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IMPROVING TB DRUG MANAGEMENT

Accelerating DOTS expansion





Organization

Stop TB Partnership

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ACCELERATING DOTS EXPANSION



Management Sciences for Health



World Health Organization



STOP TB Partnership

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INTRODUCTION

The incidence of tuberculosis (TB) is increasing in many parts of the world, and partner organizations of Stop TB recognize the significant role drug management plays in ensuring that safe, effective, quality drugs are available when and where patients need them. The workshop *Improving TB Drug Management: Accelerating DOTS Expansion* was held on 6-8 June 2002 in Washington, DC, sponsored by three organizations:

- Stop TB Partnership Secretariat, World Health Organization;
- Management Sciences for Health, through the Rational Pharmaceutical Management Plus Program (RPM Plus) and the Strategies for Enhancing Access to Medicines (SEAM) initiative;
- Royal Netherlands Tuberculosis Foundation, KNCV.

The outcome of the workshop was countryspecific action plans, developed by national TB and essential drugs managers in collaboration with TB partners and designed to improve drug management in their countries. The plans contained a description of the activity, the resources and technical assistance needed, the timeline for implementation, responsibility for implementation and completion of individual activities, and monitoring indicators based on the realities of the local situation.

A series of papers were prepared as background information and self-analysis tools for workshop participants. Contents of the papers were presented during plenary sessions and used by participants during group sessions. The papers were revised on the basis of feedback received during the workshop and are included in this report.

It is hoped that others will find these documents useful in analysing their TB drug management systems, identifying specific weaknesses, and selecting implementation activities that will improve problem areas. Titles of the papers are:

- TB drug sector survey in two developing countries;
- Harmonization of TB drugs and their presentations;
- Drug procurement for tuberculosis;
- Using indicators to monitor TB drug supply;
- Operational framework to strengthen TB drug management.

TB DRUG SECTOR SURVEY IN TWO DEVELOPING COUNTRIES

Prepared by Thomas Moore Technical Officer for Stop TB/MSH

The Stop TB Partnership Secretariat and Management Sciences for Health wish to acknowledge the following people who have contributed to the preparation of this report: Michael Derosena, Anglade Malan-Kla, Marjorie Janvier, Paul Lalvani, Andy Marsden, Keith Johnson, Rena Eichler, Joseph M'Boussa

OVERVIEW

The main objective of the survey discussed in this paper was to identify specific problems in connection with drug management and availability of drugs for treating tuberculosis (TB) at the central and peripheral levels in two developing countries, Republic of Congo and India (the state of Uttar Pradesh).

The Rational Pharmaceutical Management Plus (RPM Plus) programme, funded by the United States Agency for International Development (USAID) under cooperative agreement HRN-A-00-00-0016-00, provided support for the survey which used the assessment tool *Drug management for tuberculosis* (DMTB) developed by Management Sciences for Health (MSH). Congo and Uttar Pradesh were chosen for the following reasons:

• As an international TB partner, USAID is interested in the TB situation in developing countries.

- Congo was one of the first recipients of a TB drug grant from the Global TB Drug Facility (GDF) of the Stop TB Partnership.
- India bears one-third of the global TB burden.
- Uttar Pradesh is one of the states in India currently receiving little support from the Government.

Between 10 April and 8 May 2002, RPM Plus consultants and local personnel conducted a qualitative and quantitative survey in the two countries. The assessment focused on TB drug management aspects of the national TB programmes. The country teams collected data on the selection, procurement, distribution, and use of TB drugs based on a set of indicators described in the DMTB.

The reports on Congo and Uttar Pradesh are presented in separate sections of this paper. At the end of each section is a list of recommendations based on the survey findings.

REPUBLIC OF CONGO

Background

TB in Congo

In the past few years, TB has evolved from a serious public health problem to a public health catastrophe in this country of 3.15 million inhabitants. TB is the third most common illness in Congo, behind only malaria and acute respiratory infection. At the end of the civil war in 1997, there were 3417 cases of TB; 9880 cases were reported in 2001—nearly a three-fold increase.

As of 1999, Congo indicated that it had a TB case-detection rate of 75% and a cure rate of 70%. In order to meet the Stop TB targets, the country needs to improve its case-detection rate to at least 85% by 2005.

The French Cooperation for developing countries provided support for TB drug supply to Congo before the civil war and up to and including 1997. The Belgian Government provided timely assistance in the amount of US\$ 222 222 for 1998, and the French Cooperation provided support again from 1999 to 2002, in the amount of US\$ 453 636, for TB drug supply, laboratory products, and equipment. In 2002 GDF procured drugs worth US\$ 133 500 and granted them to the Congolese Government. An annual budget of US\$ 66 712 was proposed for TB drugs for several years by the Congolese Government, but the funds have never been released.

Data collected during the survey indicated that the average percentage of unexpired TB drugs and products available in facilities visited (n=20) was only 57%. Although health facilities were out of stock of TB drugs only 4% of the time, according to local experts, there are fears that the country will run out of TB drugs in the near future if immediate action is not taken. It is hoped that donors will be able to continue to support the national TB programme (NTP) because the Government has not procured TB drugs in many years.

TB health facilities consist of Centres for Diagnosis and Treatment (CDTs) and Centres for Directly Observed Treatment (CDOTs). TB can be diagnosed only at the CDTs but, depending on where they live, patients may be treated at either a CDT or a CDOT during the 2-month intensive phase. CDOTs do not provide a continuous-treatment phase, and their patients are therefore referred to the closest CDT for sputum (bacilloscopy) follow-up during the 6-month continuation phase. Congo currently maintains 23 CDTs and 127 CDOTs, which also function as integrated health centres for other diseases.

Survey method

The survey sample consisted of 18 randomly selected CDTs and CDOTs in the regions of Brazzaville (10), Pointe Noire (6), and Dolisie (1), and in the city of Gamboma (1). Two central medical stores, one in Brazzaville and the other in Pointe Noire, were also surveyed. Some of the sites originally proposed were eliminated because they lacked security. More centres from Brazzaville and Ponte Noire were chosen for the survey for two reasons: (1) the political situation in the country has left large areas insecure in the aftermath of the civil war, and (2) 90% of the TB patients in Congo are diagnosed and treated in Brazzaville and Pointe Noire. Approximately half of the survey was therefore carried out in the Brazzaville region and Pointe Noire.

The quantitative portion of the survey was conducted by 12 data collectors and supervisors who received practical training before visiting health facilities to begin their work. The training sessions were conducted by RPM Plus consultant Dr Michael Derosena, who was assisted by Professor Joseph M'Boussa, Director of the NTP, and Dr Daniel Yokolo, Medical Director of the Anti-Tuberculosis Centre in Brazzaville. Forms used by the data collectors for the quantitative part of the survey were adapted for use in Congo from those in the DMTB. RPM Plus technical assistant Ms. Marjorie Janvier modified the data collection forms as required and developed the data-entry software used to calculate indicators for the survey.

The qualitative portion of the survey was conducted by RPM Plus consultant Professor Anglade Malan-Kla using structured questionnaires. WHO country representatives assisted Professor Anglade in setting up interviews with local experts in drug selection, procurement, distribution, use, quality assurance, and national policy.

The TB drug tracer list used by the data collectors was developed in collaboration with NTP and includes the first-line TB drugs currently in use, as well as syringes and needles for injection of streptomycin (see Annex 1).

Survey results

Drug policy

A national drug policy for Congo was developed in 2000, but has not yet been signed or published. Among other things, it proposes a drug control and administration programme, drug registration, and licensing of pharmaceutical laboratories.

The country has published an essential drugs list that contain all drugs provided by the NTP, most of which are fixed-dose combination products.¹

Receipt of TB drugs is covered by a drug donation policy of the NTP and requires prior consent from the Government or an initial request for the donation by the Government.

Supervision of drug management and of the TB programme in general is difficult because of lack of motor vehicles or other means of transport.

Drug selection and use

The NTP implements the Directly Observed Treatment, Short-course (DOTS) strategy and treatment regimens are comparable to those proposed in DOTS literature. The treatment regimens for the different types of TB are:

- Category I. New smear-positive/negative pulmonary TB (85% of all cases), treated with an intensive phase of EHRZ,² 1–4 tablets (according to the body weight of the patient) taken daily for 2 months. The treatment is followed by a continuous phase of EH³ 1–4 tablets (also according to body weight) taken daily for 6 months.
- *Category II*. Smear-positive pulmonary relapse/failure TB (10% of all cases), treated with an intensive phase of SEHRZ,⁴ taken daily for 2 months under direct supervision, and a continuous phase of EHRZ for 6 months.
- Children. TB in children (5% of cases) is treated with an intensive drug regimen of RHZ⁵ for 2 months, and a continuation phase of RH.⁶ The number of tablets to be taken is adjusted according to the body weight of the patient.

Treatment regimens are monitored by the CDT, which keeps a file on each patient. Compliance with the national programme and treatment regimens is documented, and drugs that are not included in the standard regimens are not used.

Indicators were calculated from the data collected in the health facilities and revealed that 69% of new patients with pulmonary TB (n = 626) were prescribed correct drugs and dosages in accordance with standard treatment

- ³ HR = isoniazid (H)/300 mg + rifampicin (R)/450 mg.
- ⁴ HRZES = HRZE same as Category I + (S) streptomycin 1 g administered twice weekly.
- ⁵ HRE = isoniazid (H)/300 mg + rifampicin (R)/450 mg + ethambutol (E)/600 mg.
- ⁶ HRZ = isoniazid (H)/300 mg + rifampicin (R)/450 mg + pyrizinamide (Z)/750 mg.

¹ Fixed-dose combination products contain two, three, or four TB drugs in one tablet or capsule.

² HRZE = isoniazid (H)/300 mg + rifampicin (R)/450 mg + pyrazinamide (Z)/750 mg + ethambutol (E)/600 mg.

regimens for the intensive phase of treatment. This indicator increased to 80% (n = 435 patients) for the continuous phase. Possible reasons for these low numbers may be lack of appropriate training for prescribers and insufficient monitoring by supervisors.

As the patients left the health facility they were asked whether they had been observed by the TB provider during treatment; 69% had been observed (n = 161). The observed patients were then asked about their treatment schedule and what could happen if they did not return for a scheduled dose; 84% (n = 110) knew about their treatment schedule and the outcome if drugs were not taken. Patients who had not been observed were asked questions on more specific topics, such as drug names, dosage frequency, and consequences of not continuing to take the prescribed drugs; 59% (n = 51) provided correct responses to the questions.

The absence of copies of the official treatment guidelines in treatment facilities could contribute to prescriber non-adherence to established treatment protocols. The survey indicated that an average of only 22% of visited facilities (n = 20) could show a copy of the treatment guidelines.

Drug procurement and distribution

The NTP calculates the quantities of TB drugs needed using the information sent from districts, consisting of drugs distributed and dispensed to patients, numbers of patients in preceding years, and incidence of new cases. The drug estimates include a buffer (reserve stocks), which is a 1month supply in Brazzaville and Pointe Noire and a 6-month supply in regional centres in the interior of the country.

Even with this buffer system, data collectors found that an average of only 57% of unexpired TB drugs were available on the day the health facilities were visited (n = 20), with a range of 13–88%. The survey also found that drugs were out of stock an average of 4% of the time during the previous 12 months, with a range of 0–13% in the visited facilities (n = 20).

Theoretically, the Centrale Nationale d'Achat en Médicaments Essentiels (CENAMES), which is in charge of the import of all essential drugs for the Ministry of Health, should procure TB drugs. However, no budget to allow CENAMES to issue a tender has been released in years. Normal tender procedures would be to contact three or four suppliers of generic drugs appearing on the essential drugs list. Under present conditions, there is no prequalification of suppliers, a situation that greatly benefits the former suppliers, especially those with an acceptable record.

When essential drugs are tendered by CENAMES, they are distributed to public and private health centres on the basis of direct cash purchase. However, TB drugs received at CENAMES from GDF and the French Cooperation are free. These drugs are sent to the NTP, which supplies TB health facilities where treatment is also free. The treatment centres of Brazzaville and Pointe Noire are supplied monthly, and the centres in the interior of the country every 3 months. Drugs are distributed according to the real needs in the health centres, as expressed in monthly or trimestrial reports sent to the NTP in Brazzaville. Roads, and thus transport vehicles, are practically non-existent so directors of the treatment centres travel to the distribution points to collect their drugs. At best, this system is problematic.

The inventory control system in health facilities is simple, consisting only of the use of stock cards or registers; no other information management system is used. The need for better stock management training is apparent, since the NTP estimates a 20% loss of drugs from expiry, theft, and inaccurate inventory management. This loss estimate was also supported by data collected during the survey, which showed that only 79% of stock records (n = 152) corresponded to actual counts.

Nongovernmental organizations (NGOs) such as CARITAS (Catholic missionary hospital) exist in faith-based or public health care institutions but do not participate in the fight against TB. No NGOs are known to purchase their own TB drugs and supplies. The much-needed TB drug gift-in-kind from the GDF in 2001 was shipped in bottles of 1000 tablets, which created the problem of finding containers for drug dispensing. In the end, paper envelopes were used for drug quantities for less than 7 days' treatment, and plastic bags for drugs for a 1-month treatment. Also, no syringes were provided with the streptomycin drugs, which placed an undue burden on the NTP to find another source of these supplies.

Quality assurance

The Ministry of Health has a functioning but weak quality assurance system for drugs and no laboratory testing programme. There are no competent laboratories in the country for quality control of drugs. The Ministry does have a laboratory, but its three laboratory-trained personnel have been assigned to another department.

There is no formal system for reporting drug problems or for recalling substandard drugs. Local experts indicated that, when a drug recall is necessary, users are notified to await procedures from the manufacturer before returning the drugs. No drug has been recalled in the past 3 years.

The only control exercised by the NTP on the quality of the drugs it receives is physical verification of drug characteristics (colour, shape, size), strength and dosage form, expiry dates, and certificates of laboratory analysis supplied by the manufacturer (which are not always supplied). If drugs are donated, the donor should ensure that certificates of laboratory analysis will also be sent to the NTP; otherwise there is no guarantee that the drugs contain the expected dose of the TB drug.

Private sector

The private sector is not usually involved in TB drug treatment because the free service in the public sector includes drugs. There is little chance of finding a private pharmacy or retail outlet with all TB drugs present because such outlets are not interested in investing money in products that are given free to patients. Looking at the average percentage of unexpired TB drugs available in health facilities (57%) and health facilities out of stock of drugs (4%), it appears that patients may find themselves in situations where the treatment must be interrupted, this adds to the burden of TB and to the difficulty of treating the disease when the public sector is unable to provide sustainable support.

