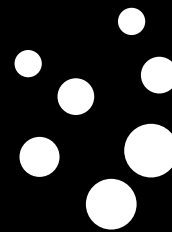


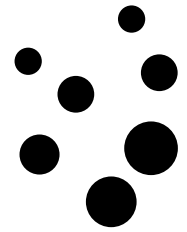
New Technologies for Tuberculosis Control:



RETOOLING
TASK FORCE

A framework for their adoption,
introduction and implementation





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- Stop TB Partnership

Abbreviations

ACSM	advocacy, communication and social mobilization
AEFI	adverse events following immunization
Aeras	Aeras Global TB Vaccine Foundation
AIDS	acquired immunodeficiency syndrome
BCG	Bacille Calmette-Guérin (vaccine)
CDC	United States Centers for Disease Control and Prevention
DFID	United Kingdom Department for International Development
DHS	demographic and health surveys
DOTS	The internationally recommended strategy for TB control until 2005, and the foundation of WHO's new Stop TB Strategy in 2006
DST	drug susceptibility testing
EML	essential medicines list
EPI	expanded programme on immunization
FDC	fixed-dose combination
FIND	Foundation for Innovative New Diagnostics
GAVI	Global Alliance for Vaccines and Immunization
GDF	Global Drug Facility
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
GLC	Green Light Committee
GMP	good manufacturing practice
GTZ	Deutsche Gesellschaft für Technische Zusammenarbeit [German Development Agency]
HIV	human immunodeficiency virus
HMIS	health management information system
MDR-TB	multidrug-resistant tuberculosis
NGO	nongovernmental organization
NTP	national tuberculosis control programme
PPM	public-private mix
RPM Plus	Rational Pharmaceutical Management Plus Program
PSM	WHO Department for Medicines Policy and Standards
QA	quality assurance
SAGE	WHO Strategic Advisory Group of Experts for vaccines and immunization
SOP	standard operating procedure
STAG-TB	WHO Strategic Technical Advisory Group for Tuberculosis
TB	tuberculosis
TB Alliance	Global Alliance for TB Drug Development
TB/HIV	TB and HIV coinfection
TDR	UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases
UNDP	United Nations Development Programme



UNICEF	United Nations Children’s Fund
Union	International Union Against Tuberculosis and Lung Disease
USAID	United States Agency for International Development
XDR-TB	extensively drug-resistant tuberculosis
WHO	World Health Organization

Preface

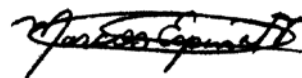
The past few years have seen remarkable successes in global TB control, resulting in an increase in the detection rate of smear-positive cases from 28% in 2000 to 60% in 2005 and a treatment success rate from 82% in 2000 to 84% in 2004. Nonetheless, 1.6 million people died from TB in 2005 and more than half of TB patients, including children, are not properly diagnosed or treated. Furthermore, the long duration of short-course chemotherapy limits treatment opportunities for many people living in poor and marginalized communities. Significant challenges to TB control remain; these are compounded by the HIV epidemic and the emergence of multidrug-resistant TB and extensively drug-resistant TB. Improvements in existing approaches and new tools are urgently needed for several reasons: the most commonly used diagnostic tool is more than a century old, the current vaccine does not confer complete protection and may present an elevated risk of adverse events in children infected with HIV, and no new drugs have been available for over 40 years.

The ability to rapidly deploy and appropriately use new tools as they become available is critical to saving lives and will require concerted and well planned efforts by the entire Stop TB Partnership, including national TB control programmes, technical partners, community members and civil society representatives, product developers, donors and international organizations. It is now more urgent than ever for national programmes and health systems to improve management capacity to prepare to seize opportunities, and to use new tools optimally to assist millions of TB patients and their families and communities.

This document provides a framework for ensuring that new tools, once available, can be expediently and efficiently adopted at the global and country levels.



Irene Koek
Chair
Stop TB Partnership Coordinating Board



Marcos Espinal
Executive Secretary
Stop TB Partnership Secretariat

¹ The internationally recommended strategy for TB control until 2005, and the foundation of the new WHO Stop TB Strategy introduced in 2006.

Foreword

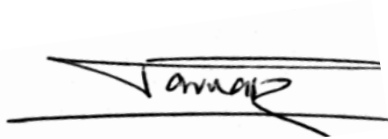
As people who have lived through TB treatment, we would like to stress that any efforts to improve tools to control the disease have also to concurrently address the importance of food security and poverty in order to truly fulfil their promise of reducing the burden of TB among our peers. Currently, 1.6 million of our comrades die every year of TB, despite TB being curable, 98% of them in resource-poor settings. Although, in theory, the recommended diagnostics and treatment can identify 70% of all smear-positive TB cases and cure 85% of them, in reality, the more than a century old smear test identified only 60% of new smear-positive pulmonary TB cases in 2005.

Many of the most vulnerable to death from TB, such as those who are coinfecting with TB and HIV or are infants, are more likely to have smear-negative or extrapulmonary TB. However, the smear test most frequently used to diagnose TB fails to identify the disease among these communities. Furthermore, although globally the rates of TB treatment success have come close to the goal of 85%, in 2004 cure rates fell far short in two WHO regions: in the African Region, the cure rate was 62% and in the European Region it was 59%. These poor outcomes are associated with the long period of treatment (6–8 months) that it takes to cure TB. Treatment is even longer and with greater side-effects when the TB is drug resistant, which is both a product and a cause of challenges to completion of treatment. Anti-TB medicines may interact with HIV medications, complicating the co-administration of treatment for TB and HIV. Furthermore, the TB vaccine does not prevent adult TB, although it does reduce some of the worst forms of childhood TB. So, although it is said that TB is curable, for many of our most vulnerable communities, this is not the case. TB is the leading cause of death in people living with HIV/AIDS, and cure rates of drug-resistant TB are shamefully low at close to 50%.

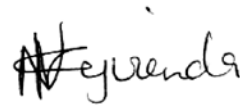
An improvement in the care of TB patients requires not only new tools that will address the current challenges of TB control but also a concurrent expansion of existing tools, while strengthening TB programmes overall so that these tools are appropriately used. After many decades of neglect, there is hope that the new technologies will be able to detect more cases and cure them in a shorter time and that treatment that can be taken with HIV medications and be effective against drug-resistant TB. In the next 10 years, there are even plans for a new anti-TB vaccine.

Retooling, which is the process of preparing health systems at the country and global levels for the uptake of new TB tools by creating policies and funding mechanisms and generating adequate and programmatically relevant data for the adoption of new tools and, most importantly, political will, is a forward thinking exercise to facilitate the availability of new technologies to the people who need them most.

We, the people who bear the burden of TB disease, as members of civil society, can play an important role in pushing for greater political will by creating a bottom-up demand for new TB tools and by working in partnership with our national TB control programmes, the Stop TB Partnership and the product developers to reduce barriers to the uptake of new tools. This document, and the hope it symbolizes, is one that we stand behind to bring improved methods of reducing the burden of TB to ensure that no more of our brothers and sisters die of this curable disease.



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Executive summary

Tuberculosis (TB) is a global problem that killed 1.6 million people in 2005. The mounting problem of drug resistance, including the emergence of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), and the growing number of TB patients who are also infected with HIV are combining to make the pandemic more deadly. These problems risk compromising the progress made in TB control during the past decade.

Beyond the current efforts to prevent, detect and cure TB, new tools are needed to radically transform the fight against TB, to contain the threat of drug-resistant strains such as MDR-TB and XDR-TB and to seriously target elimination by 2050. New technologies are urgently needed for several reasons:

- Today's first-line anti-TB medicines are more than 40 years old and must be taken for 6–9 months. Erratic or inconsistent treatment generates drug resistance.
- Today's most commonly used diagnostic tool, the light microscope, is more than 100 years old and is relatively insensitive (particularly in the presence of HIV coinfection), giving no indication of drug susceptibility.
- Today's vaccine, bacilli Calmette–Guérin (BCG), is more than 85 years old and provides acceptable protection only against disseminated forms of disease in infants and little, if any, protection beyond childhood.

Progress is being made in the development of new medicines, diagnostics and vaccines to combat the TB pandemic and eventually eliminate this disease. The Global Plan to Stop TB 2006–2015 estimated there were 27 medicines, 15 diagnostics and 8 vaccines in the production pipeline at various stages ranging from product

development to field trials. Since publication of the Global Plan in 2006, the number of candidate technologies has increased.

With the anticipated launch of the first of the new tools occurring within the next two years, the time is right to start preparing to use such tools in order to minimize the delay between licensure, availability and adoption. The goal is to spread rapidly and widely the use of new tools to care for the people who will benefit from them most. This process is termed “retooling”.

The promise of new tools

The Global Plan describes the main strategies that will be used to prevent and control TB during 2006–2015. Integral to this plan is the development and deployment of new and improved tools – medicines, diagnostics and vaccines – as they become available. The plan also commits the Stop TB Partnership to implementation of WHO's new Stop TB Strategy based on DOTS and including the International Standards for Tuberculosis Care.

The introduction of new tools for TB control and prevention should be regarded as a means of improving the quality of care by making available a wider choice of technologies to address unmet needs; it is also an opportunity to align the new tools with the capacity of health systems to deliver care, to address the changing nature of the epidemic and to meet the needs of communities with or at risk of TB.

The plans and investments made thus far by the global partnership to stop TB to accelerate the development of new tools have led to high expectations that these technologies will provide national TB control programmes with better

options to prevent, detect and treat TB. At the same time, making new tools available and accessible will require systems and procedures at global and country levels that can rapidly and effectively assess these products and incorporate them into TB control strategies and programmes where appropriate.

The Task Force on Retooling

Previous experiences with the introduction of new tools to prevent and control other communicable diseases have shown that there is often a significant delay between the availability of new tools at the global level and their eventual adoption and implementation at country level.

Recognition of the critical delay that often occurs between the time the evidence for policy-making becomes available and the implementation of policy led the Stop TB Partnership Coordinating Board to establish a Task Force on Retooling. This task force is charged with developing a framework that will encourage policy-makers and practitioners at global and national levels to accelerate the introduction of new tools into national TB control and immunization programmes. The purpose of the task force is to stimulate discussion of, and planning for, optimal, timely and appropriate introduction, adoption and implementation of new tools as they become available.

The main activities of the task force are:

- consolidating and sharing information from the working groups on drugs, diagnostics and vaccines about product pipelines as well as timelines and milestones;
- consolidating information from the working

groups on the expansion of the DOTS strategy, MDR-TB and TB/HIV to facilitate the adoption and implementation of new TB tools in the field;

- creating opportunities for consultative dialogue with stakeholders from countries with a high burden of TB, including ministries of health, nongovernmental organizations, affected communities, etc;
- facilitating the mobilization of financial and human resources for country-level introduction and deployment;
- consolidating relevant lessons learnt from other disease areas to inform TB-specific processes for adoption, introduction and implementation;
- facilitating operational research on the introduction of new tools;
- generating evidence to support the adoption of new tools;
- fast-tracking the incorporation of effective new tools into WHO's policies and national policies and guidelines;
- enhancing communication among all working groups about retooling.

Framework for the adoption, introduction and implementation of new tools

One of the first jobs of the task force was to develop a framework for the adoption, introduction and implementation of new tools. This framework provides guidance on what actions need to be taken when improvements in existing medicines, diagnostics and vaccines become available or when new tools become available. The framework is primarily intended to support national TB control and immunization programmes, and clinical laboratory diagnostic services. It is also meant

to inform the activities of the constituencies of the Stop TB Partnership, including advocacy and community-based organizations, donors, intergovernmental agencies, new product developers, national policy-makers and decision-makers, and academic and technical partners.

The framework identifies the challenges inherent in retooling and proposes key steps to be taken in order to facilitate appropriate and timely adoption and implementation. It also provides an overview of the technical and operational considerations associated with retooling at the global and national levels. Additionally, the annexes summarize technologies in the development pipeline. They also provide an illustrative list of the key actions that need to be taken so that new tools in each technology category can be adopted and their use implemented effectively. There is an illustrative generic timeline – or sequencing – of key tasks needed for adoption, introduction and implementation. A list of suggested further reading is also provided.

Specific information included in the framework is described below.

Systemic and programmatic readiness for change. The wide array of products in the development pipeline with different expected dates of availability requires systems that can manage ongoing change and rapidly integrate the newly available tools at both the global and national levels. A new tool may be superseded rapidly by a newer tool within a short time-span, where appropriate evidence exists to support it. The level of incremental improvement afforded by the new tool, and the projected availability of the next incremental improvement, will play a role in decisions regarding the investment of resources to support its adoption. The anticipated sequence of new tools becoming available may also have an impact on the resources that are allocated to

implement the newly adopted tool.

Policy-makers and decision-makers at the global and national levels will need to stay abreast of the status of the product pipeline, and to update other stakeholders on new advances that are likely to become marketed and on the approximate time frame. They will also need to consider differences in national environments and of the potential roles of the product types (medicines, diagnostics, vaccines); how they can be used together; or potential modifications of diagnostic or treatment algorithms when developing recommendations and policies. Furthermore, they will want to ensure the participation of other programmes, such as the global Expanded Programme on Immunization, the national immunization programme, and reproductive and child health programmes, in planning and implementation.

The timely and appropriate adoption, introduction and implementation of new and incrementally improved technologies for TB control face many significant challenges. These include:

- weak or non-existent legal and regulatory frameworks;
- inadequate capacity to manage clinical laboratory diagnostic services;
- inadequate capacity to manage pharmaceutical supply;
- inadequate infrastructure, equipment and support services;
- human resource constraints, in terms of sufficiency and adequacy of health workers, particularly in the public sector;
- resistance to change;
- misappropriation of resources;
- country-specific regulatory requirements;
- lack of leadership; insufficient capacity to manage change;
- financial constraints.

These challenges may be addressed by taking the following measures:

- engaging stakeholders from the beginning of the policy analysis process (for adoption) and throughout introduction and implementation;
- advanced planning and preparation, both globally and nationally;
- conducting operational research to guide adoption, introduction and implementation.

Adoption and development of new policy.

Although the development of recommendations on the use of new or improved tools for TB control at the global level and the development of new policies for the adoption and implementation of these tools at the country level are separate processes, the essential components of these processes are the same. Ideally, both processes should take place simultaneously. However, it is likely that some countries may decide to proceed with adoption and implementation without waiting for global recommendations; while others will decide to wait until guidance is available through widely accepted international organizations with a mandate for setting normative standards and providing technical assistance, such as WHO or the International Union Against Tuberculosis and Lung Disease.

The essential and interlinked components of a process for the adoption of new tools and a subsequent change in global recommendations and national policies include:

- stakeholder participation in the development of recommendations and policies;
- analysis of the needs and evidence for change;
- analysis of the risks and benefits of the new

tool and of the health system environment and capacity to adopt, introduce and implement the new tool;

- development and endorsement of the new recommendations and policies and their wide dissemination.

Introduction and implementation of new tools.

The key components of a process for implementing policy changes in both the public and private sectors, including not-for-profit institutions such as faith-based or secular nongovernmental organizations and the for-profit sector, can be divided into technical considerations, operational considerations, and monitoring and evaluation.

Technical considerations relate to the registration of products and the revision of regulations; demonstration projects; development or updating of programme guidelines, essential medicines, medical devices and related supplies lists, and recording and reporting forms; dissemination of guidelines and training of health workers and community partners providing TB care; and advocacy, communication and social mobilization.

Operational considerations include the management of tools currently in use that are to be replaced by new technologies (phase-out plan); management of supply of new tools; addressing availability in public and private sectors; development of a phase-in or roll-out plan; quantification and demand forecasting; procurement, distribution and inventory management; and ensuring quality of products and services and their safety.

Monitoring and evaluation of the adoption, introduction and implementation of new tools will provide important lessons for the uptake of incrementally improved tools.

Future work of the task force

In addition to the framework described above, the task force is engaging national and global policy-makers and stakeholders to ensure that they support retooling efforts. Documents that will be produced later in 2007 include a stakeholder engagement plan; detailed illustrative timelines for

adoption and implementation of new diagnostics, and monitoring and evaluation indicators; and pipeline updates for medicines, diagnostics and vaccines.

For more information about the Task Force on Retooling or any of these products, please contact: stoptbretooling@who.int.

1. Introduction

1.1 Background information on challenges to global TB control

DOTS¹ programmes have expanded rapidly during the past few years, leading to an increase in the detection rate of cases of tuberculosis (TB) from 28% in 2000 (1) to an estimated 60% in 2005 and a treatment success rate averaging 84% in 2004 (2). Despite this success, significant challenges remain. These include the epidemic of human immunodeficiency virus (HIV) and the emergence of multidrug-resistant tuberculosis (MDR-TB) and now extensively drug-resistant TB (XDR-TB). Improvements in existing approaches and new tools are needed to overcome these challenges and accelerate TB control, including medicines, diagnostics and vaccines. The *Stop TB Strategy* (3) recommended by the World Health Organization (WHO) includes a component to enable and promote research in order to improve current tools and make them available to TB care providers and control personnel.

1.2. The Global Plan to Stop TB

The Global Plan to Stop TB, 2006–2015 (4) describes the principal strategies that will be used to prevent and control TB over the next 10 years. These include:

- increasing access to accurate diagnosis and treatment through DOTS;
- scaling up public–private mix (PPM) approaches;
- increasing community DOTS initiatives;
- strengthening programmes to address

HIV-related TB, MDR-TB and XDR-TB.

Integral to this plan is the development and deployment of improved tools as they become available. The plan also commits the Partnership to implementing the *Stop TB Strategy*, based on DOTS and including the *International standards for tuberculosis care* (5).

Seven working groups have been delegated responsibility to plan and coordinate effective action:

- DOTS Expansion Working Group, with individual subgroups on laboratory capacity strengthening, public–private mix, childhood TB, and poverty and TB
- Working Group on MDR-TB
- TB/HIV Working Group
- Working Group on New TB Diagnostics
- Working Group on New TB Drugs
- Working Group on New TB Vaccines
- Advocacy, Communication and Social Mobilization Working Group.

These groups are responsible for mapping activities in their areas, reporting to Stop TB partners, and coordinating with partners and other groups. The issues raised by the adoption, introduction and implementation of improved and new tools for TB control are therefore of concern to each of these groups.

The plans and investments made thus far by the global partnership to stop TB to accelerate the development of new tools have led to high expectations that these new technologies will provide national TB control programmes (NTPs)

¹ DOTS is a proven approach to TB control that comprises five components: (i) political commitment with increased and sustained financing; (ii) case detection through quality-assured bacteriology; (iii) standardized treatment with supervision and patient support; (iv) an effective drug supply and management system; and (v) a monitoring and evaluation system and impact measurement. Pursuing high-quality DOTS expansion and enhancement is the first component of the WHO Stop TB Strategy.

with better options to prevent, detect and treat TB. At the same time, making new tools available will require global-level and country-level systems and procedures that can rapidly and effectively assess these products and incorporate them into TB control strategies and programmes where appropriate. The number of anticipated new and incrementally improved tools will continue to grow as newer tools emerge from the development process.

Previous experiences with the introduction of new tools to prevent and control other communicable diseases (6, 7) have shown that there is often a significant delay between the availability of new tools at the global level and their eventual adoption and implementation at country level.

1.3 The Stop TB Partnership Task Force on Retooling

Recognition of the critical delay that often occurs between the time the evidence for policy-making becomes available and the implementation of policy led the Stop TB Partnership Coordinating Board to establish a Task Force on Retooling (see Box 1.1). This task force is charged with developing a framework that will encourage policy-makers and practitioners at global and national levels to accelerate the introduction of new tools into national TB control and immunization programmes. One of the aims of the task force is to stimulate discussion of, and planning for, optimal, timely and appropriate introduction, adoption and implementation of new tools as they become available.

Box 1.1 Task Force on Retooling: composition and terms of reference

Membership

- Experts, not necessarily working group members, designated by the Chairperson of the working groups.
- Members from key subgroups (laboratory capacity strengthening, Global Drug Facility, and TB and poverty).
- Representatives of national TB control programmes from countries with high burdens of TB.
- Representatives from the WHO Stop TB Department and other relevant departments within WHO.

Purpose

- To facilitate the introduction and adoption of new tools as they become available.

Activities

- developing a workplan and timelines;
- consolidating and sharing information from the working groups on drugs, diagnostics and vaccines about product pipelines and timelines and milestones;
- creating opportunities for consultative dialogue with stakeholders from high TB burden countries, including ministries of health, nongovernmental organizations, affected communities, etc.;
- facilitating the mobilization of financial and human resources for country-level introduction and deployment;
- consolidating relevant lessons learnt from other disease areas to inform TB-specific processes for adoption, introduction and implementation;
- facilitating operational research on the introduction of new tools;
- generating evidence to support the adoption of new tools;
- fast-tracking the incorporation of effective new tools into WHO's policies as well as national policies and guidelines;
- enhancing communication among all working groups about retooling.

2. New technologies to control the spread of TB

The Global Plan estimated there were 27 medicines, 15 diagnostics and 8 vaccines in the production pipeline at various stages ranging from product development to field trials. Since publication of the Global Plan in 2006, the number of candidate technologies has increased. With the anticipated launch of the first of the new tools occurring in 2007–2008, and in recognition of the lead time required to secure adequate levels of funding and to manage procurement and supply, the time is right to start preparing for the introduction of new tools.

The introduction of new and improved tools for TB control and prevention should be regarded as a means of improving the quality of care by making available a wider choice of technologies to address unmet needs; it is also an opportunity to align the new tools with the capacity of health systems to deliver care, to address the changing nature of the epidemic and to meet the needs of the community with or at risk of TB infection.

2.1 Objectives, contents and assumptions of the framework

This document has three objectives:

- To provide a common framework to discuss the adoption and implementation of new tools for TB control.
- To identify some key issues that need to be addressed to accelerate the adoption and implementation of improved and new tools.
- To provide guidance on what actions are needed when improved existing and/or new tools become available in order to ensure optimal and appropriate adoption and implementation into TB control strategies, as well as access to, and proper use by, the community.

This framework is primarily intended to support managers of NTPs, national immunization programmes and clinical laboratory diagnostic services. It also aims to inform members of the Stop TB Partnership, including advocacy and community-based organizations, donors, intergovernmental agencies, new product developers, national policy and decision-makers, and academic and technical partners.

The document:

- identifies key challenges to adoption and implementation of new technologies;
- proposes key principles to facilitate appropriate and timely adoption and implementation;
- provides an overview of technical and operational considerations for the processes of adoption and implementation at global and national levels. The annexes include:
 - a brief overview of selected new medicines, diagnostics and vaccines in the pipeline;
 - a list of key actions for the adoption, introduction and implementation of each technology category;
 - an illustrative generic timeline for adoption, introduction and implementation;
 - a list of key readings that provide more detailed discussions of the issues and road maps.

This document starts from the assumption that the following actions will have occurred with regard to any new technology that is introduced.

- New TB protocols, medicines, diagnostics or vaccines will have undergone rigorous evaluation and met stringent standards of quality, safety and efficacy.
- For some diagnostic tests in the pipeline, field

study data will also have been provided at the time of submission for regulatory approval.

- Consequently, for the “retooling” process, a new TB technology will be considered “available” globally when adequate demonstration of its effectiveness in real-life situations in national disease control programmes also exists following efficacy studies and registration.
- Sufficient evidence will be available to enable WHO to include the new tool in global TB control policy.
- The need to adopt the new technologies will have been recognized both globally and by countries.
- Adequate financial resources will have been mobilized for the acquisition of these new products.
- Product developers and manufacturers will have formulated “win-win” situations with regard to intellectual property, technology transfer and pricing, to ensure affordability and access.

