Managing Pharmaceuticals and Commodities for Tuberculosis

A Guide for National Tuberculosis Programs

Revised August 2008

USAID FROM THE AMERICAN PEOPLE

MSH SPS Strengthening Pharmaceutical Systems

MSH MANAGEMENT SCIENCES for HEALTH

RPM Plus | Rational Pharmaceutical Management Plus

Managing Pharmaceuticals and Commodities for Tuberculosis

A Guide for National Tuberculosis Programs

Revised August 2008

USAID FROM THE AMERICAN PEOPLE

MSH SPS Strengthening Pharmaceutical Systems

MSH MANAGEMENT SCIENCES for HEALTH
RPM Plus | Rational Pharmaceutical Management Plus

This report was made possible through support provided by the U.S. Agency for International Development, under the terms of cooperative agreement number HRN-A-00-00-00016-00. The opinions expressed herein are those of the authors and do not necessarily reflect the views of the U.S. Agency for International Development.

About RPM Plus

The Rational Pharmaceutical Management Plus (RPM Plus) Program, funded by the U.S. Agency for International Development (cooperative agreement HRN-A-00-00-00016-00), works in more than 20 developing countries to provide technical assistance to strengthen drug and health commodity management systems. The program offers technical guidance and assists in strategy development and program implementation both in improving the availability of health commodities—pharmaceuticals, vaccines, supplies, and basic medical equipment—of assured quality for maternal and child health, HIV/AIDS, infectious diseases, and family planning and in promoting the appropriate use of health commodities in the public and private sectors.

Acknowledgments

Cover photos courtesy of www.stoptb.org
Cover photo, left: WHO/TB/Davenport
Cover photo, right: WHO/TB/Virot

This document was prepared by Edgar Barillas, Alix Beith, Robert Burn, Sangeeta Mookherji, Thomas Moore, Chinwe Owunna, Pedro Guillermo Suarez, and Andrey Zagorskiy. Management Sciences for Health/RPM Plus acknowledges the valuable comments and suggestions of Marta Isabel de Abrego (El Salvador), Francis Adatu (Uganda), Edith Alarcón (UNION/Peru), Cesar Bonilla (Peru), Elizabeth Ferreira (Mexico), Tomasa Sierra (Honduras), Álvaro Yañez del Villar (Chile), and David Zavala (Canadian Lung Association/ Ecuador).

Recommended Citation

Rational Pharmaceutical Management Plus. 2008. *Managing Pharmaceuticals and Commodities for Tuberculosis: A Guide for National Tuberculosis Programs.* Submitted to the U.S. Agency for International Development by the Rational Pharmaceutical Management Plus Program. Arlington, VA: Management Sciences for Health.

Rational Pharmaceutical Management Plus Program
Center for Pharmaceutical Management
Management Sciences for Health
4301 N. Fairfax Drive, Suite 400
Arlington, VA 22203
Phone: 703.524.6575
Fax: 703.524.7898
E-mail: rpmplus@msh.org

Contents

Acronyms

DOT	directly observed treatment
DOTS	directly observed treatment, short-course
DST	drug susceptibility test
E	ethambutol
FDC	fixed-dose combination
GDF	Global TB Drug Facility
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
GLC	Green Light Committee
GMP	good manufacturing practices
H	isoniazid
ICB	international competitive bidding
IDA	International Dispensary Association
INN	international nonproprietary name
ISO	International Standards Organization
MDR-TB	multidrug-resistant tuberculosis
MOH	Ministry of Health
MSH	Management Sciences for Health
NGO	nongovernmental organization
NTP	National Tuberculosis Program
PICS	Pharmaceutical Inspection Facility Scheme
R	rifampicin
S	streptomycin
SR	symptomatic respiratory
SS	safety stock
SS+	sputum-smear positive
SS–	sputum-smear negative
STG	standard treatment guidelines
TB	tuberculosis
UNICEF	United Nations Children's Fund
UNION	International Union against Tuberculosis and Lung Disease
USD	U.S. dollar
WHO	World Health Organization
WS	working stock
Z	pyrazinamide

Introduction

Why This Guide Can Be Useful for You

Typical Audience

A typical user of this guide is a National Tuberculosis Program (NTP) stakeholder, such as NTP leadership—the director and senior managers from the national and intermediate levels—as well as other Ministry of Health (MOH) units with which the NTP works closely in procuring and financing tuberculosis (TB) medicines, or both (for example, Directorate of Drugs and Medical Supplies, members of Pharmacology Committees). Nongovernmental organizations (NGOs) and donors involved in TB control are also likely to benefit from this manual. Users are expected to have varying degrees of background in tuberculosis control, and this guide should assist not only those new to TB control but also experienced managers in understanding how good pharmaceutical management can contribute to the outcomes of the TB program.

Purpose of the Guide

The purpose of this guide is to provide a step-by-step approach reviewing the most critical areas of pharmaceutical management for tuberculosis. With the guide, users should be able to identify key weaknesses in their system and mechanisms to overcome weaknesses in selection, procurement, distribution, timely use, and management support of TB medicines.

How It Works

Through a review of the algorithms, the user is expected to be able to quickly identify which areas he or she would like to learn more about. Some sections of the guide can also be used to help measure the present performance of the user's pharmaceutical management system. This introduction includes a checklist of the "ideal scenario" for which users should be aiming.

Roadmap to the Guide

The guide is divided into six sections. Most sections begin with an introduction, followed by an algorithm "roadmap" to the particular section in question. Thereafter, what sections the user refers to depend on the user's answers to the questions of the "roadmap."

Pharmaceutical Management of DOTS and DOTS-Plus Programs

Why DOTS Is the Most Efficient and Cost-Effective Approach to TB Control

The World Health Organization (WHO) declared tuberculosis a global health emergency in 1993. Although this disease causes more morbidity and mortality than any other bacterial infectious agent, it can be effectively cured when medicines are provided under the DOTS (directly observed therapy, short-course) strategy. However, despite the existence of this effective treatment, most countries have not been able to achieve the WHO global targets of detecting 70 percent of cases and curing 85 percent of those detected. In addition, an alarming situation is occurring in countries where HIV is endemic: TB rates have risen dramatically, and TB is one of the most important causes of death in persons infected with HIV.

WHO reports that nearly one-third of the global population is infected with *Mycobacterium tuberculosis* and is at risk of developing the disease. More than 8 million people develop active TB every year, and about 2 million die. More than 90 percent of global TB cases and deaths occur in the developing world, where 75 percent of cases occur in the most economically productive age group (15–54 years) of the population. On average, an adult with TB loses three to four months of work time, which can have a detrimental effect on the family or household, resulting in the loss of approximately 20 to 30 percent of annual household income and, if the patient dies of TB, an average of 15 years of lost income. In addition to the devastating economic costs, TB imposes indirect negative consequences—children leave school because of their parents' tuberculosis, and women are abandoned by their families as a result of their disease. Coinfection with HIV significantly increases the risk of developing TB.

The WHO framework for control of TB, the DOTS strategy, has been adopted by ministries of health in developing countries as the most efficient and cost-effective approach to the prevention and control of TB. The success of the DOTS strategy depends on the adequate implementation of five key components—

- *Sustained political commitment* to increase human and financial resources dedicated to TB control and to make TB control a nationwide activity integral to the national health system
- *Access to quality-assured TB sputum microscopy* for case detection among persons presenting with, or found through screening to have, symptoms of TB (most important, productive cough for two or more weeks)
- *Standardized short-course chemotherapy available for all TB cases, under proper case-management conditions including direct observation of treatment*—proper case management conditions imply technically sound and socially supportive treatment services
- *Uninterrupted supply of quality-assured medicines* with reliable pharmaceutical programming, procurement, and distribution systems

- *Recording and reporting system enabling outcome assessment* of each and every patient and assessment of overall program performance

Countries that have achieved high cure and coverage rates under DOTS include Benin, China, Guinea, Nicaragua, Peru, and Vietnam.

As mentioned previously, global targets recommended by WHO are a 70 percent case detection rate and an 85 percent treatment success rate by 2005. Although many NTPs have made great progress in this direction, a recent WHO assessment shows that, while the treatment success rate in DOTS areas is 82 percent, the case detection rate is only 37 percent (April 2005). In addition, in some parts of the world (for example, sub-Saharan African, Russia, and the Newly Independent States), TB incidence has increased considerably during recent years, suggesting that TB is not being controlled.

Table 1 outlines several advantages to using DOTS in comparison with other regimens, in terms of case detection and diagnosis, patient treatment and categorization, treatment regimens, progress toward cure, treatment follow-up, and operational results and epidemiological impact.

Table 1. Main Advantages of Using DOTS, as Compared with a Non-DOTS Approach

	Non-DOTS	DOTS
Case detection and diagnosis	Depends on unreliable, often expensive methods such as— • Excessive use of x-ray • Often ill-defined, symptomatic-based clinical diagnosis Systematic case detection of infectious cases among those exhibiting symptoms usually absent	Depends on a simple, cost-effective, and reliable method— • Two or three sputum examinations for all individuals exhibiting cough and expectoration • Limited use of x-ray for specific cases (diagnostic follow-up) • Information recorded by case detection among individuals exhibiting respiratory symptoms • Aggregate data by case detection always available; enables progress to be reliably documented
Patient categorization and treatment	Often weak As a result, the following are not well determined— • That a patient has TB • Type/degree of TB • Infectiousness • Treatment category	Strong, ensuring the following are determined, standardized, categorized— • Type of tuberculosis (pulmonary/extrapulmonary) • Sputum-smear positive (SS+) or sputum-smear negative (SS–) • Treatment category: new or retreatment (relapse, failure, retreatment, treatment interruption, chronic)
Treatment regimen	• Individualized, often inappropriate or inadequate regimens for each patient • No directly observed treatment and little patient counseling • Often centralized, specialized TB services to which patients have limited access • No structure—no flexibility or adherence to specific patient needs	• Standardized proven regimens for each case type • Directly observed treatment by a suitably trained person; patient education/counseling standard practice • Medicines may be taken daily or three times a week • Treatment can be administered at health facility, patient's home, or community center
Progress toward cure	• Information by individual sometimes available, but often not used or analyzed • Information by cohort is almost never available	• Information recorded by individual • Aggregate data by cohort always available; enables progress to be reliably documented
Treatment follow-up	• Either not done at all or done unsystematically • Findings not acted upon • Often x-ray based, which adds to expense • Main indicator is patient adherence (via the proxy: collection of medicines) • Often no record of patients' whereabouts; follow-up contact therefore impossible	• Systematic in content at fixed times • Based on inexpensive sputum-smear microscopy • Findings acted upon to achieve or improve cure prospects • Main indicator is patient outcome (cure/completion of treatment) • Location of patient is kept in the register, which allows health worker to follow up if patient misses treatment

	Non-DOTS	DOTS
Operational results and epidemiological impact	• Low case detection among those exhibiting symptoms of TB • Low treatment success in most cases • Unreliable outcome information • Poor value for money • Increasing number of chronic, uncured cases • Poor follow-up of contacts of TB cases • Increased infection • Growing medicine resistance and creation of medicine-resistant cases • High mortality from TB	• High case detection among those exhibiting symptoms of TB • High sputum-smear conversion rates at end of initial phase • High cure rates • Decreased TB incidence • Decreased prevalence of chronic cases • Good follow-up of contacts of TB cases • Decreased transmission of infection within the family and community • Prevention of medicine resistance • Low mortality from TB

Source: Adapted from WHO. 1999. "What Is DOTS? A Guide to Understanding the WHO-Recommended TB Control Strategy Known as DOTS."

How Pharmaceutical Management Is Critical to Effective DOTS Implementation

Pharmaceutical management for TB is important for the following reasons—

- It is a key component of the DOTS strategy.
- TB medicines are life-saving and have no effective substitutes.
- All first-line medicines are generics and readily available to countries worldwide.
- Successful TB control requires more than purchase of low-cost first-line medicines.
- TB medicines require a system for uninterrupted supply and a large buffer (safety) stock.
- Patients must receive good-quality medicines in the right dose for the right period of time in order to achieve cure.
- TB medicines are costly when mismanaged but cost-effective when managed well.
- TB medicines are 99 percent effective in curing TB.
- First-line medicines are cheap (USD 10–30 per full treatment course).
- Interruption of treatment or use of poor-quality medicines may have serious consequences, such as—
    - Increases in default rate and irregular TB treatment
    - Increases in morbidity
    - Increased likelihood of developing resistance
    - More expensive medicines being needed for a longer period of time to treat multidrug-resistant cases
    - Increased costs to the TB program

🕮 Suggested further reading:

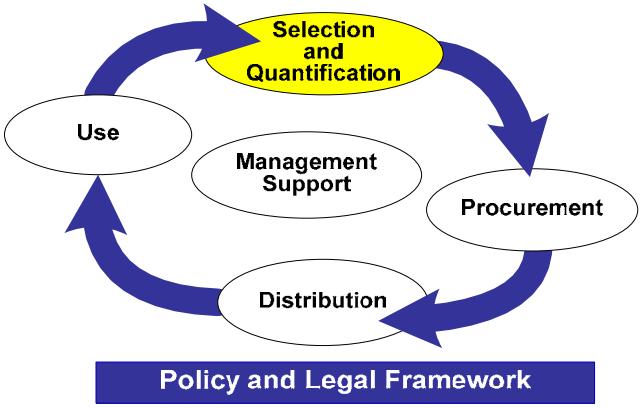
Management Sciences for Health. 2001. "Improving Drug Management to Control Tuberculosis." *The Manager: Management Strategies for Improving Health Services* 10(4). www.msh.org/projects/rpmplus/?pdf/tb_manager.pdf.

- Second-line medicines to treat multidrug-resistant tuberculosis (MDR-TB) are a last resort treatment; if they do not work, the patient can die.
- Countries that improve their pharmaceutical management systems in order to cure TB are also strengthening systems that will help them address the treatment of numerous other health problems.

Measure the Strength of Your Pharmaceutical Management System for Tuberculosis

You know that your system is functioning well if—	Is this the case in your country/program?	Learn how to improve in—
Medicines and commodities selected for treating patients are on the WHO essential medicines list.	☐ Yes ☐ No ☐ Don't know	Section 1. Selection and Quantification
Fixed-dose combinations are being used.	☐ Yes ☐ No ☐ Don't know	Section 1. Selection and Quantification
Patient kits are being used.	☐ Yes ☐ No ☐ Don't know	Section 1. Selection and Quantification
Accurate quarterly data summarizing patients' treated are available.	☐ Yes ☐ No ☐ Don't know	Section 1. Selection and Quantification
Standard treatments for TB are included in NTP Guidelines.	☐ Yes ☐ No ☐ Don't know	Section 1. Selection and Quantification
Regulatory governmental agency in the MOH has approved the pharmaceutical product (or waived registration) (for example, Directorate of Drugs and Medical Supplies).	☐ Yes ☐ No ☐ Don't know	Section 1. Selection and Quantification
Package specifications are clear (for example: FDCs in blister packs of 10 tablets/blister, RHZE as 150/75/400/275 mg, RH as 150/75mg), and special markings are described (for example: GOK for Government of Kenya, "Only for NTP use; sale of this medicine is prohibited").	☐ Yes ☐ No ☐ Don't know	Section 2. Procurement
Quality specifications for tender documents are described (for example: bioavailability of rifampicin in FDC; pharmacopeial standards for testing).	☐ Yes ☐ No ☐ Don't know	Section 2. Procurement
Lead times to procure, receive, and refill the pipeline are known.	☐ Yes ☐ No ☐ Don't know	Section 2. Procurement and Section 3. Distribution
Buffer stocks exist at central, intermediate, and local levels for 6/3/3 months respectively.	☐ Yes ☐ No ☐ Don't know	Section 3. Distribution
Port clearance fees are available to avoid delays.	☐ Yes ☐ No ☐ Don't know	Section 3. Distribution
Port clearance officials are aware of shipments prior to arrival.	☐ Yes ☐ No ☐ Don't know	Section 3. Distribution

Section 1. Selection and Quantification



Introduction

What Is Selection?

Selection is the process of establishing and using a limited list of essential medicines. It involves reviewing prevalent health problems; identifying the best clinical treatments; choosing medicines, dosages, dosage form, and special packaging needs; and deciding which medicines will be available at each level of health care.

Selection of First-Line and Second-Line TB Medicines

The process of medicine selection for national tuberculosis programs (NTPs) is based upon a variety of factors, such as standard treatment guidelines (STGs), cost, resistance to TB medicines, access to quality medicines, and management and distribution capabilities. NTP managers are required to carefully balance resources against need. Careful medicine selection is one of the most cost-effective ways of promoting a regular supply of TB medicines. For resource-poor contexts, the World Health Organization (WHO) suggests selecting five essential first-line medicines: isoniazid (H), rifampicin (R), ethambutol (E), pyrazinamide (Z), and streptomycin (S).

WHO guidelines for selection of first-line TB pharmaceuticals are those most commonly recommended. However, other guidelines or standards for selection (for example, those of the International Union against Tuberculosis and Lung Disease [UNION]) are also used in several countries worldwide. Some countries choose not to follow guidance from these international bodies. What is essential is that the method used is based on solid, regularly collected country-specific data.

Second-line medicine selection for resistant tuberculosis is recommended only after an outbreak has occurred and been documented in-country.[1] If such an outbreak has occurred and been confirmed by an independent laboratory, consider exploring the second part of this module, which addresses selection and quantification of second-line TB medicines, starting with Section 1.8.

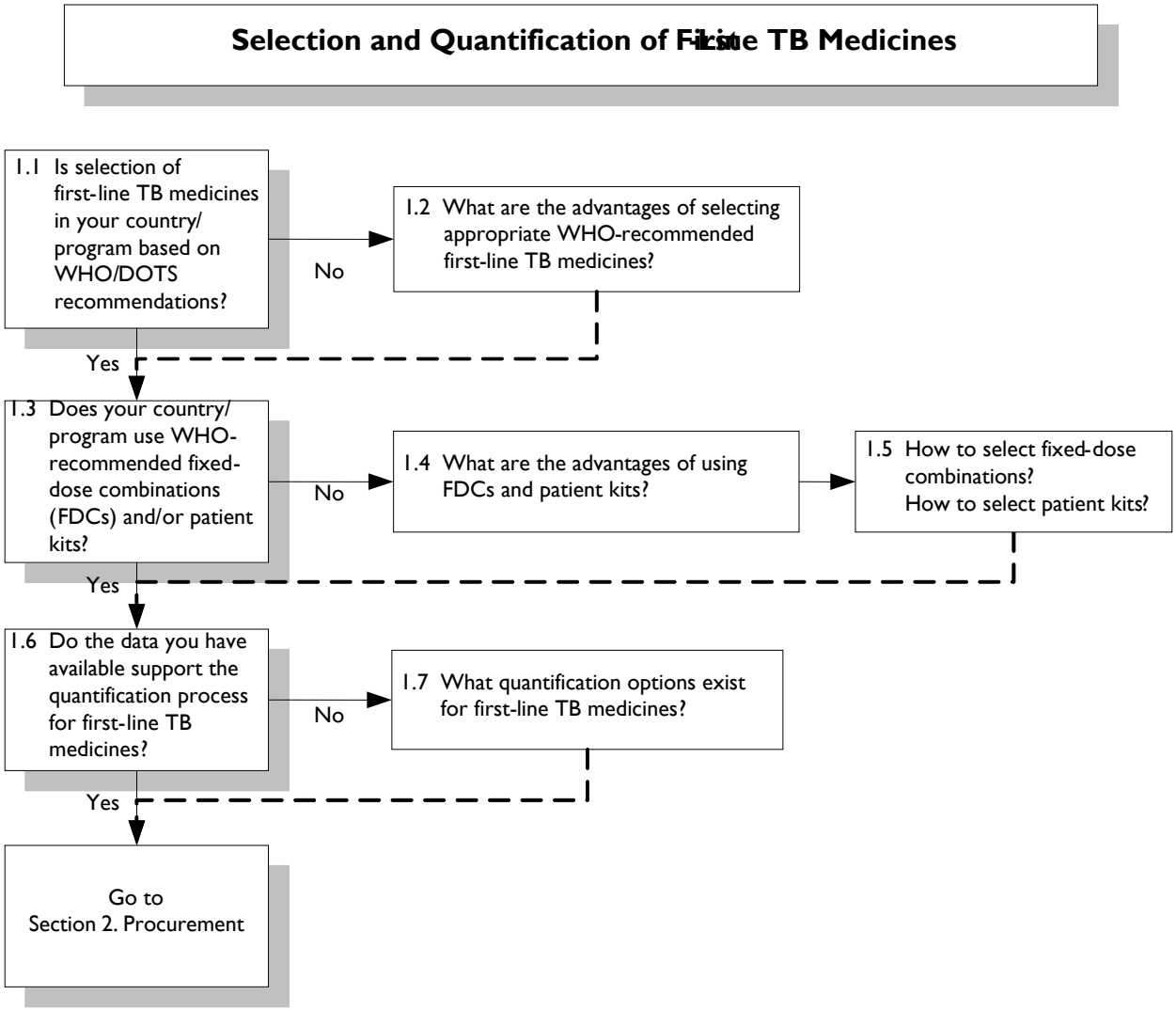
Quantification of TB Medicines

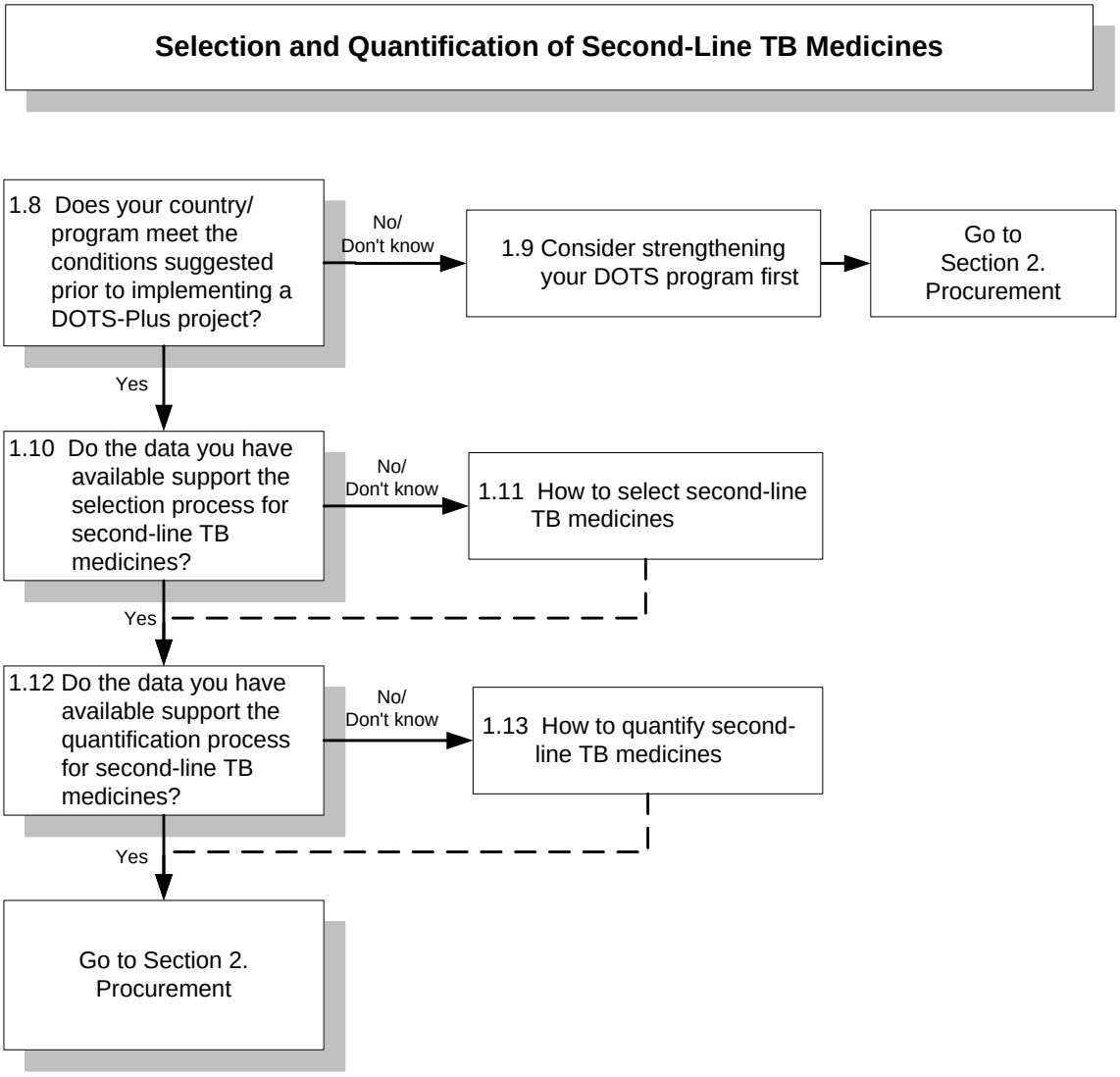
After the appropriate medicines for treating TB have been selected, accurate quantification of needs is imperative to any health system. Purchasing the right medicines in the right quantities for the various treatment regimens specific to tuberculosis is one of the first steps in reducing the incidence of the disease, death rates, and development of medicine resistance. Different quantification techniques are used depending on the accuracy of the available sources of information.

Overview and Key Issues in This Section

The first part of this section addresses key issues in selection of first-line TB medicines, such as WHO/DOTS recommendations, selecting and using fixed-dose combinations (FDCs) and patient kits, and using data for quantification purposes. The second part of this section addresses selection and quantification of second-line TB medicines in cases where it is advised that treatment of MDR-TB should occur (according to WHO guidelines).

[1] Management Sciences for Health. 2001. "Selecting Essential Drugs." *The Manager: Management Strategies for Improving Health Services* 10(4): 6–9.


Selection and Quantification of First-line TB Medicines
1.1 Is selection of first-line TB medicines in your country/ program based on WHO/DOTS recommendations?
No
1.2 What are the advantages of selecting appropriate WHO-recommended first-line TB medicines?
Yes
1.3 Does your country/ program use WHO-recommended fixed-dose combinations (FDCs) and/or patient kits?
No
1.4 What are the advantages of using FDCs and patient kits?
1.5 How to select fixed-dose combinations?
How to select patient kits?
Yes
1.6 Do the data you have available support the quantification process for first-line TB medicines?
No
1.7 What quantification options exist for first-line TB medicines?
Yes
Go to
Section 2. Procurement


Selection and Quantification of Second-Line TB Medicines
1.8 Does your country/ program meet the conditions suggested prior to implementing a DOTS-Plus project?
No/ Don't know
1.9 Consider strengthening your DOTS program first
Go to Section 2. Procurement
Yes
1.10 Do the data you have available support the selection process for second-line TB medicines?
No/ Don't know
1.11 How to select second-line TB medicines
Yes
1.12 Do the data you have available support the quantification process for second-line TB medicines?
No/ Don't know
1.13 How to quantify second-line TB medicines
Yes
Go to Section 2. Procurement

1.1 Is selection of first-line TB medicines in your country/program based on WHO/DOTS recommendations?

WHO-recommended criteria	Used in your country/program?
Are you using WHO-recommended essential first-line medicines: isoniazid (H), rifampicin (R), ethambutol (E), pyrazinamide (Z), streptomycin (S)?	☐ Yes ☐ No ☐ Don't know
Are you using fixed-dose combinations and/or patient kits?	☐ Yes ☐ No ☐ Don't know
Are you continuing to procure and stock limited amounts of separate medicines for use in special regimens for patients with drug toxicity or special requirements? (WHO recommends 2 percent of all TB patients.)	☐ Yes ☐ No ☐ Don't know
Have you received assurance of bioavailability for all TB medicines (particularly for rifampicin component) from independent labs?	☐ Yes ☐ No ☐ Don't know
Are you able to ensure the quality of the medicines, in terms of stability (shelf life)?	☐ Yes ☐ No ☐ Don't know
Are you regularly following up on medicines safety data, coordination and monitoring of treatment regimens, and control over prescribing practices to ensure a minimum amount of adverse reactions?	☐ Yes ☐ No ☐ Don't know
Are you basing needs on prevalent disease patterns?	☐ Yes ☐ No ☐ Don't know
Have you received information on the safety and efficacy of TB medicines you are using?	☐ Yes ☐ No ☐ Don't know
Are you able to ensure that health care workers can use the medicines appropriately?	☐ Yes ☐ No ☐ Don't know
Are sufficient financial resources available to procure the needed quantities of medicines?	☐ Yes ☐ No ☐ Don't know

Next Steps

If you responded "no" or "don't know" to any question in the previous exercise:

- Go to Section 1.2: What are the advantages of selecting appropriate WHO-recommended first-line TB medicines?

If you responded "yes" to all questions:

- Go to Section 1.3: Do you use WHO-recommended fixed-dose combinations and/or patient kits?

1.2 What are the advantages of selecting appropriate WHO-recommended first-line TB medicines?

Why focus on selection?

Selection of TB pharmaceuticals is the starting point of an essential TB medicines policy or pharmaceutical reform based on the health needs of a given population. Pharmaceutical selection is a process that involves careful consideration of pharmaceutical efficacy, safety, quality, and cost.

There are several key reasons why you should pay attention to how TB pharmaceuticals are selected—

- These pharmaceuticals can represent a large part of the public health budget.
- Funds are limited.
- The quality of TB pharmaceuticals in the marketplace varies.
- Keeping up to date with the large numbers of TB pharmaceuticals in the marketplace is practically impossible.