Private retail outlets were surveyed to determine whether rifampicin and streptomycin could be purchased without a prescription. A simulated purchase technique was used for this activity, with a data collector posing as a relative of a TB patient. In 32% of the outlets visited (n = 25), rifampicin was sold without a prescription, which is particularly worrisome because TB is known to rapidly develop resistance to rifampicin taken as a single drug. Rifampicin should always be taken in conjunction with other drugs and always with an order from the prescriber. In 32% of the outlets visited (n = 25), streptomycin was also sold without a prescription. Streptomycin is an injectable drug that can have long-term sideeffects and should therefore be available to patients only on the order of a physician.

Weaknesses of the TB drug management programme

Data collected during the survey revealed the following weaknesses, many of which may be attributed to lack of Government commitment to fighting TB effectively:

- Absence of roads and lack of vehicles to ensure supervision and regular supply of drugs.
- Poor stock management within storage and treatment centres for the already scarce drugs.
- High unavailability of drugs that is expected to worsen without consistent donor support.

- No Government-supplied funds to purchase TB drugs.
- Prescriber compliance with national TB treatment guidelines in need of improvement.
- Very basic quality assurance programme; donors must be informed of the need to consistently require suppliers to provide certificates of analysis for shipped drugs.
- Private-sector practices that may have adverse consequences for development of resistance to TB drugs.
- Patients' poor knowledge patients with regard to the treatment of TB during the continuation phase.

Annex 1

Republic of Congo tracer drug list

- 1. Pyrazinamide, 400 mg tablets
- 2. Streptomycin, 1 g injection
- 3. Streptomycin, 0.75 g injection
- 4. Isoniazid + ethambutol, 150 mg/400 mg tablets
- 5. Rifampicin + isoniazid, 150 mg/100 mg tablets
- 6. Rifampicin + isoniazid + pyrazinamide + ethambutol, 150 mg/75 mg/400 mg/275 mg tablets
- 7. Distilled water (water for injection), 5 ml
- 8. Syringe

UTTAR PRADESH, INDIA

Background

TB in Uttar Pradesh

The state of Uttar Pradesh (UP) has a population of 166 052 859 and contains 70 administrative districts. The national TB programme has revised its strategy for treating TB patients and instituted the Revised National Tuberculosis Control Programme (RNTCP). The RNTCP fully subscribes to the DOTS strategy and is currently implementing it in eight districts of UP; extension to another 31 districts by the end of 2002 is planned. The Government of India fully funds the RNTCP.

At the request of the Government, the RPM Plus survey was carried out only in the eight districts—population 20.6 million—where the RNTCP is already functional. In 2000–2001 the annual TB case-detection rate was 133 per 100 000 habitants, with a smear-positive case-detection rate of 56 per 100 000. The total number of treated cases was 14 994.

Under the RNTCP, four types of centres can treat TB. In decreasing order of services delivered, these are: diagnosis and treatment centre (DTC); TB unit (TBU); microscopy unit (MU); DOTS centre. The RNTCP system is organized so that one DTC has several associated TBUs, MUs, and DOTS centres.

All other districts in the state are functioning under the older scheme, called National Tuberculosis Control Programme (NTCP), which does not subscribe to DOTS and is only 50% funded by the Government. In those districts without RNTCP, it is likely that patients and their families are covering the remaining costs, which may account for the estimate by local experts that 40–50% of TB patients receive treatment in the private sector.

The cost of a 6-month course of treatment in the private sector is US\$ 102 for the drugs used with a standard DOTS regimen in the public sector. A worker earning the minimum annual salary of US\$ 1 225 (position of TB health visitor) would therefore spend one month's income on treatment. This vivdly underscores the financial burden TB places on the population if TB treatment is not free.

In the public sector there is one treatment facility for every 100 000 persons, but this figure improves dramatically to one per 5 000 persons when DOTS centres and sub-centres are included.

Survey methods

Background information was collected and an overview of TB drug management operations was prepared for use in the training of the data collectors. The Centre for Symbiosis of Technology, Environment and Management (STEM) was contracted by RPM Plus to conduct the survey.

The following sampling plan was established to capture a more comprehensive view of TB drug delivery in health facilities:

- One DTC, one TBU, two MUs, and two DOTS centres were selected in each district.
- As far as possible, TBUs, MUs, and DOTS centres were chosen at random, but medical directors sometimes decided which sites should be visited.
- The nearest retail drug outlet to each of the TB facilities was visited to determine whether streptomycin and rifampicin would be sold without a prescription.

Using this scheme, 48 TB treatment centres and 48 retail outlets were selected for survey in the following districts: Bagpat, Barabanki, GB Nagar, Ghaziabad, Lucknow, Meerut, Raibareily, and Unnao. STEM identified a team of 16 data collectors and a local coordinator familiar with drug management to assist and oversee application of the DMTB process. The qualitative survey was also coordinated by STEM, using the RPM Plus-approved local TB drug and medical expertise of Professor Joe S. Bapna and Dr. Pagnioli Dwivedi.

Training was conducted by RPM Plus consultants Andy Marsden and Paul Lalvani, who were able to identify skills, competence, and participant understanding of the purpose of the survey. Paul Lalvani was the overall coordinator for the survey in India.

The TB tracer drug list used by the data collectors was developed jointly with the state TB programme director and MSH consultants (see Annex 2).

WHO/India supported the team with local administrative logistics as needed.

Survey results

Drug policy

The drug policy of India was developed in 1986 and approved in 1994. It encourages Indian pharmaceutical companies to produce drugs at reasonable prices and emphasizes the strengthening of quality control. The policy is supported by the Identification and Recruitment Act on industrial licensing aspects, the Essential Commodities Act on drug price controls, and the Drugs and Cosmetics Act on quality and standards of medicines.

Drugs approved for TB treatment regimens are published in *Technical guidelines for tuberculosis* (New Delhi, May 1997) by the Revised National Tuberculosis Control Programme of the Central TB Division, Directorate General of Health Services.

When new drugs are introduced for the first time the are registered centrally with the Drug Controller General of India. No TB drug has been registered since 1997. To register a new drug, a supplier must pay a fee of US\$ 1 021; the fee for re-registration is US\$ 306.

TB drug selection and use

The TB drug treatment regimens used in UP under the RNTCP programme are comparable to those promoted by the DOTS strategy. For all categories of patients during the intensive phase, oral drugs are administered three times a week under the direct observation of health staff. In the continuation phase, patients are required to take the prescribed drugs three times weekly and receive the drugs in weekly blister packs, one pack at a time; drug-taking is not supervised.

Drugs are not provided as fixed-dose combination products (all drugs in one tablet) but are uniquely arranged in blister packs according to the treatment category, which facilitates understanding by both prescriber and patient of the drugs and dosages to be taken. The following treatment categories are used.

- Category I: New smear-positive pulmonary and smear-negative serious (e.g. meningitis) TB cases are given the regimen HRZE¹ for 2 months during the intensive phase, followed by HR² for 4 months.
- *Category II*: Smear-positive relapses, smearpositive failure cases, and smear-positive patients being treated after default are given the drugs HRZES³ for 2 months during the intensive phase, followed by HRZE for 1 month and HRE⁴ for an additional 5 months during the continuation phase. This category includes patients who have received TB treatment for more than 1 month in the past and who are at increased risk of having multidrug-resistant TB.

¹ HRZE = isoniazid (H)/300 mg + rifampicin (R)/450 mg + pyrazinamide (Z)/750 mg + ethambutol (E)/600 mg.

² HR = isoniazid (H)/300 mg + rifampicin (R)/450 mg.

³ HRZES = HRZE same as Category I + (S) streptomycin 1 g administered twice weekly.

⁴ HRE = isoniazid (H)/300 mg + rifampicin (R)/450 mg + ethambutol (E)/600 mg.

⁵ HRZ = isoniazid (H)/300 mg + rifampicin (R)/450 mg + pyrizinamide (Z)/750 mg.

 Category III: New cases of smear-negative pulmonary and extra-pulmonary TB that is not very serious are given RHZ⁵ for 2 months during the intensive phase, and HR for 4 months during the continuation phase.

Table 1 compares the public-sector procurement prices by each treatment category with those of the GDF published at the following Web site: http://www.stoptb.org/GDF/whatis/docs/ FactsheetGDF011205.pdf. The dosages of the fixed-dose combination tablets procured by the GDF from international sources cannot be matched exactly since the India TB programmes use the intermittent dose schedule requiring higher strengths of each drug to be taken at one time. Calculating prices for a full course of treatment for one patient makes the price comparison more meaningful. Such a comparison shows that the Government of India (GOI) procures drugs at prices as good as or slightly better than those of the GDF when the total treatment regimen is considered.

Treatment categor	y Prices	Prices in US\$		
	India	GDF		
Category I	8	10		
Category II	12	12		
Category III	7	7		

Table 1. GDF/GOI treatment pricecomparisons

The GOI prices also compare very favourably with the price of a similar treatment regimen for Category I in the private sector, estimated by local experts to be about US\$ 102 for 6 months of treatment.

An individual card for each patient undergoing TB treatment is maintained at the health unit where treatment is administered. All information related to the patient's treatment is recorded on the card.

Data collected during the survey indicated that 100% of new smear-positive patients (n = 1375) with pulmonary TB were prescribed the correct drugs in the correct dosages in accordance with

approved treatment protocols. Of the TB facilities visited, 58% (n = 47) had an official manual of treatment guidelines for TB. Apparently, prescribers have been well trained (100% correct prescribing), but the availability of treatment guidelines would help to support their training, especially in facilities where there is only one prescriber and no one else with whom to consult.

Data collectors observed patients in the intensive phase of treatment to determine whether they were directly observed by the health worker when taking their TB drugs. Direct observation took place 98% of the time in visited facilities (n=212). Although this result is good, the DOTS strategy promotes directly observed therapy 100% of the time.

Patients were interviewed as they left the treatment facilities and asked whether they understood how to take their prescribed drugs; 76% (n = 484) could correctly describe how their drugs should be taken. Improving this percentage may be an appropriate focus during DOTS expansion activities as the NTP strives to improve its cure rate. Perhaps prescribers could spend more time explaining how patients should be taking their drugs.

Drug procurement

The Central TB Division (CTBD) of the GOI quantifies drug needs on the basis of the number of TB cases detected (and reported), plus a buffer stock. The CTBD finalizes the technical specifications and delivery schedules for TB drugs.

The procurement process is in the form of a tender, which takes 7–8 months to complete; the process of drug quantification is therefore started 12–14 months before the drugs will be needed by the TB programme. The supply line of CTBD is well maintained, and there were no shortages of TB drugs in the RNTCP facilities visited. For the survey, no stock-out days were reported and 100% of the tracer drugs were available in all facilities visited.

As for all drugs, the Metallurgical and Construction Engineers Ltd (MECON) is the procurement agency for the Government of India. MECON prepares the draft bid document, which is approved by the World Bank (a World Bank loan is used to procure the drugs). MECON advertises the tender in newspapers in India and sells tender documents to interested suppliers. Manufacturers and suppliers submit bids that are evaluated jointly by MECON and the Ministry of Health. A bid evaluation report is approved by the purchase advisory committee of the CTBD and the World Bank. The bid is awarded and the contract is signed, after which the drugs are delivered and payments made in according with contract terms. MECON handles all contract disputes with suppliers.

Distribution and stock management

The transport of drugs to RNTCP facilities is by trucks and is separate from that of the essential drugs programme. Distribution moves from the central stores to states and districts with a normal frequency of 3 months. Motorcycles are used to transport TB drugs from district centres to the periphery. Personnel within the supply system in UP indicated that there is a shortage of warehousing space, although additional warehouses are now under construction.

Stocks in UP are managed by a computerized information system at all six regional warehouses. In treatment facilities stocks of TB drugs are managed through computers and ledgers. Information on expiration dates and lot numbers is available only down to the level of regional warehouses. Data collected during the survey indicated that stock records in the visited facilities differed from actual counts 83% of the time on average; this indicates a need for further training in good stock management procedures.

The CTBD receives quarterly reports by email from most of the RNTCP centres for cases treated, but these reports are sometimes incorrect and have to be verified. After verification, the reports are forwarded to MECON for drug quantification purposes.

Quality assurance

Suppliers of TB drugs have every batch of drugs tested by an approved laboratory accord-

ing to contract specifications. The batch analysis reports are provided to MECON for approval before shipment. After drugs are distributed within the public sector, random samples are collected periodically from warehouses and health centres. In UP the number of samples collected for testing in 1999 was 3 144 but only 29.7% (n = 936) were actually tested because of a lack of resources. Of the drug batches procured, 21% were tested; no failures due to poor quality were reported in any of the tests performed.

There is no reporting system for drug problems in UP, and no information about substandard or counterfeit TB drugs, or about poor-quality packaging was available to data collectors. However, local experts estimated that 1% of the TB drugs procured by the GOI were substandard.

Private pharmacies and manufacturing companies are required to be inspected at least twice a year, but there are no inspection requirements for warehouse and government pharmacies. Although data were not available for UP, an adjoining similar state has 52 inspectors who undertook inspection of 786 manufacturing companies and 11 360 private pharmacies in 1999.

Strengths of the TB drug management programme

The data collected during the survey revealed the following strengths:

- Tracer TB drugs in the RNTCP facilities were always available in the facilities visited, and no stock-out days were recorded for the tracer drugs over the past 12 months.
- Prescriber adherence to treatment guidelines for new smear-positive cases was 100% in the RNTCP facilities visited.
- The Government of India favourably procures TB drugs at a competitive price.

Weaknesses of the TB drug management programme

The data collected during the survey revealed the following weaknesses:

- Many patients were unable to describe how they should take their medications after they leave the health facility.
- Stock records were sometimes different from actual counts in all facilities visited, indicating the need to strengthen stock management training.