For all new tools, affordable pricing requires a supply strategy that will meet demand, reliable demand forecasts and early commitment to finance the tool, particularly for vaccines. Product development partnerships for the new anti-TB medicines, diagnostics and vaccines are working to address these issues.

2.2 Objectives of new technologies for TB control

Each category of new tools aims to address specific objectives for TB control. These are described below to establish a common base to guide the discussion of, and planning for, the adoption, introduction and implementation of new technologies at the global and country levels.

2.2.1 Diagnostics

The microscopic examination of sputum is still the only widely available tool in most developing countries for diagnosing TB. Unfortunately, the relatively low sensitivity of sputum smear microscopy under field conditions – more so in the presence of HIV coinfection – is a major drawback to case-finding. Limited access to microscopy, culture and drug susceptibility testing (DST) – as well as the presence of latent TB infection – add to the diagnostic challenges faced by TB control programmes.

Some of the technologies and strategies expected to improve case detection will be incremental improvements on existing technologies already available in developing countries, such as same-day smear microscopy, fluorescence microscopy or bleach sputum processing. Other technologies are tools commonly used in developed countries that are being extended to developing countries. Finally, other technologies will be completely new and radically different, such as new point-of-care tests for primary health care facilities where no diagnostic technology currently exists.

For all these tools, it will be vital that they are first assessed in a variety of operational settings in countries highly endemic for TB to demonstrate their performance before they are recommended for adoption and wide application.

The objectives for improving current diagnostic tools and developing new cost-effective ones that perform well in people infected with HIV are:

- To simplify and improve detection of TB cases, including smear-negative and extrapulmonary TB, through increased sensitivity and specificity and improved accessibility.
- To develop simple, accurate and rapid inexpensive tests that can be performed at

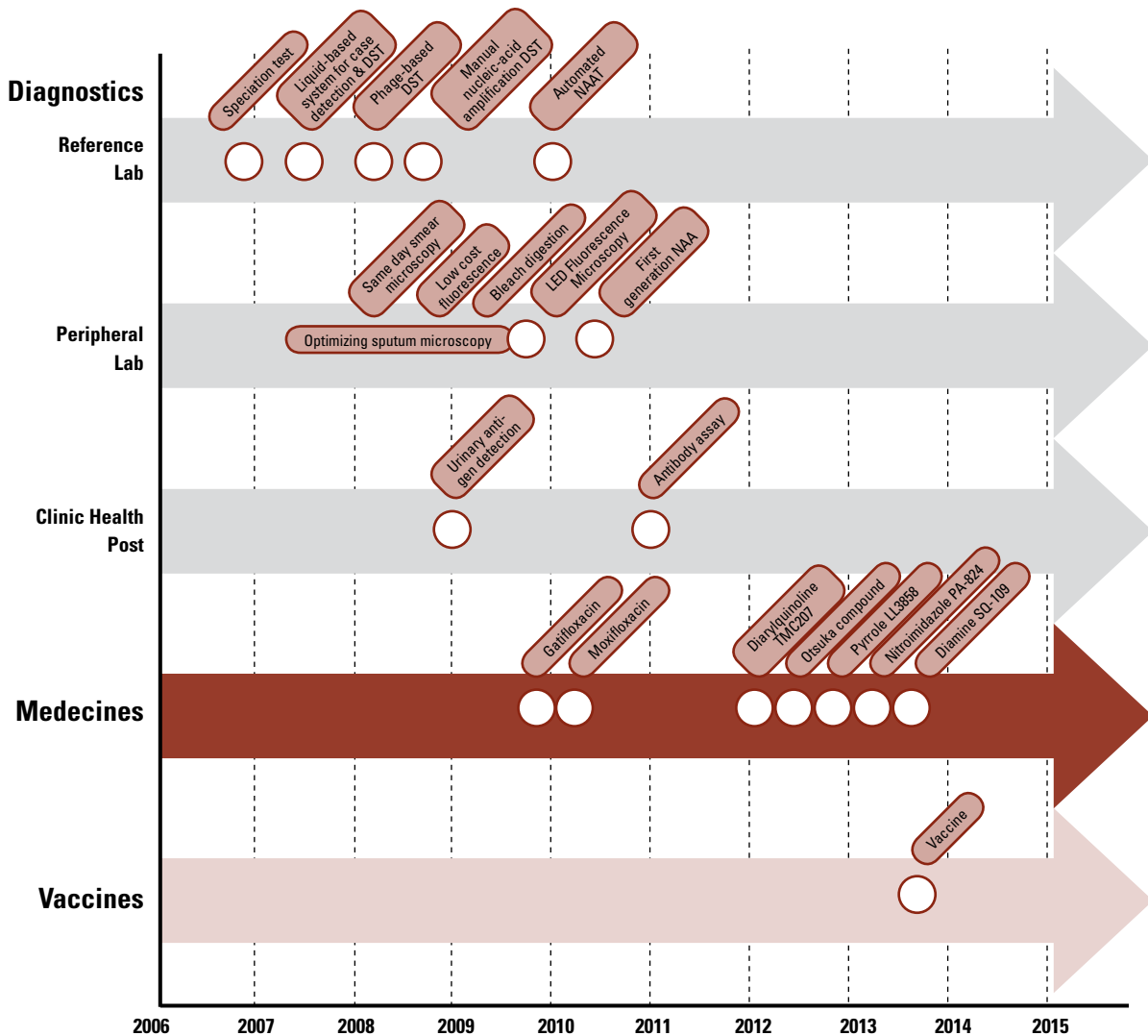


Figure 2.1 Examples of products in the pipeline currently under evaluation (see Annex 1)

DST, drug susceptibility testing; NAA, nucleic acid amplification; NAAT, nucleic acid amplification test.

Note: the time point indicated on the timescale represents end of field studies (“demonstration phase”) for diagnostics or end of Phase III clinical trials for drugs and vaccines, if evaluation is successful.

the point-of-care level of the health care system and that produce quick results on the same day.

- To monitor treatment.
- To rapidly identify drug resistance (improved DST) to both first- and second-line anti-TB medicines.
- To reliably identify latent TB infection and determine the risk of progression to active disease, enabling the rational use of preventive therapy.

2.2.2 Medicines

Despite the availability of efficacious treatment, challenges for the DOTS strategy include the number of pills and the length of treatment required to cure TB. These challenges frequently result in poor adherence to treatment and the emergence of multidrug resistance. The objectives for the development of new medicines are:

- To simplify or reduce treatment duration to two months or less.
- To effectively treat multidrug resistance (MDR-TB and XDR TB).
- To treat patients with latent TB infection.

The new medicines should be compatible with antiretroviral therapy for HIV/AIDS patients.

2.2.3 Vaccines

The current anti-TB vaccine, Bacille Calmette-Guérin (BCG), provides acceptable protection against only disseminated forms of the disease in infants; its efficacy against pulmonary TB is questionable. This highlights the need for a better vaccine regimen. The objectives for development of a new vaccine are:

- To prevent TB infection from occurring (pre-exposure prophylaxis) in all age groups.
- To prevent progression of latent TB infection to active disease in adolescents and

adults.

- To assist in the treatment of active disease, as immunotherapy, as an adjunct to conventional treatment.

2.3 Expected timeline for new technologies

Continued increases in funding for the discovery, research and development of new medicines, diagnostics and vaccines have expanded the pipeline of new tools in all three categories. Figure 2.1 identifies some of the products in the pipeline that are likely to become available by 2015, and their estimated launch date. This information is for illustrative purposes only, as these candidate products are currently undergoing trials in humans and must satisfy criteria of quality, safety and efficacy before they can be approved for marketing. It is possible that some of these products may not reach the regulatory evaluation stage or that they may not meet criteria for marketing approval.

The estimated dates for new medicines and vaccines refer to the expected time when Phase III clinical trials will be completed and an application for market approval will be filed with a regulatory agency. Some new anti-TB medicines may be introduced as novel combinations rather than as a single drugs. For diagnostics, the estimated dates refer to the expected time when studies conducted under actual service delivery conditions (demonstration studies) are completed for the identified tools and submitted with product studies for technical assessment by WHO and by the respective country health technology assessment bodies.

Annex 1 summarizes the tools in the pipeline, including information on sponsors, rationale, product description, stage of development,

regulatory status and other considerations. Other technical reviews are identified in the list of further reading.

The wide array of products in the pipeline with different expected dates of availability requires systems that can manage ongoing change and rapidly integrate the newly available tools at the global and national levels. A new tool may be superseded rapidly by a newer tool within a short time span, where appropriate evidence is available to support its adoption. The level of incremental improvement afforded by the new tool, and the projected availability of the next incremental improvement, will play a role in decisions regarding the investment of resources to support its adoption. The anticipated sequence of availability of the newly adopted tool may also impact upon the resources that are allocated for its implementation.

Policy-makers and decision-makers at the global and national levels will need to:

- stay abreast of the status of the product pipeline and update other stakeholders on new advances that are likely to become marketed and on the approximate time frame.
- consider potential modifications of diagnostic or treatment algorithms when developing recommendations and policies, differences in national environments and the potential roles of the technology types (medicines, diagnostics, vaccines) and how they can be combined.
- engage other programmes, such as the global Expanded Programme on Immunization (EPI), national immunization programmes and reproductive and child health programmes in planning and implementation.

2.4 Challenges to timely and appropriate adoption, introduction and implementation

The timely and appropriate adoption, introduction and implementation of new and incrementally improved technologies for TB control face many significant challenges. These include:

- weak or non-existent legal and regulatory frameworks;
- insufficient capacity to manage laboratory and diagnostic services;
- inadequate capacity to manage pharmaceutical supply;
- poor infrastructure, equipment and support services;
- human resource constraints, in terms of sufficiency and adequacy of health workers, particularly in the public sector;
- resistance to change;
- misappropriation of resources;
- country-specific regulatory requirements;
- absence of leadership;
- lack of capacity to manage change;
- financial constraints.

2.5 Actions that facilitate timely and appropriate adoption, introduction and implementation

2.5.1 Engaging stakeholders from the beginning of the policy analysis process (for adoption) and through introduction and implementation

Identifying stakeholders at the global and country levels – across the public and private sectors; among community-based groups and people living with TB, from donors, pharmaceutical and laboratory suppliers as well as manufacturers, professional bodies, and academic and research institutions – and keeping them updated on advances and early engagement in the adoption (policy change) process can facilitate both the decision-making process and the implementation of the new policy. The benefits of engaging the community in retooling also include opportunities for them to contribute to monitoring and evaluation activities, including pilot and feasibility studies, facilitating community group discussions to determine the acceptability of the new tool or to identify adverse drug reactions, advocacy to “move things along” throughout the policy development and implementation process, as well as advocacy for improved availability and increased government financial allocation.

It may be important to develop a strategy to engage the private health sector, which can include a wide range of providers and institutions from whom TB patients seek diagnosis and treatment outside of the publicly managed facilities, ranging from individual private practitioners to corporate enterprises to faith-based and secular not-for-private organizations. In many countries, the private sector accounts for a significant proportion of TB diagnosis and case management. WHO has established and documented PPM for DOTS implementation (8)

and has developed tools and approaches for implementing PPM.

Specific issues relevant to the private sector may have to be considered. These include:

- ensuring quality, both for the products used and for the services provided;
- developing formal guidelines to help the NTP structure collaborations with the private sector;
- adapting training materials to ensure that diagnosis and treatment practices conform with national guidelines;
- including professional medical associations as key partners in the introduction and implementation process;
- formulating strategies to provide incentives to encourage the cooperation of the private sector.

2.5.2 Advanced planning and preparation, both globally and nationally

The potential availability of some of these tools within the next 2–3 years makes it urgent for the Stop TB Partnership to define processes to facilitate appropriate adoption and implementation of the new technologies at both the global and national levels. Policy analysis and decision-making and planning for implementation processes take time, if they are to effectively engage all key stakeholders (users, health care providers, managers, policy-makers, suppliers, product developers, donors). The current pipeline suggests that policy-makers and decision-makers at the global and national levels will need to closely monitor its status in order to update other stakeholders on new advances that are likely to become available and to anticipate needs for information required for decision-making.

At the country level, knowledge about potential technical and operational implications of tools in the pipeline, combined with timely and realistic assessment of the health system environment and capacity, will contribute to guiding operational research, identifying critical system weaknesses, initiating efforts to address human resource constraints, and mobilizing financial resources and technical assistance as needed. Some countries may satisfy technical assistance needs with national resources, while others may require international assistance. In many countries, strengthening systems, particularly infrastructure development and refurbishment of premises for clinical diagnostic laboratory services, will require the deployment of significant effort, resources and time to prepare them for the optimal uptake of the new tools.

2.5.3 Operational research to guide adoption, introduction and implementation

Operational research on the introduction of new

technologies into disease control programmes to assess their effectiveness and impact will be needed to better understand their advantages and limitations and support their uptake into policy. Additional evidence will be needed to determine alignment of product characteristics and programmatic requirements with the needs of users, providers, managers, and policy- and decision-makers. Operational research can provide the information required by decision-makers in order to integrate the new technologies into programmes, such as the capacity to provide high-quality care and the social context of TB care. Phased implementation could allow the assessment of organizational and operational adaptations that may be needed to ensure high-quality care, including adequate supply and appropriate use. Effective mechanisms for data collection and dissemination of lessons learnt will need to be established.

3. Adoption and development of new policies at global and country levels

Although the development of recommendations on the use of new or improved tools at the global level and the development of new policies for the adoption and implementation of these tools at the country level are separate processes, the essential components of these processes are the same. Ideally, these two processes should take place simultaneously. However, it is likely that some countries may decide to proceed with adoption and implementation without waiting for global recommendations, while others will decide to wait until guidance is available through widely accepted international mechanisms such as WHO, or through professional associations such as the International Union Against Tuberculosis and Lung Disease (the Union). In this discussion, differences between country-level and global-level components of the adoption and policy development processes will be highlighted where relevant.

3.1 Essential components

The essential components of a process for the adoption of new tools and the subsequent changes in global recommendations and national policies can be summarized as follows:

- stakeholder participation in the development of recommendations and policies;
- analysis of the needs and evidence for change;
- analysis of the risks and benefits of the new tool, including appraisal of the options;
- analysis of the health system environment and capacity to adopt, introduce and implement the new tool;
- development and endorsement of the new recommendations and policies and their wide dissemination.

These steps should not be considered in sequence; they represent processes that are interlinked.

3.1.1 Stakeholder participation in the development of recommendations and policies

Engaging stakeholders from the wide range of constituencies affected by, and concerned with, TB-related issues will be essential in developing appropriate recommendations and policies. These constituencies represent a wide range of sectors and disciplines, from intergovernmental agencies to national governments to patient organizations. Boxes 3.1 and 3.2 provide an illustrative list of stakeholders at the global and country levels.

Keeping NTP managers and national policy-makers abreast of ongoing discussions of, and progress towards, the availability of improved or new tools will be a key strategy for accommodating differences between the global and country levels. Some of these individuals, particularly those from countries with a high burden of TB, will have been involved in, and contributed to, the policy-making process to adopt new tools at the global level through various mechanisms and fora, including WHO advisory groups. In addition, many of them may have been involved in the design and conduct of clinical trials and studies in their countries to evaluate the efficacy and/or programme effectiveness of the new tool. A high level of participation by countries early in the evaluation process will facilitate their own analyses of

Box 3.1 Illustrative list of stakeholders at global level

Stop TB Partnership

Intergovernmental agencies

- World Health Organization
- United Nations Children's Fund
- United Nations Development Programme
- Joint United Nations Programme on HIV/AIDS
- UNICEF/UNDP/World Bank/WHO Special Programme for Research Training in Tropical Diseases

Funding agencies

- Multilateral and regional donors and development banks: Global Fund, World Bank, African Development Bank, Asian Development Bank, etc.
- Bilateral donors: Canadian International Development Agency, Danida, United Kingdom Department for International Development, Directorate General for International Cooperation, Norad, Sida, United States Agency for International Development, etc.
- United States National Institutes of Health
- European & Developing Countries Clinical Trials Partnership
- Philanthropic and other funding organizations: Bill & Melinda Gates Foundation, Rockefeller Foundation, Global Alliance for Vaccines and Immunization, Open Society Institute, Wellcome Trust, etc.
- New financial mechanisms: International Finance Facility, UNITAID, etc.

Pharmaceutical companies

- Private research and development firms
- State-owned enterprises

International suppliers

- Procurement agencies (Crown Agents, International Dispensary association, GTZ, Global Drug Facility)
- Private health care providers and institutions

Professional organizations and technical partners

- International Union Against Tuberculosis and Lung Disease
- United States Centers for Disease Control and Prevention
- KNCV Tuberculosis Foundation
- Other associations (American Thoracic Society, European Centres for Disease Control, European Respiratory Society)
- Academic institutions

Advocacy and community-based organizations

- Global Care Council, International Treatment Preparedness Coalition, RESULTS Educational Fund, Treatment Action Campaign, Treatment Action Group

Product development partnerships

- Aeras Global TB Vaccine Foundation
- Foundation for Innovative New Diagnostics
- Global Alliance for TB Drug Development

Box 3.2 Illustrative list of stakeholders at country level

(This list should be tailored to the specific context in each country.)

Ministry of Health

- National TB Control Programme
- National AIDS Control Council
- Joint HIV/TB Committee
- Medicines Regulatory Authority
- National Immunization Programme
- National Public Health Laboratory
- Pharmacy and Essential Medicines Department
- Department of Planning
- Director of Primary Health Care
- Health Education Department
- Provincial and District Health Officers
- Training department

Ministry of Finance

- Director of Health Budgets

Professional organizations

- Laboratory Technologists Association
- Medical and Paediatrics Associations
- Nurses Association
- Pharmacists Association

Private sector

- Manufacturers of TB control products
- Importers and wholesalers
- Private hospitals and pharmacies including NGOs
- Drug shops
- Traditional healers

Academic, research and training institutions

- Medical college
- Research institute
- Training institute

Other

- Community-based organizations
- National health policy-makers
- Global Fund country coordinating mechanisms
- National TB association
- Patients organizations
- Collaborating partners including multilateral (WHO, UNICEF, World Bank, etc.) and bilateral (USAID, PEPFAR, DFID, etc.) partners

countries, briefing papers, guidance documents¹ or other channels for disseminating information on new tools (e.g. through WHO country offices, the work of other technical partners, the World Wide Web and other means) could help national policy-makers examine these issues.

At both the global and country levels, ways of engaging the communities of those affected by, or at high risk of, TB in the analysis and decision-making processes should be found to ensure that their needs and perspectives are appropriately addressed.

At the global level, WHO has several specific mechanisms that can play a key role in the development of recommendations for new tools.

First, in 2001 WHO established an advisory committee called the Strategic and Technical Advisory Group for Tuberculosis (STAG-TB). This group is comprised of 18 members who represent a wide range of constituencies and expertise, including health systems, treatment issues, public and private sector issues and the affected community. STAG-TB provides scientific and technical guidance to WHO. The group meets once a year, and the results of its deliberations may form the basis of WHO recommendations. Subcommittees are sometimes created to provide advice to WHO on specific topics. Through consultation and collaboration, WHO could provide input, through its subcommittees, to ensure that effectiveness studies are appropriately designed, and to facilitate the analysis of available evidence prior to meetings of the full STAG-TB. This early engagement can help ensure that the package of evidence that will be presented to the full group for a decision meets the requirements and expectations of the wider group.

Second, in order to inform the development of guidelines for the introduction of new anti-TB vaccines, it will be necessary to engage the WHO Department of Immunization, Vaccines and Biologicals. This department convenes another advisory committee, the Strategic Advisory Group of Experts (SAGE) for vaccines and immunization. SAGE advises WHO on global policies and strategies for all vaccine-preventable diseases. Its mandate ranges from research and development concerns to delivery of immunization and linkages with other health interventions. Members of SAGE also span a range of constituencies, including members of the research and vaccine development communities, operational research experts, epidemiologists and programme managers. Like the Stop TB Department, SAGE can be informed through collaboration with WHO working groups established around specific topics. SAGE is currently being reorganized to make its structure and processes more formal.

Third, the Stop TB Partnership follows WHO guidelines and recommendations on global TB control policy, which are disseminated through its seven working groups. These groups are already collaborating to evaluate and demonstrate the effectiveness of new technologies, as in the case of the DOTS expansion and new TB diagnostics working groups. The Stop TB Secretariat supports collaboration among the groups.

As the Global Plan calls for “prompt approval of new tools for adoption by WHO and in countries”, it will be necessary to clarify and communicate how WHO can be engaged as early as possible in the evaluation of new technologies and their inclusion in new policy guidelines and recommendations where appropriate. Clear information on how to approach WHO regarding new technologies and their possible inclusion

¹ Examples of briefing documents prepared to assist countries in decision-making on adopting and introducing four-drug fixed-dose combination tablets include: *Frequently asked questions about the 4-drug fixed dose combination tablet recommended by the World Health Organization for treating tuberculosis (9)* and *Operational guide for national tuberculosis control programmes on the introduction and use of fixed-dose combination drugs (10)*.

in new WHO guidelines and recommendations must be transparent and clearly communicated to companies and other organizations that are developing new and improved technologies.

At the country level, political will is essential for the timely implementation of recommendations and for policy change. Some of the factors influencing the political environment for decision-making process include the following:

- Pressure on the government to demonstrate its commitment to fighting TB.
- Likely impact of the policy change on support for the programme. For example, the ability to obtain first-line fixed-dose combination (FDC) medicines free of charge was one of the factors that influenced the policy change to FDCs in countries purchasing from the Global Drug Facility (GDF). It may be possible to leverage additional funding for strengthening health care systems such as through the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund).
- Reassurance that the policy change can be sustained at least in the medium term. Obtaining medicines free of charge for one year may not be a sufficient incentive for change when the transition process itself is likely to take up to two years, or when the medicines are expensive and the cost will have to be borne by the ministry of health.
- Other national policy and guideline changes that are under way. For example, an initiative to update the national essential medicines list (EML) can be an incentive to update the NTP's standard treatment guidelines first in order to minimize the costs in updating and reprinting the EML at a later date.
- Opportunity to introduce multiple TB programme changes to minimize transition

costs. For example, updating a TB diagnostic algorithm in parallel with introducing a new TB diagnostic tool can minimize the costs of updating the operational manual and conducting training.

- Opportunity to integrate the policy change with initiatives to strengthen health systems. This factor may be a major consideration for introducing new TB diagnostic tests that will require strengthening of laboratory services in the country, especially at the peripheral level, to ensure appropriate diagnosis, treatment and adherence to therapy.
- Continued development of new tools which may supersede existing tools. Policy-makers may be reluctant to invest in the transition costs associated with adopting a new tool if it is expected to be replaced by a superior tool in a year or two. Further exploration of the considerations that affect policy decisions at the country level could help in the development of tools that could provide guidance in this area.
- Cost savings or efficiency gains to be achieved by using new tools.
- Opportunity to improve on TB control indicators.

3.1.2 Analysis of the needs and evidence for change

The Global Plan contains a comprehensive discussion of the importance and role of new tools in meeting the challenges of TB control. The need to develop these tools and the evidence behind these needs have been well documented and compiled by both the Stop TB Partnership and WHO, and are understood and accepted at the global level. Epidemiological evidence and information on the improved efficacy and performance of new tools are important for developing global recommendations. However,

other considerations, including those related to risks and cost–benefit, capacity to incorporate the new tool, capacity to provide high-quality care, and user needs and perspectives as well as responsiveness to national control needs are likely to be country-specific.

