POLICY IMPLEMENTATION PACKAGE

FOR NEW TB DRUG INTRODUCTION

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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

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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).

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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).

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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).

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6. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. (WHO/HTM/TB/2014.11) Geneva, World Health Organization. 2014. (apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf, accessed 14 October 2014).

7. Minimum requirements for a functional pharmacovigilance system. Geneva: Global Fund to Fight AIDS, TB and Malaria and World Health Organization; 2010. (http://www.who.int/medicines/areas/quality_safety/safety_efficacy/PV_Minimum_Requirements_2010_2.pdf, accessed 5 June 2014).

8. A practical handbook on the pharmacovigilance of medicines used in the treatment of tuberculosis. Enhancing the safety of the TB patient. Geneva: World Health Organization; 2012. (http://www.who.int/medicines/publications/Pharmaco_TB_web_v3.pdf, accessed 5 June 2014).

a   Adverse drug reaction: a response to a medicine that is noxious and unintended, and that occurs at doses normally used in people.

b   Adverse drug event: any untoward medical occurrence that may present during treatment with a pharmaceutical product, but that does not necessarily have a causal relationship with this treatment.

Annex: Meeting the minimum requirements for introduction of new TB drugs/regimens: a readiness assessment checklist

The introduction of new drugs/regimens should always take place within a functional national TB programme (NTP) organized according to WHO recommendations, including a functional programmatic management of MDR-TB (PMDT). In order to guide countries to assess their level of preparedness and develop appropriate plans for the rational introduction of new TB drugs/regimens, the current package includes a **checklist** that outlines the *minimum conditions* that countries should have in place as a *prerequisite* for introduction and implementation of a new TB drug or drug regimen.

Much of the required information already exists as part of the routine documentation of the NTP or PMDT programme into which the new drugs/ regimens are being introduced. The checklist is articulated into seven domains, that need particular attention during the preparatory phase, and highlights for each of them key elements that need proper checking:

1) Health and regulatory environment

2) Laboratory capacity

3) Drug procurement system

4) Case management

5) Monitoring & evaluation

6) Pharmacovigilance

7) Financial resources and country support

HOW TO USE THE CHECKLIST?

The checklist should be compiled and used by the NTP/partners as a tool to assess whether all essential aspects are in place or need to be improved or established prior to the introduction of new drugs/regimens.

Once information is gathered, it should be evaluated by a specifically appointed national Implementation Task Force (see **Element 2**) together with national and international partners, to streamline the preparation phase, planning and implementation.

If the minimum requirements are not met or are not in place at the time of preparation, a specific plan and timeline for addressing the gaps and weaknesses should be developed by the Task Force. Progress should be periodically assessed to ensure all minimum requirements are in place and functional.

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Checklist for country preparedeness and planning

DOMAIN	MINIMAL REQUIREMENTS FOR COUNTRY IMPLEMENTATION OF NEW DRUGS/REGIMENS	IN PLACE / AVAILABLE	TO BE STRENGTHENED	TO BE SET UP / ESTABLISHED
Health and regulatory environment	Background information on health system infrastructure			
	Background information on national TB programme (NTP) infrastructure			
	Background information on programmatic management of MDR-TB (PMDT) in the country *(1,2)*			
	TB burden indicators			
	NTP performance indicators			
	Background information on TB case management at country level			
	Background information on national drug regulatory process			
Laboratory capacity	**At national level**			
	Background information on general laboratory infrastructure			
	Background information on TB laboratory infrastructure			
	WHO/ISTC standards *(3)* requirements for TB diagnosis			
	Decentralized access to rapid molecular tests			
	Reference laboratory with sufficient capacity for culture			
	Drug susceptibility testing (DST) to determine resistance to first-line drugs (at least rifampicin and isoniazid) and second-line drugs (at least ofloxacin, moxifloxacin, amikacin/kanamycin, capreomycin) *			
	Quality assurance system through an established link with a Supranational Reference Laboratory			
	At implementing site level			
	Sputum smear microscopy or other WHO-accepted initial diagnostic test			
	Rapid molecular tests: Xpert MTB/RIF and/or LPA[†] technology			
	Culture (solid and/or liquid)			
	Access to DST to first and second line drugs (as per national treatment protocol)*			
	Haematology (white blood count, hemoglobin, platelet count)			
	Biochemistry (kidney function tests, liver function tests, pancreatic function tests, electrolytes)			
	HIV test, CD4 cells count, HIV viral load			
	Pregnancy test			
	Other tests as per treatment protocol (e.g. TSH, audiometry, serum glucose)			
Drug Supply and Procurement system	Procurement and supply chain management (PSCM) system in place to guarantee regular drug supply and distribution			
	Absence of stock-outs for 1 year			

