DOC 2.06-10.2

NEW TECHNOLOGIES FOR TB CONTROL: A GUIDE FOR THEIR ADOPTION, INTRODUCTION, AND IMPLEMENTATION

NOVEMBER 2006

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Funding Sources

- Global Alliance for TB Drug Development (TB Alliance)
- Foundation for Innovative New Diagnostics (FIND)
- UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR)
- United States Agency for International Development (USAID), through its Rational Pharmaceutical Management Plus Program (Cooperative Agreement HRN-A-00-00-00016-00)

ABBREVIATIONS

ACSM	Advocacy, Communication and Social Mobilization
ADIP	Accelerated Development and Introduction Plan
ADRs	Adverse Drug Reactions
AEFI	Adverse events following immunization
Aeras	Aeras Global Tuberculosis Vaccine Foundation
AIDS	Acquired immunodeficiency syndrome
AMC	Advanced market commitment
ART	Antiretroviral therapy
BCG	Bacille Calmette-Guérin (vaccine)
BMGF	Bill & Melinda Gates Foundation
CCM	Country Coordinating Mechanism
CDC	Centers for Disease Control and Prevention (USA)
CIDA	Canadian International Development Agency (Canada)
CMS	Central Medical Store
DEEP	Diagnostics Evaluation Expert Panel
DFID	Department for International Development (UK)
DOMI	Diseases of the Most Impoverished Programme
DOTS	DOTS expansion is the first component of the WHO Stop TB Strategy. DOTS is a proven approach that comprises political commitment with increased and sustained financing; case detection through quality-assured bacteriology; standardized treatment with supervision and patient support; an effective drug supply and management system; and a monitoring and evaluation system and impact measurement.
DST	Drug susceptibility testing
EML	Essential Medicines List
EMDL	Essential Medicines Device List
EPI	Expanded Programme on Immunization
FAQ	Frequently Asked Questions
FDC	Fixed-dose combination
FIND	Foundation for Innovative New Diagnostics
G-6-PD	Glucose-6-phosphate dehydrogenase deficiency
GAVI	Global Alliance for Vaccines and Immunization
GCP	Good Clinical Practice
GCLP	Good Clinical Laboratory Practice
GDF	Global Drug Facility
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
GMP	Good Manufacturing Practices
GLC	Green Light Committee

GTZ	Deutsche Gesellschaft fur Technische Zusammenarbeit [German Development Agency]
HiB	Haemophilus influenza B vaccine
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IDPF	International Drug Purchase Facility
IFFIM	International Finance Facility for Immunization
ISTC	International Standards for Tuberculosis Care
IVD	In vitro diagnostic
IVR	WHO Initiative for Vaccine Research
IUATLD	International Union Against Tuberculosis and Lung Disease
KNCV	Koninklijke Nederlandse Centrale Vereniging ter Bestridjing van Tuberculose [Royal Netherlands Tuberculosis Foundation]
LTBI	Latent tuberculosis infection
MSH	Management Sciences for Health
MDG	Millennium Development Goal
MDR-TB	Multi-drug resistant tuberculosis
MRA	Medicines Regulatory Authority
MOH	Ministry of Health
MYP	Multi Year Plan (for immunization)
NAAT	Nucleic acid amplification test
NGO	Nongovernmental organization
NIAID/NIH	National Institute of Allergy and Infectious Diseases/ National Institutes of Health (USA)
NRA	National Regulatory Authority
NRL	National Reference Laboratory
NTP	National Tuberculosis Program
PAL	Practical Approach to Lung Health
PAHO	Pan American Health Organization
PATH	Program for Appropriate Technology in Health
PDP	Product Development Partnership
PPM	Public-private mix
PneumoADIP	Pneumococcal Accelerated Development and Introduction Plan
R & D	Research and development
RED	Reaching Every District
RF	Rockefeller Foundation
RPM Plus	Rational Pharmaceutical Management Plus Program
QA	Quality assurance
SAGE	Strategic Advisory Group of Experts for Vaccines and Immunization

STAG	WHO Strategic Technical Advisory Committee for TB
STB	WHO Stop Tuberculosis Department
STGs	Standard Treatment Guidelines
TB	Tuberculosis
TB Alliance	Global Alliance for TB Drug Development
TB/HIV	TB and HIV co-infection
TBCAP	TB Control Assistance Program
TDR	UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases
TFR	Task Force on Retooling
UNDP	United Nations Development Programme
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
VCT	Voluntary Counseling and Testing
VPB	Vaccine Procurement Baseline
XDR-TB	Extensively drug-resistant tuberculosis
WHO	World Health Organization

FOREWORD

[PENDING: BY A TB PATIENT TO BE PROVIDED BY JAVID SYED]

PREFACE

[TO BE DETERMINED: MARCOS ESPINAL?]

Illustrative Text

The past decade is remarkable for the success in TB control leading to an increase in the case detection rate of smear positive TB from 27% to 60%, and treatment success rate to 84%. The DOTS expansion might have reversed the increasing trend of incidence of TB to negative. However, what we found after the decade of enormous efforts by DOTS with conventional tools are that we still have 1.6 million deaths a year. More than half of TB patients, including children, remain in the community without proper diagnosis and treatment; still long "short course chemotherapy" deprives lots of opportunities especially for the poor, directly and indirectly. Significant challenges remain, and they are accelerated by the HIV epidemic, multi-drug resistant tuberculosis (MDR-TB), and now extensively resistant tuberculosis (XDR-TB). Improvements in existing approaches and new tools are needed as the diagnostic currently in use is more than 100 years old, the current vaccine is not protective in most adults and may present an elevated risk of adverse events in children infected with HIV/AIDS, and there have been no new drugs for over 40 years.

The ability to urgently deploy and appropriately use new tools as they become available is critical to saving lives, and will require a concerted and well planned effort by the entire Stop TB Partnership, including the NTPs, technical partners, community members and civil society representatives, product developers, donors and international organizations. It is more urgent than ever for NTPs and health systems to improve the management capacity to prepare to seize opportunities, and 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 both the global and country levels.

EXECUTIVE SUMMARY

The Promise of New Tools

The Stop TB Partnership's Global Plan to Stop TB (2006-2015) describes the principal strategies that will be used for TB prevention and control over the next 10 years. 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 new WHO-recommended Stop TB Strategy, based on DOTS and including the International Standards for TB Care.

The large investments that have been made to accelerate the development of new medicines, diagnostics and vaccines for TB have led to high expectations that these new technologies will provide National TB Programmes (NTPs) with better options and more choices for improving TB prevention, detection and treatment. At the same time, availability of new tools will also require country-level systems and procedures that can rapidly and effectively assess and incorporate them into their TB control strategies and programmes.

Past experience with the introduction of new tools for prevention and control in malaria and hepatitis B and other disease areas has shown that there is often a significant delay between availability of new tools at the global level and their eventual adoption and implementation at country level.

The Global Plan to Stop TB 2006-2015 estimated there were 27 medicines, 15 diagnostics, and eight vaccines in the "pipeline" at various stages ranging from product development to field trials. Since its publication, the number of candidate technologies has increased. With the anticipated launch of the first of the new tools in 2007 or 2008, and the lead time required to secure adequate levels of funding and manage procurement and supply, the time is right to start preparing for introduction of new tools.

The introduction of new and improved medicines, diagnostics and vaccines for TB control and prevention should be regarded as a means to improve the quality of care by making available not only a wider choice of technologies to address unmet need, but also opportunity to align the new tools with the capacity of health systems to deliver care and to the needs of the community of people with TB infection.

Objectives and Content of the Guide

Recognizing this wide time lag between evidence and policy implementation, the Stop TB Partnership Coordinating Board established the Task Force on Retooling to develop a framework for catalyzing global and national level policy makers and practitioners towards accelerated introduction of new tools into TB control programmes. One of the aims of TFR is to stimulate discussions and planning for optimal, timely and appropriate introduction, adoption and implementation of these tools as they become available.

This document aims to provide a common framework to discuss the adoption and implementation of new tools for TB control; identify some key issues that need to be addressed to accelerate the adoption and implementation of improved and new tools; and

provide guidance on what actions are needed when improved existing and/or new medicines, diagnostics and vaccines become available.
It is primarily intended to support managers of national TB control programmes, national immunization programmes, and clinical laboratory and diagnostic services. It is also aimed 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 for facilitating appropriate and timely adoption and implementation; and provides an overview of technical and operational considerations for the processes of adoption and implementation at global and national levels.

The annexes provide a brief overview of new medicines, diagnostics and vaccines in the development pipeline; an illustrative list of key actions for the adoption and implementation for each technology category; an illustrative generic timeline, or sequencing of key tasks, for adoption, introduction and implementation; and a list of key readings that provide more detailed discussions of the issues and road maps.

System and Programme Readiness for Change

The wide array of products in the pipeline with different expected dates of availability means that systems that can manage on-going change and enable rapid integration of newly available tools will be required at both the global and national levels. A new tool may be rapidly superseded by a newer tool within a short time span, if there is appropriate evidence 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 investment of resources to support its adoption. The anticipated sequence of new tool availability may also impact the resources that are allocated for the implementation of the newly adopted tool.

Policy makers and decision makers at 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 make it to market and 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 modification of diagnostic or treatment algorithms when developing recommendations and policies; and ensure the participation of other programmes, such as the global Expanded Programme on Immunization (EPI), 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: weak or non-existent legal and regulatory frameworks; inadequate capacity to manage laboratory and 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; lack of capacity to manage change; and financial constraints.

Key actions that will facilitate their timely and appropriate adoption, introduction and implementation include: engaging stakeholders from the beginning of the policy analysis process (for adoption) and through introduction and implementation; advanced planning and preparation, both globally and nationally; and conducting operations research to guide adoption, introduction and implementation.

