

# DISCUSSION

ANTI-TUBERCULOSIS DRUG RESISTANCE IN THE WORLD

## CHAPTER

# 4

### 4.1 MAGNITUDE OF DRUG-RESISTANT TUBERCULOSIS

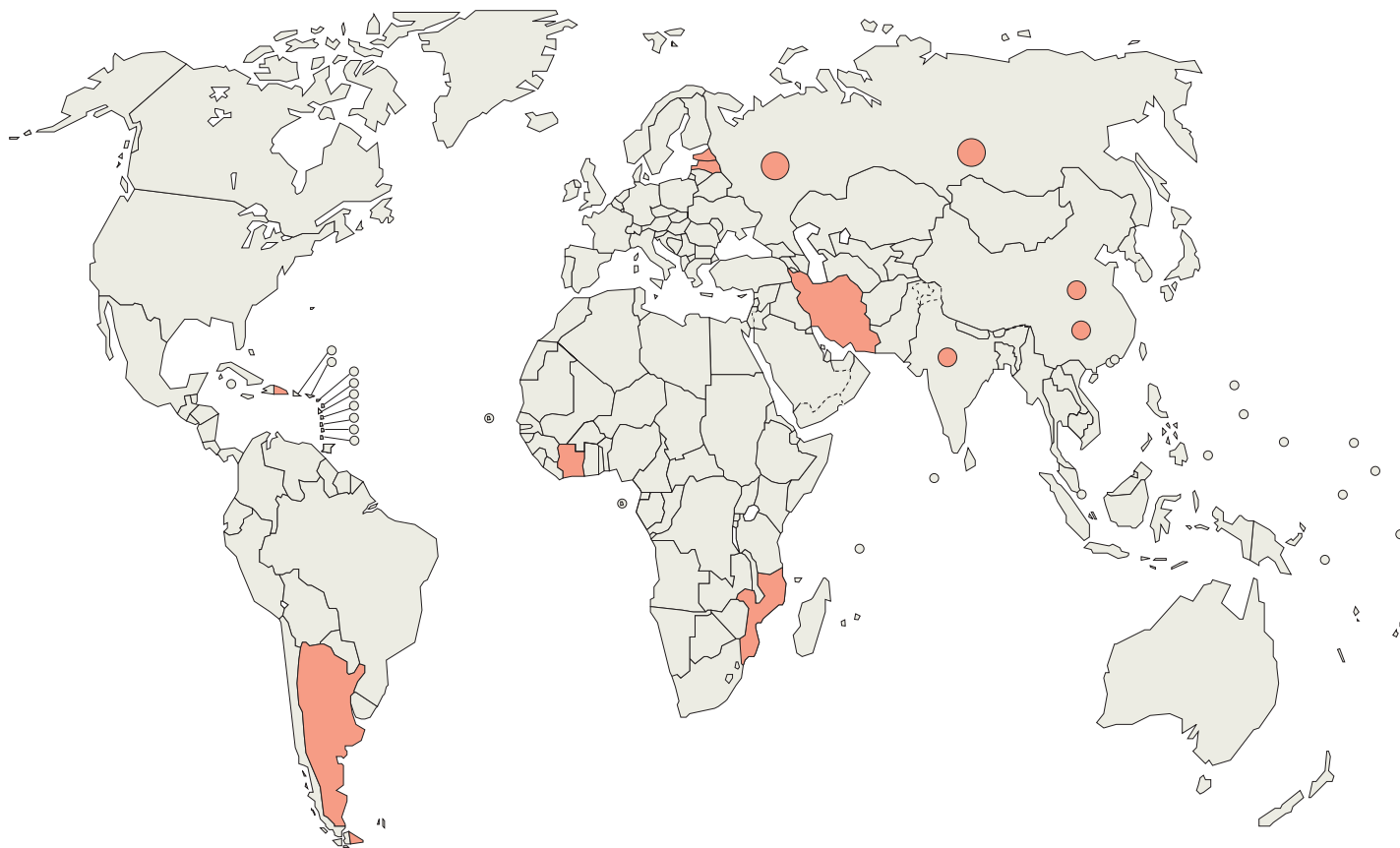
The Global Project has evolved and several countries now consider surveillance for drug-resistant TB an essential tool to assess performance of their NTP. The number of countries participating has increased, and the SRL network has achieved remarkable results in proficiency testing. Much has been learned since the beginning of the project in 1994. The data generated in this phase reinforced the findings of the first phase that drug-resistant TB varies widely across regions and countries.<sup>1,2</sup> Its presence in every geographical setting participating in the Global Project underlines the need for the expansion and strengthening of TB control efforts worldwide. Elimination of drug-resistant TB will not be possible unless TB is eradicated. Thus, containing and decreasing resistance at the lowest possible prevalence levels through the implementation of sound TB control should be the goal of every country.