At the global level, the Stop TB Partnership Secretariat has a catalytic role to play in articulating and communicating these issues in order to engage partners around the world. This is important in order to stimulate and maintain commitment among partners, particularly among those who could potentially play a role in developing new tools.

3.1.3 Analysis of the risks and benefits of the new tool

Determination of the risks and benefits of a new tool requires a careful examination of the evidence. This will include evidence not only of the *efficacy* of a new tool under the conditions of controlled clinical trials but also of its *effectiveness* under actual use conditions. To achieve this requires early engagement with NTPs in high TB burden countries. In the case of new medicines, it is anticipated that they will be introduced as combinations of new medicines rather than as single entities to be combined with, or added to, existing treatment protocols, or replacing “old” medicines in current regimens. This will have significant implications for study requirements, as the new treatment combinations will have to be directly compared with the existing regimens.

Information on the performance of existing tools is needed as a starting point, but other aspects of the new tool will have to be considered. These include:

- costs and cost–benefit analysis (costs will include not only direct product acquisition costs for governments and for

patients but also the costs of programme implementation, continued support and other costs to the patient);

- product characteristics (shelf-life, storage, and transportation and temperature requirements);
- need for consumables and other devices (needles and syringes, laboratory reagents, replacement parts);
- requirements or implications on the other tools (medicines on laboratory and patient monitoring supplies);
- information management needs of the NTP (for example, if peripheral-level health centres become engaged with the diagnosis of TB);
- required knowledge and skill levels (for performing tests, handling medicines and vaccines, etc.) and implications for staff retraining, as well as production and distribution of materials for providers, patients and the community.

For anti-TB medicines, tool-specific considerations include:

- acceptability to patients, including factors that influence adherence to treatment (multiple dosing and the availability of FDC products, patient kits, the duration of therapy and the need for adjustments of dosages for weight in different age groups and between sexes);
- potential for cross-resistance with other anti-TB medicines;
- likelihood of drug resistance developing;
- drug interactions with commonly used medicines, including other anti-TB

medicines, medicines commonly used in individuals infected with HIV and with widely used traditional medicines such as herbs;

- side-effects, including both severity and incidence, and additional need for laboratory or provider monitoring (for example, glucose monitoring for medicines that affect glucose metabolism);
- contraindications with common conditions (e.g. patients receiving antiretroviral therapy, people with glucose-6-phosphate dehydrogenase deficiency, diabetes, alcohol dependency or those who are malnourished) and additional need for laboratory investigations to exclude contraindications;
- use in special groups, including children, infants and pregnant women;
- need for prepackaging.

For diagnostics, considerations include:

- acceptability to patients, including factors that contribute to patient adherence in the diagnostic pathway;
- quality assurance (QA) requirements, including internal and external quality control programmes;
- level of health system where the tool is to be used, as well as potential coverage in the public and private sectors;
- human resource needs, including the time taken to collect the sample, conduct the test and the skills needed to perform the test;
- infrastructure, equipment and supply needs, including requirements to collect, store and process the sample;
- ease of the procedure, interpretation of the test results and quick turnaround time.

For vaccines, considerations include:

- vaccine presentation (number of doses per vial) and trade-off between the wastage from multi-dose vials, which may have lower costs per dose and less burden on the cold chain but higher wastage rates (11);
- proper reconstitution of vaccine using the appropriate diluent;
- disease surveillance capacity after administering the vaccine;
- adverse events following immunization (AEFI);
- programme implementation issues, such as errors in storage, preparation or administration;
- method of vaccine delivery (e.g. oral, injection);
- safety and efficacy in people infected with HIV.

After examining these issues, the options for policy-makers may include:

- recommendation of adoption and implementation of the new tool;
- provision of a qualified recommendation, such as use of the tool only in certain circumstances; or
- request for further evidence of effectiveness.

3.1.4 Analysis of the health systems environment and capacity to adopt, introduce and implement the new tool

This analysis requires an understanding of the different sectors of health systems, including the public, not-for-profit private and for-profit sectors, because capacity differs both between sectors and among different levels within a given sector. For example, diagnostic tools which require high

degrees of skill to use and/or a sophisticated infrastructure such as biocontainment facilities may only be suitable for introduction into the higher level of health services. Similarly, introduction of new medicines where systems are inadequate to ensure appropriate diagnosis and treatment could lead to rapid development of resistance.

On the other hand, if the innovations simplify diagnosis and treatment, they could be ideal for introduction into weak infrastructures and programmes. Therefore, the constraints faced by health systems in developing countries need to be recognized when developing recommendations for the introduction and use of new tools at the global level. This development process offers Stop TB partners the opportunity to work together to identify countries' needs, and to develop strategies to address these needs. For example, the introduction of liquid culture media for species identification and DST will require laboratories performing this testing to have access to appropriate biocontainment facilities. New global recommendations or standards for the use of liquid culture, in turn, will have to take into consideration the availability of this infrastructure in countries, or the feasibility of installing, operating and maintaining biosafety equipment in developing countries.

At the country level, an analysis to ascertain if sufficient capacity exists in the health system to enable the NTP to realize the full benefit of the new TB control technology and to determine the necessary inputs is a key component of the decision-making process. This feasibility study should assess both technical and management capacity,¹ as well as determine the location and capacity of health facilities in the public and private sectors. Investigations of field acceptability and feasibility should be planned and budgeted for early in the process. In addition to the data from

small-scale studies, a countrywide analysis to identify and quantify the impact of the factors that may constrain successful implementation may be needed.

Box 3.3 contains some of the tool-specific considerations.

3.1.5 Development and endorsement of the new recommendations and policies and their wide dissemination

Following completion of the analyses of the needs and evidence for change, of the risks and benefits of the new tool and of the capacity of health systems, the next step is to develop new recommendations at the global level and new policies at the country level.

At the global level, this can be done through submission to WHO with a view to possible inclusion of a new technology in revised guidelines and recommendations. WHO may choose to seek advice from STAG-TB and SAGE in formulating such revisions. In the case of the Stop TB Department, WHO has taken the approach of developing new recommendations and disseminating the associated information through communication channels such as the World Wide Web and previously scheduled meetings and training programmes, rather than waiting until the development or revision of the full set of new programmatic guidelines. In the case of the WHO Department of Immunization, Vaccines and Biologicals, SAGE recommendations are typically interpreted and developed into position papers to provide guidance.

At the country level, a decision has to be made whether to endorse a new tool and, if so, whether to develop a new policy or update the existing policy. Ideally, a comprehensive policy document should be developed that presents the

¹ The following manual can assist users to assess the aspects of the pharmaceutical management system that are critical to ensuring the availability and proper use of new anti-TB medicines: *Pharmaceutical management for tuberculosis: assessment manual (12)*.

Box 3.3 General resource considerations for new technologies

For medicines, some key considerations may include the available capacity to:

- diagnose different forms of TB, including TB in HIV/AIDS, MDR-TB and XDR-TB;
- perform essential laboratory monitoring;
- provide the appropriate quality of medical care;
- detect contraindications and adverse drug reactions;
- provide support to patients to adhere to and complete treatment;
- store products appropriately;
- minimize losses and theft;
- carry out pharmacovigilance.

Some key considerations for diagnostics may include:

- availability of trained staff to perform the test;
- effectiveness of regulatory/monitoring oversight for laboratories (including quality assurance);
- location in remote areas and access to spare parts and consumables;
- availability of in-country technical support;
- resources for maintenance contracts;
- state of communications systems and infrastructure for transmitting test results;
- logistics and storage requirements for laboratory equipment and consumables, for example, cold chain and uninterrupted supply of electricity;
- environmental conditions, such as ambient temperature and humidity;
- availability of appropriate medicines once diagnosis has been confirmed.

For vaccines, some key considerations may include:

- requirement for booster doses;
- skills to give vaccine (e.g. intradermal administration);
- availability of trained staff;
- integrating a vaccine for pre-exposure TB into the global expanded programme on immunization;
- incorporation of vaccine into health care delivery systems for adolescents and adults;
- adherence to safe injection practices;
- the ratio of coverage versus vaccine wastage in existing programmes;
- adequacy and availability of cold-chain storage;
- adequacy of surveillance and response systems post vaccine administration (especially in decentralized health systems).

background to the policy change and explains the details of the new recommendations. However, countries will have to consider the future need to incorporate the rapid, successive availability of new tools into their decision about whether to develop a set of new policies and guidelines, or to revise existing documents. The development of decision aids such as algorithms or decision trees could help provide guidance in this area. It will be critical that all stakeholders are active participants in this process and kept updated. In particular, NTP managers and technical partners in countries, who are more likely to be informed of the latest options in the TB “toolkit”, will have to ensure that senior-level decision-makers within the ministry of health are briefed fully on the new recommendations so that they are able to explain the changes to professional organizations, donors,

nongovernmental organizations (NGOs) and other key stakeholders to encourage their endorsement of new policies.

New mechanisms that could help facilitate the development of global recommendations and national policy development include the Task Force on Retooling and the country coordinating mechanisms, which have been established in many countries for soliciting and providing oversight over grants from the Global Fund. The broad representation of a variety of stakeholders on each of these bodies could represent an opportunity to enable a wide range of constituencies to participate in the discussions which will be necessary to secure final development and endorsement of guidelines and new policies.

4. Introduction and implementation of new technologies

This section focuses on the key considerations for integrating new technologies, including medicines, diagnostics and vaccines, with the other recommendations for TB control with NTPs. The implementation of policy changes in both the public and the private sectors, including not-for-profit institutions such as faith-based or secular NGOs and the for-profit sector, is addressed. The key considerations, listed in Box 4.1, can be divided into technical considerations, operational considerations, and monitoring and evaluation.

Technical considerations incorporate the activities related to the regulation and appropriate

use of the tool through the development and dissemination of guidelines, and the development and use of appropriate training and advocacy, communication and social mobilization (ACSM) strategies. Operational considerations include the activities related to procurement and supply management, which ensure that the tools are available at the points of service delivery.

Although the steps are presented sequentially, the activities need not be carried out in sequence but in parallel to facilitate faster implementation.

Box 4.1 Key considerations for implementing policies for new technologies

Technical considerations

- Registration of products and revision of regulations.
- Development/updating of programme guidelines, the essential medicines list, the essential medical devices and supplies list, and recording and reporting forms.
- Dissemination of guidelines and training of health workers and community partners providing TB care.
- Advocacy, communication and social mobilization targeting the community.

Operational considerations

- Management of products currently in use that are to be replaced by new technologies:
 - development of a phase-out plan.
- Management of supply of new products:
 - availability in the public and private sectors;
 - development of a phase-in or roll out plan;
 - forecasting of demand and quantification;
 - procurement;
 - distribution;
 - inventory management.
- Product quality and safety surveillance:
 - monitoring product quality;
 - clinical event surveillance (pharmacovigilance).

Monitoring and evaluation

4.1 Technical considerations

4.1.1 Regulation and registration

The regulatory changes required for the introduction of a new medicinal, diagnostic or vaccine product into a country include registration and revision of regulations relating to the prescribing, dispensing or use and sales. Box 4.2 outlines the key questions to be asked during the policy change process.

Regulation is a fundamental step required by countries before a new product is authorized to enter the country and be integrated into the health care system. In most countries, the product registration process includes submission of a dossier containing information on efficacy, safety and other properties. In some countries, a site visit to the manufacturer is required. Information on the additional registration requirements for medicines such as FDCs and co-packaged combinations must be obtained in good time to ensure that products arrive in the country to meet the implementation schedule. Manufacturers will usually be required to provide documentation of

satisfactory bioavailability for the product. Some countries may require local clinical trials to be done. However, if manufacturers and/or promoters such as the product development partnerships have carried out appropriate effectiveness studies, albeit in other countries, and if WHO through its committees has certified validity of the evidence, regulators at country level should critically consider whether there is real need to redo them locally.

The requirements for, and process of, registering diagnostic products vary from country to country, and a regulatory framework may not be in place in many developing countries. Moreover, expertise to evaluate the submitted dossiers may not be available.

Depending on how frequently the registration committee in the country meets, and the extent of the backlog of applications, the registration process can take six months or longer; it may take years in the case of new products. The submission of incomplete dossiers and the time taken to conduct site visits contribute to delays.

Box 4.2 Key questions on product regulation for new technologies

1. What is the registration status of the new products for TB control in the country?
2. If the programme is donor funded and is required to meet donor requirements for quality assurance, are the products:
 - (a) registered in a country with a stringent drug regulatory authority, or
 - (b) prequalified by WHO?
3. Are the regulations regarding the distribution and sale of the new products consistent with the new policy?
4. Are the regulations related to the prescribing, dispensing and/or use of the new products in the country consistent with the new policy?

For example, in one country, registration of anti-TB drug FDCs to support a policy change to FDCs took 10 months, in part due to delays in sending the samples by the manufacturer, the incompleteness of the dossier submitted and the time taken by the regulatory team to inspect the facility. The GDF now requires approved manufacturers to keep dossiers of documents on file for rapid transmittal to national regulatory authorities. Efforts are under way to harmonize regulatory requirements for new TB control products because country-specific requirements, for example for efficacy and stability studies, can significantly delay the process of policy implementation.

To address the constraints faced by insufficient capacity to conduct dossier evaluation or manage the registration workload, fast-track mechanisms (prioritizing evaluation and processing of new TB technology registration application) and/or recognition of efficacy and safety evaluation (“proxy evaluation”) by another medicines regulatory authority, particularly for countries participating in the International Conference on Harmonization, may be a more efficient way of accelerating and shortening the registration process. Although issuing a waiver for products procured under a GDF grant can be an effective temporary measure, this is not a long-term solution. Strengthening the national regulatory authority to facilitate a national registration process for new TB control products will require significant technical assistance, including streamlining the process, developing and implementing appropriate standard operating procedures (SOPs), training staff, establishing a product registration database, and overcoming the resistance to harmonizing technology registration and mutual recognition. As this can be one of the longest and most difficult steps in the policy change process, it is critical that programme managers work with manufacturers

and product development partnerships to initiate the process of registering products early.

The Global Training Network on Vaccine Quality¹ is an example of a global initiative to improve vaccine regulation and production through a series of nine training courses conducted by 16 training centres in three different languages. This network provides national regulatory authorities, national quality control laboratories and vaccine producers with training on good manufacturing practice (GMP), laboratory quality systems, quality control testing, regulation for vaccines and surveillance for AEFI.

As noted earlier, many countries have minimal or no regulatory oversight over diagnostics. This deficiency calls for investments to strengthen this area. Establishment of internationally recognized standards for evaluating and testing could help those countries that lack their own regulatory mechanism.

Regulatory changes may include amending regulations and policies to ensure that the qualifications and training of staff who prescribe and dispense medicines, administer vaccines or perform diagnostic testing are consistent with the new policy. In order to ensure that the new tools are available at public and private health facilities, and at different levels of the health care system including community organizations, in line with the updated TB policy, the NTP will need to work with the national formulary committee and the medicines regulatory authority to schedule or assign an appropriate legal classification for the medicine, diagnostic or vaccine (e.g. prescription-only medicine, over-the-counter). For example, it may be considered necessary to reclassify an anti-TB medicine that is already in use as an antibiotic as a TB-prescription-only medicine to reduce the potential for use in other

¹ http://www.who.int/immunization_standards/vaccine_quality/gtn_index/en/index.html.

infectious conditions or its inappropriate use, as a measure to delay the development of resistance, but commitment is needed to enforce this.

4.1.2 Revision of programme guidelines, essential medicines and supplies lists, and recording and reporting forms

Some key questions related to the revision of programme guidelines, essential medicines and supplies lists and recording and reporting forms are laid out below in Box 4.3.

All programme guidelines, including national standard treatment guidelines, immunization guidelines, diagnostic testing algorithms, and basic training materials and modules will need to be revised quickly after the new policy has been adopted. It is therefore important to identify and secure adequate funding early to complete the process in good time. A request to include the new product in the national EML and essential

medical and devices list and essential health supplies list, where they exist, will also need to be submitted promptly, as these essential lists guide the selection of medicines, diagnostic kits, equipment, reagents and other associated supplies for national procurement.

The national TB five-year plan and national comprehensive immunization multi-year plans, TB diagnosis and treatment guidelines, as well as the TB sections of HIV guidelines and immunization schemes, may need to be updated along with national operational manuals, handbooks and job aids for programme managers and health workers, curricula and training materials, and SOPs and manuals for laboratories. Cross-checking the information included in the operational manual with the team responsible for developing procurement specifications and negotiating contracts is essential to avoid errors and subsequent reprinting costs. For example,

Box 4.3 Key questions on programme guidelines, essential medicines, vaccines, medical devices and other health supplies lists, and recording and reporting forms

1. What existing programme guidelines and associated training materials need to be updated for different levels of health care workers?
 - national TB treatment guidelines
 - national HIV treatment guidelines, for example, for prevention and treatment of opportunistic infections, and HIV/TB coinfection
 - national tuberculosis operational manual
 - national operational manual for management of drug-resistant TB
 - national laboratory manual
 - national standard operating procedures for laboratories
 - national immunization guidelines.
2. Who will be responsible for updating the guidelines or developing new ones?
3. Has an application to add the new products been submitted to the corresponding essential technology selection committee?
4. Who is responsible for updating the recording and reporting forms?
5. Who is responsible for updating the training materials?

in one country, the operational manual was prepared with instructions for dispensing anti-TB FDCs in 30-tablet packages, only to discover when the supplies arrived that the product packages contained 28 tablets.

Revision of the guidelines should be coordinated with the development of ACSM strategies to ensure that the same messages are communicated to health care workers, community partners providing care and the public, especially where treatment schedules vary. The revision of guidelines and associated materials to include new technologies can often provide an opportunity to incorporate other changes, for example to support national DOTS expansion. It is important that additional proposed changes are identified, planned and budgeted for early so that the process of implementing the new technologies is not delayed.

The recording and reporting forms used by the NTP and the national immunization programme will need to be revised to include the new tools, and then field-tested and printed. Relevant changes to the health management information system and other health system forms will also be required. This process needs to be started in good time, as the forms will need to be incorporated into national operational guides and training materials. The process of revising and printing forms for governmental TB control programmes, particularly where they have to be printed by government printers, can take up to six months. One approach to avoid delays is to use draft forms during the transition phase, which also offers the advantage of allowing thorough field-testing of the forms, including obtaining feedback from users. It is important to anticipate the time needed to develop the materials, as this, together with the availability of the product, will determine the schedule for disseminating guidelines and

training health workers and community partners.

Changes to guidelines will also result in changes to the monitoring and evaluation system. For example, new point-of-care diagnostics laboratory registers may not be centrally located, and new indicators and ways of capturing data and monitoring performance will be needed.

4.1.3 Dissemination of guidelines and training of health workers and community partners providing TB care

Dissemination of the revised guidelines to programme managers and front-line TB workers in both the public and private sectors will need to be accompanied by sensitization and/or training of health care workers in both sectors, and also of community partners providing TB care where relevant. For some new tools, such as new second-line drugs to treat drug-resistant TB or new diagnostic technology for rapid culture or DST, the sensitization and training of staff in the one or two centres in the country where treatment for drug-resistant TB is provided, or the national laboratory where the test will be performed, will be relatively simple. For other tools, such as a new first-line treatment for TB or a new point-of-care diagnostic test, training activities will need to be carefully coordinated with supply management, essential infrastructure changes and the development of laboratory-specific SOPs, particularly where tools are being introduced in phases in the country. It is important that training and sensitization activities of health care and community workers are done shortly before the new tool is available at the service delivery point, as providers may forget key messages if distribution of the product is delayed.

A training plan needs to be developed that lays out the strategy for training and the approach for assuring the quality of training. Countries may choose to have a pool of trainers to train future

trainers or to retain a central or regional pool of trainers to conduct all the training. The plan will also need to include a strategy for training community treatment supporters.

In many high-burden countries, the severe shortage of health care workers makes it difficult for managers to release front-line TB workers from their facilities to attend the training. Similarly, releasing laboratory staff from facilities with one or two qualified staff can pose challenges. It is important to ensure that adequate notice of one month or longer is given to the facility management team for the training and to plan for the repetition of training. In addition, identifying a pool of dedicated trainers at the central level can be problematic in under-resourced TB control programmes. This can be a major limiting factor to the speed of implementing a policy change. The implementation strategy may involve the following:

- ensuring that all the central level TB programme staff are competent to deliver all aspects of the training;
- dedicating a core of 2–3 staff to organize and deliver the training;
- releasing other staff to assist in the intensive phase of training where possible.

Strategies for monitoring the quality of the training may include observation of dispensing practices or of staff performing a TB diagnostic test. Laboratory performance indicators and other tools for supportive supervision will also have to be updated or adapted.

Training materials will need to be developed and field-tested to meet the needs of different audiences. Such materials have to be developed in the context of the *International standards for tuberculosis care* (5). Technical assistance may

be needed to appropriately develop these training materials or adapt materials prepared by global partners.

Materials for health care workers and community treatment supervisors are needed well in advance. One approach to prepare materials for health care workers can be to extract information from the TB operational manual. The NTP may decide to take the opportunity to offer additional training to support other aspects of the national TB control strategy, such as HIV/TB service delivery integration. It is important that these decisions are made early on so that the complete training package is ready to meet the time line for implementation. Information packages may need to be developed for some target audiences, such as private sector physicians. Training alone may be insufficient to convince private practitioners to adopt the new recommendations. The professional associations will need to be involved early in the process to pave the way for adoption of the new policy by private practitioners. The NTP will also need to work with the pre-service training institutions in the country to incorporate revisions related to the new technologies for TB control in their curricula. Similar changes need to be made to TB, HIV, laboratory, immunization and other in-service training curricula. All staff involved in immunization will need to review their capacity to deliver the new anti-TB vaccine in the context of their health system. Capacities need to be strengthened in the area of planning, management, and monitoring and evaluation, including the key technical areas of immunization operations such as logistics, vaccine supply and quality (13). In-service training in particular needs to be strengthened at the district level to ensure quality of delivery of immunization services.

Some key questions to consider on the communication components are included in Box 4.4.

Box 4.4 Key questions on the communication components of implementing the new policy

1. How will the revised guidelines be disseminated within the public and private sectors?
2. Which groups of health-care workers and/or community partners caring for TB patients need to be trained in the new recommendations?
3. Who will develop the materials and carry out the training for the health-care and community workers in both the public and private sectors?
4. Who is responsible for the development of advocacy, communication and social mobilization strategies, and how will this be coordinated with the development, dissemination and training of the revised guidelines?
5. How long will it take to train all appropriate personnel in the national TB control programme?

4.1.4 Advocacy, communication and social mobilization targeting the affected community

ACSM strategies will be needed to support the implementation of the new TB control recommendations, especially those that introduce diagnostic tests or treatment with which providers, and particularly patients, have little or no experience. Multiple approaches, including printed advocacy and information materials, mass media and e-information, should be used to increase public awareness about the new recommendations, and the strategies will need to be coordinated with the sensitization or training of health workers and community partners in TB care to ensure that consistent messages are communicated. Issues of treatment adherence, information on potential side-effects, special requirements of medicines such as routine laboratory monitoring, and the concerns regarding testing for TB should be addressed as relevant. This applies also for vaccines, because negative perceptions about immunization arising out of rumours, AEFI or cultural and religious beliefs must be addressed. Communication and advocacy skills must be strengthened for EPI programmes and heads of provincial and district-level programmes. Resources for developing a communication strategy have been published by WHO and the Stop TB Partnership (14) and by the

Global Alliance for Vaccines and Immunization (GAVI) (15).