Adoption and New Policy Development

Although the development of recommendations on the use of improved or new tools for TB control at the global level and the development of new policies for 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 organizations with a mandate for setting normative standards and providing technical assistance, such as WHO or the Union.

The essential and interlinked components of a process for adoption of new tools for TB 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, analysis of the health system environment and capacity to adopt, introduce and implement the new tool; and 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 the private sector, including not-for-profit institutions such as faith-based or secular NGOs and the for-profit sector, can be divided into technical considerations, operational considerations, and monitoring and evaluation.

Technical considerations relate to registration of products and revision of regulations; development or updating of programme guidelines, essential medicines, medical devices and related supplies lists, 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 product and service quality and safety. Monitoring and evaluation of the adoption, introduction, and implementation of new TB tools will provide important lessons for the uptake of incrementally improved tools.

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. In particular, its Working Groups can facilitate collaboration to:

- Keep stakeholders informed about products in the development pipeline;
- Strengthen frameworks and processes for product regulation and registration, particularly for diagnostics;
- Strengthen pharmaceutical management, laboratory infrastructure and services;
- Increase capacity to conduct operations research to guide adoption, introduction and implementation;
- Address human resource constraints; and
- Mobilize adequate financial resources.

Stop TB Partners should work collaboratively to develop and/or widely disseminate practical guidance documents and training materials on:

- Engaging stakeholders;
- Submission of new technology applications to WHO;
- Comparative assessment of options;
- Specific road maps for adoption and introduction of highly promising new tools;
- Tool specific materials for advocacy, communication, and social mobilization; and
- Monitoring and evaluation system, including indicators for adoption, introduction and implementation of new TB tools; and
- International standards and related guidance documents for assessing and regulating technologies.

BACKGROUND

While the past few years are remarkable for the successes in DOTS expansion leading to an increase in the case-detection rate from 27%[1] to an estimated 60% by 2005, and a treatment success rate averaging 82%[2], significant challenges remain, especially those posed by the HIV epidemic and multi-drug resistant tuberculosis (MDR-TB), and now extensively drug-resistant tuberculosis (XDR-TB). Improvements in existing approaches and new tools are needed to address these challenges and accelerate TB control; these new tools include medicines, diagnostics, and vaccines. The new Stop TB Strategy[3] recommended by the World Health Organization (WHO) includes a component that specifically aims at promoting research as an integral approach to ameliorate current tools available to TB care providers and control personnel.

The Stop TB Partnership's Global Plan to Stop TB (2006-2015)[4] describes the principal strategies that will be used for TB prevention and control over the next 10 years. These include:

- Increasing access to accurate diagnosis and treatment through DOTS;
- Scaling up the public-private mix approach;
- Increasing community DOTS initiatives; and
- Strengthening programmes to address MDR-TB, XDR-TB and HIV-related 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 new WHO Stop TB Strategy, based on DOTS[5] and including the International Standards for TB Care[6].

[1] Dye C, Watt CJ, Bleed D. Low access to highly effective therapy: a challenge for international tuberculosis control. ***Bull WHO*** 2000;80:437-444.
[2] World Health Organization. ***WHO Report 2006: G lobal Tuberculosis Control; Surveillance, Planning, Financing***. WHO/HTM/TB/2006.362. Geneva: World Health Organization, 2006.
[3] Stop TB Partnership and World Health Organization. ***The Stop TB Strategy. Building on and Enhancing DOTS to meet the TB-related Millennium Development Goals***. Geneva: World Health Organization, 2006.
[4] Stop TB Partnership and World Health Organization. ***Global Plan to Stop TB 2006-2015***. Geneva: World Health Organization, 2006.
[5] DOTS is a proven approach to TB control that comprises political commitment with increased and sustained financing; case detection through quality-assured bacteriology; standardized treatment with supervision and patient support; an effective drug supply and management system; and 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.
[6] Tuberculosis Coalition for Technical Assistance. ***International Standards for Tuberculosis Care (ISTC***). The Hague: Tuberculosis Coalition for Technical Assistance, 2006.

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

- 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; and
- Advocacy, Communications and Social Mobilization Working Group.

These working 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 are therefore of concern to each of these groups.

The large investments that have been made to accelerate the development of new medicines, diagnostics and vaccines for TB have led to high expectations that these new technologies will provide National TB Programmes (NTP) with better options and more choices for improving TB prevention, detection and treatment. At the same time, availability of new tools will also require country-level systems and procedures that can rapidly and effectively assess and incorporate them into their TB control strategies and programmes. The number of anticipated new and incrementally improved tools will continue to grow as newer tools emerge from the development process.

Past experience with the introduction of new tools for prevention and control in malaria, hepatitis B and other disease areas[7,8] has shown that there is often a significant delay between availability of new tools at the global level and their eventual adoption and implementation at country level.

Recognizing this wide time lag between evidence and policy implementation, the Stop TB Partnership Coordinating Board established the Task Force on Retooling (TFR, see Box 1) to develop a framework for catalyzing global and national level policy makers and practitioners towards accelerated introduction of new tools into TB control programmes. The aim of TFR is to stimulate discussions and planning for optimal, timely and appropriate introduction, adoption and implementation of these tools as they become available.

[7] Mahoney RT, Maynard JE. ***The introduction of new vaccines into developing countries***. Vaccine. 1999 Feb 26;17(7-8):646-52.
[8] Mutabingwa, TK. ***Artemisinin-based combination therapies (ACTs): best hope for malaria treatment but inaccessible to the needy!*** Acta Trop. 2005 Sep;95(3):305-15.

Box 1: Task Force on Retooling: Composition and Terms of Reference

Membership

- Experts, not necessarily working group members, designated by the Chairman of the working groups
- Members from key subgroups (laboratory, GDF, poverty)
- Representatives from high burden country NTPs
- 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 work plan and timelines
- Consolidating and sharing information from the diagnostics, drugs and vaccines working groups on current product pipelines and timelines/milestones
- Creating opportunities for consultative dialogue with stakeholders from high burden countries, including ministries of health, NGOs, affected communities, etc.
- Facilitating the mobilization of financial and human resources for country level introduction and deployment
- Consolidating relevant lessons learned form other disease areas to inform TB-specific processes for adoption, introduction and implementation
- Facilitating operations research on introduction of new tools
- Generating evidence to support the adoption of new tools
- Fast-tracking their incorporation in WHO and national policies and guidelines
- Enhancing communication among all Working Groups around the theme of retooling

INTRODUCTION

The Global Plan to Stop TB 2006-2015 estimated there were 27 medicines, 15 diagnostics, and eight vaccines in the "pipeline" at various stages ranging from product development to field trials. Since its publication, the number of candidate technologies has increased. With the anticipated launch of the first of the new tools in 2007 or 2008, and the lead time required to secure adequate levels of funding and manage procurement and supply, the time is right to start preparing for introduction of new tools.

The introduction of new and improved medicines, diagnostics and vaccines for TB control and prevention should be regarded as a means to improve the quality of care by making available not only a wider choice of technologies to address unmet need, but also opportunity to align the new tools to the capacity of health systems to deliver care and to the needs of the community of people with TB infection.

Objectives

This document aims to:

- Provide a common framework to discuss the adoption and implementation of new tools for TB control;
- Identify some key issues that need to be addressed to accelerate the adoption and implementation of improved and new tools; and
- Provide guidance on what actions are needed when improved existing and/or new medicines, diagnostics and vaccines become available, to ensure optimal and appropriate adoption and implementation into TB control strategies, and access and proper use by the community.

This guide is primarily intended to support managers of national TB control programmes, national immunization programmes, and clinical laboratory and diagnostic services. It is also aimed 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.

Contents

This document:

- Identifies key challenges to adoption and implementation of new technologies;
- Proposes key principles for facilitating appropriate and timely adoption and implementation; and
- 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;
- Listing of key actions for the adoption, introduction and implementation of each technology category;
- An illustrative generic timeline for adoption, introduction and implementation; and
- A list of key readings that provide more detailed discussions of the issues and road maps.

Assumptions

The document starts from the assumption that the following will have occurred with regard to any new technology 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 be provided at the time of submission for regulatory approval.
- Consequently, for "the retooling" process a new TB technology is considered "available" globally when it also has adequate demonstration of its effectiveness in real-life situations in national disease control programmes 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 is recognized both globally and by countries.
- It will be possible to mobilize adequate financial resources for the acquisition of these new products.
- Product developers and manufacturers will have worked out "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 (PDP) for the new anti-TB medicines, diagnostics and vaccines are working to address these issues.

TB Control Objectives for New Technologies

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

Diagnostics

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

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

For all these tools it will be vital that they are first assessed in a variety of operational disease control programmes in high-endemic countries 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 HIV-infected persons are to:

1) Simplify and improve detection of TB cases, including smear negative and extra-pulmonary TB, through increased sensitivity and specificity and improved accessibility;

2) Develop simple, accurate and rapid inexpensive tests that can be performed at point of care level of the health care system and that produce quick results on the same day;

3) Monitor treatment;

4) Rapidly identify drug resistance (improved drug susceptibility testing) to both first- and second-line medicines; and

5) Reliably identify latent TB infection and determine the risk of progression to active disease, enabling the rational use of preventive therapy.

Medicines

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

1) Simplify or reduce treatment duration to two months or less;

2) Effectively treat multi-drug resistant TB (MDR-TB, XDR TB); and

3) Treat patients with latent TB infection.

The new medicines should also be compatible with HIV/AIDS anti-retroviral therapy.