DOMAIN	MINIMAL REQUIREMENTS FOR COUNTRY IMPLEMENTATION OF NEW DRUGS/REGIMENS	IN PLACE / AVAILABLE	TO BE STRENGTHENED	TO BE SET UP / ESTABLISHED
Case management	**At national level**			
	WHO/ISTC standards *(3)* for treatment			
	Clinical Review Committee (e.g. MDR-TB Consilium)			
	Appropriate case holding strategy			
	At implementing site level			
	Access to information and education on TB and TB treatment			
	Availability of ancillary drugs			
	Measures to maximize treatment adherence			
	Chest X-ray			
	ECG			
	Audiology*			
	Visual acuity tests*			
	Psychosocial evaluation			
	Access to psychiatric evaluation if needed*			
	Access to neurologic evaluation if needed*			
	Access to bronchoscopy if needed*			
	Access to surgery and histopathology if needed*			
	Access to continous ECG monitoring if needed*			
	Access to ultrasound if needed*			
Monitoring and Evaluation	Recording and reporting (R&R) in line with revised WHO recommendations *(4,5)*			
	Electronic R&R system			
	Minimum indicators routinely generated			
	Regular supervision plan (minimum 2 rounds/year) to each implementing site			
	Regular cohort data analysis			
	Drug resistance surveillance (DRS) in the last 2–3 years			
	Plan to repeat DRS 3–5 years after new drug/regimen introduction or to establish continuous DRS**			
Pharmacovigilance (PV)	Background information on PV system at national level			
	Minimum requirements in place *(6,7)*			
	Cohort event monitoring system			
Financial resources and country support *(8)*	Background information on NTP budget			
	Budget for introduction of new drug/regimen developed			
	Funds for new drug/regimen introduction secured			
	Technical assistance partners identified			
	Plan for technical assistance developed			

* These are the required tests and diagnostics at the implementing site level during the pilot phase of introduction; as more experience is gained with new drugs/regimens, the country may consider allowing scale-up sites without some of these tests to use new drugs/regimens, provided they are able to refer patients, send samples, and receive results in a timely fashion.

** Continuous surveillance is defined as routine diagnostic drug susceptibility testing of all patients with tuberculosis.

† LPA: Line probe assay

References

1. Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 Update (WHO/HTM/TB/2011.6). Geneva: World Health Organization; 2011.

2. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. (WHO/HTM/TB/2014.11). Geneva, World Health Organization. 2014 (apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf, accessed 13 October 2014).

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8. Planning and Budgeting Tool for tuberculosis control (version 6, updated May 2013) and User Manual part I and II. Geneva, World Health Organization (http://www.who.int/tb/dots/planning_budgeting_tool/download/en/index.html, accessed 13 October 2014).

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2 A national implementation plan for introduction of new TB drugs or regimens

Background

The conditions for the introduction of a new tuberculosis (TB) drug or regimen are shaped by a number of factors, in particular the characteristics of the new TB drug or regimen, the indications for use, and the country context - i.e. the national health environment, the specifics of the TB epidemics and the means of control.

Objective

Building on the assessment of minimum requirements (see **Element 1** and **checklist**), to outline the practical steps for preparing the introduction of new TB drugs and regimens that can be tailored to the national environment and the conditions of introduction.

Key steps

1. Establish a national framework for introduction of new TB drugs or regimens

A. Involve national leadership and establish working group to lead the implementation

The national TB programme (NTP) is best placed to be the focal point for the introduction of new TB drugs and regimens.

The creation of a high-level National Implementation Task Force is strongly recommended to ensure planning and coordination of the introduction process across different policy-makers and implementers within the health system. The mandate of this task force is to oversee the preparation, planning and implementation of the introduction of the new TB drug or regimen and its evaluation. It should be chaired by a representative of the Ministry of Health (MoH), have its secretariat within the NTP and be composed of representatives from the MoH and related bodies, technical stakeholders, donors, civil society and international partners.

In addition, it is advised to set up a *Technical Working Group* (TWG) to plan, conduct and supervise the various steps in the introduction of a new TB drug or regimen. This group, led by the NTP, could be a subset of the above committee and include NTP staff, academics, clinicians, microbiologists, pharmacists as well as national and international technical partners. It would focus on supporting the NTP to pursue adaptation of World Health Organization (WHO) guidance on new drugs or regimens, revision of national treatment guidelines and clinical tools, development of training materials, and revision of recording and reporting forms, etc. The TWG would also provide support during the training of medical staff and the supervision of pilot implementing centres.

B. Coordinate with the national regulatory authority

The NTP should liaise with the national regulatory authority (NRA) to enable action by the relevant body to:

- ensure timely filing and drug registration (including temporary import permissions if needed) so that the drug is available at the time of planned introduction;
- prepare inclusion in the national essential medicines list (if applicable);
- discuss plans for the required pharmacovigilance system (see **Element 3**);
- discuss plans to promote responsible use of the new drugs, including access by the private sector (see **Element 4**).

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C. Engage in dialogue with drug developer

The MoH should be informed on international pricing and filing strategies for relevant products and explore options for obtaining quality assured generic versions early on. Topics for discussion with drug developers at country level include:

- filing for registration;
- prescription and sale in the private sector;
- promotion of appropriate marketing;
- application of internationally agreed prices;
- need for assessment of resistance to the new drug(s) with appropriate transfer of technology.