Annex 2

Uttar Pradesh tracer drug list

- 1. Isoniazid, 100 mg tablets
- 2. Isoniazid, 300 mg tablets
- 3. Rifampicin, 150 mg capsules
- 4. Rifampicin, 450 mg capsules
- 5. Pyrazinamide, 500 mg tablets
- 6. Ethambutol, 600 mg tablets
- 7. Ethambutol, 800 mg tablets
- 8. Streptomycin, 750 mg injection vial
- 9. Streptomycin, 1000 mg injection vial
- 10. Thiacetazone, 50 mg tablets
- 11. Isoniazid + rifampicin, 600 mg/450 mg tablets and capsules
- 12. Isoniazid + rifampicin, 50 mg/100 mg kit
- 13. Isoniazid + rifampicin + pyrazinamide, 600 mg/450 mg/1500 mg tablets and capsules
- 14. Isoniazid + rifampicin + pyrazinamide, 300 mg/450 mg/750 mg blister pack, kit
- 15. Isoniazid + rifampicin + pyrazinamide + ethambutol, 300 mg/450 mg/1500 mg/800 mg tablets
- 16. Isoniazid + rifampicin + pyrazinamide + ethambutol, 600 mg/450 mg/1500 mg/1200 mg blister pack: tablets, capsules
- 17. Isoniazid + rifampicin + ethambutol, 600 mg/450 mg/1200 mg blister pack: tablets, capsules
- 18. Isoniazid + ethambutol, 300 mg/800 mg tablets
- 19. Isoniazid + thiacetazone + pyridoxine HCl, 75 mg/37.5 mg/75 mg tablets
- 20. Ethionamide, 250 mg tablets
- 21. Cycloserine, 250 mg capsules, tablets

HARMONIZATION OF TB DRUGS AND THEIR PRESENTATIONS

Prepared by **Peter Evans**

The Stop TB Partnership Secretariat and Management Sciences for Health wish to acknowledge the following people who have contributed to the preparation of this paper: Virginia Arnold, Robert Matiru, Ian Smith, Thomas Moore

OVERVIEW

Current guidelines of the International Union Against TB and Lung Diseases (IUATLD) and WHO allow for a wide range of acceptable ways to treat TB, all of which are considered valid under the umbrella of DOTS. This flexibility may work well for countries with strong infrastructure and sufficient financial resources but proves an unnecessary burden on the poorer countries.

Individual countries have interpreted these guidelines and in many cases undertaken operational research. Several have found different ways to improve programme performance through the choice of drug or presentation:

- Choosing fixed-dose combinations (FDCs) overcomes the problem of the excessive number of tablets that a patient must take. Use of FDCs also reduces the number of drugs that have to be stocked, selected, dispensed, and observed.
- Choosing drugs presented in packages designed to contain the entire treatment when the patient first arrives overcomes the problem of failed treatment due to stock

		TB treatment	
TB treatment	TB nationts	Initial phase ¹	
category	ib patients	Daily (28 doses/month)	3 times per week (12 doses/month)
I	New smear-positive patients; new smear-negative pulmonary TB with extensive parenchymal involvement; severe concomitant HIV disease or severe forms of extra-pulmonary TB	2 (RHZE) ^b = 56 doses of RHZE	$2 H_3 R_3 Z_3 E_3^{b}$ = 24 doses of RHZE
II	Previously treated sputum smear-positive pulmonary TB: — relapse; — treatment after interruption; — treatment failure ^c	2 (RHZE)S/1 (RHZE) = 84 doses of RHZE plus 56 doses of S	2 H ₃ R ₃ Z ₃ E ₃ S ₃ / 1 H ₃ R ₃ Z ₃ E ₃ = 36 doses of RHZE plus 24 doses of S
III d	New smear-negative pulmonary TB (other than in Category 1) and less severe forms of extra-pulmonary TB	2 (RH) Z = 56 doses of RHZ	2 R ₃ H ₃ Z ₃ = 24 doses of RHZ

shortages. Forecasting and stock control can be simplified.

- Choosing drugs packed as daily treatments, usually in blister packs, reduces the possibility of dispensing error. Use of blister packs also provides an additional record for the health worker and supervisor of what has been dispensed.
- Choosing formulations designed to provide patients with the same number of tablets at each visit, no matter where they are in the treatment schedule, reduces the possibility of error. The 4-drug fixed dose combination

(4FDC) tablet makes it easier to adjust dose to the patient's body weight.

• Colour-coding products to match training materials provides an additional visual indication to the health worker that the correct drug is being dispensed.

The Global Drug Facility should make easily and rapidly available to all national DOTS expansion programmes TB drug formulations and package designs, of known good quality, at affordable prices, which provide the maximum possibility of enhancing TB drug management.

regimens				
Continuation phase ^a				
Daily (28 doses/month)	3 times per week (12 doses/month)			
4 (RH) = 112 doses of RH or 6 (HE) = 168 doses of HE	4 (RH) ₃ = 48 doses of RH			
5 (RH) E = 140 doses of RHE	5 (RHE) ₃ = 60 doses of RHE			
4 (RH) = 112 doses of RH or 6 (HE) = 168 doses of HE	4 (RH) ₃ = 48 doses of RH			

- Direct observation of treatment intake is always required for treatments including rifampicin
- ^b In meningitis ethambutol should be replaced by streptomycin
- ^c Failures of Regimen I that include rifampicin in the continuation phase are more likely resistant to H and R and have a lower chance of cure with regimen II, which includes only one new drug. Alternatives to Regimen II are strengthening the regimen by adding 1-2 reserve drugs or using regimen IV in failure patients with proven MDR, according to the resources and capacity to keep patients on treatment
- ¹ Countries may choose to use regimen I also for Category III patients, to simplify training and drug supply. This however results in unnecessary medication and may reduce the priority that should be given to infectious cases

TREATMENT FOR TUBERCULOSIS: THE IMPORTANCE OF STANDARDIZATION AND SIMPLIFICATION

Introduction

Current IUATLD/WHO guidelines allow for a wide range of acceptable ways to treat TB, all of which are considered valid under the umbrella of DOTS. The variations in interpretation allow flexibility of choice at the national programme level. However, little guidance is available on packaging of drugs.

This flexibility may work well for countries with strong infrastructure, capable of independently determining the best drugs and treatment regimens, preparing training materials, evaluating manufacturers, conducting quality assurance, and tendering internationally to obtain best prices. However, it works poorly for countries that lack the infrastructure or funds to make such independent determinations.

Even for strong programmes, the cost of independence is high. TB drugs are more expensive than necessary (2-4), training programmes have to be established independently, programmes are unable to build upon the experience of, or compare their performance with, other programmes, and there is considerable duplication of effort in finding suitable suppliers.



- 3 treatment categories
- 2 recommended dosages—daily and intermittent
- 3 weight categories (not always consistent)
- Variety of packaging: blisters, foil-wrapped, loose tablets

All countries should choose drugs and treatment regimens that meet the needs of their programmes. The choice of regimens, drugs, and drug package presentations has a significant impact on programme management.

The Global Drug Facility (GDF) of the Stop TB Partnership acts as an international supply mechanism and assists in providing suitable presentations. Standardization and the combining of orders for similar drugs have many benefits for TB control.

This paper illustrates the impacts of drug choice on management issues at all levels. Situations from the health centre level, the central level, and the GDF are provided.

The programme

Crucially, the achievement of a curative TB programme within a public health system depends on the successful interaction between the health worker and the patient. The programme and the drugs must therefore be designed to that ensure this relationship is as successful as possible.

The patient

For patients to come to a health centre for treatment, they must know that they are sick, know that there are drugs that are safe, effective, and able to cure them, and know that these drugs will always be available when needed. A patient is more likely to complete a course of treatment if it is short-lasting, if the drugs are easy to take, and if the treatment is affordable.

If drugs are not available when patients attend the health centre, the likelihood of their returning for every appointment and their belief that treatment must be completed to be effective will diminish.

- 1. Some programmes have introduced fixeddose combinations, so that fewer tablets have to be taken (5).
- 2. Some programmes concentrate on intermittent therapy to reduce the number of visits to the health centre. Some have chosen the fixed combination product isoniazid/rifampicin (RH) in the continuation phase to reduce the total duration of treatment.
- 3. Some programmes reserve the entire treatment when the patient first registers, thus ensuring availability of the drugs whenever that patient comes in. Reserving drugs under a patient's name at registration transfers ownership of the drugs from the health centre to the patient; that is, the drugs become the patient's drugs. Patients are more likely to continue treatment so that they may receive all of their drugs.
- 4. Some programmes use tablets in blister packs, which are seen by many patients as being of higher quality than foil-wrapped or loose tablets; this enhances patients' perception of the treatment.

The health worker

The health worker must ensure that the correct drugs are available, dispensed, and taken—on schedule—in the correct dosages. Direct observation by the health worker or other designated individual remains paramount. For these apparently simple tasks to be achieved, many things must be in place. The following discussion indicates for which tasks the health worker must bear the responsibility, although sometimes they may need to rely on other experts.

Know the patient's status

The health worker must know the needs of the patient and whether the patient has been following the necessary treatment schedule. He or she must also know the patient's TB treatment category and body weight and the stage of the treatment regimen reached. It is equally important to know when patients have failed to come for scheduled treatment; such patients must be identified within a day or two and encouraged to continue treatment to avoid relapse which can promote development of multidrug-resistant TB (MDR-TB). These processes are normally controlled through a record-keeping system.

- 1. Some programmes use patient boxes to help health workers with these tasks; the "patient pack" used in India is an example. One pack is reserved for the patient at the beginning of treatment and is identified with the patient's name. Thereafter the health worker need only match patient with pack to identify needs and status. Once the patient has been matched with his or her pack, the next blister pack of drugs is opened and the contents given to the patient. The packs are stacked in one designated place at the beginning of the day and moved to a second place when TB drugs have been administered. Any packs that do not move during the day serve to identify missing patients so that follow-up can be initiated (6).
- 2. Some programmes use tablets packed in blisters as an indicator of each patient's treatment status: used blisters are retained as a record of what drugs have been taken.

Dispense correctly

Some regimens require that different quantities of up to five drugs are counted out and given to each patient on each occasion. The number of tablets to be counted out, vary according to the patient's body weight. Some treatment recommendations require tablets to be broken in half.

While counting out two, three, or four tablets of each of three or four drugs may seem a simple task for trained health workers, errors do occur. It is relatively easy to select the wrong drug from the shelf when there are many to choose from, or to mistakenly select two tablets of one drug and three of a second instead of three of the first and two of the second. If one or two drugs of a four-drug combined treatment are unavailable, there may be a temptation to give the patient only partial treatment rather than explain why drugs are being withheld. Partial treatment is unacceptable when simultaneous administration of multiple drugs is the norm for successful treatment and for reducing the likelihood of MDR-TB.

- 1. Some programmes have standardized on combination products to reduce the possibility of dispensing errors. The number of products available to the health worker is reduced and fewer tablets have to be counted out (5).
- 2. Some programmes chose formulations that allow the patients to take the same number of tablets at every visit, regardless of what stage of the treatment schedule has been reached.
- 3. Some programmes colour-code the products to provide extra visual reassurance to the health worker that the right drugs have been chosen.
- 4. Some programmes have standardized on patient boxes, which separate the treatment into periodic requirements. Health workers need only identify each patient and locate his or her box. They can then dispense the next treatment by taking out the tablets for that day—no need to identify drugs, no need to count tablets (6).

Replenishment of stocks

The health worker has a responsibility to ensure that drugs are available when needed. He or she must therefore have some background knowledge of drugs used and patients treated, and must know whether and how future drug needs will change, what stocks are on hand and on order, and when the delivery after next will arrive. Because forecasting future TB cases is notoriously difficult, many programmes require health workers to hold reserve drug stocks equal to the quantity used during one order period, so as to avoid stock shortages.

Determining whether the stocks on hand are sufficient and in the right proportions for future patients is difficult. Estimating how many patients can be treated from a partially full bulk container of tablets requires good documentation of the receipt and dispensing of drugs. Stock shortages of one or more drugs in the past are a sign of weakness, possible in forecasting, at some level within the system; no matter the origin of the error, subsequent forecasting at the health centre becomes especially difficult.

In countries that have standardized on patient packs, knowledge of stock used by health workers becomes a matter of knowing the number of patients treated in each category. Disease burden and treatment data become synonymous. Stock in hand can be determined by counting packs. Counting stock in terms of patient treatments rather than assessing it from bulk containers of tablets makes stock control simpler at all levels but especially at the health centre (6).

National TB programme manager

The manager of the national TB programme (NTP) is responsible for the programme's success. The manager must both establish the objectives of the NTP and ensure that those objectives are being achieved

In a standardized programme the NTP manager can take lessons learned from the successful aspects of the programme and apply them to the less successful aspects. On a global scale, lessons learned in one country may be applied to another—but only if the same regimen and the same drugs are being used in both.

A key indicator of success is the smooth and uninterrupted flow of TB drugs from the central receiving area to patient treatment centres. For many programmes it is difficult to oversee this flow, and part of the problem lies in the way information is handled. Patients treated are counted and recorded in one set of registers, and containers of tablets received and dispensed are recorded in another. Reconciling the two records is further complicated by the need to adjusting drug quantities according to patients' body weights. However, while it is not always easy, or even possible, to achieve this reconciliation, this need not be the case.

Some programmes forecast, order, and dispense drugs in terms of numbers of patients rather than numbers of tablets. Thus the register of patients and the register of drugs used can be matched and can be self-correcting. It then becomes much easier for the manager to have an overview of treatments needed and treatments provided.

CENTRAL NEEDS AND THE GDF

Finance office and regulatory authority

The range of TB drugs acceptable to the country and the standards that apply are the responsibility of the national regulatory authority (RA) and controlled through the process of registration. Every drug that is used within the country should be officially registered. Changing drugs and producers frequently overburdens the RA: when drugs are changed, supporting documentation from the manufacturers of all chosen drugs must be made available for examination.

The health system's finance office needs to know the cost of the approved quantity of drugs; its job is complicated by unexpected increases in drug costs due either to price changes or to increased demand. While the finance office may focus on affordability, it is usually unpredictability that causes the greatest problems.

- 1. The GDF assists registration by requiring that approved manufactures keep available, for rapid transmittal on demand, a file of documents designed for registration of standard items,. This registration file, together with data of the registration and use of the same drugs in other countries, will facilitate registration.
- 2. The GDF has published prices of a selection of standard TB drugs (4) to provide a benchmark for programmes and finance offices. Prices may vary but should be comparable to the benchmark. If the programme finds costs are significantly higher than GDF prices, the GDF may be requested to assist in the supply process.

Manufacturer

The manufacturer aims to produce drugs at the lowest possible cost and sell at the highest possible price. For most generic drugs in the public sector, the manufacturer must offer better prices than anyone else to obtain orders but must still be able to make a reasonable profit. Lowering production costs is in the best interests of both buyer and seller—and is the key to allowing the manufacturer to sell at the lowest possible price.