Vaccines

Although the only currently available TB vaccine Bacille Calmette-Guérin (BCG) provides protection against disseminated disease in neonates and young children, 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:

1) Prevent TB infection from occurring (pre-exposure prophylaxis) in all age groups;

2) Prevent progression of latent infection (LTBI) to active disease in adolescents and adults; and

3) Assist in treatment of active disease, as immunotherapy as an adjunct to conventional treatment.

Expected Timeline for New Technologies

Continued increases in funding for the discovery, research, and development of new anti-TB medicines, TB diagnostics, and anti-TB vaccines has expanded the pipeline of new tools in all three categories. Figure 1 identifies some of the products in the pipeline which are likely to be become available by 2015 and their estimated launch date. This information is for illustrative purposes, 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 quite possible that some of these 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 expected time when phase III studies will be completed and an application for market approval will be filed with a regulatory agency. Some new TB medications may be introduced as novel combinations, rather than single drugs. For diagnostics, the estimated dates refer to expected time when studies conducted under actual service delivery conditions (demonstration studies) are completed for the identified tools and submitted along with product studies for technical assessment by the World Health Organization (WHO) and by the respective country health technology assessment bodies.

Annex 1 provides a summary of 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 recommended readings.

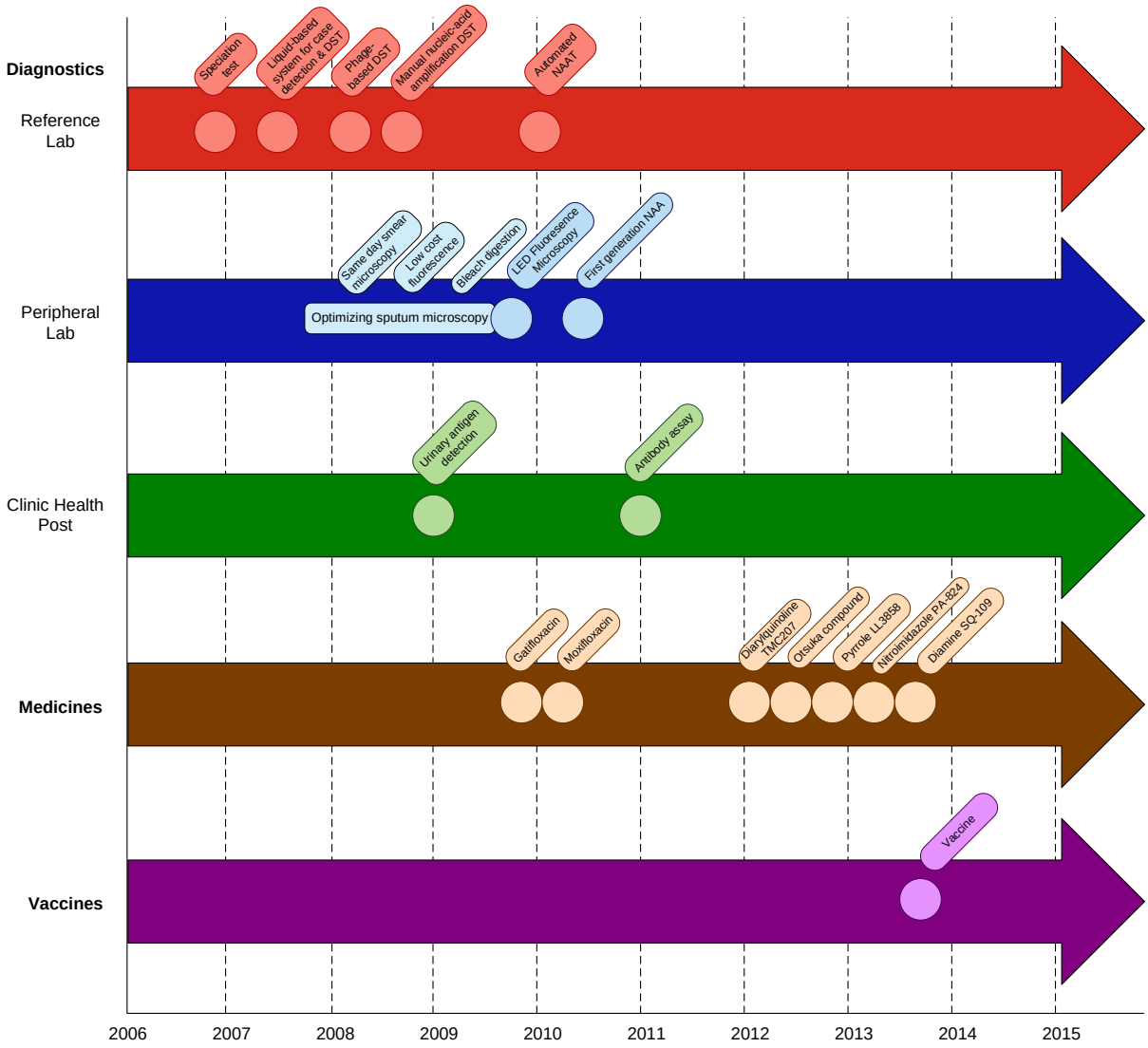


Figure 1. Examples of products in the pipeline currently under evaluation (see Annex 1).

Note: the time point indicated on the time scale represents end of field studies ("demonstration phase") for diagnostics or end of Phase III trials for drugs and vaccines, if evaluation is successful.
DST=drug susceptibility testing, NAA=Nucleic acid amplification, NAAT=Nucleic acid amplification test.

The wide array of products in the pipeline with different expected dates of availability means that systems that can manage on-going change and enable rapid integration of newly available tools will be required at both the global and national level. A new tool may be rapidly superseded by a newer tool within a short time span, if there is appropriate evidence 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 investment of resources to support its adoption. The anticipated sequence of new tool availability may also impact upon the resources that are allocated for the implementation of the newly adopted tool.

Policy makers and decision makers at 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 make it to market and the approximate time frame; and

- Consider potential modification of diagnostic or treatment algorithms when developing recommendations and policies; and differences in national environments and of the potential roles of the technology types (medicines, diagnostics, vaccines); how they can be used together;

- Engage other programmes, such as the global Expanded Programme on Immunization (EPI), the national immunization programmes, and reproductive and child health programmes in planning and implementation.

Challenges to Timely and Appropriate Adoption, Introduction and Implementation of New Technologies for TB control

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 laboratory and 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;

- Lack of capacity to manage change; and

- Financial constraints.

Actions that Facilitate Timely and Appropriate Adoption, Introduction and Implementation of New Diagnostics, Medicines and Vaccines

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

Identifying global and country level stakeholders, across the public and private sectors, community-based groups and people living with TB, donors, pharmaceutical and laboratory suppliers and manufacturers, professional bodies, and academic institutions and keeping them updated on advances and early engagement in the adoption (policy change) process can facilitate both the decision making process and also the implementation of the new policy.

The benefits of engaging the community in retooling also include the opportunity 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 (ADRs); advocacy to "move things along" throughout the policy development and implementation process, and 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 public-private mixes (PPM) for DOTS implementation[9], and has developed tools and approaches for implementing PPM.

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

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

2. *Advanced planning and preparation, both globally and nationally*

The potential availability of some of these tools within the next two or three years makes it urgent for the Stop TB Partnership to define processes to facilitate appropriate adoption and implementation of the new technologies at both 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 it will be necessary for policy makers and decision makers at the global and national levels to closely monitor the status of the product pipeline, and to update other stakeholders on new advances that are likely to become available, and 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 guide operations research, identify critical system weaknesses, initiate efforts to address human resource constraints and mobilize financial resources and technical assistance, as needed. Some countries may satisfy technical

[9] TB Strategy and Operations, Stop TB Department. ***Public-Private Mix for DOTS: Practical Tools to Help Implementation.*** WHO/CDS/TB/2003.325. Geneva: World Health Organization, 2003.

assistance needs with national resources, while others may require international assistance. In many countries, strengthening systems, particularly infrastructure development and refurbishing of premises for diagnostic and laboratory services, will require significant effort, resources, and time to prepare them for optimal uptake of the new tools.

3. *Operations research to guide adoption, introduction and implementation*

Operations research on the introduction of new medicines, diagnostics, and vaccines 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, policy and decision-makers. Operations research can provide the information that decision-makers need to consider in order to integrate the new technologies into programmes, such as the capacity to provide 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 quality of care, including adequate supply and appropriate use. Effective mechanisms for data collection and dissemination of lessons learned will need to be established.

ADOPTION AND NEW POLICY DEVELOPMENT AT GLOBAL AND COUNTRY LEVELS

Although the development of recommendations on the use of improved or new tools for TB control at the global level and the development of new policies for 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 professional associations such as IUATLD. In this discussion, differences between country-level and global level components of the adoption and policy development processes will be highlighted where relevant.

Essential Components

The essential components of a process for adoption of new tools for TB and a subsequent change 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 wide dissemination

These steps should not be considered in sequence, but represent processes that are interlinked.

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 to develop appropriate recommendations and policies. These constituencies represent a wide range of sectors and disciplines, from intergovernmental agencies to national governments to patient organizations. Illustrative stakeholders at global and country levels are listed in Boxes 2 and 3.

A key strategy to accommodate differences between the global and the country levels will be to keep national TB programme managers and national policy makers aware of the ongoing discussions and progress towards availability of improved or new tools. Some of these individuals, particularly those from high burden countries, will have been involved in and contributed to the policy making process to adopt new TB control 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 of improved new tools will facilitate their own analyses of the needs and evidence for change. For other countries, briefing papers, guidance documents,[10] or other channels for disseminating information on new tools (e.g. through WHO country offices, and through the work of other technical partners, through the web, and other means), could help national policy makers examine these issues.