2. Develop a national implementation plan

Once all basic requirements have been checked (see **Element 1**, **Annex**), and following the establishment of the national framework, countries should develop a national implementation plan. To assist with this, WHO has developed a generic *Implementation plan for the introduction of new TB drugs and regimens* (see http://www.who.int/tb/new_drugs/ParentImplementationPlan). It is recommended that countries adapt this plan to the type of drug or regimen to be introduced, and to their specific environment and settings. As an example, the parent implementation plan for introduction of new TB drugs has been adapted to the case of bedaquiline (see http://www.who.int/tb/new_drugs/bdq_implementationplan).

A. Select an implementation model

Depending on the national context, the type of new drug or regimen, and the availability of appropriate diagnostics, an adaptive model of introduction should

be selected. Box 1 provides a framework for possible introduction models for each country to consider.

B. Revise technical guidelines

The NTP with technical partners should revise the national treatment guidelines, based on the WHO policy guidance for the use of the new TB drug or regimen. Plans should be made for dissemination and related capacity building activities.

C. Prepare the national implementation plan

The NTP, assisted by the TWG, should develop the national implementation plan, describing in detail the various phases of introduction of the new TB drug or regimen at country level (Box 1). This implementation plan (with relevant budget) should address all aspects of introduction, including drug procurement and supply management; diagnostic needs; training and system strengthening (diagnostic capacities, information systems); case management; treatment support; and pharmacovigilance. The implementation plan should also include an efficient and functional monitoring and reporting system on clinical use, safety and the programmatic performance of the introduction. The plan should outline the means of introduction – for instance an initial phase of piloting in specifically selected sites followed by a scale-up phase – as well as a phase-out plan for the old drug(s) or regimen(s) if replacement is being advised.

Early dialogue should be initiated with the national body responsible for domestic financing as well as potential or existing international donor(s) supporting TB control, programmatic management of multidrug-resistant TB, and drug procurement, to ensure effective and equitable access to the new TB drug or regimen.

BOX 1: DEVELOPMENT OF A NATIONAL PLAN FOR THE INTRODUCTION OF A NEW TB DRUG OR REGIMEN

The national implementation plan should address the following aspects of introduction of a new TB drug or regimen:

- rationale for the introduction of the new drug or regimen at country level;
- development and/or update of clinical guidelines, including:
  - information on patient eligibility and exclusion criteria;
  - optimal use of the new TB drug and selection of companion drugs;
  - case management;
  - treatment monitoring;
- recording and reporting;
- monitoring and evaluation;
- pharmacovigilance;
- ethical aspects;
- training of managers and staff;
- human resources development;
- timeline development;
- budget development.

Table 1: Models to be considered in designing the introduction of new TB drugs or regimens

	NEW MDR-TB DRUG ADDED TO EXISTING REGIMEN	NEW MDR-TB REGIMEN	NEW DS-TB REGIMEN	NEW DS/DR-TB REGIMEN
Expected number of patients	Small–Medium	Medium	Large	Large
Setting	Specialized centres; part or all of existing MDR-TB sites (if use is uncomplicated)	Existing MDR-TB sites; additional sites if new regimen is simpler than existing regimen	Existing DS-TB treatment level	Existing DS-TB treatment level or subset of these sites (if management more complex than current short course)
Means of introduction	Initially in specialized sites only	Initially in specialized sites or by certified MDR-TB treatment providers	Physician prescription or provision by certified TB treatment provider	Physician prescription or provision by certified TB treatment provider
Monitoring options:				
a) if conditional regulatory approval	a) Patient registry, compassionate use or expanded access programme	a) Patient registry, clinical/operational research	a) Basic management unit TB register	a) Patient registry, clinical/operational research for specific sub-group of patients
b) if fully approved	b) Spontaneous pharmacovigilance	b) Spontaneous pharmacovigilance	b) Spontaneous pharmacovigilance	b) Spontaneous pharmacovigilance
Phased introduction	Depending on context: begin at tertiary/referral level or trial sites then scale up	Depending on context: begin at tertiary/referral level, or at certified MDR-TB treatment sites, then scale up	Begin as pilot, then scale up	Begin as pilot, then scale up
Laboratory implications	**High** Need to align with appropriate DST availability	**High** Need to align with appropriate DST availability	**Moderate** Need to align with appropriate DST availability	**High** Need to align with appropriate DST availability

DR-TB = drug-resistant TB, DS-TB = drug-susceptible TB, MDR-TB = multidrug-resistant TB, DST = drug susceptibility test.

3 Monitoring and evaluation of new drugs and regimens, including pharmacovigilance and drug resistance surveillance

Background

Most countries introducing new tuberculosis (TB) drugs and regimens have a routine monitoring and evaluation (M&E) system in place as part of their programmatic management of drug-susceptible or drug-resistant TB. Some aspects of these systems might need to be reinforced to enable rational introduction of new drugs or regimens, prevention of misuse, and collection of reliable data on safety and effectiveness. Documenting the way that patients respond to treatment is essential to guiding country decisions in terms of implementation and scale-up. Patients receiving new drugs or regimens should be regularly monitored during and after treatment, using the standard monitoring schedules *(1, 3)*. At programmatic level, evaluation of treatment response of an initial cohort of patients will assist in the evaluation of the overall performance of the new drug or regimen and in the planning for scale-up as appropriate.

