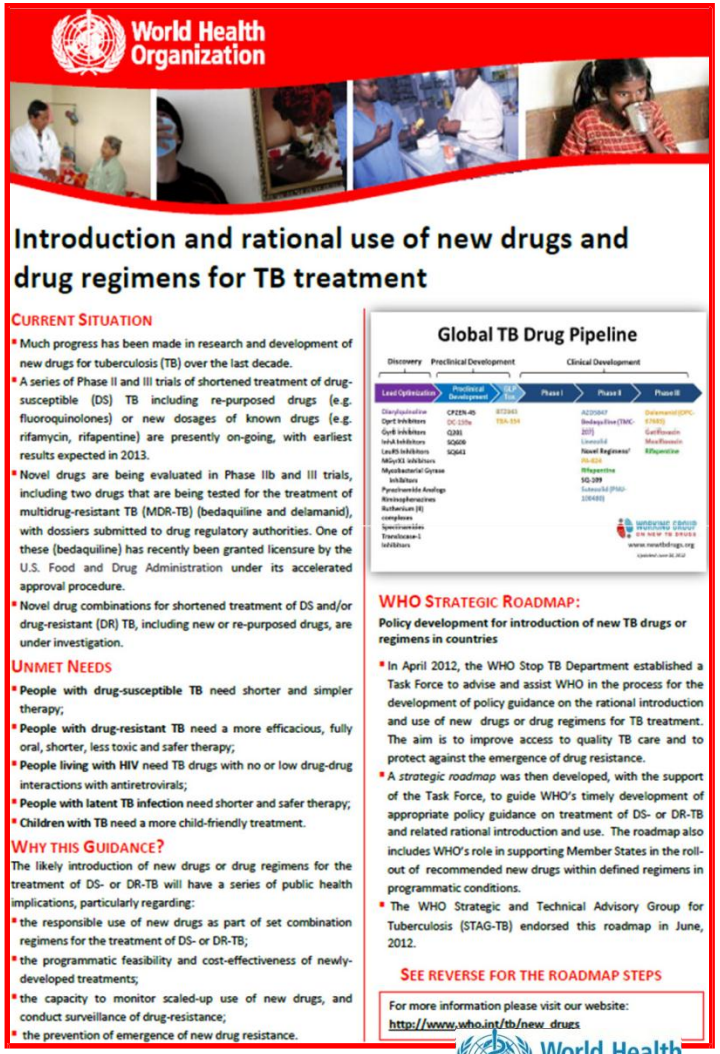
Describes key elements of a process aimed at:

- 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 implement these recommendations

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



World Health Organization

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

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

World Health Organization

The WHO Strategic Plan

5 steps:

1. Determination of the type of evidence & data to be required by WHO to recommend the use of new drug(s) / regimen(s) for the treatment of TB, and production of technical information notes
2. Development of a "Policy Development Framework" to establish recommendation for the introduction of new TB drugs / regimens in countries
3. Series of Expert consultations to evaluate new TB drugs / regimens coming out of the pipeline and revise / update treatment guidelines as appropriate
4. Issuance of Recommendations
5. Technical assistance for introduction in countries

Production of information notes

- Aimed at facilitating the evaluation of new drugs / regimens and production of policy ad–hoc recommendations for the treatment of TB (all forms)

- Information notes:
  - to countries
  - to drug / regimen developers
  - to regulators

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

Introduction in countries

Country preparedness

• Background information on health system and NTP infra structures, and on epidemiological data ("know your epidemics")

Country support to enable access to new drugs

• Strengthened capacity for diagnosis (including drug resistance), treatment and safety monitoring

• Sustained system for supply of QA drugs

• Discuss control mechanisms / regulations to prevent irresponsible use of drugs, particularly in the private sector

• Develop "Pilot projects" for initial deployment of new drugs with harmonised methods and surveillance

• Community / patients' representatives contribution

• Strong collaboration between key stakeholders

Key issues for introduction of new TB drugs or regimens

Main issues to address:

– delivery of and access to treatment (by whom ? how ?)

– risks to individuals (ADRs, DDIs) and implications

– risk of irrational use (off-label, inadequate combinations, inadequate doses or duration, etc.)