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

[10] Examples of briefing documents prepared to assist countries in decision making on adopting and introducing four-drug fixed-dose combination tablets include:

- Stop TB Partnership Secretariat Global Drug Facility. ***Frequently Asked Questions about the 4-drug Fixed Dose Combination Tablet Recommended by the World Health Organisation for Treating Tuberculosis***. WHO/CDS/STB/2002.18 Rev 1. Geneva, Switzerland: World Health Organization, 2003.
- ***Operational Guide for National Tuberculosis Control Programmes on the Introduction and Use of Fixed-dose Combination Drugs***. WHO/CDS/TB/2002.308 and WHO/EDM/PAR/2002.6. Geneva, Switzerland: World Health Organization, 2002.

Box 2: Illustrative list of stakeholders at global level

Stop TB Partnership

Intergovernmental agencies

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

Funding agencies

- Multilateral and regional donors and development banks: Global Fund, World Bank, African Development Bank, Asian Development Bank, etc.
- Bilateral donors: CIDA, Danida, DFID, DGIS, Norad, Sida, USAID, etc.
- National Institutes of Health (NIH),
- European & Developing Countries Clinical Trials Partnership (EDCTP)
- 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 R&D firms
- State-owned enterprises

International suppliers

- Procurement agencies (Crown Agents, International Dispensary association, GTZ, Stop TB Global Drug Facility)
- Private healthcare providers and institutions

Professional organizations and Technical partners

- International Union Against Tuberculosis and Lung Disease (The Union)
- Centers for Disease Control and Prevention (CDC)
- 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 TB Vaccine Foundation
- Foundation for Innovative New Diagnostics (FIND)
- Global Alliance for TB Drug Development (TB Alliance)

Box 3: 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 Program
- 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
- GFATM Country Coordination Mechanisms
- National TB Association
- Patients Organizations
- Collaborating partners including multilateral (WHO, UNICEF, World Bank, etc.) and bilateral (USAID, PEPFAR, U.K. Department for International Development, etc.) partners

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

First, in 2001 WHO established an advisory committee called the Strategy and Technical Advisory Group for Tuberculosis (STAG), 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. The STAG provides scientific and

technical guidance to WHO, and meets once a year; the results of these deliberations can become the basis of WHO recommendations. Subcommittees are sometimes formed to provide advice to WHO on specific topics. Through consultation and collaboration, WHO could provide input, through its sub-committees, to ensure that effectiveness studies are appropriately designed, and to facilitate the analysis of available evidence prior to meetings of the full STAG. 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 Vaccines and Immunization. This Department convenes another advisory committee, the Strategic Advisory Group of Experts (SAGE), as well as the STAG. SAGE has the responsibility of advising 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 the SAGE also span a range of constituencies, including members of the research and vaccine development communities; operational research experts; epidemiologists; and programme managers. Similarly as for the STAG, it is also possible to inform the SAGE through collaborating 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 and disseminates them through the Partnership's seven Working Groups. These groups are already collaborating together to evaluate and demonstrate new technologies, as in the case of the DOTS Expansion and New Diagnostics Working Groups. The Stop TB Secretariat supports the 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 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 medicines (FDCs) free of charge was one of the factors that influenced the policy change to FDCs in countries purchasing from the GDF. It may be possible to leverage additional funding for strengthening healthcare systems such as through the Global Fund to Fight AIDS, TB and malaria.

- 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 underway. For example, an initiative to update the national essential medicines list (EML) can be an incentive to update the TB programme standard treatment guidelines (STGs) first 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 previous ones. Policy makers may be reluctant to invest in the transition costs associated with adopting a new TB control 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.

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 has been well documented and compiled both by the Stop TB Partnership and WHO, and is understood and accepted at the global level. Epidemiological evidence and information on the improved efficacy and performance of new tools is 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 quality care, user needs and perspectives, and 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.

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 not only evidence of the *efficacy* of a new tool under the conditions of controlled clinical trials, but also evidence of the *effectiveness* of a new tool under actual use conditions. To achieve this requires early engagement with NTP in high burden countries. In the case of new medicines, it is anticipated that they will be introduced as combinations of new medicines, rather than single entities to be combined 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 that will have to be considered, including:

- 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, 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 health centers become engaged with the diagnosis of TB); and
- Required knowledge and skill levels (for performing tests, handling medicines and vaccines, etc.) and implications for staff retraining, 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 (multiple dosing and the availability of fixed dose combination products, patient kits; the duration of therapy, and the need for dose adjustment for weight in different age groups and between sexes);
- Potential for cross-resistance with other TB drugs;
- Likelihood of resistance developing;
- Drug interactions with commonly used medicines, including other TB drugs, 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);

- Contra-indications with common conditions (e.g. patients taking antiretrovirals, people with glucose-6-phosphate dehydrogenase deficiency, diabetes, alcoholism, or those who are malnourished), and additional need for laboratory investigations to exclude contra-indications;

- Use in special groups, including children, infants, and pregnant women; and

- Need for prepackaging.

For diagnostics, considerations include:

- Acceptability to patients, including factors that contribute to patient adherence in diagnostic pathway;

- Quality assurance requirements, including internal and external quality control programmes;

- Level of health system where the tool is to be used and potential coverage in public and private sectors;

- Human resource needs, including time taken to collect the sample, conduct the test, and skills needed to perform the test;

- Infrastructure, equipment and supply needs, including requirements to collect, store and process the sample; and

- Ease of the procedure, interpretation of test results, and quick turn around 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 have higher wastage rates; [11]

- Proper reconstitution of vaccine using 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); and

[11] See Annex 2. WHO. Vaccine Introduction Guidelines: Adding a vaccine to a national immunization program: decision and implementation. Geneva: World Health Organization; 2005, http://www.who.int/vaccines-documents

- 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;
- Providing a qualified recommendation, such as use of the tool only in certain circumstances; or
- Requesting further evidence of effectiveness.

Analysis of the Health Systems Environment and Capacity to Adopt, Introduce, and Implement the New Tool

This analysis requires understanding the different sectors of health systems, including the public, not-for-profit private, and for-profit sectors, because capacity differs both between sectors and between 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 hogher 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 drug sensitivity testing 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[12], 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.

[12] 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 TB medicines. Rational Pharmaceutical Management Plus Program. ***Pharmaceutical Management for Tuberculosis: Assessment Manual***. Edited by A. Zagorskiy, C. Owunna, and T. Moore. Submitted to the United States Agency for International Development by the Rational Pharmaceutial Management Plus Program. Arlington, VA: Management Sciences for Health, 2005.

Box 4 contains some of the tool specific considerations:

Box 4: General resource considerations for medicines, diagnostics, and vaccines

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 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 (ADRs)
- Provide support to patients to adhere to and complete treatment
- Store products appropriately
- Minimize losses and theft
- Carry out pharmacovigilance

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 Expanded Program on Immunization (EPI)
- Incorporation of vaccine into healthcare delivery systems for adolescents and adults
- Adherence to safe injection practices
- The ratio of coverage versus vaccine wastage in existing programs
- Adequacy and availability of cold chain storage
- Adequacy of surveillance and response systems post vaccine administration (especially in decentralized health systems)

Development and Endorsement of the New Recommendations and Policies and Wide Dissemination

Once the analyses of needs and evidence for change; of the risks and benefits of the new tool; and of the capacity of health systems are completed, the next step is to develop new recommendations at the global level and 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 of the STAG and the 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 Web, previously scheduled meetings and training programmes, rather than wait until the development or revision of the full set of new *programme guidelines*. In the case of the WHO Department of Vaccines and Immunization, 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 anew 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 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 for TB into their decision over whether or not to develop a set of new policy 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 organisations, donors, 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 TFR and the Country Coordinating Mechanisms (CCMs) 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.

INTRODUCTION AND IMPLEMENTATION OF NEW TOOLS FOR TB

This section focuses on the key considerations for integrating new technologies, including medicines, diagnostics and vaccines with the other recommendations for TB control to NTPs. The implementation of policy changes in both the public and the private sector, including not-for-profit institutions such as faith-based or secular NGOs and the for-profit sector are addressed. The key components, included in Box 5, can be divided into technical considerations, operational considerations, and monitoring and evaluation.

Box 5. Key considerations for implementing policies for new technologies for TB control

1. **Technical considerations**
- Registration of products and revision of regulations
- Development/updating of program guidelines, the essential medicines list (EML), 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 (ACSM) targeting the community

2. **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)

3. **Monitoring and evaluation**

The technical considerations incorporate the activities related to the regulation and the 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. The operational considerations include the activities related to procurement and supply management, which ensure that the tools are available at the service delivery points.

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

Technical Considerations

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 the sale of a product. The key questions to ask during the policy change process are outlined in Box 6.

Box 6: Key product regulation questions

1. What is the registration status of the new products for TB control in the country?
2. If the program is donor funded and if the program 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?

Regulation is a fundamental step required by countries before they allow a new product to enter the country and be integrated into the health care system. In most countries, the product registration process includes submission of a dossier with 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 fixed-dose combinations (FDC) 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 appropriate effectiveness studies have been done by manufacturers and/or promoters like the product development partnerships (PDPs), 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 requirement and process for registering diagnostic products varies from country to country, and there may be not be a regulatory framework in place in many developing countries. Moreover, expertise to evaluate the submitted dossiers may not be available.

Depending on how often the registration committee in the country meets and 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 time taken to conduct site visits contribute to delays. For example, in one country, registration of anti-TB drug FDCs to support a policy change to FDCs took ten 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 Global Drug Facility now requires approved manufacturers to keep dossiers of documents on file for rapid transmittal to national regulatory authorities. Efforts are underway to harmonize regulatory requirements

for new TB control products as country-specific requirements, for example, for efficacy and stability studies, can significantly slow down the process of policy implementation.
To address constraints faced by insufficient capacity to conduct dossier evaluation or manage the registration work load, 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 countries participating in the International Conference on Harmonization (ICH), may be a more efficient way to accelerate and shorten the registration process. Although issuing a waiver for products procured under a Global Drug Facility grant can be effective as a temporary measure, this is not a long-term solution. Strengthening the national regulatory authority to facilitate national registration process for new TB control products will require significant technical assistance, including streamlining the process, developing and implementing appropriate standard operating procedures, staff training, and 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 the PDPs to initiate the process of registering products early.