4.2 Operational considerations

4.2.1 Management of products currently in use that are to be replaced by new technologies: developing a phase-out plan

The first step is to determine whether the new TB control product will be a replacement for any medicines, vaccines or diagnostic tests currently in use or an addition to the currently recommended tools. For example, a country may change its policy to introduce a new medicine to treat drug-resistant TB to supplement the existing range of tools held at the national referral centre. In this case, none of the existing tools will need to be phased out. On the other hand, a change in policy in order to introduce a new first-line product will probably require the existing products held in stock to be phased out or, at a minimum, to be reduced substantially. The next generation of anti-TB vaccines may provide either an addition or a booster to the BCG vaccine that is commonly given at birth, or a recombinant BCG not currently in use, or both.

Planning for the phasing out of the products being

replaced is critical because decision-makers are often reluctant to implement policy changes when significant stocks of “old” medicines, vaccines or diagnostics remain in the system. Countries with large public sector TB programmes typically hold 9–12 months of buffer stock of first-line anti-TB medicines. Some key questions that must be asked in developing a plan for phasing out the current technologies from the system are listed in Box 4.5.

If a phase-out plan is necessary, the first step is to map out which of the tools to be phased out are currently available in the country, and where. The next step is to compile accurate estimates of the current products in stock and in the supply chain, and to develop a plan for adjusting future procurements to ensure that when the switch to the new product is made there is not a large stock of the previous used products in the system.

However well planned the phase out is, some stocks of the previously used products will usually be left over in public health stores and facilities when the new products become available. In some cases, small quantities of the products may be retained for continuing use, for example in patients who experience side-effects to the new first-line anti-TB medicine.

It is critical to carefully monitor the phasing-

in/phasing-out process during the transition phase and to adjust the timing for phasing out of old products as necessary. For example, in one country the lead time to procure anti-TB FDC products to support a policy change to FDCs took eight months instead of the expected four months. Fortunately, stock of the single drug products was sufficient to cover the unanticipated delay in implementing the policy change due to this extended lead time. In the transitional stage of policy implementation, it is better to retain some stocks of the obsolete products than to run out before the new products arrive.

The techniques used to phase out products in the public sector can also be used in the not-for-profit private sector. However, phasing out obsolete products from the for-profit private sector is much more complex. For countries that supply the private sector with anti-TB tools, the feasibility of approaches, which may include compensating retail outlets by the government or through the wholesaler, may need to be explored. It will be very important to carefully document and share with other countries all experiences with the phasing out of tools, whether in the public or the private sectors.

Box 4.5 Key questions on developing a phase-out plan for removing current technologies from the health system

1. Is a phase-out plan needed?
2. Will the new product be a replacement or an addition to products currently used in the country?
3. How will stocks of currently used products be removed from public sector facilities once the new TB control products are available?
4. What, if anything, will be done about the existing stocks of the currently used products in the not-for-profit and for-profit sectors?

4.2.2 Management of supply of the new tools

Availability in the public and private sectors. A critical decision for procurement planning is whether the public sector will procure and supply the new products to both the public and the private sectors, and to develop budgets and quantify needs accordingly. In some countries, the public sector TB control programme already supplies many anti-TB products to the not-for-profit sector. As countries move forward with strategies to strengthen NTPs and expand DOTS, including implementing PPM approaches (16), the private sector may become increasingly important in rolling out the new technologies. For example, an NTP may decide that a new rapid TB diagnostic kit should be supplied by the public sector to nongovernmental HIV voluntary counselling and testing centres to improve TB case-finding. One consideration is that the lack of availability of the new TB control tool in the private sector may either encourage leakage from the public sector or use of inappropriate or non-recommended tools.

Once this decision has been made, the next step is to prepare the phase-in plan in which the innovation is introduced gradually, or a roll-out plan in which the innovation is introduced everywhere simultaneously within a country.

Developing a phase-in or nationwide roll-out plan. There are two approaches to implementing a new policy that involve the introduction of new TB control tools: either a phased approach or an immediate nationwide roll out. The degree of planning will depend on the option chosen. For some new tools, a phased approach will not be appropriate. For example, the introduction of a new rapid culture test and DST for referral laboratories may not need to be phased in. Similarly, a new medicine with the potential to significantly decrease mortality from MDR-TB will usually be made available immediately to the few

referral centres in a country that treat cases of MDR-TB. However, with tools such as new first-line anti-TB medicines, phased implementation is often recommended by WHO in order to enable NTPs and ministries of health to evaluate and adjust their approaches as needed. The WHO operational guide for NTPs on the introduction and use of FDC medicines is a useful guide for developing a phase-in plan (10).

Phased implementation could be geographical, with some areas or districts with high TB case-loads selected for early implementation. Alternatively, it could take place according to health system level, with some levels selected for early implementation. For example, a tool to be used at all levels of the health system could begin with the national reference and provincial health facilities first, and then the district, before the health centre level. This will allow for strengthening the district and proximal levels, while implementation takes place at referral levels.

Phased implementation offers the following advantages:

- lower start-up costs for the implementation;
- enables countries to field-test materials, such as training and ACSM strategies and materials, as well as recording and reporting forms, and to identify and correct any problems;
- lower human resources requirements at the central level to manage implementation; this is particularly important where the available human resources at central level for training and to support implementation are limited;
- the uptake of the new recommendations in the first phase can be monitored and used to improve forecasting of the demand for the new tool in following phases;

- provides an opportunity to engage stakeholders in the community in the process of retooling; the community can contribute to the phasing-in process by assisting the NTP to identify sites to begin monitoring patients, identifying side-effects and adverse reactions to new medicines through community discussion groups, and identifying ways in which the community can support service delivery, particularly in a context of severe health worker shortages.

Although phased implementation is usually preferred, a nationwide roll out may be more appropriate for simple (point-of-care) technologies, geographically small countries, when immediate coverage is desired (new vaccine) and where sufficient resources are available. However, nationwide implementation requires greater start-up costs, good pre-testing of ACSM and training materials, as well as better coordination of all activities to ensure successful implementation.

Implementation guides for specific tools, such as the WHO *Operational guide for national tuberculosis control programmes on the introduction and use of fixed-dose combination drugs (10)*, are valuable resources to help countries develop a country-specific phasing-in or nationwide roll-out plan.

Forecasting demand and quantification. Forecasting needs is also a critical step for justifying and securing an adequate budget to procure products regardless of whether the source of funding is the national government or a grant from external sources. Initially, new tools such as vaccines may be produced by a limited number of suppliers, and the global supply may be limited. It will therefore be important to forecast the potential needs carefully before starting the

phase-in. It may be difficult to obtain additional products in time to avoid stock-outs caused by unanticipated requirements, such as wastage of reagents which have a limited shelf-life once the product is opened, or multi-dose vials for an anti-TB vaccine.

For anti-TB treatment, sufficient supplies of new medicines must be correctly quantified so that every patient can begin treatment without delay and complete treatment without interruption. Accurate record keeping and timely reporting of consumption data are key to proper quantification for a need and demand-driven supply system. It is also important to identify early on how the procurement of the new products will be financed – through the ministry of health, through donors and others – to ascertain budget restrictions and how the tender process may impact the quantification process.

Key questions to ask when making the forecasts for new TB control technologies are listed in Box 4.6.

The initial step is to define the coverage and objectives for the forecasts. For example, is the demand forecast for the public sector network alone or will it also include the private sector? For what levels of the health care system are estimates needed? What is the objective of the forecasting exercise? For example, is it to prepare preliminary estimates for manufacturers, organize finances or determine quantities to be procured?

Several different methods can be used to compile a forecast of demand, based on historic consumption data, morbidity data or a combination of both. For new tools, data on previous consumption are not available, and the morbidity method is used to forecast needs. However, accurate forecasting is usually constrained by the lack of good-quality data on morbidity and

Box 4.6 Key questions on forecasting the potential demand for new technologies

1. What will the impact of new TB control technologies be on demand for existing products? How will new diagnostic tests affect the needs for anti-TB medicines? Will new vaccines decrease the need for diagnostic tests and medicines? By how much and over what period of time?
2. What data are available for forecasting needs?
3. What method is currently used for forecasting needs of TB control products?
4. How are the forecasts validated?
5. What method of quantification will be used to estimate the demand for new TB control products and what are the data limitations?
6. Have needs for special populations, for example, for children and pregnant women, been considered?
7. Are adequate buffer stocks planned at relevant levels? Have stocks to fill the supply chain been included in the estimate?
8. Are parallel efforts for national procurement and grants appropriately coordinated to avoid duplication and to ensure that all products and supplies needed to make up a drug regimen, perform a test or administer a vaccine are available simultaneously and in adequate quantities?
9. Have the ancillary medicines and supplies for identifying and managing adverse effects to anti-TB medicines or vaccines been included in the forecasts?
10. Will the implementation be pilot tested in a few districts then scaled up gradually throughout the country or will there be a nationwide rollout?
11. What is the expected uptake of the new TB control policy over time within each health facility and/or district?

estimates must be made from whatever data do exist. It is important that programme planners have a clear understanding of the limitations of the data used and utilize data collected from pilot studies or phased implementation to improve estimates of the potential demand before nationwide implementation. If the new tool is to replace an existing product, initial forecasts can be based on the consumption of previously used first- and second-line treatments,¹ diagnostics and vaccines.

It is important to consider how the introduction of new TB technologies may impact the use

sensitive diagnostic test (resulting in enhanced case detection) may increase the need for anti-TB medicines. These new medicines will require tests to identify resistance, or may also increase the need for laboratory testing to detect potential side-effects or exclude contraindications. For example, as discussed earlier, the introduction of a new medicine that affects glycaemic control may increase the need for reagents and supplies to support blood glucose screening in TB-infected patients. Moreover, demand for more effective or simpler first-line anti-TB medicines may in turn increase the use of diagnostics.

Experience from the introduction of antiretroviral therapy has shown that a team approach to developing assumptions and forecasting demand for new tools contributes to producing meaningful estimates. Including stakeholders from the national immunization programme or the laboratory services as appropriate, as well as the NTP team and central medical stores personnel, and from the private sector if they will be involved in using the new tool, should be considered.

Although forecasting and quantification tools have been developed to estimate needs of existing TB control tools, they may not be widely used. Strategies to assist countries to successfully implement new policies must include developing new tools or adapting existing ones to quantify needs for new TB control technologies and provide technical assistance to compile forecasts, particularly before applications are made to the Global Fund, the GDF, GAVI and other funding organizations. In particular, assistance may be needed to develop the assumptions for quantifying requirements and using existing tools. For example, the GDF has developed tools to assist countries in quantifying their needs for both the anti-TB medicines and the laboratory kits that it procures. The GDF provides technical assistance to countries in quantifying needs through its partners. The district vaccine data management tool defines critical indicators and describes how to monitor the management of immunization supplies.

Procurement. Procurement is the process of acquiring medicines and supplies, including those obtained by purchase and donation. An effective procurement process ensures the availability of the appropriate tools, in the correct quantities, at reasonable prices and at recognized standards of quality. The key questions that need to be asked in developing a procurement plan for the new TB control tools are listed in Box 4.7.

Box 4.7 Key questions on procuring the new technologies

1. What do the treatment guidelines call for?
2. What are the national procurement regulations?
3. Does the current system allow procurement directly from international agencies and/or sole source procurement? Are there published procurement procedures for competitive procurement? What funds are to be used for the purchase of the new products?
4. Is there a local source of the new product or will it be imported?
5. Is the product registered in the country?
6. Are the products prequalified by WHO?
7. Are international supply mechanisms available? (Global Drug Facility and Green Light Committee, Pan American Health Organization Strategic Fund, US President's Emergency Plan for AIDS Relief, etc.)
8. What is the average lead time (the time taken between ordering the product and the time when it is available for use) for the new product?
9. What systems are in place to assure the quality of the new tool?
10. Is there a need for special packaging specifications?

The systems for procuring new technologies for NTPs vary considerably. In some countries, procurement is centralized and is done either for anti-TB medicines alone or integrated with procurement of essential medicines; in other countries, procurement is completely decentralized and is a responsibility of individual TB facilities and health centres. Between these two options are various other arrangements, including those in which the NTP selects products and quantifies

¹ Methodologies for quantifying anti-TB medicines are outlined in: *Managing pharmaceuticals and commodities for tuberculosis: a guide for national tuberculosis programs (17)*.

needs, leaving procurement and distribution to the essential medicines programme; or others in which procurement is the responsibility of an agency nominated by the donor paying for the products. National immunization programmes may purchase their vaccines from UNICEF¹ or directly from manufacturers. In addition, the procurement of laboratory reagents and equipment may be managed by the national laboratory system. In some countries, the procurement of TB tools by the public sector is small relative to the private sector.

Often, actual procurement and financing of the procurement occur in different departments or ministries or through donors. There is a need therefore to synchronize the availability of funding to meet the requirements of the procurement cycle. For procurement using funds from the Global Fund or GAVI, countries are required to adhere to Global Fund and GAVI policies on procurement and supply management, which emphasize the purchase of products that have been prequalified by WHO (or which have been produced according to GMP). Procurement of second-line medicines with funds from the Global Fund can be done only via the Green Light Committee (GLC). It is therefore essential that timely planning, communication and required lead times are adhered to.

Given the complexity of the procurement requirements and systems in current use, it is important to establish a communication mechanism that includes all of the key stakeholders who will contribute to managing the procurement of the new tools. The first task for the working group responsible for coordinating the introduction of the new technology should be the development of a procurement plan that considers the distribution strategy (including the public and private sectors as appropriate)

to support the implementation of the new policy. The plan should also include information on the procurement method to be used. To obtain the best prices, competitive procurement is generally recommended. However, the limited number of suppliers of a new TB technology may mean that countries are limited to a single supplier. It is important that the managers of the transition process work closely with the procurement team and adjust the phase-in or roll-out plan as needed to manage unanticipated events, such as extended lead time due to production difficulties or a natural disaster in the exporting country.

Regardless of whether products are sole-sourced, systems need to be put in place to verify the quality of products as well as to monitor supplier performance and resolve any identified problems. Some new diagnostics may have short shelf-lives, so consideration should be given to procuring or scheduling deliveries of smaller quantities more frequently to obtain more recently manufactured stock.

A useful resource for procuring anti-TB medicines is *Managing pharmaceuticals and commodities for tuberculosis: a guide for national tuberculosis programs (17)*.

The Global Drug Facility and the Green Light Committee. The GDF and the GLC play a unique role in the expansion of access to, and the availability of, high-quality anti-TB medicines to facilitate global DOTS expansion and enhancement. The GDF is housed in WHO headquarters in Geneva, Switzerland, and managed by a small team at the Stop TB Partnership Secretariat. Since its establishment in 2001, the GDF has been a primary source of first-line anti-TB medicines for countries that meet specific requirements set out by the GDF, including the use of effective treatment protocols.

¹ UNICEF is the principal purchaser of vaccines for national programmes. It also works with countries to strengthen their forecasting plans to ensure that such information is readily available to manufacturers. UNICEF invites WHO prequalified manufacturers to bid for multi-year purchase agreements for direct delivery to countries that use UNICEF procurement.

The GDF works to:

- link demand for quality-assured medicines to timely supply and monitoring, via grant and direct procurement services, outsourcing all contracts to partners on a competitive basis;
- use product packaging and standardization to simplify management of medicines;
- link grants to TB control programme performance;
- stimulate industry to produce sufficient quality-assured, internationally-recommended anti-TB medicines at the most competitive prices.

In addition to supplying adult and paediatric formulations of anti-TB medicines, the GDF has also begun to provide second-line medicines as a result of its convergence with the GLC. Furthermore, the GDF has already begun preparations to supply diagnostic kits to NTPs. These kits are expected to begin arriving in countries in mid-2007.

The GLC was established in 2001 when the former Working Group on DOTS-Plus for MDR-TB identified access to second-line anti-TB medicines as one of the major obstacles to the implementation of DOTS-Plus pilot projects. The working group made arrangements with the pharmaceutical industry to provide lower-priced second-line anti-TB drugs to DOTS-Plus pilot projects that met the standards outlined in the *Guidelines for establishing DOTS-Plus pilot projects for the management of MDR-TB (18)*. The DOTS-Plus pilot projects have now evolved into MDR-TB management programmes (19). The GLC is responsible for reviewing applications from potential MDR-TB management programmes and advising WHO on projects eligible to receive concessionally-priced, second-line anti-TB medicines (20).

Both the GDF and the GLC provide extensive

technical assistance to countries in managing medicines and laboratory kits in support of DOTS expansion and DOTS-Plus programmes, including market forecasting and monitoring of anti-TB drug use. In addition, the GDF has assisted several countries in transitioning from single-drug first-line medicines to FDCs and is therefore well positioned to assist countries in introducing new medicines and diagnostics.

The GDF's role with respect to improved or new tools for TB control will be to ensure the continuous supply of quality-assured products through excellent procurement practices, including competitive tendering to obtain the lowest possible prices, while ensuring high quality of products. It does not have its own policy regarding the addition of products to its procurement list. Instead, it generally follows the recommendations of STAG-TB and the WHO Department for Medicines Policy and Standards (PSM) on QA. If manufacturers or other entities approach the GDF with requests for adding products, independently of STAG-TB and PSM, the GDF will generally seek advice from the WHO Stop TB and PSM departments.

While historically it has focused only on procurement of anti-TB medicines, the GDF has recently added laboratory supplies for performing microscopy to its procurement list, and also worked with partners to develop quality standards for reagents. The GDF's day-to-day decision-making process is usually by consensus of its 12-member staff, which meets every two weeks; however, the Stop TB Partnership's Executive Secretary and Coordinating Board play important roles when it comes to decisions with resource implications or when significant changes in procedures are being considered. The GDF also provides short-term forecasts (three months) to manufacturers, which could be of limited usefulness for the suppliers of new tools. If the GDF is to expand its role to

Box 4.8 Key questions on distributing the new technologies

1. Is there a comprehensive distribution strategy and a detailed distribution plan that addresses special storage and handling requirements including cold chain?
2. Does the distribution plan address all the supplies and products that are needed to use the new products appropriately, for example to make up a drug regimen, perform a test or administer a vaccine?
3. Does the plan ensure that products will reach service delivery points in time to be consumed before the expiry date?
4. Does the plan allow for effective coordination/collaboration between the public and private sectors?
5. Is there existing capacity (public and private) to implement the distribution plan?
6. Are the storage capacity and conditions at the store adequate and appropriate? If not, what plans exist to improve them?
7. What is the distribution and transportation capacity and is it adequate?

prepare and communicate a guidance document or manual on its criteria and procedures for adding new products to its supply catalogue.

The GDF will also play an important role in supporting prequalification of new medicines via the WHO Procurement, Quality and Sourcing Project: Access to Anti-Tuberculosis Drugs of Acceptable Quality (TB prequalification project), which was initiated in 2002. This project aims to facilitate access to anti-TB medicines of acceptable quality through the assessment of products and their manufacturers for compliance with WHO-recommended standards.

The GDF is currently a principal supporter of the TB prequalification project, providing:

- a major source of its funding for manufacturer site inspections, product dossier evaluations, publications of Invitations of Expressions of Interest in Prequalification and supplier training workshops on prequalification requirements/procedures;
- technical guidance on the list of anti-TB medicines eligible for prequalification;

- identification of political support for the TB prequalification project.

In order to expedite prequalification of new anti-TB medicines, the GDF, in conjunction with WHO/PSM and other interested partners, will need to pursue initiatives such as:

- determining the feasibility of mobilizing retired inspectors from ICH/PICS¹ countries to form a pool of consultants to assist manufacturers to respond adequately to inspection remarks and submit answers to queries on their product dossiers;
- training workshops for manufacturers participating in the prequalification project.

Distribution. The steps in the distribution of new technologies will differ from country to country, depending on how the public and private distribution systems are organized, and whether distribution is centralized or decentralized to states or districts. In addition, new medicines, diagnostics and vaccines may all move through different distribution channels. Some new

¹ International Conference on Harmonization/Pharmaceutical Inspection Cooperation Scheme.

Box 4.9 Key questions on managing the inventory of new technologies

1. What inventory control system is in place and is it reliable? Is a physical check of medicines carried out at least annually?
2. What is the average stock turnover time, and is there a policy and practice of issuing stock according to first expiry/first out at all levels?
3. Are there functional management information systems to track product flow?
4. How well is the shelf-life of products managed throughout the existing supply chain? What systems are in place for dealing with expired products?
5. Are adequate security measures in place to prevent theft of stored products?

medicines and diagnostic supplies may have a relatively short shelf-life of two years or less, and it will be imperative that distribution systems function effectively to avoid product loss due to the expiry of stock. In addition, new technologies requiring cold-chain management during distribution and storage, such as vaccines, are likely to present particular challenges for the distribution system. Some key questions to address are included in Box 4.8.

The distribution strategy should be developed as part of the phase-in or roll-out plan and integrated into the overall distribution plan; it should also take into account the private sector as appropriate. It is important to ensure that all the products needed to use the new tool are addressed in the distribution plan. Even when the new products are in stock at the central medical store, distribution to the peripheral level can take 2–4 weeks or longer. In one country, it took 2–3 months to deliver medicines from the central level to the regional and then district level to support the phased introduction of first-line FDCs, as stores' staff wanted to consolidate the delivery of the new products with other consignments at each level. It is therefore important to submit the request for distribution well in advance to coordinate the arrival of the drugs with training of

health care workers and/or community partners.

Inventory management. It is important that inventory management measures are assessed and upgraded, or established if they do not already exist, at all health facilities to ensure that stocks of the new tools are managed appropriately to prevent stock-outs and minimize wastage due to expiry.¹ Upgrading the storage facilities, particularly in the peripheral-level laboratories of many countries where new diagnostic kits and supplies are to be introduced, may be necessary and should be factored into the implementation budget and plan. For products that require cold storage, for example vaccines, additional refrigerated space may need to be identified during the transition phase and also potentially to meet increased demand for the product. WHO's vaccine volume calculator enables countries to plan for their space requirements before introducing new vaccines (22). Some key questions to consider are included in Box 4.9.

The introduction of new technologies into health facilities or departments that have been long under-resourced, such as the peripheral-level laboratories, may provide an opportunity to integrate DOTS expansion with overall health system strengthening. Joint plans may need to be

¹ Useful resources on inventory management include: *Managing pharmaceuticals and commodities for tuberculosis: a guide for national tuberculosis programs (17)* and *Guidelines for the storage of essential medicines and other health commodities (21)*.

developed with other health system departments and programmes that focus on improving inventory management systems, infrastructure and staff capacity and use funding synergistically to achieve benefits for all programmes.

Store management tools such as stock cards may need to be introduced in bulk storage areas and mechanisms established to ensure that records are maintained and that physical checks are performed regularly. In addition, the store may need to be adequately secured to prevent theft. It will be important to ensure that products do not expire before they are used; mechanisms for recalling short-expiry products in districts or facilities with low utilization and transferring them to those areas with high utilization may need to be established.

4.2.3 Ensuring product and service quality and safety

Ensuring the quality and service of products and their safe use is a shared responsibility that will require close collaboration among manufacturers, suppliers, health regulatory authorities, procurement agencies, supply chain operators, providers and people infected with TB. Key questions for product QA and pharmacovigilance are included in Box 4.10.