Manufacturers can obtain lower prices on raw materials if they commit to large orders, even if the materials will be delivered over an extended period. Production costs can be lowered: by manufacturing a small number of large batches rather than a large number of small batches; if drugs are produced, tested, and packed to the same standards and specifications; if production takes place when there is spare capacity rather than having to interrupt the manufacture of another item; if uncertainty about future orders can be removed.

- 1. To assist the manufacturer in lowering his costs, the GDF makes long-term forecasts for a specified number of TB drugs, with continual new advice as new information on the size of the market is received.
- 2. The ability to provide accurate forecasts is dependent on having a large client base and a limited list of standard TB drugs.

THE GDF



The nature of the market place is such that, the fewer suppliers and the more customers there are, the stronger is the position of the seller. Many marketing approaches are thus designed to result in segmentation of the market and increased market share in each of the segments. The opposite is true for the buyer. Buyers benefit when there are more sellers and fewer buyers; they are empowered by standardizing specifications and consolidating orders. These two opposites will be in constant tension, with either the buyer or the seller sharing power according to the market split.

For the GDF to maximize its impact it should standardize TB drugs to the greatest extent possible and consolidate orders from as many smaller buyers as possible. It should also ensure that there is a pool of quality producers competing for the business. In this way, power will shift from seller to buyer and the GDF will be able to do more for Stop TB. As the buyer's power increases, it becomes possible to stabilize prices and to design products that more closely meet programme needs rather than simply accept what is available.

GDF philosophy and purpose

The GDF is a drug supply mechanism, established to ensure that TB drugs would be available for DOTS expansion. It ensures the availability of drugs when needed, of known good quality, and at prices that are an efficient use of donor funds—in all respects meeting the needs of a TB programme. Whenever the GDF has a comparative advantage, it encourages TB programmes to use the services it offers, which fall into three areas:

- · Grants of drugs
- Procurement services
- A "white list" of suppliers of drugs of known good quality.

It is expected that each country will only use the supply services it needs.

Because the GDF suppliers and prices have been published, countries with sound finances and good infrastructure for procurement and quality assurance can approach their preferred companies directly and, using the GDF prices as a benchmark, should be able to purchase drugs at similar prices. If they cannot prices as favourable as those available to the GDF they may choose to use the GDF services.

Countries that are financially sound and have good procurement mechanisms but that lack a robust quality assurance system may choose to purchase only from companies used by the GDF, knowing they will receive drugs of known good quality.

Countries that are financially sound but that lack both good procurement and quality assurance systems may use the procurement services of the GDF, knowing that they will receive drugs of known good quality at low cost.

Finally, countries that are dependent on donors for some or all of their drug supply and

that wish to expand their DOTS programmes may apply for grants and receive drugs free of charge (7)

For each of these situations the GDF aims to adopt standards of excellence so that it will at least match any other option that a country programme may choose. However, the GDF is not a national procurement agent but an international agent. Where the national agent serves the priority needs of a single country, the GDF is an international agent and balances needs and benefits for all countries.

Areas of standardization

There are several components of TB drug treatment where standardization will be effective.

- 1. Regimens: drugs, dosage, duration of treatment and patient weight ranges
- 2. Products: drugs, strengths, combinations, packaging presentations, standards, and testing.
- 3. Calculations of quantities of drugs to .

It is not necessary for a programme to redefine policy, but merely to show that within existing policy, standardization has operational advantages, making DOTS expansion easier.

Example regimen (daily)

Category	2 months intensive (daily)	4 months continuation (daily)
I	2 (RHZE)	4 (RH)
II	2 (RHZE) + S/1 (RHZE)	5(RH) + E
Ш	2 (RH) + Z	4 (RH)

While many possibilities for drugs and regimens exist with the WHO/IUATLD guidelines, each country will choose one regimen, set of drugs, and presentation style. The more countries make the same choices, the more the GDF can do to influence manufacturers to meet the needs of the programme.

Example of recommended drugs

- RHZE, combination tablets, supplied as H 75 mg + E 275 mg + R 150 mg + Z 400 mg in blisters of 28 tablets and boxes of 12 blisters.
- RH, combination tablets, supplied as H 75 mg + R 150 mg in blisters of 28 tablets and boxes of 24 blisters.
- Z, tablets, supplied as Z 400 mg in blisters of 28 tablets and boxes of 12 blisters.
- E, tablets, supplied as E 275 mg in blisters of 28 tablets and boxes of 30 blisters.
- S, injectable, supplied as vials of 750 mg together with 3 ml of diluent, syringe. and disposal box in boxes of 112 treatments.

With just five drugs, all adult patients, of all weights, in all categories can receive individualized treatment that fully meets IUATLD/ WHO recommendations.

Recommended weight bands

For all drugs and all treatment categories

Patients of very low body weight, < 25 kg	one tablet a day
Patients of low body weight, weight 25–39 kg	two tablets a day
Patients of average body weight, 40–55 kg	three tablets a day
Patients of high body weight, 56–70 kg	four tablets a day
Patient of very high body	five tablets a day

Streptomycin is provided to patients of average weight as 750 mg, diluted in 3 ml. This may be considered equivalent to 3 doses of 250 mg/ml. If necessary, the dose may be adjusted—in accordance with a patient's weight—to actually be equivalent to the number of tablets. Thus a patient of lower weight, requiring only two tablets a day, would also require only 2 ml of the diluted streptomycin.

Recommended standards

While many standards are acceptable, the GDF recommends that drugs are manufactured to United States Pharmacopoeia standards and tested according to USP protocols, when they exist. This makes production and testing of drugs consistent. For the GDF, tablets are subjected to bioavailability testing of the active ingredient at a laboratory recommended by WHO; producers and drugs will be examined according to new WHO standards for TB drugs supplied internationally.

GDF has adopted standards for blister design, including layout, materials, markings, identity by unique colouring, and package inserts.

Recommended calculation: patients not bottles or tablets

Because of the risk of drug resistance it is recommended that a patient does not start on a course of treatment with assurance that sufficient drugs will be available to complete the course without interruption. The health worker must therefore view stock levels as numbers of complete treatments rather than numbers of bottles or tablets, and drugs should be supplied in formats that lend themselves to this kind of calculation. One approach is to distribute drugs in patient boxes, each containing sufficient drugs for a full course of treatment. Once the box has been selected for the patient, the drugs are reserved for that patient and only that patient. The advantages of this approach are obvious, but it does require either that patients of all weights receive the same treatment or that drug packages suitable for all weights are kept in stock. Trying to ensure that the right balance of treatments for different weights is always available can be complex.

Another approach has been devised, designed to meet the needs of both health workers and patients. Drugs are provided in master boxes, which—when needed—are converted at the health centre to individual patient boxes to meet individual patient requirements. Blisters of 28 tablets, for example, are taken from the master box and placed in a patient box, which is then reserved for a particular patient.

Weight	2 (RHZE) tablets	Blisters	4(RH) tablets	Blisters
Very light	1	1 x 2	1	1 x 4
Light	2	2 x 2	2	2 x 4
Average	3	3 x 2	3	3 x 4
Heavy	4	4 x 2	4	4 x 4
Very heavy	5	5 x 2	5	5 x 4

Blisters for individual patients

Points to note

- The number of tablets to be taken is the same for both (all) drugs.
- Calculation for blisters needed is tablets per day x months of treatment.
- If there are insufficient blisters available the patient's treatment is not started.

Inventory control systems, tendering, ordering, and stock on hand should be based on or calculated as patient treatments.

While these drugs may be used in the same manner as other TB drugs, including bulk supplies, the GDF design allows for programmes to introduce and use a simplified forecasting and ordering system. Thus:

- 50 boxes of RHZE combination blisters could be counted as 50 patient treatments (category 1 intensive)
- 50 boxes of HE combination blisters could be counted as 50 patient treatments (category 1 continuation), etc.

Delivery

The GDF standard is to make drugs available to countries through the grant mechanism within 60 days from the date of application to receipt of goods or 30 days from order placement to delivery of drugs to the consignee. In addition, it is intended that every step of the delivery process be transparent. The shipment delivery date will be confirmed at the time of order placement; the country will be able to track the progress of the order at any time using webbased information or weekly from status reports provided by fax or email.

Guaranteeing such rapid delivery necessitates the stockpiling of drugs in advance of firm requests. In turn, this requires a focus on a limited number of items with an expected high turnover, and means that programmes must want the drugs that are stockpiled. Drugs not stockpiled may still be made available but will have to be produced and undergo independent quality assurance testing—a process that will take 4–5 months.

Quality

The GDF standard demands the best available independent quality assurance system. The GDF has arranged for the newly initiated WHO scheme to be the main focus of the quality assurance system. Using the system recommended by the "Expert Committee on the Selection and Use of Essential Medicines" selection, products and producers will be examined by a WHO-appointed team and the findings published. Samples selected randomly from finished goods will still be sent for independent laboratory analysis, and all shipments will be inspected to ensure that they match both the purchase order and country needs. Countries receiving goods through the GDF will be assured that the drugs are of known good quality.

Prices

The GDF standard is to have TB drugs of known good quality always available, at a price equal to or lower than that charged by any other mechanism providing TB drugs internationally. The GDF seeks out as many producers of good quality drugs as possible. It also consolidates the requests for TB drugs from several countries to make an interesting quantity for the manufacturer; this has ensured significant competition for GDF business and resulted in price reductions.

Low prices are dependent on high volumes of standard drugs, manufactured as efficiently as possible. The GDF reduces risk to the producer by a precise and advantageous payment system and by a constant information flow on both short-term and long-term demand.

NEW OPPORTUNITIES

Fixed-dose combinations

The availability of fixed-dose combinations (FDCs), particularly the 4FDC, at prices—even for drugs provided in blisters—that are the same as or lower than those of other TB drugs is a recent and welcome development. It offers a rare opportunity for national programmes to switch to FDCs, making DOTS easier in many respects:

- Easier to finance—the per-treatment cost is lower than previous costs.
- Easier to dispense—fewer drugs are needed to be selected and counted. This will help in avoiding the development of drug resistance. Drugs for individual patients are counted in a similar manner across different weight categories.
- Easier for the patient—fewer tablets are taken.
- Easier to buy—drugs are available at low cost from a limited number of suppliers who have been closely examined.
- Easier to stock at all levels—just five drugs may be suitable for all categories and all patient weights.
- Easier to assure quality—the few suppliers will be examined according to WHO standards and centrally monitored.
- Easier to adjust dosage by weight.

Because of the operational advantages to the programme, the GDF is focusing on FDCs.

Blisters

GDF has received numerous requests for drugs to be supplied in blisters. However, there was no consistency in what was being requested and no internationally accepted standards for blister designs. Although still supplying tablets in bulk, the GDF wished to meet this demand for blisters for a variety of reasons:

- Many patients and health workers perceive blister-packed drugs as being of higher quality than foil-wrapped or loose tablets.
- Blisters provide better protection for the tablets once the main container has been opened.
- Blisters have the same shelf-life as foilwrapped and loose drugs, at very similar cost.
- Blisters packed face to face occupy about the same space as tablets packed in bulk.
- Blisters help the health worker to identify the drugs needed and to count the tablets to be dispensed.
- Keeping empty blisters can provide a permanent record for the health worker of what each patient has taken.
- Keeping empty blisters can provide a permanent record for the supervisor of what the health worker has been doing.

Blister-packed drugs can be used in all situations in which foil-wrapped and loose drugs are used. Because of their operational advantages to the programme, the GDF is focusing on blister packs.

Blister pack design

The design of the blister pack opens up other opportunities. Drugs may be provided in continuous strips, enabling any number of tablets to be extracted when required. However, it is possible to design the pack into blister cards to assist the health worker in counting and dispense drugs.

Each card contains 28 tablets—enough for one tablet a day for 4 weeks. If the patient is of average weight, and therefore receives 3 tablets a day of RHZE combination for 2 months, 3 x 2 cards are selected; 6 cards provide complete treatment for the average patient in the intensive phase.

For the continuation phase, the same patient needs 3 tablets a day of RH combination for 4 months, and 3 x 4 cards are selected; 12 cards

provide complete treatment for the average patient in the continuation phase.

If the patient is of lighter weight and needs only 2 tablets a day, $2 \ge 2$ cards of RHZE combination will be needed for the intensive phase, and $2 \ge 4$ cards of RH combination for the continuation phase.

In general, number of tablets per day x months of treatment = number of cards needed.

Once the first daily dose is extracted from the blisters, the empty shells provide the health worker with an extra check on the number of tablets to be provided and a permanent record of what was dispensed.

The same principle also applies to streptomycin. The dose for a patient of average weight is 0.75 g and the dilution volume varies between 2 and 5 ml. If the diluent volume is standardized as 3 ml, a patient who would require 3 tablets will require 3 ml of diluted streptomycin. A lighter patient who would require only 2 tablets daily should receive 2 ml of streptomycin diluted in the standard manner.

As the DOTS programme expands the use of community-based treatment supporters increases. Blister packs and blister cards are a convenient way of providing drugs to the community-based treatment supporter, helping both the responsible health worker and the community observer to count and dispense the correct dosage. Returning the empty blisters to the health worker provides a record of treatment given.

Because of the operational advantages to the programme, the GDF focuses on blister cards containing 28 tablets.

Patient boxes

TB differs from many public health problems in that, if the patient is not treated properly or does not complete treatment, the result—from a public health perspective—is worse than no treatment at all. The partially treated patient may have no symptoms but remain infectious, infecting first his or her family, then friends, and then the community at large with TB organisms that may be drug-resistant. A contributing factor to incomplete treatment is the frequent stock shortages of TB drugs in some programmes. A patient's treatment should not be started without assurance that sufficient drugs will be available for completion of the course.

Reserving the full treatment as soon as a new patient present is quite easy when blister cards are used. The drugs are put into a box marked with the patient's details (at least name, date, and number of tablets). The patient is told that these are his or her drugs and that they will not be given to anyone else. The patient now has all the drugs needed to complete the course of treatment and will be unaffected by changes in drugs, regimens, or stock shortages.

The GDF provides FDCs in adjustable patient boxes. These can be used only with blistered products with all product information included on the blister sheet. Each box holds a complete average treatment. Adding or removing blisters, according to the number of tablets needed, allows the health worker to create a patient box for patients of higher or lower body weight. It allows each drug to be dispensed according to the patient's weight but still requires stocking only one prepackaged patient box per category. Because of the operational advantages to the programme, the GDF focuses on drug presentations that can be effectively managed as patient boxes.