– risk for resistance development

– feasibility and potential public health impact

– cost-effectiveness

Great variability of national contexts (TB epidemics, health system and infrastructure, logistics, finance)!

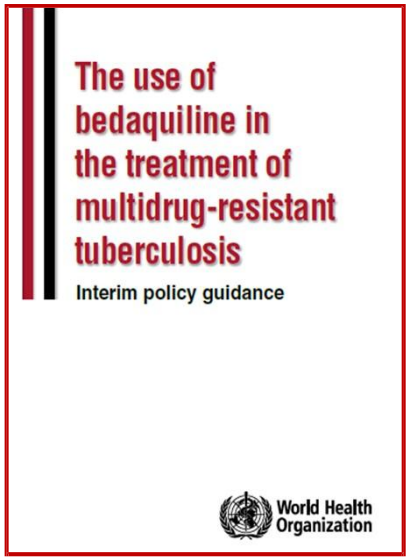
Guidance on the use of new TB drugs

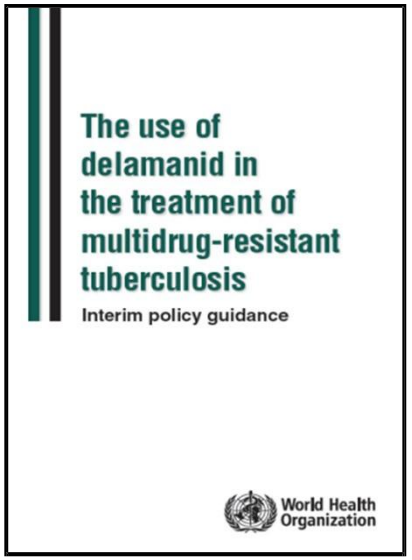
Expert consultations to evaluate new TB drugs / regimens coming out of the pipeline and revise / update treatment guidelines as appropriate

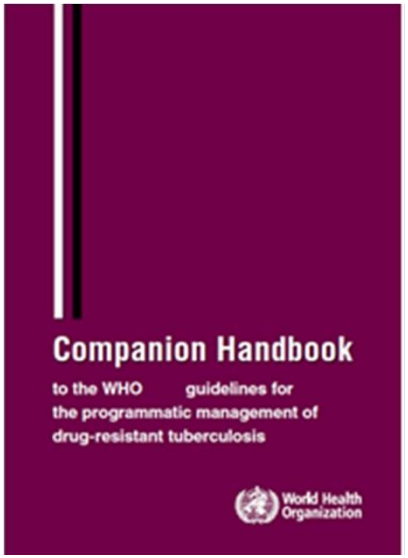
→ development of interim WHO guidance for use of bedaquiline

→ development of interim WHO guidance for use of delamanid

Backed-up by the WHO Companion Handbook on guidelines for PMDT







Interim policy guidance on the use of bedaquiline

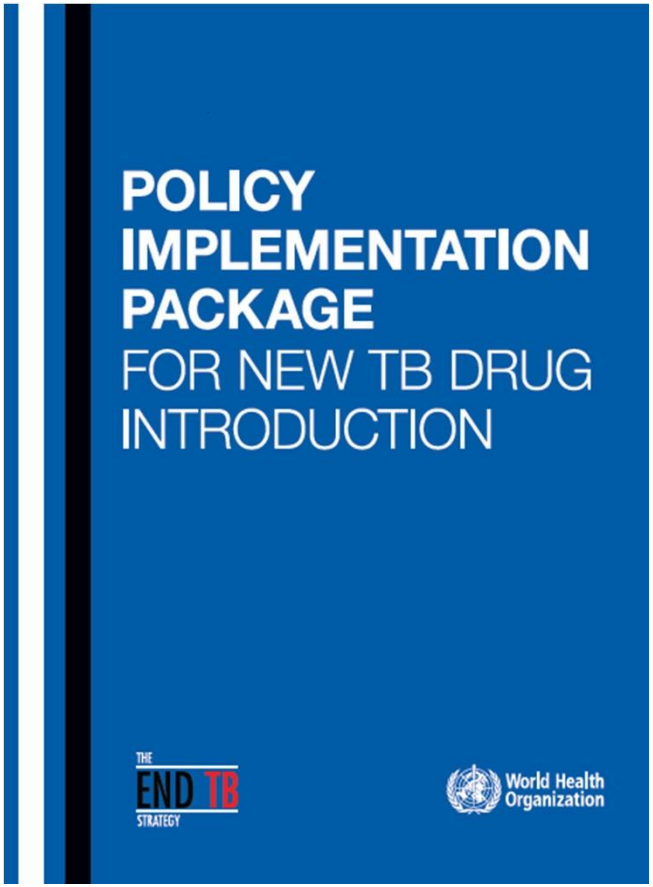
"Bedaquiline may be added to a WHO- recommended regimen in adult patients with pulmonary MDR-TB, under five specific conditions", "conditional recommendation, very low confidence in estimates of effect", WHO in June 2013