Monitoring product and service quality. Integrating surveillance of product quality at all levels of the health system can ensure that the new technologies available in the market are of the appropriate quality. For diagnostics, ensuring quality also includes the development of systems for internal quality control and external quality assessment. A comprehensive system includes ensuring quality during product registration, procurement, distribution and storage through the public and private sectors; it also includes a mechanism for removing from the supply chain any products found to be of poor quality and that pose

a danger to the health of those who use them (23). While many countries have functional systems for assessing the quality of products at the time of registration, systems for monitoring the quality of products in the marketplace are generally weak. Building capacity in existing structures that collect similar information for other essential medicines or diagnostic tests could be considered to make the best use of available human resources.

Ideally, new diagnostic tests should be integrated into laboratories with a comprehensive internal and external quality management system to ensure the reliability of laboratory performance. In reality, most laboratories will require considerable investments in resources to improve infrastructure, refurbish equipment, establish appropriate operating procedures, and improve management capacity to ensure not only the high-quality performance of diagnostic testing but also the safe use and disposal of diagnostic reagents, consumables and other materials.

Clinical event monitoring (pharmacovigilance). Mechanisms for surveillance of adverse events associated with the use of new medicines and vaccines should be developed within the systems for monitoring adverse events for other medicines and vaccines, where they exist. Forms for recording adverse events will need to be provided to the service delivery points. Sensitization and training of health workers to capacitate them to recognize adverse events and encourage them to report the events will need to be a key component of the policy implementation. Appropriate communication channels will need to be established to effectively report and receive feedback between those reporting and those collecting and analysing reports centrally. The introduction of the new tools will be an excellent opportunity to strengthen existing but weak systems or to develop systems where they are lacking (24). Effective communication

Box 4.10 Key questions on assuring quality and pharmacovigilance of new technologies

1. Is there a system or procedure in place for verifying the quality of products registered and/or procured?
2. Is there a system or procedure in place for monitoring the quality of products already in the market? Are samples regularly tested by a qualified laboratory?
3. Is there a system to assess and monitor the quality of laboratory service provision?
4. Is there a system or procedure in place for monitoring drug resistance to anti-TB medicines?
5. Is there a system or procedure in place for reporting adverse clinical events associated with the use of the new products?
6. Is there a programme to promote safe injection practices?

mechanisms should also be established with the WHO Collaborating Centre for International Drug Monitoring so that information on previously unsuspected adverse reactions to medicines and vaccines can be shared.

4.3 Monitoring and evaluation

Monitoring and evaluation is an essential part of the policy implementation process and should be ongoing throughout planning and implementation. Planning for monitoring and evaluation needs to be done early and integrated throughout the implementation process so that monitoring data can be used to guide any changes in implementation strategies by the NTP, governments and external stakeholders. Monitoring and evaluation is particularly important for new tools because health care workers have little experience with their use.

Some key questions related to the development of monitoring and evaluation systems are listed in Box 4.11.

It may be necessary to develop specific indicators to monitor the uptake of the new tools. If these cannot be collected through the existing health

information system, a new system may be needed.

Data for monitoring and evaluation can be obtained from existing surveys, such as demographic and health surveys (DHS) and health management information system (HMIS) data, or through special studies. The decision on which information source(s) to use depends on each country context and the type of information systems available. Where possible, data for monitoring and evaluation of TB control should be collected through routine systems. Types of information systems include:

- *DHS*. DHS are nationally representative household surveys that provide data for a wide range of monitoring and impact evaluation indicators. Typically, these surveys are conducted every five years in most endemic countries.
- *HMIS*. Most countries have an existing HMIS that provides basic information on mortality and morbidity rates.
- *Logistics management information systems*. Logistics management information systems may provide details on the management of supplies of medicines, vaccines and diagnostic kits and supplies.

Box 4.11 Key questions on monitoring and evaluation of new technologies

1. Is the current monitoring and evaluation system capable of tracking the implementation process? What elements/indicators/procedures are lacking?
2. Is there an monitoring and evaluation plan to track implementation progress and performance relative to defined/established targets?
3. What information sources exist for monitoring, and what needs to be developed?
4. How will performance of the roll-out be evaluated?
 - internal versus external evaluation?
 - process versus outcomes evaluation?

- *Surveillance system.* Some countries may use sentinel sites to collect routine data on TB control indicators. Data on medicines and vaccine availability and drug resistance may be incorporated into these systems.
- *Vaccine surveillance system.* Some countries may have a system for reporting suspected AEFI.
- *Adverse drug reaction/pharmacovigilance reporting systems.* These systems are used to collect and provide data about adverse drug reactions experienced by patients under actual use conditions. This information may then be used to help drug regulatory authorities and others in the health community to modify the regulations pertaining to the medicine or vaccine.
- *Special studies.* In the absence of good data to monitor the uptake of the policy, it may be necessary to carry out special research to obtain particular data. Such data are collected every five years in most endemic countries.

Work is under way to develop a standard framework for the development of a range of guidelines and tools for monitoring and evaluation, including a summary of agreed upon illustrative core indicators for TB control, and references to more detailed indicator manuals on specific programme areas (25). Indicators can be developed and/or adapted to individual national or programme needs, and the introduction of new technologies will require that the indicators be periodically revised and updated.

5. The way forward

The timely and appropriate adoption, introduction and implementation of new TB control technologies into TB control programmes will require strong and coordinated support from the Stop TB Partnership. Its working groups can facilitate collaboration to:

- keep stakeholders informed about products in the development pipeline;
- consolidate frameworks and processes for product regulation and registration, particularly for diagnostics;
- strengthen pharmaceutical management, and laboratory infrastructure and services;
- increase capacity to conduct operational research to guide adoption, introduction and implementation;
- address human resource constraints;
- mobilize adequate financial resources.

Members of the Stop TB Partnership should work together to develop and/or widely disseminate practical guidance documents and training materials on:

- engaging stakeholders;
- international standards and related guidance documents for assessing and regulating diagnostics;
- submission of new technology applications to WHO;
- comparative assessment of options;
- product-specific road maps for adoption and introduction of highly promising new tools;
- product-specific materials for ACSM;
- monitoring and evaluation systems, including indicators, for adoption, introduction and implementation of new tools.

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Annex 1: What is in the TB pipeline (November 2006)?

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Summary table of current anti-TB products in the pipeline, by stage of development, 2006–2015
SELECTED NEW ANTI-TB MEDICINES

Stage of development	Product	Sponsor	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	
CLINICAL TESTING	Gatifloxacin	European Commission OFLUTOB Consortium; Lupin Ltd; NIAID TBRU; TDR; TRC	Phase II				Phase III ^a						
	Moxifloxacin	Bayer HealthCare AG; CDC TB Trials Consortium; EDCTP; FDA Orphan Products Division; Johns Hopkins University; MRC; TB Alliance; UCL	Phase II/III				Phase III						
	Diamine (SQ-109)	Sequella Inc.; NIH	Phase I				Phase III						
	Nitroimidazole derivative OPC-67683	Otsuka Pharmaceutical Company	Phase II					Phase III					
	Pyrrrole LL3858 (Sudoterb)	Lupin Ltd	Phase I					Phase III					
	Diarylquinoline (TMC-207)	Tibotec Pharmaceuticals Limited	Phase I						Phase III				
	Nitroimidazole (PA-824)	TB Alliance; Novartis, NIH National Institute of Allergy and Infectious Diseases	Phase I						Phase III				
	Dipiperidine (SQ-609)	Sequella Inc.	Preclinical									Phase III	
	Synthase inhibitor FAS200313	FASgen Inc.	Preclinical									Phase III	
	Translocase I inhibitors	Sequella Inc.; Sankyo Ltd	Preclinical									Phase III	
DISCOVERY	Nitroimidazole Analog Program	TB Alliance; University of Auckland, New Zealand; University of Illinois, Chicago	Discovery									Phase III	
	Quinolones	TB Alliance and KRICI; Yonsei University, Seoul	Discovery									Phase III	
	AstraZeneca Portfolio	AstraZeneca	Discovery									Phase III	

^a "Phase III" means anticipated completion of Phase III clinical trials.

CDC, United States Centers for Disease Control and Prevention; EDCTP, European and Developing Countries Clinical Trials Partnership; FDA, United States Food and Drug Administration; KRICI, Korea Research Institute of Chemical Technology; MRC, United Kingdom Medical Research Council; NIAID TBRU, National Institute of Allergy and Infectious Diseases TB Research Unit; NIH, United States National Institutes of Health; TB Alliance, Global Alliance for TB Drug Development; TDR, UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases; TRC, Tuberculosis Research Centre; UCL, University College London.

Note: new compounds may be introduced in combination rather than as single drugs.

SELECTED NEW TB DIAGNOSTICS

Status	Product	Sponsor	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
REFERENCE LABORATORY	Liquid culture system for case detection and DST	FIND and BD	CU		AA							
	Speciation test	FIND and Tauns Co. Ltd	DP		AA							
	Phage-based DST	FIND and Biotec Laboratories		DP	AA							
	Manual NAAT	FIND and HAIN Lifescience GmbH	EP				AA					
	Automated NAAT	FIND and Cepheid					AA					
PERIPHERAL LABORATORY	Urinary NAA	FIND; UCL; Spaxen	EP						AA			
	Same day sputum smear microscopy	TDR	EP		AA							
	Low-cost fluorescence microscopy	TDR	EP	DP	AA							
	Bleach digestion of sputum	TDR			DP	AA						
	LED fluorescence microscopy	FIND	DP			AA						
HEALTH POST	First-generation isothermal NAA	FIND and EIKEN Chemical Co., Ltd	DP					AA				
	Urinary antigen detection	FIND and partners	DP				AA					
	Antibody detection tests	FIND and partners	DP						AA			

AA, earlier date for availability for adoption in the public sector; BD, Becton, Dickinson and Company; CU, already in use in countries; DP, demonstration phase; DST, drug susceptibility testing; EP, evaluation phase; FIND, Foundation for Innovative New Diagnostics; NAA, nucleic acid amplification; NAAT, nucleic acid amplification testing; TDR, UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases; UCL, University College London.

SELECTED NEW ANTI-TB VACCINES

Type of vaccine	Product	Sponsor	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
VIRAL VECTORED VACCINES	MVA85A	University of Oxford with funding from Wellcome Trust and European Commission	Phase I									Phase III ^a
	AERAS-402	Crucell Holland B.V. and Aeras	Phase I									Phase III
MODIFIED-RECOMBINANT BCG	AERAS-X03	Aeras	Preclinical development	Phase I								Phase III
	RBCGHLy	VPM under license from the Max Planck Society	Preclinical development	Phase I								Phase III
PROTEIN SUBUNIT VACCINES	M72	GlaxoSmithKline and Aeras	Phase I									Phase III
	HyVac 4	Statens Serum Institute, Intercell and Aeras	Preclinical development	Phase I								Phase III
	Hybrid-1	Statens Serum Institute and European TB Vaccine Project	Phase I									Phase III
BACTERIA-VECTORED VACCINES	AERAS-X05	Aeras	Preclinical development	Phase I								Phase III

^a Phase III means anticipated completion of Phase III clinical trials.

Aeras, Aeras Global TB Vaccine Foundation; VPM, Vakzine ProjektManagement GmbH

Chapter 1 NEW ANTI-TB MEDICINES

Current short-course (six-month) combination therapy for tuberculosis (TB) is effective when administered reliably. However, TB control is hindered by the lengthy and complex treatment required by current drugs, and is further complicated by the disease's deadly interaction with HIV/AIDS and the rise of multidrug-resistant TB (MDR-TB). These factors underscore the urgent public health need for new anti-TB therapies.

The Working Group on New TB Drugs established as its goal the development of new, affordable anti-TB drugs that would: (i) simplify or reduce the necessary duration of treatment to two months or less; (ii) effectively treat MDR-TB; and (iii) provide treatment for patients with latent TB infection. It must be recognized that drug development in general is a slow and careful process (8–12 years) that emphasizes safety and efficacy in a phased approach to the clinical development pipeline. Phase I is the first examination of a new chemical entity in humans, and is conducted under careful supervision on a small number of healthy volunteers with escalating doses of a new drug. Phase II is for continued safety plus efficacy testing in infected patients (20–50) and establishes an appropriate dose range for more expanded evaluations. For TB, Phase II may include an early bactericidal assay to detect quantitative effects in reducing the number of sputum bacilli. Phase III, a large study of infected patients (>300), is often conducted at multiple sites, determines efficacy with clinical outcomes and may be the pivotal study for official registration of a new anti-TB drug. It must be noted that throughout this course of evaluations, the attrition rate for drugs of all types is very high, in the order of 1/100 successfully completing safety testing.

For the first time in 40 years, there is a coordinated portfolio of promising new compounds in the pipeline, some of which have the potential to become the cornerstone drugs for the control and possible eventual elimination of TB in the future. These new drugs may be introduced as new combinations, thus revolutionizing anti-TB therapy.

A. CLINICAL TESTING

1. Gatifloxacin
Sponsors
European Commission (EC) OFLUTOB Consortium; Lupin Ltd; National Institute of Allergy and Infectious Diseases TB Research Unit (NIAID TBRU); Tuberculosis Research Centre (TRC); UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR)
Programme description
Fluoroquinolones have been shown to have bactericidal activity in vitro against <i>Mycobacterium tuberculosis</i> , which has been confirmed in animal models (1–4). They are rapidly absorbed and have high oral bioavailability. They are highly concentrated in respiratory tract tissues, pulmonary secretions and inside lung macrophages.
In humans, the fluoroquinolone class of drugs is well tolerated over extended periods; thus they have been proposed in the treatment of TB (5). Among the various fluoroquinolones, gatifloxacin is particularly active against Gram-positive organisms and achieves plasma concentrations higher than the minimal inhibitory concentration obtained with other fluoroquinolones.
The Phase II trial results of a gatifloxacin-containing regimen are demonstrating good potential. This trial was conducted by the South African Medical Research Council in Durban, South Africa, in patients with newly diagnosed pulmonary TB with and without HIV coinfection. It was designed to measure the anti-TB activity of the treatment in the first two months of therapy when compared with standard WHO-recommended treatment and two other similar regimens which contained either ofloxacin or moxifloxacin. Treatment with either the gatifloxacin- or moxifloxacin-containing regimen was shown to be significantly more active than either the standard regimen or the ofloxacin-containing regimen after two months of treatment.
A multi-centre Phase III clinical trial is planned to definitively assess whether the four-month gatifloxacin-containing regimen is equivalent to the current standard six-month short-course regimen. Study sites are in Benin, Guinea, Kenya, Senegal and South Africa.
Anticipated completion of Phase III
2010

2. Moxifloxacin
Sponsors
Bayer HealthCare AG; United States Centers for Disease Control and Prevention (CDC) TB Trials Consortium; European and Developing Countries Clinical Trials Partnership (EDCTP); United States Food and Drug Administration (FDA) Orphan Products Division; Johns Hopkins University; United Kingdom Medical Research Council (MRC); TB Alliance for TB Drug Development (TB Alliance); University College London
Programme description
<p>Moxifloxacin is a fluoroquinolone – a subset of the quinolone class of antibiotics. Developed by Bayer HealthCare AG, moxifloxacin has demonstrated efficacy for the treatment of several acute respiratory infections. It also has an excellent safety record, having been used in more than 42 million patient treatments in 104 countries.</p> <p>Moxifloxacin’s mechanism of action differs from that of the drugs currently used to treat TB. It acts by inhibiting an enzyme called DNA gyrase, which is essential for bacterial survival. At the same time, moxifloxacin has little interaction with the cytochrome P450 enzyme system. Cytochrome P450 is heavily involved in the metabolism of some of the antiretroviral drugs (ARVs) used to treat HIV/AIDS. Rifampicin, a cornerstone of the current TB regimen, induces certain cytochrome P450 enzymes, causing some ARVs to be metabolized too quickly. This drug–drug interaction can complicate the treatment of people coinfecting with TB/HIV. Moxifloxacin avoids this interaction, making it easier to use when patients are also receiving drugs which are affected by the cytochrome enzyme systems.</p> <p>Several animal studies have shown that moxifloxacin may be effective against <i>M. tuberculosis</i>. Results indicate that substituting moxifloxacin for one of the current standard anti-TB drugs may eliminate TB infection faster than today’s standard treatment protocol. In preclinical studies commissioned by the TB Alliance in 2002–2003, investigators at Johns Hopkins University found that substituting moxifloxacin for isoniazid in a mouse model system decreased the amount of time needed to eradicate TB infection by two months.</p> <p>On 25 August 2005, the TB Alliance and Bayer HealthCare AG signed an historic agreement: to conduct a global clinical development programme seeking to register moxifloxacin for a TB indication. Should these trials prove successful, the agreement includes a joint commitment to ensuring the drug’s affordability for TB patients in the developing world. Bayer is donating moxifloxacin for each trial site and will sponsor regulatory filings. With Bayer, the TB Alliance is managing the overall clinical trial programme, ensuring the coordination of information and results towards the goal of registration. Financial support for the programme comes from the TB Alliance, and from CDC, the FDA Orphan Products Development Center and the EDCTP.</p> <p>Moxifloxacin is currently in clinical trials for the treatment of pulmonary TB. The clinical development programme includes four late-stage clinical trials that together will enrol more than 2000 TB patients. Sites are in Africa, Europe and the Americas, including 10 American states. Two drug regimens are being evaluated, each substituting moxifloxacin for one of the drugs in the standard four-drug treatment regimen. The first substitutes moxifloxacin for ethambutol, and the second substitutes moxifloxacin for isoniazid.</p> <p>The goal of this programme is to register moxifloxacin for a TB indication. The initial focus is the treatment of drug-sensitive, adult, pulmonary TB. Successful trials will allow moxifloxacin to contribute to an optimized first-line anti-TB treatment regimen. Supplementary studies will be carried out as appropriate, based on the results of these initial investigations.</p>
Anticipated completion of Phase III
2010

3. Diamine (SQ-109)
Sponsors
Sequella Inc., United States National Institutes of Health (NIH)

Programme description
Developed in partnership with the NIH, SQ-109 is a new diamine anti-TB drug. It could replace one or more drugs of the existing first-line TB drugs in the intensive-phase regimen.
With a mechanism of action distinct from other antibiotics used in TB therapy (including isoniazid, ethambutol, and ethionamide), SQ-109 inhibits cell wall synthesis in a select group of microorganisms with excellent in vitro activity against both drug-susceptible and drug-resistant TB bacteria, including extensively drug-resistant TB (XDR-TB). SQ-109 also enhances, both in vitro and in vivo, the activity of the anti-TB drugs isoniazid and rifampicin, thereby shortening the time required to cure mice of experimental TB by 25%.
The Phase I dose-escalation study is enrolling 46 healthy normal volunteers. The patients will be divided into five ascending dose groups of eight, plus an additional group of six in an effect of food group, to evaluate the safety and pharmacokinetics of SQ-109. Increased dose levels will be administered approximately 10 days apart to allow for clinical safety measurements. The trial will run for approximately 3–4 months.
SQ-109 has completed all IND-directed preclinical toxicology, pharmacology and safety studies in two animal species. The IND was filed with the FDA in August 2006.
Anticipated completion of Phase III
2010

4. Nitro-dihydro-imidazooxazole derivative OPC-67683
Sponsor
Otsuka Pharmaceutical Company
Programme description
OPC-67683 has potent in vitro activity against <i>M. tuberculosis</i> , may shorter duration of therapy in active TB and MDR-TB and is more effective than current drugs for anti-TB therapy.
A mycolic acid biosynthesis inhibitor found to be free of mutagenicity and to possess highly potent activity against TB, including MDR-TB. In comparison with rifampicin, isoniazid, ethambutol, streptomycin, pyrazinamide and PA-824, OPC showed an exceptionally low minimum inhibitory concentration (MIC) range (0.006 to 0.024 ug/mL) in culture experiments and highly effective therapeutic activity at low doses in animal studies. In a mouse model of TB, OPC did not produce antagonistic effects in combination with other anti-TB drugs, and the combination of OPC with rifampicin and pyrazinamide exhibited the strongest effect, showing at least a two-month quicker eradication of viable TB bacilli in the lung than seen with the existing standard TB regimen. Other in vitro experiments have shown that OPC was not affected by, nor did it affect, the activity of liver microsome enzymes, suggesting that OPC may possibly be used in combination with drugs (including ARVs) that induce or are metabolized by cytochrome P450 enzymes. OPC was also found to be highly active in mice with SCID, which mimics the immune deficiency seen in AIDS patients. OPC is currently in Phase II clinical development in TB patients, but no results have been published to date.
Anticipated completion of Phase III
2011

5. Pyrrole LL3858 (sudoterb)
Sponsors
Lupin Ltd
Programme description
Sudoterb has demonstrated in vitro and in vivo anti-mycobactericidal activity against both sensitive and resistant strains of <i>M. tuberculosis</i> . Complete killing of <i>M. tuberculosis</i> has been observed to occur as early as 19 days when combined with isoniazid, rifampicin and pyrazinamide. The molecule is also expected to have a post antibiotic effect. Preclinical toxicology studies have established the safety of the molecule.

Phase I clinical development of the molecule is being undertaken. Randomized, double-blind, placebo-controlled single, dose-escalation studies conducted in healthy adult male volunteers have so far proven to be safe, well tolerated and well absorbed following oral administration. Randomized, double-blind, placebo-controlled, multiple, dose-escalation studies are in progress.

Phase II clinical development for the novel drug, administered alone or in combination with isoniazid, rifampicin and pyrazinamide, may be conducted in patients suffering from TB to establish efficacy and safety.

Anticipated completion of Phase III

2011

6. Diarylquinoline (TMC-207)

Sponsors

Tibotec Pharmaceuticals Limited

Programme description

The diarylquinolines specifically inhibit adenosine triphosphate (ATP) synthesis in *M. tuberculosis*, thus blocking its energy producing mechanism. The drug's unique mechanism of action explains the lack of cross-resistance observed in preclinical studies to any of the current anti-TB drugs, including moxifloxacin. In cell culture and mice studies, TMC has extremely potent anti-TB activity, more active than the combination of rifampicin, isoniazid and pyrazinamide, even when used as a monotherapy. When substituted for either rifampicin or isoniazid in combination therapy, TMC-207 halved treatment time, leading to complete TB sterilization within two months.

Preliminary studies in healthy human volunteers suggest that the drug may be safe and has a half-life of more than 24 hours, which may permit intermittent dosing. The drug is currently in early clinical activity studies in patients with TB. A Phase II trial focusing on MDR-TB will commence in mid-2007. Based on the available non-clinical safety assessment, the initial treatment duration will be two months. A solid dosage form is available for this trial. No recent published peer-reviewed data are available on clinical trials of TMC-207 (6–11). Recent advances and developments on TMC were presented at the 37th IUATLD World Conference.

Anticipated completion of Phase III

2012

7. Nitroimidazole (PA-824)

Sponsors

TB Alliance, Novartis and the NIH National Institute of Allergy and Infectious Diseases

Nitroimidazole analogs: TB Alliance, University of Auckland, University of Illinois, Chicago

Programme description

PA-824 is a nitroimidazole, a class of novel antibacterial agents. As a potential TB therapy, it has many attractive characteristics – most notably its novel mechanism of action, its activity in vitro against all tested drug-resistant clinical isolates, and its activity as both a potent bactericidal and a sterilizing agent in mice. In addition, the compound shows no evidence of mutagenicity in a standard battery of genotoxicity studies, no significant cytochrome P450 interactions, and no significant activity against a broad range of Gram-positive and Gram-negative bacteria.