What criteria should be taken into account during the selection process?

According to the World Health Organization, selection criteria for TB pharmaceuticals include—

- Basing need on prevalent disease patterns
- Being able to demonstrate and document the safety and efficacy of TB medicines
- Being able to ensure the quality of the medicines, both in terms of bioavailability and stability (shelf life)
- Ensuring that authorized personnel are capable of using the medicines
- Ensuring financial resources are available
- Basing therapeutic equivalence of pharmaceuticals (generic products) on efficacy, safety, quality, price, and availability
- Taking into account the proven advantage of combination products over separate products
- Taking into account the total cost of treatment, not only the unit cost of the medicines

What first-line medicines are recommended by WHO for treatment of TB?

WHO-recommended essential first-line medicines are—

- Isoniazid (H)
- Rifampicin (R)
- Ethambutol (E)
- Pyrazinamide (Z)
- Streptomycin (S)

Why select WHO-recommended TB medicines?

The advantages of selecting appropriate WHO-recommended TB medicines are many; for example, appropriate formulation selection—

- Facilitates prescriptions of standardized chemotherapy (rational use)
- Obtains better prices by limiting the number of formulations purchased (pricing)
- Simplifies management of supplies and stock (distribution and inventory control)
- Facilitates quality control of medicines (quality assurance)
- Allows access to WHO prequalified suppliers for WHO-recommended dosage forms (very important for FDCs)

If TB pharmaceuticals are selected rationally, procurement and transaction costs will be reduced, medicine availability will be improved, and health outcomes will improve because of a regular supply of quality medicines.

How does the selection process work?

First: Review patterns of TB morbidity, drug resistance, and populations affected.

Second: Design standard treatments for TB patients (WHO-recommended regimens preferred), and include them within NTP guidelines, endorsed as a national policy of the MOH for TB control.

Third: Develop a list of essential medicines and supplies to ensure these standard treatments—specify medicine, generic name (international nonproprietary name, or INN), strength, and dosage form.

Next: You are ready to procure first-line TB medicines.

What specifications should be included?

The specifications for selecting pharmaceuticals should include—

- Selection by generic or international nonproprietary name
- Dosage form (for example, tablet, ampoule for injection)
- Strength (for example, rifampicin 150 mg + isoniazid 75 mg)
- Package presentations, quantity of basic units (for example, blisters containing 10 tablets each, with 10 blisters per pack)
- Level of health care where the pharmaceuticals will/should be used (taking into account the capability of health workers). For example, oral medicines should be available in all treatment centers, whereas injectables should be available only where a clinician or nurse is available.

Next Steps

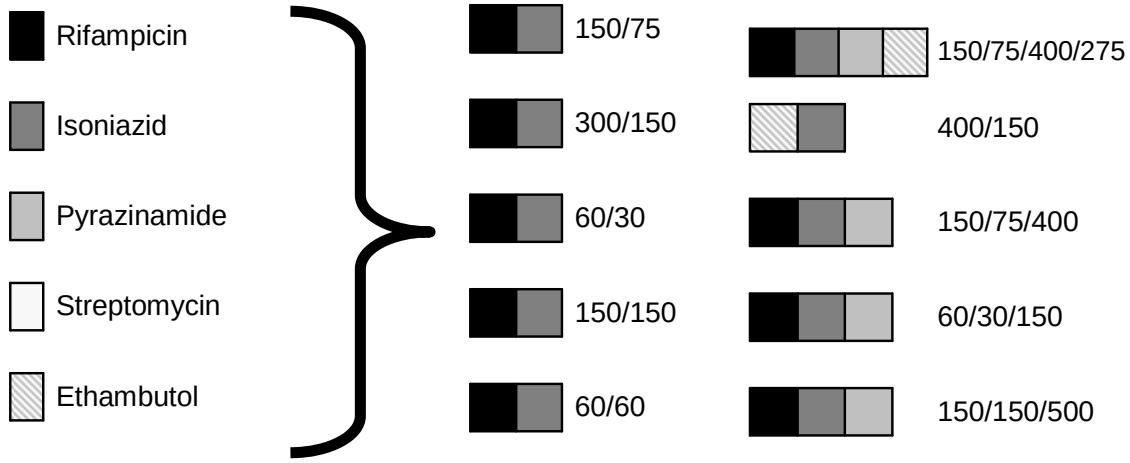
Go to Section 1.3: Does your country/program use WHO-recommended FDCs and/or patient kits?

1.3 Does your country/program use WHO-recommended FDCs and/or patient kits?

Common FDCs used in tuberculosis control

A *fixed-dose combination* is the combination in a single tablet of two, three, or four TB medicines.[2]

WHO-Recommended Tuberculosis Agents and Fixed-Dose Combinations



Source: Adapted from WHO. 2002. *Operational Guide for National TB Control on the Introduction and Use of Fixed-Dose Combinations.* Geneva: WHO.

Please specify whether your country/program is using—		
• The two-medicine H+R combination	☐ Yes	☐ No
• The two-medicine H+E combination	☐ Yes	☐ No
• The three-medicine combination	☐ Yes	☐ No
• The four-medicine combination	☐ Yes	☐ No
• A patient kit containing FDCs	☐ Yes	☐ No

[2] A four-medicine FDC in a single-dose sachet is currently in clinical trials.

Next Steps

If you responded "yes" to any/several/all questions in the previous exercise and do not use any other treatment regimen:

- Go to Section 1.6: Do the data you have available support the quantification process for first-line TB medicines?

If you responded "no" to all questions:

- Go to Section 1.4: What are the advantages of using FDCs and patient kits?

1.4 What are the advantages of using FDCs and patient kits?

Advantages of using FDCs and patient kits

The following are advantages to using fixed-dose combinations and patient kits—

- FDCs may increase patient adherence to treatment.
- The two-, three-, or four-medicine combinations (R + H; R + H + E; R + H+ Z; R + H + Z + E) reduce the risk of monotherapy with bactericidal medicines and thus decrease the threat of resistance to treatment.
- The two-medicine combination (E + H) is useful because it can be self-administered during the second (continuation) phase of TB treatment.[3] However, this combination may be less effective than R + H. For this reason, the R + H combination is usually recommended, but only where directly observed therapy is practiced.
- FDCs simplify dose calculations and procurement.
- FDCs provide the patient with fewer tablets to swallow.
- A patient kit contains a full course of treatment for TB (all medicines needed through treatment completion, be it 6 months for category I treatment or 8 months for category II).

Some disadvantages of using FDCs and patient kits may, depending on particular country's circumstances, include the following—

- Even though they are simpler to use, personnel still need to be retrained in quantification and use.
- Identifying the medicine causing any adverse effect and therefore adjusting the regimen to avoid adverse effects (less than 2 percent of patients) may be lengthy.
- FDCs may not be immediately available in local markets.

Next Steps

Go to Section 1.5: How to select fixed-dose combinations? How to select patient kits?

[3] Self-administration is recommended only in exceptional cases in particular country settings.

1.5 How to select fixed-dose combinations? How to select patient kits?

Selecting FDCs

When selecting FDCs, keep in mind that—

- Fixed-dose combination medicines are only fully efficacious when—
  - The correct dose of each prescribed medicine is present.
  - Proven full medicine absorption occurs.
- A statement of bioavailability should be provided by supplier/manufacturer.
- Follow-up is needed on medicine safety data, coordination and monitoring of treatment regimens, and control over prescribing practices.
- The use of FDCs does not preclude the need to purchase and stock limited amounts of separate medicines for use in special regimens for patients with drug toxicity or special requirements. WHO suggests that on average 2 percent of TB patients may need separate medicines

📖 To learn more about FDCs, see WHO. 2002. *Operational Guide for NTPs on the Introduction and Use of Fixed-Dose Combination Drugs* (WHO/CDS/TB 2002.308), at http://whqlibdoc.who.int/hq/2002/WHO_CDS_TB_2002.308.pdf) (available in English and French).

The following tables from the WHO's 2002 *Operational Guide for NTPs on the Introduction and Use of Fixed-Dose Combination Drugs* are a useful guide for the selection of treatment regimens using FDCs.

Table 1.1 Recommended Dosage of Essential First-Line Anti-TB Medicines

Medicine (Abbreviation)	Mode of Action	Recommended Dose (Dose Range) in mg/kg Body Weight	
		Daily	Intermittent (3 Times per Week)
Rifampicin (R)	Bactericidal	10 (8–12)	10 (8–12)
Isoniazid (H)	Bactericidal	5 (4–6)	10 (8–12)
Pyrazinamide (Z)	Bactericidal	25 (20–30)	35 (30–40)
Streptomycin (S)	Bactericidal	15 (12–18)	15 (12–18)
Ethambutol (E)	Bacteriostatic	15 (15–20)	30 (25–35)

Table 1.2 WHO-Recommended FDCs (from the WHO Model List of Essential Medicines, revised May 2005)

Medicine	Dose Form	Strength for Daily Use	Strength for Intermittent Use (3 Times per Week)
Rifampicin + isoniazid [RH]	Tablets	150 mg + 75 mg 300 mg + 150 mg	150 mg + 150 mg
	Tablets or packets of granules[a]	60 mg + 30 mg	60 mg + 60 mg
Ethambutol + isoniazid [EH]	Tablets	400 mg + 150 mg	—
Rifampicin + isoniazid + pyrazinamide [RHZ]	Tablets	150 mg + 75 mg + 400 mg	150 mg + 150 mg + 500 mg
	Tablets or packets of granules[a]	60 mg + 30 mg + 150 mg	—
Rifampicin + isoniazid + pyrazinamide + ethambutol [RHZE]	Tablets	150 mg + 75 mg + 400 mg + 275 mg	— —

Note: — = not applicable

[a] For pediatric use.

Table 1.3 Recommended Treatment Regimens for Each Treatment Category

Tuberculosis Diagnostic Category	Tuberculosis Patients	Tuberculosis Treatment Regimens	
		Initial Phase (Daily or 3 Times per Week)[a]	Continuation Phase (Daily or 3 Times per Week)[a]
I	New smear-positive patients; new smear-negative patients pulmonary TB with extensive parenchymal involvement; severe concomitant HIV disease or severe forms of extrapulmonary TB	2RHZE[b]	4RH[c]
II	Previously treated sputum smear-positive pulmonary TB: • relapse • treatment after interruption • treatment failure[d]	2RHZES/1RHZE	5RHE
III	New smear-negative pulmonary TB (other than in Category 1) and less severe forms of extrapulmonary TB	2RHZE[e]	4RH[c]

Note: Standard code for TB treatment regimens. Each anti-TB medicine has an abbreviation (shown in the preceding tables). R = rifampicin; H = isoniazid; Z = pyrazinamide; E = ethambutol; S = streptomycin. A regimen consists of two phases. The number before a phase is the duration of that phase in months. A number in subscript (for example, $_3$) after a letter is the number of doses of that medicine per week. If there is no number in subscript after a letter, then treatment with that medicine is daily. For example: 2RHZE/4(RH)$_3$. The duration of the initial phase is 2 months and medicine treatment is daily, with rifampicin (R), isoniazid (H), pyrazinamide (Z), and ethambutol (E). The continuation phase is 4(RH)$_3$. The duration is 4 months, with rifampicin (R) and isoniazid (H) three times per week.

[a] Direct observation of treatment intake is required for the initial phase in smear positive cases, and always when treatment includes rifampicin.

[b] Streptomycin may be used instead of ethambutol.

[c] 4RH may be replaced by 6EH daily when supervision of treatment is not possible. However, preliminary data from a recent clinical trial have shown that 6EH is much less effective than 4RH in terms of cure, with higher failure and relapse rates. In meningitis: 2RHZS/4RH or 2RHZS/4(RH)$_3$, replacing ethambutol with streptomycin.

[d] Whenever possible, medicine sensitivity testing is recommended before prescribing category II treatment in failure cases.

[e] Ethambutol may be omitted for patients with noncavitary, smear-negative pulmonary TB who are known to be HIV-negative, patients who are known to be infected with fully medicine-susceptible bacilli. Young children with primary TB should be given three-medicine combination only (without ethambutol).

Table 1.4 Dosage Schedules for Adults

Patient Body Weight (kg)	Initial Phase			Continuation Phase[a]		
	2 Months			4 Months		or 6 Months
	Daily	**or Daily**	**or 3 Times per week**	**Daily**	**or 3 Times per week**	**Daily**
	RHZE[b] 150 mg + 75 mg + 400 mg + 275 mg	RHZ 150 mg + 75 mg + 400 mg	RHZ 150 mg + 150 mg + 500 mg	RH 150 mg + 75 mg	RH 150 mg + 150 mg	EH 400 mg + 150 mg
30–39	2	2	2	2	2	1.5
40–54	3	3	3	3	3	2
55–70	4	4	4	4	4	3
71 and more	5	5	5	5	5	3

Note: R = rifampicin; H = isoniazid; Z = pyrazinamide; E = ethambutol.

[a] 4RH may be replaced by 6EH daily when supervision of treatment is not possible. However, preliminary data from a recent clinical trial have shown that 6EH is much less effective than 4RH in terms of cure, with higher failure and relapse rates.

[b] Maximum recommended daily dose of rifampicin in FDCs is 750 mg.

Table 1.5 Dosage Schedules for Smear-Negative Children

Patient Body Weight (kg)	Initial Phase	Continuation Phase	
	2 Months	4 Months	
	Daily	**or Daily**	**or 3 Times per Week**
	RHZ 60 mg + 30 mg + 150 mg	RH 60 mg + 30 mg	RH 60 mg + 60 mg
< 7	1	1	1
8–9	1.5	1.5	1.5
10–14	2	2	2
15–19	3	3	3
20–24	4	4	4
25–29	5	5	5

Note: R = rifampicin; H = isoniazid; Z = pyrazinamide.

📖 To address frequently asked questions about 2-, 3-, and 4-medicine FDCs:

See http://www.stoptb.org/gdf/documents/whatis/documents/FAQ-brochure.pdf

Selecting patient kits

A TB patient kit is a preassembled box containing all the anti-TB medicines for a full DOTS treatment course. Usually there are two types of kits: one for Categories I and III, and the other for Category II. Kit packages include medicines for both the intensive and continuation phases.

Some countries buying loose medicines assemble packages for each patient at the health-facility level, often using plastic containers. This method is a good operative option if the country cannot purchase preassembled kits.

Some of the advantages and limitations of using kits include the following.

Advantages	Limitations
• *Standardized treatment:* allows health workers to select a single container that has the predetermined medicines, strengths, and quantities (the TB patient kit for administering to the patient), limiting confusion and wastage. • *Quantification for procurement or ordering*: improves ease of estimating medicine needs whereby 1 patient = 1 patient kit. • *Distribution of TB medicines:* improves ease of logistics in that fewer items are being transported. • *Stock management and inventory control:* improves ease of managing stocks and documentation of stock movement because one product is being handled. • *Patient adherence:* whereas medicine stockouts cause patients to lose confidence in the health system, the patient kit assures the TB patient that his or her medicines will be available from start to finish of treatment. In addition, the patient may feel ownership of the patient kit and will likely complete the full course of treatment since he or she can see how many medicines must still be taken to achieve cure during visits to the health center or dispensary.	• Larger storage space may be needed in central and local warehouses. • Personnel should be trained in the adjustment of kits according to body weight, inventory methods, and repacking. • If TB packs are reconstituted, loose medicines must be collected, packing materials must be available, an area should be available for reconstitution in the warehouse, and procedures such as "Good Storage Practices" should be in place and followed.

Next Steps

Go to Section 1.6: Do the data you have available support the quantification process for first-line TB medicines?

1.6 Do the data you have available support the quantification process for first-line TB medicines?

Using data to support quantification of first-line TB medicines

How is your country/program currently forecasting upcoming need/demand for first-line TB medicines?
• By using past use (consumption) of TB medicines to project future need/demand ☐ Yes ☐ No ☐ Don't know If yes, describe where this information is collected from and with what frequency: _____ _____
• By using morbidity data to determine the number of expected cases ☐ Yes ☐ No ☐ Don't know If yes, describe where this information is collected from and with what frequency: _____ _____
• Some combination of the two methods: ☐ Yes ☐ No ☐ Don't know If yes, describe what information is collected, from where and with what frequency: _____ _____

Next Steps

If you responded "yes" to any/several/all questions in the previous exercise and do not use any other treatment regimen:

- Go to Section 2. Procurement.

If you responded "no" to all questions:

- Go to Section 1.7: What quantification options exist for first-line TB medicines?

1.7 What quantification options exist for first-line TB medicines?

What is quantification?

Quantification is the process of estimating the amount of medicines needed to ensure an uninterrupted supply to fully cover estimated TB treatment requirements over a period of time (usually one year).

What is quantification used for?

You can use quantification to—

- Prepare and justify a medicine budget
- Avoid stockouts
- Plan for new and expanding tuberculosis programs
- Optimize medicine budgets based on TB cases to be treated and the most cost-effective treatment approaches
- Calculate emergency needs for disaster relief and epidemics
- Replenish an existing supply network that has become depleted of products
- Compare current consumption of medicines with tuberculosis treatment priorities and use in other health systems
- Estimate needs for bulk purchase
- Forecast long-term needs for manufacturers or suppliers
- Estimate needs for proposal funding, such as from the Global Fund to Fight AIDS, TB and Malaria

What steps should you consider as part of the quantification process?

- Prepare an action plan for quantification
    - Appoint an official or department in charge
    - Form a quantification team to coordinate activities
    - Define quantification coverage and objectives
    - Examine available data and select the best quantification method to use based on data availability and quality

  - Estimate and obtain resources
  - List and assign tasks
  - Update STGs if necessary and use STGs to develop the medicines or commodity list
  - Develop a workplan with realistic timelines for the quantification process

- Decide if quantification will—

  - Be centralized or decentralized
  - Use manual or computerized methods

- Estimate time requirements, including procurement period and safety stock

- Fill the supply pipeline

- Consider the impact of lead time

- Adjust for program growth and for losses due to waste and theft

- Cross-check estimates produced with those for previous years or alternative methods

- Estimate total procurement cost

- Adjust and reconcile final quantities in accordance with available funds

What quantification methods exist?

Three options exist for quantification, each of which has its advantages and disadvantages—

- *Morbidity based*: This WHO-recommended method bases estimates on the number of expected symptomatic respiratory (SR[4]) and TB cases.

- *Consumption based*: This alternative method is available to systems with a functioning pharmaceutical management information system to base estimates on past consumption. To use the consumption method, the program needs quantities actually dispensed from health facilities and existing quantities from the storerooms and warehouses throughout the system.

- *Adjusted-consumption based*: This method is used where the estimation of TB cases is difficult. Quantification estimates are based on data from a similar region or health service where the number of expected TB cases is known.

[4] An SR case is defined as any person who has had cough and expectoration (sputum) for more than two or three weeks.

A "quick" comparison of the two preferred methods: morbidity and consumption (note the two types of morbidity method)

	Morbidity		Consumption
	Historical	**Expected SR[5] Cases**	
Context	• For existing programs	• For new and existing programs	• More appropriate in established supply systems
Data used during quantification process	• Estimate number of cases of each category of TB to be treated in one year using quarterly reports	• Estimate number of expected SR cases to be identified at the health-facility level over a one-year period	• Inventory records • Pipeline requirements • Unit costs of medicines • Supplier lead time
Limitations/ Requirements	• Accurate attendance data • Standard treatments • Computer analysis for large databases	• Programming module • Baseline information of number of attendees at health facilities	• Accurate consumption data
Advantages	• Easy analysis	• Accurate and useful information	• Similar to the method used for other medicines and commodities in the health facility

How to use the historical morbidity method

An example is provided below of how to use the morbidity method. The example is based on a 2(RH)ZE/4RH daily regimen for a middle weight-band patient (40–54 kg)[6] and considers only category I TB patients.

The following assumptions were considered during quantification—

- Each patient requires 28 doses a month for a daily regimen.
- Three tablets each for RH and Z and two tablets for E are required for the weight band used.
- The following adjustments were considered—
    - Procurement Period [PP] (time from placing one order to the next) = 12 months
    - Safety Stock period [SS] (reserve stock kept to avoid stockouts) = 6 months

[5] This method is used by certain Latin American and Caribbean countries, and according to the programming modules included in their respective NTP guidelines, SR cases are a proportion (usually 5–10 percent) of patients, 15 years of age or older, attending health facilities. Expected TB cases are about 10 percent of SR cases.
[6] R = rifampicin; H = isoniazid; Z = pyrazinamide; E = ethambutol; S = streptomycin.

- Lead Time period [LT] (time between when the order is prepared and when it is available for issue in the country) = 6 months
- Total PP + SS + LT = 24 months or 2.0 years

- Total stock on hand and stock on order for each medicine is—

  - RH = 24,300
  - Z = 8,400
  - E = 4,200

- Package specifications and unit cost

  - RH 150 mg/75 mg box of 672 tablets in 24 blister sheets = $17.20
  - Z 400 mg box of 1,000 tablets/units = $8.45
  - E 400 mg box of 1,000 tablets/units = $13.20

If you choose, you can complete the right-hand side of the chart with your country/program's information to determine whether you have sufficient (accurate) data to use this method.

Sample quantification using historical morbidity method

	Step	Example	Your country/program's data
1	Estimate the number of expected TB cases per disease category in the projected year	1,000 category I cases over 12 months	
2	Identify the number of tablets of each medicine selected for complete treatment of one patient on category I TB treatment	1. 504 rifampicin/isoniazid (RH 150/75 mg) combination tablets 2. 168 pyrazinamide (Z 400 mg) tablets 3. 112 ethambutol (E 400 mg) tablets	
3	Multiply the number of tablets required by the total estimated cases	1. 1,000 category I cases x 504 units isoniazid/rifampicin = 504,000 2. 1,000 category I cases x 168 units pyrazinamide = 168,000 3. 1,000 category I cases x 112 units ethambutol = 112,000	
4	Adjust for Procurement Period (PP), Safety Stock (SS), and Lead Time (LT)*	PP + SS + LT = 24 months or 2 years 504,000 tablets of RH x 2 years = 1,008,000 units 168,000 tablets of Z x 2 years = 336,000 units 112,000 tablets of E x 2 years = 224,000 units	
5	Subtract stock on hand and stock on order; the result is amount to procure	1. RH 1,008,000 – 24,300 = 983,700 2. Z 336,000 – 8,400 = 327,600 3. E 224,000 – 4,200 = 219,800	
6	Determine final quantities to procure by packs by dividing basic units for each medicine by package size	1. RH 983, 700 ÷ 672 units/pack = 1,464 2. Z 327,600 ÷ 1,000 units/pack = 328 3. E 219, 800 ÷ 1,000 units/pack = 220	
7	Multiply pack price for each medicine by required number of packs and sum totals to obtain total cost of procurement	1. RH 1,464 × $17.20 = $25,181 2. Z 328 × $8.45 = $2,772 3. E 220 × $13.20 = $2,904 4. Total = $30,857	
8	Cross-check estimates obtained by using another method or comparing previous year's estimate; reconcile and adjust quantities according to available budget		

*Note that other adjustments for losses or waste can be made in step 4.

Model Table for Quantification of Essential Tuberculosis Medicines Using Morbidity Method

Medicine Name (add medicine strength)	Treatment Category	(A) Estimated Cases for Year	(B) Basic Units per Case (e.g., tab, vial)	(C) Basic Units Needed (each category) (A x B)	(D) Total Basic Units per Product (sum of C per product)	(E) Adjusted Order Factor *	(F) Quantity to Procure (D x E)	(G) Units per Container/ Blister	(H) Number Containers/ Blisters to Buy (F ÷ G)	(I) Container/ Blister Price	(J) Total Price (H x I)
	Cat. I										
	Cat. II										
	Cat. III										
	Cat. I										
	Cat. II										
	Cat. III										
	Cat. I										
	Cat. II										
	Cat. III										
	Cat. I										
	Cat. II										
	Cat. III										
	Cat. I										
	Cat. II										
	Cat. III										
	Cat. I										
	Cat. II										
	Cat. III										

* Adjusted order period in years equals months to cover plus lead time plus safety stock (for example, 12 months + 5 months + 1 month = 18 months = 1.5 years).

How to use the SR morbidity method

An example (from the Latin American and Caribbean region) is provided below on how to use the SR morbidity method.

Assumptions considered during quantification include the following—

- Regimen considered for category I TB patients is 2(HR)ZE/4$(HR)_3$ and for category II patients is 2(HR)ZES/1(HR)ZE/5$(HR)E_3$.
- Average adult patient weight band used for calculation is 40–54 kg.
- For TB prophylaxis with H, average weight band used for calculation is 30 kg (5mg/kg/day).
- Each patient requires 28 doses a month for daily regimen (intensive phase) and 12 doses per month for intermittent regimen (continuation phase of treatment). For TB prophylaxis with H, 30 doses per month is considered in this calculation.
- Three tablets each for RH and Z and two tablets for E are required for considered weight band. For TB prophylaxis with H, half a tablet of 300 mg is considered for each patient.

If you choose, you can complete the right-hand side with your country/program's information to determine whether you have sufficient (accurate) data to use this method.

🕮 Further Resources:

A quantification exercise with the details on arithmetic procedures is included in WHO. 2002. *Operational Guide for National Tuberculosis Control Programs*. WHO/CDS/TB/2002.308-WHO/EDM/PAR/2002.6.

Sample quantification using SR morbidity method

	Step	Example	Your country/ program's data
1	Calculate the number of patients, 15 years of age or older, who attended health facilities during the previous year (e.g., 2004)	100,000 patients attending in 2004	
2	Calculate the number of expected SR cases in the projected year (e.g., 2005)	Usually this figure represents 5 percent of all patients 15 years of age or older who attended health facilities 100,000 x 0.05 = 5,000 SR cases expected for 2005	
3	Calculate the number of expected diagnosis sputum smear (SS) tests for the projected year	Usually 3 SS are estimated for each SR case identified 5,000 x 3 = 15,000 diagnosis SS expected	
4	Estimate the number of expected total TB cases per disease category in the projected year	1. Usually the total number of TB cases represents 10 percent of the SR cases expected 5,000 x 0.10 = 500 total TB cases 2. New TB cases (category I) would be 85 percent of total TB cases number 500 x 0.85 = 425 TB cases category I 3. Previous TB cases (category II) would be 15 percent of total TB cases number 500 x 0.15 = 75 TB cases category II *Note*: We assume that category I TB treatment includes new pulmonary TB SS+, pulmonary TB SS–, and extrapulmonary TB. Category II TB treatment includes relapses, treatment after default, and failure of category I treatment.	

	Step	Example	Your country/ program's data
5	Identify the number of tablets of each medicine selected to treat one patient of category I TB treatment	If the NTP uses the category I TB treatment 2(HR)ZE/4$(HR)_3$ and decides to use FDCs, you would calculate the following number of tablets for each treatment: 1. 168 isoniazid/rifampicin (HR) combination tablets (75/150 mg) 2. 144 isoniazid/rifampicin (HR) combination tablets (150/150 mg) 3. 168 pyrazinamide (Z) tablets (400 mg) 4. 112 ethambutol (E) tablets (400 mg)	
6	Multiply the number of tablets required by the number of estimated individuals requiring category I TB treatment	1. 425 category I TB treatment x 168 units HR (75/150 mg) = 71,400 units 2. 425 category I TB treatment x 144 units HR (150/150 mg) = 61,200 units 3. 425 category I TB treatment x 168 units Z = 71,400 units 4. 425 category I TB treatment x 112 units E = 47,600 units	
7	Identify the number of tablets or vials of each medicine selected to treat one patient for category II TB treatment	If the NTP uses the category II TB treatment 2(HR)ZES/1(HR)ZE/5$(HR)_3E_3$ and decides to use FDCs, you would calculate the following number of tablets or vials: 1. 252 isoniazid/rifampicin (HR) combination tablets (75/150 mg) 2. 180 isoniazid/rifampicin (HR) combination tablets (150/150 mg) 3. 252 pyrazinamide (Z) tablets (400 mg) 4. 408 ethambutol (E) tablets (400 mg) 5. 56 streptomycin (S) vial injectable (1 gr)	
8	Multiply the number of tablets (or other units) required by the estimated number of individuals requiring category II TB treatment	1. 75 category II TB treatment x 252 units HR (75/150 mg) = 18,900 units 2. 75 category II TB treatment x 180 units HR (150/150 mg) = 13,500 units 3. 75 category II TB treatment x 252 units Z = 18,900 units 4. 75 category II TB treatment x 408 units E = 30,600 units 5. 75 category II TB treatment x 56 units S = 4,200 units	
9	Calculate the total number of TB medicines required for individuals on category I and II TB treatment in the projected year	1. 71,400 + 18,900 = 90,300 units HR (75/150 mg) 2. 61,200 + 13,500 = 74,700 units HR (150/150 mg) 3. 71,400 + 18,900 = 90,300 units Z 4. 47,600 + 30,600 = 78,200 units E 5. 4,200 = 4,200 units S	

	Step	Example	Your country/ program's data
10	Identify the quantity of H that the NTP needs to guarantee the H prophylaxis in children under 5 years who have contact with a pulmonary TB SS+ Prophylaxis is given for at least 6 months at a dose of 5mg/kg/day. The maximum recommended dose of H is 300 mg/day.	You would estimate one child for each TB patient in category I TB treatment 425 x 1 = 425 children with prophylaxis expected A 30 kg child will require 150 mg of H per day = ½ tablet of 300 mg. For 6 months at 30 doses per month, one 30 kg child will require 90 tablets of H, 300 mg. 425 x 90 = 38,250 units H (300 mg per tablet)	
11	Using the number of SS expected, calculate the quantity of slides, sputum containers, and other lab reagents that the NTP needs	For this example you would include in the NTP requirements (from step 3 above)— • 15,000 sputum containers • 15,000 slides	

Follow steps 4 to 8 from the historical morbidity method to calculate the final procurement quantities and cost.

