

# INTRODUCTION

## ANTI-TUBERCULOSIS DRUG RESISTANCE IN THE WORLD

# CHAPTER 1

### 1.1 THE THREAT OF ANTI-TUBERCULOSIS DRUG RESISTANCE

In 1994 the World Health Organization (WHO), the International Union Against Tuberculosis and Lung Disease (IUATLD), and several partners launched the Global Project on Anti-tuberculosis Drug Resistance Surveillance (DRS) (herein referred to as the “Global Project”). Results of the first phase (1994–1997) of this project were released in 1997.<sup>1,2</sup> Although drug-resistant tuberculosis (TB) had been recognized immediately after the introduction of effective chemotherapy in 1947,<sup>3–7</sup> the Global Project was the first attempt to collect accurate, standardized and representative data worldwide. Data from 35 geographical settings\* confirmed that drug-resistant TB was ubiquitous. The Global Project also confirmed the existence of multidrug-resistant tuberculosis (MDR-TB), defined as resistance to, at least, isoniazid (INH) and rifampicin (RMP), in all countries surveyed (except Kenya). Some of these geographical settings had a prevalence of MDR-TB in new cases exceeding 3%.<sup>1,2</sup> While the existence of MDR-TB was known, previous reports, including those of several outbreaks in TB patients infected with the human immunodeficiency virus (HIV) in the United States<sup>8–15</sup> and in Europe,<sup>16–18</sup> were not representative of the wider population of TB patients.<sup>19</sup> Of all patterns of drug resistance, MDR-TB is the one that focused international attention because of the reduced response to standard short-course chemotherapy (SCC) with first-line drugs, leading to higher mortality and treatment failure rates and increased periods of transmissibility.<sup>20–22</sup>

The detection of geographical settings with a high prevalence of MDR-TB prompted WHO to establish an initiative known as “DOTS-PLUS”, to study the feasibility and cost-effectiveness of treatment regimens with second-line drugs for the management of this variant of TB in countries with limited resources.<sup>23,24</sup> This initiative was conceived to protect the efficacy of DOTS (directly observed treatment, short-course), the WHO strategy for the control of TB which, if implemented correctly, has been shown to be effective in curing up to 85% of all TB cases under programme conditions.<sup>25–27</sup> Pilot projects are currently underway to gather data to design evidence-based policy guidelines for the management of MDR-TB.

Despite the success of the first phase of the Global Project in bringing together accurate and representative data on the magnitude of anti-tuberculosis drug resistance in 35 geographical settings, several questions remained unanswered. Thus, continuation and expansion of the Global Project were considered a priority for WHO, IUATLD and their numerous partners.

### 1.2 THE NEED TO EXPAND THE GLOBAL PROJECT

The overall goal of the Global Project is to improve the performance of National Tuberculosis Programmes (NTP) through policy recommendations. The specific objectives

\* Geographical settings refer to countries, territories or geographic sub-units within countries such as states, provinces, oblasts, or regions

are: (i) to collect data on the extent of anti-tuberculosis drug resistance in a standardized manner by country, particularly in those countries identified as priorities for assistance; (ii) to help countries develop a system of surveillance of drug resistance; (iii) to improve the diagnostic capacity of laboratories; and (iv) to revise policy on anti-tuberculosis treatment based on the analysis of the results.

The main goal of the first phase of the Global Project was to obtain an overview of the prevalence of anti-tuberculosis drug resistance using standard, internationally-accepted, methods. This goal was successfully achieved in 35 geographical settings in five continents around the world.<sup>1,2</sup> However, it was clear that the coverage of the Global Project needed to be expanded, since several of the most populous countries, e.g., People's Republic of China (China), India, and the Russian Federation, where the burden of TB is very high, were only surveyed in one or two administrative units. Thus, the magnitude of the problem was not fully ascertained. Furthermore, not all regions of the world were surveyed during the first phase of the Global Project; in particular, no country from WHO's Eastern Mediterranean Region participated.

In addition, only one data point on anti-tuberculosis drug resistance from each geographical setting was available in the first phase of the Global Project. Thus, the assessment of trends was not possible. Since the current recommendation of the Guidelines for Surveillance of Drug Resistance in Tuberculosis is to do continuous surveillance or repeat the surveys every three to five years,<sup>28,29</sup> many of the geographical settings participating in the first phase required more time to assess trends.