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DRUG PROCUREMENT FOR TUBERCULOSIS

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OVERVIEW

This paper aims to explain procurement practices specific to tuberculosis (TB) drugs. The information it contains is meant to provide a basic understanding of the components of procuring good-quality TB drugs in global markets. The process of procurement is often complicated by lack of experience among personnel, the unpredictability of drug availability from many global manufacturers, weak quality assurance systems among some manufacturers, and the poor management of some national quality assurance programmes. Although not specific to TB, the interagency guidelines, Operational principles for good pharmaceutical procurement (1) served as the basis for this paper.

Complexity of TB drug procurement

In national health systems the infrastructure for procuring TB drugs varies considerably. In some countries TB drug procurement is a purely vertical programme in which staff select, procure, and distribute only TB drugs and supplies-and do so quite separately from selection, procurement, and distribution of other essential drugs. In contrast, procurement of TB drugs in other countries is managed jointly with procurement of other drugs. Between these two scenarios are various other drug management options, such as those in which the national TB programme selects TB drugs and quantifies drug needs, but the essential drugs programme carries out procurement and distribution, or those in which procurement is the responsibility of an agency nominated by the donor paying for the drugs.

Regardless of the method, TB drug procurement is a complicated process and can involve many different agencies within a country as well as outside (in the case of international procurements). Procurement takes from 12 to 24 months on average and requires specific knowledge if it is to be successful.

Objectives of TB drug procurement

Regardless of the structure of the health system within a country, the objective of TB drug procurement remains the same — to purchase quality drugs from reliable suppliers at the best possible prices. To promote this objective, a TB programme manager should be aware of how successful procurement is accomplished and should, where appropriate, facilitate specific procurement activities.

Checklist of procurement activities for good TB drug management

The following checklist summarizes the common components of a comprehensive TB drug procurement system. The TB programme manager can use this list and the subsequent discussion of each component to understand and promote improved procurement activities.

- Management support through political commitment and a viable management information system.
- A drug selection mechanism for establishing and approving Directly Observed Treatment, Short-course (DOTS) drug treatment regimens, ideally using fixed-dose combination drugs (FDCs), and updating the national essential drugs list with the TB drugs included in the treatment regimens.
- Drug quantification methods that accurately estimate TB drug needs for all categories of TB patients.
- Competitive procurement practices that not only use appropriate tender methods to foster competition but also assure the quality of TB drugs and supplies (for example, by providing suppliers with product quality and packaging specifications required for TB drugs).
- Supplier selection and qualification procedures that allow assessment of suppliers'

capacities for providing quality drugs in a timely manner.

• A quality assurance system that defines requirements and requires documentation of quality assurance procedures used by the manufacturer to ensure provision of goodquality TB drugs. The Ministry of Health (MOH) can use a quality assurance system to monitor the quality of drugs received from the suppliers and during storage in MOH facilities until drugs are dispensed to the patient. A good system will also allow tracking of drugs within the MOH supply system in the event that a manufacturer recalls a drug product. Optimally, a national quality assurance programme would also have the resources to inspect suppliers for good manufacturing practices (GMPs).

- A supervision and monitoring mechanism that uses validated indicators to measure the performance of the TB drug procurement system.
- A strategy allowing facilitated procurement through the Global TB Drug Facility (GDF), and other non-profit suppliers, or other donor organizations to fill TB drug availability gaps for those TB programmes that have insufficient resources to procure on their own good-quality TB drugs in a timely manner.

COMPONENTS of TB DRUG PROCUREMENT

A well-functioning TB drug procurement system will have adequate management support to guide the various components of the system. Ideally, such guidance is sustained by a responsive management system within the programme, with visible support from political and administrative superiors. In typical procurement systems, activities are ideally divided among different offices, committees, and individuals, each with appropriate expertise and resources to allow the effective execution of the following procurement activities:

- *Drug selection:* Selecting the most appropriate drug treatment regimens and products for the TB programme, based on DOTS.
- *Drug quantification:* Estimating drug requirements based on epidemiological data, and using a systematic method such as morbidity-based (the approach recommended by the World Health Organization) or consumption-based quantification.
- Competitive procurement methods: Establishing a restricted procurement process with pre-qualification of suppliers.

- Supplier selection and qualification: Identifying and qualifying local and international suppliers.
- *Quality assurance:* Ensuring acceptable drug product quality and packaging for TB drugs.
- *Monitoring and supervision:* Monitoring supplier quality and performance, and supervising and monitoring the procurement system with regular evaluation

Procurement activities should be transparent, and personnel should follow written guidelines based on established, proven procedures to avoid being perceived as corrupt and losing the confidence of the public, donors, and other potential suppliers in the TB control programme. Development of an efficient procurement service requires planning and monitoring activities throughout the procurement cycle.

Management support for DOTS, quantification, and management information system

It is important that the government adopt the DOTS strategy recommended by WHO in order to support a well-functioning TB drug procurement service. Five components are involved:

- Government commitment to sustained TB control activities.
- *Case-detection by sputum-smear microscopy* among symptomatic patients self-reporting to health services.
- *A standardized treatment regimen* of 6–8 months for at least all sputum smear-positive cases, with directly observed therapy for at least the first 2 months.
- *A regular, uninterrupted supply* of all essential TB drugs.
- A standardized recording and reporting system that allows assessment of treatment results for each patient and of the overall performance of the TB control programme.

An uninterrupted supply of essential TB drugs requires accurate data on numbers of expected cases of the different categories of TB in the next procurement cycle, consumption data from the previous cycle, financial commitment for resources and drugs needed by the TB control programme, and diligence in seeking appropriate resources from donors and global initiatives to fill the resource gaps.

The backbone for obtaining appropriate data for procurement activities is a management information system (MIS) that provides data for accurately quantifying drug needs and for monitoring procurement activities. Without accurate data, TB drug estimates will be compromised, leading to stock-outs of drugs that are needed by patients. Drug availability is crucial in the treatment of TB: four or five drugs have to be taken simultaneously, on a daily basis, for 6–8 months without interruption to effect a successful cure and prevent development of drug resistance and consequent relapse.

Drug selection

Following the selection and implementation of workable treatment regimens such as DOTS, drug products for a national TB programme (NTP) need to be selected by an expert committee, ideally composed of a TB medical specialist, a pharmacologist, a TB programme manager, an epidemiologist, a pharmacist, and a nurse. Drug selection encompasses identification of treatment regimens, strengths of drugs, and dosage schedules to be used in the programme. It also includes choosing the appropriate packaging configuration for the TB drugs (such as loose tablets, patient boxes, or blister packs) and the FDC drugs that will be made available.

Experts generally recommend that FDC tablets be used wherever possible for treatment of both children and adults. Many experts feel that FDCs contribute directly to the likelihood of rational prescribing of anti-TB regimens because all the required drugs are included in one tablet. In addition, FDCs should make dispensing easier because there are fewer tablets or capsules to handle, which in turn should improve adherence by patients who take fewer numbers of tablets or capsules at any one time. FDCs come in two-, three-, and fourdrug combinations and are appropriate treatment regimens to consider if their selection is based on the morbidity profile of a given population. Because fewer tablets need to be stocked, FDCs occupy less storage space in warehouses and dispensing areas and facilitate stock rotation to keep the drugs fresh.

Standardizing—and thereby harmonizing treatment regimens within a TB control programme offers the added advantage of limiting the products that need to be procured. In decentralized health systems, where district managers have the authority to procure their own TB drugs, inappropriate and potentially incorrect drugs and dosages could be procured. Whether drugs are procured centrally or at lower levels, TB drugs should always be included in the national essential drugs list once they have been approved by the health system. Because of the complicated treatment regimens necessary for breaking the transmission of TB, having the right drugs in the right quantities available when the patient needs them is of utmost importance.

Drug quantification

Drug quantification means estimating the number of expected cases of all categories of TB to be treated in the upcoming year and multiplying the projected number of cases in each category by the number of single-drug or fixed-dose combination tablets required for that category. Inaccurate quantification is one of the biggest obstacles to good procurement, and the NTP manager must understand where to obtain the data and how to calculate drug needs accurately.

The two methods best suited to estimating TB drug needs are morbidity-based and consumption-based. Using both methods is a good idea, especially in countries where drug information systems are inadequate. Regardless of the quantification method used, however, the general approach is to calculate enough of each drug for 12 months. The quantities to be procured can be adjusted up or down according to the availability of funds.

TB drug treatment regimens comprise four or five drugs that are taken for the first 2 months (the intensive phase of treatment), followed by two to four drugs taken over the next 4-6 months (the continuous phase). Use of the morbidity-based method to estimate needs, requires the NTP manager to know the population of the country, the overall incidence of TB, the ability of the health system to detect TB cases, and the number of expected cases of TB for all categories. Although the number of expected cases can be based in part on the number of patients treated in the past, managers may need to pay attention to special circumstances within the country, such as rapidly increasing TB incidence due to HIV, or known migratory populations moving into the country. The morbidity-based method is defined by WHO in the Tuberculosis handbook (2) and is suited to countries with inadequate drug MIS for providing data on drug distribution, dispensing, stock-out, and expiry.

A well-functioning MIS is imperative for the consumption-based method, which relies on

accurate data from storerooms and pharmacy outlets for drugs distributed and dispensed; number of days out of stock; and number of drugs lost through expiry, diversion, and poor stock management. Few countries have a wellfunctioning MIS, but when these data are available, drug quantification is usually more accurate since numbers are based on real historical data rather than on expected numbers of patients as with the morbidity method. Some countries use data on number of drugs issued during the previous procurement cycle, but this is not quite as good as actual consumption data described above. The consumption-based method is described in the Drug management for tuberculosis tool developed by Management Sciences for Health.

When quantifying TB drug requirements, the NTP manager should also determine the preferred packaging (e.g., blister-packed drugs, patient boxes, loose tablets) and the exact formulations (e.g. which FDC tablets) needed to help ensure greater drug availability and adherence to treatment regimens. In the case of blister packs, the drugs for a full day or full week of treatment can be packaged in one blister. An example is the multidrug blister pack developed by India's TB control programme, which uses blister packing for a daily dose and for patient boxes. This packaging makes prescribing, dispensing, and securing patient adherence to therapy much easier.

Patient boxes, which have been tries by a number of countries on a pilot basis, may be useful in TB control programmes that have trouble maintaining an adequate supply of the TB drugs needed by patients under treatment. All of the drugs needed for both intensive and continuous phases of treatment of a specific patient, usually 6–8 months' supply depending on the category of TB patient, are placed in a box that is labelled with that patient's name. The drugs in the box are used only for that patient, and the supply of medicines needed to complete therapy for that patient is ensured. This approach works well if patients do not move around during treatment.

After a reliable quantification has been completed, it may still be necessary to adjust

the quantities that can be procured to conform to available funding. Having fewer drugs than needed for full treatment of an individual patient may promote the development of multidrugresistant TB (MDR-TB); before the treatment of a given patient begins, therefore, all drugs must be available for both the intensive and continuous phases of treatment. Should drug quantities need to be reduced for a particular procurement cycle, they should be adjusted on a per-patient basis.

Competitive procurement methods

Competition is the best way for a TB programme to obtain the most cost-effective, quality TB drugs possible. The task is not easy since TB drugs are all off patent and there are many suppliers worldwide, with unit prices that vary wildly. The recommended method for procuring TB drugs is through restricted tender with pre-qualification and performance monitoring of suppliers.

At the outset, the TB drug procurement department must determine government policy on international procurement and to what extent local TB drug manufacturers must be used. Moreover, if funding for the purchase of the TB drugs is through a World Bank loan, Bank procurement procedures must be followed; these explicitly support international competitive bidding, with supplier prequalification, and a small percentage of the loan being allowed for local procurement.

Potential suppliers must be qualified for service reliability and product quality before the drug tender is prepared and the procurement service can invite bids only from such suppliers.

Once the contract is signed, performance monitoring of the supplier can begin, based on the quality and delivery terms of the contract.

Countries that do not have fully functional procurement systems may also acquire TB drugs by facilitated procurement from the Global Drug Facility (GDF) and non-profit suppliers. The GDF programme is described later in this paper. Advantages of this method are competitive prices, products of good quality, timely deliveries, and procurement by experienced professionals.

Supplier selection and qualification

Although restricted tender with prequalification is recommended for procuring TB drugs, a procurement service may choose to qualify suppliers after tendering. This "post-qualification" must be planned and carried out well in advance of actual tenders to avoid delays in receiving drugs. Even so, pre-qualification of suppliers tends to reduce the complexity of the tender process. Whichever method is chosen, buyers should:

- require certificates from manufacturers and regulatory agencies indicating that the manufacturers are licensed and inspected by local authorities;
- obtain financial reports showing that the suppliers are established and able to fulfil the drug order;
- gather information on suppliers' reliability and the quality of their products based on past performance;
- inspect samples of products; and
- if necessary, conduct laboratory tests of drugs that may be unstable or have low bioavailability.

To gather much of the information needed to determine suppliers' qualifications, buyers can use both the "Quality of a Product Moving in International Commerce" certificate, developed by WHO, and drug batch analysis certificates. More information is available on the following web site: http://www.who.int/ medicines/library/theme/theme_qual.shtml.

To avoid confusion in tender documents to pre-qualify suppliers of TB drugs, the procurement department should use criteria established by the NTP and the national regulatory authority and include in the terms and conditions the exact strengths of the single-dose and FDC drugs, as well as quality specifications for each drug product. Appropriate standards for packaging must also be specified to indicate appropriate labelling and to protect drug products during shipment and storage. Reference should be made in the terms and conditions to the pharmacopoeias that manufacturers are required to use to test their products (e.g. US Pharmacopoeia (USP), British Pharmacopoeia (BP), and International Pharmacopoeia (IP)). Packaging of TB drugs can also be complicated when special blister packs are requested for improving patient and prescriber compliance. Quality issues with rifampicin-only tablets and rifampicin in FDCs have been noted by both WHO and the International Union Against TB and Lung Disease (IUATLD), and are discussed below, in the "Quality assurance" section.

In the absence of prequalification, supplier reliability may be determined only after purchase, that is, when the supplier delivers the required quantities of drugs according to the specifications and dates in the contract. Procurement departments in neighbouring countries may prove to be a valuable resource if they are able to provide information about their experiences with certain suppliers. However, whether pre- or post-qualification of suppliers is effected, appropriate monitoring of performance will help to eliminate undesirable suppliers.

Quality assurance

Quality assurance involves many areas within the national TB control programme, but discussion here is limited to those areas specific to drug registration and procurement.