Sample Programming Module

Province/geographical area/unit	**Year**
Municipality	
Health facility	
Institution	

Total population		**Population > 14 years of age**	
Population < 5 years of age		**Consultations > 14 years of age**	
		Previous year	

Case detection

Number of consultations > 14 years of age	Expected number of SR = A x 5%	Expected number of sputum-smear diagnoses = B x 3
(A)	(B)	(C)

Case diagnosis

Total number of expected TB cases = B x 10%	New TB cases = D x 85%	Previously-treated TB cases = D x 15%
(D)	(E)	(F)

Case management

Sputum-smear control among new TB cases = E x 6	Sputum-smear control among previously treated TB cases = F x 8	Total expected number of individuals undergoing sputum-smear control = G + H
(G)	(H)	(I)

TB medicine requirements

Medicines	Short-course TB treatment	Retreatment case	Chemoprophylaxis	Total
Isoniazid x 300 mg[7]				
Rifampicin x 300 mg				
Pyrazinamide x 500 mg				
Ethambutol x 400 mg				
Streptomycin x 1 gram				
Isoniazid x 100 mg[8]				

Laboratory supply requirements for conducting sputum-smear microscopy

Total number of sputum smears = C + I	Number of plastic containers = J	Number of slides = J	Applicator sticks = J	Immersion oil = J x 0.04 cc	Basic Fuchsin = J x 0.02 cc
(J)					

Crystalized phenol = J x 0.04gr	Alcohol 95 = J x 7.8 cc	Clorhidric acid = J x 0.04cc	Methylene blue = J x 0.01cc	Sodium hypochlorite = J x 0.01 gm	Filter paper = J x 0.01 cm

[7] 360 tablets of 300 mg isoniazid are programmed for chemoprophylaxis of HIV-positive individuals.
[8] 180 tablets of 100 mg isoniazid are programmed for chemoprophylaxis of children who are less than 5 years of age.

How to use the consumption method

An example is provided below on how to use the consumption method. Assumptions considered in the illustration include the following—

- Total annual consumption of rifampicin/isoniazid 150 mg/75 mg = 259,200.
- Procurement Period [PP] (time from placing one order to the next) = 6 months.
- Safety Stock period [SS] (reserve stock kept to avoid stockouts) = 3 months.
- Lead-Time period [LT] (time between when the order is prepared and when it is available for issue in the country) = 4 months.
    - Total PP + SS + LT = 13 months.
- No stockouts during the review period considered (12 months). If stockouts had occurred, for example, 20 days during the review period, the average monthly consumption would be adjusted to include the days out of stock as follows—
    - 259,200 ÷ (12 months – (20 days ÷ 30.5 days in a month) = 22, 857
- Total stock on hand and stock on order for RH = 24,000.
- RH 150 mg/75 mg box of 672 tablets in 24 blister sheets = $17.20.

If you choose, you can complete the right-hand side of the chart with your country/program's information to see whether you have sufficient (accurate) data to use this method.

Sample consumption method quantification

	Step	Example	Your country/ program's data
1	Divide total annual consumption of specific medicine units by 12 to get average monthly consumption; do this for each medicine	Isoniazid/Rifampicin = 259,200 ÷ 12 = 21,600 units/month	
2	Calculate additional number of units required, taking into account safety stock, procurement period, and lead time	PP + SS+ LT =13 months: 21,600 x 13 = 280,800 additional units	
3	Combine total annual consumption with additional amounts for the total number of units that need to be ordered	259,200 + 280,800 = 540,000 units total	
4	Subtract stock on hand and stock on order	540,000 – 24,000 = 516,000 units	
5	Calculate quantity to procure in packs by dividing by number of units per pack	516,000 ÷ 672 = 768 packs	
6	Total cost of procurement	768 × $17.20 = $13,210 for RH	

What to do when data are unavailable or when unreliable data inhibit use of the consumption or morbidity method

When neither consumption nor morbidity method is feasible, the adjusted-consumption method can be used.

How to use the adjusted-consumption method

This option uses data (disease incidence, consumption or use, and/or expenditures) from a standard supply system to extrapolate the consumption in a target supply system or another region or health system. Two possible alternatives exist.

- Population-based (medicine use for each case × estimated incidence in target system)
- Service-based (medicine use per specific patient case or rural health center × estimated number of patients in reference service area)

A combination of the two methods could also be used with different denominators for different products.

The adjusted-consumption method is useful for estimating needs when rolling out services to new sites or when starting new programs.

Next Steps

Has a confirmed (by an independent laboratory) outbreak of MDR-TB occurred in you country?

- If yes, go to Section 1.8: Does your country/program meet the conditions suggested prior to implementing a DOTS-Plus project?
- If no, go to Section 2. Procurement.

1.8 Does your country/program meet the conditions suggested prior to implementing a DOTS-Plus project?

In areas where the prevalence of multidrug-resistant TB (MDR-TB) is sufficiently high to threaten the success of TB control and the basic DOTS program has been successfully implemented, the WHO formally recognizes the need for the specific management of MDR-TB. "Sufficiently high prevalence of MDR-TB" must be interpreted with some flexibility because of the complex set of variables that may determine the threshold at which a DOTS-Plus approach is warranted. *In general, a prevalence of MDR-TB above 3 percent among cases never treated previously may constitute a reasonable level to consider the necessity of a DOTS-Plus approach.* This threshold, however, is not the only issue to be considered when deciding whether to implement a DOTS-Plus pilot project. Economic issues, the status of current TB control efforts, and TB case-management priorities also need to be taken into consideration (WHO. 2002. *Guidelines for Establishing DOTS-Plus Pilot Projects for the Management of MDR-TB.* WHO/CDS/TB/2000.279).

Before initiating a DOTS-Plus project, the following conditions should be met—	**Does your country/program meet these conditions?**
• Considerable political will exists to support the project (as evidenced by guaranteed financial support by the government and/or donors, long-term investment of staff and resources, and coordination of efforts among stakeholders involved).	☐ Yes ☐ No ☐ Don't know
• DOTS is being implemented in more than 90 percent of health facilities.	☐ Yes ☐ No ☐ Don't know
• A continuous supply of first-line TB pharmaceuticals is available.	☐ Yes ☐ No ☐ Don't know
• Combined default and transfer rates are less than 6 percent.	☐ Yes ☐ No ☐ Don't know
• A plan for project administration, including written operational procedures (TB program manuals) and an effective monitoring and evaluation system, exists.	☐ Yes ☐ No ☐ Don't know
• Laboratory services, including for drug susceptibility tests (DSTs), exist.	☐ Yes ☐ No ☐ Don't know
• A treatment strategy and a specialized unit for managing MDR-TB patients have been developed.	☐ Yes ☐ No ☐ Don't know
• Reliable information systems exist and are functioning well.	☐ Yes ☐ No ☐ Don't know
• Ability to collect and analyze cohort data exist.	☐ Yes ☐ No ☐ Don't know

Next Steps

If you responded "yes" to all questions in the previous exercise and prevalence of MDR-TB is above 3 percent among cases never treated previously in your country, it is appropriate for you to consider introducing a strategy to treat MDR-TB.

- Go to Section 2. Procurement.

If you responded "no" to any question, OR the prevalence of MDR-TB is below 3 percent among cases not previously treated in your country, it is recommended that you do not yet consider introducing a strategy to treat MDR-TB. Instead:

- Go to Section 1.9: Consider strengthening your DOTS program first.

1.9 Consider strengthening your DOTS program first

MDR-TB arises when TB is improperly managed with incorrect treatment regimens or under inappropriate program conditions. Prevention of MDR-TB is achieved through the implementation and/or expansion of TB control under adequately structured programs.

Thus, an effective DOTS-based TB control program must be in place in an area before investing the considerable resources necessary for the treatment of MDR-TB.

A well-implemented DOTS program is the best strategy to control the emergence of new cases of MDR-TB. From a public health point of view, it is better not to launch a DOTS-Plus project if the performance of the basic DOTS program needs improvement. If a DOTS-Plus project is launched under suboptimal conditions, resistance to second-line medicines is likely to emerge rapidly.

Next Steps

If your program meets the conditions to implement a DOTS-Plus project:

- Go to Section 1.10: Do the data you have available support the selection process for second-line TB medicines?

If your program does no meet the conditions to implement a DOTS-Plus project:

- Go to Section 2. Procurement.

1.10 Do the data you have available support the selection process for second-line TB medicines?

Using data to support selection of second-line TB medicines

Please complete the following table to get a sense of whether the data you have available support the selection process for second-line TB medicines.

Question	Answer
• Is there a successful DOTS program implemented in the country?	☐ Yes ☐ No ☐ Don't know
• Does the NTP have recent studies about TB pharmaceutical susceptibility profile?	☐ Yes ☐ No ☐ Don't know
• Are the second-line TB medicines likely to be used in your country registered by national authorities?	☐ Yes ☐ No ☐ Don't know
• Is epidemiological information available about the number of MDR-TB patients that may potentially be treated?	☐ Yes ☐ No ☐ Don't know
• Are there national or international providers that can ensure a continuous supply of second-line TB medicines after the DOTS-Plus project is launched?	☐ Yes ☐ No ☐ Don't know
• Are you regularly following up on medicines safety data, coordination and monitoring of MDR-TB treatment regimens, and control over prescribing practices to ensure a minimum amount of adverse reactions?	☐ Yes ☐ No ☐ Don't know
• Are you able to demonstrate and document the safety and efficacy of second-line TB medicines?	☐ Yes ☐ No ☐ Don't know
• Are you able to ensure that authorized personnel are capable of using the second-line TB medicines?	☐ Yes ☐ No ☐ Don't know
• Are sufficient financial resources available to procure needed second-line TB medicines?	☐ Yes ☐ No ☐ Don't know
• Do you base therapeutic equivalence of pharmaceuticals on efficacy, safety, quality, price, and availability?	☐ Yes ☐ No ☐ Don't know

Next Steps

If you responded "yes" to the previous questions:

- Go to Section 1.13: How to quantify second-line TB medicines.

If you responded "no":

- Go to Section 1.11: How to select second-line TB medicines.

1.11 How to select second-line TB medicines

How the selection process differs from that for first-line medicines

The selection process for second-line medicines differs considerably from selection of first-line treatment because—

- Only a limited supply of second-line treatments is available.
- More medicines are needed for longer periods of time (up to 24 months) than with first-line treatment.
- Second-line medicines are much more expensive (up to 100 times more) than first line.

Web Resource:

Use the online version of MSH's *International Drug Price Indicator Guide* to compare prices of second-line TB medicines in your country with prices obtained by other countries and offered by other organizations.
See http://erc.msh.org/mainpage.cfm?file=1.0.htm&module=DMP&language=English.

- Second-line medicines are more toxic than first line.
- Second line-medicines are not as effective as first line.

WHO-recommended second-line medicines

WHO-recommended second-line medicines include—

- Capreomycin
- Cycloserine
- Para-aminosalicylic acid
- Ethionamide
- Prothionamide
- Amikacin
- Kanamycin
- Ciprofloxacin
- Ofloxacin
- Levofloxacin

Criteria for selection

Clear recommendations and STGs for the treatment of MDR-TB are only now being developed. Qualified specialists should make decisions for selecting second-line medicines for the country, based on drug-resistance patterns.

Four different types of second-line regimens are possible—

- Individualized
- Empiric and later individualized
- Standardized
- Standardized, then individualized if standardized fails

Note that comparative effectiveness has not been determined for any of the methods.

How to determine which type of regimen to use

Steps to follow to determine which type of regimen you should use within your MDR-TB project—	Does your country/program meet these conditions?	Most appropriate type of regimen
Do you have regular access to a laboratory with drug susceptibility testing capacity?	☐ Yes	Individualized
	☐ No	Standardized
	☐ No, but expect to have in the near future	Empiric

Individualized regimens

An individualized regimen requires laboratory support.

- Sputum-smear microscopy through a laboratory network
- Culture for *Mycobaterium tuberculosis*
- Drug susceptibility tests (DSTs) for isoniazid, rifampicin, streptomycin, and ethambutol
- Information management system
- Collaboration with supranational reference laboratory (for DSTs of second-line medicines)

The individualized regime must be designed selecting the proper combination of the medicines from the following medicine groups—

First-line agents	Injectable	FQ	Second-line agents	Third-line agents
H	S	Cx	Et	Amx/Clv
R	Km	Ox	Cs	Clofazamine
Z	Cm	Lx	PAS	Clarithromycin
E	Am	Mx	Th	
		Gx		

Group 1: Oral (first-line medicines)

- Isoniazid, rifampicin, pyrazinamide, ethambutol
- Most efficacious and well tolerated
- Use maximum doses
- Isoniazid 900 mg orally twice weekly in cases of resistance at low concentrations

Group 2: Injectables (first- and second-line medicines)

- Streptomycin, kanamycin, amikacin, capreomycin (these medicines are called aminoglycosides)
- Aminoglycosides and capreomycin are bactericidal and should be included
- Use maximum doses
- Treat until culture negative for six consecutive months

Group 3: Fluoroquinolones (second-line medicines)

- Ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, gatifloxacin
- Bactericidal

Group 4: Bacteriostatics (mostly second-line medicines)

- Cycloserine
- Para-aminosalicicylic acid
- Ethionamide
- Prothionamide
- Thiacetazone

Note: Bacteriostatics are less efficacious than fluoroquinolones.

Group 5: Third-line agents

- Amoxicillin + clavulanate
- Clofazamine
- Clarithromycin

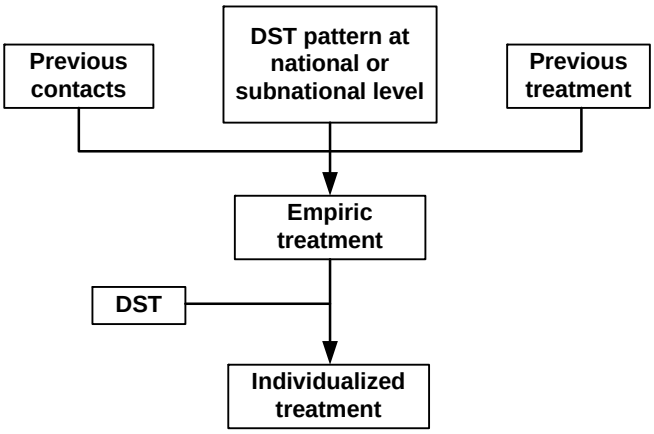
Note: Agents are active in vitro but limited data exist on their activity in vivo.

How to select second-line TB medicines for individualized regimens—

- Use where valid and reliable first- and second-line anti-TB DST is readily available
- Include first-line medicines to which infecting strain is susceptible
- Include a minimum of five medicines, including three second-line medicines not previously used
- Use high-end dose
- Use parenteral (injection) therapy for extended period (6 months after culture conversion)
- Do not rely on medicines to which resistance is suspected (the amplification effect)
- Administer daily for at least 18 months after culture conversion
- Observe all doses
- Aggressively treat all side effects

Empiric regimens

Empiric regimens are used until the DSTs are available; then the individualized regimen can be designed.

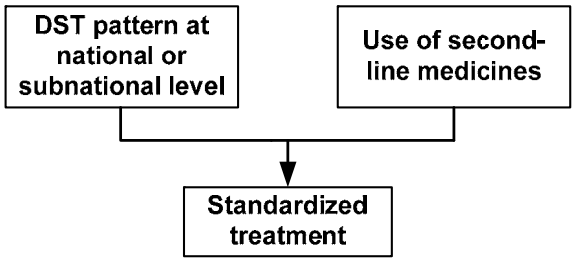


Standardized regimens

You will need to consider introducing a standardized regimen where "real time" valid and reliable first- and second-line anti-TB DST results are not available to guide individual treatment decisions. These regimens are based on DST pattern and history of use of second-line TB medicines in the patient population area.

All patients enrolled in the project are placed on this regimen for the duration of treatment. Giving two or three treatments before switching to an adequate regimen will result in more amplification, less-effective regimens, more side effects, and higher cost.

Standardized regimens with second-line medicines can be dangerous if not well designed.



Next Steps

Go to Section 1.12: Do the data you have available support the quantification process for second-line TB medicines?

1.12 Do the data you have available support the quantification process for second-line TB medicines?

Using data to support quantification of second-line TB medicines

• Is epidemiological information about the number of MDR-TB patients that may potentially be treated available, such as—	
o Percentage of failures of category I and/or category II treatments	☐ Yes ☐ No ☐ Don't know
o Percentage of chronic patients	☐ Yes ☐ No ☐ Don't know
o Prevalence of MDR-TB according to national surveillance	☐ Yes ☐ No ☐ Don't know
o Number of identified MDR-TB patients on a "waiting list" for treatment	☐ Yes ☐ No ☐ Don't know
• Are sufficient financial resources available to procure needed second-line TB medicines?	☐ Yes ☐ No ☐ Don't know

Next Steps

If you responded "no" or "don't know," to the preceding questions:

- Go to Section 1.13: How to quantify second-line TB medicines.

If you responded "yes":

- Go to Section 2. Procurement.

1.13 How to quantify second-line TB medicines

What is quantification of second-line medicines used for?

- Prepare and justify the budget for a DOTS-Plus project
- Resupply an existing DOTS-Plus project with subsequent orders

📖 A model list of pharmaceuticals and supplies that may be required is included in Annex 1.1.

How does quantification of second-line medicines differ from quantification of first-line medicines?

- Shelf life is usually short: 24–36 months for most medicines.
- Treatment duration may even exceed shelf life.
- The lead time may be longer because no local manufacturers may be located in the country.
- Ancillary medicines and supplies for managing adverse effects should be considered.
- DOTS-Plus projects are new and expanding in most countries, unlike first-line TB treatment, where countries have trained personnel with many years of experience estimating drug requirements.
- Reliable epidemiological data for MDR-TB are not as readily available as for first-line treatment.
- Data needed for quantification where individualized regimens are used are more difficult to collect, aggregate, and use for estimating medicines requirements.

What quantification methods exist?

- For a new project using standardized regimens, the first six-month order should be based on morbidity (number of cases × standardized regimen adopted). Following six-month orders should be adjusted by consumption.
- For new projects using empiric/individualized treatments, the requirements are difficult to predict. The project may need to buy a reasonable stock (six-month consumption estimate) for all the medicines that may be needed.

Use the following three worksheets to quantify second-line TB medicines.

Next Steps

Go to Section 2. Procurement.

Step 1: Calculating total quantities and costs

Sample MDR-TB Treatment Regimen: 6_____ / 18_____	**Basic unit**	**Number basic units needed (per day)**	**Duration of treatment (days = 26x6)**	**Basic units needed per treatment phase**	**Estimated number of cases to treat**	**Total basic units needed to order for full regimen**	**Green Light Committee unit price USD**	**Total cost**	**Budget available**	**Budget deficit/ surplus**
		A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**
Intensive phase:										
Example Thiacetazone 250 mg	tab	3	156	468						
Continuation phase:			**(days = 26 × 6 × 3)**							
Example Thiacetazone 250 mg	tab	3	468	1404						
								_		
					Total cost medicines					
					Freight + insurance 10%			_		
					Grand total cost medicines					
					Medicine cost for one patient					

Step 2: Calculating order for first six months, quantities and costs

What to do:

1. Determine basic units needed for first six-month period: (= Column E intensive phase previous exercise) fill in column **A**.
2. Fill in package size per item in column **B**.
3. Calculate total number of packs to order. Fill in column **C**.
4. Fill in Green Light Committee (GLC) or other unit price.
5. Calculate cost per pack under column **E**.
6. Calculate total cost per item under column **F**.
7. Calculate freight and insurance costs for this order and determine total costs in **F**.
8. Fill in total budget available under column **G**. and determine remaining budget under column **E**.

	Basic unit	Total basic units to cover first six months (intensive phase)	Package size (number basic units/pack)	Total number packs to order	GLC unit price USD	Cost per pack	Total cost	Budget available	Remaining budget
		A	B	C	D	E	F	G	E
							-		
Total costs medicines									
Freight + insurance 10%							-		
Grand total costs medicines									

Step 3: Calculating the second, third, and fourth six-month orders, quantities and costs per six-month order

What to do:

1. Determine basic units needed for second, third, and fourth six-month periods: (= Column E continuation phase exercise step 1, divided by 3 because the total in column E is for 18 months); fill in column **A**.
2. Fill in package size per item in column **B**.
3. Calculate total number of packs to order. Fill in column **C**.
4. Fill in GLC unit price from handout in column **D**.
5. Calculate cost per pack in column **E**.
6. Calculate total cost per item in column **F**.
7. Sum total costs in **F** and calculate freight and insurance costs for this order.
8. Fill in budget brought forward after previous order under column **G**, and determine remaining budget in column **H**.
9. As in item 8, determine costs for the third and fourth six-month orders and enter in column F.
10. Discuss in your subgroup how to handle changes in regimen by physician during treatment.

	Basic unit	Total basic units to cover 2nd, 3rd, 4th six months	Package size (number basic units/pack)	Total number packs to order	GLC unit price USD	Cost per pack	Total cost	Remaining budget brought forward	Remaining budget
		A	B	C	D	E	F	G	H
Total costs medicines									
Freight + insurance 10%									
Grand total costs medicines 2nd order									
Grand total costs medicines 3rd order									
Grand total costs medicines 4th order									

Annex 1.1 Ancillary Medicines for Managing Adverse Effects to First- and Second-Line TB Medicines

- Antiemetics: chlorpromazine, promethazine, metoclopramide, dimenhydrinate, lorazepam, diazepam
- Antiulcer agents: antacids (magnesium and aluminium hydroxide), H2-blockers (ranitidine)
- Antifungal agents: fluconazole or clotrimazole
- Antidiarrheals: loperamide
- Dehydration agents: oral rehydration salts and intravenous fluids
- Antidepressants: amitriptyline, fluoxetine
- Anxiolytics: diazepam, clonazepam
- Hypnotics: diphenhydramine, lorazepam
- Antipsychotics: haloperidol
- Anticonvulsants: diazepam, phenytoin, carbamazepine
- Prophylaxis of neurological complications: pyridoxine (vitamin B6)
- Agents to treat peripheral neuropathy: amitriptyline, ibuprofen
- Agents to treat vestibular symptoms: meclizine
- Agents for headaches: opioid and nonopioid analgesics
- Agents for cutaneous reactions: corticosteroid creams (hydrocortisone), anti-pruritus lotions (calamine)
- Analgesics for arthralgias and arthritis: ibuprofen, acetaminophen
- Thyroid replacement hormones: levothyroxine
- Diuretics: furosemide, amiloride
- Agents for bronchospams: bronchodilators (albuterol), inhaled corticosteroids (beclomethasone)
- Agents for systemic hypersensitivity reactions: diphenhydramine, prednisone, dexamethasone, epinephrine

Supplies needed to manage adverse medicine reactions

- Water for injection
- Needles and syringes
- Disinfectants, soaps, towels, and tissues
- Gloves and face masks
- Sputum cups
- Forms and labels
- Zinc stains and other chemicals
- Microscopes
- Slides
- Filter and lens paper
- Applicator sticks
- Miscellaneous equipment for microscopy
- Culture media, Petri plates
- Autoclave, incubator, sterilizer
- BCG, PPD
- X-ray machine, film developer, and fixer
- Intramuscular and intravenous injection supplies
- Intravenous administration sets
- Visual field and color vision testing charts
- Audiometers
- Bedside commode, emesis basins
- Resuscitation equipment

Annex 1.2 Additional References

Creese, A., and D. Parker. 1994. *Cost Analysis in Primary Health Care*. Geneva: World Health Organization.

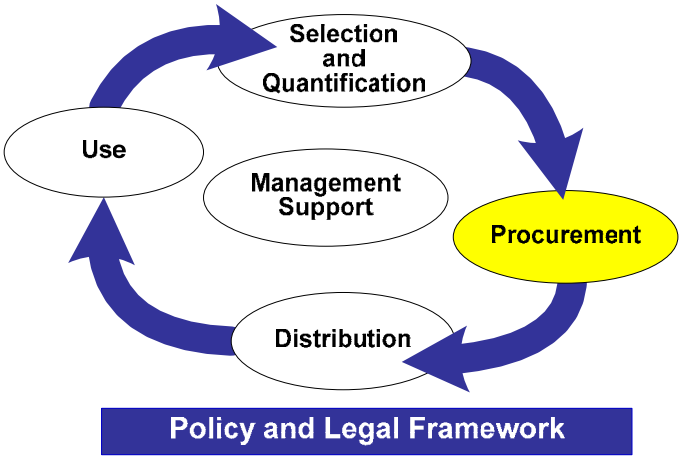
Management Sciences for Health and the World Health Organization. Chapter 14, "Quantifying Drug Requirements." In *Managing Drug Supply: The Selection, Procurement, Distribution, and Use of Pharmaceuticals*. 2nd edition. West Hartford, CT: Kumarian Press, Inc.

Pio, A., and P. Chaulet. 1998. *Tuberculosis Handbook*. Geneva: World Health Organization. WHO/TB/98.253.

World Health Organization. 1997. Chapter 4, "Available Drugs for MDR Tuberculosis." In *Guidelines for the Management of Drug-Resistant Tuberculosis*. Geneva: World Health Organization.

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

Section 2. Procurement



Introduction

What Is 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 medicines in the right quantities at reasonable prices, and at recognized standards of quality.

Procurement of First-Line TB Medicines

The primary objective of tuberculosis medicine procurement is to provide regular delivery of adequate quantities of high-quality medicines at the lowest cost. First-line tuberculosis medicines are usually cheap and often procured through local providers. However, in recent years, the Global TB Drug Facility (GDF),[9] established by the Stop TB Partnership, has been a strong source for first-line TB medicines.

In order to receive these medicines, countries must meet specific requirements set out by the GDF, including use of effective treatment protocols. By the end of 2004, 58 countries, NGOs, and states had received GDF support. Of the 4.4 million patient treatments ordered by GDF, 3.45 million were with GDF grants and 1.028 million through direct procurement using recipients' funds.[10]

[9] To learn more about the Global TB Drug Facility, see www.stoptb.org/gdf.
[10] http://www.stoptb.org/gdf/documents/GDF%204X4-final.pdf (accessed on January 3, 2006).

If your country lacks GDF support or you are responsible for procuring TB medicines, you should—

- Understand effective pharmaceutical procurement practices
- Identify the level of competition among suppliers
- Choose the most appropriate procurement method
- Determine qualifications of suppliers
- Provide specifications for TB medicines and packaging
- Know the length of time that registration takes
- Assure TB medicine quality
- Monitor suppliers' performance

Procurement of Second-Line TB Medicines

Second-line TB medicines are expensive and often not immediately available, even in international markets. The Green Light Committee (GLC),[11] a committee of the DOTS-Plus Working Group within the Stop TB Partnership, offers a reliable source for these TB medicines for countries with limited means of procuring and certifying the quality of second-line medicines.

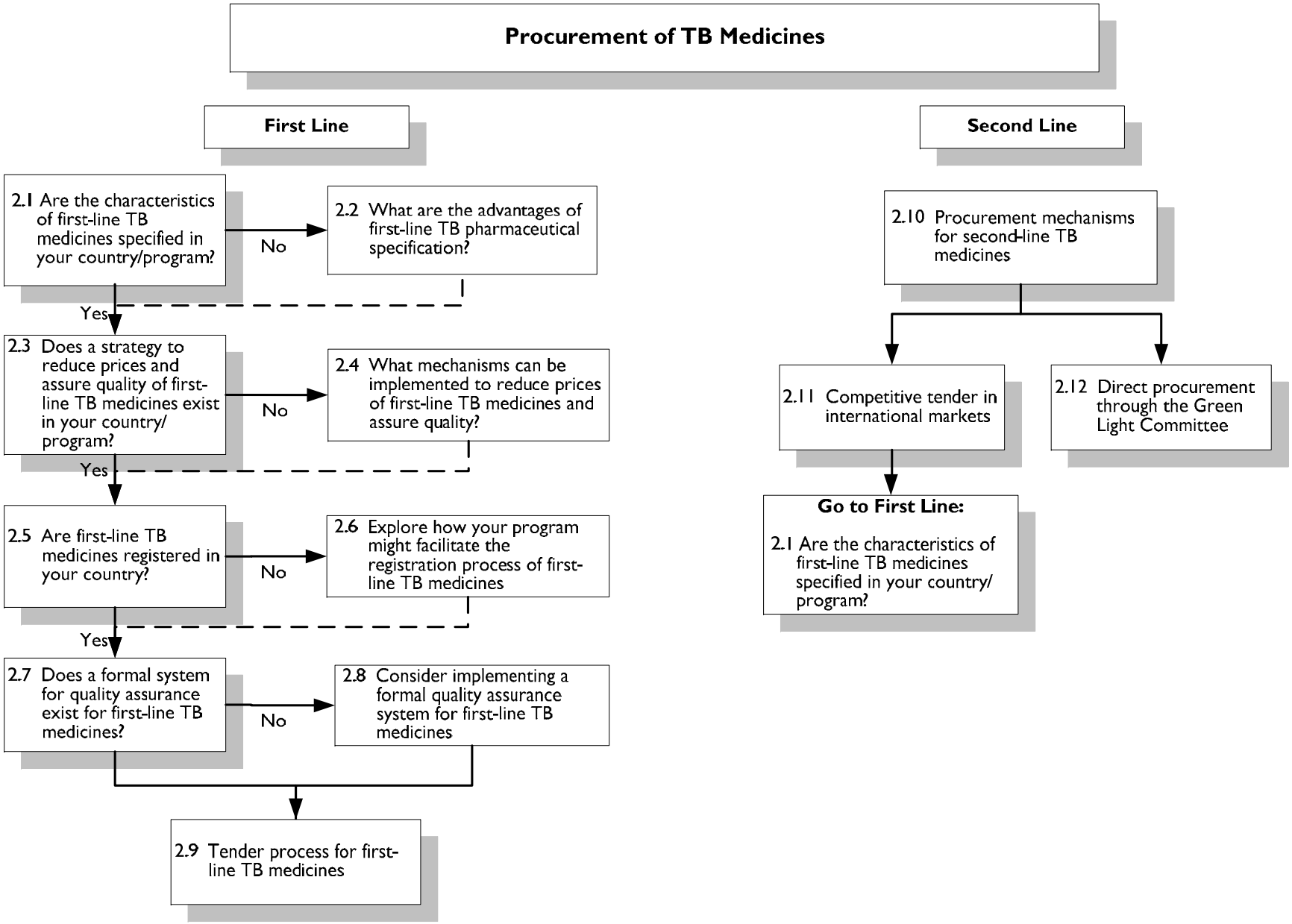
Several conditions should be in place, however, before a country/program considers introducing a DOTS-Plus project. As mentioned in Section 1 on selection and quantification, selection of second-line medicines for multidrug-resistant TB (MDR-TB) is recommended only *after* an outbreak has occurred, been documented in-country, and preferably been confirmed by an independent laboratory. To confirm that your country/program meets the conditions suggested before a DOTS-Plus project should be implemented, you should go to Section 1.8 of the selection and quantification module and complete the checklist exercise.