Other important questions related to anti-tuberculosis drug resistance also needed to be answered. The report released in 1997 included only aggregated data from each setting;<sup>1</sup> no inference could be drawn regarding potential determinants of anti-tuberculosis drug resistance based on individual patient data. Likewise, the effect of migration on the levels of anti-tuberculosis drug resistance had also been suggested for assessment.<sup>30,31</sup>

In view of the above, the second phase (1996–1999) of the Global Project focused on the following topics:

- expansion to other geographical settings in order to obtain a more detailed understanding of the magnitude of anti-tuberculosis drug resistance in the world;
- assessment of trends of drug resistance;
- assessment of the impact of migration on the prevalence of anti-tuberculosis drug resistance;
- thorough analysis of determinants of drug resistance based on individual patient data;
- correlation of drug resistance with indicators of TB control.

The findings are summarized in this second report of the Global Project.

### 1.3 MECHANISMS OF AND FACTORS ASSOCIATED WITH ANTI-TUBERCULOSIS DRUG RESISTANCE\*

Resistance of *Mycobacterium tuberculosis* (*M. tuberculosis*) to anti-tuberculosis drugs is a man-made amplification of a natural phenomenon. Wild strains of *M. tuberculosis* that have never been exposed to anti-tuberculosis drugs are almost never resistant, though natural resistance to specific drugs has been documented for *M. bovis* (pyrazinamide [PZA]). However, for the purpose of drug resistance surveillance, the interest focuses on the random process of genetic mutations that leads to the emergence of clinical resistance to anti-

\* (To aid the reader, this section is reproduced in part from the first global report published in 1997, Publication No. WHO/TB/97.229)

tuberculosis treatment.

During bacterial multiplication, resistance develops through spontaneous mutation and with a frequency that has been defined. Mutations resulting in resistance of *M. tuberculosis* to RMP occur at a rate of  $10^{-10}$  per cell division and lead to an estimated resistance prevalence of 1 in  $10^8$  bacilli in drug-free environments; the rate for INH is approximately  $10^{-7}$  to  $10^{-9}$ , resulting in resistance in 1 in  $10^6$  bacilli.<sup>32</sup> Bacillary populations greater than  $10^7$  are common in lung cavities in infected patients.<sup>5</sup> Thus, resistant organisms (or mutants) evolve in the absence of antimicrobial exposure, but they are diluted within the majority of drug-susceptible mycobacteria. The presence of antimicrobials provides the selective pressure which favours a resistant cell which then multiplies to become predominant, especially in patients with a large load of bacilli, e.g., those with extensive cavitation disease.<sup>33,34</sup>

Exposure to a single drug—due to irregular drug supply, poor drug quality, inappropriate prescription and/or poor adherence to treatment—suppresses the growth of bacilli susceptible to that drug but permits the multiplication of drug-resistant organisms.<sup>34</sup> This phenomenon is called *acquired resistance*. Subsequent transmission of such bacilli to other persons may lead to disease which is drug-resistant from the outset, a phenomenon known as *primary resistance* (Figure 1). Every drug active against *M. tuberculosis* is bound to select for resistance.<sup>5</sup>

Multiple drug resistance due to spontaneously occurring mutations is virtually impossible, since there is no single gene involved in such a process, and mutations resulting in resistance to the various different classes of drugs are genetically unlinked. For example, the likelihood of spontaneous mutations resulting in resistance to both INH and RMP is the product of the individual probabilities, i.e., 1 in  $10^{14}$  ( $10^6 \times 10^8$ ).<sup>35</sup> This is in fact one of the essential reasons for the use of multidrug regimens in the treatment of tuberculosis.<sup>36,37</sup>

The emergence of drug-resistant *M. tuberculosis* in a population has been associated with a variety of management, health provider and patient-related factors.<sup>38</sup> In many countries, management factors may include the lack of availability of a standardized therapeutic regimen, or poor implementation compounded by frequent or prolonged shortages of drug supply in areas with inadequate resources or political instability. Use of anti-tuberculosis drugs of unproven quality is an additional concern, as is the sale of these medications over the counter and in the black market.

The emergence of drug resistance may involve departures by providers from the correct management of individual cases. Difficulties occur in selecting the appropriate chemotherapeutic regimen, sometimes due to lack of recognition of prior treatment, and ignorance of the importance of standardized regimens.<sup>39,40</sup> In addition, providers may not monitor patients appropriately while on therapy. Patients' non-adherence to prescribed treatment also contributes to the development of drug resistance.<sup>41-44</sup> Non-adherence is difficult to predict from demographic or social characteristics but is less likely to occur if directly observed therapy (DOT) is in use.<sup>45</sup>

Finally, a crucial element in the emergence of drug resistance is the lack of a properly organised system to ensure prompt diagnosis and effective treatment.<sup>46</sup> For this reason, the level of anti-tuberculosis drug resistance in a population is an indicator of the effectiveness of a NTP.

**Fig. 1. The development and spread of drug- and multidrug-resistant tuberculosis**