The data presented in this report also show that MDR-TB is a problem in certain areas of the world. The median prevalence of MDR-TB among new TB cases tested in this phase was 1%. The coverage of geographical settings almost doubled that of the first phase of the Global Project without major variations in this figure.<sup>1</sup> MDR-TB was again found highly prevalent in some countries of Eastern Europe, mainly those of the former Soviet Union (Estonia, Latvia, Ivanovo and Tomsk Oblasts in the Russian Federation), but also in other areas outside of this region (Henan Province in China and the Islamic Republic of Iran). Furthermore, relatively high prevalences of any RMP resistance, the most powerful anti-tuberculosis drug and a key determinant of MDR-TB, were reported among new cases in Henan and Zhejiang Provinces (China), Estonia, the Islamic Republic of Iran, Latvia, Mozambique, Ivanovo and Tomsk Oblasts (Russian Federation), Thailand and Tamil Nadu State (India). These findings suggest that MDR-TB may become a more significant problem in these settings in the near future. Furthermore, the findings of relatively low prevalence of MDR-TB in some of the settings that participated in this phase of the Global Project does not mean that these countries may not face a more important problem in the future. This will depend very much on how TB arises in a given setting (i.e. primary disease in people newly infected, endogenous reactivation, or exogenous re-infection). In geographical settings where endogenous reactivation disease is a major contributor, rapid changes should not be expected. On the contrary, where primary disease and exogenous re-infection are main contributors to morbidity, changes may be seen rapidly.

In geographical settings where MDR-TB is relatively high (see following box and Map 8), the implementation of proper TB control as well as measures directed to decrease the level of circulating MDR strains should be considered.<sup>23,24</sup> Pilot projects testing feasibility and cost-effectiveness of managing MDR-TB cases in national programmes are beginning

The designations employed and the presentation of material on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines represent approximate border lines for which there may not yet be full agreement.

**Map 8. Prevalence of MDR-TB greater than 3% among new cases in geographical settings surveyed between 1994-1999**



### Geographical settings with a prevalence of MDR-TB greater than 3% among new cases, 1996–1999

• Estonia	14.1%
• Henan Province (China)	10.8%
• Latvia	9.0%
• Ivanovo Oblast (Russian Federation)	9.0%
• Tomsk Oblast (Russian Federation)	6.5%
• Islamic Republic of Iran	5.0%
• Zhejiang Province (China)	4.4%
• Mozambique	3.5%
• Tamil Nadu State (India)	3.4%

in several of these locations, as part of WHO's "DOTS-PLUS for MDR-TB" initiative.<sup>23–24, 67</sup> However, no strategy to manage MDR-TB will achieve success if patients with drug-susceptible TB, who are the majority, are not properly treated within well-organized TB control programmes. Thus, countries that are not able to guarantee proper case-management of drug-susceptible TB with inexpensive, highly successful, treatment regimens with first-line drugs,<sup>25, 68–78</sup> should not undertake specific management of MDR-TB cases using second-line drugs until a sound TB control strategy is implemented.

There were also reassuring news in this phase of the Global Project. The prevalence of MDR-TB among new cases in geographical settings that have implemented sound TB control does not appear to be increasing. However some of these findings were based on limited data, usually only two data points.