In 2002, the TB Alliance and Chiron Corporation, a biotechnology company based in California, signed a landmark agreement to develop PA-824 and, potentially, other nitroimidazole derivatives for TB. PA-824 became the first compound in the TB Alliance portfolio. The TB Alliance received worldwide exclusive rights to PA-824 and its analogs for the treatment of TB, and Chiron pledged to make the technology royalty-free in endemic countries. Chiron retained the right to develop and commercialize the compounds for non-TB indications.

The TB Alliance immediately outlined plans to advance the development of this class of compounds. With support from the NIH National Institute of Allergy and Infectious Diseases, the TB Alliance engaged the Research Triangle Institute to assist in the management of the development project. In its first two years of development, PA-824 successfully passed all major preclinical milestones. In June 2005, the compound entered Phase I clinical trials to evaluate its safety, tolerability and pharmacokinetics in healthy volunteers.

As PA-824 moved through its preclinical phases, 15 contract research organizations conducted a full range of toxicology, pharmacokinetic and production assessments, all the while managed by TB Alliance staff and the Research Triangle Institute. Preclinical development was designed to assess both the efficacy and the safety of PA-824. While early data indicated PA-824's efficacy against both drug-sensitive TB and MDR-TB, the preclinical phase of development assessed PA-824's efficacy compared to, and in combination with, current anti-TB drugs. This phase was designed to assess the compound's non-clinical pharmacokinetic and safety profile to determine its suitability for entry into clinical trials.

PA-824 completed its preclinical milestones in approximately two years, and is now in Phase I clinical development. The Phase I programme is evaluating the safety, tolerability, pharmacokinetics and ADME (absorption, distribution, metabolism and excretion) properties of single and multiple doses of PA-824 in healthy adult volunteers.

To date, three Phase I studies have been conducted. These include: a randomized, double-blind, single ascending dose study in healthy male volunteers; a randomized, double-blind, multiple ascending dose study in healthy male and female volunteers; and a single dose study with radio-labelled PA-824 to assess its absorption, distribution, metabolism and excretion in healthy volunteers of both genders.

Once Phase I studies have been successfully completed, PA-824 will be subjected to a Phase II early bactericidal activity study, conducted in TB patients. This will provide proof-of-concept of the efficacy of PA-824 in adult patients with sputum smear-positive, pulmonary TB. The TB Alliance has also initiated an investigation of PA-824 nitroimidazole analogs, currently in the discovery phase of development.

Nitroimidazole Analog Program

Any drug candidate is likely to encounter some difficulties during clinical development. Therefore, in addition to its work with PA-824, the TB Alliance has instituted an analog program on several tracks, seeking to maximize the potential of the novel nitroimidazole class. Working with researchers at the University of Auckland in New Zealand and the University of Illinois at Chicago, the TB Alliance aims to discover new nitroimidazopyrans that may have improved profiles over PA-824. This program has two conceptual purposes:

- (i) With the assumption that PA-824 will ultimately prove to be clinically useful, second-generation compounds may be even better.
- (ii) If PA-824 fails to develop into a commercial drug, there may be superior nitroimidazole compounds capable of overcoming any difficulties that precluded regulatory approval of PA-824.

The chemistry group, led by Professor Bill Denny at the University of Auckland, has synthesized many new pharmacophores, several of which have demonstrated potent anti-TB activity. Further optimization of these pharmacophores may lead to new nitroimidazoles that have in vitro activity better than PA-824. In addition, some of these compounds have been scaled up for in vivo proof-of-principle studies in mice. A new, commercially viable synthesis has also been developed.

The project team will focus on the development of structure–activity relationships to address both mutagenicity and QT prolongation issues. Compounds that meet the in vitro potency criteria, and are free of mutagenicity and hERG inhibitory activity, will be advanced to in vivo efficacy and pharmacokinetic studies.

Anticipated completion of Phase III

- For PA-824: 2012
- For Nitroimidazole Analog Program: 2015

B. PRECLINICAL

1. Dipiperidine (SQ-609)
Sponsors
Sequella Inc.
Programme description
This new class of antibiotic compounds, dipiperidines, has promising in vitro and in vivo anti-TB activity. SQ-609 was identified as a lead candidate in this series. Product profile attributes: Potent in vitro activity against <i>M. tuberculosis</i> ; kills <i>M. tuberculosis</i> by interfering with cell wall biosynthesis; low in vitro toxicity in cultured mammalian cells; oral bioavailability; antimicrobial activity in vivo in two different mouse models of TB; significantly prolongs therapeutic effect after the withdrawal of drug therapy in mice; favourable in vitro safety pharmacology profile.
Anticipated completion of Phase III
2014

2. Synthase inhibitor FAS200313
Sponsors
FASgen Inc.
Rationale and product profile
FASgen has designed and synthesized a series of novel compounds that not only inhibit the biosynthesis of the tubercle bacillus' waxy outer coating but also interfere with a vital step in the organism's energy-generating metabolic pathways.
Anticipated completion of Phase III
2014

3. Translocase I inhibitors
Sponsors
Sequella Inc., Sankyo Ltd
Programme description
Sequella licensed the Translocase I inhibitors from Sankyo, Ltd (November 2004). Sankyo identified the compound class and performed extensive research and preliminary preclinical development on three selected inhibitors. Sequella has exclusive worldwide rights to the series of Translocase I inhibitors for the treatment of TB and all other indications.
Anticipated completion of Phase III
2014

C. DISCOVERY STAGE

1. Quinolones
Sponsors
The TB Alliance in collaboration with the Korea Research Institute of Chemical Technology (KRICT) and Yonsei University, Seoul.
Programme description
Quinolones are one of the few classes of antimicrobial agents that are totally synthetic in origin. The first quinolone, nalidixic acid, was introduced in the 1960s as a narrow-spectrum agent used primarily for the treatment of urinary tract infections.

Quinolones possess many desirable attributes as a first-line therapeutic agent against TB. These include potent bactericidal activity against both replicating and non-replicating *M. tuberculosis*, favourable long-term safety indicators, oral bioavailability and an ability to penetrate macrophages. Moxifloxacin, a proven and effective antibiotic developed by Bayer HealthCare AG, is a third-generation quinolone compound that has demonstrated effective sterilizing activities against *M. tuberculosis*. The TB Alliance, in collaboration with Bayer, is currently conducting moxifloxacin clinical trials, evaluating the drug as a potential agent to treat TB. However, the quinolone class has not been extensively optimized for a TB indication.

In 2003, the TB Alliance initiated a lead identification and optimization project with the goal of identifying a new generation of quinolones with enhanced efficacy against TB. Based on data from animal models and the preliminary clinical evaluation of quinolones marketed for other antimicrobial indications, this class of compounds has the potential both to shorten the time required to treat TB and to increase the effectiveness of widely spaced, intermittent therapy.

The objective of the quinolone project is to develop a new generation of DNA gyrase inhibitors that will be effective in shortening anti-TB therapy, while maintaining an excellent safety and tolerability profile. The new agents should also be suitable for the treatment of MDR-TB and TB/HIV coinfections without prohibitive drug-drug interactions with ARVs. To achieve these goals, the TB Alliance is collaborating with KRICT and Yonsei University, where scientists are synthesizing and testing novel quinolones, and have discovered several promising compounds that are being evaluated for their potential to be further developed as drug candidates.

This collaboration seeks to achieve the following profile:

- potent activity against both replicating and non-replicating *M. tuberculosis*;
- efficacy in both acute and chronic animal models of TB;
- pharmacokinetics that would support once-daily dosing;
- acceptable safety;
- low cost of goods.

Researchers at KRICT have synthesized more than 600 quinolone analogs, which have then been tested for activity against *M. tuberculosis* in the laboratories of Professor Sang-Nae Cho at the Yonsei University Department of Microbiology. As a result of this effort, several promising leads have been identified, including compounds of the subclass of quinolones known as quinolizinones. These lead compounds are highly active against mycobacteria and have desirable solubility and pharmacokinetic properties. Such traits are the result of chemical modifications, focused on a key position in the quinolone molecule known for its important effects on antimicrobial potency, pharmacokinetics and safety profiles.

Compounds that have acceptable potency in the in vitro screens will be scaled up and further evaluated in second- and third-tier biological assays to determine whether they meet the criteria for development as candidates for clinical evaluation.

Anticipated completion of Phase III

2015

2. AstraZeneca Portfolio

Sponsors

AstraZeneca

Programme description

This is a preclinical portfolio of projects with programmes in different phases, including lead identification and optimization.

AstraZeneca's research is focused on finding new therapies for TB that will either act in drug resistant disease and/or reduce the complexity or the duration of treatment. Thus the programme has three specific goals:

- shortening the duration of therapy to improve patient compliance;
- eradicating disease, even latent disease, and therefore reducing the chances of relapse
- developing new agents which act on drug resistant strains and have no adverse drug–drug interactions.

The portfolio of projects covers lead identification and lead optimization. Preclinical evaluation of compounds is a continuing activity. The development phase for successful compounds is targeted by 2010.

Anticipated completion of Phase III

2015

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Chapter 2 NEW TB DIAGNOSTICS

Health services have been divided into three levels based on consideration of the intended level of the health system where the new tools are to be used: reference laboratory, peripheral laboratory and health post.

A. **Reference laboratory** is defined as a regional, tertiary or national level laboratory with mycobacterial culture capability.

B. **Peripheral laboratory** is defined as a laboratory at health centre or higher level where sputum smear microscopy is conducted, and where auxiliary equipment such as biosafety cabinets, centrifuges and incubators is unlikely to be present.

C. **Health post** is defined as a primary health care facility with no on-site access to microscopy or other laboratory testing.

The selected technologies described below as examples are grouped according to their intended level of implementation. These examples were selected as being illustrative of a process which involves submission to STAG-TB for consideration.

In general, the highest impact on case-finding will accrue from implementation at the lowest level of health services.

Some of the diagnostic tools expected to be introduced into control programmes will be incremental improvements on existing technologies, while others will be radically new. The speed and extent of adoption of new technologies will depend on the balance between the benefits they bring and the degree of disruption their implementation causes. For instance, a simplified microscopy method may see greater adoption than a novel alternative that necessitates changes in the way testing or case notification are carried out. On the other hand, a new method that rapidly identifies all smear-positive and many smear-negative cases might, if suitably robust and specific, see widespread use and substantially replace microscopy.

A. REFERENCE LABORATORY

1. Liquid culture system for case detection and drug susceptibility testing (DST)
Type of product
Liquid culture system
Product
Mycobacterium growth indicator tube (MGIT-TB) and MGIT-DST
Developers
Foundation for Innovative New Diagnostics (FIND) and Becton, Dickinson and Company (BD)
Rationale
It is recognized that direct smear microscopy has limited sensitivity, especially in some patient groups such as children and individuals coinfected with HIV. Culture is substantially more sensitive than microscopy. Liquid culture systems are more rapid and more sensitive than solid culture.
Product profile
The MGIT-TB culture system allows for the rapid growth and detection of <i>M. tuberculosis</i> . The average time to detection is 10–14 days as opposed to 3–4 weeks with traditional solid egg or agar-based culture.
MGIT can also be used to diagnose multidrug-resistant TB (MGIT-DST). FIND, together with BD, is evaluating MGIT-DST to determine the feasibility and impact of its wider use in disease-endemic settings.

Stage of development
Both of these products are already in use in wealthier countries and in the private sector of some developing countries. Currently, MGIT-TB culture and MGIT-DST are being evaluated in demonstration projects to assess their effectiveness, efficiency and impact in the field situation in national control programmes of low-income countries with high TB prevalence.
Considerations
Limitations: tests intended for use where culture and biosafety facilities exist or can be built. Additional care is required to minimize contamination of culture.
Earlier date for availability for adoption in public sector
Beginning of 2008

2. Speciation test
Type of products
Test for confirming <i>M. tuberculosis</i> grown in culture
Product
Capilia TB
Developers
FIND and Tauns Co. Ltd
Rationale
Not all AFB grown in culture are <i>M. tuberculosis</i> . Existing tests for confirming identification of <i>M. tuberculosis</i> are time consuming and complex. The Capilia TB test is a simple and fast lateral flow technology that allows the confirmation of <i>M. tuberculosis</i> in cultures in 15 minutes.
Product profile
The Capilia test is a lateral flow (strip test) detecting a TB-specific antigen.
Stage of development
The test is in the demonstration phase to assess effectiveness in real-life disease control programmes.
Considerations
Limitations: tests intended for use where culture facilities exist or can be built.
Earliest date for availability for adoption in the public sector
Late 2008

3. Phage-based DST
Type of product
Phage-based test
Product
FASTPlaque-Response test
Developers
FIND and Biotec Laboratories
Rationale
Conventional detection of multidrug resistance requires isolation of <i>M. tuberculosis</i> in culture prior to DST. This leads to a long turnaround time of weeks to months. The FASTPlaque-Response assay is applied directly to sputum smear-positive samples, with rifampicin-susceptibility results obtained in just two days.
Product profile
The FASTPlaque assay is bacteriophage-based and allows detection of rifampicin resistance directly from smear-positive sputum or indirectly from culture. Rifampicin resistance in most settings serves as a marker for multidrug resistance.

Stage of development
The test is in the demonstration phase in selected countries where its efficiency and effectiveness are to be assessed.
Considerations
Limitations: tests intended for use where culture and biosafety facilities exist or can be built.
Earliest date for availability for adoption in the public sector
End of 2008

4. Manual nucleic acid amplification DST
Type of product
Molecular technique
Product
PCR-based assay
Developers
FIND and HAIN Lifescience GmbH
Rationale
The rapid detection of multidrug resistance could facilitate early initiation of correct treatment or appropriate measures to prevent transmission. The manual-based nucleic acid amplification DST detects rifampicin and isoniazid resistance in one day.
Product profile
PCR-based line-probe assay
Stage of development
The test is entering the evaluation phase.
Considerations
Limitations: tests intended for use where culture, biosafety and polymerase chain reaction (PCR) capabilities exist or can be built. Requirement for specialized equipment (Thermocycler) and training. The sensitivity of the assay for isoniazid resistance is only 60–70%.
Earliest date for availability for adoption in public sector
2008

5. Automated nucleic acid amplification test DST
Type of product
Molecular technique
Product
PCR-based
Developers
FIND and Cepheid
Rationale
Molecular amplification is a proven technology for the detection of <i>M. tuberculosis</i> . Current test methods, however, are too complex for routine widespread implementation in developing countries. Sample processing and DNA extraction adds significantly to this complexity. An assay that automates all of these steps could make nucleic acid amplification testing (NAAT) much simpler to implement. Molecular detection of rifampicin resistance could speed targeted treatment and other measures for controlling MDR-TB.
Product profile
FIND and Cepheid are working to develop an automated method to integrate sputum processing, DNA extraction as well as amplification and detection of TB DNA and rifampicin-resistance encoding mutations.
Stage of development
Under development

Considerations
Limitations: requirement for specialized equipment and limited training; security; electricity.
Earliest date for availability for adoption in the public sector
2010

6. Urinary nucleic acid amplification
Type of product
Molecular technology
Product
PCR-based test for <i>M. tuberculosis</i> DNA in urine
Developers
FIND, University College London, Spaxen
Rationale
Fragments of <i>M. tuberculosis</i> DNA have been shown to be excreted in urine. Urine is less variable and easier to collect than sputum and may be safer to handle. These characteristics may make this method applicable in less complex settings if paired with an appropriately simple amplification method.
Product profile
This is a method, not a product, and will need to be applied to an existing molecular amplification platform.
Stage of development
This method is under development.
Considerations
Limitations: tests intended for use where PCR capabilities exist or can be built. Requirement for specialized equipment (Thermocycler) and training.
Earliest date for availability for adoption in the public sector
2011

B. PERIPHERAL LABORATORY

1. Same-day sputum smear microscopy
Type of product
Optimizing sputum microscopy
Product
Same-day two-smear strategy
Developers
TDR
Rationale
The current sputum smear microscopy strategy requires direct examination of three sputum specimens obtained on 2–3 different days. This strategy delays the diagnosis and leads to patient drop-out during the diagnostic process.
Product profile
The same-day approach requires a patient to produce two separate sputum samples to curtail patient drop-out, thereby increasing case detection.
Stage of development
Under evaluation in operational settings; moving towards demonstration.
Considerations
More cases require links with treatment centre/drugs. Possible cost saving/consumables. Reorganization of the laboratory workflow to maximize benefit.

Earliest date for availability for adoption in the public sector
End of 2008

2. Low-cost fluorescence microscopy
Type of product
Sputum microscopy
Product
Fiber-optic-based fluorescence microscopy system
Developers
TDR
Rationale
Fluorescence microscopy increases the sensitivity of direct smear microscopy. The expense of the conventional fluorescence microscopy system precludes its widespread use at peripheral level. This system offers a cheaper alternative. Potential exists for further optimization of smear microscopy by combining low-cost fluorescence microscopy with bleach digestion and/or same-day approaches.
Product profile
A simple objective with light filters that can be fitted to most standard makes of microscopes and is connected by a fiber-optic cable to a halogen light source.
Stage of development
The product is already available and in use by some organizations in the field. Evaluation in operational settings and a move to demonstration projects are planned for 2007.
Considerations
Requires training. As yet, no guidelines for external quality assessment (EQA). Fluorescence microscopy may represent a broad platform, with advantages in the diagnosis of other diseases. Considerable time will be saved in microscopic examination of smears.
Earliest date for availability for adoption in the public sector
End of 2008

3. Bleach digestion of sputum
Type of product
Sputum smear microscopy
Product
Bleach
Developers
TDR
Rationale
Digestion of sputum with bleach (sodium hypochlorite) prior to the preparation of smears has been shown to increase the sensitivity of smear microscopy.
Product profile
Bleach digestion of sputum. Various methods of bleach digestion have been described involving different digestion times and supplementary processes.
Stage of development
Developing a standardized bleach digestion method to be put into demonstration projects in 2008.
Considerations
The expected reduction in biohazard resulting from bleach digestion will be evaluated prior to demonstration projects.
Earliest date for availability for adoption in the public sector
End of 2009

4. LED fluorescence microscopy
Type of product
Fluorescent microscope
Product
LED microscope
Developers
FIND and commercial partner
Rationale
Existing conventional fluorescence systems increase the sensitivity of direct smear microscopy. The LED microscope lamp is inexpensive in comparison to mercury vapour or the halogen lamp used in the regular fluorescent microscope and may have a lifespan of more than 50 000 hours.
Product profile
Simple binocular microscope incorporating LED light source.
Stage of development
Microscope in development phase.
Considerations
Training; as yet no EQA system for fluorescence microscopy; may represent a broad platform, with advantages in the diagnosis of other diseases; considerable time-savings in microscopic examination.
Earliest date for availability for adoption in the public sector
2009

5. First-generation isothermal nucleic acid amplification
Type of product
Molecular technique
Product
First-generation LAMP-based assay (loop-mediated isothermal amplification technology platform).
Developers
FIND and EIKEN Chemical Co. Ltd
Rationale
A simple DNA amplification method that does not require an expensive thermocycler or detection system and that allows visual detection of amplification could allow sensitive molecular methods to be used at lower levels of the health system.
Product profile
Preliminary data suggest high sensitivity and specificity. Modifications of the assay may be suitable for implementation at microscopy level. It is envisaged that the method may be applied to sputum, urine and blood specimens.
Stage of development
This product is in the development phase.
Considerations
Cross-disease platform; training required; somewhat more complex than microscopy, but with potential for further simplification and implementation at peripheral laboratory.
Earliest date for availability for adoption in the public sector
2010

C. HEALTH POST

No tests are currently available for use at the health post level of the health system. Bringing diagnostics to this level would be a tremendous achievement, with great implications for the ability of a control programme to increase case detection. In general, the technology best suited for this level is lateral flow or other immunochromatographic strip test.

1. Urinary antigen detection
Type of product
Antigen detection test
Product
LAM (mycobacterial lipoarabinomannin) antigen detection in urine.
Sponsors
FIND and partners
Rationale
<i>M. tuberculosis</i> LAM has been shown to be excreted in the urine of TB patients. Urine is an easier specimen to collect than sputum, and may be less variable in quality and safer to handle.
Product profile
There are several versions of this assay in development, including in-tube ELISA and dipstick methods. Urinary antigen detection may be of particular value in diagnosing TB in HIV-coinfected patients. There is potential for further development and simplification, resulting in a lateral flow test.
Stage of development
This test is under development.
Considerations
Lateral flow test – implementation could significantly increase case-finding through improved access to testing. The ELISA format has potential to increase case-finding if combined with smear microscopy and/or culture in settings of high HIV prevalence. Possible improvements in the diagnosis of paediatric and extrapulmonary TB.
Earliest date for availability for adoption in the public sector
2010

2. Antibody detection tests
Type of products
Antibody detection tests
Product
Development pending identification of suitable antigens
Sponsors
FIND and partners
Rationale
TB patients often have detectable antibodies to a variety of <i>M. tuberculosis</i> antigens. Currently, the commercially-available serological tests have been shown to perform poorly. A limited number of potential diagnostic antigens have been evaluated. FIND is systematically interrogating the proteome of <i>M. tuberculosis</i> for potential diagnostic antigens.
Product profile
The likely final product would be an immunochromatographic lateral-flow or flow-through test.
Stage of development
Antigen identification stage.
Considerations
Antibody detection may not perform well in patients with HIV-mediated immunosuppression.
Earliest date for availability for adoption in the public sector
2011

Chapter 3 NEW ANTI-TB VACCINES

According to the *Global Plan to Stop TB, 2006–2015*, the introduction of new, effective TB vaccines will be an essential component of any strategy to eliminate TB by 2050. New TB vaccines to prevent childhood and adult forms of TB, to prevent progression of latent infection to active disease and to shorten drug treatment regimens will fundamentally alter approaches to TB control.

The Working Group on New TB Vaccines was established to foster and coordinate collaborative efforts to develop novel vaccination approaches that are effective in reducing the burden of TB disease. The goal of the working group is to have a safe, effective, licensed vaccine available at reasonable cost by 2015.

It is anticipated that the next generation of vaccines will work by complementing the immune response induced by the current BCG vaccine or a modified recombinant BCG (rBCG). New vaccines could be delivered together with BCG to young children before they are exposed to TB, as a separate booster to young adults or as an adjunct to chemotherapy.