Two specific aspects deserve particular attention: pharmacovigilance and drug-resistance surveillance.

I. Pharmacovigilance

During TB treatment, the occurrence of adverse drug reactions (ADRs) can contribute to additional morbidity, treatment interruption before completion, treatment failure, emergence of drug-resistance, reduced quality of life, or death. When introducing a new drug or regimen, pharmacovigilance is essential to record in a reliable way the evidence of ADRs or drug–drug interactions.

Pharmacovigilance is defined as the "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem" *(4, 5)*. The aim of pharmacovigilance is to enhance patient care and safety in relation to the use of medicines and to support public health programmes by providing reliable information for the effective assessment of the risk–benefit profile of medicines. This informs policy decisions, clinical guidelines and treatment recommendations.

Objective

Active pharmacovigilance methods are recommended to ensure that the safety of new TB drugs and/or regimens is successfully monitored within national TB programmes.

Establishing an active pharmacovigilance system requires systematic screening for significant clinical events (through patient interview and clinical testing) and the recording of relevant information in relation with drug intake on standard forms. Cohort event monitoring (CEM) is the best-suited method of pharmacovigilance for the introduction of new drugs and regimens *(4)*. It is an active form of surveillance, similar in design and management to an observational cohort study, with baseline and periodic measurement of patient parameters prospectively. The basic function of CEM is to act as an early warning system for problems with new medicines. The cohort approach reduces the likelihood of bias in selection of patients or in measurements of events and is best suited to make preliminary conclusions about the potential association of an event with the given exposure. Lastly, it provides denominators and baseline data for analysis. Confirmed or suspected associations need to be notified to the national body responsible for drug safety.

Key steps

Before implementing CEM, it is necessary to assess what pharmacovigilance experience exists in the country. Most countries will not have existing programmes for active pharmacovigilance in TB but may have such systems in place for other diseases (e.g. malaria, HIV) *(6)*.

The nine steps to implement a CEM are as follows:

1. Creation of a national CEM committee representing the various constituencies to steer the creation and continued functioning of the CEM.
2. Development of a CEM protocol defining clearly the activities and the standard operating procedures for the study, as well as respective roles and responsibilities, with a clear budget and options for resource mobilization.

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3. Ethical approval of CEM protocol is required before the start of activities.

4. Management and supervision of CEM should be preferably carried out by the unit of the national TB control programme devoted to the management of drug-resistant TB.

5. Training for staff at different levels

6. Creation of data collection material, based on WHO guidance *(4).*

7. Collection of data at initiation and during treatment review, with adequate liaison with laboratories and other diagnostic units.

8. Creation/adaptation of an electronic database to ensure proper safekeeping of the data. This is indispensable for the analysis of data and will facilitate the sharing of data between centres. The electronic register will include all data elements needed for monitoring of effectiveness, adverse events and feasibility (ideally inclusive of costs) *(2).*

9. Identifying signals and data analysis

II. Drug-resistance surveillance

Patients treated for TB should be closely monitored to detect drug resistance early enough to ensure that an adequate regimen is used. The availability of reliable drug-susceptibility testing (DST) for new classes of drugs that have not been in wide use usually lags behind the release of the drugs themselves. Once new DST methods become available they need to be accurate and feasible to be used in low-resource settings. Drug resistance surveillance is crucial to the protection of new medications and their rational use.

Objective

Surveillance of drug resistance is mandatory when piloting the introduction of new regimens for the treatment of TB, in order to:

(i) assess baseline levels of resistance to existing TB drugs in the population targeted to receive the new drug or regimen;

(ii) monitor the emergence or amplification of resistance to the drugs that are part of a new regimen.

Key steps

To meet these objectives, two different but complementary surveillance approaches should be considered *(7)*:

- **Population-representative drug resistance surveys.** These are routinely conducted in most countries. Countries should be invited to store the survey strains so that when new regimens are planned to be introduced, baseline levels of resistance to the new or re-purposed drug(s) can be assessed. This information provides the rationale for the piloting of a new regimen in a country. Surveys should be repeated every 3–5 years to monitor time trends in drug resistance in the population. All phenotypic and molecular tests endorsed by WHO may be used for this purpose.

- **Continuous surveillance of drug resistance in patients piloting the new regimen.** All patients receiving a new treatment regimen should be closely monitored to detect promptly the emergence or amplification of drug resistance. Ideally, DST should be performed before treatment initiation and on any monthly positive culture to assess amplification. When resources are limited, DST may be done every 3 months on any positive culture. At the end of treatment, a specimen should be collected for culture and a DST performed if positive. Should laboratory capacity for DST for selected drugs not be available in the country, the strains should be sent to the appropriate supra-national reference laboratory for testing. All phenotypic and molecular tests endorsed by WHO may be used for this purpose. All strains should be stored for further testing and analysis.