1. Proper patient selection
2. Patient informed consent required
3. Treatment design based on WHO recommendations
4. Treatment under close monitoring
5. Active pharmacovigilance

WHO Policy Implementation Package for introduction of new TB drugs or regimens in countries (1)

The goal of the Policy Implementation Package is to support countries in preparing for introduction of new TB drugs and/or regimens, based on WHO policy guidance, in order to better serve patients and communities in need.

WHO in Oct 2014



WHO Policy Implementation Package for introduction of new TB drugs or regimens in countries (2)

1. Minimum requirements for country preparedness and planning
2. Implementation plan for introduction of new TB drugs or regimens
3. Pharmacovigilance and drug resistance surveillance
4. Private sector engagement
5. Systems approach for ensuring uninterrupted supply of quality-assured medicines
6. Operational research

Implementation Plan for Introduction of Bedaquiline in Countries

Step 1: Establish the framework for the introduction of bedaquiline at country level

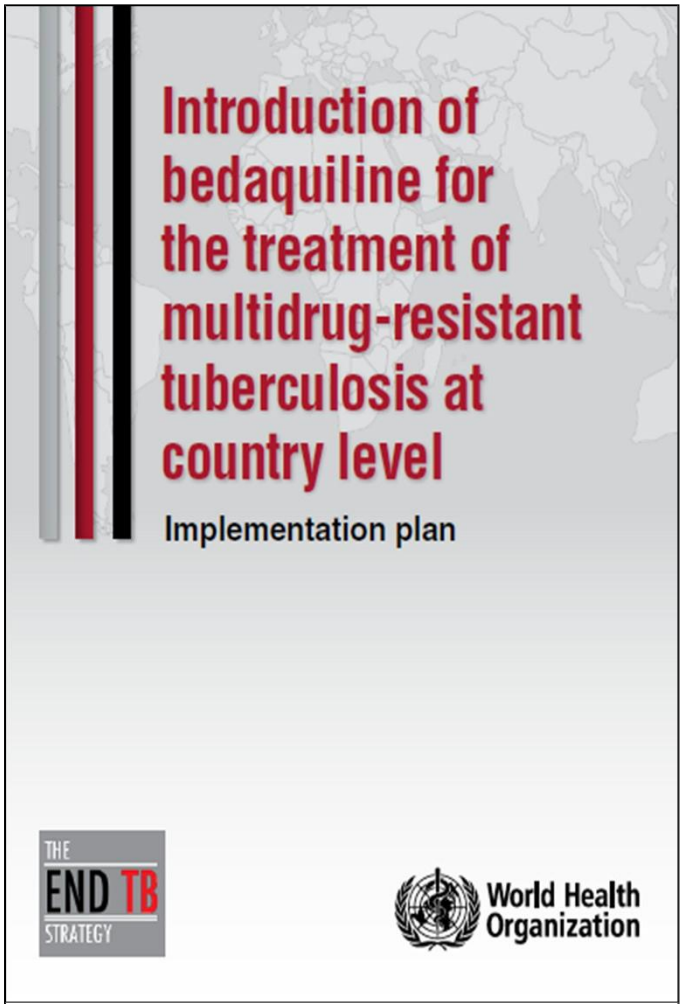
Step 2: Meet the minimal requirements for introduction of bedaquiline