If you respond "yes" to all questions in that exercise, and prevalence of MDR-TB is above 3 percent[12] among cases never treated previously in your country, it is appropriate for you to consider introducing a strategy to treat MDR-TB. If that is the case, please go to Section 2.10 toward the end of this module to learn more about procurement of second-line TB medicines.

Overview and Key Issues in This Section

The goals of TB medicine procurement are to procure the most effective medicines in the right quantities, to select reliable suppliers of high-quality products, to ensure timely delivery, and to achieve the lowest possible cost for all medicines. This section addresses key issues in procurement of both first- and second-line TB medicines, such as prequalification, bulk procurement, quality assurance, and standard bidding documents, and provides an overview of the roles of the GDF and GLC in increasing access to low-cost, high-quality TB medicines.

[11] To learn more about the Green Light Committee, see http://www.who.int/tb/dots/dotsplus/management/en/.
[12] An MDR-TB threshold is not the only factor to consider when deciding whether to implement a DOTS-Plus pilot project. Economic issues, status of current TB control efforts, and TB case-management priorities should also be considered (WHO/CDS/TB/2000.279).


Procurement of TB Medicines
First Line
Second Line
2.1 Are the characteristics of first-line TB medicines specified in your country/program?
No
2.2 What are the advantages of first-line TB pharmaceutical specification?
Yes
2.3 Does a strategy to reduce prices and assure quality of first-line TB medicines exist in your country/ program?
No
2.4 What mechanisms can be implemented to reduce prices of first-line TB medicines and assure quality?
Yes
2.5 Are first-line TB medicines registered in your country?
No
2.6 Explore how your program might facilitate the registration process of first-line TB medicines
Yes
2.7 Does a formal system for quality assurance exist for first-line TB medicines?
No
2.8 Consider implementing a formal quality assurance system for first-line TB medicines
2.9 Tender process for first-line TB medicines
2.10 Procurement mechanisms for second-line TB medicines
2.11 Competitive tender in international markets
2.12 Direct procurement through the Green Light Committee
Go to First Line:
2.1 Are the characteristics of first-line TB medicines specified in your country/ program?

2.1 Are the characteristics of first-line TB medicines specified in your country/program?

When procuring TB (and other) medicines, a precise description of the characteristics of the medicines to be procured, along with any special requirements, should be provided to potential bidders. This detailed description is called the "technical specifications" of the given product and, if made clear and respected during the bidding process, these specifications can lead to optimal procurement in terms of achieving better prices and higher-quality medicines.

Ideally, your country/program should provide a positive answer to the following recommended specifications.

Recommended specification	Currently specified in your country/program?
• Is the generic (international nonproprietary) name specified?	☐ Yes ☐ No ☐ Don't know
• Is the desired presentation of each TB medicine (capsule, tablet, vial, blister, or loose) specified?	☐ Yes ☐ No ☐ Don't know
• Is the desired dose (mg per tablet, capsule, or vial) specified?	☐ Yes ☐ No ☐ Don't know
• Is the desired labeling (listing medicines' content, language, and any special instructions or recommendations) specified?	☐ Yes ☐ No ☐ Don't know
• Is the minimum shelf life that the medicine should have when delivered to the program clearly specified?	☐ Yes ☐ No ☐ Don't know

Next Steps

If you responded "no" or "don't know" to any question:

- ➢ Go to Section 2.2: What are the advantages of first-line TB pharmaceutical specification?

If you responded "yes" to all questions in the exercise above:

- ➢ Go to Section 2.3: Does a strategy to reduce prices and assure quality of first-line TB medicines exist in your country/program?

2.2 What are the advantages of first-line TB pharmaceutical specification?

Why focus on specifications?

If TB medicine characteristics are not specified in the bidding documents, the TB program should elaborate these for each medicine, share them with the procurement officer, and ensure that they are included in the bidding documents.

The following specifications should be made clear as noted—

- *Name:* List the generic (international nonproprietary) name because using generics can increase competition among providers and result in lower prices. Also specify quality standards, not specific brands, for medicines with bioavailability problems, such as rifampicin.

- *Presentation:* Specify the presentation (capsule, tablet, in blister or loose, vial, and so forth) of each type of TB medicine you would like to procure, and the secondary (outer) packaging characteristics. Including these specifications should result in a smoother tendering and procurement process (for example, bidders should understand up front that shipments of different presentations will not be accepted).

- *Dose:* Describe the dosage strength of each medicine for which you are tendering (milligrams per tablet, capsule or vial, and so forth). This specification also should help ensure a smoother tendering and procurement process.

- *Labeling:* Specify content, local language, and special instructions or recommendations (for example, *property of the Ministry of Health, not to be sold*) to be included in labeling. By specifying these instructions and recommendations clearly, medicines are more likely to be used appropriately after they reach the health facility.

- *Expiration date:* Establish the minimum shelf life that each TB medicine should have when delivered to the program. This requirement is the first step in ensuring that quality medicines reach patients before expiry. A medicine's shelf life should be at least 75 percent of the label's expiration date. For most medicines an effective shelf life of at least two years is usually required.

Next Steps

Go to Section 2.3: Does a strategy to reduce prices and assure quality of first-line TB medicines exist in your country/program?

2.3 Does a strategy to reduce prices and assure quality of first-line TB medicines exist in your country/program?

What mechanisms does your country/program use to improve prices and quality of TB medicines?

Strategies to assure TB medicine *quality*:	**Being used in your country/program?**
• Procurement of TB medicines is limited to essential medicines list or formulary list.	☐ Yes ☐ No
• Supplier prequalification: Only prequalified suppliers are allowed to compete in restrictive tenders. This strategy can be used both to assure quality and decrease procurement time.	☐ Yes ☐ No
• Formal supplier qualification based on medicine quality, service, and financial viability as well as formal monitoring of suppliers to ensure continued qualification.	☐ Yes ☐ No
• Product quality assurance program.	☐ Yes ☐ No
• Other: _____	☐ Yes ☐ No

Strategies to reduce TB medicine *prices*	**Being used in your country/program?**
• Bulk procurement: is there a strategy to consolidate requirements and conduct a single tender?	☐ Yes ☐ No
• Competitive bidding is used on all but very small or emergency purchases.	☐ Yes ☐ No
• Suppliers are evaluated after submission of bids in open tenders.	☐ Yes ☐ No
• Transparency and written procedures, including the separation of key functions that require different expertise, ensure that the person or office responsible for awarding the tender is not the same as the person or office paying the supplier. This separation introduces transparency in the process, which can result in increased competition and decreased prices.	☐ Yes ☐ No
• Reliable payment and good financial management.	☐ Yes ☐ No
• Other: _____	☐ Yes ☐ No

How do prices for TB medicines in your country/program compare with prices obtained by others?

The *International Drug Price Indicator Guide*, published by Management Sciences for Health (MSH) since 1986, provides a spectrum of prices from pharmaceutical suppliers and procurement agencies, based on their current catalogs or acquisition prices. This guide, accessible online, can be used to compare the prices that you are obtaining through your procurement process to the prices that others are obtaining.

To access the TB-medicine-specific information, see http://erc.msh.org/dmpguide/classresult.cfm?language=english&year=2003&class_code=06.2.4.&class_code2=06.2.4.&class_name=Antituberculosis%20medicines&action=class&display=yes.

Next Steps

If you responded "no" to any questions in the previous exercise, or if you would like to learn more about different possible mechanisms to reduce the prices and improve the quality of TB medicines:

- Go to Section 2.4: What mechanisms can be implemented to reduce prices of first-line TB medicines and assure quality?

If you responded "yes" to most/all questions:

- Go to Section 2.5: Are first-line TB medicines registered in your country?

2.4 What mechanisms can be implemented to reduce prices of first-line TB medicines and assure quality?

Mechanisms to reduce prices and assure quality of TB medicines[13]

During the tendering process, several steps can be taken in order to obtain high-quality and low-priced TB medicines. Following are useful strategies to assure quality of TB medicines.

Strategies to assure quality

Supplier prequalification

By means of prequalification, a list of acceptable suppliers is qualified before procurement. During prequalification, suppliers provide evidence that they can reliably supply the needed quantity of medicines and that the medicine supplies will meet quality standards. The prequalification process should be transparent and open equally to domestic and international companies. Ideally you will develop documents that specify your program's or country's prequalification requirements but, until these are developed, you can use documents developed by the World Bank to guide this process, or those developed by MSH.[14]

To prequalify a supplier, you should—

- Review medicine certificates provided by the manufacturer and regulatory authority of the manufacturing country. The "Certificate of a Pharmaceutical Product Moving in International Commerce," which follows guidelines of the World Health Organization (WHO), tells you whether the manufacturer is licensed to operate, has been inspected, and has conducted appropriate tests on its medicines.

- Require suppliers to provide references from other buyers, information on contracts with other programs or countries, information on quality control procedures and capacity, data on medicine recalls, and a list of licenses from the manufacturer to sell its products.

- Complete a full, independent audit of the factory's manufacturing practices, or obtain the results of an audit completed by a strong drug regulatory authority or reputable organization or inspector such as a PICS country.[15]

- Require data, both before and after qualification, showing ongoing monitoring of the finished product's quality through batch certification (testing each batch of a product after it is produced).

[13] This section has been adapted from the 2001 *Manager* 10(4); see http://www msh.org/projects/rpmplus/pdf/tb_manager.pdf.
[14] For a copy of tender documents, contact rpmplus@msh.org.
[15] PICS countries' regulatory authorities are members of the Pharmaceutical Inspection Cooperation Scheme; see www.picscheme.org.

- Request and test for quality several samples from the manufacturer that are representative of the manufacturing process being used.

- Require the supplier's financial reports, a letter from tax authorities, and bank references to establish the supplier's financial viability.

Formal supplier qualification and monitoring

Establish and use formal supplier qualification, which should be based on medicine quality, service reliability, and financial viability.

Ideally, a formal system for monitoring suppliers' performance should be in place. Many supply programs rely instead on informal impressions from procurement personnel when selecting suppliers; however, procurement personnel may be unaware of problems that users have had with the TB medicines of specific suppliers.

A system for monitoring suppliers should therefore be based on simple indicators that take into account all activities in the pharmaceutical management cycle. These indicators should monitor—

- Lead time (the waiting period from the time an order is placed until it arrives in-country) to ensure compliance with quoted delivery times

- Product quality, based on a review of the packaging, labeling, and expiration date, as well as results from a laboratory analysis

- Customer service, including each supplier's response to inquiries, provision of documents, and provision of additional services

Product quality assurance program

Establish and maintain a formal system for product quality assurance that includes—

- Product certification
- Inspection of shipments
- Targeted laboratory testing
- Reporting of suspect products

See Section 2.8 for more information on this subject.

Strategies to reduce prices

Bulk procurement

By pooling amounts of TB medicines to be purchased for a number of facilities or regions, your country/program is likely to be able to achieve more favorable prices. However, a contract award to a single supplier for all TB medicines required does not mean that all medicines covered by the contract must be shipped in one order—instead, your country/program should be careful to specify in the contract the number of shipments, when these should take place, and the quantities required (often to multiple delivery points).

Competitive bidding

Inducing supplier competition can result in more favorable pricing. Therefore, if multiple suppliers of TB medicines exist in a given market, public-sector TB programs should strive to use some sort of competitive bidding program for all but very small purchases (for example, emergency).

In restrictive tenders, only prequalified suppliers compete, whereas in open tenders, all suppliers must be evaluated after submission of bids.

Consider alternative providers for direct procurement

When competitive procurement is not a viable or logical option (for example, quantities required are very small or a single provider exists in the country), considering alternative providers makes sense. Request and make price comparisons, and compare with international reference prices. Alternative providers may include WHO, GDF, the United Nations Children's Fund (UNICEF), and the International Dispensary Association (IDA).

Increase transparency, ensure that written procedures are followed, and, if possible, separate key procurement functions

It is essential that the procurement process be as transparent as possible. Written procedures should be followed throughout the tender, and formal, explicit criteria should be used to make procurement decisions. Separation of key functions means that the team (or person) that prepares the bidding documents should not be the same that awards the tender and pays the provider. To the extent possible, information on the tender process, on the results, and on how the decision(s) were made should be made available to the public.

The importance of reliable payment and good financial management

It is critical to develop and implement mechanisms to ensure prompt, reliable payment for TB medicines procured. One way is to make sure funding is available for the quantities to be purchased before placing an order. Prompt payment may bring down prices of medicines as much as bulk discounts. Exploring alternative financial mechanisms for payment for pharmaceuticals might be worthwhile: for example, mechanisms that establish separate medicine

accounts (for example, revolving drug funds) may allow the procurement cycle to operate on a separate schedule from the treasury cycle.

Effect of implementing strategies to reduce prices and increase quality

Putting the described mechanisms into place effectively should not only increase quality and lower cost of TB medicines, but also lower total costs. For example, while the visible cost of the necessary first-line TB medicines for a short-course regimen of 6–8 months may be between USD 10 and USD 30 per treatment course, the hidden costs could easily be twice as much. Hidden costs, or costs usually associated with shortages and poor supplier or procurement office performance can include[16]—

- Increased acquisition costs caused by emergency procurement, such as when a TB medicine is ordered too late or the supplier fails to deliver on time
- Replacement costs when goods are lost or must be discarded because of poor packaging, improper shipping conditions, rapid spoilage, or expired shelf life
- Replacement costs for short shipments, wrong dosage forms, and the like
- Storage or port charges and administrative expenses caused by inefficient clearing procedures, or lack of funds or proper documentation
- Health and economic costs of stockouts resulting from delay or default on delivery

A combination of the previously described strategies can be used. The performance of the procurement process should be based on an analysis of the conditions in which the program operates, a baseline analysis of the price, and the quality of the medicines being purchased as well as annual audits and regular reporting thereafter.

Next Steps

Go to Section 2.5: Are first-line TB medicines registered in your country?

[16] Adapted from MSH. 1997. *Managing Drug Supply: The Selection, Procurement, Distribution, and Use of Pharmaceuticals*. 2nd ed. West Hartford, CT: Kumarian Press, 167.

2.5 Are first-line TB medicines registered in your country?

Registration of TB medicines

In order to be procured, distributed, and dispensed, TB medicines usually first need to be registered in your country. This requirement should be made explicit in the bidding documents.

Does your country/program require the registration of TB medicines before procurement?	☐ Yes ☐ No ☐ Don't know

You should find out whether your country has a rapid registration process for TB medicines in case the suppliers who win your procurement have not registered their medicines in your country. Ignoring the time needed for TB medicines registration can cause shipments to be delayed, jeopardizing the availability of medicines in health facilities.

Next Steps

If you responded "yes" to the previous question:

- Please go to Section 2.6: Explore how your program might facilitate the registration process of first-line TB medicines.

If you responded "no":

- Go to Section 2.7: Does a formal system for quality assurance exist?

2.6 Explore how your program might facilitate the registration process of first-line TB medicines

What might you do to facilitate the registration process?

Private distributors of medicines are responsible for the registration of their products. If the National TB Program (NTP) is procuring medicines through the Global TB Drug Facility, or any other international nonprofit organization, facilitating the registration process may be necessary, requesting the required documentation from the supplier for the pharmaceutical registration office before delivery of the product shipment in the country and serving as an intermediary for any consultation.

Next Steps

Go to Section 2.7: Does a formal system for quality assurance exist for first-line TB medicines?

2.7 Does a formal system for quality assurance exist for first-line TB medicines?

What is quality assurance?[17]

Quality assurance is defined here as "the management activities required to ensure that the TB medicine that reaches the patient is safe, effective, and acceptable to the patient." A comprehensive quality assurance program includes both technical and managerial activities, spanning the entire supply process from medicine selection to patient use.

Although quality assurance activities are particularly concentrated in procurement, they are a relevant element of selection, distribution, use, and management support. Medicines should be selected on the basis of safety and efficacy, in a dosage form with the longest possible shelf life. Sections 1.1, 1.2, and 1.10 discuss the importance of selection of quality-assured first- and second-line medicines.

Medicines received from commercial suppliers and donors should meet specified quality standards at the time of delivery. Packing should meet contract requirements to withstand handling and storage conditions. Sections 3.2, 3.6, and 3.8 discuss the importance of receipt, inspection, storage, and transportation of the products to assure their quality throughout the distribution process.

Product quality concerns reported by prescribers, dispensers, and consumers should be addressed and resolved. Sections 4.3, 4.4, and 4.6 introduce the importance of good dispensing practices for quality assurance.

Finally, quality assurance should be an element in a comprehensive plan to mobilize resources and monitor the performance of the pharmaceutical management system. Section 5.4 presents a synthesis of the quality assurance system used by international agencies such as the GDF, and Section 5.6 presents some indicators that can be used to monitor and evaluate the quality assurance system.

[17] This section has been adapted from MSH. 1997. *Managing Drug Supply: The Selection, Procurement, Distribution, and Use of Pharmaceuticals*. 2nd ed. West Hartford, CT: Kumarian Press, 167.

What are the essential components of a strong quality assurance program?

A quality assurance system must include, at a minimum, the following elements.

Component	Currently conducted as part of your country/program?
• Product certification	☐ Yes ☐ No ☐ Don't know
• Inspection of shipments upon arrival (having each medicine inspected for appearance of the product and packaging)	☐ Yes ☐ No ☐ Don't know
• Laboratory testing (having laboratory tests conducted on samples to test the quality of the medicine's active ingredient)	☐ Yes ☐ No ☐ Don't know
• Reporting of suspected poor quality products (formal procedure should exist and be known in order to facilitate this process)	☐ Yes ☐ No ☐ Don't know

The product certification is only as reliable as the agency issuing it. If the certification is well performed, the procurement office should be able to learn the following information through the scheme—

- Whether a product is licensed to be placed on the market in the exporting country, and if not, the reasons why
- Whether the supplier manufacturers the dosage forms and packages or only labels finished dosage forms and distributes the medicines manufactured by an independent company, or is involved in none of these activities
- Whether the manufacturer of the product has been inspected and the periodicity of inspection
- Whether the quality certificate is provisional, pending technical review
- Whether the information submitted by the supplier satisfies the certifying authority on all aspects of manufacture of the product if it is performed by another party

Next Steps

If you responded "no" or "don't know" to any of the questions above:

- ➢ Go to Section 2.8: Consider implementing a formal quality assurance system for first-line TB medicines.

If you responded "yes":

- ➢ Go to Section 2.9: Tender process for first-line TB medicines.

2.8 Consider implementing a formal quality assurance system for first-line TB medicines

Why should your country/program consider implementing a formal quality assurance program for TB medicines?

A strong quality assurance program is extremely important for successfully combating TB: effective, unharmed, unexpired medicines are essential to cure patients and minimize development of resistance. The purpose of quality assurance in TB pharmaceutical supply systems is to ensure that TB medicines reaching a patient are safe, effective, and of standard quality. To function effectively, this program must be an integral part of all components of medicine supply, starting with careful product selection and being integrated into procurement practices, distribution, and use. The quality of TB pharmaceutical products is ensured by more than laboratory testing of medicine samples, because a comprehensive quality assurance program includes both technical and managerial activities. Quality assurance in TB medicines supply is not the same as quality control in manufacturing.

What are the key components of a formal quality assurance system?

- TB pharmaceutical product certification
- Good manufacturing practices certification and other product quality information
- Inspection of shipments of TB medicines
- Contract specifications
- Laboratory testing of TB medicines

In order to ensure the quality of TB medicines, the program's tender documents and contract specifications should ensure that potential suppliers provide laboratory testing samples and information regarding the following.

TB pharmaceutical product certification

Certification—

- Verifies registration of the given TB medicines in manufacturer's country
- Provides evidence that the product/supplier has obtained a WHO-type certificate from the drug control agency/authority of the exporting country
- Includes a batch analysis certificate from the manufacturer or international quality control organization of the given TB medicines

Good manufacturing practices certification

Good manufacturing practices (GMP) require that manufacturers, processors, and packagers of medicines, medical devices, food, and blood take proactive steps to minimize or eliminate instances of contamination, mix-ups, and errors to ensure that their products are safe, pure, and effective.

Suppliers should obtain GMP certification from the national drug regulatory authority in their country, UNIPAC, or other international PICS organization.[18] GMP certification requires documented evidence that personnel, facilities, equipment, materials, manufacturing operations, labeling, packaging, quality control, and stability and validation testing are appropriate for the product. Your country/program should ensure that the suppliers from whom you are procuring TB medicines have received GMP certification from a reliable source. This information should be provided by the supplier; if the supplier cannot provide GMP certification, consider using another supplier. As a last resort, you could request recent reports of GMP inspections and medicine recall histories from national drug regulatory agencies of the countries in which the suppliers are located. For those suppliers providing International Standards Organization (ISO)[19] certification, make sure the certificate includes the section on good manufacturing practices.

Other product quality information

The supplier should provide other documents, such as a certificate of analysis provided by the manufacturer stating the test results from a particular batch are in accordance with reference specifications such as the British Pharmacopoeia (BP), United States Pharmacopeia (USP), or International Pharmacopeia.

Inspection of shipments certificate[20]

Each shipment of TB pharmaceuticals should be physically inspected through verification of adherence to contract specifications and order completeness and also through inspection of samples of all items to spot any gross abnormalities. Inspection of TB medicines can sometimes be arranged to take place in the exporting country prior to shipment through an independent agency (one example is SGS, Société Générale de Surveillance) and can result in cost savings because noncompliance with contract terms or defective products can be identified relatively early in the procurement process.

Contract specifications

Details that should be specified in the contract and with which the shipment of delivered TB medicines must conform in order for the provider to accept the delivery include—

[18] PICS is the Pharmaceutical Inspectorate Cooperation Scheme composed of various countries interested in improving their capacity in drug regulation and GMP inspections. See http://www.picscheme.org/index.htm.
[19] ISO is a nongovernmental organization comprising a network of the national standards institutes of 153 countries that defines specifications that products, including pharmaceuticals, and services will be expected to meet on export markets. For more information, see http://www.iso.org/iso/en/aboutiso/introduction/index.html#five.
[20] This section has been adapted from MSH. 1997. *Managing Drug Supply: The Selection, Procurement, Distribution, and Use of Pharmaceuticals*. 2nd ed. West Hartford, CT: Kumarian Press, section 18.4.

- Pharmacopeial reference standard
- Local language for product label
- Minimum information to provide on label (medicine name, strength of medicine, INN, expiration date, manufacturer's name and location)
- Any other additional information required
- Standards for packaging to meet specific storage and transport conditions, such as thickness of outer packaging

Laboratory testing[21]

If possible, laboratory testing of batch samples upon arrival at the country/program is usually recommended for all TB medicines coming from most national or international providers. Comparative dissolution tests are recommended for all components. Fixed-dose combination (FDC) TB medicines, especially combinations containing rifampicin, require special monitoring to assure quality, including laboratory testing and verifying bioavailability in humans. In countries that lack clearly defined, functional quality assurance programs or skilled specialists, managers may need to compare data from tests of FDC products with data from tests of single-ingredient medicine products using accepted international pharmacopeial standards and good manufacturing practices.

Be aware that some suppliers have inaccurately promoted their products as FDCs containing WHO-approved combinations of medicines and strengths. Some have even attached WHO treatment guidelines to medicine shipments, falsely attempting to validate their products. When selecting FDCs, managers always need to verify that these medicines comply with approved treatment standards.

TB medicines procured through the GDF/GLC: GDF and GLC quality assurance procedures are strict enough so that in-country laboratory testing may be unnecessary.

Other components that contribute to an effective quality assurance system include appropriate storage, transport, dispensing, and use of TB medicines, as well as establishment and implementation of a TB product monitoring and reporting system. These components are discussed in the following sections of the manual.

Next Steps

➢ Go to Section 2.9: Tender process for first-line TB medicines.

[21] This section is adapted from "Improving Drug Management to Control Tuberculosis," *The Manager*, see www msh.org/projects/rpmplus/pdf/tb_manager.pdf.

2.9 Tender process for first-line TB medicines

What possible procurement methods exist and what are the advantages of each?

Various procurement methods exist and can be used to procure TB medicines; however, more-competitive methods are generally preferred over direct procurement, given that competition usually brings prices down. Direct procurement is justified when few suppliers exist or when an international agency can ensure best quality at lowest price.

In most countries the tender process is a direct responsibility of Ministry of Health procurement departments. After the NTP specifies the medicines and quantities to be purchased, it should be involved in the procurement process to ensure that specified medicines are purchased at the best quality and price.

Common procurement methods include the following.

Open tender: Bidding is open to all interested national or international suppliers. Different types of open tenders include—

- National Competitive Bidding
- International Competitive Bidding (ICB)

Restricted tender: Participation of suppliers is limited to those who have registered with the government or who are prequalified. A limited competitive bidding is a restricted tender with prequalification. This method is usually recommended for tuberculosis medicines.

Prequalification is usually necessary for tuberculosis medicines and supplies. The following steps should be considered in a prequalification process[22]—

- List documentation that will be required for prequalification of manufacturers, agents, and middlemen
- List documentation that will be required to establish supplier eligibility
- Advertise prequalification criteria (journals, embassies, newspapers)
- Notify qualified and unqualified applicants

Competitive negotiation: The buyer approaches a small number of potential suppliers and bargains for specific price or service arrangements.

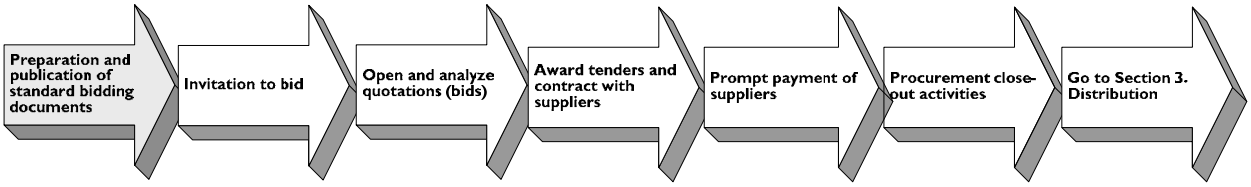
[22] WHO has set up a prequalification process for suppliers of medicines to treat AIDS, malaria, and tuberculosis; see http://mednet3.who.int/prequal/.

Direct procurement: A purchase from a single supplier at the quoted price (as in emergency or small purchases in national markets). Among alternative international options to procure first-line medicines directly are—

- The Global TB Drug Facility: Governments and organizations have been able to obtain (in some cases free) high-quality, first-line TB medicines through this mechanism since 2001. For more information about GDF procurement methods and grants, see www.stoptb.org/gdf.

- International agencies such as the Pan American Health Organization, UNICEF, and nonprofit suppliers (IDA and others).

If your country decides to procure TB medicines through an open tender, the following steps should be followed—



Note: The arrow will be shaded in subsequent sections discussing information relating to the subject matter indicated.

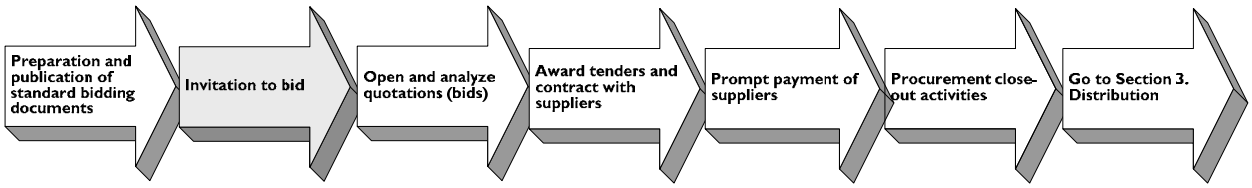
Instructions: For all tables that follow in this section, complete the checklists to assess your program or to record progress as steps are taken to implement the various listed activities.

