

## CHAPTER 1

# Background information on drug-resistant tuberculosis

### 1.1 Chapter objectives

This chapter summarizes key information on the emergence of drug-resistant TB, its public health impact, experience gained in patient management and strategies for addressing drug resistance within national TB control programmes.

### 1.2 Recent developments and the Stop TB Strategy

The original basic package of DOTS provisions for TB control has recently been expanded while retaining the five essential components (see Chapter 2, section 2.2).

The new Stop TB Strategy continues to emphasize the basic package and includes components that tackle additional challenges:

#### 1.2.1 Pursuing high-quality DOTS expansion

- a. Political commitment with increased and sustained financing
- b. Case detection through quality-assured bacteriology
- c. Standardized treatment with supervision and patient support
- d. Effective drug supply and management system
- e. Monitoring and evaluation system and impact measurement

**1.2.2 Addressing TB/HIV, MDR-TB and other challenges** by implementing collaborative TB/HIV activities, preventing and controlling MDR-TB, and addressing prisoners, refugees and other high-risk groups and situations.

**1.2.3 Contributing to health system strengthening** by collaborating with other health-care programmes and general services, e.g. by mobilizing the necessary human and financial resources for implementation and impact evaluation, and by sharing and applying achievements of TB control.

**1.2.4 Involving all care providers**, including public, nongovernmental and private providers, by scaling up public-private mix (PPM) approaches to ensure adherence to international standards of TB care, with a focus on providers for the poorest and most vulnerable groups.

**1.2.5 Engaging people with TB, and communities** by scaling up community TB care and creating demand through context-specific advocacy, communication and social mobilization.

**1.2.6 Enabling and promoting research** to improve programme performance and to develop new drugs, diagnostics and vaccines.

Emphasis on expanding laboratory capacity (sputum smear microscopy first, then culture or drug susceptibility testing (DST)) and the use of quality-assured drugs across all programmes are important aspects of this comprehensive approach to TB control.

### **1.3 Integration of diagnostic and treatment services to control tuberculosis**

Detection and treatment of all forms of TB, including drug-resistant forms, should be integrated within national TB control programmes. In the past, many public health authorities reasoned that scarce resources should be used for new patients with drug-susceptible TB because the cost of detecting and treating the disease was 10- to 100-fold lower than for MDR-TB. However, it has now proved feasible and cost-effective to treat **all** forms of TB, even in middle- and low-income countries. Untreated or improperly treated patients with resistant TB are a source of ongoing transmission of resistant strains, resulting in future added costs and mortality. The framework for the management of drug-resistant TB presented in these guidelines can be adapted to all national TB control programmes and integrated within the basic DOTS strategy.

### **1.4 Causes of drug-resistant tuberculosis**

Although its causes are microbial, clinical and programmatic, drug-resistant TB is essentially a man-made phenomenon. From a microbiological perspective, resistance is caused by a genetic mutation that makes a drug ineffective against the mutant bacilli. An inadequate or poorly administered treatment regimen allows a drug-resistant strain to become the dominant strain in a patient infected with TB. Table 1.1 summarizes the common causes of inadequate treatment.

Short-course chemotherapy for patients infected with drug-resistant strains may create even more resistance to the drugs in use. This has been termed the “amplifier effect” of short-course chemotherapy.

Ongoing transmission of established drug-resistant strains in a population is also a significant source of new drug-resistant cases.

### **1.5 Addressing the sources of drug-resistant tuberculosis**

Any ongoing production of drug-resistant TB should be addressed urgently before embarking on any programme designed for its control. The framework

TABLE 1.1 Causes of inadequate antituberculosis treatment (1)

HEALTH-CARE PROVIDERS: INADEQUATE REGIMENS	DRUGS: INADEQUATE SUPPLY/QUALITY	PATIENTS: INADEQUATE DRUG INTAKE
Inappropriate guidelines	Poor quality	Poor adherence (or poor DOT)
Noncompliance with guidelines	Unavailability of certain drugs (stock-outs or delivery disruptions)	Lack of information
Absence of guidelines	Poor storage conditions	Lack of money (no treatment available free of charge)
Poor training	Wrong dose or combination	Lack of transportation
No monitoring of treatment		Adverse effects
Poorly organized or funded TB control programmes		Social barriers
		Malabsorption
		Substance dependency disorders

approach described in these guidelines can help to identify and curtail possible sources of drug-resistant TB.