A. VIRAL VECTORED VACCINES

1. MVA85A
Type of product
Modified vaccinia Ankara virus expressing AG85A (MVA85A)
Sponsors
MVA85A was developed in Adrian Hill's laboratory at the University of Oxford, with funding from the Wellcome Trust and the European Commission.
Product description
MVA is a highly attenuated strain of vaccinia virus. It was used to immunize some 120 000 humans during the smallpox eradication campaign and has an excellent safety record.
Stage of development
MVA85A has been evaluated in multiple Phase I trials in Gambia, South Africa and the United Kingdom, in BCG-naive and BCG-vaccinated healthy adults as well as in HIV-infected adults.
Considerations
As judged by the number of trials as well as paradigms tested, MVA85A can be considered the most advanced of the new anti-TB vaccine candidates in the clinical development pipeline.
Expected date for completion of Phase III trials
2015

2. AERAS-402
Type of product
Replication-incompetent adenovirus 35 vector expressing <i>M. tuberculosis</i> antigens Ag85A, Ag85B and TB10.4.
Sponsors
AERAS-402 is being developed by Crucell Holland B.V. and the Aeras Global TB Vaccine Foundation (Aeras).
Product description
Adenovirus 35 is an advanced adenoviral vector system for the induction of antigen-specific CD4+ and CD8+ T-cell responses.
Stage of development
AERAS-402 is being evaluated in Phase I safety trials in the USA.
Expected date for completion of Phase III trials
2015

B. MODIFIED-RECOMBINANT BCG

1. AERAS-X03
Type of products
Recombinant BCG, overexpressing <i>M.tuberculosis</i> antigens Ag85A, Ag85B, Rv3407 and TB10.4 as well as an endosomalytic perfringolysin from <i>Clostridium perfringens</i> and a urease deletion mutation.
Sponsors
AERAS-X03 is being developed by Aeras.
Product description
Aeras-X03 is a recombinant BCG expressing a mutated perfringolysin as a mechanism to induce antigen-specific CD4+ and CD8+ T-cells via escape of mycobacterial antigens from the endosome for access to Class I presentation.
Stage of development
Aeras-X03 is in late-stage preclinical development and is scheduled to enter Phase I clinical trials in 2007.
Expected date for completion of Phase III trials
2015

2. RBCGHly
Type of product
Recombinant BCG expressing listeriolysin as well as carrying a urease deletion mutation.
Sponsors
RBCGHly is being developed by Vakzine Projekt Management GmbH (VPM) under license from the Max Planck Society. It was initially developed by the group of Professor S. Kaufmann from the Max Planck Institute for Infection Biology (Berlin, Germany).
Product description
RBCGHly is a recombinant BCG expressing listeriolysin as a mechanism to induce antigen-specific CD4+ and CD8+ T-cells via escape of mycobacterial antigens from the endosome. Urease has been deleted as a means of providing the optimal pH for listeriolysin function.
Stage of development
RBCGHly has completed preclinical development and is currently under GMP production. Phase I clinical trials are planned for 2007.
Expected date for completion of Phase III trials
2015

C. PROTEIN SUBUNIT VACCINES

1. M72
Type of product
Recombinant protein composed of a fusion of <i>M. tuberculosis</i> antigens Rv1196 and Rv0125.
Sponsors
M72 is being developed by GlaxoSmithKline (GSK) and Aeras.
Product description
M72 is a fusion of separate <i>M. tuberculosis</i> protein antigens delivered in GSK proprietary adjuvant AS02.
Stage of development
M72 is in Phase I clinical trials in Europe and in the USA.
Expected date for completion of Phase III trials
2015

2. HyVac 4
Type of product
Adjuvanted recombinant protein composed of a fusion of <i>M. tuberculosis</i> antigens Ag85B and TB10.4.
Sponsors
HyVac 4 is being developed by the Statens Serum Institute, Intercell and Aeras.
Product description
HyVac 4 is a fusion of separate <i>M. tuberculosis</i> protein antigens delivered in Intercell proprietary adjuvant IC31.
Stage of development
HyVac 4 is in late-stage preclinical development (non-human primates). Phase I clinical trials are scheduled for 2007.
Expected date for completion of Phase III trials
2015

3. Hybrid-1
Type of products
Adjuvanted recombinant protein composed of <i>M. tuberculosis</i> antigens Ag85B and ESAT-6.
Sponsors
Hybrid-1 is being developed by the Statens Serum Institute and the European TB vaccine project (TBVAC).
Product description
Hybrid-1 is a fusion of separate <i>M. tuberculosis</i> protein antigens delivered in Intercell proprietary adjuvant IC31.
Stage of development
Hybrid-1 is being evaluated in Phase I safety trials in the Netherlands.
Expected date for completion of Phase III trials
2015

D. BACTERIA-VECTORED VACCINES

1.AERAS-X05
Type of product
AERAS-X05 is a <i>Shigella</i> -delivered recombinant double-stranded RNA nucleocapsid encoding <i>M. tuberculosis</i> antigens Ag85A, Ag85B and Rv3407.
Sponsors
AERAS-X05 is being developed by Aeras.
Product description
<i>Shigella</i> -delivered nucleocapsids represent an inexpensive means of manufacturing oral delivery vaccines capable of expressing multiple TB antigens and inducing high levels of CD8+ T-cells.
Stage of development
Aeras-X05 is in late-stage preclinical development. Phase I clinical trials are scheduled for late 2007.
Expected date for completion of Phase III trials
2015

Annex 2: Key actions for new anti-TB regimens (illustrative)

Global adoption and new policy development

Issues	Key actions	Technical/operational lead	Estimated timeline	Resource requirements
Global policy development	Engage key stakeholders and facilitate discussion at global level on the inadequacies of existing medicines and strategies and the need and potential strategies for change			
	Ensure partners and stakeholders have a common understanding of the process and mechanism for decision-making for policy development on adoption of new tool			
	Assemble and submit information on the risks and benefits of the new tool to WHO			
	Scientific and technical guidance for the decision-making group developed by STAG-TB and the need for additional studies identified			
	Analyse the capacity of health systems in Member countries to adopt, and appropriately manage and use the new tool; identify needs for further studies/operational research			
	Review scientific and technical guidance as well as study results in order to decide whether to develop a new policy to recommend adoption of the new tool			
	Develop, endorse and communicate the new policy			
	Determine costs and responsibilities for updating and dissemination of international guidelines and associated technical materials and tools			
	Update and print guidelines; develop, budget and implement a strategy to communicate recommendations			
	Submit an application to add the new tool to the WHO EML; communicate decision to the country level			
International TB guidelines and materials	Identify, update and field test training materials and other technical tools			
	Develop, field test and disseminate an operational guide and a package of tools to assist countries and decision-makers to adopt and implement the new recommendations			
Registration	Determine approaches to assist countries in registering the new tool			
WHO prequalification	Inform manufacturers of the requirements for WHO prequalification of the new product; provide information on an acceptable dossier			
	Encourage manufacturers to begin the process of assembling the dossier and submitting the application in good time			

Issues	Key actions	Technical/ operational lead	Estimated timeline	Resource requirements
Manufacturing and supply	Develop initial global forecasts			
	Initiate large-scale production of active pharmaceutical ingredient and finished product (single medicine and/or FDC)			
	Transfer technology to increase geographical distribution of producers; determine need to provide technical assistance to manufacturers to meet GMP standards			
	Decide if new tool will be made available from international sources such as GDF			
Financing	Assist countries to identify potential sources of funding; provide technical assistance to capacitate countries to develop proposals			
Monitoring and evaluation	Identify priorities for operational research; assist countries to secure budgets, and implement and disseminate research			
	Determine approaches to assist countries to strengthen post-marketing surveillance systems for product quality, adverse drug reactions and emerging drug resistance			

Issues	Key actions	Technical/ operational lead	Estimated timeline	Resource requirements	
Country policy development	Establish mechanisms to engage with and contribute to global policy adoption and development process for new anti-TB medicines; identify approaches to enable ongoing scanning for tools and treatment strategies that may impact NTP programming				
	Engage decision-makers and facilitate discussion at national level on the inadequacies of existing medicines and/or strategies and the potential strategies for change				
	Identify key partners and stakeholders and select a mechanism (committee or working group) to engage them in the policy development process				
	Inform policy-makers and key stakeholders of ongoing discussions at global level and progress in development of new anti-TB medicines				
	Assemble and analyse information on the risks and benefits of the new anti-TB medicine or treatment strategy; determine the relevance to the country and appraise the options, e.g. for maintaining the status quo				
	Determine the need for additional in-country studies to inform decision-making; secure funding, and implement and present results to the committee/working group				
	Review national regulations and policies to identify potential barriers to implementation				
	Analyse the capacity of the health care system to appropriately manage and use the new tool; key considerations may include capacity to: <ul style="list-style-type: none"> • diagnose • perform essential laboratory monitoring • provide the appropriate quality of medical care • detect contraindications and adverse drug reactions • provide support to patients to adhere to and complete treatment • store products appropriately • minimize losses and theft 				
	Identify opportunities for leveraging funding for the policy change and to introduce other TB control programme or health system strengthening activities to minimize transition costs				
	Determine the full costs of adopting and implementing a new policy to introduce the new anti-TB medicine or treatment strategy				
Review the information and study results in order to decide whether to develop a new policy to adopt the new tool or treatment strategy					
Develop and endorse the new policy					

Country implementation

Issues	Key actions	Technical/ operational lead	Estimated timeline	Resource requirements
Registration	Register the new medicine using a fast-track mechanism, if available			
	Where exemptions are given for the initial procurement, ensure that an application to register the product is submitted in good time to allow follow-on procurement to proceed promptly to avoid stock-outs			
	Amend regulations and policies to assign appropriate scheduling for the tool and/or address any constraints to implementation			
Planning	Identify an existing committee or establish a new committee to manage the transition			
	Establish working group or task force and appoint members; develop terms of reference and mechanisms for coordination and communication with other key bodies			
	Make key decisions on: <ul style="list-style-type: none"> the level of the health care system and/or sector (e.g. public and private) where the new product will be available method of introduction of the new tool – phasing in or introduction through a full national roll-out need to phase out currently used tools criteria for a facility to start using the new tool 			
	Determine the first possible arrival date for the new tool; develop roll-out or phase-in plan			
	Develop a phase-out plan, if appropriate			
	Set schedule to review implementation progress and to adjust plans as needed; identify standards to determine whether introduction at a site is successful			

Issues	Key actions	Technical/ operational lead	Estimated timeline	Resource requirements
Financing	Develop multi-year budget for: <ul style="list-style-type: none"> new medicines, including buffer stocks and stock to fill the pipeline; consider costs for transport, insurance, QA testing and clearing other recurrent costs associated with the use of the medicine, e.g. laboratory test to monitor for adverse drug reactions, medicines to manage side-effects 			
	Develop budget for transition including costs for: <ul style="list-style-type: none"> establishing and convening working groups developing and disseminating new treatment guidelines revising and printing new operational manuals, tools and reporting and recording forms preparing training materials and ACSM materials training health-care providers and community partners establishing QA testing for new products addressing infrastructure needs withdrawal and incineration of obsolete products operational research and ongoing monitoring and evaluation 			
	Map out potential resources at national level; evaluate current spending and redirect funds if necessary			
	Determine the funding gap			
	Map out potential international resources, e.g. Global Fund, GDF, multilateral and bilateral donors, foundations, and develop a funding strategy			
	Develop/revise proposals for Global Fund, GDF and other donors			
	Secure commitments from ministry of health departments and from donors			
	Develop/review mechanisms for financial accountability			
	Evaluate cost-sharing and exemption mechanisms and develop strategies to address inequities			
	Receive funds disbursed by donors; prepare next proposal for funding			
	Determine which programme guidelines, tools and associated materials need to be updated; decide if amendments will be incorporated into the existing guidelines and materials or published as an addendum			
	Determine costs and responsibilities for updating the guidelines and associated tools			
	Update and disseminate guidelines and materials; coordinate process with training and implementation of ACSM strategies			
	Submit an application to add the new tool to the national EML; publish revised EML or addendum			
Revise recording and reporting forms; field test, print and disseminate				
Revise programme guidelines, EML and reporting and recording forms				

Issues	Key actions	Technical/ operational lead	Estimated timeline	Resource requirements
Training of health workers and community partners	Develop training strategy, budget and plan; coordinate with dissemination of guidelines, implementation of ACSM strategies and delivery of supplies			
	Develop and field test training materials; adapt tools for supportive supervision to incorporate the new guidelines			
	Train core team of trainers			
	Implement training plan; monitor quality of training			
	Revise pre-service and in-service curricula to incorporate the new recommendations into ongoing training			
	Develop and budget BCC and ACSM strategies; coordinate implementation with dissemination of guidelines and training			
	Develop and implement ongoing BCC and ACSM strategies to support rational use of the new tool			
	Identify dosage forms in use and estimate quantities in the pipeline at central and peripheral levels and on order			
	Calculate expected stock-out date and adjust future procurement of the currently used medicines to ensure that large pipelines of the currently used medicine do not accumulate during Phase-in or roll-out of the new medicine			
	Implement Phase-out plan; coordinate with Phased or nationwide implementation and adjust timeline as needed			
Phase-out medicines being replaced	Withdraw obsolete tool and redistribute or dispose of as appropriate			
	Define coverage and objectives for the forecast; identify budget restrictions or factors that may impact the forecast, such as procurement by other partners			
	Determine availability and limitations of consumption and/or morbidity data; select quantification method(s) that will be used to develop an initial forecast			
	Calculate needs for a Phased or nationwide implementation; determine size of buffer stocks for the different levels and requirements to fill the pipeline			
	Calculate needs for ancillary medicines and supplies for identifying and managing adverse effects to anti-TB medicines			
	Utilize data from pilot sites and/or Phased implementation to adjust estimates of the potential demand and uptake; refine forecasts and set schedule for quantifying ongoing needs			
	Determine procurement mechanisms available for the procurement; review donor and/or government requirements and restrictions for the procurement			
	Ascertain the lead time for the products and the estimated shelf-life on delivery			
	Set quality assurance (QA) standards and verification methods			
	Determine procurement method and develop a procurement plan; set procurement calendar			
Procurement	Assure financing for goods, transport, insurance, QA testing and clearing			
	Implement procurement; pay invoices and claim damages (if any)			
	Monitor the procurement process and supplier performance. Communicate information on potential delays to the committee/working group managing the transition			

Issues	Key actions	Technical/ operational lead	Estimated timeline	Resource requirements
Distribution	Develop a distribution strategy that synchronizes distribution of the new product and any ancillary medicines and supplies with Phased or nationwide implementation; identify resource needs for the transition, e.g. for additional deliveries			
	Integrate the distribution of the new product and ancillary supplies into the overall distribution plan			
	Verify clearing/importation requirements and arrange timely exemptions			
	Receive and clear stock; comply with QA procedures			
Health system strengthening	Implement distribution plan; receive and redistribute old products as per phase-out plan			
	Monitor the distribution process and communicate information on potential delays to the committee/working group managing the transition			
	Identify resources and develop a plan for strengthening health care systems to meet criteria for a site to start using the new product. Considerations may include capacity building to: <ul style="list-style-type: none"> properly store the medicines provide appropriate quality of care perform laboratory tests to screen for contraindications and/or for adverse effects produce reliable, valid and timely data on uptake, consumption and outcomes and to track the products through the system manage the supplies of products to avoid stock-outs or wastage promote the rational use of medicines 			
	Integrate capacity building activities to support the availability and appropriate use of the new anti-TB medicine with other initiatives to strengthen health systems			
Quality and safety	Synchronize timing of capacity building activities with the phased or nationwide implementation plan to ensure sites meet criteria for start up			
	Adhere to registration requirements to assure safety, efficacy and quality of the new TB product			
	Set quality assurance standards and verification methods for procurement; identify and secure funding to implement testing			
	Develop a plan for post-marketing product quality surveillance; secure resources and implement			
Quality and safety	Where a functioning national system for monitoring and reporting adverse drug reactions exists, integrate reporting for the new TB tool into the system			
	Where systems do not exist, explore the potential to monitor adverse events to the new tool through other mechanisms, e.g. through the recording and reporting forms for the TB control programme as an interim measure			
	Develop a plan for ongoing surveillance to monitor for emergence of resistance to the new anti-TB medicine			

Issues	Key actions	Technical/ operational lead	Estimated timeline	Resource requirements
Monitoring and evaluation	Explore the use of pilot sites and operational research to guide the appropriate implementation of the policy to introduce the new anti-TB medicine			
	Identify standards to determine whether introduction at a site is successful			
	Develop a monitoring plan to collect, analyse and report data on success of implementation; solicit feedback from health care staff, patients and other stakeholders. Take timely corrective action as needed			
	Prepare a report on findings at the end of each phase of the transition process			
	Prepare a final report on the introduction process; share experiences and lessons learnt with other countries			
	Set up a system to monitor for new tools and technologies that may impact NTP programming and use of the recently introduced anti-TB medicine			

Annex 3: Key actions for new TB diagnostics (illustrative)

Issues	Key actions	Technical/operational lead	Estimated timeline	Resource requirements
Global policy development	Engage key stakeholders and facilitate discussion at global level on the inadequacies of implementation of existing laboratory diagnostics and the need and potential strategies for change			
	Continue advocacy for and work towards streamlining and standardizing regulation of in vitro diagnostics for infectious diseases			
	Inform and engage key stakeholders during the development and execution of demonstration phase studies of impact and optimal use			
	Ensure partners and stakeholders have a common understanding of the process and mechanism for decision-making for policy development on adoption of the new tool			
	Demonstration of impact and optimal use studies completed (Phase IV)			
	Assemble and submit information on the risks and benefits of the new tool to WHO			
	Scientific and technical guidance for the decision making group developed by STAG-TB and the need for additional studies identified			
	Analyse the capacity of health systems in Member countries to adopt, and appropriately manage and use the new tool; identify needs for further studies/operational research			
	Based on STAG-TB recommendations, Stop TB Partnership develops guidelines			
	Develop, endorse and communicate the new recommendations and guidelines/standards, covering:	<ul style="list-style-type: none"> • laboratory assessment tools • staffing and training levels • infrastructure and equipment • biosafety aspects • generic SOPs manual • supervisory guidelines and checklists • information storage and recording • QA guidelines (both external and internal programmes) covering <ul style="list-style-type: none"> o proficiency testing o rechecking o supervision o internal quality control and quality improvement 		

Issues	Key actions	Technical/ operational lead	Estimated timeline	Resource requirements
International TB guidelines and materials	Determine costs and responsibilities for updating and dissemination of international guidelines and associated technical materials and tools			
	Update and print guidelines; develop, budget and implement a strategy to communicate recommendations/guidelines			
	Submit an application to add the new tool to the WHO Essential List of Laboratory Equipment and Supplies for TB (if such exists); communicate decision to the country level			
	Identify, update and field test training materials and other technical tools			
Registration	Develop, field test and disseminate an operational guide and a package of tools to assist countries and decision-makers to adopt and implement the new recommendations			
	Determine approaches to assist countries to register the new product			
	Continue efforts to develop a framework for a WHO regulatory-quality diagnostics evaluation system			
Manufacturing and supply	Develop initial global forecasts			
	Initiate large-scale production of equipment and consumables			
	Transfer technology where appropriate to increase geographical distribution of producers and of after-market support services; determine need to provide technical assistance to manufacturers to meet GMP standards			
Financing	Engage GDF to determine if improved or new tools will be included in procurement lists			
	Assist countries to identify potential sources of funding; provide technical assistance to capacitate countries to develop proposals			
Monitoring and evaluation	Identify priorities for operational research; assist countries to secure budgets, and implement and disseminate research			
	Determine approaches to assist countries to strengthen post-marketing surveillance systems for product quality, adverse drug reactions and emerging drug resistance			

Issues	Key actions	Technical/operational Lead	Estimated timeline	Resource requirements
Country policy development	Establish mechanisms to engage with and contribute to global policy adoption and development process for new or improved TB diagnostics; identify approaches to enable ongoing scanning for products and treatment strategies that may impact NTP programming			
	Engage decision-makers and facilitate discussion at national level on the inadequacies of existing laboratory tools and approaches and the potential strategies for change, using an integrated approach which considers the impact of new drugs and vaccines on the national strategy for TB control			
	Ensure participation of national reference laboratory with NTP in planning and budgeting activities			
	Identify key partners and stakeholders and select a mechanism (committee or working group) to engage them in the policy development process			
	Inform policy-makers and key stakeholders of ongoing discussions at global level and progress in improved/new laboratory diagnostic development, new drugs and new vaccines			
	Assemble and analyse available information on the risks and benefits of the improved/new laboratory diagnostic; determine the relevance to the country, and appraise the options, including the benefits/risks of maintaining the status quo. Analysis must include an assessment of the impact of new drugs and vaccines and consider the pipeline of potential new products			
	Determine the need for additional in-country studies to inform decision-making; secure funding, and implement and present results to the committee/working group			
	Review national regulations and policies to identify potential barriers to implementation and need for reinforcement of regulatory framework and oversight			
	Analyse the capacity of the health care system to appropriately manage and use the new tool; key considerations may include:			
	<ul style="list-style-type: none"> • laboratory infrastructure requirements, including those associated with biosafety (addressing those appropriate for the different levels of the laboratory system, i.e. health post/district/reference laboratories) • role of private laboratories • QA requirements, including those for internal and external QA, and supervision • role of private laboratories • human resource and training requirements • after-market support needs, including consumables, equipment maintenance • requirements for recording and communicating information • minimizing losses and theft 			
Identify opportunities for leveraging funding for the policy change and to introduce other TB control programme or health system strengthening activities to minimize transition costs, including the possible advantages of cross-platform technology which could improve diagnostic capacity for other diseases				
Determine the full costs of adopting and implementing a new policy to introduce the improved/new TB diagnostic				
Review the information from the preceding steps and decide whether to develop a new policy to adopt the improved/new TB diagnostic				
Develop and endorse the new policy				

Country implementation

Issues	Key actions	Technical/ operational Lead	Estimated timeline	Resource requirements
Registration	Register the new diagnostic			
	Continue work with international bodies on developing and implementing a regulatory framework for in vitro diagnostics			
	Amend regulations and policies to assign appropriate scheduling for the tool and/or address any constraints to implementation			
Planning	Identify an existing committee or establish a new committee to manage the transition			
	Establish working group/or task force and appoint members; develop terms of reference and mechanisms for coordination and communication with other key bodies			
	Make key decisions on: <ul style="list-style-type: none"> the level of the health care system (e.g. clinic/health post, peripheral lab, reference lab) and/or sector (e.g. public and private) where the new tool will be available method of introduction of the new tool – phasing in or introduction through a full national rollout need to phase out currently used products criteria for a facility to start using the new tool 			
	Determine the first possible arrival date for the new tool; develop roll-out or phase-in plan			
	Develop laboratory improvement plans in conjunction with NTP strategic plan			
	Develop a phase-out plan, if appropriate			
	Set schedule to review implementation progress and to adjust plans as needed; identify standards to determine whether introduction at a site is successful			

Issues	Key actions	Technical/ operational Lead	Estimated timeline	Resource requirements
Financing	<p>Develop multi-year budget for:</p> <ul style="list-style-type: none"> • equipment purchase • equipment maintenance and operating costs • consumables(specimen containers/slides, reagents, etc.) supply and re-supply, including buffer stocks and stock to fill the pipeline; including costs for transport, insurance, QA testing and clearing • recruitment and training of new personnel • supervision and monitoring costs • QA-related costs (both internal and external QA) • recurrent training costs to maintain proficiency in performance of tests • systems and networks for recording, storage and communication of information (i.e. test results) 			
	<p>Develop budget for transition including costs for:</p> <ul style="list-style-type: none"> • establishing and convening working groups • developing and disseminating new diagnostic protocols • revising and printing new operational manuals, tools and reporting and recording forms • preparing training materials and ACSM materials • training laboratory providers and supervisors • establishing QA testing for new tools (internal and external QA) • addressing infrastructure needs • withdrawal and incineration of obsolete tools • proper disposal of used products (i.e. specimen containers, slides, dipsticks) • operational research and ongoing monitoring and evaluation 			
	Map out potential resources at national level; evaluate current spending and redirect funds if necessary			
	Determine the funding gap			
	Map out potential international resources, e.g. Global Fund, GDF, multilateral and bilateral donors, foundations, and develop a funding strategy			
	Develop/revise proposals for Global Fund, GDF and other donors, ensuring that funding requests include needs associated with laboratory improvements (e.g. equipment, consumables, training, supervision, QA, after-market support)			
	Secure commitments from ministry of health departments and from donors			
	Develop/review mechanisms for financial accountability			
	Evaluate cost-sharing and exemption mechanisms and develop strategies to address inequities			
	Receive funds disbursed by donors; prepare next proposal for funding			