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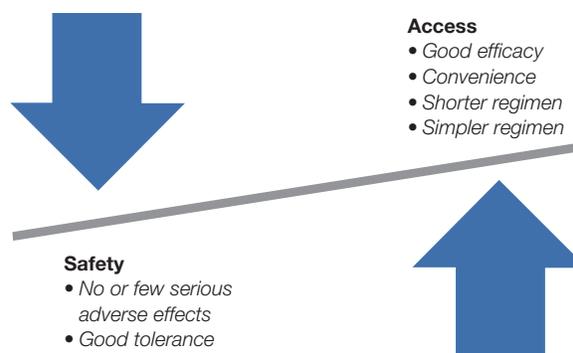
4 Private sector engagement

Background

When considering the introduction of new tuberculosis (TB) drugs or regimens in countries, it is crucial to engage with the private sector, particularly in countries where this sector is serving a significant proportion of the general population, so as to ensure responsible use of the new drug or regimen. For this, effective enforcement of regulatory authority is key; regulatory approaches may include mandatory case notification and restrictions on the indiscriminate sale of TB drugs in the private sector. The effective introduction and regulation of a new drug through the private sector requires the ability to distinguish between a wide array of providers.[a] It also necessitates mechanisms to ensure that those providers distribute the drug and treat patients in accordance with recognized international standards of care and effective treatment control recommendations. This requires a mechanism that enables pre-approval or validates providers who meet these characteristics.

Objective

To describe the key steps that countries should have in place for the rational introduction and responsible implementation of a new TB drug or regimen in the private sector.

Figure 1: Balance between safety and access

Access
- *Good efficacy*
- *Convenience*
- *Shorter regimen*
- *Simpler regimen*

Safety
- *No or few serious adverse effects*
- *Good tolerance*

Key steps

Before engaging the private sector, some guiding principles should be taken into consideration. Engaging the private sector in the introduction of new TB drugs should build on existing collaboration, beginning with those providers that are already collaborating with TB management programmes. This baseline of collaboration with the private sector is crucial to determine the pathway for the new drug. Balancing safety of and access to the new drug depends on its characteristics (i.e. a drug with safety concerns would lead to a different balance than a drug that is well tolerated) and whether or not this is a pilot or scale-up phase (see Figure 1).

Table 1: Definitions of licensure, accreditation and certification

PROCESS	ISSUING ORGANIZATION	COMPONENTS/REQUIREMENTS	STANDARDS
Accreditation (voluntary)	Recognized tools (often NGO)	Compliance with published standards, on-site evaluation; compliance not required by law and/or regulations	Set at a maximum achievable level to stimulate improvement over time
Licensure (mandatory)	Government authority	Regulations to ensure minimum standards, on-site evaluation	Set at a minimum level to ensure an environment with minimum risk to health and safety
Certification (voluntary)	Authorized body (either government or NGO)	Demonstration that the organization has additional services, technology or capacity	Set by national professional or specialty boards

NGO = nongovernmental organization.
Source: Shaw 2004 *(1)*

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a Including those qualified and competent to manage TB such as general physicians and chest specialists, and non-qualified health practitioners such as traditional healers, those trained in alternative systems of medicine and pharmacists.

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Balancing safety and access is primarily controlled through the regulatory approval of the drug and through the establishment of a controlled introduction process – including certification, licensure and accreditation of providers (see Table 1).

The various steps to be taken for the rational introduction of a new TB drug in the private sector are outlined below (and further in Table 2).

1. Initial dialogue

The Ministry of Health (MoH) should facilitate initial dialogue between key stakeholders to discuss policy guidance, regulatory requirements and introduction strategy, in particular in the private sector, through various public–private mix (PPM) approaches (2). This would include a discussion of the balance around PPM strategy, involving all stakeholders.

2. Strategy formulation

Following initial dialogue, the MoH should formulate a strategy for the initiation of the new drug or regimen in the private sector through the following activities:

A. Assess the situation including the performance of ongoing PPM initiatives (close link between procurement and supply systems).

B. Define the goals of the introduction (e.g. maximize access or maximize safety or carry out limited use to build evidence, etc.). The goals defined in the strategy will affect the model and introduction strategies (see Table 2).

C. Design a suitable model of PPM engagement with appropriate policy framework and guidance, and define the respective roles of key stakeholders described in initial dialogue.

3. Planning and implementation

A. Determine a reasonable timeline of activities that takes into account needed modifications to the current paradigm (particularly in the case of assessment or accreditation of providers (see Table 2)).

B. Consider the procurement implications of the working model proposed and the necessary training.

C. Ensure appropriate training is provided, particularly with the use of external assessment of providers.

4. Support and supervision

A. Provide support to private providers more closely in the initial stages of implementation. Private sector may need assistance to ensure strict adherence to the diagnostic and treatment protocols, and in providing counselling and support to patients.

B. Supervisory visits to collaborating private providers should be undertaken regularly and should be used to review all aspects of care and support. Particular attention should be paid to the documentation and maintenance of essential records and reports. Supervisory visits should also be used to address any problems providers may face in care delivery, in accordance with recommended standards.