The Global Training Network on Vaccine Quality (GTN/VQ) is an example of a global initiative to improve vaccine regulation and production through a series of nine training courses conducted by 16 training centers in three different languages. The GTN/VQ provides national regulatory authorities, national quality control laboratories, and vaccine producers training on Good manufacturing Practices (GMP), laboratory quality systems (LQS), quality control testing, regulation for vaccines, surveillance for adverse events following immunization
(http://www.who.int/immunization_standards/vaccine_quality/gtn_index/en/index.html).

As noted earlier, many countries have minimal or no regulatory oversight over diagnostics. This deficiency calls for investments in strengthening 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 staff who can prescribe and dispense medicines, administer vaccines, or perform diagnostic testing is 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 infectious conditions or its inappropriate use, as a measure to slow down the development of resistance, but commitment is needed to enforce this.

Revision of Programme Guidelines, Essential Medicine and Supply Lists, 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 7.

Box 7: Key questions on programme guidelines, essential medicines, vaccines, 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 healthcare workers?
   - National Tuberculosis treatment guidelines
   - National HIV treatment guidelines, for example, for prevention and treatment of opportunistic infections, and HIV/TB co-infection
   - National Tuberculosis operational manual
   - National operational manual for management of drug-resistant tuberculosis
   - 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?

All programme guidelines, including national standard treatment guidelines (STGs), 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 medicines, diagnostics and vaccines in the national EML and essential medical device list (EMDL), 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 5-year plan and national comprehensive immunization multi-year plans, TB diagnosis and treatment guidelines and 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 standard operating procedures 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, 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 the ACSM strategies to ensure that the same messages are communicated to health care workers, community partners providing care and the public, especially if treatment schedules are different. The revision of guidelines and associated materials to include new technologies can often be the opportunity to incorporate other changes, for example, to support DOTS expansion in country. It is important that additional changes to be made to the documents 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 government forms for TB 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 along with availability of product will determine the schedule for disseminating guidelines and training health workers and community partners.

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

Dissemination of Guidelines and Training of Health Workers and Community Partners Providing TB Care

The dissemination of the revised guidelines to the programme managers and the front line TB workers in both the public and private sectors will need to be accompanied by sensitization and/or training of the health care workers in both sectors and also of the 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 drug susceptibility testing, 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 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 standard operating procedures, particularly where tools are being introduced in phases in the country. It is important that training and sensitization activities of healthcare 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 have a central or regional pool of trainers 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 can make 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 be a challenge. It is important to ensure that adequate notice of one month or longer is given for the training to the facility management team 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 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; and 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 (ISTC). Technical assistance may be needed for appropriate development of these training materials or the adaptation of materials developed 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 TB vaccine in the context of their health system. Capacities need to be strengthened in the area of planning, management, monitoring and evaluation including the key technical areas of immunization operations such as logistics, vaccine supply and quality[13]. In-service training particularly needs to be strengthened at district level to ensure quality of immunization service delivery.

Some key questions to consider on the communication components are included in Box 8.

Box 8: Key questions on the communication components in implementing the new policy

1. How will the revised guidelines be disseminated within the public and private sector?
2. Which groups of health care workers and/or community partners in TB care 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 the ACSM 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 NTP?

[13] WHO/AFRO Vaccine Preventable Disease Unit. ***New Vaccine Introduction in the Africa Region: Lessons learnt***. Harare 2004. Harare, Zimbabwe: WHO Regional Office for Africa, 2004.

Advocacy, Communication and Social Mobilization (ACSM) Targeting the Affected Community

Advocacy, communication and social mobilization (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/training of health workers and community partners in TB care to ensure that everyone is receiving the same messages. Issues of 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 is also true for vaccines because negative perceptions about immunization arising out of rumours, adverse events following immunizations (AEFIs), or cultural and religious beliefs must be addressed. Communication skills 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 the Global Alliance for Vaccines and Immunization[15].

Operational Considerations

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 if the new TB control product will be a replacement for any medicines, vaccines, or diagnostic tests currently in use or if it will be an addition to the currently recommended tools. For example, a country may change its policy to introduce a new drug 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 policy change to introduce a new first-line product for TB 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 TB vaccines may provide either an addition or 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 they have significant stocks of "old" medicines, vaccines or diagnostics in the system. Countries with large public sector TB programmes typically hold between nine to 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 TB control tools from the system are listed in Box 9.

[14] ACSM Subgroup at Country Level. ***Advocacy, Communication and Social Mobilization to Fight TB: a 10-year Framework for Action***. WHO/HTN/STB/2006.37. WHO/Stop TB Partnership. WHO: 2006.
[15] Global Alliance for Vaccines and Immunization (GAVI). 2001. ***Advocacy for immunization : how to generate and maintain support for vaccination programs.*** Produced by the Bill and Melinda Gates Children's Vaccine Program at PATH (Program for Appropriate Technology in Health). Seattle: GAVI

Box 9: Key questions in developing a phase-out plan for removing the current TB control products 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 one 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?

If a phase out plan is necessary, the first step is to map out which of the TB control tools that are 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, a small quantity 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 unexpected delay in implementing the policy change due to this extended lead time. In the transitional stage of policy implementation it is better to be left with 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 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 phasing out tools, whether in the public or the private sectors.

Management of Supply of the New Tools

Availability in the Public and Private Sectors

A decision that is critical for procurement planning is to decide if the public sector will procure and supply the new products to both the public and the private sector and to develop budgets and quantify needs accordingly. In some countries, the public sector TB programme already supplies many TB control products to the not-for-profit sector. As countries move forward with strategies to strengthen NTPs and expand DOTS, including implementing

public-private approaches[16], the private sector may become increasingly important in rolling out new technologies. For example, an NTP may decide that a new rapid TB diagnostic kit should be supplied by the public sector to non-governmental HIV voluntary counselling and testing (VCT) 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 Rollout Plan

There are two approaches to implementing a new policy that involves the introduction of new TB control tools, either a phased approach or through an immediate nationwide rollout. 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 new rapid culture and drug susceptibility testing for referral laboratories may not need to be phased in. Similarly, a new medicine with the potential to significantly decrease mortality due to 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 TB programmes and Ministries of Health to evaluate and adjust their approaches as needed. The ***Operational Guide for National Tuberculosis Control Programmes on the Introduction and Use of Fixed-dose Combination Drugs*** is a useful guide for developing a phase-in plan[17].

Phased implementation could be geographical, with some areas or districts with high TB caseloads selected for early implementation. Alternatively, it could take place according to health system level, with some levels of the health system selected for early implementation. For example, the 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, 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.

[16] Uplekar M, Lonnroth K (for the Stop TB Partnership Subgroup on PPM for DOTS Expansion). ***Engaging All Health Care Providers in TB Control. Guidance on Implementing Public-Private Mix Approaches***. WHO/HTM/TB/2006.360. Geneva, Switzerland: World Health Organization, 2006.

[17] ***Operational Guide for National Tuberculosis Control Programmes on the Introduction and Use of Fixed-dose Combination Drugs***. WHO/CDS/TB/2002.308 and WHO/EDM/PAR/2002.6. Geneva: World Health Organization, 2002

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

The development of specific tool implementation guides, such as the WHO Operational Guide for National Tuberculosis Programmes on the *Introduction and Use of Fixed-Dose Combination Drugs*[18] is a valuable resource for helping countries develop their country-specific phasing in or nationwide rollout 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 for TB control 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 might 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 a TB vaccine.

For TB treatment, sufficient supplies of new anti-TB medicines must be correctly quantified so that every TB 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 TB control products will be financed—through the Ministry of Health, through donors, and others—to ascertain what 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 10.

[18] ***Operational Guide for National Tuberculosis Control Programmes on the Introduction and Use of Fixed-dose Combination Drugs***. WHO/CDS/TB/2002.308 and WHO/EDM/PAR/2002.6. Geneva: World Health Organization, 2002

Box 10. Key questions to consider when forecasting the potential demand for new TB control 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 piloted 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?

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 include the private sector as well? 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 TB control tools, data on past 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 treatment seeking behaviour and reasonable 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 the nationwide implementation. If the new tool is replacing an existing product, initial forecasts can be based on the consumption of previously used first- and second-line treatments[19], diagnostics and vaccines.

It is important to consider how the introduction of new TB technologies may impact the use of other existing tools. For example, a more sensitive diagnostic test (resulting in enhance

[19] Methodologies for quantifying anti-TB medicines are outlined in Rational Pharmaceutical Management Plus Program. ***Managing Pharmaceuticals and Commodities for Tuberculosis: A Guide for National Tuberculosis Programs***. Submitted to the United States Agency for International Development by the Rational Pharmaceutical Management Plus Program. Arlington, VA: Management Sciences for Health, 2005

case detection) may increase the need for anti-TB medicines. New TB 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 glycemic control may increase the need for reagents and supplies to support blood glucose screening in TB-infected patients. Also 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 (ART) 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, in addition to the NTP team and central medical stores personnel, and also 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 providing technical assistance to compile forecasts particularly before applications are made to the GFATM, 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 to quantify needs for both anti-TB drugs and for laboratory kits it procures. GDF provides technical assistance to countries to quantify 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 right TB control tools, in the right 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 11.