Issues	Key actions	Technical/ operational Lead	Estimated timeline	Resource requirements
Revise SOPs, essential laboratory supplies list and reporting and recording forms	Determine which SOPs, tools and associated materials need to be updated; decide if amendments will be incorporated into the existing guidelines and materials or published as an addendum			
	Determine costs and responsibilities for updating the guidelines and associated tools			
	Update and disseminate guidelines and materials; coordinate process with training and implementation of ACSM strategies			
	Submit an application to add the new tool to national EML; publish revised EML or addendum			
Training of laboratory providers	Revise recording and reporting forms; field test, print and disseminate			
	Develop training strategy, budget and plan; coordinate with dissemination of new SOPs, implementation of ACSM strategies and delivery of supplies			
	Develop training curricula and test training materials; field test training materials; adapt tools for supportive supervision to incorporate the new guidelines			
	<ul style="list-style-type: none"> test performance (microscopy, culture, DST) equipment operation and maintenance QA (internal and external) laboratory management, including planning and budgeting 			
ACSM strategies	Train core team of trainers			
	Implement training plan; monitor quality of training			
	Revise pre-service and in-service curricula to incorporate the new recommendations into ongoing training			
	Develop and budget ACSM strategies; coordinate implementation with dissemination of guidelines and training			
Phase-out laboratory equipment and supplies being replaced	Develop and implement ongoing ACSM strategies to support rational use of new tool			
	Identify forms in use and estimate quantities in the pipeline at central and peripheral levels and on order			
	Calculate expected stock-out date and adjust future procurement of the currently used diagnostics or related supplies to ensure that large pipelines do not accumulate during phase-in or roll-out			
	Implement phase-out plan; coordinate with phased or nationwide implementation and adjust timeline as needed			
Forecasting and quantification	Withdraw obsolete tools and supplies and redistribute or dispose of as appropriate			
	Define coverage and objectives for the forecast; identify budget restrictions or factors that may impact the forecast, such as procurement by other partners			
	Determine availability and limitations of consumption and/or morbidity data; select quantification method(s) that will be used to develop an initial forecast			
	Calculate needs for a phased or nationwide implementation; determine size of buffer stocks for the different levels and requirements to fill the pipeline			
Forecasting and quantification (continued)	Utilize data from pilot sites and/or phased implementation to adjust estimates of the potential demand and uptake; refine forecasts and set schedule for quantifying ongoing needs			

Issues	Key actions	Technical/operational Lead	Estimated timeline	Resource requirements
Procurement	Determine procurement mechanisms available for procurement of laboratory equipment and supplies; review donor and/or government requirements and restrictions for the procurement			
	Ascertain the lead time for the tools and the estimated shelf-life of reagents on delivery			
	Set QA standards and verification methods			
	Determine procurement method and develop a procurement plan; set procurement calendar			
	Assure financing for goods, transport, insurance, QA testing and clearing			
	Implement procurement; pay invoices and claim damages (if any)			
	Monitor the procurement process and supplier performance. Communicate information on potential delays to the committee/working group managing the transition			
	Develop a distribution strategy that synchronizes distribution of the new equipment and consumables (including specimen containers, reagents, etc.) with phased or nationwide implementation; identify resource needs for the transition e.g. for additional deliveries			
	Integrate the distribution of the new tool and ancillary supplies into the overall distribution plan			
	Verify clearing/importation requirements and arrange timely exemptions			
Distribution	Receive and clear stock; comply with QA procedures			
	Implement distribution plan; receive and redistribute old tools as per phase-out plan			
	Monitor the distribution process and communicate information on potential delays to the committee/working group managing the transition			
Laboratory system strengthening	Identify resources and develop a plan for strengthening laboratory systems to meet criteria for a site to start using the new tool. Considerations may include capacity building to—			
	<ul style="list-style-type: none"> • Upgrade laboratory infrastructure • Properly store and maintain the equipment and associated supplies • Perform diagnostic procedures • Perform internal quality controls • Perform supervisory activities • Develop laboratory management capacity • Produce reliable, valid and timely data on uptake, consumption and outcomes and to track the tools through the system • Manage the supplies of reagents and other supplies to avoid stock-outs or wastage • Promote the appropriate use of testing 			
	Integrate capacity building activities to support the availability and appropriate use of the improved/new diagnostic with other initiatives to strengthen health systems			
	Synchronize timing of capacity building activities with the phased or nationwide implementation plan to ensure sites meet criteria for start up			
	Ensure capacity for equipment maintenance and upgrading is in place			

Issues	Key actions	Technical/ operational Lead	Estimated timeline	Resource requirements
Quality and safety	Adhere to registration requirements to assure safety, efficacy and quality of the new tool			
	Set quality assurance standards and verification methods for procurement; identify and secure funding to implement testing			
	Develop a plan for supervision at all levels of the laboratory system that are included in the NTP strategy			
	Design and develop internal QA programmes			
	Design country-specific external QA programmes			
Monitoring and evaluation	Explore the use of pilot sites and operational research to guide the appropriate implementation of the policy to introduce the improved or new diagnostic tools			
	Identify standards to determine whether introduction and implementation at a site is successful			
	Develop a monitoring plan to collect, analyse and report data on success of implementation; solicit feedback from health care staff, patients and other stakeholders. Take timely corrective action as needed			
	Prepare a report on findings at the end of each phase of the transition process			
	Prepare a final report on the introduction process; share experiences and lessons learnt with other countries			
	Set up a system to monitor for new tools and technologies that may impact NTP programming and use of the recently introduced diagnostic			

Annex 4: Key actions for new anti-TB vaccines (illustrative)

Issues	Key actions	Technical/ Operational Lead	Estimated Timeline	Resource Requirements
Development and/or revision of global recommendations	Engage key stakeholders and facilitate discussion at global level on the need for the new anti-TB vaccine and potential strategies for change			
	Ensure partners and stakeholders have a common understanding of the process and mechanism for decision-making for policy development on adoption of the new vaccine			
	Assemble and submit information on the harms and benefits of the new tool to WHO			
	Scientific and technical guidance developed by SAGE			
	Analyse the capacity of health systems in GAVI and non-GAVI countries to adopt, and appropriately manage and use the new vaccine; identify needs for further studies/operational research			
International guidelines and materials	Review scientific and technical guidance as well as study results in order to decide whether to develop a new policy to recommend adoption of the new vaccine. Position paper on the new vaccine to be developed			
	Develop, endorse and communicate the new recommendation or revised strategy			
	Determine costs and responsibilities for updating and dissemination of international recommendations/guidelines and associated technical materials and tools			
	Update and print (written, CD, web site) guidelines/recommendations; develop, budget and implement a strategy to communicate recommendations			
	Identify, update and field test training materials and other technical tools			
Registration WHO prequalification	Develop, field test and disseminate an operational guide and a package of tools to assist countries and decision-makers to adopt and implement the new recommendations			
	Determine approaches to assist countries to register the new tool			
	Initiate process for WHO prequalification			

Issues	Key actions	Technical/ Operational Lead	Estimated Timeline	Resource Requirements
Manufacturing and supply	Develop initial global forecasts			
	Transfer technology if appropriate to increase geographical distribution of producers; determine need to provide technical assistance to manufacturers to meet GMP standards			
Financing	Engage UNICEF for inclusion of new tool on its procurement list			
	Assist countries who request assistance to identify potential sources of funding and provide technical assistance if requested to help countries develop funding proposals			
Monitoring and evaluation	Identify priorities for operations research; assist countries to secure budgets, implement and disseminate research			
	Determine approaches to assist countries to strengthen post-marketing surveillance systems for AEFI			

Issues	Key actions	Technical/ operational lead	Estimated timeline	Resource requirements
Country policy development	<p>Establish interagency coordinating committees or working groups on anti-TB vaccines as a strategy to develop strong partnerships within country and with those outside the country</p> <ul style="list-style-type: none"> • Assemble data on TB disease burden to aid decision-makers to introduce the new vaccine • Determine options to phase-in the pre-exposure anti-TB vaccine into EPI programme • Determine priority target population for post-exposure anti-TB vaccine and how it may impact NTP programming <ul style="list-style-type: none"> • Determine the costs and benefits of the new vaccine and how it may impact national health budget • Determine immunization schedules and identify approaches for integrating the new vaccine in EPI • Assess potential impact of the new vaccine on EPI delivery structure • Determine how delivery of the new vaccine will be integrated in other health services • Review competing priorities of other new vaccines being delivered • Conduct interviews with key experts in public and private sectors to assess possible barriers for introduction of new anti-TB vaccines • Determine the feasibility for introducing the new vaccine <p>In-country stakeholder consensus:</p> <ul style="list-style-type: none"> • Inform policy-makers and key stakeholders of global recommendations and potential of new anti-TB vaccines • Identify key partners and agencies to form a committee or working group to guide the introduction process 			

Country implementation

Issues	Key actions	Technical/ operational lead	Estimated timeline	Resource requirements
Registration	<p>Working group to monitor registration and regulation of vaccines</p> <p>Register the new vaccine using a fast-track mechanism (if available)</p> <ul style="list-style-type: none"> Develop introduction plan for the new vaccine at national, district and facility levels Design timeline for implementation of required activities before introduction (e.g. procurement, in-country stakeholder consensus, community awareness, training at all levels, monitoring tools, recording and reporting forms) Establish dates for official ceremony and launch of vaccine for actual administration throughout the country Develop plan for monitoring AEFI Review existing practices for vaccine “bundling” policy Determine staffing plans as needed at all levels (EPI, NTP, etc) 			
Introduction plan	<ul style="list-style-type: none"> Develop objectives and plans for immunization system strengthening in lieu of new vaccine introduction Establish criteria for vaccination of adolescents and adults Develop guidelines for use of anti-TB vaccines at all levels of the health system (national, district and facility level) Develop national EPI policies, plans, guidelines and standards Revise EPI guidelines and reporting and recording forms Review injection safety policy at all levels of the health system Develop visual aids and posters on injection safety 			

Issues	Key actions	Technical/ operational lead	Estimated timeline	Resource requirements
Financing	<p>External sources of financing</p> <ul style="list-style-type: none"> Map out potential international resources, e.g. GAVI/Vaccine Fund, Vaccine Independence Initiative, International Financial Facility for immunization <p>Develop/revise proposals for international funding agencies</p>			
	<p>Develop budget for programme costs:</p> <ul style="list-style-type: none"> training at national, provincial and district levels developing and disseminating ACSM documents and training materials infrastructure, such as cold chain, storage space, etc. operational research for ongoing monitoring and evaluation <p>Transportation costs for extended delivery and surveillance</p>			
	<p>Before introduction:</p> <ul style="list-style-type: none"> Revise national budget for allocation of new anti-TB vaccine based on expected coverage Calculate additional costs of programme implementation to accommodate new vaccine training, logistics, cold chain, ACSM, etc. Revise the comprehensive multi-year plan for immunization Determine sources of external financial assistance and plan for appropriate financing before introduction of vaccine Develop financial sustainability plan to accommodate long-term provision of anti-TB vaccines Develop/review mechanisms for financial accountability 			
	<p>After introduction:</p> <ul style="list-style-type: none"> Monitor trends in availability of funds at all levels Strengthen surveillance systems at national/regional level, including surveillance-specific personnel and training 			

Issues	Key actions	Technical/ operational lead	Estimated timeline	Resource requirements
<p>Training plan</p>	<p>For EPI managers and NTP managers:</p> <ul style="list-style-type: none"> Conduct training and focus-group discussions in functions of planning, organizing, leadership and management of EPI and NTP operations at all levels in lieu of new anti-TB vaccine introduction In the context of rapid change of health sector reform, consider strengthening management roles in areas such as motivation, communication and coordination Develop curricula, training materials and follow-up plan to monitor effectiveness of cascade training for health workers and community partners: Secure funding for training and related materials Ensure adequate amount of samples are ready for training (e.g. new vaccine samples, auto-disable (AD) syringes, safety boxes) If AD syringes are still new in certain districts or regions, ensure demonstration activity to minimize wastage of AD syringes Include updates of other aspects of EPI programme in training strategy Train health care workers on interpersonal communication skills and counselling skills for new anti-TB vaccines Generate institutional support for training (e.g. academic universities) Sensitize health workers on new immunization policies Establish regional teams for sustained capacity building and training activities, including post-training evaluation 			
<p>ACSM strategies</p>	<p>Advocacy strategies:</p> <ul style="list-style-type: none"> Invite multidisciplinary stakeholders to inform process and reach common agreement on new anti-TB vaccine immunization Ensure participation of in-country/regional scientific and research community, including partnerships with professional associations and concerned groups Gain support from media, sport stars, film stars or other well known personalities for endorsing the new vaccine Increased education on efficacy and safety of anti-TB vaccines <p>Communication strategies:</p> <ul style="list-style-type: none"> Provide technical material on the new vaccine and its benefits to media and generate awareness for use in print, radio, television, street plays, etc. Create display materials/immunization posters on new anti-TB vaccine Radio announcements in locally relevant language disseminated weeks before introduction of the new vaccine Celebrate TB vaccine health day or “village health day” <p>Social mobilization:</p> <ul style="list-style-type: none"> Perform situational analysis to determine psychosocial acceptance of vaccine Inform key community groups and social, religious and cultural leaders on benefits of the new vaccine Address problems with community demand for immunization, including negative perceptions/experiences about immunization arising out of rumours, AEFI or cultural and religious beliefs 			

Issues	Key actions	Technical/operational lead	Estimated timeline	Resource requirements
Forecasting and quantification	<ul style="list-style-type: none"> Plan for demand of the new vaccine from all levels of health facility Forecast based on needs of identified target population as determined in immunization strategy Forecast also based on capacity of health systems to deliver new anti-TB vaccines Quantify number of annual doses and supplies with projection for the next five years. Ensure that available or committed funding will be available to purchase doses and supplies Assess need for both small and large vial sizes in relation to minimizing vaccine wastage and capacity in health systems 			
	Determine what other factors might affect uptake of anti-TB vaccines (system readiness, staff recruitment, etc.) and plan for phased supply of vaccines			
Procurement	Review available procurement mechanisms and analyse donor and/or government requirements and restrictions for the procurement			
	Ascertain the lead time for the tools and the estimated shelf-life on delivery			
	Decide on appropriate choice of vaccine presentation (e.g. 1, 2, 5 or 10 dose vial presentation)			
	Set QA standards and verification methods			
	Determine procurement method and develop a procurement plan; set procurement calendar			
Distribution	Monitor the procurement process and supplier performance. Communicate information on potential delays to working group managing the transition			
	Promote communication with manufacturers or other suppliers on number of doses needed			
	Establish a TB Vaccine Distribution Plan related to the immunization strategy decided by the working group			
	Establish indicators for TB vaccine distribution at all levels of health facility			
	Monitor the distribution process and communicate information on potential delays to the committee/working group managing the transition			
Health system strengthening	Integrate capacity building activities to support the availability and appreciate use of the new vaccine			
	Assess need for strengthening health systems in lieu of new anti-TB vaccine introduction (e.g. cold chain, reporting mechanisms, safe injection practices, monitoring and evaluation)			
	<p>Storage and cold-chain capacity and readiness</p> <ul style="list-style-type: none"> Determine how the new vaccine will impact storage and cold-chain capacity Determine if storage space needs to be expanded, especially at district and facility levels Assess quality of cold chain equipment and if old ones need replacement <p>Vaccine logistics and management:</p> <ul style="list-style-type: none"> Ensure adequate amount of AD syringes and safety boxes, especially if supplied vaccines are from non-GAVI sources Periodically assess storage capacity, especially when there is influx of new or underutilized vaccines along with anti-TB vaccine Monitor effective use of vaccine vial monitors for temperature check and implementation of multi-dose vial policy Determine balance between TB vaccine utilization rate and TB vaccine wastage rate Adopt multi-dose vial policy and vaccine vial monitors 			

Issues	Key actions	Technical/ operational lead	Estimated timeline	Resource requirements
Quality and safety	Adhere to registration requirements to assure safety, efficacy and quality of the new vaccine			
	Set quality assurance standards and verification methods for procurement, identify and secure funding to implement testing			
Vaccine surveillance	Develop a plan for post-marketing product quality surveillance; secure resources and implement			
	<ul style="list-style-type: none"> Strengthen regional and district surveillance for measuring vaccination coverage and impact on TB disease burden Establish surveillance where none exists Develop feasible reporting mechanisms for AEFI and ensure availability of reporting forms for AEFI Facilitate monitoring and assessment of efficacy of vaccines during field use Develop national and regional epidemiological networks to monitor disease eradication due to vaccination 			
Monitoring and evaluation	Develop post-introduction evaluation plan to assess impact on EPI programme			
	Establish process indicators to identify challenges and constraints			
	Solicit feedback from health care staff, patients and other stakeholders			
	Use data and information to implement corrective action			
	Prepare documentation to share lessons learnt from introduction of vaccine and successful strategies			
Monitoring and evaluation	Cohort studies to assess impact of vaccine on disease incidence			
	<p>At all facility levels:</p> <ul style="list-style-type: none"> Develop and implement standard checklist of actions Follow-up supportive supervision, especially at low-performing health facilities Written documentation on observations or assessment with recommendations during a supervisory visit 			

Annex 5: Timeline for adoption and implementation (illustrative)

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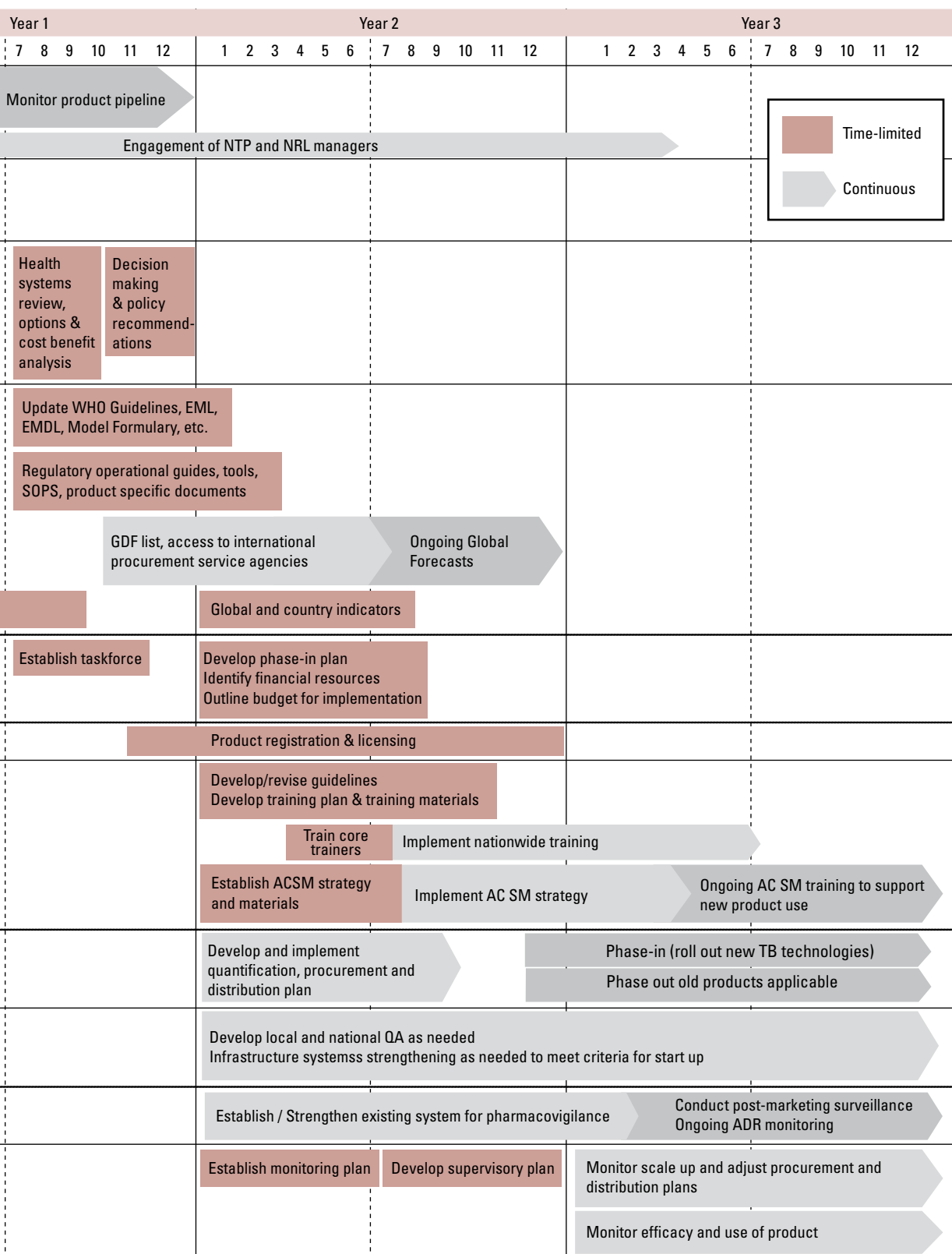
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- Global Policy
- Manufacturing Arrangements
- National Policy Development
- Global support for implementation
- NATIONAL IMPLEMENTATION
- Planning & Budgeting
- Regulatory
- Guidelines, Training, and AC SM
- Procurement and Distribution
- Quality Assurance
- Pharmacovigilance
- Monitoring and Evaluation

Pre-launch						
	1	2	3	4	5	6
Stakeholder discussion, compile evidence, build consensus, establish policy, develop guidelines, and recommendations						
Pricing Global Forecasts Supply Agreements						
Engagement global policymaking Operations research						
						WHO prequalification



Annex 6: Further reading

Strategic plan documents

The Stop TB Strategy: building on and enhancing DOTS to meet the TB-related Millennium Development Goals. Geneva, World Health Organization, 2006 (WHO/HTM/TB/2006.368).

The Global Plan to Stop TB, 2006–2015. Geneva, World Health Organization, 2006 (WHO/HTM/STB/2006.35).

GIVS Global Immunization Vision and Strategy 2006–2015. Geneva, World Health Organization and United Nations Children's Fund, 2005 (WHO/IVB/05.05).

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Operational guide for national tuberculosis control programmes on the introduction and use of fixed-dose combination drugs. Geneva, World Health Organization, 2002 (WHO/CDS/TB/2002.308 and WHO/EDM/PAR/2002.6).

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Kettler H, White K, Hawkes S. *Mapping the landscape of diagnostics for sexually transmitted infections: key findings and recommendations*. Geneva, UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, 2004 (TDR/SDI/IDE/04.1).

Diagnostics for tuberculosis: global demand and market potential. Geneva, UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, 2006.

General references

Plafker K. *Promoting drug development and access: some lessons from WHO past experiences and new strategies for the future*. Geneva, World Health Organization, 1998 (DAP/98.6).

Camp R et al. *What's in the pipeline: new HIV drugs, vaccines, microbicides, HCV and TB therapies in clinical trials*. New York, NY, Treatment Action Group, 2006 (available at: <http://www.hepcan.org/DrugsinthepipelineHCVTAGPipeline2006.pdf>; accessed March 2006).

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Simmons R, Brown J, Diaz M. Facilitating large-scale transitions to quality of care: an idea whose time has come. *Studies in Family Planning*, 2002; 33:61–75.

The safety of medicines in public health programmes: pharmacovigilance an essential tool. Geneva, World Health Organization

Stop TB Partnership



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