Table 2: Guidance for PPM considerations for the introduction of new TB drugs or regimens

IMPLICATIONS FOR:		INTRODUCTION OF NEW TB DRUG(S) OR REGIMEN(S)
Private sector provision, in settings with:	Limited private sector	Consider initial use only in public sector to inform broader roll-out
	Extensive private sector	Consider first involving providers already collaborating as part of PPM initiatives; use a form of external assessment (Table 1) to ensure appropriate use; licensure may be best, particularly for an all-new regimen
National regulatory authority (NRA)		Ensure restricted availability of the drug/regimen to the public sector and collaborating private sector providers
Engagement with pharmaceutical industry		Pursue early discussions to restrict direct marketing of the drug.

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5 Systems approach for ensuring uninterrupted supply of quality-assured drugs

Background

A functional procurement and supply chain management (PSCM) system is key for ensuring sustainable access to new tuberculosis (TB) drugs and regimens. The readiness of a country is established through a comprehensive analysis of the current medicines policies and supply practices, using the frameworks of pharmaceutical management and access.
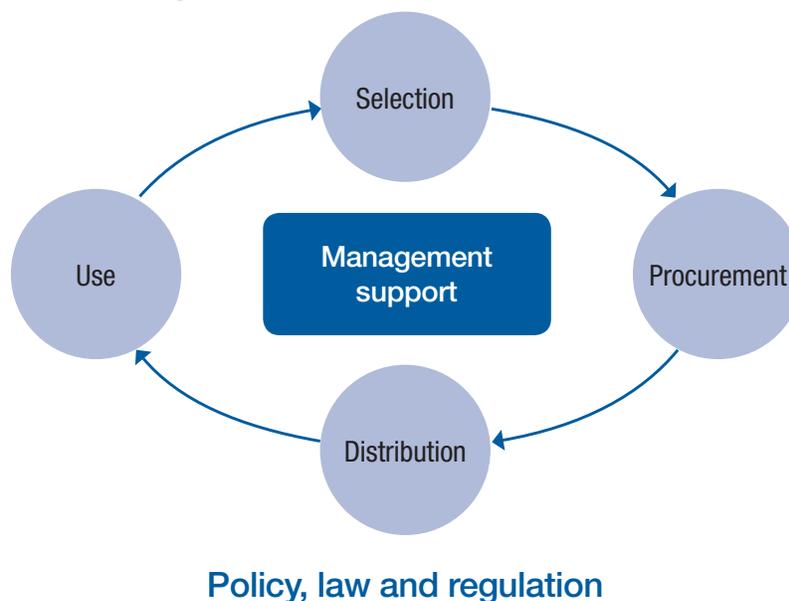
The TB pharmaceutical management system involves four basic functions: selection, procurement, distribution and use. Each function builds on the next, forming the pharmaceutical management cycle, a critical sub-system of a national health system. Selection, procurement and distribution functions are all closely connected to health service delivery, and use includes the provision of quality care and services that support rational use of the TB medicine (Figure 1) *(1)*. The TB pharmaceutical management system relies on a foundation of appropriate policies, laws and regulations. In this context, any planning for the introduction of new TB medicines or regimens must be cognizant of existing TB pharmaceutical management practices *(2, 3)*.

Objective

This document summarizes a generic process to assess, monitor and improve the pharmaceutical management system, with the view to achieve an uninterrupted supply of both new and existing quality-assured medicines.

Figure 1: Pharmaceutical management

Source: Adapted from Management Sciences for Health (2011) *(4)*

Key steps

1. Analysis of the existing TB pharmaceutical management system

An analytical process is necessary to generate evidence on the strengths and weaknesses of current TB pharmaceutical management practices (in both public and private sectors). These practices are critical to ensure availability and proper use of TB medicines (details of this analytical process can be found in references 1 and 3). Such evidence is expected to provide decision-makers with data for the design of an operational plan to support the introduction of new medicines, including budget planning. A step-by-step approach, reviewing the most critical areas of the TB pharmaceutical management system, is described elsewhere *(2)*. Through this process, decision-makers should be able to identify key weaknesses in their system, and mechanisms to overcome shortcomings in selection, procurement, distribution, timely use and management support for new TB medicines. The analysis is followed by interventions to ensure minimum requirements for proper adoption, introduction and implementation of new medicines or regimens.

## 2. Definition of key stages to ensure access to new drugs

The following stages are described in reference 4.

Stage 1: Adoption. This is a multisector process resulting in an explicit global and/or country policy decision to access and use new TB drugs or regimens, following the analysis of:

- the benefits, risks and costs of new medicines or regimens;
- the health system's capacity to finance, manage and appropriately use the medicines;
- the pharmaceutical management system's capacity to ensure timely procurement, quality assurance, inventory control and sustainable access;
- acceptance of new technologies by domestic markets, providers and interests groups.

