POLICY IMPLEMENTATION PACKAGE FOR NEW TB DRUG INTRODUCTION

THE END TB STRATEGY

World Health Organization

Acknowledgements:

This document was developed by a team led by Christian Lienhardt and Diana Weil. The core work was produced by the Task Force on New TB Drug Policy Development (Jennifer Cohn, Margareth Dalcolmo, Gerry Davies, Viet Nhung Nguyen, Christophe Perrin, Michael Rich, Giorgio Roscigno, Holger Schunemann, Alena Skrahina, Soumya Swaminathan, Andrew Vernon; Chair: Gavin Churchyard), with the contribution of Janet Ginnard, Richard Hafner, Andrew Jones, Joel Keravec, Michael Kimerling, Niranjan Konduri, Ya-Diul Mukadi, Andre Zagorski and WHO/GTB staff Dennis Falzon, Mukund Uplekar, Matteo Zignol, Fraser Wares, Ernesto Jaramillo. Overall guidance was provided by the Director of the Global TB Programme, Mario Raviglione.

The Bill and Melinda Gates Foundation is acknowledged for its support to the development of this document through grant project number OPP1052577.

Printed in France

WHO/HTM/TB/2014.22

Editing and design by Inís Communication - www.iniscommunication.com

Summary

The landscape of drug development for treatment of tuberculosis (TB) has evolved dramatically over the past 10 years. Newly developed and re-purposed drugs are being investigated in clinical trials, and novel drugs have been approved by stringent regulatory authorities under accelerated or conditional procedures. Promising novel regimens are being tested for the treatment of drug-susceptible and drug-resistant TB, and regimen development will likely accelerate with the introduction of new TB drugs into the market.

Reaching populations in need rapidly and equitably when a new drug or drug regimen has demonstrated evidence-based benefits is a priority for WHO. In its new *End TB Strategy* with targets to end the Global TB Epidemic by 2035, WHO advocates for rapid uptake of new drugs and associated research to optimize implementation and impact.

To address challenges in preparing and enabling safe and effective uptake of new drugs or regimens under programmatic conditions, WHO has developed a *Policy Implementation Package* (PIP).

The goal of the PIP 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.

The PIP provides the key elements of a roadmap for introduction of new TB drugs and/or regimens and aims to complement existing and new policy guidance on the use of new drugs for the treatment of TB or MDR-TB. There are **six elements** in this package:

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

This package provides briefing notes on steps to be considered in addressing each of these elements, and accompanying checklist and background documentation. Further implementation guidance will be provided through model national implementation plans, which build on these notes.

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Introduction

New drugs and regimens are urgently needed to enable faster, safer, less toxic and more effective treatments for people with tuberculosis (TB). Treatment of drug-susceptible TB relies on a combination of four drugs given for six months, which may challenge the capacity of patients and health providers to maintain adherence until completion. Although current treatment is recognized as being much more cost effective compared to many other priority health interventions, the burden on health systems and patients is enormous.

Furthermore, drug-resistant TB is a major threat to global care and control. The World Health Organization (WHO) estimates that about 480 000 new multidrug-resistant TB (MDR-TB)[a] cases occurred in the world in 2013. Of these, only 97 000 were reported to WHO to be enrolled in treatment. This gap is largely the result of shortfalls in diagnostic and treatment capacity in most countries *(1)*. Furthermore, on average, an estimated 9.0% of people with MDR-TB have extensively drug-resistant TB (XDR-TB) – an even more lethal form of drug-resistant TB[b] *(1)*. Current treatment regimens for drug-resistant TB are far from satisfactory: most MDR-TB patients require treatment for 20 months or more with daily administration of drugs that are more toxic and less effective than those used to treat drug-susceptible TB.

Lastly, there is a great need for shorter and more effective treatment for latent TB infection in order to prevent the emergence of disease in, and transmission from, the estimated 1 billion people infected with *Mycobacterium tuberculosis* – the germ that causes TB disease – in the world today.

The landscape of drug development for treatment of TB has evolved dramatically over the past 10 years. Newly developed and re-purposed drugs are being investigated in clinical trials, and some drugs have already been approved by stringent regulatory authorities under accelerated or conditional procedures. Promising novel regimens are being tested and regimen development will likely accelerate with the introduction of new TB drugs into the market. WHO recognizes the significant economic and logistic implications of the introduction of new or re-purposed drugs for the treatment of TB, as well as the personal and public health consequences if the process is not managed well. A number of key issues need to be addressed:

- Reaching populations in need rapidly and equitably when a new drug or regimen has demonstrated benefit to a group of patients.
- Ensuring responsible use of new drugs, as part of combination regimens for the treatment of TB.
- Building capacity to monitor scaled-up use of new drugs or regimens, and ensuring sound pharmacovigilance and surveillance of drug resistance.
- Ensuring the safety of patients exposed to new drugs while at the same time preventing the emergence of resistance to these new compounds.
- Assessing the programmatic feasibility and cost-effectiveness of newly developed TB treatment regimens.