Box 11. Key questions on procurement of the new TB control 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 TB control 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? (GDF and GLF, PAHO Strategic Fund, PEPFAR-type, etc)
8. What is the average lead time (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 TB tool?
10. Is there a need for special packaging specifications?

The systems for procuring TB tools for national programmes vary considerably. In some countries procurement of TB tools is centralized, and is done either for TB medicines alone or is integrated with procurement of essential medicines; in others the procurement of TB products 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 national TB programme selects products and quantifies 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 TB control products. National immunization programmes may purchase their vaccines from UNICEF[20] 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 to synchronize the availability of funding to meet the requirements of the procurement cycle. For procurement using GFATM or GAVI funds, countries are required to adhere to GFATM & 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 Good Manufacturing Practices [GMP]). Second-line medicines procurement with GFATM funds can be done only via the GLC). Therefore, it is essential that timely planning, communication and required lead times are adhered to.

Given the complexity of procurement requirements and systems in use, it is important to establish a communication mechanism that includes all the key stakeholders who will contribute to managing the procurement of the new TB control 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 for the new TB technologies that considers the distribution strategy (including the public and private sectors as appropriate) to support the implementation of the new policy. The procurement plan must 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/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 product quality as well as to monitor supplier performance and for resolving any identified problems. Some new TB 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.

[20] 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.

A useful resource for procuring anti-TB medicines is *Managing Pharmaceuticals and Commodities for Tuberculosis: A Guide for National Tuberculosis Programs.*[21]

The Global Drug Facility (GDF) and the Green Light Committee (GLC)

The GDF and GLC play a unique role in the expansion of access to, and the availability of, high-quality TB medicines to facilitate global DOTS Expansion and enhancement. The GDF is housed in WHO headquarters in Geneva and managed by a small team at the Stop TB Partnership secretariat. The GDF has been a primary source of first-line anti-TB medicines since it was established in 2001 for countries that meet specific requirements set out by the GDF, including the use of effective treatment protocols.

The GDF works to:

- Link demand for quality 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 medicines management;
- Link grants to TB programme performance; and
- Stimulate industry to produce sufficient quality assured, internationally recommended anti-TB medicines at the most competitive process.

In addition to medicines, the GDF also supplies diagnostic kits to TB programmes and later in 2006 will be a source of second-line anti-TB medicines when the GDF and the Green Light Committee (GLC) converge their procurement activities.

The GLC was established in 2000 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 meet the standards outlined in the Guidelines for Establishing DOTS-Plus Pilot Projects for the Management of MDR-TB[22]. The GLC is tasked with reviewing applications from potential DOTS-Plus pilot projects and advising WHO/DOTS Plus on which projects should receive the specially priced, second-line TB medicines[23].

Both the GDF and the GLC provide extensive technical assistance to countries in managing TB control 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 anti-TB

[21] Rational Pharmaceutical Management Plus Program. ***Managing Pharmaceuticals and Commodities for Tuberculosis: A Guide for National Tuberculosis Programs***. Submitted to the United States Agency for International Development by the Rational Pharmaceutical Management Plus Program. Arlington, VA: Management Sciences for Health, 2005

[22] World Health Organisation. ***Guidelines for establishing DOTS-Plus pilot projects*** (WHO/CDS/TB/2000.279) Geneva, Switzerland: World Health Organization 2006

[23] ***Instructions for Applying to the Green Light Committee for Access to Second-line Anti-Tuberculosis Drugs*** (WHO/HTM/TB/2006.369). Available at http://whqlibdoc.who.int/hq/2006/WHO_HTM_TB_2006.369_eng.pdf [Accessed October 27, 2006]

medicines to FDCs and so is well positioned to assist countries to introduce new TB control medicines and diagnostics.

The GDF's role with respect to improved or new tools for TB will be to assure the continuous supply of quality products through excellent procurement practices, including competitive tendering to obtain the lowest possible prices, while ensuring 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 the STAG and WHO's Department for Policy and Medicines Standards (PSM) on quality assurance. If manufacturers or other entities approach the GDF with requests for adding products, independently of the STAG and WHO/PSM, the GDF will generally seek advice from the WHO Stop TB and PSM departments. While historically the GDF has only focused on TB medicines procurement, it 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 the 12 member staff, which meets every two weeks, although the Executive Secretary and Coordinating Board of the Stop TB Partnership play important roles when it comes to decisions with resource implications or when significant changes in procedures are being considered. An additional role that the GDF plays is in providing short-term forecasts (three months) to manufacturers, which could be of limited usefulness for the suppliers of new TB tools. If GDF is to expand its role to include the supply of new TB tools, it will need to 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 have an important role to play in terms of supporting prequalification of new anti-TB 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 at facilitating access to anti-TB medicines of acceptable quality through the assessment of products and 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 TB medicines eligible for prequalification; and
- Identification of political support for the TB Prequalification Project.

In order to catalyse 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 PIC/S and ICH 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; and
- Training workshops for manufacturers participating in the prequalification project.

Distribution

The steps in the distribution of new TB control 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, TB control medicines, diagnostics and vaccines may all move through different distribution channels. Some new TB 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 that require 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 12.

Box 12. Key questions for distribution of new TB control 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 get to 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?

The distribution strategy should be developed as part of the phase in or rollout 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 TB control 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 two to four weeks or more. In one country, it took two to three months to move 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 TB control tools are managed appropriately to prevent stock-outs and to minimize wastage due to expiry[24]. Upgrading the storage facilities, particularly in peripheral 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[25]. Some key questions to consider are included in Box 12.

Box 13. Key questions for inventory management of new TB control 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?

The introduction of new TB technologies into health facilities or departments that have been long under-resourced, such as the peripheral level laboratories may be an opportunity to integrate DOTS Expansion with overall health system strengthening. Joint plans may need to be 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 kept and updated regularly, and that physical checks are regularly performed. In addition, the store may need to be adequately secured to prevent theft of high value items. It will be important to ensure that products do not expire before they are used and 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.

[24] Useful resources on inventory management include

- Rational Pharmaceutical Management Plus Program. ***Managing Pharmaceuticals and Commodities for Tuberculosis: A Guide for National Tuberculosis Programs***. Submitted to the United States Agency for International Development by the Rational Pharmaceutical Management Plus Program. Arlington, VA: Management Sciences for Health, 2005
- ***Guidelines for the Storage of Essential Medicines and Other Health Commodities*** JSI/DELIVER/WHO/UNICEF 2003)

[25] Vaccine volume calculator. An aid for the introduction of new vaccines (WHO/V&B/01.24) Available from http://www.who.int/vaccines-documents/excel/Volume_calculator_December_2004.xls. [Accessed October 27, 2006]

Ensuring Product and Service Quality and Safety

Ensuring product and service quality and safe use of the new TB technologies is a shared responsibility and will require close collaboration among manufacturers, suppliers, health regulatory authorities, procurement agencies, supply chain operators, providers and people with TB infection. Key questions for product quality assurance and pharmacovigilance are included in Box 14.

Box 14. Key questions for quality assurance and pharmacovigilance

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 procedures 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 new TB control products?
6. Is there a program to promote safe injection practice?

Monitoring Product and Service Quality

Integrating product quality surveillance at all levels of the health system can assure that the new TB control medicines, vaccines and diagnostic devices and reagents 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[26]. While many countries have functional systems for assessing the quality of products at the time of registration, systems for monitoring quality of products in the marketplace are generally weak. Building capacity in existing structures that collect similar information for other essential medicines, 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 systems for ensuring the reliability of laboratory performance. In reality, most laboratories will require considerable investment in resources to improve infrastructure, refurbish equipment, establish appropriate operating procedures, and improve management capacity to ensure not only quality performance of diagnostic testing but also the safe use and disposal of diagnostic reagents, consumables, and other materials.

[26] U.S. Pharmacopeia in collaboration with other partners. ***Ensuring the Quality of Medicines in Low-Income Countries. An Operational Guide***. Draft for field testing. Rockville, MD: The United states Pharmacopeial Convention, 2005.

Clinical Event Monitoring (Pharmacovigilance)

Mechanisms for surveillance of adverse events associated with the use of new TB control 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 TB 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 analyzing reports centrally. The introduction of the new TB tools will be an excellent opportunity to strengthen existing but weak systems or develop one where there it is lacking[27]. Effective communication 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 with others.

Monitoring and Evaluation

Monitoring and evaluation (M&E) is an essential part of the policy implementation process and should be ongoing throughout planning and implementation. Planning for M&E 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. M&E is particularly important for new TB control medicines, vaccines and diagnostic tools because health care workers have little experience with their use.

Some key questions related to the development of M&E systems are listed in Box 15.

Box 15. Key questions for monitoring and evaluation

1. Is current M&E system capable of tracking implementation process? What elements/indicators/ procedures are lacking?
2. Is there an M&E 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 rollout be evaluated?
   - Internal versus external evaluation?
   - Process versus outcomes evaluation?

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 Survey (DHS) and health management information system (HMIS) data, or through special studies. The decision on which information source(s) to use depends

[27] ***The Safety of Medicines in Public Health Programmes: Pharmacovigilance an essential tool***. Geneva: WHO, 2006.

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 surveys are nationally representative household surveys and 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*: These may provide information on management of supplies of medicines, vaccines and diagnostic kits and supplies

- *TB 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 adverse events following vaccination.

- *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 underway to develop a standard framework for the development of a range of M&E guidelines and tools, including a summary of agreed upon illustrative core indicators for TB, and references to more detailed indicator manuals on specific programme areas[28] 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.