Adoption is a key step: lack of analysis and understanding of a health system will impede introduction and implementation (see **Element 1**). At the core of access is the need to provide medicines and pharmaceutical services that are safe, efficacious, cost effective and quality assured (Figure 2). Often, it is

Figure 2: Increasing access to products and services
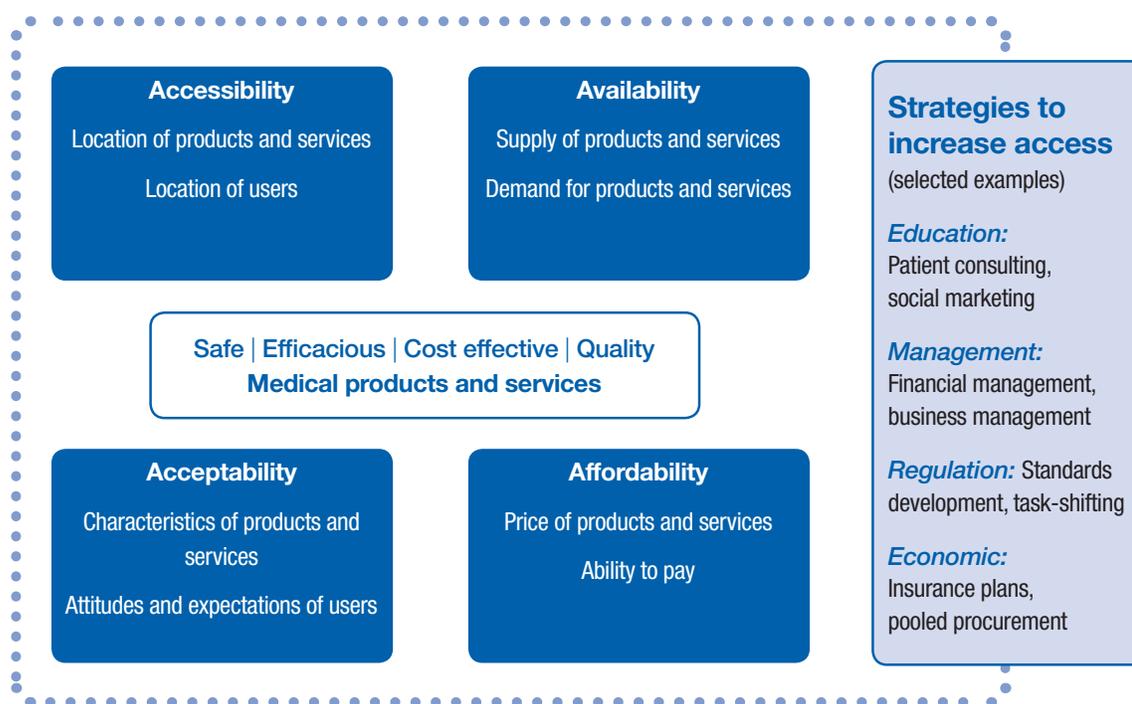
assumed that if medicines are in stock, then positive outcomes will naturally result. But availability is only one aspect of ensuring access to medicines; equally important are accessibility (geography and convenience), affordability (price and ability to pay for medicines and services) and acceptability (cultural and personal preferences).

Stage 2: Introduction. **This stage is driven by a set of coordinated activities that are carried out to prepare for effective and sustainable access to the new medicine or regimen. This includes:**

- preparation of a plan for addressing the gaps and weaknesses of the health and medicines management system;
- appropriate new medicines and/or regimens regulation and registration;
- preparation and execution of phase-in and phase-out plans for procurement and supply management (i.e. may include phasing-out of older drugs as the new drug is introduced);
- revision of guidelines, tools and training materials;
- financial resources mobilization;
- staff training;
- advocacy, communication and social mobilization activities.

Stage 3: Implementation.

This stage relies on a set of activities that put into effect the above policy and plan, and monitor and evaluate the progress of these activities and their impact on TB control. Implementation activities include:

- execution of the implementation, phase-in and phase-out plans;
- ongoing technical assistance programmes;
- execution of supply management procedures;
- monitoring and evaluation of programme implementation and new TB technology performance and impact;
- corrective actions as needed.

3. Minimum requirements for procurement and supply chain management to introduce new TB drugs

Countries with well-functioning PSCM systems may not need any significant strengthening interventions to ensure access to new TB medicines and regimens, but only the product or regimen-specific amendments to the existing policies and procedures outlined below. However, countries with weak systems and a history of access problems should first develop a comprehensive plan, informed by the assessments done at the adoption stage, for strengthening PSCM practices and establishing missing elements, if any.

Key elements include:

- a national PSCM coordination group (or task force) with clear terms of reference;
- policies for the selection and use of new medicines and regimens endorsed by key players;
- secured multi-year finance for all functions of PSCM (e.g. development of PSCM guidelines, capacity building programmes, logistics management information systems linked with reporting and recording systems);
- a national PSCM plan for new medicines and regimens, including a detailed phase-out and phase-in approach;
- quality assurance policy and standard operating procedures (SOPs) supporting selection, procurement, distribution and use;
- strategic long-term forecasting for the procurement of new medicines, and phasing out old medicines;
- formal registration of medicines or importation waivers and other requirements;
- monitoring and evaluation, including: performance indicators, data sources and data collection SOPs, reporting format and schedules;
- SOPs for medicine management available in pilot and roll-out sites;
- SOPs for inventory management (minimum, maximum and buffer stock levels for new products, logistics management information systems);
- a functional early warning system for preventing stock-outs and over-stocking.