To address these issues, WHO has initiated a process to develop ad-hoc policy recommendations for the treatment of TB with new drugs *(2)* and assist countries to prepare for safe and effective uptake of these new drugs or regimens under programmatic conditions. A *Policy implementation package* (PIP) for new TB drugs has been developed to support country efforts in preparing and implementing the use of recommended drugs and/or regimens. The PIP provides an overview of the key elements to be

a MDR-TB is caused by organisms that are resistant to the most effective TB drugs (isoniazid and rifampicin). MDR-TB results from either infection with organisms that are already drug-resistant, or may develop in the course of a patient's treatment.

b XDR-TB is a form of TB caused by organisms that are resistant to isoniazid and rifampicin (i.e. MDR-TB) as well as a fluoroquinolone and one of the second-line, injectable TB drugs (amikacin, kanamycin or capreomycin).

considered in preparing for the rational introduction and use of new TB drugs and/or regimens in countries; it aims to complement WHO policy guidance on the treatment of TB or MDR-TB. WHO recognizes that there will be variability in implementation processes, given the country context, the nature of the TB drugs and/or regimens proposed, and the relevant WHO guidance on their use. Therefore, the PIP is conceived as a *generic tool* to orient and frame actions by national governments and their partners.

The PIP covers **six elements** needed to be addressed for introduction of new TB drugs or drug regimens:

1) Minimum requirements for country preparedness and planning: This first element outlines the essential basic health and programmatic capacities that must be in place at country level for the optimal introduction and implementation of a new TB drug or drug regimen according to WHO policy recommendations. A check-list is provided to assess these requirements.

2) National implementation plan for introduction of new TB drugs or regimens. This element describes the various steps in the development of a national implementation plan, taking into account the various operational models for introduction of new TB drugs or regimens, depending on the TB epidemics situation and the level of preparedness in a country, and the type of drug or regimen to be introduced.

3) Monitoring and evaluation of new TB drugs or regimens, including pharmacovigilance and drug resistance surveillance. Introduction of new TB drugs or regimens requires careful monitoring in terms of safety (particularly if drugs are being introduced following conditional regulatory approval), and emergence of drug resistance. This element introduces a basic framework for establishment of pharmacovigilance for new TB drugs and monitoring of drug resistance.

4) Private sector engagement. Introduction of new TB drugs requires a set of best practice regulations by ministries of health to provide rational access to and protection of new drugs. This element addresses key issues for effective introduction of new TB drugs in the context of substantial involvement of the private sector in TB care, usually referred to as 'public–private mix'.

5) Systems approach for ensuring uninterrupted supply of quality-assured medicines. This element describes the need for a clearly established procurement and supply chain management system at country level with the view to achieve an uninterrupted supply of both new and existing quality-assured medicines.

6) Operational research. This element addresses how operational research will be particularly important for the rational and responsible introduction of new TB drugs or regimens and can assist countries in the implementation and scale-up processes. Operational research is also helpful to evaluate the public health impact, through the collection of relevant information to measure feasibility, cost effectiveness, acceptability and impact.

Based on this PIP, WHO is working with partners to develop model implementation plans and other tools based on implementation experience (see **Element 2**).

In preparing this package, WHO has benefitted from the advice of the WHO Task Force for New Drug Policy Development to guide its approach to developing new treatment policy and to support countries with initial preparation and rational introduction of new drugs. WHO staff and members of the Task Force served as the writing group for this PIP. The writing group has also drawn upon a range of WHO policy guidance and tools, as well as research, tools and best practices drawn from country and partner experience in TB and in related fields of public health and disease prevention and control.

See http://www.who.int/tb/new_drugs/en/index.html
for links to available materials (includes factsheet on introduction of new TB drugs, and related information notes for drug and drug regimen developers, regulatory agencies and TB control programmes).

References

1. Global tuberculosis report 2014 (WHO/HTM/TB/2014.08). Geneva: World Health Organization; 2014.
2. Introduction and rational use of new drugs/regimens for the treatment of tuberculosis in countries. Geneva: World Health Organization; 2014. (http://www.who.int/tb/new_drugs/en/index.html, accessed 7 June 2014).
3. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: Interim policy guidance. Geneva: World Health Organization; 2013. (http://www.who.int/tb/challenges/mdr/bedaquiline/en/, accessed 14 October 2014).

1 Minimum requirements for country preparedness and planning

Background

National governments are responsible for introducing new tuberculosis (TB) drugs and regimens in a way that guarantees their safe and responsible use, assures equitable access and minimizes emergence of drug resistance. It is widely acknowledged that the means by which this is achieved depends on the nature of the TB drugs or regimens introduced, the conditions of use and the specific country context and health infrastructure.

Objective

To describe suggested minimum requirements for countries' preparedness for the safe and responsible introduction and use of a new TB drug or regimen according to WHO recommendations, ensuring equitable access for patients in need.