Keep in mind that, in order to guarantee a successful tender and avoid stockouts, the planning process should consider the time required to complete each of the mentioned phases. In most countries the preparation of the tender process usually requires at least six months (from the preparation of the bidding documents to the distribution of the medicines).

Preparation and publication of standard bidding documents

Before the invitation to bid, the procurement office should take the following steps.

Step	Done (Date)
• Verify budget estimates and availability of funds	☐
• Prepare procurement requirements	☐
• Determine selection criteria; obtain approval from tender committee	☐
• Open procurement files on each product	☐
• Ensure that pertinent information is in one place for easy reference	☐
• Prepare bid evaluation system; agree on merit/point system for (1) technical compliance, (2) contractual merit, (3) commercial merit and (4) financial merit	☐



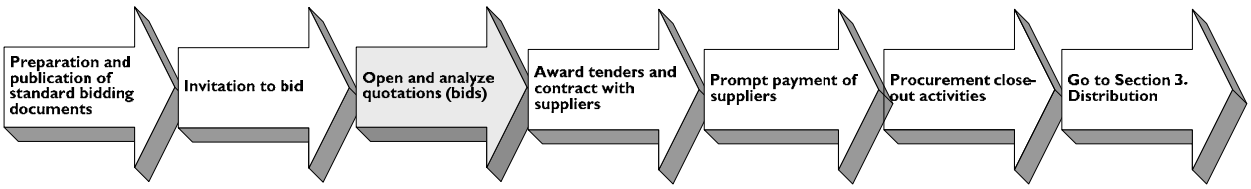
Invitation to bid

In competitive tenders the invitation to bid is usually published in local newspapers, international publications, and on the Internet. The invitation usually explains where and when a copy of the bidding documents can be obtained.

The bidding documents should include, but not be limited to, the following terms.

Term	Included in presently used TB medicines bidding documents?
• Eligibility	☐
• Technical specifications	☐
• Licensing	☐
• Quantity	☐
• Delivery date	☐
• Shipping terms and documentation	☐
• Payment terms	☐
• Certificate of analysis, protocols, signed by National Drug Regulatory Authority	☐
• Copies of package inserts	☐
• Prices itemized	☐
• Validity of offer	☐
• Offer must be signed by authorized representative	☐
• Samples	☐
• Date of submission	☐
• Registration forms for licenses or prequalification	☐
• Warranty for discrepancies caused by supplier	☐
• Delays in supplier's performance	☐
• Liquidated damages	☐
• Termination for default, insolvency, convenience	☐
• Resolution of disputes	☐
• Taxes and duties	☐
• Signing of contract	☐
• Annex of terms and conditions, schedule of requirements	☐

Models of standard bidding documents are available by contacting MSH at the following e-mail address: rpmplus@msh.org.



Open and analyze quotations (bids)

Establishing a transparent, thorough supplier selection process can help—

- Minimize the costs of TB medicines procured
- Ensure that medicines procured meet desired quality standards
- Ensure that suppliers are reliable and will deliver the specified quantity and quality of TB medicines within the expected delivery period
- Encourage the participation of more suppliers

When selecting a TB medicine supplier, the following routine criteria should be taken into consideration.

Criteria that should be taken into consideration when determining which TB medicine supplier to use	**Presently taken into consideration as part of the process to determine TB medicine supplier?**
• All the costs are visible (taxes, shipment, etc.)	☐
• Medicine quality is reliable	☐
• Service is reliable (delivery date is met for other clients)	☐
• Product specifications are complied with	☐
• Contract specifications are complied with	☐

Additional criteria may depend on local situation or special circumstances but also weigh in the decision of which TB medicines supplier to use.

Other criteria that may need to be taken into consideration	**Presently taken into consideration as part of the process to determine TB medicine supplier?**
• Local preference	☐
• Supplier performance (local and international)	☐
• Intergovernmental trade agreements (policy)	☐
• Donor agency restrictions	☐

The bid-opening process should be as transparent as possible in order to lend credibility and legitimacy to the entire process. Ideally the following steps are taken—

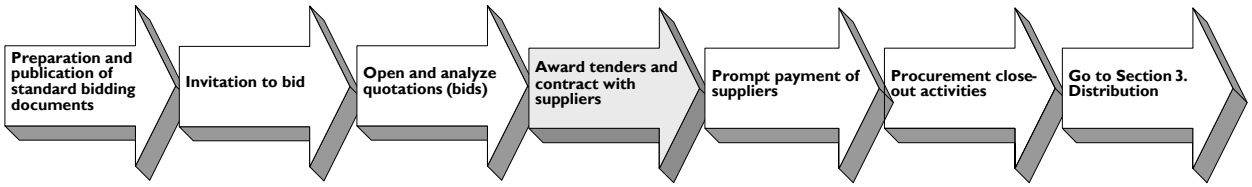
Step	Presently included as part of the bid-opening process?
• Prepare a form for recording bid opening	☐
• Hold a formal bid opening at time and place specified in the bid documents	☐
• Record attendance (name, address, company, signature)	☐
• Open bids: read aloud, sign/stamp all pages of all bids	☐
• Record proceedings and summary of quotations	☐
• Record responsiveness	☐
• After public opening of bids, conduct bid examination to catch any errors	☐
• Collect and record bid securities	☐
• Complete and sign record of bid examination	☐

The best method for evaluating and comparing submitted bids requires that a systematic stepwise process should be followed. The following elements should be included in this process—

Step	Presently included as part of the bid evaluation and comparison process?
• Prepare a bid summary for each bid response received	☐
• Attach a detailed bid summary and record the bid summary for each responsive bidder	☐
• Prepare a merit/point system, if applicable, considering a proper balance among quality, price, and opportunity	☐
• Prepare adjudication forms for comparison of bids	☐
• Prepare documents for tender review committee	☐

The selection process should focus on the following elements.

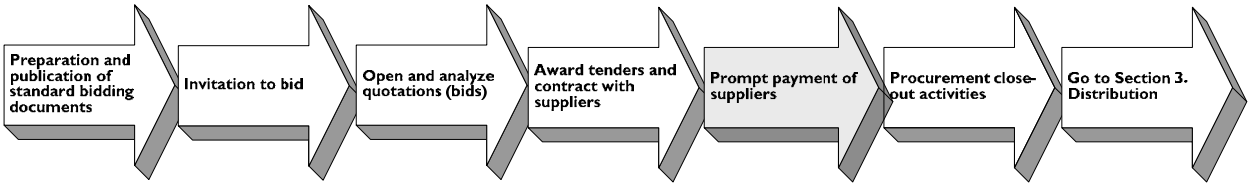
Step	Presently included as part of the selection process?
• Documents presented for tender review	☐
• Review and compare bids: technical, contractual, and financial merits of each option	☐
• Determine whether further action or investigation is needed	☐
• Make first tentative recommendations	☐
• Review merit/point system again and assign ranking	☐
• Adjudicate bids and record committee's decision	☐
• Obtain signatures from tender committee	☐
• Secure additional approvals (Ministry of Health, Ministry of Finance, NTP, others)	☐



Award tenders and contract with suppliers

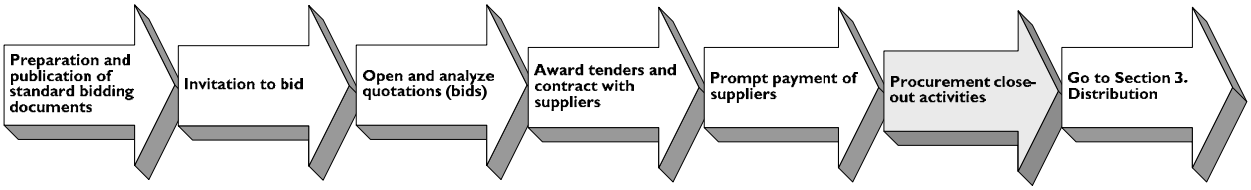
Ideally, in order to have an efficient and transparent bid-awarding process, the following steps should be included.

Step	Presently included as part of the bid award process in your country/program?
• Notify successful bidder	☐
• Resolve contract issues	☐
• Negotiate any changes and secure approvals	☐
• Add any modifications to the original contract	☐
• Prepare an addendum if required	☐
• Prepare an official bid award letter and contract form for signature by official(s)	☐
• Transmit award letter with general shipping conditions	☐
• Contract with suppliers	☐
• Notify unsuccessful bidders	☐



Prompt payment of suppliers

Prompt payment of TB medicine suppliers is essential to the credibility of your program and will play a large role in suppliers' decisions to maintain your program as a client. In order to ensure consistent and reliable prompt supplier payment, you should consider a release of funds arrangement with your program's finance unit or funding organization or request and verify a down payment or a letter of credit from your program's finance unit or central bank. A letter of credit is a banking tool extensively used in national and international trade. It can function as a tool to enforce quality assurance, inspection, certificates, and authorization of shipments. It guarantees payment to the seller, while allowing the buyer to retain funds in its bank until the seller has complied with the contract terms.



Procurement close-out activities

After a bid has been awarded, a number of factors should be monitored and recorded on a regular basis, including the following—

Monitoring and recording	Presently taking place?
• Overall contract performance	☐
• Shipping authorizations and timelines	☐
• Customs clearance and delivery	☐
• Product performance (usually done through the National Drug Regulatory Authority)	☐

In addition, supplier history forms and warranty records should be kept.

Next Steps

- If there is a DOTS-Plus Project, go to Section 2.10: Procurement mechanisms for second line TB medicines.
- If not, go to Section 3: Distribution.

2.10 Procurement mechanisms for second-line TB medicines

Procurement of second-line TB medicines

From a public health point of view, it is better not to launch a DOTS-Plus project if appropriate conditions are not in place, such as—

- The ability to collect and analyze cohort data
- A combined default and transfer rate under 6 percent
- A continuous supply of first-line anti-TB medicines
- Application of DOTS in 90 percent of cases

If these conditions are not in place, resistance to second-line medicines is likely to emerge rapidly, and cure will become extremely difficult or impossible. See Section 1.8 for a more detailed explanation on when to consider implementing a DOTS-Plus project.

If your country/program has already decided to implement a DOTS-Plus project, one of the first and most important steps is to select the supplier and the procurement mechanism for second-line TB medicines. Two options exist—

- A competitive tender in international markets using procedures similar to those described for first-line pharmaceuticals

- Direct procurement using the Green Light Committee mechanism

2.11 Competitive tender in international markets

The advantages, disadvantages, and recommended procedures for procuring first-line TB medicines in international markets through competitive tender have already been described in Section 2.9. These issues are similar for procurement of second-line TB medicines; therefore, if a country chooses to procure second-line TB medicines through a competitive international tender, it should consult that section.

Please also bear in mind that, in addition to second-line medicines, a DOTS-Plus project requires an adequate supply of medicines to treat adverse reactions; supplies for injectables, such as syringes; IV administration sets; and reagents/standards for laboratory testing.

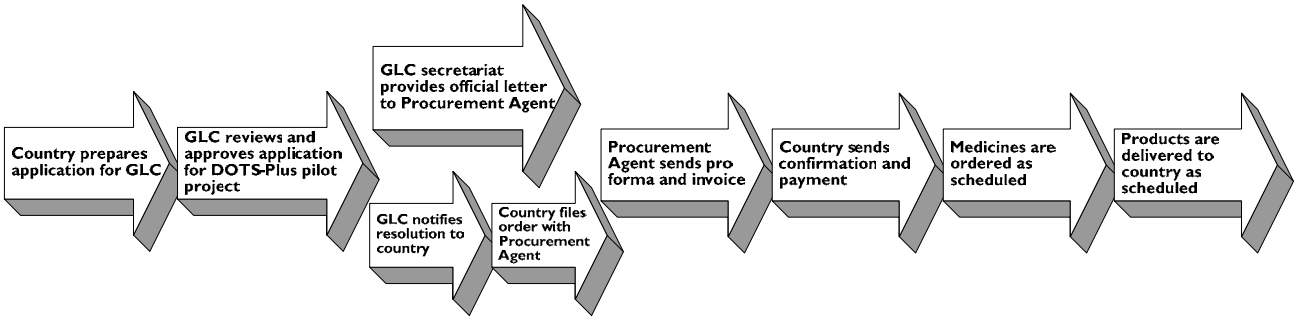
2.12 Direct procurement through the Green Light Committee

Direct procurement is an adequate mechanism when market forces fail, as is the case for second-line TB medicines. This market failure can be explained by the fact that little demand exists for second-line medicines, which means few suppliers are interested in meeting the low demand; as a result, little competition exists, which, in turn, implies higher prices.

Given that each country seeking second-line medicines has few MDR-TB patients to treat, each alone does not have the purchasing power to command low prices. A possible solution to this problem is pooled procurement by an organization that procures on behalf of several countries, thus increasing the number of patients who require second-line medicines and bringing down the price.

The Green Light Committee was established with that purpose in mind. It functions as a pooled procurement mechanism for second-line TB medicines and in addition provides extensive technical assistance to DOTS-Plus projects.

Direct Procurement through the Green Light Committee



Features of the GLC

The GLC is a technical panel of the Stop TB/WHO working group on DOTS-Plus for MDR-TB. Its members are WHO, the U.S. Centers for Disease Control and Prevention (CDC), the Medical Research Council (MRC), the International Union against TB and Lung Disease (UNION), the NTPs of Estonia and Latvia, and Harvard Medical School. The GLC secretariat that coordinates the work of the GLC is located within the Stop TB department at WHO.

The GLC's primary function is to review applications from TB programs wanting to implement a DOTS-Plus project and advise WHO/DOTS-Plus on which projects should benefit from specially priced, quality-assured second-line TB medicines. A country must comply with WHO standards (*Guidelines for Establishing DOTS-Plus Pilot Projects for the Management of MDR-TB*[23]) to be accepted for participation in the GLC pooled procurement process. The GLC performs procurement activities for second-line medicines through its procurement agent,

[23] See http://www.who.int/docstore/gtb/publications/dotsplus/dotspluspilot-2000-279/english/foreword.html.

currently the IDA, a nonprofit foundation. IDA is responsible for negotiation with suppliers, procurement, quality assurance, and distribution of second-line TB medicines and adds a 7 percent margin to the purchase prices to covers its operating expenses. The GLC is considering the feasibility of joint procurement activities with the Global TB Drug Facility.

Technical assistance is arranged through the GLC technical panel for TB programs wanting to establish a DOTS-Plus project. The GLC monitors approved projects, providing for technical assistance as needed, and collects global evidence for developing policy in controlling MDR-TB.

GLC preapplication phase

Before applying to the GLC, the potential DOTS-Plus project needs to fulfill a number of steps. If your country/program is considering applying to the GLC, please complete the following table to ensure that you have a good chance of having your application approved.

Step	Presently the case in your country/program?
• The DOTS strategy is in place and functioning well	☐ Yes ☐ No ☐ Don't know
• Government commitment and adequate funding for a DOTS-Plus project exist	☐ Yes ☐ No ☐ Don't know
• A coordinated project management plan exists	☐ Yes ☐ No ☐ Don't know
• Adequate laboratory services have been established	☐ Yes ☐ No ☐ Don't know
• A rational treatment strategy for second-line medicines has been approved	☐ Yes ☐ No ☐ Don't know
• A functioning information management system has been developed	☐ Yes ☐ No ☐ Don't know
• Second-line medicines that your country/program plans to request are registered in your country	☐ Yes ☐ No ☐ Don't know
• A plan has been developed for dealing with local customs procedures when importing medicines	☐ Yes ☐ No ☐ Don't know

How to apply to the GLC

After the previous elements are in place, the applicant should follow these steps—

Step	Completed (Date)
• Prepare and submit an application to the GLC using "Instructions for Applying to the Green Light Committee for Access to Second-Line Anti-Tuberculosis Drugs" (see http://www.who.int/docstore/gtb/policyrd/PDF/GLC_Application_Instructions.pdf)	☐
• Respond to GLC comments, questions, requests for additional information or instructions resulting from the review of the application within the next three months	☐
• Facilitate a site visit, if requested by the GLC	☐
• Agree to specific terms and conditions as outlined in the Letter of Agreement with WHO/Dots-Plus	☐

GLC quality assurance

The GLC can feel confident that high-quality second-line TB medicines are being procured under IDA because IDA uses good distribution practices (according to WHO guidelines) and prequalifies manufacturers (it assesses quality assurance systems, audits manufacturing plants, performs laboratory analysis on batch samples, and sends information and documentation to facilitate registration of medicines in-country).[24]

GLC operational process

DOTS-Plus country projects that are approved by the GLC sign a contract with WHO/Dots-Plus. The GLC secretariat then introduces the approved project to the procurement agent through an official letter. The approved country project sends confirmation of order and payment to the procurement agent, and medicines are delivered to the site designated by the country of the DOTS-Plus project. Enrollment, treatment, and monitoring of the cohort on second-line treatment then begins, periodic data and reports are sent to WHO, and monitoring visits by the GLC and consultants are conducted. Technical assistance from members of the Working Group is provided to projects as needed.

Some challenges that countries have faced while procuring second-line medicines through the GLC have been noted.

- It usually takes four months from the time an order is placed until the second-line medicines are delivered because no medicines are kept in stock by the procurement agent and manufacturers of second-line TB medicines produce these medicines on demand.

- Special attention needs to be paid to inventory control because capreomycin and cycloserine have a particularly short shelf life, or expiry date (18 months from one supplier).

[24] As suppliers continue to be qualified by the WHO/Medicines prequalification project for medicines to treat first-line TB, HIV/AIDS, and malaria, soon there will be a list of suppliers for second-line TB medicines as well. This list of suppliers will help GLC further assure the quality of the medicines it procures.

Annex 2.1 Additional References

Management Sciences for Health and World Health Organization. 1997. Chapter 13, "Managing Procurement." In *Managing Drug Supply: The Selection, Procurement, Distribution, and Use of Pharmaceuticals*. 2nd edition. West Hartford, CT: Kumarian Press, Inc.

Pio, A., and P. Chaulet. 1998. *Tuberculosis Handbook*. Geneva: World Health Organization. WHO/TB/98.253.

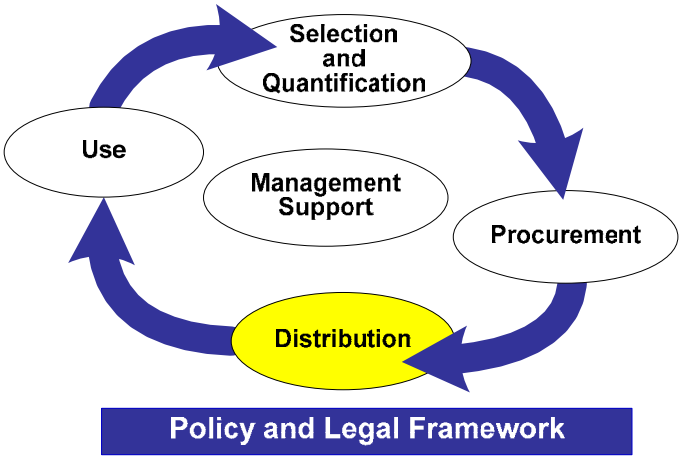
World Bank. 2000 (revised 2001, 2002, 2003). Standard Bidding Documents: Procurement of Health Sector GoodsWashington, DC.
http://siteresources.worldbank.org/PROCUREMENT/Resources/health-ev4.doc.

World Health Organization. 2000. *Guidelines for Establishing DOTS Plus Pilot Projects for the Management of Multi-Drug-Resistant Tuberculosis (MDR-TB).* WHO/CDS/2000.279.

World Health Organization. 2002. "Instructions for Applying to the Green Light Committee for Access to Second-Line Anti-Tuberculosis Drugs." WHO/CDS/TB/2001.286 Rev.1.

World Health Organization. 2003. *Procurement Manual for the DOTS-Plus Projects Approved by the Green Light Committee.* WHO/HTM/TB/2003.328.

Section 3. Distribution



Introduction

What Is a Distribution System?

A *distribution system* ensures a continuous flow of supplies from a central point to the end-user facilities. It is composed of four major elements: the system's design (degree of centralization, push versus pull ordering, geographic or population coverage, number of different levels); an information system (inventory control, records and forms, consumption reports, information flow); appropriate storage (locations, building design, materials handling systems, and order picking systems); and delivery (collection versus delivery, choice of transport, vehicle procurement, vehicle maintenance, routing, and scheduling of deliveries).

Distribution of First-Line TB Medicines

The distribution activity of the pharmaceutical management cycle must ensure that TB medicines are available in the quantities needed for all patients during all treatment phases. The distribution phase of the cycle includes clearing medicines through customs, transporting them, making timely deliveries, keeping records, maintaining adequate storage levels, and following appropriate storage procedures in all facilities (see figure 3.1).

Unlike most medicines, first-line TB medicines do not have effective substitutes if stock runs out. Good distribution ensures that all first-line TB medicines are available in the quantities needed, at all points of administration to patients, at all times.

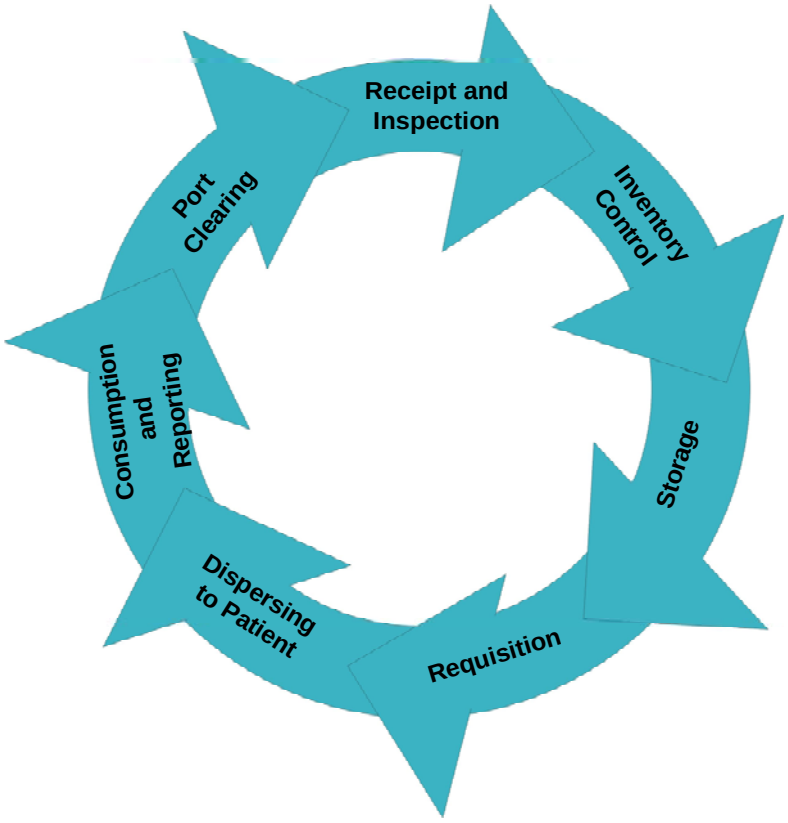


Figure 3.1 Distribution Cycle

Medicine storage and delivery costs are a significant component of national TB program (NTP) budgets. Transportation costs to remote locations can represent several times the value of medicines distributed. In addition to TB medicines, TB storage and distribution logistics include laboratory materials and recording and reporting forms.

The most important elements to be considered in a distribution system are design (centralized or decentralized), information systems, storage conditions, and delivery mechanism. This section analyzes each of these elements and discusses various options for improving the efficiency of the entire system.

Distribution of Second-Line TB Medicines

In this section, second-line TB medicines are considered alongside first-line medicines, because distribution mechanisms do not differ in every aspect. Some differences do exist, however. For example, second-line medicines have a shorter shelf life than first-line medicines, and medicines for treating adverse reactions should be kept in stock. Another difference is that inventory control and reordering of second-line medicines is based on consumption not morbidity (see Section l.13 for more information), because even standardized regimens may be modified throughout a treatment course if results are poor or adverse reactions develop.

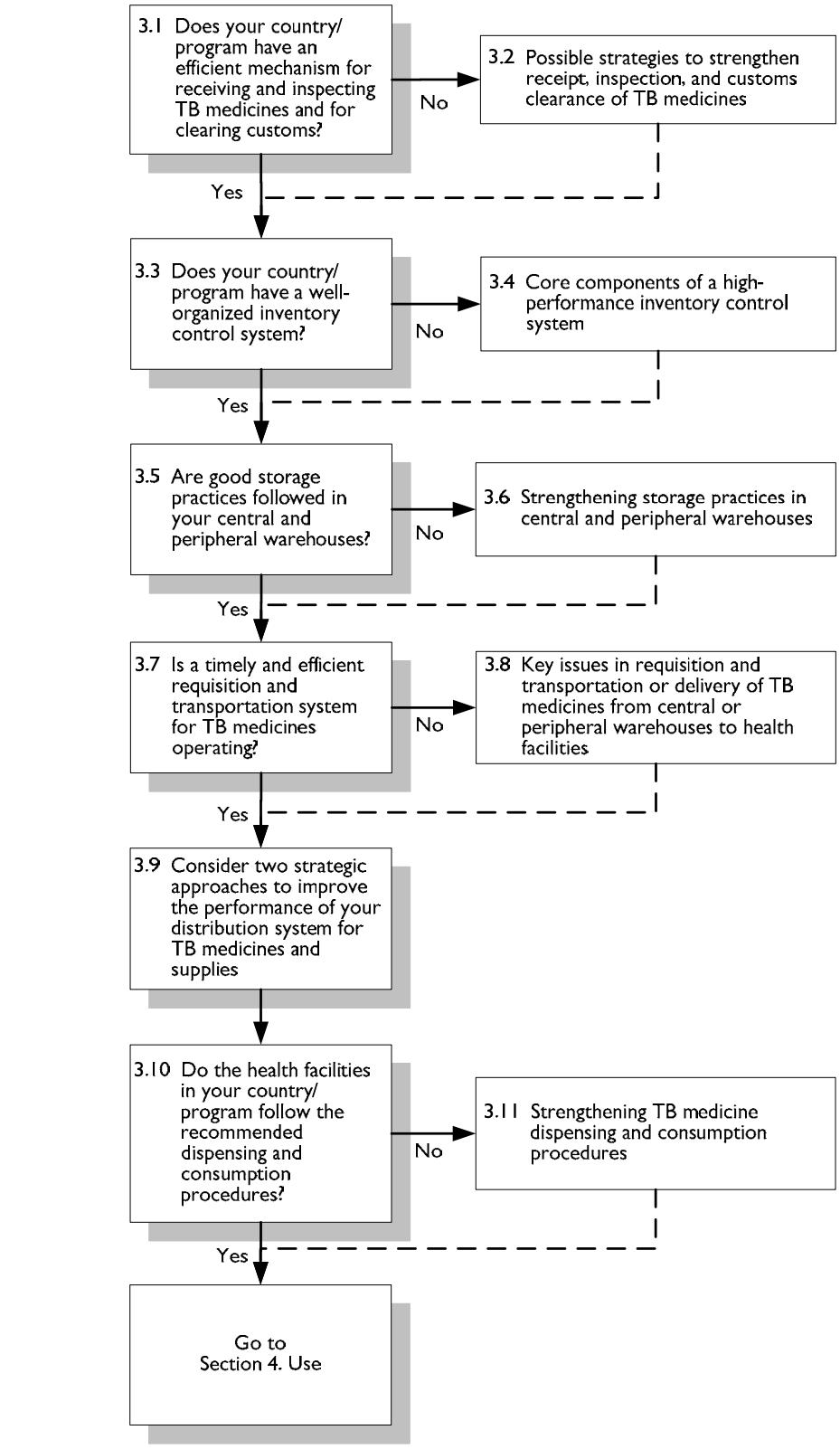
Characteristics of a Well-Managed Distribution System

You know that your country/program's distribution system is well-managed when—	
• A constant supply of TB medicines is maintained to avoid stockouts	☐
• Medicine quality is conserved throughout the distribution process	☐
• Loss of TB medicines is minimized	☐
• Accurate inventory records are maintained	☐
• Storage points for TB medicines are rationalized	☐
• Available transportation resources are used efficiently	☐
• Theft and fraud are reduced	☐
• Information required for forecasting medicine needs is generated	☐

Overview and Key Issues in This Section

This section addresses key issues in distribution, such as port clearance of TB medicines, timely and effective transportation, essentials of good storage practices, inventory control, requisition, receipt and inspection procedures, and distribution at the health-facility level. The section also addresses advantages and disadvantages of working solely with the public sector compared with developing a collaborative or contractual relationship with private organizations who in turn take on some or all of the distribution responsibility. At the end of the section, a checklist is provided that addresses all aspects of distribution of TB medicines; this checklist can be used to comprehensively assess your country's performance against a number of criteria that contribute to an effective and efficient distribution system (see Annex 3.2).

Distribution of TB Medicines



3.1 Does your country/program have an efficient mechanism for receiving and inspecting TB medicines and for clearing customs?

Common problems in receipt, inspection, and customs clearance of TB medicines

The following table outlines common problems in receipt, inspection, and customs clearance of TB medicines. Please complete the table to get a sense of potential areas of weakness in the process used by your country/program to receive and inspect TB medicines and to clear these medicines through customs.