THE IMPORTANCE OF A FUNCTIONAL EARLY WARNING SYSTEM FOR THE INTRODUCTION OF NEW MEDICINES

Early warning is the dynamic monitoring of the supply pipeline, based on clear SOPs for each element of supply chain and inventory management, valid and useful indicators, and informative dashboards. Key processes include ongoing quantification of needs (e.g. automated, monthly, quarterly) based on actual and projected case enrolment data, medicines utilization, available on-hand and expected deliveries data, and information on lead times throughout the entire supply chain. A good early warning system signals impending stock-outs, over stock or expiry of medicines in a timely manner allowing NTPs time to react and take action.

A free downloadable tool for forecasting, quantification and early warning, *QuanTB*, has been developed for national TB programmes by the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program in conjunction with the Stop TB Partnership Global Drug Facility. This tool is designed to prevent stock-outs and plan for phase-out and phase-in of new TB medicines and regimens under various enrolment scenarios. *QuanTB* is interfaced with the Stop TB Global Forecasting and Early Warning System, which allows global TB initiatives to implement market shaping interventions to ensure global availability of quality assured TB medicines, and better react to rapidly changing country needs.

QuanTB can be downloaded from http://siapsprogram.org/quantb/

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6 Operational research

Background

Operational research (OR) is defined variously as the "use of systematic research techniques for programme decision-making to achieve specific outcomes" *(1)* or as "the search for knowledge on interventions… that can enhance the quality, effectiveness, or coverage of programmes…"*(2).* In the context of introduction of new drugs, OR can be useful to assess the effectiveness, acceptability, feasibility and affordability of interventions under routine or real world programme conditions. In this context, OR seeks to understand setting-specific factors relevant for successful introduction, as well as those applicable across different settings. OR will thus be particularly important in the piloting of the introduction of new tuberculosis (TB) drugs or regimens in countries and this experience can usefully guide others in implementation and scale-up.

Objective

To outline the steps in using operational research methods to assist national TB programmes in the introduction of new TB drugs or drug regimens.

Key steps

Some issues requiring OR are predictable in advance of implementation, while others will be generated as experience with implementation develops. Research topics for OR will be developed through collaboration with experts and country programme leadership. The following steps need to be considered in order to conduct appropriate operational research:

1. Capacity to conduct OR successfully: This requires experience in study design and protocol development, data collection and analysis, and preparation of reports and manuscripts. The ability to ensure protection of human subjects is also

essential. It may require conforming to principles of good clinical practice *(3, 4)* and good laboratory practice *(5, 6)* as applied in the clinical trial context. Many activities concerned with monitoring and evaluation and with pharmacovigilance, rely on good recording and reporting systems. Capacity to conduct OR will be required early in the process of rational introduction, and should be planned at both central and local levels *(7).*

2. Relevant study designs: These include basic descriptive designs as well as cohort approaches – such as the cohort event monitoring used in pharmacovigilance activities (see **Element 3**). Recommended designs for a series of specific questions are described in the WHO/STP document: *Priorities in operational research to improve tuberculosis care and control (7).* This may reasonably rely on translation and adaptation of existing, internationally standardized forms, with modification as needed to address local issues *(8–10).* Attention to standardization of question and variable formats at an early stage will facilitate cross-country analyses that are likely to be valuable; this may particularly apply to collection of laboratory data, for which early attention is needed.

3. Identification of problems or questions: Proper and robust application of OR is expected to assist in resolution of many of the early challenges to rational introduction of TB drugs. It will help to identify which approaches are most or least successful, by identifying common obstacles (and their solutions) to implementation. In the context of rational introduction of new TB drugs or regimens, OR will address two types of challenges:

- those that are generally applicable to the implementation of rational introduction approaches – for example:

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- What are the best approaches for public–private mix engagement (accreditation or certification in different settings)?
- What are the best strategies to assure monitoring of acquired resistance to new agents?
- What are the most common failures in maintaining suggested protocol and programme operations?
- What do patients and physicians report on the experience of rational introduction approaches?
- What is the frequency of stock-out of standard drugs, and what is the impact on care for patients with multidrug-resistant and extensively drug-resistant TB?

• those which are applicable to specific new agents or regimens – for example:
- What is the distribution of patients who would most likely benefit from the new drug or regimen? (Answering this question may entail assessment of the rates and types of resistance in different patient groups or the geographic distribution of drug resistance.)
- Which types of adverse events are experienced and with what frequencies (e.g. how to monitor for cardiotoxicity, hepatotoxicity, ototoxicity or neurotoxicity for certain drugs, etc.). This includes identifying increased mortality due to serious adverse effects.
- What features are associated with acquisition of resistance to a specific new drug?

Lastly, OR will allow the evaluation of patient, programme and population level impact of new TB drugs or regimens, including the cost-effectiveness and impact on TB transmission. The use of pragmatic, cluster-randomized designs should be considered, as well as mathematical modelling to help inform policy for implementation *(7)*.

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The goal of the 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.

www.who.int/tb/new_drugs

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