Like other drugs, TB drugs should be registered in the country where they are to be used to ensure that they are safe and effective. The national drug regulatory authority usually conducts registration. Most countries have such an authority, but where none exists the MOH should establish an agency to be responsible for registration. The registration criteria specific to TB drugs have been published in the International Journal of Tuberculosis and Lung Disease (3) and include evidence that FDCs are tested as required by WHO and IUATLD. Other quality assurance issues specific to TB drugs are the criteria that should be stated in tender documents, that is, a signed statement from the manufacturer containing the following information:

- Comparative bioavailability results for rifampicin in single-drug and FDC products not older than 3 years, and the laboratories at which the tests were performed. Laboratory tests must be equivalent to rifampicin single-drug standard methods in order to comply with recognized pharmacopoeial standards.
- Comparative dissolution tests for all components of FDC products.
- A declaration of consistency between the starting and subsequent batches.
- A correlation over time between dissolution tests of different batches.
- A statement that the raw materials are in accordance with reference specifications.

Even after drug registration, and with appropriate documentation in hand showing that manufacturers have followed good manufacturing practices, the appropriate MOH departments should verify the quality of shipped drugs and supplies using physical and laboratory tests. If laboratory services are unavailable or inadequate, random sampling with testing by a WHO reference laboratory is suggested. A quality assurance department may also want to consider laboratory screening by thin-layer chromatography, which requires fewer resources and provides quick identification and measures content uniformity of a drug. At a minimum, a physical inspection should be made to ensure that drugs appear adequate (not crushed or discoloured, for example) and are labelled and packaged according to specifications (e.g. blisters or requested configuration of FDCs in the blister).

In summary, with an appropriate quality assurance system in place, the TB programme will receive drugs with the correct ingredients, with the potency specified on the label, in the required dosage form and in the packaging configuration ordered, and with active ingredients that are bio-available.

Monitoring and supervision

The need for continual planning and monitoring throughout the procurement process is not

unique to TB drug procurement but is worthy of mention here. The procurement process is cyclical: when the NTP has received one order of TB drugs, the next cycle of procurement must be started by collecting quantification data and pre-qualifying additional suppliers. In addition, supplier performance must be monitored to determine reliability of delivery and quality specifications agreed upon in the contract.

Personnel supervision is one method of monitoring, but the collection of standardized data to measure specific indicators is also an appropriate way of quantitatively assessing performance of the procurement system. Those indicators are presented in another paper in this document, *Using indicators to monitor TB drug supply*.

Facilitated procurement from the Global Drug Facility

National TB control programmes may be using a variety of mechanisms to procure TB drugs, including working with suppliers who participate in national tenders, those who participate in international tenders, and international not-forprofit suppliers. While NTPs should always strive to be as self-sufficient as possible, those countries without available resources and experience may find it advantageous to purchase TB drugs through global initiatives like the GDF. The GDF is an initiative of the Stop TB Partnership that provides a mechanism for increasing access to, and availability of, highquality TB drugs to facilitate global DOTS expansion. The advantages of using the GDF include the following:

- Competitive prices can be expected.
- Procurement is done by others.
- Quality products are assured.
- Timely deliveries are made.
- Ongoing development of packages such as FDCs and blisters promotes patient compliance.
- Linkage exists with the DOTS expansion programmes of WHO Member States providing the greatest benefit of drug use within the country.

The GDF has a grants-in-kind mechanism to fill the gap in TB resources of countries using the DOTS scheme, and in 2002 established the direct procurement mechanism to meet yet another demand. To use this direct procurement mechanism, countries must meet specific criteria: details are available on the Stop TB web site at http://www.stoptb.org/GDF/ drugsupply/Direct_procurement_process.doc, which specifies the sale of drugs only to those organizations and countries that follow DOTS guidelines and are committed to using TB drugs procured through the GDF only in DOTS programmes. To continue purchasing from the GDF, countries must submit routine annual DOTS programme performance reports to WHO.

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USING INDICATORS TO MONITOR TB DRUG SUPPLY

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OVERVIEW

To ensure a reliable supply of TB drugs, managers must pay attention to four key components of the drug supply system selection, procurement, distribution, and use within their countries—which need to be supported by appropriate financing and a management information system to feedback strategic information. The activities covered by each of these components are described in another of the papers in this document, *Operational framework to strengthen TB drug management*.

Why monitor?

Monitoring is an integral part of TB drug supply; it should be performance-based and involve an ongoing review of activities to determine the extent to which established targets are being met. Indicators will help policy-makers to make more informed decisions relative to their national programmes. Moreover, with a monitoring system in place, action can be taken immediately to rectify any problems that occur (1).

Although the indicators suggested in this paper are intended for in-country monitoring of drug supply, some can also be used for reporting to partners and global TB initiatives such as the Global Drug Facility (GDF) and the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM).

Using indicators

There are several methods for monitoring a TB drug supply system—direct supervision of personnel is one of them. Direct supervision, or even periodic supervisory visits, can be problematic in some developing countries because of lack of resources. A supplemental method is the use of indicators, which is described in this paper.

To calculate indicators, data about the programme are needed. These data should be available within the TB information system for vertically managed TB programmes, and within the drug information system of the essential drugs programme in countries where TB drug supply is integrated with other health programmes. If all the drug supply and use data are not readily available in the country's TB drug information system, the programme manager may want to seek technical assistance from TB partners in setting us a viable system.

When selecting which monitoring indicators to use for the first time, managers commonly choose too many. Some of the indicators may then not be used, or prompt feedback may not be given to those involved, causing personnel to lose faith in the monitoring system and perhaps rendering it ineffective. It may be best to identify all the indicators that would useful, and then select one or two core indicators for each component of the TB drug supply system (selection, procurement, distribution, use, financing, quality assurance, and national drug policy). Once the monitoring system is fully established, more indicators can be added, as feasible, or some of the core indicators can be replaced with others.

Taking action

If indicators are to be used effectively, the TB drug supply manager should take action appropriate to the nature of any problem identified: this may take the form of positive feedback or corrective feedback. It may also involve reassigning staff, adjusting TB drug supply targets, or requesting additional information to provide a better understanding of the problem. With a good monitoring system in place, managers make optimal use of scarce resources.

The next section discusses in more detail the use of monitoring indicators in TB drug supply. The last section, "Illustrative TB drug management indicators", provides a list of indicators to consider for use in monitoring a TB drug programme.

CHOOSING INDICATORS FOR MONITORING

Introduction

All countries have national drug policies which are published in laws, regulations or procedures. These may vary from country to country but generally have the same objectives: making effective, safe, low-cost, essential drugs available and affordable, meeting the needs of the entire population, and ensuring that the drugs are of good quality and used rationally. With a good drug monitoring system in place, a TB drug management programme can promote the accomplishment of the national drug policies.

In some countries the TB drug supply system is vertically managed by the national TB programme, while in others it is part of the essential drugs programme. In countries with decentralized health systems, it is managed at the district level. Regardless of the type of TB drug supply system, effective monitoring can help managers to achieve the goals of the national drug policy and the TB control programme. Monitoring is also important as a means of reporting progress to partners and global initiatives such as the World Health Organization, the Stop TB Partnership, and GFATM.

Several types of monitoring system are described in the publication *Managing drug* supply (1), but it is not the intention to discuss them all here. The purpose of this paper is to discuss drug management indicators in the context of TB drug supply.

The four main components of the drug management cycle—selection, procurement, distribution, and use—can be used to break down TB drug management into more discreet activities to provide a better understanding of what should be monitored.¹ For example, the following core indicators might be chosen for each of the components:

- *Selection*—proportion of TB drugs used that are in the standard treatment guidelines.
- *Procurement*—supplier contract delivery times.
- *Distribution*—number of stock-outs in TB drug storerooms.
- *Use*—percentage of patients given their TB drugs in directly observed therapy.

Indicators are a viable choice for monitoring drug management activities, having been around since the early 1990s (1). Drug management indicators specific to TB are the same as those used by essential drugs programmes but adapted to the specifics of TB drugs. Some drug management indicators have been tested in various countries and others have been adapted for specific national or global programmes.

TB drug management indicators take several forms: some are merely data that can be summed, such as "numbers of TB drugs that failed quality tests", while others are averages, percentages, or proportions and require calculation, such as "percentage of stock-outs of TB drugs in health facilities". Indicators measured at only one point in time are less useful than those that are measured on a regular basis and allow trends to be monitored over time. More comprehensive information on drug management indicators is available in *Indicators for monitoring national drug policies* (2).

Selecting TB drug management indicators

Setting up a monitoring system without clear connection to the drug management programme, as often happen, can lead to the selection of too many or inappropriate indicators. At the outset, using many indicators may mean the collection of useful data, but if time cannot be found to analyse those data and provide feedback for appropriate action, the monitoring

¹ See also the final paper in this document, *Operational framework to strengthen TB drug supply*.

programme is likely to fail. To avoid this, TB drug programmes may want to start small and expand the number of indicators only when the system is well established. It may be a good approach to start by selecting just one or two core indicators at each level of TB drug supply —central, district, treatment centre—and then expand to include more or different indicators once the monitoring system is well established.

When selecting indicators for TB drug management, it is important to ensure both that they are meaningful and understandable by those whose activities are being measured and that the data are readily available or retrievable. Data collection for monitoring indicators must become part of regular monthly or quarterly activities. However, if the TB drug information system is not functioning well, the first step is to improve its performance so that indicator data will be reliable. Even with a sub-optimal information system, indicators should be chosen for the data that are currently available, and an annual survey should be undertaken to fill the gap for data that are unavailable. One useful way to set up an indicator monitoring system is to select strategic sentinel sites or a smaller set of health facilities for reporting. However, if a sentinel system is used, there is still the possibility of problematic sites remaining undetected.

Collecting data to calculate indicators

The number of drug products needed for TB programmes is small when compared with the hundreds of products involved in essential drugs programmes. For that reason, the TB drug monitoring system may include all drugs used in the national TB programme. However, if the monitoring system needs to start small, a tracer list of TB drugs—which should be those drugs that are available at all levels of the health system—can be selected. In this case the tracer list may consist of all drugs used to treat patients in Categories I, II, III of the WHO/DOTS strategy (*3*), since all drugs must be available at all times for successful treatment and prevention of drug-resistant TB.

In countries where the private sector is important in TB drug supply, the national programme may want to include retail pharmacies or private clinics in the routine monitoring—but certainly in periodic surveys.

There are other reasons governing the selection of drugs to monitor. Perhaps the TB programme is expanding its use of fixed-dose combination products or of blisters packaged especially for patient boxes. In this case, the products to monitor at the central warehouse, local storerooms, and treatment centres may be the different drug combinations or packaging configurations. Other choices may be drugs that have caused difficulties in the past, because of quality problems with the active ingredients of the tablets themselves or with the product packaging.

Information needed to calculate indicators

Depending on whether the indicators are prepared as summed data or need to be calculated, the following information must be given to determine the feasibility of their adoption within a TB drug system.

- Name of the indicator or monitoring point
- Rationale for the indicator
- Definition of the indicator
- Data that constitute the numerator and denominator (for summed data only the numerator data are given)
- Where to go to get the data
- Whom to ask for the data
- What data must be collected and reported
- How data are to be analysed.

In the data collection tool *Drug management* for tuberculosis (DMTB) developed by Management Sciences for Heath (MSH), several drug management indicators have been adapted for monitoring TB drug supply. The tool is still in draft form, however, and the indicators are currently being field-tested in two countries; test results should be available by the end of 2002. In the interim, the DMTB tool may serve as a guide to understanding the components of a drug management indicator.

In the MSH training guide *Drug* procurement for tuberculosis (4), indicators for the procurement of drugs for a national TB programme have been suggested. These are also being field-tested, but results may not be available for some time because of the need to track long procurement periods.

Illustrative TB drug management indicators

Several TB drug indicators are listed below for consideration by national TB programmes. They are purely illustrative, although some have been tested through a general essential drugs programme. For better understanding they are grouped under the appropriate components of the drug management cycle. To assist in identifying what data must be collected and where, and how the indicator should be calculated, reference can be made to the documents cited above and also to Indicators for monitoring national drug policies (2). TB partners may be able to provide technical assistance to national programmes in setting up a TB drug monitoring system based on local requirements.

Indicators marked with an asterisk (*) are core indicators established by the GDF for monitoring countries with which it has agreements.

Drug legislation, regulation, and policy related indicators

- Percentage of a set of TB drugs that are registered in the country as compared with the contract delivery dates.
- Average number of days to register TB drugs.
- Percentage of TB treatment facilities visited that have the latest official manual of treatment guidelines for TB.

Selection-related indicators

• Percentage of first-line TB drugs on the *WHO Model list of essential drugs (5)* included on the national essential drugs list.

Procurement-related indicators

- *Costs of drugs procured as a percentage of costs if GDF drugs were used.
- Dates the different shipments of TB drugs arrived in country.
- Average time required to clear shipments of TB drugs from the port of entry.
- Percentage of mean international price paid, CIF¹/ex-factory, for a set of TB drugs that was part of the last regular Ministry of Health (MOH) procurement.
- Percentage of drugs purchased by international tender over the past 3 years.

Distribution and storage related indicators

- *Average percentage of time out of stock for a set of TB drugs in MOH storage and treatment facilities at different levels of the health system.
- Average percentage of a set of unexpired TB drugs available in MOH storage and treatment facilities on the day of inspection.
- Average percentage of stock records that correspond with physical counts for a set of TB drugs in MOH storage and TB facilities on the day of inspection.
- Number of drugs beyond expiry date out of total of number of TB drugs surveyed on the day of inspection.

Drug use related indicators

- *Percentage of new smear-positive patients with pulmonary TB who were prescribed correct drugs in correct dosages in accordance with treatment standards adopted by the country.
- Percentage of TB patients who could correctly describe how the prescribed medication should be used (for the continuation phase of treatment).

¹ CIF: cost, insurance, freight.

- Percentage of prescribed TB drugs actually dispensed.
- Percentage of private drug retail outlets where rifampicin and streptomycin were available without a prescription.
- Percentage of private retail outlets where TB drugs are sold.
- Cost (CIF/ex-factory) of drugs prescribed as a percentage of costs if DOTS norms for treatment were followed.

Quality control related indicators

• *Number of TB drug samples that failed quality control testing out of the total number of TB drug samples tested.

- Total number of quality problems reported during the year by storeroom, prescriber, and dispensing personnel and patients.
- Percentage of shipments received over the past 3 years that were physically inspected for quality defects.

Financing related indicators

- Average number of days to pay suppliers after receipt of TB drugs for the last three procurements.
- Average percentage of expenditures for all TB drugs paid for by the government.