Common problems with port and customs clearance	Occurs in or frequency of occurrence in your country/program
• It is clear who should take charge for port and customs clearance of TB medicines.	☐ Yes ☐ No ☐ Don't know
• Responsible staff members are able to attend to port and custom clearance duties within 1–2 days after arrival of TB medicines.	☐ Every procurement ☐ Often ☐ Seldom ☐ Never ☐ Don't know
• Customs tax payments are arranged before arrival of the shipment so delays are avoided.	☐ Every procurement ☐ Often ☐ Seldom ☐ Never ☐ Don't know
• Documents are prepared in advance, thus avoiding delays.	☐ Every procurement ☐ Often ☐ Seldom ☐ Never ☐ Don't know
• Medicines are registered before receipt in-country, thus avoiding delays.	☐ Every procurement ☐ Often ☐ Seldom ☐ Never ☐ Don't know
• Storage conditions for medicines during clearance are sufficient and maintain quality.	☐ Every procurement ☐ Often ☐ Seldom ☐ Never ☐ Don't know

Next Steps

If, from your completion of the previous table, you feel that receipt, inspection, and customs clearance of TB medicines could be strengthened in your country/program:

- Go to Section 3.2: Possible strategies to strengthen receipt, inspection, and customs clearance of TB medicines.

If, on the other hand, the mechanisms in your country seem to be quite efficient:

- Go to Section 3.3: Does your country/program have a well-organized inventory control system?

3.2 Possible strategies to strengthen receipt, inspection, and customs clearance of TB medicines

Port clearance of TB medicines

TB programs alone, or in conjunction with other parts of the Ministry of Health (MOH), are usually responsible for port clearance of imported TB medicines. In some cases, if the TB program or the MOH does not have the experience or resources to conduct port clearance, this activity may be transferred to the pharmaceutical distributor (or a private pharmaceutical provider).

Clearance through customs includes the following activities—

- Identifying and locating the arrival of shipments of TB medicines
- Storing medicines in a quality manner until they leave the port
- Obtaining clearance documents
- Inspecting shipment for losses or damage

Identifying and locating the arrival of shipments of TB medicines

Who is responsible for port clearance of TB medicines in your program/country?

Responsible for port clearance	First-line TB medicines	Second-line TB medicines
TB program alone	☐	☐
TB program and MOH Department:	☐	☐
MOH department alone Name:	☐	☐
Pharmaceutical distributor Name:	☐	☐
Private pharmaceutical provider Name:	☐	☐
Other (type of organization and name):	☐	☐
Don't know	☐	☐

In order for the port clearance activities to be efficient, responsibility for port clearance must be clear, staff members must have the time to participate in port clearance activities after medicines arrive in-country, and payments must be anticipated and documents prepared beforehand to avoid unnecessary delays at the port. Delays will reduce shelf life and will increase the potential for theft of TB medicines, unexpected storage fees, and stockouts, resulting in the need for emergency purchases and incurring higher-than-necessary costs to the program.

Not all of these functions necessarily need to be taken on by the TB program. Instead, the contract can stipulate that the supplier is responsible for port clearance or, alternatively, responsibility for port clearance can be contracted out to a private provider.

Storing medicines properly until they leave the port

Appropriate storage conditions should be ensured for TB medicines stored at each and all possible storage points during distribution (before clearance from the port, at central/peripheral warehouses, and at individual health facilities). Products should be protected from heat, direct sunlight, humidity, and theft. See Section 3.6 for more details about appropriate storage practices for TB medicines.

Obtaining clearance documents

Often these documents are provided by a specific department within the MOH and the customs office. In both cases, the NTP should coordinate this process.

Inspecting shipment for losses or damage

Complete the following table to get a better sense of what areas need improvement in order to strengthen receipt and inspection practices in the central and peripheral warehouse(s) in your country/program.

Mechanisms to improve TB receipt and inspection in central or peripheral warehouse(s)	Practice is followed?
• Check that the supplier's invoice corresponds to the original purchase order	☐ Yes ☐ No ☐ Don't know
• Visually inspect, at random, that quantities of containers, packages, and items in each package are correct	☐ Yes ☐ No ☐ Don't know
• Visually inspect, at random, that TB medicines, dosages, form, and strength are all correct	☐ Yes ☐ No ☐ Don't know
• Visually inspect packages at random to ensure no tablets have been crushed and/or no vials have been broken	☐ Yes ☐ No ☐ Don't know
• Visually inspect, at random, that medicines are correct color and correctly labeled and that any other unique identifiers (codes for example) are present	☐ Yes ☐ No ☐ Don't know

Next Steps

Go to Section 3.3: Does your country/program have a well-organized inventory control system?

3.3 Does your country/program have a well-organized inventory control system?

What are inventory and inventory control?

Inventory is the total of all products kept on hand at any storage point. A good distribution system must aim at protecting against uncertainty of quantities needed, permit bulk purchasing, minimize waiting time, increase transportation efficiency, and buffer against seasonal fluctuations.

Inventory control is the function of supply management that focuses on providing sufficient stocks of medicines while minimizing handling costs; inventory control includes requisitioning and issuing products, financial accounting, and preparing the consumption and stock balance reports necessary for procurement.

Common pitfalls in TB medicine inventory control

The following table outlines common problems in inventory control for TB medicines at treatment centers and warehouses. Please complete the table to get a better sense of what areas need improvement to strengthen inventory control procedures in your country/program.

Element of inventory control	Takes place in my country
• Document when new TB medicines arrive at facility	☐ Yes ☐ No ☐ Don't know
• If relevant, document when TB medicines are sent to lower-level facilities	☐ Yes ☐ No ☐ Don't know
• Use first-expiry, first-out (FEFO) method for stock rotation to avoid expired TB medicines, then use first-in, first-out (FIFO) method	☐ Yes ☐ No ☐ Don't know
• Calculate average monthly or quarterly consumption (annual consumption divided by 12 or 4)	☐ Yes ☐ No ☐ Don't know
• Calculate safety stock (number of months to order and receive stock)	☐ Yes ☐ No ☐ Don't know

Next Steps

If, from your completion of the previous table, you feel that inventory control of TB medicines could be strengthened in your country/program:

- Go to Section 3.4: Core components of a high-performance inventory control system.

If, on the other hand, the inventory control mechanisms in your country seem to be quite efficient:

- Go to Section 3.5: Are good storage practices followed in your central and peripheral warehouses?

3.4 Core components of a high-performance inventory control system

How to establish a high-performance inventory control system

Inventory should be strictly controlled to ensure that the distribution system always contains the right goods in the correct quantities. Good inventory control is essential for requisitioning and issuing medicines, financial accounting, and preparing consumption and stock balance reports. Thoroughly trained staff members are critical to successful inventory control.

The components of an effective inventory control are—

- Keeping a balance between service and stock levels
- Following a well-designed policy on reordering frequency
- Using standard methods to calculate reordering quantities
- Controlling costs associated with inventory management
- Maintaining records that track receipt and distribution of all shipments of TB medicines to clearinghouses and health facilities

TB programs should establish the appropriate working and security stock for each administrative level of the system, taking into account consumption, transportation services, lead time, warehouse storage capacity, and frequency of deliveries of TB medicines. In some countries, for instance, the security stock level may be equivalent to three months of consumption in health facilities, three months in provincial warehouses, and six months in the central warehouse.

Figure 3.2 shows the importance of inventory holding and the costs associated with it.

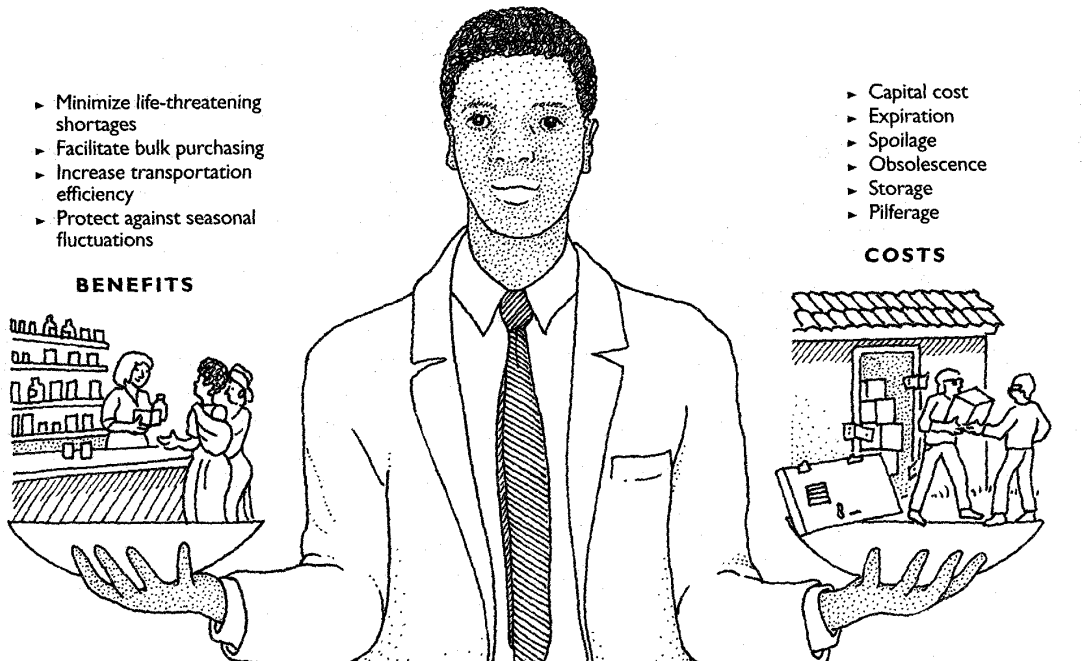


Figure 3.2 Benefits and Costs Associated with the Inventory

The amount of the safety stock required depends on several country-specific conditions, such as administrative support to the NTP, predictability of the budget for the purchase of medicines, physical accessibility of remote locations, and reliability of suppliers. If these conditions are difficult to predict, the safety stock tends to be higher. If health facilities have become almost depleted of stock, the NTP might consider the order of a one-time 100 percent buffer stock to fill the pipeline and then reduce to three to six months' buffer for subsequent annual orders.

Working stock depends heavily on monthly medicine consumption and lead time. In most countries, working stock is equivalent to three to four months of consumption.

Please see figure 3.3 and note that—

- Working stock is determined by the minimum and maximum stock levels needed.
- Average inventory = safety stock (SS) + ½ working stock (WS).
- Reduction in average inventory reduces holding costs.
- Holding costs[25] can be reduced by cutting back the SS or the WS.

[25] Holding costs include cost of medicine and overhead to maintain the storage facility.

- *If the quantity to be ordered is reduced, more frequent deliveries are needed.*
- Reducing quantity ordered may reduce holding costs but increases procurement and transportation costs.

The basic data to generate this information must be registered in electronic or manual records (bin cards).

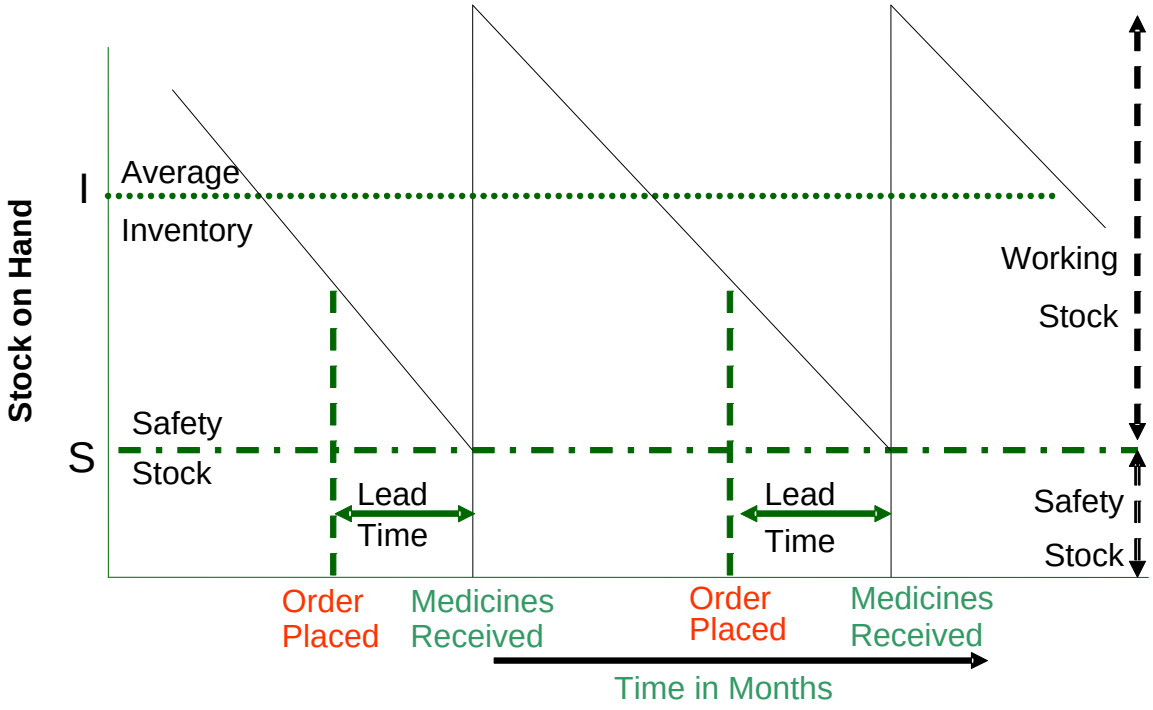


Figure 3.3 Ideal Inventory Control Method

A special note regarding inventory control and frequency of delivery for second-line TB medicines

Distribution of second-line medicines deserves special consideration. Because these medicines have a shorter shelf life, safety stock should be nonexistent or minimal. Very strict inventory control and frequent deliveries are usually necessary to ensure maximum efficiency. This element is critical when designing and beginning implementation of a DOTS-Plus project.

Next Steps

Go to Section 3.5: Are good storage practices followed in your central and peripheral warehouses?

3.5 Are good storage practices followed in your central and peripheral warehouses?

Common problems with storage of TB medicines

The following table outlines common problems with storage of TB medicines at central and peripheral warehouses. Please complete the table to get a better sense of what areas need improvement to strengthen storage practices in warehouses in your country/program.

Mechanisms to improve TB stock management in central or peripheral warehouses	**Practice is followed**
• The stock area is divided into zones for easy location of different products.	☐ Yes ☐ No ☐ Don't know
• An area is designated for second-line TB medicines.	☐ Yes ☐ No ☐ Don't know
• Stock rotation follows a FEFO (first-expiry, first-out) approach.	☐ Yes ☐ No ☐ Don't know
• Cleanliness of area is ensured.	☐ Yes ☐ No ☐ Don't know
• The environment of the warehouse protects medicines from factors that could inhibit their effectiveness or use, such as sunlight, heat, cold, moisture, pests, and theft.	☐ Yes ☐ No ☐ Don't know

Next Steps

If, from your completion of the preceding table, you feel that storage practices for TB medicines could be strengthened in your country/program:

- Go to Section 3.6: Strengthening storage practices in central and peripheral warehouses.

If, on the other hand, the storage practices in your country/program seem to be quite efficient:

- Go to Section 3.7: Is a timely and efficient requisition and transportation system for TB medicines operating?

3.6 Strengthening storage practices in central and peripheral warehouses

Steps to strengthen storage practices in central and peripheral warehouses in your country/program

After port clearance, TB medicines are transported from the port of entry to the NTP or MOH warehouse. If the MOH was not responsible for port clearance, at this point the MOH usually assumes full responsibility of the medicines. Upon arrival of the medicines at the central and peripheral warehouses (in decentralized systems), the responsible body must verify many factors related to the purchase order and the TB medicines themselves.

If the delivery complies with the specifications included in the signed contract, the MOH transfers the medicines to the storage area (almost certainly a central or peripheral warehouse, depending on the extent of centralization or decentralization within the country). In some cases, and depending on the provider and the terms of the contract, the medicines may first be transferred to a "quarantine area" until the laboratory certifies the quality of the product (by conducting laboratory analysis for correct medicine, strength, and dissolution time). In these cases, the medicines are officially accepted by the responsible authority and transferred to the general storage area only following laboratory certification and approval.

Unlike first-line medicines that in most cases are used exclusively for TB, second-line medicines may be used for the treatment of other infections. It is best if they can be reserved exclusively for the use of multidrug-resistant-TB patients and kept in a secure separate area.

Good storage practices in warehouses are essential to ensure that TB medicines are handled efficiently, waste is limited, and loss caused by expiry is kept to a minimum.

Next Steps

Go to Section 3.7: Is a timely and efficient requisition and transportation system for TB medicines operating?

3.7 Is a timely and efficient requisition and transportation system for TB medicines operating?

Common problems with requisition and transportation or delivery of TB medicines

The following table outlines common problems with requisition and transportation or delivery of TB medicines from central and peripheral warehouses to treatment clinics. Please complete the table to get a better sense of what areas need improvement to strengthen requisition, transportation, and delivery practices within your country/program.

Common problems with TB medicine requisition, transportation, and delivery	**Takes place in my country/program**
• TB medicines don't arrive at the peripheral health facilities on time.	☐ Yes ☐ No ☐ Don't know
• TB medicines don't arrive at the peripheral health facilities at regular intervals; instead their delivery is sporadic.	☐ Yes ☐ No ☐ Don't know
• Health facilities often run out of TB medicines.	☐ Yes ☐ No ☐ Don't know
• Health facilities often have an oversupply of TB medicines, possibly leading to expiry of these medicines.	☐ Yes ☐ No ☐ Don't know

Next Steps

If, from your completion of the previous table, you feel that requisition, transportation, or delivery of TB medicines could be strengthened in your country/program:

- Go to Section 3.8: Key issues in requisition and transportation or delivery of TB medicines from central or peripheral warehouses to health facilities.

If you are comfortable with the performance of your country/program with respect to requisition, transportation, and delivery, but you feel that your country/program would benefit from exploring further options for strengthening its distribution system, particularly the areas of receipt, customs clearance, storage, requisition, and delivery of TB medicines:

- Go to Section 3.9: Consider two strategic approaches to improve the performance of your distribution system for TB medicines and supplies.

If you are comfortable with the performance of your country/program with respect to all of the mentioned criteria:

- Go to Section 3.10: Do the health facilities in your country/program follow the recommended dispensing and consumption procedures?

3.8 Key issues in requisition and transportation or delivery of TB medicines from central or peripheral warehouses to health facilities

Options for requisition, transportation, and delivery of TB medicines within your country/program

In completely decentralized systems, medicines and supplies may be delivered directly to provincial warehouses or health facilities. In centralized environments, two systems are used to establish medicine needs: the "push system" and the "pull system."

- In a "push system," supply personnel at the central level determine what medicines in what quantities are needed in peripheral health facilities based on demographics, morbidity, and consumption estimates.

- In a "pull system," each administrative level (usually health facility) determines its needs based on monthly consumption of each medicine and periodically send its requests to central (or provincial) warehouses.

Although a pull system is preferable, because it is a truer reflection of actual need, it requires a highly competent staff, sufficient supplies, financial resources, and a good management information infrastructure at both health facility and central levels.

Regardless of the level at which needs are established, two options exist for transporting TB medicines to health facilities. In a *collection system*, health facilities send their trucks to the central or peripheral level to pick up the medicines, whereas in a *delivery system*, the central or peripheral warehouses transport the supplies in their own trucks to the health facilities.

In TB programs with no access to central or provincial storage facilities, health clinics must store all TB medicines themselves. See the following table for a list of advantages and challenges of the collection and delivery systems.

System	Advantages	Challenges
Delivery	If proper delivery routes, order intervals, and delivery schedules are in place, the total cost of transport will be less. Deliveries of supplies can be combined with other important scheduled and mandatory visits to the field. Medicine selection, assembly, and packing operations can be scheduled and accomplished efficiently.	Needs reliable transport facilities. Outright purchase or leasing of vehicles gives rise to high capital and operating costs. If the delivery route is long, the possibility of product breakage and loss of quality exists. In many instances, security lapses may occur because of the lack of a responsible officer accompanying goods. Health facilities may be closed when the delivery truck arrives, or a responsible officer may not be on hand to receive supplies. The delivery truck may be in a hurry to get to the next destination, making it difficult to check for short shipments, damage, and other problems before the truck departs.
Collection	Provides an opportunity for issuing personnel to meet people from the field and discuss common problems, and for field officers to meet and exchange ideas among themselves. Frees central-level staff from providing transport facilities to the field. Provides greater incentive to obtain supplies regularly because the facility is responsible for collecting supplies. Allows field personnel to attend to other business in town. Offers the possibility of a greater choice of methods of transport. Allows for better checking, handling, and security of goods received.	Takes up a lot of health facility staff members' time. Time may be wasted waiting for assembly of the order, or supplies might not be ready for collection on the first visit. Total cost of transport may be high. Budget line items may be too small. Health center personnel may tend to increase the frequency of visits for various reasons.

It is important to keep in mind that intermediate storage levels may increase inventory costs without adding advantages to the system.

The number of deliveries required is determined by taking into account calculated working and security stocks (see Section 3.7), transportation services, and storage capacity. Logically, an inverse relation exists between the frequency of deliveries and storage capacity.

Delivery Schedules

↑ Frequency	↓ Storage Capacity
↓ Frequency	↑ Storage Capacity

Use of patient kits: distribution issues

If a country uses patient kits for the treatment of tuberculosis, all medicines necessary for a full course must be included in a "box" (see figure 3.4) and the medicines must be adjusted to correspond with the dosage required for the patient's weight. Where TB patient kits are used, the inventory control and requisition mechanism uses the "box" as the accounting unit.

Figure 3.4 TB Patient Kit

Both the push or pull system and the collection or delivery system also apply to patient kits. Kits may be prepared by the country's health system or purchased directly from a manufacturer. Keep in mind, however, that there are advantages and challenges to using patient kits, primarily in terms of distribution, storage, and medicine use.

Some main advantages and disadvantages of using patient kits include the following.

Advantages	Challenges
• Easier to count inventory • Easier to distribute • Easier to monitor regularity of treatment • Prevents supply breakdowns for individual patients	• Requires more storage space • Requires training health workers in the reconstitution of the kits • Repacking materials are required

Next Steps

If you feel that your country/program would benefit from exploring further options for strengthening your distribution system, particularly the areas of receipt, customs clearance, storage, and requisition and transportation or delivery of TB medicines:

- Go to Section 3.9: Consider two strategic approaches to improve the performance of your distribution system for TB medicines and supplies.

If, on the other hand, you are comfortable with the performance of your country/program in the given criteria:

- Go to Section 3.10: Do the health facilities in your country/program follow the recommended dispensing and consumption procedures?

3.9 Consider two strategic approaches to improve the performance of your distribution system for TB medicines and supplies

Other options to explore to further strengthen distribution of TB medicines within your country/program

Two major strategies exist for improving the performance of any TB pharmaceutical and supplies distribution system: contract private providers or integrate specialized distribution systems. No decision should be made without a serious study of the costs and advantages (and challenges) of each alternative.

Option 1. Explore the cost-effectiveness of including private providers in the distribution process compared with only public providers

In most countries, local private providers of port clearance, storage, and transportation services exist. These alternatives should be considered if private providers offer better performance at lower prices than the estimated costs and expected performance of public systems. No optimal mix exists: different functions can be taken on by different public or private players, and numerous combinations are possible depending on the existence and availability of local providers and the results of cost-effectiveness studies.

For example, private providers may assume responsibility for port clearance and transportation of TB medicines, while public authorities retain responsibility for storage and inventory control functions, as shown in table 3.1.

Table 3.1 Public/Private Mix for Distribution of TB Pharmaceuticals and Supplies (example)

Distribution Component	Public	Private
Port clearance		X
Storage	X	
Inventory control	X	
Transportation		X

If an NTP decides to initiate a contractual agreement with a private provider, expected performance should be clearly stated in the contract, including service to be provided, indicators of performance, conditions for payment, and the like.

When the scale of operation is limited, as often is the case in TB programs, private suppliers may not be interested in providing services to public institutions. Integration of specialized distribution systems (TB, malaria, family planning, and so forth) may be a more realistic alternative to increasing the effectiveness of the entire system.

Option 2. Explore the cost-effectiveness of maintaining a specialized system compared with an integrated one

TB programs can consider exploring the cost-effectiveness of integrating distribution systems for TB medicines with other specialized programs or with the distribution system used by the MOH for all other medicines and supplies. Careful analysis of the performance of alternate systems is needed to ensure that supply of TB medicines will not be disrupted.

An integrated system should keep in mind a few particular demands of TB programs—

- Reserving the exclusive use of TB medicines, particularly rifampicin-containing products and second-line medicines, for TB patients, and implementing NTP procedures in order to ensure that these medicines do not end up being used for alternative purposes

- Implementing necessary security for first- and second-line TB medicines

Next Steps

Go to Section 3.10: Do the health facilities in your country/program follow the recommended dispensing and consumption procedures?

3.10 Do the health facilities in your country/program follow the recommended dispensing and consumption procedures?

Overview of good dispensing and consumption procedures for TB medicines

The following table lists good dispensing and consumption procedures for TB medicines. Please complete the table to get a better sense of what areas need improvement in order to strengthen dispensing and consumption procedures in your country/program.

Dispensing/consumption element	Frequency of occurrence?
• The treatment is directly observed within the program.	☐ Always ☐ Never ☐ Don't know ☐ Only in certain parts of the country (what %, where?): _____
• Administration of medicines to patients is registered on the proper forms.	☐ Always ☐ Sometimes ☐ Never ☐ Don't know
• Consumption records at health-facility level are requested by and sent to higher levels in the system for reporting and future quantification purposes.	☐ Annually ☐ Biannually ☐ Quarterly ☐ Monthly ☐ Never ☐ Don't know ☐ Other: _____
• Regular inspection of health facilities takes place.	☐ Annually ☐ Biannually ☐ Quarterly ☐ Never ☐ Don't know ☐ Other: _____

Next Steps

If, from your completion of the previous table, you feel that dispensing and consumption procedures for TB medicines could be strengthened in your country/program:

- ➢ Go to Section 3.11: Strengthening TB medicine dispensing and consumption procedures.

If, on the other hand, the dispensing and consumption procedures in your country/program seem to be quite efficient:

- ➢ Go to Section 4. Use.

3.11 Strengthening TB medicine dispensing and consumption procedures

What are good TB medicine dispensing and consumption recording practices?

Dispensing consists of all the activities that occur between the time the prescription is presented and the medicine is issued to the patient. Dispensers (usually pharmacists, doctors, nurses, or other health care workers) should check patients' understanding of instructions for taking the given medicines by asking each patient to repeat the instructions.

According to the DOTS strategy, administration of TB medicines should be directly observed (DOT, or directly observed treatment). Although, in practice, DOT is usually undertaken by the prescriber or dispenser, under some circumstances a family member or a community worker may perform this observation. The dose taken should be recorded on the proper forms immediately in order to accurately control medicine consumption.

Consumption reporting records are an essential component of an efficiently run dispensary. They serve primarily to—

- Help verify stocks used
- Assist with tracing problems in medicines issued to patients (who may have adverse side effects, for example)
- Place orders (using the consumption method, see Section 1.7)

Reporting methods include retaining the prescription, entering data into a record book, and using computers during the dispensing process.

Ideally, when health facilities determine how much stock to order, the amount of stock already on hand should be considered, together with the expected delivery time of stock ordered. When medicines and supplies are delivered to the health facilities, personnel should follow the same receipt and inspection procedures as those recommended for the central or peripheral warehouses.

Next Steps

Go to Section 4. Use.

Annex 3.1 Additional References

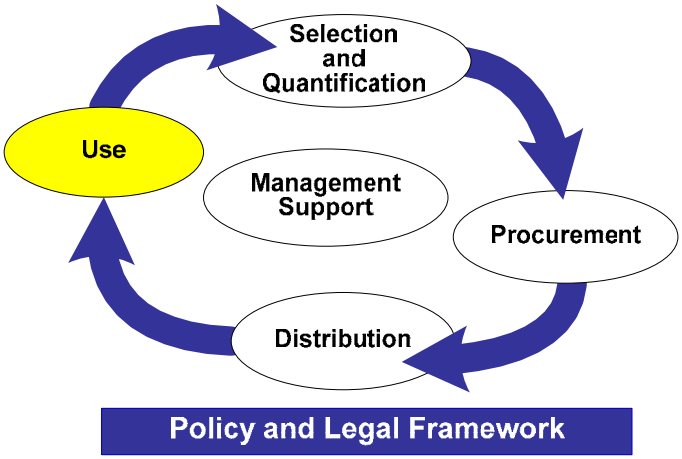
- Management Sciences for Health and World Health Organization. 1997. Chapter 21, "Managing Distribution." In *Managing Drug Supply: The Selection, Procurement, Distribution, and Use of Pharmaceuticals*. 2nd edition. West Hartford, CT: Kumarian Press.

- Management Sciences for Health. 2001. "Improving Drug Management to Control Tuberculosis." *The Manager* 10 (4).

Annex 3.2 Comprehensive Distribution Checklist

Elements of Distribution Management Cycle	Conditions to Be Met	Used in My Program?	
		Yes	No
Port clearing	Customs tax covered before arrival		
	Medicines already registered		
	Good storage space until cleared		
	Others:		
Receipt and inspection	Visually inspect package for:		
	• Correct quantity received		
	• Crushing		
	• Correct medicine and strength		
	• Correct dosage form		
	• Correct color and labeling		
	Conduct laboratory analysis for:		
	• Correct medicine and strength		
	• Dissolution time		
	Special coding		
	Correct language		
	Others:		
Storage	Environment protects medicines from:		
	• Heat or cold		
	• Sunlight		
	• Moisture		
	• Pests		
	• Theft		
	Divided into zones for easy access		
	Designated area for second-line medicines		
	Other:		
Requisition	Facilities determine how much to order		
	Amount of stock on hand is considered		
	Delivery time is considered		
	Other:		
Transportation	Frequent deliveries made to minimize stockouts and avoid expired medicines in facilities		
	System exists to document receipts and deliveries		
	Other:		
Inventory control	Document when received and when arrives		
	Use FEFO principle for stock rotation to avoid expired medicines		
	Calculate average monthly consumption (annual consumption divided by 12)		
	Calculate safety stock (number of months to order and receive stock)		
	Other:		

Section 4. Use



Introduction

What Exactly Does "Use" Mean?[26]

The Conference of Experts on the Rational Use of Drugs, convened by the World Health Organization (WHO) in Nairobi in 1985, defined rational use as follows: "the rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community." Depending on the context, however, many factors influence what is considered rational.