The factors that may be contributing to the development of new drug-resistant cases should be reviewed (see Table 1.1 for a list of possible factors) (1). Well-administered first-line treatment for susceptible cases is the best way to prevent acquisition of resistance. Timely identification of drug-resistant TB and adequate treatment regimens (Category IV regimens) administered early in the course of the disease are essential to stop primary transmission. Integration of DOTS with treatment of drug-resistant TB works synergistically to eliminate all the potential sources of TB transmission.

### 1.6 Magnitude of the MDR-TB problem

The incidence of drug resistance has increased since the first drug treatment for TB was introduced in 1943. The emergence of MDR-TB followed the widespread use of rifampicin since the 1970s.

The WHO Stop TB Department estimates the number of incident cases (including new and re-treatment cases) occurring worldwide in 2003 alone to be 458 000 (95% confidence limits, 321 000–689 000) (2). Prevalent cases worldwide could be two or three times higher than the number of incident cases (3).

The objectives of the WHO/IUATLD Global Project on Antituberculosis Drug Resistance Surveillance are to gather data on drug resistance using a standard methodology and to determine the global magnitude of resistance to four first-line antituberculosis drugs: isoniazid, rifampicin, ethambutol and streptomycin (4). The standard methodology includes representative sampling of patients with adequate sample sizes, standardized data collection distinguishing between new and previously treated patients and quality-assured laboratory DST supported by a network of supranational TB reference laboratories. By 2003, three rounds of the global project had been completed

covering 109 countries or regions within large countries (5). Despite these surveillance data, the magnitude of drug resistance is not yet known in many areas of the world with high burdens of TB, such as most of China, India, Indonesia, Nigeria and countries of the former Soviet Union. Nevertheless, evidence from half the world's nations confirms that drug resistance is a serious problem worldwide.

The third global report on antituberculosis drug resistance surveillance has documented that many areas of the world face endemic and epidemic MDR-TB, and in some areas resistance is alarmingly high. In patients never previously treated, the median prevalence of resistance to any of the first-line drugs, most commonly streptomycin and/or isoniazid, was 10.7% (range 0–57.1%); 20 survey sites exceeded 20%. The median prevalence of MDR-TB was 1.2% (range 0–14.2%); 11 sites exceeded the 6.5% threshold for extreme values, including 7 in the former Soviet Union. In patients previously treated, the median prevalence of any resistance was 23.3% (range 0–82.1%) and of MDR-TB, 7.7% (range 0–58.3%).

Drug resistance was strongly associated with previous treatment. In previously treated patients, the probability of any resistance was over 4-fold higher, and of MDR-TB over 10-fold higher, than for untreated patients. The overall prevalence of drug resistance was often related to the number of previously treated cases in the country. Among countries with a high burden of TB, previously treated cases ranged from 4.4% to 26.9% of all patients registered in DOTS programmes. In the two largest high-TB burden countries (China and India), re-treatment cases accounted for more than 20% of sputum smear-positive cases (6).

Many identified MDR-TB cases have resistance to drugs other than both isoniazid and rifampicin. In fact, one third of MDR-TB cases had resistance to all four of the first-line drugs tested in the global survey.

Moreover, MDR-TB patients often live for several years before succumbing to the disease (7). Prevalence of MDR-TB may therefore be three times greater than its incidence (3), suggesting that the true number of MDR-TB cases in the world today may approach or exceed one million.

### **1.7 Management of drug-resistant tuberculosis, the Green Light Committee and the global response to MDR-TB**

The WHO Working Group on DOTS-Plus for MDR-TB was established in 1999 to lead the global effort to control MDR-TB. This working group, part of the Stop TB Partnership, formed the GLC in 2000 to provide technical assistance to DOTS programmes, promote rational use of second-line drugs worldwide and improve access to concessionally-priced quality-assured second-line drugs.

The GLC has developed a mechanism to assist countries in adapting the

framework described in these guidelines to country-specific contexts. Countries that meet the framework requirements, with a strong DOTS foundation and a solid plan to manage drug-resistant TB, can benefit from quality-assured second-line drugs at reduced prices. The GLC also offers technical assistance before implementation of programmes for control of drug-resistant TB (DR-TB control programmes) and monitors approved projects.

A well-functioning DOTS programme is a prerequisite for GLC endorsement and for continuation of GLC support. Experience has shown that implementing a DR-TB control programme substantially strengthens overall TB control for both drug-susceptible and drug-resistant cases (8).

For control of drug-resistant TB worldwide, WHO and its partners recommend integrating management of the disease into essential services for TB control and expanding treatment for drug-resistant TB as rapidly as human, financial and technical resources will allow.

Patients who meet WHO diagnostic Category IV criteria (see Chapter 4) are treated with regimens designed to treat MDR-TB. These regimens are referred to as “Category IV regimens” throughout the guidelines.

## References

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