[28] ***Monitoring and Evaluation Toolkit: HIV/AIDS, Tuberculosis and Malaria. Draft 14/01/2004***. WHO, UNAIDS, The Global Fund to Fight AIDS, Tuberculosis and Malaria, USAID, CDC, UNICEF and the World Bank. 2004

THE WAY FORWARD

The timely and appropriate adoption, introduction, and implementation on 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;
- Strengthen frameworks and processes for product regulation and registration, particularly for diagnostics;
- Strengthen pharmaceutical management, and laboratory infrastructure and services;
- Increase capacity to conduct operations research to guide adoption, introduction and implementation;
- Address human resource constraints; and
- Mobilize adequate financial resources.

Stop TB Partnership members should work collaboratively 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 advocacy, communication, and social mobilization; and
- Monitoring and evaluation system, including indicators, for adoption, introduction and implementation of new TB tools.

ANNEX 1: WHAT IS IN THE TB PIPELINE (NOVEMBER 2006)?

TO BE DISTRIBUTED AT THE COORDINATING BOARD MEETING

ANNEX 2: KEY ACTIONS FOR NEW ANTI-TB DRUGS (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 the 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 WHO's Strategy and Technical Advisory Group for Tuberculosis (STAG) and the need for additional studies identified			
	Analyze 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 and study results and decide to develop a new policy to recommend adoption of the new tool (or not)			
	Develop, endorse and communicate the new policy			
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			
	Submit an application to add the new tool to WHO EML; communicate decision to country-level			
	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 to register 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			
Manufacturing and supply	Develop initial global forecasts			
	Initiate large scale production of API and finished product (single drug and/or FDC)			

Issues	Key Actions	Technical/ Operational Lead	Estimated Timeline	Resource Requirements
	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 operations research; assist countries to secure budgets, implement and disseminate research			
	Determine approaches to assist countries to strengthen post marketing surveillance systems for product quality, adverse drug reactions and emerging resistance			

Country Policy Development

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 the 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 new anti-TB medicine development			
	Assemble and analyze 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, implement and present results to the committee/working group			
	Review national regulations and policies to identify potential barriers to implementation			
	Analyze the capacity of health care system to appropriately manage and use the new tool; key considerations may include capacity to: ▪ Diagnose ▪ Perform essential laboratory monitoring ▪ Provide the appropriate quality of medical care ▪ Detect contraindications and adverse drug reactions ▪ Provide support to patients to adhere and complete treatment ▪ Store products appropriately ▪ Minimize losses and theft			
	Identify opportunities for leveraging funding for the policy change and to introduce other TB 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 and decide to develop a new policy to adopt the new tool or treatment strategy (or not)			
	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 stockouts			
	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— ▪ 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 rollout ▪ 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 if introduction at a site is successful			
Financing	Develop multi-year budget for— ▪ 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 ADR, medicines to manage side effects			
	Develop budget for transition including costs for— ▪ 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 quality assurance testing for new products ▪ Addressing infrastructure needs ▪ Withdrawal and incineration of obsolete products ▪ Operations research and ongoing monitoring and evaluation			
	Map out potential resources at national level; evaluate current spending and redirect funds if necessary			

Issues	Key Actions	Technical/ Operational Lead	Estimated Timeline	Resource Requirements
	Determine the funding gap			
	Map out potential international resources e.g. GFATM, GDF, multilateral and bilateral donors, foundations, and develop a funding strategy			
	Develop/revise proposals for GFATM, GDF and other donors			
	Secure commitments from MoH 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			
Revise programme guidelines, EML and reporting and recording forms	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 EML; publish revised EML or addendum			
	Revise recording and reporting forms; field test, print and disseminate			
Training of health workers and community partners	Develop training strategy, budget and plan; coordinate with dissemination of guidelines, implementation of BCC/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 on-going training			
ACSM strategies	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 new tool			
Phase out medicines being replaced	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/roll out of the new medicine			
	Implement phase out plan; coordinate with phased or nationwide implementation and adjust timeline as needed.			
	Withdraw obsolete tool and redistribute or dispose of as appropriate.			
Forecasting and quantification	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			

Issues	Key Actions	Technical/ Operational Lead	Estimated Timeline	Resource Requirements
	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)	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			
Procurement	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 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			
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			
	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			
Health system strengthening	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— ▪ 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 stockouts or wastage ▪ Promote the rational use of medicines			
	Integrate capacity building activities to support the availability and appropriate use of the new anti-TB drug with other initiatives to strengthen health systems			

Issues	Key Actions	Technical/ Operational Lead	Estimated Timeline	Resource Requirements
	Synchronize timing of capacity building activities with the phased or nationwide implementation plan to ensure sites meet criteria for start up			
Quality and safety	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			
	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 programme as an interim measure			
	Develop a plan for ongoing surveillance to monitor for emergence of resistance to the new anti-TB medicine			
Monitoring and Evaluation	Explore the use of pilot sites and operations research to guide the appropriate implementation of the policy to introduce the new anti-TB drug.			
	Identify standards to determine if introduction at a site is successful			
	Develop a monitoring plan to collect, analyze 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 learned 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)

Global Adoption and New Policy Development

Issues	Key Actions	Technical/ Operational Lead	Estimated Timeline	Resource Requirements
Global policy development	Engage key stakeholders and facilitate the discussion at global level on the inadequacies of the 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 disease			
	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 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 WHO's Strategic Technical Advisory Group (STAG) and the need for additional studies identified			
	Analyze 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 recommendations, Stop TB Partnership develops guidelines			
	Develop, endorse and communicate the new recommendations and guidelines/standards, covering: • 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 o Proficiency testing o Rechecking o Supervision o Internal QC 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 WHO Essential List of Laboratory Equipment and Supplies for TB (if such exists); communicate decision to country-level			
	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 to register the new product			
	Continue efforts to develop framework for 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			
	Engage GDF to determine if improved or new tools will be included in procurement lists			
Financing	Assist countries to identify potential sources of funding; provide technical assistance to capacitate countries to develop 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 product quality, adverse drug reactions and emerging resistance			

Country Policy Development

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 improved/new TB diagnostics; identify approaches to enable ongoing scanning for products and treatment strategies that may impact NTP programming			
	Engage decision makers and facilitate the 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 TB strategy			
	Ensure participation of National Reference Lab 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 analyze available information on the risks and benefits of the improved/new lab 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, 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			
	Analyze the capacity of health care system to appropriately manage and use the new tool; key considerations may include: • 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 • Quality Assurance 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			

Issues	Key Actions	Technical/ Operational Lead	Estimated Timeline	Resource Requirements
	Identify opportunities for leveraging funding for the policy change and to introduce other TB 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 to develop a new policy to adopt the improved/new TB diagnostic (or not)			
	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— • 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 if introduction at a site is successful			
Financing	Develop multi-year budget for— • Equipment purchase • Equipment maintenance and operating costs • Consumable(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 • Quality Assurance 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)			
	Develop budget for transition including costs for— • Establishing and convening working groups • Developing and disseminating new diagnostic protocols • Revising and printing new operational manuals, tools and reporting and recording forms			

Issues	Key Actions	Technical/ Operational Lead	Estimated Timeline	Resource Requirements
	• Preparing training materials and ACSM materials • Training laboratory providers and supervisors • Establishing quality assurance testing for new tools (internal and external QA) • Addressing infrastructure needs • Withdrawal and incineration of obsolete tools • Proper disposal of used poducts (i.e. specimen containers, slides, dipsticks) • Operations 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. GFATM, GDF, multilateral and bilateral donors, foundations, and develop a funding strategy			
	Develop/revise proposals for GFATM, 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 MoH 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			
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 EML; publish revised EML or addendum			
	Revise recording and reporting forms; field test, print and disseminate			
Training of laboratory providers	Develop training strategy, budget and plan; coordinate with dissemination of new SOPs, implementation of ACSM strategies and delivery of supplies			
	Develop training curriculum and test training materials; field test training materials; adapt tools for supportive supervision to incorporate the new guidelines • Test performance (microscopy, culture, DST) • Equipment operation and maintenance • Quality Assurance (internal and external) • Laboratory management, including planning and budgeting			
	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 on-going training			

Issues	Key Actions	Technical/ Operational Lead	Estimated Timeline	Resource Requirements
ACSM strategies	Develop and budget ACSM strategies; coordinate implementation with dissemination of guidelines and training			
	Develop and implement ongoing ACSM strategies to support rational use of new tool			
Phase out laboratory equipment and supplies being replaced	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/roll out of the new medicine			
	Implement phase out plan; coordinate with phased or nationwide implementation and adjust timeline as needed.			
	Withdraw obsolete tool and redistribute or dispose of as appropriate.			
Forecasting and quantification	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			
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 quality assurance 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			
Distribution	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			
	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			

Issues	Key Actions	Technical/ Operational Lead	Estimated Timeline	Resource Requirements
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— ▪ 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 stockouts 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			
Quality and safety	Adhere to registration requirements to assure safety, efficacy and quality of the new TB 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 operations research to guide the appropriate implementation of the policy to introduce the improved and new TB diagnostic tools.			
	Identify standards to determine if introduction and implementation at a site is successful			
	Develop a monitoring plan to collect, analyze 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 learned 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 TB diagnostic			

ANNEX 4: KEY ACTIONS FOR NEW ANTI-TB VACCINES (ILLUSTRATIVE)