Ideally *rational use of medicines* should be used in a biomedical context that includes the following criteria—

- Correct medicine
- Appropriate indication—that is, the reason to prescribe is based on sound medical considerations
- Appropriate medicine, considering efficacy, safety, suitability for the patient, and cost
- Appropriate dosage, administration, and duration of treatment
- Appropriate patient—that is, no contraindications exist and the likelihood of adverse reaction is minimal

[26] This section has been taken from MSH. 1997. *Managing Drug Supply: The Selection, Procurement, Distribution, and Use of Pharmaceuticals*. 2nd ed. West Hartford, CT: Kumarian Press.

- Correct dispensing, including appropriate information for patients about the prescribed medicines

- Patient adherence to treatment

Use of First-Line TB Medicines

Using standardized short-course chemotherapy for all TB cases under proper case management conditions is one of the five key components of the DOTS strategy. WHO guidelines[27] provide the most widely available and effective set of protocols for controlling TB and cover most relevant issues regarding the use of TB medicines. This section therefore only highlights key issues in the use of first-line medicines (primarily adherence) and focuses more prominently on issues concerning the use of second-line medicines.

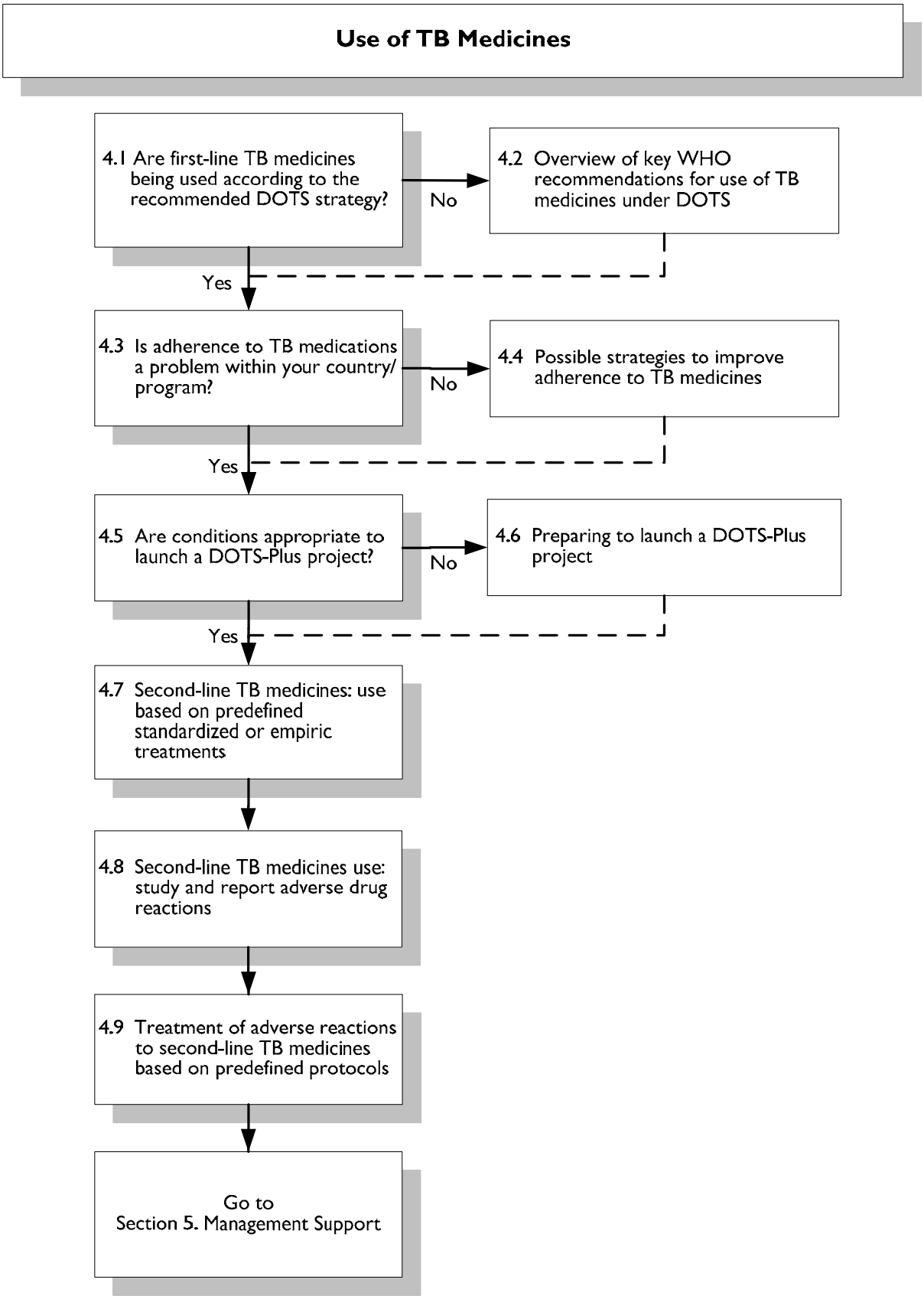
Use of Second-Line TB Medicines

In contrast to first-line medicines, where treatment regimens are standardized and promoted internationally through the DOTS strategy, multiple individualized and standardized treatments are used for treatment of multidrug-resistant tuberculosis (MDR-TB). Furthermore, because second-line medicines are usually highly toxic, initial empiric or standardized regimens must be modified based on each patient's individual reactions to individual medicines and to the medicines' sensitivity tests**.** DOTS-Plus projects must have functioning systems in place to identify adverse reactions, report them, and treat them properly. Adherence to second-line treatment must also be carefully monitored to avoid further development of resistance.

Overview and Key Issues in This Section

As mentioned, this module focuses primarily on use of second-line TB medicines, in particular on their side effects, treatment of such side effects, and the need to develop and implement a monitoring system for both medicine consumption and treatment of adverse drug reactions. Antibacterials used to treat MDR-TB are discussed in Section 1 on Selection and Quantification of this guide.

[27] WHO. 2003. *Treatment for Tuberculosis: Guidelines for National Programs,* 3rd ed. Geneva: WHO. Full document available on www.who.int/tb/publications/cds_tb_2003_313/en.


Use of TB Medicines
4.1 Are first-line TB medicines being used according to the recommended DOTS strategy?
No
4.2 Overview of key WHO recommendations for use of TB medicines under DOTS
Yes
4.3 Is adherence to TB medications a problem within your country/ program?
No
4.4 Possible strategies to improve adherence to TB medicines
Yes
4.5 Are conditions appropriate to launch a DOTS-Plus project?
No
4.6 Preparing to launch a DOTS-Plus project
Yes
4.7 Second-line TB medicines: use based on predefined standardized or empiric treatments
4.8 Second-line TB medicines use: study and report adverse drug reactions
4.9 Treatment of adverse reactions to second-line TB medicines based on predefined protocols
Go to Section 5. Management Support

4.1 Are first-line TB medicines being used according to the recommended DOTS strategy?

DOTS strategy recommendations regarding TB medicine use

Effective TB pharmaceutical management achieves rational medicine use when patients receive medicines appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community.

The DOTS strategy makes the following recommendations for use of TB medicines.

Recommendation	Currently occurs in your country/program?
• Ingestion of first-line TB medicines should be directly observed, at least during the initial two months of treatment. Directly observed treatment (DOT) can play a large role in increasing adherence.	☐ Yes ☐ No ☐ Don't know
• Adequate information about TB medicines is provided to prescribers, patients, and the public.	☐ Yes ☐ No ☐ Don't know
• A variety of measures to strengthen adherence should be considered, including among others—	
o Training prescribers	☐ Yes ☐ No ☐ Don't know
o Monitoring prescribing practices	☐ Yes ☐ No ☐ Don't know
o Establishing relationships with private providers	☐ Yes ☐ No ☐ Don't know
o Providing unit dose packages such as blister packs	☐ Yes ☐ No ☐ Don't know
o Educating patients and communities	☐ Yes ☐ No ☐ Don't know
o Developing appropriate incentives and enablers for patients and/or providers to encourage or incite greater adherence levels (see Section 4.4 for more information about these strategies)	☐ Yes ☐ No ☐ Don't know

TB medicine information for providers can be provided through national medicine information bulletins, national formularies, training programs, and guidelines on standardized regimens.

Whether you are a TB program manager or a manager of prescribers and dispensers of TB treatment, you need to promote the fact that TB can be successfully treated with first-line TB medicines only if these medicines are taken appropriately and consistently for the full course of treatment.

Next Steps

If the preceding recommendations for DOTS implementation are not presently being followed by your country/program:

- Go to Section 4.2: Overview of key WHO recommendations for use of TB medicines under DOTS.

If DOTS is being implemented in most or all health facilities in your country/program:

- Go to Section 4.3: Is adherence to TB medications a problem within your country/program?

4.2 Overview of key WHO recommendations for use of TB medicines under DOTS

WHO recommendations for use of TB medicines under DOTS[28]

Given that patient adherence to TB treatment can be a considerable challenge, WHO recommends that TB programs implement a number of measures to facilitate the treatment process.

These measures include the following—

- *Providing free TB medicines*, so that costs of treatment do not inhibit patient access (although, of course, other indirect costs still exist, such as transportation to a clinic or the opportunity cost of time off work, which might still inhibit patient access).

- *Using a patient-centered approach* through which treatment access is facilitated and patient choice is a main variable in determining when and where the patient will receive treatment. In addition to bringing the service closer to the patient, other goals of a patient-centered approach include providing sputum-smear controls free of charge, reducing patient time and cost of obtaining treatment, and providing good and rapid attention.

- *Using directly observed therapy*: as mentioned previously, the DOTS approach advocates that treatment is observed "in a way that is sensitive and supportive to the patient's needs." In practice, observation can take place in an inpatient setting (hospital/sanatorium) or outpatient setting and is usually done by a health worker, community member, or family member. The aim, once again, is to maximize patient convenience in order to improve adherence. Therefore DOT ideally occurs as close to the patient's home or workplace as possible.

- *Use of fixed-dose combinations (FDCs)*: as discussed in Section 1.4, WHO advocates the use of FDCs for first-line TB treatment because these medicines significantly reduce a patient's pill burden and can significantly improve adherence levels.

Next Steps

As DOTS is being introduced or expanded within your country/program, you should further consider the issues in this section. Start by going to:

➢ Section 4.3: Is adherence to TB medications a problem within your country/program?

[28] This section has been adapted from WHO. 2003. *Treatment for Tuberculosis: Guidelines for National Programs.* 3rd ed. Geneva: WHO.

4.3 Is adherence to TB medications a problem within your country/program?

The challenge of treatment adherence

Adherence to TB treatment is a key challenge of TB medicine use. The reasons for poor adherence can be multiple, for example—

- Factors associated with the health facility
    - TB medicine stockouts: If a patient has to attend a clinic each day during the first two months of TB treatment, but medicines are available only half (or less) of the time, he or she may choose not to present for treatment because time could be more valuably spent.
    - Poor organization of service delivery: Lack of privacy, inconvenient opening hours, and long waiting times are all factors that create barriers for patients trying to access treatment.
    - Poor quality of medical care: Absent or inconsistent supervision of health facility staff, expired medicines and reagents, and poor attitudes of the health staff members to patients all contribute to low-quality services and ineffective treatment.
    - Barriers to optimal performance: Systemic factors may be preventing facility staff members from performing their best—for example, a lack of budget for transport may be preventing them from tracking defaulters. A lack of supportive supervision may discourage staff members from providing quality TB treatment.
- Factors associated with the patient
    - After they have started treatment, patients usually start to feel better rather quickly. At that point, patients may decide that they lose more (time, income, transport costs) than they gain from TB treatment and decide to skip doses or stop treatment altogether.
    - In the absence of adequate counseling and support from health staff, adverse reactions to TB drugs may result in similar patient behavior.
    - Patients may not believe the treatment is having any effect and thus discontinue medicine intake.

How to know whether adherence is a problem in your country/program and to determine the extent of the problem

Recommendation	Currently occurs in your country/program?
• Does evidence exist in your country/program of less than optimal adherence?	☐ Yes ☐ No ☐ Don't know
• If yes, what type of evidence?	☐ Cohort studies / DOTS monitoring reports ☐ Other quantitative studies ☐ Qualitative studies ☐ Other, describe: _____
• If no concrete evidence exists, do you suspect that adherence may be a problem within your country/program?	☐ Yes ☐ No ☐ Don't know
• If yes, what causes this suspicion?	☐ High case detection rates being achieved, yet treatment success levels low ☐ High default rates ☐ Other, describe: _____

Next Steps

If evidence exists of a TB medicine adherence problem in your country/program:

- Go to Section 4.4: Possible strategies to improve adherence to TB medicines.

If available evidence shows no adherence problem in your country/program (and, additionally, you suspect none):

- Go to Section 4.5: Are conditions appropriate to launch a DOTS-Plus project in your country?

4.4 Possible strategies to improve adherence to TB medicines

What mechanisms might your country/program use to try to improve adherence to TB treatment?[29]

If your program has already ensured a continuous supply of first-line medicines and a documented problem of adherence still exists, one or a number of the following strategies can be tried.

Recommended strategy	Currently used in your country/program?
• Training providers/prescribers of TB medicines	☐ Yes ☐ No ☐ Don't know
• Training dispensers of TB medicines	☐ Yes ☐ No ☐ Don't know
• Setting up a system for the direct observation of TB medicine administration and ensuring that DOT is occurring in practice	☐ Yes ☐ No ☐ Don't know
• Monitoring prescribing practices	☐ Yes ☐ No ☐ Don't know
• Monitoring through use of indicators	☐ Yes ☐ No ☐ Don't know
• Providing TB patient kits	☐ Yes ☐ No ☐ Don't know
• Educating patients and communities	☐ Yes ☐ No ☐ Don't know
• Considering implementation of appropriate incentives and enablers to encourage and/or incite higher treatment completion	☐ Yes ☐ No ☐ Don't know
• Establishing relationships with private providers and considering mechanisms to involve them further in the treatment process	☐ Yes ☐ No ☐ Don't know

Training prescribers

It is important to develop initial and continuing training programs on appropriate prescribing for physicians, nursing staff, and dispensers of TB medicines. Such training must involve reviewing prescription writing and documentation in medical records in the health facility. If coupled with monitoring and feedback, training can help reduce variations in prescribing in countries that have few or no treatment standards and also encourage appropriate treatment for patients, based on their different treatment categories. Finally, training can help providers both support patients who cope with medicine reactions and withstand the pressure of using heavily promoted, but inappropriate, medicines.

[29] This section has been adapted from "Improving Drug Management to Control Tuberculosis," *The Manager*. See http://www msh.org/projects/rpmplus/pdf/tb_manager.pdf.

Setting up a system for direct observation of patients who are taking medicines

Developing a system where the provider or other authorized observer can directly observe and document that patients are taking the medicines in the health facilities is also very important, at least during the initial phase of treatment. During the continuation treatment phase, this person should verify patients' timely visits to the health facility for additional medicines.

Monitoring prescribing practices

Provider prescribing should be continuously monitored to ensure that DOTS standards are being followed. DOTS forms, which are available from WHO, can be used for monitoring adherence. Careful monitoring of medical records will help determine whether each provider understands the treatment regimen and whether each patient is adhering to prescribed treatments. To be most effective, monitoring and training programs must work together.

Providing TB patient kits

TB patient kits containing a complete treatment regimen can improve patient adherence to treatment (see Section 1.5). Although these kits should always be accompanied by easy-to-understand instructions, ingestion of the TB medicines still requires direct observation.

Educating patients and communities

Patient education should be required for all TB programs. Like providers, patients must understand their role in treating TB and limiting its transmission to other people. Your strategies for public health and medicine education should provide individuals and communities with the information, skills, and confidence necessary to both use TB medicines appropriately, safely, and effectively and decrease TB's spread. The Stop TB Partnership provides ideas to organize an educational program and teaching materials, many of which are available online at http://www.stoptb.org/resource_center/documents.asp.

Considering development and implementation of incentives and enablers for patients, providers, or both to improve treatment completion

Understanding what factors are influencing patient and provider behavior is the key to identifying appropriate mechanisms that might improve treatment adherence. Incentives or enablers (for example, food support, transport vouchers, monetary bonuses for cured patients) can be designed for a variety of purposes: for example, to enable patients to overcome barriers in completing treatment, to motivate providers to properly supervise treatment or trace defaulters, or to encourage providers to refer persons suspected of having TB to testing centers. See

Stop TB, WHO, the World Bank, and RPM Plus have developed a participatory "motivations mapping tool" that facilitates the identification of current program performance problems, focusing on the underlying stakeholder motivators that contribute to those problems and the prioritization of potential interventions (including incentives and enablers) to address the motivational challenges.

The tool is available online at http://www.msh.org/projects/rpmplus/pdf/Mapping_Motivations.pdf.

www.msh.org/projects/rpmplus/3.5.htm to learn more about how incentives and enablers are being used in TB control around the world for improving case detection and treatment adherence rates.

Establishing relationships with private providers

If private providers play a considerable role in TB treatment in your country, it is important that you gain support for the government's TB treatment protocols from the medical, pharmacy, and nursing associations. Organizing presentations at association meetings and distributing government materials on selected medicines and treatment protocols for first-line treatment could be useful. As a result, arrangements may develop whereby private providers diagnose patients and send them to government facilities for free medicines, or where the government reimburses private providers for TB treatment.

For more about how providers are being increasingly engaged in the TB case detection and treatment process, see WHO's Public-Private Mix for DOTS Expansion Web site: http://www.who.int/tb/dots/ppm/en/.

Next Steps

Go to Section 4.5: Are conditions appropriate to launch a DOTS-Plus project in your country/program?

4.5 Are conditions appropriate to launch a DOTS-Plus project in your country?

What are the optimal conditions for launching a DOTS-Plus project?

A well implemented DOTS program is the best strategy to control the emergence of new cases of MDR-TB. From a public health point of view, it is better not to launch a DOTS-Plus project if the performance of the basic DOTS program to treat first-line TB needs improvement. If a DOTS-Plus project is launched in suboptimal conditions, resistance to second-line medicines is likely to emerge rapidly.

Optimal conditions that should exist before implementation of a DOTS-Plus project include—

Condition	Currently exists in your country/program?
• Ability to collect and analyze cohort data	☐ Yes ☐ No ☐ Don't know
• Combined default and transfer rates under 6 percent	☐ Yes ☐ No ☐ Don't know
• Continuous supply of first-line anti-TB medicines	☐ Yes ☐ No ☐ Don't know
• Application of DOTS in at least 90 percent of cases	☐ Yes ☐ No ☐ Don't know

Next Steps

If you responded "no" or "don't know" to any/all of the above questions:

- Go to Section 4.6: Preparing to launch a DOTS-Plus project.

If you responded "yes":

- Go to Section 4.7: Second-line TB medicines: use based on predefined standardized or empiric treatments.

4.6 Preparing to launch a DOTS-Plus project

What steps need to be taken during preparation?

In addition to needing a well-implemented DOTS program, before beginning second-line treatment a DOTS-Plus project must ensure the following steps are taken.

Checklist

Step	Current status within your country/program
• Create a specialized unit for managing MDR-TB patients	☐ Exists ☐ Doesn't exist ☐ Don't know
• Ensure that laboratory services, including drug susceptibility tests (DSTs), are available	☐ Yes ☐ No ☐ Don't know
• Design an appropriate treatment strategy based on DSTs	☐ Exists ☐ Doesn't exist ☐ Don't know
• Ensure an uninterrupted supply of second-line quality medicines	☐ Yes ☐ No ☐ Don't know
• Ensure that patient adherence is maximized by making directly observed second-line treatment a requirement	☐ Yes ☐ No ☐ Don't know
• Establish and implement an effective monitoring and evaluation system	☐ Exists ☐ Doesn't exist ☐ Don't know

Detailed information about how to launch a DOTS-Plus project can be found in:

WHO. 2000. *Guidelines for Establishing DOTS-Plus Projects for the Management of Multi-Drug Resistant Tuberculosis (MDR-TB).* Scientific Panel of the Working Group on DOTS-Plus for MDR-TB. WHO/CDS/TB/2000.279. http://www.who.int/docstore/gtb/publications/dotsplus/dotspluspilot-2000-279/english/foreword.html

Next Steps

After all of the previously mentioned steps have been taken and the conditions they establish are in place, your country/program is considered ready to implement a DOTS-Plus project, therefore:

- Go to Section 4.7: Second-line TB medicines: use based on predefined standardized or empiric treatments.

4.7 Second-line TB medicines: use based on predefined standardized or empiric treatments

What mechanisms should be in place to strengthen management of second-line TB medicines?

Section 1.11 of this manual describes how to select second-line TB medicines according to standardized or individualized treatment regimens. Both options rely on medicine susceptibility patterns, either collective or individual.

A DOTS-Plus project should develop expertise in a number of areas in order to be able to properly manage use of second-line TB medicines. These areas include development of local competence in—

Checklist

Step	Current status within your country/program
• Sputum-smear microscopy through use of a well-functioning laboratory network	☐ Expertise exists ☐ Expertise does not exist ☐ Don't know
• Culture of *Mycobacterium tuberculosis*	☐ Expertise exists ☐ Expertise does not exist ☐ Don't know
• DST for isoniazid, rifampicin, streptomycin, and ethambutol	☐ Expertise exists ☐ Expertise does not exist ☐ Don't know
• Information management	☐ Expertise exists ☐ Expertise does not exist ☐ Don't know
• Drug resistance surveillance in a representative sample of patients	☐ Expertise exists ☐ Expertise does not exist ☐ Don't know

Although local competence in DST for second-line anti-TB medicines need not necessarily be developed, the WHO recommends that, at a minimum, access to a qualified laboratory should be available for this purpose.[30]

After selection, procurement, and distribution, rational use of second-line TB medicines depends primarily on the following, all of which you should aim to implement as part of your project.

[30] WHO. 2000. *Guidelines for Establishing DOTS-Plus Pilot Projects for the Management of Multidrug-Resistant Tuberculosis (MDR-TB).* Scientific Panel of the Working Group on DOTS-Plus for MDR-TB. WHO/CDS/TB/2000.279.

Checklist

Step	Current status within your country/program
• Patient and provider education on the importance of not interrupting treatment, on the long duration of treatment required, and on the high probability of severe adverse reactions to second line medicines	☐ Yes, takes place ☐ No, does not take place ☐ Don't know
• A well-designed system to identify, report, and treat adverse drug reactions	☐ Yes, exists ☐ No, does not exist ☐ Don't know
• Direct observation of TB medicine ingestion throughout the entire treatment course (18–24 months)	☐ Yes, takes place ☐ No, does not take place ☐ Don't know
• Prohibition of use of second-line medicines for clinical cases other than MDR-TB	☐ Yes ☐ No ☐ Don't know

Next Steps

Go to Section 4.8: Second-line TB medicine use: study and report adverse drug reactions.

4.8 Second-line TB medicine use: study and report adverse drug reactions

Adverse drug reactions: frequent manifestations and consequences

One of the most common reasons for nonadherence to MDR-TB treatment is the emergence of severe adverse drug reactions.

Adverse drug reactions may be classified as follows—

- Minor
- Moderate
- Severe

Some of the most frequent adverse reactions and their suspected causative agents are included in table 4.1. A form to report adverse drug reactions is presented in Annex 4.1.

Table 4.1 Frequency and Consequences (781 patients in Estonia, Latvia, the Philippines, and Tomsk Oblast, Russian Federation)

Adverse Reaction	Suspected Agent(s)	Percentage Affected	Percentage Interrupted	Percentage Stopped	Percentage Changed Regimen
Nausea/vomiting	cicloserine, ethionamide, fluoroquinolone, isoniazid + thiacetazone, ofloxacin, para-aminosalicylic acid (PAS), prothionamide, Z	29.7	4.1	0	1
Diarrhea	augmentin, PAS, prothionamide	16.9	1.4	1.3	0.3
Arthralgias	isoniazid + thiacetazone, capreomycin, cicloserine, ofloxacin, Z, PAS, prothionamide	16.3	5.1	0	0.1
Abdominal pain	cicloserine, ethionamide, fluoroquinolone, PAS, prothionamide, Z	11	0.3	0	5.1

Adverse Reaction	Suspected Agent(s)	Percentage Affected	Percentage Interrupted	Percentage Stopped	Percentage Changed Regimen
Dizziness/vertigo	amikacin, capreomycin, cicloserine, ethambutol, fluoroquinolone, isoniazid + thiacetazone, kanamycin, PAS, prothionamide, streptomycin	10.1	1	1.2	1.2
Sleep disturbances	cicloserine, fluoroquinolone, PAS, prothionamide	9.1	0	0.3	1.5
Hearing disturbances	amikacin, capreomycin, kanamycin, streptomycin	7.4	0.8	1.4	3.6
Electrolyte disturbances	capreomycin, kanamycin, PAS	7.3	1.4	0.4	2.3
Headaches	cicloserine, fluoroquinolone, kanamycin, ofloxacin, prothionamide	5.4	0.3	0.1	0.3

Source: WHO. 2000. *Guidelines for Establishing DOTS-Plus Projects for the Management of Multi-Drug Resistant Tuberculosis (MDR-TB).* Scientific Panel of the Working Group on DOTS-Plus for MDR-TB. WHO/CDS/TB/2000.279.

Product problem reporting system

In addition to ensuring that health workers observe for signs and symptoms of adverse reactions to the medicines in patients, the health system should establish a formalized product problem-reporting system the components of which would include—

- Standardized forms for reporting adverse reactions
- Written procedure for how to fill out the form
- Who should report the product problem
- Where and to whom the form should be sent
- What additional measures need to be taken, such as sending a sample of the product
- What follow-up information should be provided to the reporting person

- What action to take based on analysis of the problem, such as taking no action, notifying other health professionals of the adverse drug reaction, removing the medicine from the health system, notifying the manufacturer of the problem

For more information and an example of a product reporting form, please refer to *Managing Drug Supply*.[31]

Next Steps

Go to Section 4.9: Treatment of adverse reactions to second-line TB medicines based on predefined protocols.

[31] MSH. 1997. Chapter 18, "Procurement." In *Managing Drug Supply: The Selection, Procurement, Distribution, and Use of Pharmaceuticals*. 2nd ed. West Hartford, CT: Kumarian Press, 284–85.

4.9 Treatment of adverse reactions to second-line TB medicines based on predefined protocols

How best to treat adverse reactions?

Because second-line medicines are the last resource for the treatment of TB and the standardized or individualized regimens usually include the most potent medicines that the strain is susceptible to, not many options exist for a change of regimen or even for lowering the dose of one or more medicines. Adverse drug reactions must, therefore, be identified rapidly and treated aggressively. Given these considerations, WHO recommends the following[32]—

- Direct management of adverse reactions with standardized algorithms
- Reducing dosage of suspected medicine(s) one medicine at a time
- Removal of some medicines from regimens for the treatment of adverse drug reactions

This final option, however, should be chosen only as a last resort. The following algorithm may be used a general reference.

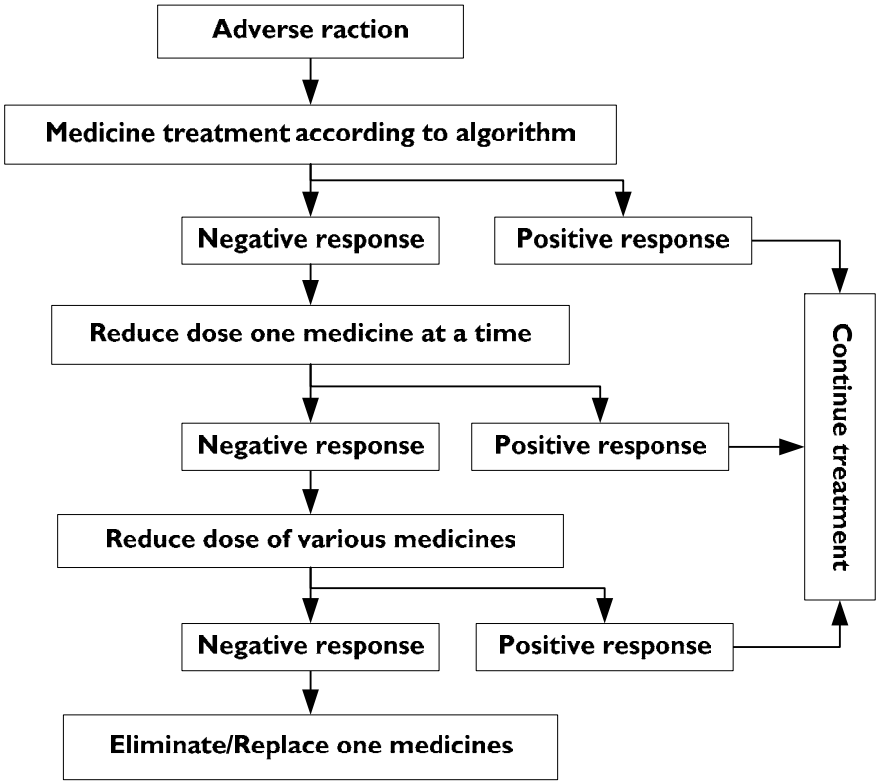


Figure 4.1 Algorithm for treating adverse drug reactions

[32] WHO. 2000. *Guidelines for Establishing DOTS-Plus Pilot Projects for the Management of Multi-Drug Resistant Tuberculosis (MDR-TB).* Scientific Panel of the Working Group on DOTS-Plus for MDR-TB. WHO/CDS/TB/2000.279.