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OPERATIONAL FRAMEWORK TO STRENGTHEN TB DRUG MANAGEMENT

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OVERVIEW

Introduction

This paper provides a strategic framework that can be used by TB programme managers, Ministry of Health (MOH) TB drug managers and local TB partner organizations to develop a comprehensive action plan for improving weaknesses in drug procurement and supply for the national TB programme (NTP). For best use of the framework, the first step is to identify specific weaknesses in the programme. Identifying drug management problems can be done in several ways:

- Using personal knowledge and experience from working within the national programme.
- Through a special workshop or committee bringing together both individuals familiar with the NTP and experts in TB drug management.
- Formally, through an assessment such as that provided by data collection tool *Drug* management for tuberculosis (DMTB), developed by Management Sciences for Heath (MSH), which quantifies the extent of the problems.

Each of the methods will produce a different level of understanding of TB programme weaknesses. Once it has good knowledge of specific problems, the TB programme can use the framework provided in this paper and select appropriate activities to implement for strengthening drug management capacity.

This framework was developed for the Stop TB/MSH drug management meeting in Washington, DC, in June 2002. Using the framework, participants of the meeting will select specific activities, establish a realistic timeline, person(s) responsible for carrying out each activity, and the resources needed. Using this methodology resource gaps will be documented so that partners understand how they can best provide specific assistance to the TB programme.

Objectives of drug management

TB drug management activities must be designed to support the NTP; providing drugs from approved standard treatment regimens for TB patients of Categories I, II and III when needed should be the primary objectives. It is no simple task to procure and supply drugs since there are many suppliers in local and international markets, prices and quality vary tremendously, and drug procurement and supply personnel may not have the necessary training, experience, financial resources, or appropriate established procedures. In addition, TB treatment regimens are complicated and it is difficult for patients to continue taking the 4–5 drugs required throughout the 6–8-month treatment period.

Operational framework and activities for strengthening TB drug procurement and supply

The procurement and supply of TB drugs is a recurring process, and using the drug management cycle illustrated below is a good way to understand the various components of the process and their interrelationships. Those components are selection, procurement, distribution, use, and management Support, all of which are supported by a **"Policy and legal framework":**



Once managers have a full understanding of the cycle they can more easily identify existing gaps and shortcomings in their own programmes and recommend specific improvements for ensuring the uninterrupted procurement and supply of TB drugs. The next section in this paper outlines the strategic framework for strengthening TB drug procurement and supply, and the final section describes specific activities that managers can choose to overcome the weaknesses they identify in their TB programmes. For each implementation activity, the expected outcome or benefit is also provided.

OPERATIONAL FRAMEWORK TO STRENGTHEN TB DRUG PROCUREMENT AND SUPPLY

Components of drug management

To address TB drug management appropriately, managers need to know the specific roles of each component of the drug management cycle, since any flaw that interrupts the patients' timely use of TB drugs may lead to treatment failure and promote the spread of multidrug-resistant TB (MDR-TB). There are four major components of the cycle:

- Selection of essential TB drugs
- Procurement of selected drugs
- Distribution of procured drugs
- Use of distributed drugs.

Each component of the cycle is supported by a policy and legal framework and a management support system.

Management support

Management support is an integral part of each of the components of the cycle, and manager responsibilities will be spread throughout several departments of the MOH in a typical NTP. For example, the NTP control manager may be directly involved in the selection of drugs and regimens, estimation of quantities of each drug needed, and distribution of drugs to treatment facilities.

The essential drugs manager may also be involved in the selection of drugs and regimens, and may—instead of the NTP manager—be responsible for receipt of TB drugs and their distribution to treatment facilities. The procurement manager is usually involved in selecting and qualifying of local and international suppliers, tendering for good-quality, costeffective drugs, and monitoring supplier contract performance. The receipt and clearance of TB drugs from the port of entry could be the responsibility of any of these managers.

Prescribers and patients are responsible for *using* the TB drugs. It is the prescriber who must first diagnose that the patient has TB, then prescribe the drugs and treatment periods according to treatment guidelines, and then directly observe the patient taking the drugs, especially during the first 2 months of treatment. The patient is also responsible for rational drug use and must comply with the complicated treatment regimen necessary to combat TB.

Verifying the quality of TB products is the responsibility of the national drug regulatory authority. This involves carrying out registration of suppliers' drug products, ensuring that suppliers use good manufacturing practices, and monitoring the quality of received products through physical inspection and laboratory analysis.

A viable drug management information system (MIS) must be in place to provide the specific programme data needed to manage each component of the cycle. To monitor effectiveness of treatment and provide feedback information for ongoing TB programme needs, prescribers must record all case data using standardized patient care and reporting forms. The programme will need patient case data to determine needed resources for the programme, to quantify TB drug needs for the next procurement cycle, and to report to local and global partners such as the WHO Stop TB Partnership.

Finally, the NTP should have in place strategies to monitor the effectiveness of the TB drug management programme. Monitoring can take the form of supervision of employees and use of indicators to track trends in drug procurement and supply. Indicators are especially useful for demonstrating to stakeholders and TB partners alike the status of drug management within the programme. With such data a programme may be able to obtain more assistance—technical expertise, and human and financial resources—to improve TB drug procurement and supply.

Policy and legal framework

The success of a TB control programme depends largely on political commitment from the government and from doctors and other health professionals to support a DOTS programme. Government commitment takes the form of drug policy activities for allocating budgets, promoting education initiatives, defining the role of the public and private sectors, and responding to global initiatives for procurement, supply, and use of TB drugs. Commitment of the health provider consists in diagnosing, prescribing, and administering approved treatment regimens for Categories I, II, and III patients, directly observing drug-taking by the patient, patient education, and documentation of TB drug use and compliance. The DOTS strategy promoted by WHO outlines the commitment needed by an NTP:

- Government commitment to sustain TB control activities.
- Case detection by sputum-smear microscopy among symptomatic patients who report to health facilities voluntarily.
- Standardized treatment regimen of 6–8 months for all patients with positive sputum smears and directly observed therapy for at least the initial 2 months.

- A regular, uninterrupted supply of all essential TB drugs.
- A standardized recording and reporting system that allows assessment of treatment results for each patient and of the overall performance of the TB control programme.

With both management support and a policy and legal framework in place, the four components of the drug management cycle are easier to manage. Activities specific to each of the four components (selection, procurement, distribution, and use) are discussed in the following sections.

Selecting TB drugs

Selecting drugs for TB programmes usually involves a team of people with different backgrounds—the NTP manager, a medical specialist in TB treatment, a pharmacologist, a procurement specialist, a pharmacist, and a nurse, for example. The team reviews patterns of TB morbidity and resistance and, using the DOTS regimens as a basis, identifies treatments of choice, and selects the drugs and dosage forms that will be available in TB treatment facilities.

In selecting specific drugs and drug combinations, the team must also consider the structure of the health system, the ratio of providers to TB patients, and the accessibility of health facilities to patients. WHO recommends that the TB patient should be directly observed while taking the TB drugs during the first 2 months of treatment: this is greatly facilitated by the use of fixed-dose combination (FDC) products, which WHO and its partners have supported for several years. In addition to 2- and 3-drug combination products, a 4-drug product (4FDC) has recently become available, which contains all the drugs needed by the Category I patient during the initial phase of treatment. Based on the patient's weight, one or more 4FDC tablets are taken daily, making drug calculations easier for the prescriber and drug-taking easier for the patient. The 4FDC is also useful for the Category II patient to whom it can be jointly administered with the fifth drug needed for treatment-injectable streptomycin.

Another consideration for the selection team is the packaging of drugs. Until quite recently, blister-packed drugs were much more costly than loose tablets in multi-dose bottles of 100 or 1 000 tablets; now, however, with improved technology and greater competition, the price difference is practically negligible. Blister packaging is thus a viable alternative for TB programmes, helping prescribers to give patients a better understand of their treatment regimens. For example, the blister pack may contain all TB drugs or FDCs needed for 1 day, 1 week, or longer.

Some TB programmes have experimented with patient boxes—containers, marked with each patient's name, into which all the drugs for at least the first 2 months of treatment are placed. This system was developed to avoid the problem of starting a patient on the intensive phase of treatment and then having to interrupt treatment (and risk the development of MDR-TB) because of stock-outs.

Once the drugs are selected, they should be included on the national essential drugs list. This helps to enforce the procurement of only approved drugs, especially in decentralized health systems where drugs can be purchased at local levels.

Procuring TB drugs

Procurement of TB drugs involves obtaining a regular supply of adequate quantities of highquality drugs at the lowest possible cost. As mentioned in the previous section, stock-outs cause the interruption of patients' treatment and can lead to the development of MDR-TB. The need for timely procurement to promote availability of drugs in the health system is thus obvious. Details of the following procurement activities are described in another paper in this document, *Drug procurement for tuberculosis*:

• *Drug selection:* Serving as a member of the team that selects the most appropriate drug treatment regimens and products for the TB programme, the procurement manager can provide background information on such matters as expected costs, availability in the market place, and which drugs are already registered in the country.

- *Drug quantification:* Estimating drug requirements on the basis of epidemiological data, and using a systematic method such as morbidity-based (recommended by WHO) or consumption-based quantification. Depending on the programme, responsibility for quantification may rest with the NTP or with procurement personnel. Estimating the quantities of each needed drug is critical for ensuring that drugs are available when and where needed by the patient.
- Competitive procurement methods: Understanding the advantages of the restricted procurement method with pre-qualification of suppliers. There are several procurement methods, but only this method is recommended for TB drugs; it involves a formal process of collecting data about potential suppliers before tendering for the drugs themselves. With a limited list of suppliers with known potential for producing drugs of good quality, the procurement department has fewer tender bids to review, reducing lead time for receiving the drugs.
- Supplier selection and qualification: Identifying and qualifying local and international suppliers. TB drugs have been on the market for more than 30 years, are available as generic formulations from many producers worldwide, and have shown quality problems with the drug rifampicin in FDC products. Through pre-qualification, a procurement manager must be able to identify the best suppliers for the TB programme based on their ability to produce and deliver the drugs when needed, using acceptable quality standards, at an optimum price. Prequalification allows a procurement manager to prevent undesirable suppliers from bidding, thereby saving time and resources.
- *Quality assurance:* Understanding quality aspects of drug and packaging specifications for TB drugs. Many things can go wrong in the attempt to provide drugs of good quality, and all those involved in the procurement process must contribute to overcoming these potential problems. Manufacturers must follow validated processes, using the same ingredients and the same equipment, with trained

personnel. The drug packaging must be tested to ensure that it will preserve the quality of the drugs at least until the expiry date specified on the labelling. The national regulatory authority can verify this through on-site inspections or through the use of the *WHO certification scheme on the quality of pharmaceutical products moving in international commerce (1)*.

Shippers must use procedures that maintain product quality until delivery to the TB programme, such as meeting the manufacturer's specified conditions for temperature extremes and humidity. The TB programme must then maintain product quality during distribution to the facilities and storage within health facilities until drugs are given to the patient.

Despite prequalification of suppliers, the TB programme must still inspect and test the products for quality assurance purposes. It should establish receiving procedures for sampling of the shipment for physical inspection to determine whether the drugs have deteriorated, been crushed, or changed colour and whether they are labelled appropriately, and laboratory testing to establish that drugs contain the correct active ingredient(s) in the dosages specified.

Monitoring and supervision: Monitoring supplier quality and performance, monitoring and supervising the procurement system. Supervising personnel is one method of monitoring, but can be time-consuming and subjective. A supplemental method is monitoring through the use of indicators to quantitatively demonstrate performance of the procurement system. Depending on the indicators chosen, they can measure the procurement lead time, contract delivery times by suppliers, number of quality problems found by the system, percentage of drugs out of stock in TB drug facilities, and percentage of drugs past their expiry dates. Potential indicators are described in detail in another paper in this document, Using indicators to monitor TB drug supply.

Distributing TB drugs

Distribution comes into play once drugs are appropriately selected and the drug quantities calculated and procured. The process begins with rapid clearance through customs to avoid deterioration of drugs waiting at the port of entry in inappropriate storage conditions. Once drugs have passed quality inspections they can be delivered to warehouses and treatment facilities.

Timely provision of TB drugs relies on information from local warehouses and health facilities on quantities of existing stocks and the number of additional drugs needed. To deliver orders promptly, the distribution manager must establish a transportation schedule that takes account of the geography of the country, the availability of vehicles, and the condition of the roads. Provision should be made for emergency orders with a safeguard to prevent overuse of the emergency system as a result of poor inventory control.

Good inventory control procedures must be used at all levels in the programme to avoid stock-outs and to supply reliable data for estimation of drug needs for the next procurement. The following procedures for good stock management should be followed to promote the availability of TB drugs when they are needed by the patients and in the prescribed quantities:

- The receiving warehouse should document receipts and deliveries of all drug shipments to TB depots and health facilities when they occur.
- Local warehouses and treatment centres should document receipts of all drug deliveries when they occur.
- Treatment centres should document quantities of each drug dispensed or administered to patients every day.
- Warehouses and treatment centres should store drugs in an appropriate way so they are easy to find, protected from pilferage, and protected from deterioration from sunlight and moisture.
- Warehouses and treatment centres should rotate stocks, putting drugs that will expire first at the front; this avoids exceeding the

shelf life and therefore loss of drugs (FEFO—first to expire, first out).

Using TB drugs

To promote rational drug use, health care providers must prescribe the appropriate TB drugs in the right doses and patients must adhere to the drug regimens prescribed. The rational use of drugs is facilitated by other components of the drug management cycle, as described above, with drugs being selected from approved treatment regimens and made available at treatment centres in the quantities and at the times needed by patients. It is also facilitated by the development work of WHO and its partners, who continue to study ways of improving TB treatment regimens. One outcome of such work, the use of FDCs, has already been (see "Selection" above).

With the lengthy and complex treatment regimens necessary to fight TB, use of FDCs greatly facilitates the job of the prescriber and enhances patient compliance. For the prescriber, FDCs simplify the calculation of doses, making the task of matching numbers of tablets to the patient's body weight much easier. For the patient treated with FDCs, fewer tablets have to be taken at one time.

The direct observation of patients that is involved in the DOTS (directly observed treatment, short course) scheme also promotes the rational use of TB drugs. Patients are observed while taking their drugs, at least during the first 2 months of treatment, and this helps in avoiding relapse or failure. Any relapse or treatment failures that occur put affected patients in danger of developing MDR-TB, leading to both the necessity of using more costly antibiotics and, sometimes, death.