Key steps

Introduction of a new TB drug or regimen requires that minimum baseline conditions be in place in various organizational, technical, programmatic and logistical areas to enable optimal implementation. Assessing the presence of these **minimum requirements** will help countries to identify the areas that need strengthening or upgrading. These minimum requirements are categorized in seven key areas:

1. The national health context

At baseline, it is necessary to assess the health environment in which the new TB drug or regimen will be introduced, understand how the national TB programme (NTP) operates, and appreciate the epidemiological background. The structure of the country's health care system should be reviewed *(1)* including the structure and organization of the NTP, its financing and human resources, together with its performance indicators. Data are also needed on key epidemiological indicators, such as TB notification, estimated TB incidence, mortality, treatment outcomes, drug resistance (for first- and second-line drugs), and TB/HIV co-infection. *Countries should only consider introduction of new treatments if there is evidence that appropriate capacity and infrastructure are in place to support adequate performance in basic TB control efforts.*

2. Laboratory

Appropriate tests are essential for reliable diagnosis of TB and multidrug-resistant TB (MDR-TB), monitoring of response to treatment, and surveillance of resistance. The capacity of the TB laboratory network to provide tests at all levels of care (national, regional and district) must be evaluated to ensure that the new drug can be rationally introduced. Methods for monitoring resistance to novel drugs will need to be introduced. Isolates from patients with treatment failure should be stored in designated laboratories until drug-susceptibility testing, on- and off-site, can be performed. Laboratory facilities are needed to support monitoring of drug-specific toxicities. The minimum set of TB laboratory tests and their placement at various levels of the health system will vary depending on the new TB drug or regimen.

3. Drug supply and management

A well-managed and sustainable procurement system is key for optimal introduction of new TB drugs. Aspects pertaining to regulatory process, licensure, quality assessment, procurement and importation of drugs should be examined. Information is needed from key bodies involved in the procurement and distribution of TB drugs, including national regulatory authorities, national medical stores, implementing partners and drug distributors. WHO-endorsed standard procedures for procurement of TB drugs within the NTP and collaborative treatment sites should be in place, together with appropriate quality assurance policies, reliable forecasting and distribution logistics, as well as a functional recording system to track drugs through the supply chain. Ensuring these items are firmly in place will help optimize drug introduction and the ability to reach patients in need.

4. Case management

National guidelines should be updated according to WHO recommendations on use of new drugs in TB treatment, and case management should respect the International Standards for TB Care *(2)*. Health care providers, especially staff involved in diagnosis and treatment of MDR-TB should benefit from continuing education on updates and changes in clinical and programmatic practice. For MDR-TB, programmatic

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management requires regular supervision by a specialized team, due to the frequency of serious adverse events, the risk of newly acquired drug resistance, as well as other challenges to patients' adherence. Social support measures tailored to individual patient needs should be available. Adequate resources should be available for clinical monitoring (such as: electrocardiography (ECG), audiometry, biochemical testing and neuropathic assessment) as per WHO guidance.

5. Monitoring and evaluation

A strong monitoring and evaluation (M&E) system is required to ensure rational use of a new TB drug or regimen and prevent the emergence of resistance. The existing M&E framework for drug-susceptible and drug-resistant TB should be evaluated to identify areas requiring strengthening. The minimum M&E activities that must be in place include: use of the WHO recording and reporting system (preferably using electronic formats); a data management system that interfaces smoothly with the existing or planned pharmacovigilance system; regular collection of data for periodic cohort analysis; supportive supervision; and a drug resistance surveillance system *(3–6).*

6. Pharmacovigilance

Adverse drug reactions[a] and adverse events[b] can contribute to treatment failure, avoidable morbidity and death, and/or creation of drug resistance. Pharmacovigilance is critical given the complexity of regimens for MDR-TB, the toxicity of some of the drugs and the concomitant use of antiretroviral therapy in patients with HIV-associated TB. In preparing for the introduction of new TB drugs, background information is needed on the existing pharmacovigilance system and its structure. Requirements include standards for centralized data collection, and establishment of an active pharmacovigilance system with an individual patient database *(7, 8).*

7. Financing

Implementation of a new TB drug or regimen requires identification of adequate financial resources (from the government or donors). A budget should be prepared to account for additional activities to be carried out, including the incremental costs of additional or adjusted commodities purchase, training, diagnosis and care, as well as monitoring and evaluation.

A checklist for country readiness assessment

As indicated in **Element 2**, it is advised that a national implementation Task Force be established to oversee the process of introduction of new TB drugs or regimens. To assist the work of the Task Force, a **checklist** has been prepared that reviews details for each of the areas above – see Annex.

Related WHO documents on introduction of new TB drugs and drug regimens can be found at the following link: http://www.who.int/tb/new_drugs/en/index.html

The guidelines on the programmatic management of drug-resistant TB (5) and the companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis (6) provide the information on MDR-TB management that can serve as a basis for the assessment of preparedness for introduction of new drugs or regimens for MDR-TB.

References

1. Monitoring the building blocks of health systems: A handbook of indicators and their measurement strategies. Geneva: World Health Organization; 2010. (http://www.who.int/healthinfo/systems/monitoring/en/, accessed 7 June 2014)