A comprehensive set of protocols for treating adverse drug reactions can be found in the *Partners in Health Guide to the Medical Management of Multidrug-Resistant Tuberculosis* (http://www.pih.org/library/mini-mdrtb/index.html).

Next Steps

Go to Section 5. Management Support.

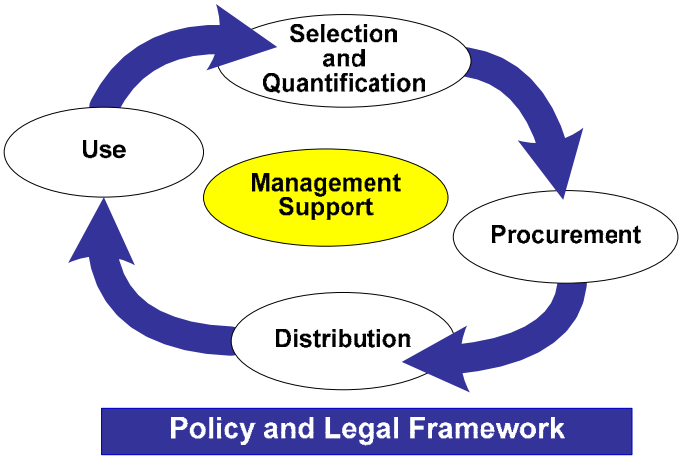
Annex 4.1 Additional References

Management Sciences for Health and World Health Organization. 1997. Chapter 21, "Managing Distribution." In *Managing Drug Supply: The Selection, Procurement, Distribution, and Use of Pharmaceuticals*. 2nd edition. West Hartford, CT: Kumarian Press.

Partners in Health. 2003. *Partners in Health Guide to the Medical Management of Multidrug-Resistant Tuberculosis*. Boston: http://www.pih.org/library/mini-mdrtb/index.html.

World Health Organization. 2000. *Guidelines for Establishing DOTS-Plus Pilot Projects for the Management of Multidrug Resistant Tuberculosis (MDR-TB).* WHO/CDS/TB/2000.279.

Section 5. Management Support



Introduction

What Is Meant by Management Support within the Context of the Pharmaceutical Management Cycle?

In addition to routine TB pharmaceutical supply management, the coordinator of the National TB Program (NTP) usually faces multiple challenges that typically include decisions concerning the introduction of fixed-dose combinations, the implementation of patient kits, and the procurement of medicines for the treatment of multidrug-resistant TB (MDR-TB). A TB coordinator must balance his or her time and effort between routine administration and long-term development of the pharmaceutical component of the national tuberculosis program.

Management support is located at the center of the pharmaceutical management cycle, which represents its central, crucial nature as the engine that drives the other components of the cycle. Effective management support is required during all activities in the cycle and at all organizational levels, from the national program level down to where the TB medicines are prescribed and dispensed to patients.

Management support includes various subcomponents—

- Organization and management
- Financing and sustainability
- Information management
- Human resources management

For example, when planning for improvements in TB pharmaceutical management, the leader of a TB control program will need to develop these plans, mobilize internal and/or external funding

support, implement the plans (taking into consideration management issues of organization, financing, information flow, and human resources), and monitor and evaluate the program's performance prior to and following implementation of proposed changes. Indicator-based monitoring is an essential activity that should be routinely conducted by national tuberculosis programs.

When seeking to strengthen management support, TB program managers should consider the institutional context, describe the desired performance, identify gaps between desired and actual performance, and select interventions to close the gaps during implementation (figure 5.1).

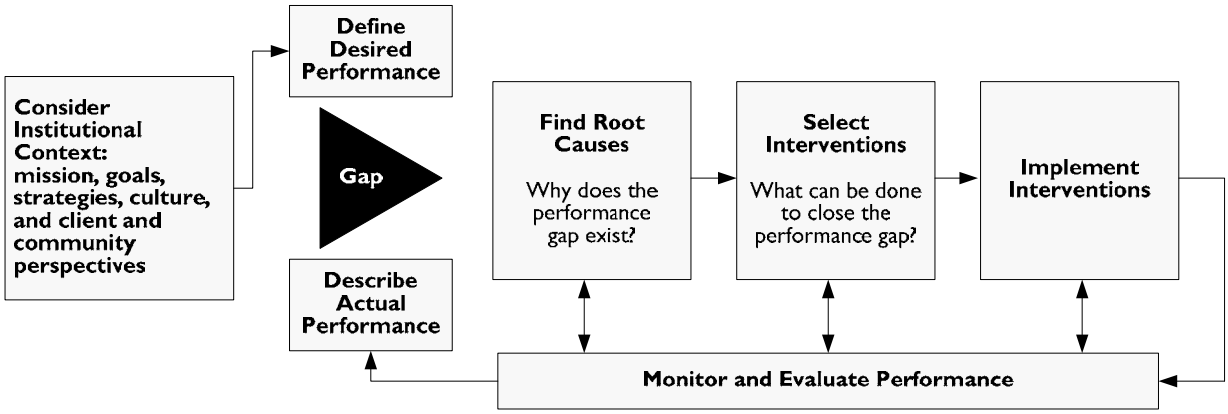
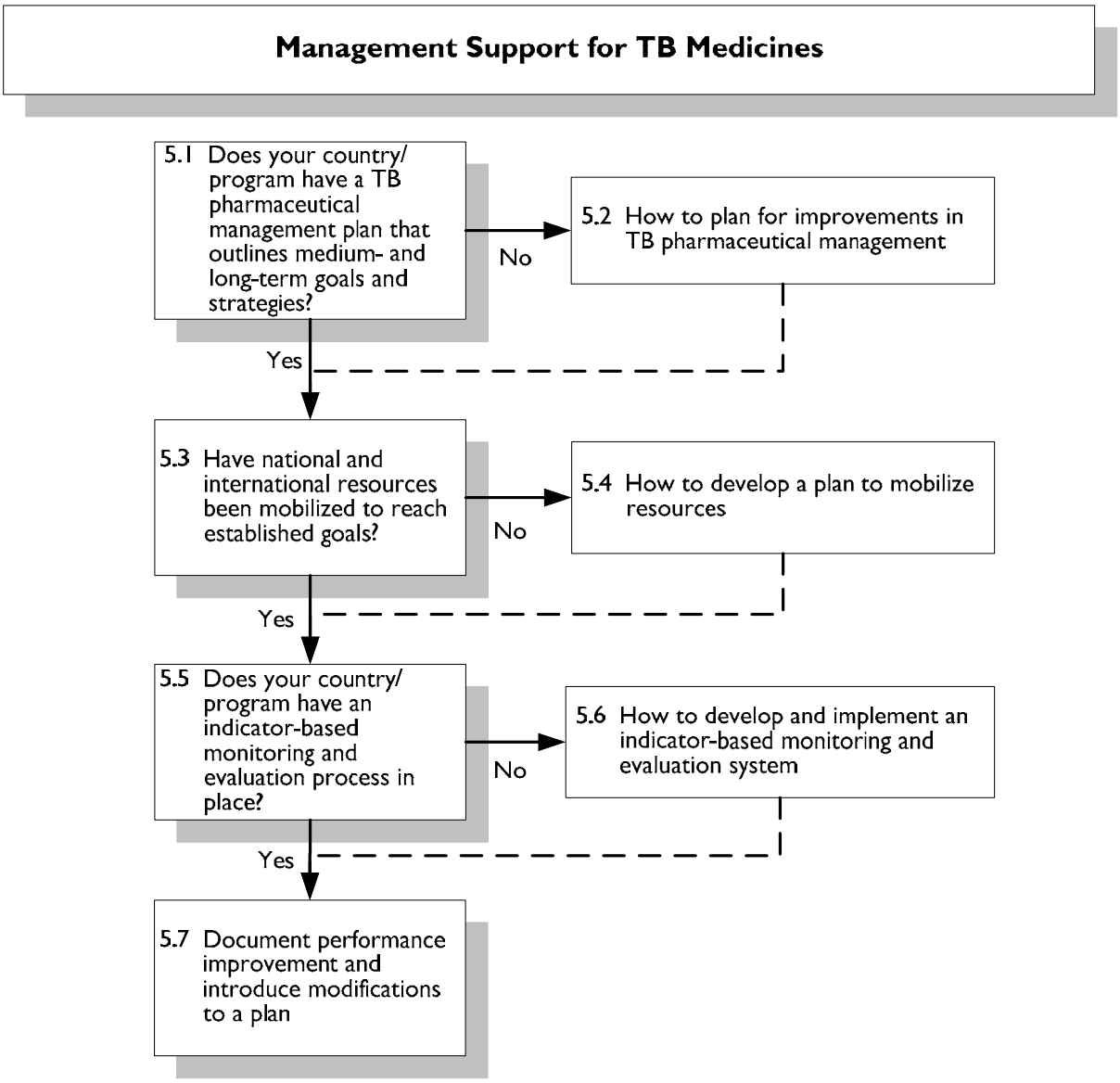


Figure 5.1 Steps to Consolidate Management Support

Overview and Key Issues in This Section

This module addresses key issues in providing effective management support for a TB program.



5.1 Does your country/program have a TB pharmaceutical management plan that outlines medium- and long-term goals and strategies?

Why develop a plan?

A written plan is usually a critical component of effectively organizing and ensuring a constant supply of TB pharmaceuticals. The following questions may help you evaluate the current status of your program in this area:

Recommended	Currently used in your country/program?
• Does your program have a pharmaceutical supply management plan?	☐ Yes ☐ No
• Has your program established medium- and long-term goals?	☐ Yes ☐ No
• Has a strategy been developed to pursue these goals?	☐ Yes ☐ No

Next Steps

If you responded "no" to any question:

- Go to Section 5.2: How to plan for improvements in pharmaceutical management for tuberculosis.

If you responded "yes" to all questions in the previous exercise:

- Go to Section 5.3: Have national and international resources been mobilized to reach established goals?

5.2 How to plan for improvements in TB pharmaceutical management

How to develop a plan

In order to effectively plan for improvements in TB pharmaceutical management, national TB programs should take the following steps—

- Analyze the current situation and assess needs over the short, medium and long term
- Establish goals and set objectives and targets for each of these time frames
- Determine the most appropriate and effective strategies to move forward and activities to implement these strategies
- Define responsibilities and identify and mobilize resources required (from national and international sources) to translate strategies into action

In principle, *strategic planning* addresses longer-term development planning (5 to 10 years) and emphasizes overall effectiveness and direction, while *program planning* is more medium-term planning (3 to 5 years) that focuses on major objectives, activities, and resources needed. *Work planning* tends to be short-term planning (usually 6 to 12 months) that involves identifying target outputs, required tasks, and inputs (in terms of human and other resources) required for effective accomplishment of each major objective.

Next Steps

Go to Section 5.3: Have national and international resources been mobilized to reach established goals?

5.3 Have national and international resources been mobilized to reach established goals?

Sources of funding

Please complete the following table (the examples are illustrative), listing prioritized anticipated changes that will occur in your country/program with respect to pharmaceutical management for TB, expected time frame, and source of funding, in order to identify gaps in funding.

Anticipated change in order of priority (highest priority first)	Time frame	Source of funding
(example #1: expansion of DOTS program to cover 6 more districts or an estimated 4,000–8,000 more cases; will need assured supply of TB medicines in all public TB facilities in these 6 districts)	Next calendar year (Jan–Dec 2006)	☐ National ☐ International cooperation agencies ☐ GFATM ☐ Other _____
(example #2: have new data on HIV/AIDS patients contracting TB, which increases to 16 percent of patients next year)	Next calendar year (Jan–Dec 2006)	☐ National ☐ International cooperation agencies ☐ GFATM ☐ Other _____
		☐ National ☐ International cooperation agencies ☐ GFATM ☐ Other _____
		☐ National ☐ International cooperation agencies ☐ GFATM ☐ Other _____

Next Steps

If you cannot identify a source of funding for one of more "anticipated changes":

- Go to Section 5.4: How to develop a plan to mobilize resources.

If you responded "yes" to all questions:

- Go to Section 5.5: Does your country/program have an indicator-based monitoring and evaluation process in place?

5.4 How to develop a plan to mobilize resources

What potential funding sources exist to support improvements in TB pharmaceutical management in your country/program?

How you will go about mobilizing national and international resources is an essential component of your strategy. International financial support and technical assistance should complement (and not substitute) national efforts to control TB.

When planning for the mobilization of international resources to support pharmaceutical management for tuberculosis, the NTP should consider the following possibilities—

- Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM): With the aim of providing essential medicines and other health products to as many people as possible, the GFATM has adopted a set of policies and principles on procurement and supply management. For additional information check: http://www.theglobalfund.org/pdf/guidelines/pp_guidelines_procurement_supplymanagement_en.pdf.

  Although resources provided through the GFATM mechanism can be used to procure first-line TB medicines from any (local, national, or international) source, procurement of second-line TB medicines for the treatment of MDR-TB using GFATM resources must be procured through the Green Light Committee (GLC; see below for more information). Specifically, GFATM guidelines state that "to help limit resistance to second-line TB drugs and to be consistent with the policies of other international funding sources, all procurement of medications to treat Multi-Drug Resistant TB (MDR-TB) must be conducted through the Green Light Committee (GLC) of the Stop TB Initiative."[33] More information on the GLC can be obtained from the World Health Organization (WHO) representative in each country or from http://www.stoptb.org/wg/dots_plus/.

- Global TB Drug Facility (GDF): The GDF, a project of the Stop TB Partnership, managed by a secretariat housed at the WHO in Geneva, was established in 2001 as an initiative to increase access to high-quality TB medicines for DOTS implementation. The GDF is an innovative, nontraditional approach that seeks to link demand for TB medicines to supply and monitoring, outsources all services to partners on a competitive basis, uses product packaging to simplify TB pharmaceutical management, and links grants of TB medicines to actual program performance. Specifically, the GDF provides—

  - Grants of first-line TB medicines to support DOTS expansion
  - A direct procurement mechanism for countries and nongovernmental organizations within the context of DOTS programs
  - A White List of prequalified manufacturers of high-quality TB medicines

[33] http://www.theglobalfund.org/pdf/guidelines/pp_guidelines_procurement_supplymanagement_en.pdf.

- Ongoing technical support and an annual monitoring mission
- Standardized medicine products and user-friendly packaging

More information about the GDF is available on http://www.stoptb.org/gdf/.

- Green Light Committee: The GLC, a subgroup of the WHO Working Group on DOTS-Plus for MDR-TB, reviews country-specific projects and advises WHO on which projects should benefit from preferentially priced, quality-assured second-line TB medicines; monitors approved projects; and collects evidence to develop international policy on second-line TB pharmaceuticals. The members of the GLC are the WHO, the U.S. Centers for Disease Control and Prevention (CDC), the Medical Research Council, the International Union against Tuberculosis and Lung Disease (UNION), the NTPs from Estonia and Latvia, and Harvard Medical School.

  GLC procures second-line TB medicines through its procurement agent.

  DOTS-Plus country projects that are approved by the GLC sign a contract with WHO, after which the GLC secretariat introduces the approved project to the procurement agent through an official letter. The country then requests a catalog from the procurement agent in order to explore products, prices, and conditions. GLC-approved country projects send confirmation of order and payment to the procurement agent (see Figure 5.2). Generally it takes four months from the time an order is placed for TB medicines to be delivered. The lead time is explained by the fact that second-line TB medicines are not usually kept in stock by the procurement agent or the manufacturer because of short shelf life and low demand. Manufacturers instead usually produce such second-line medicines on demand. This potential time-lag needs to be incorporated into program planning.

  More information on the GLC is available on http://www.stoptb.org/wg/dots_plus/.

  Figure 5.2 illustrates the GLC procurement process.

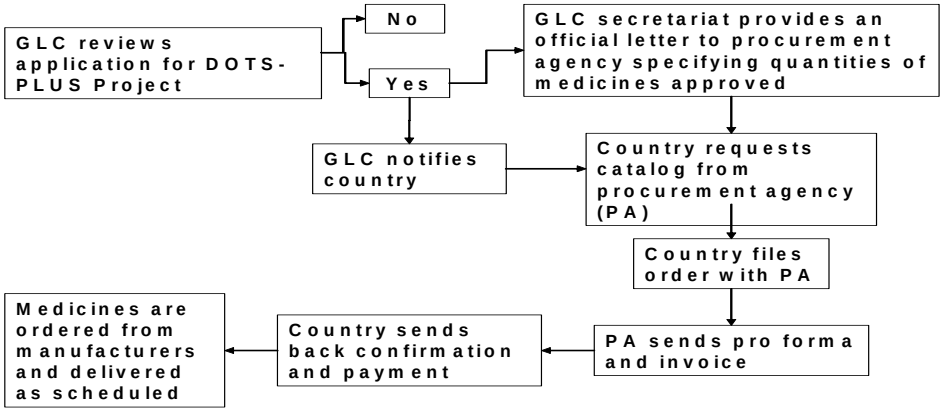


Figure 5.2 Procurement Process through GLC

Next Steps

Go to Section 5.5: Does your country/program have an indicator-based monitoring and evaluation process in place?

5.5 Does your country/program have an indicator-based monitoring and evaluation process in place?

Why use indicators?

Indicators provide the most solid base for monitoring and evaluation of the TB pharmaceutical supply system. They provide information about the rate at which the program is reaching the intended goals. Please answer the following questions to evaluate how your program is doing in this area.

Recommended	Currently used in your country/program?
• Have indicators been developed for the monitoring of TB pharmaceutical management?	☐ Yes ☐ No
• Are the indicators regularly used during monitoring or evaluations visits?	☐ Yes ☐ No
• Are the indicators analyzed for decision making?	☐ Yes ☐ No
• Are the results of the monitoring and evaluation visits disseminated and analyzed with the TB staff members?	☐ Yes ☐ No

Next Steps

If you responded "no" to one or more of the previous questions:

- Go to Section 5.6: How to develop and implement an indicator-based monitoring and evaluation system.

If you responded "yes" to all of them:

- Go to Section 5.7: Document performance improvement and introduce modifications to plan.

5.6 How to develop and implement an indicator-based monitoring and evaluation system

Why monitor and evaluate?

After plan design, including development of resource-mobilization strategies, managers usually dedicate most of their time to plan implementation—the process of carrying out the plan by organizing and directing the work, which involves managing people, money, information, and other resources to achieve the intended results.

Plan implementation performance should be subject to monitoring and evaluation so that—

- Progress is reviewed, comparing actual performance against target performance.
- Feedback is provided to demonstrate the value and importance of information gained and to break the "poor quality data cycle" (which often occurs when managers don't trust the quality of the information received by health facilities and therefore don't use it, which results in workers at the health facility becoming discouraged from collecting the data because it is not being fed back into decision making).
- Prompt follow-up action can be taken early on, if required, if actual performance is not reaching targeted levels.

Monitoring contrasted with evaluation: what is the difference?

Whereas *evaluation* is the review of progress toward meeting established objectives, goals, and future plans, *monitoring* is the ongoing review of the degree to which program activities are completed and targets are met.

How to monitor performance of the TB pharmaceutical management system in your country/program

Various complementary methods should be used to monitor the performance of the pharmaceutical management system—

- Routine reporting: The core of a monitoring system, this reporting focuses on TB medicine supply, finance, training, quality assurance, and medicine use.
- Supervisory visits: Such visits reinforce routine reporting requirements and should be used to provide in-service training and feedback.

- Sentinel reporting: This type of reporting supplements routine reporting and is most useful when a system is undergoing rapid or substantial change because it can detect unexpected or unintended outcomes. Sentinel sites (treatment centers) are chosen so as to represent the whole TB program.

- Special studies: This type of study is recommended when additional information is needed about the program that requires the use of experts to design and conduct the study.

The importance of using indicators as part of monitoring and evaluation

Indicators are a core part of monitoring and evaluation used to assess the extent to which the targets and objectives of a program or project are being or have been met. Indicators offer standardized and objective measurements and allow comparison of measurements between countries and at various periods in time, depending on the sample size.

When selecting an indicator, keep in mind that indicators are most effective when they are—

- Clear: easily understood by everyone

- Useful: reflect an important dimension of performance

- Measurable

    - Quantitative: such as rates, ratios, percentages, common denominator (for example, population)

    - Qualitative: "yes," "no"

- Reliable: can be collected consistently by different data collectors

- Valid: represent a true measure

Examples of pharmaceutical management indicators include—

Component	Indicator
Procurement	Percentage of median international prices paid for TB medicines from last regular procurement
Distribution (inventory control)	Average percentage of time out of stock for a set of TB tracer commodities in TB facilities
	Average percentage of stock records that correspond with physical counts for TB medicines
	Average percentage of TB commodities available in TB facilities and medical stores
Use	Number of medicines for the treatment of adverse reactions per MDR-TB patient
	Percentage of MDR-TB patients who could correctly describe how the prescribed medication should be used
	Percentage of new smear-positive patients with pulmonary TB who were prescribed correct medicines in conformity with the standard treatment guidelines in the country
Quality	Percentage of TB medicine samples that failed quality-control testing out of the total number of TB medicine samples tested during the past year
	Percentage of TB medicines received in the past three shipments that were accompanied with a batch certificate

For a complete list of indicators for TB pharmaceutical management, see Annex 5.2. Additional information about the mathematical calculation (formula), data collection methods and instruments, issues to consider during interpretation, and limitations of these and other indicators may be obtained by contacting rpmplus@msh.org and requesting a list from the *Pharmaceutical Management for Tuberculosis Assessment Manual*.

Next Steps

Go to Section 5.7: Document performance improvement and introduce modifications to plan.

5.7 Document performance improvement and introduce modifications to plan

How to use information to improve performance

As shown in figure 5.3, all the raw data collected should be analyzed and fed back into the decision-making process because decisions based on sound evidence should lead to improved performance of the program, and if necessary, modifications to the plan.

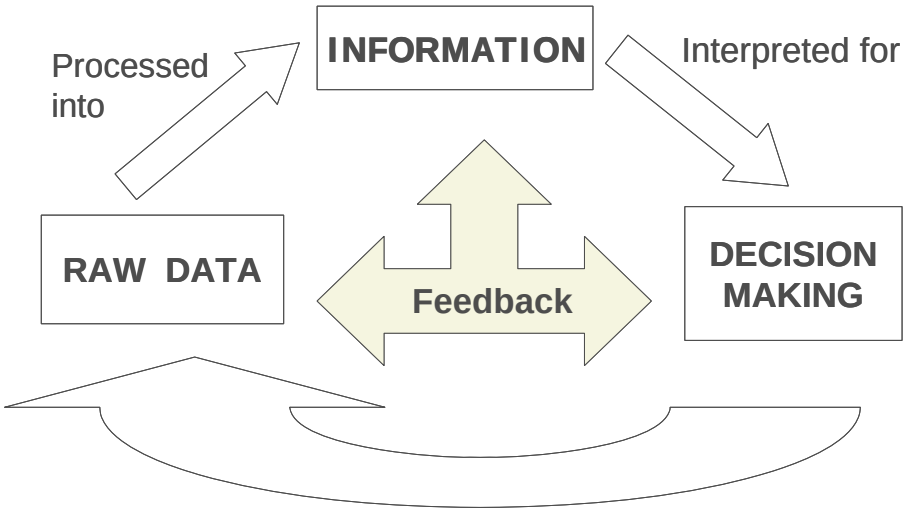


Figure 5.3 Information for Decision Making

Monitoring and evaluation are also needed to accumulate replicable experience in pharmaceutical management of first-line and second-line medicines, to determine availability of medicines and adherence to treatment, and to satisfy GLC and GFATM (and other international organizations') requirements for continuing support.

If the information shows that medicine stockouts are the problem, measures can be taken to improve inventory control procedures, quantification, and ordering. Or if improper treatment is the problem, then the improvement strategy might include more training of prescribers and education of patients.

The GLC, for instance, requires the following information to modify (or discontinue) a DOTS-Plus project based on performance—

- Tracking of pharmaceutical orders: compare dates/quantities ordered with those received
- Tracking of program medicine usage: quantity consumed by patients during quarter and quantity remaining in stock

- Tracking patient treatment outcomes: cured cases, treatment completions, deaths, failures, defaults

With a strong management support system, gaps or weaknesses found in TB pharmaceutical management will be brought to light and measures such as those mentioned throughout the guide can be used to implement solutions.

Annex 5.1 Additional References

Management Sciences for Health and World Health Organization. 1997. Chapter 21, "Managing Distribution." In *Managing Drug Supply: The Selection, Procurement, Distribution, and Use of Pharmaceuticals*. 2nd edition. West Hartford, CT: Kumarian Press.

Partners in Health. 2003. *Partners in Health Guide to the Medical Management of Multidrug-Resistant Tuberculosis*. Boston: http://www.pih.org/library/mini-mdrtb/index.html.

Rational Pharmaceutical (RPM) Plus Program. 2004. *Pharmaceutical Management for Tuberculosis Assessment Manual*. Revised edition of *Drug Management for Tuberculosis Assessment Manual*. Edited by A. Zagorskiy, C. Owunna, and T. Moore. Submitted to the U.S. Agency for International Development by the RPM Plus Program. Arlington, VA: Management Sciences for Health.

World Health Organization. 2000. *Guidelines for Establishing DOTS-Plus Pilots Projects for the Management of Multidrug-Resistant Tuberculosis (MDR-TB).* WHO/CDS/TB/2000.279.

World Health Organization. 2004. *Compendium of Indicators for Monitoring and Evaluating National Tuberculosis Programs*. WHO/HTM/TB/2004.344.

Annex 5.2 Illustrative TB Pharmaceutical Management Indicators

Several TB medicine indicators are listed here for consideration by national TB programs. Several have been tested through general essential medicines programs. The Stop TB partnership has selected four core indicators it will use for global monitoring of national TB programs. National TB programs may find these useful as well to improve their TB pharmaceutical management activities.

For clarity, the indicators are grouped under corresponding components of the pharmaceutical management cycle. The number assigned to each indicator corresponds to the detailed description of indicators in Annex 2 of the RPM Plus publication (2004) *Pharmaceutical Management for Tuberculosis Assessment Manual*. The description of the indicators may help identify what data need to be collected and where and how to calculate the indicator. Note that if the indicator number contains a *K* or *C*, the indicator is *key* (always needs to be collected) or *complementary* (used to broaden the monitoring of TB pharmaceutical management activities).

The indicators without a number may also be used by your program. TB partners may be able to provide the necessary technical assistance in setting up a TB medicine indicator system based on local requirements.

Drug Policy

C-4. Percentage of TB facilities visited where the most recent official manual of treatment guidelines for TB was present

C-1. Percentage of NTP medicine products included on the national essential medicines list

C-2. Percentage of NTP medicine products included on the WHO tuberculosis essential medicines list

Existence of a national TB medicine policy to support national TB program goals

Number of suppliers of TB medicines registered in the country

Average number of days to register or re-register TB medicines

Cost of TB medicine registration (single dose, combo pack, FDC)

Percentage of TB medicines that are registered in the country

Procurement

K-5. Percentage of median international price paid for a set of TB commodities that was part of the last regular procurement

C-8. Number of days that a person has to work at minimum wage to pay for a complete TB treatment course taking into account the price of medicines in the public or private market

Costs of TB medicines prescribed per course (by patient category) as a percentage of costs if the GDF medicines were used

Average lead time for orders placed for TB medicines from international sources during the last three procurements measured from the time order is submitted to procurement department or office for purchasing to the time order is received in warehouse

Average lead time for orders placed for TB medicines from local sources during the last three procurements

Average lead time to submit procurement order for TB medicines to suppliers measured from the time order is submitted to the procurement department until order is placed with the suppliers

Average lead time to receive approvals for an order of TB medicines, measured from the time the procurement department prepares the order, subsequent to tendering, until the order is approved for placement with suppliers

Distribution

K-1. Average percentage of time out of stock for a set of TB tracer commodities in TB facilities

K-2. Average percentage of a set of TB commodities available in TB facilities and medical stores

C-7. Average percentage of stock records that correspond with physical counts for a set of TB tracer commodities in TB storage facilities

Percentage of facilities that store TB medicines according to standard TB storage specifications

Value of expired TB medicines last quarter

Drug Use

K-3. Percentage of new smear-positive patients with pulmonary TB who were prescribed correct medicines in conformity with the standard treatment guidelines used in the country

C-6. Percentage of TB patients who reported regular observation by a health care worker during medicine intake

C-5. Percentage of TB outpatients who could correctly describe how the prescribed medication should be used

Percentage of drug retail outlets where rifampicin and streptomycin were available without a prescription (and/or for indications other than TB)

Cost of medicines prescribed as a percentage of costs if DOTS norms for treatment were followed (only meaningful if regimens other than DOTS are followed)

Quality Control

K-4. Percentage of TB medicines in the past three shipments that were accompanied with a batch certificate

C-3. Percentage of TB medicine samples that failed quality-control testing out of the total number of TB medicine samples tested during the past year

RPM Plus Program
Center for Pharmaceutical Management
Management Sciences for Health
4301 North Fairfax Drive, Suite 400
Arlington, VA 22203 USA

www.msh.org/rpmplus