Some TB programmes have experimented with the use of incentives for both prescribers and patients. For prescribers, incentives have included bonuses for every patient treated successfully or recognition in the community as a successful TB practitioner. For patients, incentives have taken the form of food supplements or of stipends for successfully treated patients who become spokespersons in their communities promoting good TB control (2).

It is crucial to make private sector becoming more involved in TB treatment prescribers and dispensers as aware as possible of government TB treatment programmes.

ACTIVITIES TO STRENGTHEN MANAGEMENT OF TB DRUG PROCUREMENT AND SUPPLY

In order to identify weakness in drug management, TB programmes can compare their organizational structure and procedures with the model provided by the operational framework described above. Appropriate solutions can then be selected. This section contains a variety of problems and activities for overcoming drug management weaknesses. To better use the information, programme managers should create a table to organize the outcome of their drug management analysis. For each problem and activity selected they can indicate the resources needed, resources available, resource gaps, person responsible to carry out the activity, and potential TB partners who could provide financial and technical assistance.

Activities to advocate for needed changes in the national drug policy

• **Problem**: There is no policy for promoting rational drug use or for updating personnel training to promote rational drug use.

- Activity: Hold strategic meeting with policy-makers and demonstrate both the need and the positive outcomes if drug policy were to include human resource capacity building and the rational use of TB drugs.

- *Expected outcome:* Drug policy will be updated to affirm government support for rational TB drug use, including training for good procurement practices, good stock management and inventory control, and appropriate use by prescribers. The TB programme budget will cover regular training for appropriate staff that includes supervisory activities.

• **Problem:** Current drug registration procedures are too lengthy and affect the availability of TB drugs in the national programme.

- *Activity:* Hold strategic meetings with the national drug regulatory authority (NDRA) and discuss acceptable ways to coordinate TB drug registration dossiers.

- *Expected outcome:* The NDRA will adopt procedures such as fast-track registration¹ and agreement on a model drug registration dossier. The NDRA will share registration procedures with authorities of other countries within the region when registering TB drugs from the same suppliers.

Activities that can promote overall drug management support

• **Problem:** The programme wishes to change from using single drugs to FDC products.

- Activity: Justify the change to FDCs with decision-makers, then provide technical assistance in establishing and implementing a changeover plan. The plan should include announcement of the changeover decision to TB programme personnel; training for all personnel who will select, procure, distribute, and use the new TB products; ensuring that

only products of good quality will be procured and used; updating the documentation system to accommodate the FDCs; and a mechanism to monitor implementation (for example, procurement personnel will need to understand specifics of FDCs related to quality and packaging of 2-, 3-, and 4-drug FDCs and potential blister-pack configurations). The plan must also cover the phasing-out of remaining single-drug products.

- *Expected outcome*: The changeover to FDCs will be smooth and avoid interrupting appropriate treatment of TB patients.

• **Problem:** The management information system (MIS) is weak and unable consistently to feedback the number of treated cases and therefore the quantities of drugs needed for the next procurement cycle.

- Activity: Seek and provide technical assistance in developing an MIS that has appropriate reporting forms and a computerized or manual tracking system; assistance should include training for appropriate personnel in analysis and interpretation of the data. Train personnel on TB drug quantification using both the morbidity- and consumption-based methods. Quantities from the two methods can then be compared to improve estimates of real drug needs.

- *Expected outcome:* Programme data will be available in a timely manner for national programme reviews by TB partners, reporting to global initiatives such as Stop TB and DOTS expansion, and identification of problem areas by the TB drug procurement and supply managers

• **Problem:** The NTP does not have an optimum system for monitoring its drug management activities.

- Activity: Seek and provide technical assistance in establishing a system that combines the drug supply reporting mechanisms with supervisory checklists, selecting appropriate drug management programme indicators, and training programme personnel to calculate indicators as well as interpret the data. The system may include the use of sentinel sites for surveillance and indicator monitoring.

¹ Fast track drug registration involves the issuance of conditional permission for a supplier to market a drug in-country. Prequalification of the supplier has usually taken place, the drug is used, and the supplier's product is monitored for quality by the NDRA during the conditional period, often 6–12 months.

- *Expected outcome:* The NTP will be able to monitor critical activities and take action when problems occur.

Activities that can improve selection of appropriate TB drugs

• **Problem:** The TB drug selection committee has little experience in, or needs updating on, currently accepted therapies such as FDCs (the committee may be the same as the essential drugs committee).

- Activity: Provide specialized training for the TB drug selection committee in currently accepted therapy including, for example, FDC use, packaging, and function within the DOTS strategy.

– Expected outcome: Standard treatment guidelines (STGs) are updated with appropriate therapies for Categories I, II, and III patients.

• **Problem:** TB or essential drugs selection committee has not updated the STGs for TB in several years, and there have been recent changes in national demographics and TB incidence, or newer therapies have been introduced.

- *Activity:* The selection committee is supported by partners to update the STGs and establishes a regular system for keeping the STGs current, such as ad hoc meetings held at least yearly to evaluate whether any conditions have changed.

- *Expected outcome:* STGs are updated with appropriate therapies for Categories I, II, and III patients.

• **Problem:** There is no TB drug selection committee in the country and STGs need to be established, approved, and adopted.

- *Activity:* Provide technical assistance to establish and implement the use of STGs. Where an essential drugs committee exists, use it for this activity.

– Expected outcome: STGs are developed and approved by the NTP for Categories I, II and III patients; these may be country-specific STGs or STGs for the WHO DOTS strategy.

• **Problem:** Drugs listed in the currently approved STGs are not all on the national essential drugs list (EDL).

- *Activity:* Essential drugs committee is supported by partners to update the EDL with all currently approved TB drugs based on national STGs.

- *Expected outcome:* In both vertical and decentralized TB programmes, having an EDL limits the drugs that can be procured for TB and promotes cost-efficiency, efficacy of treatment, and quality assurance activities.

Activities that can improve quantification (estimation) of drug needs

• **Problem:** Quantification personnel are new to the TB programme and do not understand how to estimate drug needs using morbidity data, which is the method supported by WHO and many of its partners.

- *Activity:* Provide training for the new quantification personnel in both morbidityand consumption-based methods. Training will include comparison of quantities calculated by the two methods to improve estimates of drug needs.

- *Expected outcome:* Estimates of TB drug needs calculated by the new quantification personnel will be more accurate and will minimize stock-outs of TB drugs in the programme.

• **Problem:** Quantification activities for the NTP were recently decentralized to the district level; personnel are new to TB and do not understand how to use morbidity data.

- Activity: Provide district personnel with training in estimating drug needs using the morbidity- and consumption-based methods, and in other TB programme policies and procedures that affect them. Establish a supervisory monitoring programme to follow their progress.

- *Expected outcome:* The estimates of TB drug needs calculated by the district personnel will be more accurate and minimize stock-outs of drugs in treatment facilities in their districts.

• **Problem:** Quantification personnel at national, district, or facility levels are providing poor estimates of drug needs for procurement.

- *Activity:* Provide all appropriate personnel with technical assistance and practical training in the morbidity- and consumption-based methods.

– Expected outcome: Estimates of TB drug needs will be more accurate and stock-outs attributable to quantification weaknesses will be reduced.

Activities that can improve procurement of TB drugs

• **Problem:** The procurement department has never purchased TB drugs or has little experience in purchasing TB drugs on the international market, but is responsible for drug acquisition for the NTP.

- Activity: Seek assistance from TB partners for training in purchasing TB drugs, including identification and qualification of international suppliers, tendering and contracting, quality assurance of TB drugs procured from local and international sources, and use of restricted tender with supplier prequalification (reference the DMTB data collection tool). TB partners will provide technical assistance during the first few procurements.

- *Expected outcome:* Personnel will be able to locate and select appropriate TB drug suppliers, conduct an international tender, establish a viable contract, and monitor supplier performance; appropriate TB drugs will be procured.

• **Problem:** The procurement department has some experience in purchasing TB drugs on the international market but needs assistance in selected areas such as locating and prequalifying TB suppliers, assuring quality of TB drugs, preparing tender documents, conducting and adjudicating tenders, contracting, or monitoring suppliers.

- Activity: From TB partners seek technical assistance for procurement personnel in specified areas of procurement; this may

involve training and hands-on assistance.

- *Expected outcome:* Procurement personnel will become more proficient in procuring TB drugs and will be able to reduce drug management problems related to procurement.

• **Problem:** The TB programme consistently orders more drugs than available funds can procure at any one time; suppliers have grown weary of this and unit prices have risen on successive tenders to compensate for late payments.

- Activity: Provide technical assistance for quantification and procurement personnel to improve their understanding of methods of reconciling TB drug estimates with available funds (estimating on a per-patient basis is best for TB, for example), and of establishing mechanisms (for example, letter of credit or escrow accounts) to assure suppliers of payment.

- *Expected outcome:* Quantities of drugs ordered each time will be only what the programme can afford, suppliers will be assured of timely payment, and TB drug unit prices will probably decrease.

• **Problem:** The country recently received a World Bank (WB) loan and the NTP needs to procure TB drugs using a part of the loan; procurement personnel have never purchased drugs using a WB loan.

- Activity: Provide technical assistance to procurement department in following WB procurement requirements for health sector goods, using restricted tender with prequalification of suppliers.

- *Expected outcome:* WB approval will be obtained more rapidly and may prevent stockouts of TB drugs.

• **Problem:** The NTP was recently given funding by TB partners but does not have the human resources necessary to procure the drugs.

- *Activity:* Provide information and technical assistance on using the facilitated procurement activity of the GDF of the Stop TB partnership or procure directly from non-profit suppliers.

- *Expected outcome:* The TB programme will be able to purchase quality drugs and receive them in a timely manner so as to prevent stock-outs and promote DOTS expansion in their country.

Activities that can improve distribution and stock management within the country

• **Problem:** There is no established system for distributing TB drugs to local treatment facilities; either the NTP relies on vehicles from other health services or has vehicles but seems unable to catch up with delivery needs.

- Activity: Provide technical assistance to the NTP in developing an appropriate transportation system and delivery schedule, including potential need for capital equipment such as more vehicles.

- *Expected outcome:* TB drugs will be available in appropriate dosage forms and quantities when needed for patient treatment.

• **Problem:** Local warehouse personnel seem unable to manage stocks so that correct of drugs are always available for delivery to treatment facilities when needed.

– Activity: Provide training and technical assistance in good stock management procedures, including documentation of all quantities of drugs moving into the warehouse and from the warehouse to treatment facilities, and calculation of buffer stocks and minimum quantity levels to trigger an order, for example.

– Expected outcome: Stock levels will be maintained so that needed quantities will always be available for delivery to treatment facilities

• **Problem:** There has been a significant loss of drugs due to pilferage, expiry, and deterioration over the previous 2 years.

- Activity: Provide training and technical assistance in good storage practices such as avoidance of excessive moisture and direct sunlight, exclusion of pests, provision of secure storage areas, and prevention of drug expiry using the FEFO (first to expire, first out) method of stock rotation.

- *Expected outcome:* Drug losses will diminish, relieving this expensive burden on the NTP.

Problem: The receiving warehouse and the local warehouses do not have a management information system (MIS) that will track drug requirements, drug orders, and existing stock levels in health facilities; there have been many drug stock-outs as a result.

– Activity: Provide technical assistance in establishing an MIS.

- *Expected outcome:* Warehouse personnel will be able to more accurately control the movement of TB drugs from receiving warehouse to local warehouses and from local warehouses to treatment facilities when needed.

Activities that can improve use of TB drugs

• **Problem:** Not all prescribers are following the STGs approved by the NTP or not consistently documenting that they use directly observed therapy.

- Activity: Provide technical assistance to establish a prescriber monitoring system (may include periodic documentation reviews, use of indicators, comparison of drug quantities consumed versus number of patients who should have been treated).

- *Expected outcome:* Prescribers will understand the need to follow STGs as established by the programme; number of patients treated will be reported; and patients will be treated more appropriately, leading to fewer relapses and treatment failures.

• **Problem:** Many patients are not following the prescribed treatment regimens and are developing MDR-TB.

-*Activity:* Provide technical assistance in developing and implementing an incentive plan for all patients to encourage adherence to the prescribed treatment (may include training, recognition in a TB programme

ceremony as a "successfully treated patient", or financial reward for successful completion of therapy (2)).

- *Expected outcome:* Number of relapses and treatment failures will decrease.

Activities that can improve quality assurance of TB drugs

 Problem: Drug-testing laboratories have few resources for random testing of TB drugs received from local and international suppliers.

- Activity: Provide technical assistance in establishing the optimum use of resources, such as use of thin-layer chromatography test methods, and limiting laboratory testing to the most problematic drugs (e.g. rifampcin in FDCs, or those drugs with quality problems found during physical inspection at port of entry).

- *Expected outcome:* Laboratory testing concentrates on the most problematic products, offering the best possible quality assurance programme for the NTP with the limited resources available.

• **Problem:** Storeroom personnel, patients, and prescribers alike are complaining about the quality of the products they receive, such as too many crushed tablets, discoloration, or empty blisters (i.e. containing no tablets).

- Activity: Provide technical assistance in establishing a two-tier TB drug sampling system, first to physically inspect products for approval of shipments from suppliers, and second to collect samples from health facilities. Samples collected from the field would be physically inspected and tested in the laboratory as appropriate. Problematic suppliers would be identified and then, depending on the nature of the quality problems, notified that they may be removed from the approved list of suppliers. - *Expected outcome:* The number of quality problems would diminish.

• **Problem**: The NDRA has limited resources for registering drugs from new suppliers and monitoring the quality of drugs in the market place.

- Activity: Provide technical assistance to the NDRA in establishing a targeted programme of activities such as using fast-track drug registration, establishing a model dossier to register drug products from local and international sources, or targeting local manufacturers, distributors, and retail pharmacies that have been problematic in the past.

- Expected outcome: Drug registration will be well controlled and timely and will not delay procurement decisions, and inspection personnel will use their time more wisely by inspecting known offenders against drug laws.

Activities for conducting a comprehensive assessment of the TB drug sector

• **Problem/situation:** There are many problems in the private and public TB drug sectors, and previous assessments have consisted of only partial reviews; both the NTP and TB partners are interested in identifying weaknesses of drug selection, procurement, distribution, and use.

- *Activity:* Use the DMTB tool to comprehensively quantify and document actual weaknesses in the TB drug sectors (public and private).

 Expected outcome: The NTP and partners understand specific weaknesses in drug management and can discuss the appropriate levels of support and technical assistance needed.

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