· checklist to assist in country preparedness

Step 3: Develop a national plan for the introduction of bedaquiline

Step 4: Implement the introduction of bedaquiline in pilot sites

Step 5: Generate evidence for scale up



Step 1: Establishing the Framework

- Assess the national context / environment
- Create a national Implementation Task Force (chaired by MoH Rep, includes national stakeholders i.e. NTP, regulatory agency, procurement groups, PV, CSO, etc.)
- Establish a Technical Working Group (NTP-led)
- Coordinate with National Regulatory Authority
- Dialogue with pharma / drug developer(s)
- Ensure appropriate procurement
- Initial sensitization workshop

Step 2: Meeting the minimal requirements for introduction of bedaquiline

- Laboratory capacity
- Drug resistance assessment
- Clinical Review Committee
- Case management
- Recording & Reporting
- Monitoring & Evaluation
- Drug Safety monitoring
- Budget
- Drug supply system

Step 3: Develop a national plan for introduction of bedaquiline

- Update national treatment guidelines
- Selection of Pilot Sites (MDR-TB treatment centres)
- Patient eligibility
- Optimal use and selection of companion drugs
- Laboratory needs
- Case management (adherence, treatment monitoring specifics,…)
- Recording and reporting
- Monitoring and evaluation
- Drug Safety monitoring
- Ethical aspects
- Human resources development, incl training of managers and staff
- Timeline

Step 4: Implement the introduction of bedaquiline in pilot sites

- Identify patients eligible for treatment with bedaquiline
- Obtain informed consent
- Consult with Clinical Review Committee
- Initiate treatment
- Ensure active Drug Safety Monitoring – cohort based

(detection, management and reporting of adverse events)

- Monitor treatment response (outcome, individual drug resistance)

Step 5: Generate evidence for scale up

- Implementing Bdq introduction: screening, consent, review committee consultation, initiation, monitoring, AEs & ADRs, individual DST
- Generating evidence for scale-up: safety, effectiveness, tolerability, costs, process/barriers
- Needs to be done rapidly but carefully to avoid erroneous conclusions
  - Outcome indicators
  - Process indicators

Laboratory needs

- Access to DST to first and second line drugs (as per national treatment protocol)
- Rapid molecular tests: Xpert MTB/RIF and/or LPA technology
- Tests for FQ and SL INJ resistance
- Rapid communication of results
- Storage for isolates for later testing for resistance to Bdq
- Additional chemistry / laboratory tests according to drugs specifics

Ethical aspects

- This is programme implementation

  - not a trial, even if countries may need to implement 'under OR conditions'

- Patient informed consent: beware “exceptionalized” drug
- Locally relevant patient information and consent form needs to be created

Lessons learnt from work with early implementing countries

- Introduction of Bdq according to WHO recommendations seems to work and countries are very much willing to do this;
- Process requires careful planning, including reinforcement of structures (lab, R&R, M&E) and training;
- Inevitable delays/hurdles and logistical challenges at national (e.g. high level approval, waiver for drug import, regulatory approval) and international levels (drug order approved by GF, etc.);
- Long term view to improve the way new drugs are introduced: find right balance given urgent needs and slow implementation process;
- Model can be used for other new drugs and regimens as they become available;
- Need to streamline process for more countries and other new drugs;
- Train consultants, need to deliver updated information to donors and regulators; and
- rGLCs may play a key role to advise countries appropriately on ability to introduce new TB drugs/regimens and related activities.

Key messages

Key messages for WHO/GTB are:

- to engage with and support national authorities and stakeholders early in the preparation of policies for introduction of new TB medicines at programmatic level (including quality, procurement aspects, etc.);
- to ensure that new TB medicines / regimens are introduced in an optimal way to give maximum benefit to patients in need, to protect patients and the drug from misuse, and to prevent the emergence of resistance; and
- to ensure that introduction of new medicines follows international / national policy recommendations and appropriate plans are made to ensure feasibility and inform policy-making
- to ensure feasibility under programmatic use
- collect due information (safety, feasibility, effectiveness, …) to
  - inform national/global policy-making
  - expand and scale-up (country-wide; private sector)

Thank you for your attention !