Global Adoption and New Policy Development

Issues	Key Actions	Technical/ Operational Lead	Estimated Timeline	Resource Requirements
Development and/or revision of Global recommendations	Engage key stakeholders and facilitate the discussion at global level on the need for the new 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 new TB vaccine			
	Assemble and submit information on the harms and benefits of the new tool to WHO).			
	Scientific and technical guidance developed by WHO's Strategy Advisory Group of Experts (SAGE)			
	Analyze 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			
	Review scientific and technical guidance and study results and decide to develop a new policy to recommend adoption of the new vaccine (or not). Position paper on new TB vaccine to be developed			
	Develop, endorse and communicate the new recommendation or revised strategy			
International guidelines and materials	Determine costs and responsibilities for updating and dissemination of international /recommendations/ guidelines and associated technical materials and tools			
	Update and print (written, CD, website) guidelines/recommendations; develop, budget and implement a strategy to communicate recommendations			
	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 to register the new tool			
WHO prequalification	Initiate process for WHO prequalification			
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			
	Engage UNICEF for inclusion of new tool on procurement list			
Financing	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 adverse effects following immunization			

Country Policy Development

Issues	Key Actions	Technical/ Operational Lead	Estimated Timeline	Resource Requirements
Country policy development	Establish Interagency Coordination Committees (ICC) or Working Groups for TB vaccines as a strategy to develop strong partnerships within country and with those outside the country ▪ Assemble data on TB disease burden to aid decision makers to introduce TB vaccine ▪ Determine options to phase in the pre-exposure TB vaccine into EPI programme ▪ Determine priority target population for post-exposure TB vaccine and how it may impact NTP programming			
	▪ Determine the costs and benefits of new TB vaccine and how it may impact national health budget ▪ Determine immunization schedules and identify approaches for integrating the new TB vaccine in EPI ▪ Assess potential impact of new TB vaccine on EPI delivery structure ▪ Determine how new TB vaccine delivery? will be integrated in other health services ▪ Review competing priorities of other new vaccines being delivered ▪ Conduct interviews with key experts of public and private sector to assess possible barriers for introduction of new TB vaccines ▪ Determine the feasibility for introducing the new TB vaccine			
	In-country stakeholder consensus:- ▪ Inform policy makers and key stakeholders of global recommendations and potential of new TB vaccines ▪ Identify key partners and agencies to form a committee or working group to guide the introduction process			

Country Implementation

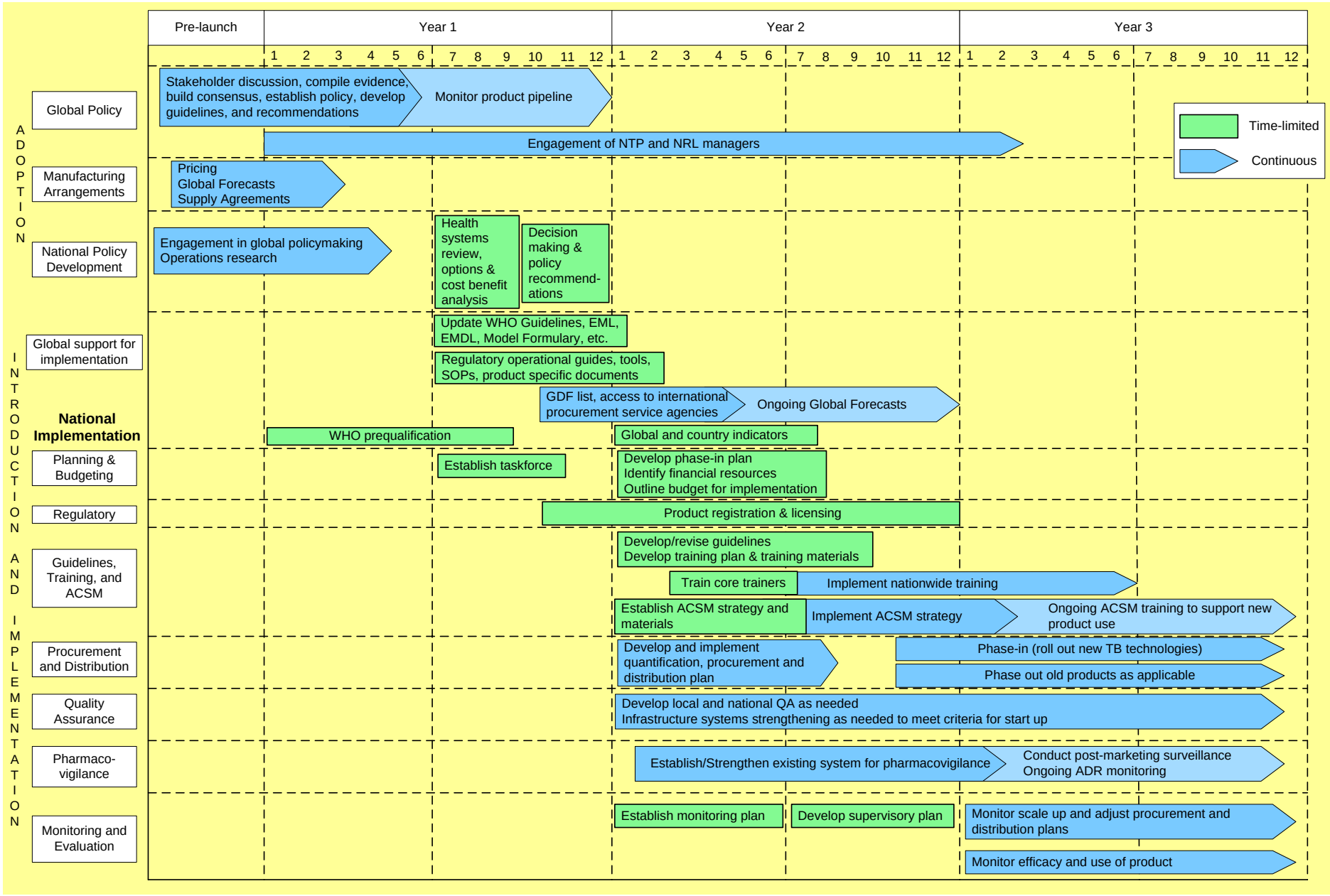
Issues	Key Actions	Technical/ Operational Lead	Estimated Timeline	Resource Requirements
Registration	Working group to monitor registration and regulation of vaccines			
	Register the new vaccine using a fast track mechanism if available			
Introduction Plan	▪ Develop introduction plan for new TB vaccine 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, etc. ▪ Establish dates for official ceremony and launch of vaccine for actual administration throughout the country ▪ Develop plan for monitoring adverse events following immunization (AEFI) ▪ Review existing practices for vaccine "bundling" policy ▪ Determine staffing plans as needed at all levels (EPI, NTP, etc)			
	▪ 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 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, reporting and recording forms ▪ Review injection safety policy at all levels of health system ▪ Develop visual aids and posters on injection safety			
Financing	External sources of financing ▪ Map out potential international resources: e.g. GAVI/Vaccine Fund, Vaccine Independence Initiative (VII), International Financial Facility for immunization (IFFIm), etc Develop/revise proposals for international funding agencies			
	Develop budget for programme costs:- ▪ Training at national, provincial and district level ▪ Developing and disseminating ACSM documents and Training materials ▪ Infrastructure such as cold chain, storage space, etc ▪ Operations research for ongoing monitoring and evaluation Transportation costs for extended delivery and surveillance			

Issues	Key Actions	Technical/ Operational Lead	Estimated Timeline	Resource Requirements
	Before introduction ▪ Revise national budget for allocation of new 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 it before introduction of vaccine ▪ Develop financial sustainability plan to accommodate long term provision of TB vaccines ▪ Develop/review mechanisms for financial accountability			
	After introduction ▪ Monitor trends in availability of funds at all levels ▪ Strengthen surveillance systems at national/regional level including surveillance specific personnel and training			
Training plan	For EPI Managers and NTP Managers ▪ 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 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, 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, AD syringes, safety boxes, etc) ▪ 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 counseling skills for new 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			
ACSM strategies	Advocacy strategies ▪ Invite multidisciplinary stakeholders to inform process and reach common agreement on new 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 new TB vaccine ▪ Increased education on efficacy and safety of TB vaccines			

Issues	Key Actions	Technical/ Operational Lead	Estimated Timeline	Resource Requirements
	Communication strategies ▪ Provide technical material on TB 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 TB vaccine ▪ Radio announcements in locally relevant language disseminated weeks before introduction of TB vaccine ▪ Celebrate TB vaccine health day or "village health day" Social Mobilization ▪ Perform situational analysis to determine psychosocial acceptance of vaccine ▪ Inform key community groups and social, religious and cultural leaders on benefits of TB vaccine ▪ Address problems with community demand for immunization including negative perceptions/experiences about immunization arising out of rumors, AEFIs or cultural and religious beliefs			
Forecasting and quantification	▪ Plan for demand of TB 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 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 TB vaccines (e.g. system readiness, staff recruitment, etc) and plan for phased supply of vaccines			
Procurement	Review available procurement mechanisms and analyze donor and/or government requirements and restrictions for the procurement			
	Ascertain the lead time for the tools and 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 quality assurance standards and verification methods			
	Determine procurement method and develop a procurement plan; set procurement calendar			
	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			
Distribution	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	Integrate capacity building activities to support the availability and appreciate use of new TB vaccine			

Issues	Key Actions	Technical/ Operational Lead	Estimated Timeline	Resource Requirements
strengthening	Assess need for strengthening health systems in lieu of new TB vaccine introduction (e.g. cold chain, reporting mechanisms, safe injection practices, monitoring and evaluation, etc)			
	Storage and cold-chain capacity and readiness ▪ Determine how new TB 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 Vaccine Logistics & Management ▪ Ensure adequate amount of auto-disable 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 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 (MDVP) and vaccine vial monitors (VVM)			
Quality and safety	Adhere to registration requirements to assure safety, efficacy and quality of new TB vaccine			
	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			
Vaccine Surveillance	▪ 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 learned from introduction of vaccine and successful strategies			
	Cohort studies to assess impact of vaccine on disease incidence			
	At all facility levels ▪ 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)



ANNEX 6: FURTHER READINGS
DRAFT

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