- Data from 28 countries/geographical settings showed that MDR-TB in new cases is significantly increasing only in Estonia
- Countries with sound TB control have been able to prevent increases in the prevalence of MDR-TB
- The availability of only two data points in most geographical settings limits the ability to assess the future impact of drug resistance on TB control efforts

The analysis among previously treated cases was also affected by the availability of only two data points. While several geographical settings showed decreasing prevalences of MDR-TB among previously treated cases, such decreases could be related to differences in sample size across surveys. Sample size for surveys of drug resistance is normally calculated only for new cases, because the proportion of previously treated cases is usually a small fraction of the total cases registered for treatment in the geographical setting. The current recommendation is to sample 100% of previously treated cases until the sample size for new cases is completed or for a fixed period of one year.<sup>28,29</sup> This could be the case of settings with very different samples of previously treated cases across surveys, e.g. Republic of Korea, Sierra Leone. It is also important to acknowledge that good TB control in a given setting should result in a reduction of previously treated cases over time due to high cure rates of new cases.<sup>79</sup> Such a reduction could reflect a paradox on the magnitude of MDR-TB because the decline is usually at the expense of non-MDR-TB previously treated cases. Thus, the remaining pool of previously treated cases contains proportionately more patients with MDR-TB. Although the prevalence of MDR-TB among previously treated cases may appear high, the absolute number is really very low (e.g. Cuba, Czech Republic, Puerto Rico, Uruguay).

#### 4.1.1 Magnitude of the problem by continents

All WHO regions were represented in this new phase of the Global Project. Thus the magnitude of the problem is defined to a greater extent than in the previous phase.<sup>1</sup> For instance, in the Americas more than 90% of the target population has been covered, and the data indicate that the burden of MDR-TB is of limited importance throughout the region. New countries surveyed, including Canada, Chile, Colombia, Mexico, Nicaragua, Uruguay and Venezuela, showed low prevalence (below 3%) of MDR-TB in new TB cases, suggesting that MDR-TB is not a major public health problem in these countries. Furthermore, data on trends from six countries showed no significant increase in any of the locations surveyed. While in Peru 3% of new cases studied had MDR-TB, this prevalence was not significantly different from the prevalence reported in the survey carried out in 1995–1996. Peru also reported a statistically significant reduction in the level of any drug resistance (all types), any INH resistance, and any RMP resistance among previously treated cases. This is probably linked to a reduction of the total number of previously treated cases over the years due to proper case-management of new cases. However, since the numbers of previously treated cases sampled in the two surveys are very different, sampling bias cannot be ruled out. Cuba and Chile, countries with a long history of good TB control, were also relatively free of MDR-TB.<sup>80,81</sup> Long-term trends (over 15 years) from Chile suggest that MDR-TB among new and previously treated cases is not, and will probably never become, a public health problem, provided the performance of NTP remains at the present level.<sup>82</sup> A significant decrease of MDR-TB in the United States is the result of several factors. These include the introduction of sound TB control, specially direct observation of treatment, infection control measures, and most likely the controlled use of second-line drugs.<sup>83</sup> Countries in the American Region with high prevalence of MDR-TB, as reported previously by the Global Project, were Argentina and the Dominican Republic.<sup>84,85</sup> A new survey is underway in Argentina; however, data are not yet available. The Dominican Republic has initiated laboratory quality control activities in order to repeat the survey done in 1994.

In Africa, drug-resistant TB appears to be minimal at this time. New geographical settings surveyed did not show major problems. With the exception of Mozambique, where MDR-TB needs to be closely monitored, six other locations surveyed (Bangui in the Central African Republic, Botswana, Guinea, Sierra Leone, Mpumalanga Province in South Africa, and Uganda) are not yet seriously affected by this problem at the moment. Mozambique is a country that has been recently affected by war and political turmoil. New data will be needed in order to properly assess trends in this country. New surveys from Sierra Leone and Botswana showed no differences as compared with the first surveys. Nevertheless, several high TB incidence countries in Africa have not been surveyed including Ethiopia, the Democratic Republic of Congo, and Nigeria. Thus, generalization to the whole continent cannot be made yet.

Despite the increase of HIV-related TB,<sup>86–88</sup> most African countries have not seen an upsurge of MDR-TB. This could be the result of different factors, including that RMP has only recently been introduced into these countries, the use of rifampicin-free treatment regimens in the continuation phase of therapy, and the growing presence of DOT. In Benin, for instance, RMP was introduced in 1983 and twelve years later there was no MDR-TB.<sup>89</sup> This is also the case for Botswana and Kenya. In contrast, the Côte d'Ivoire introduced rifampicin in 1985 and MDR-TB was found to be a problem in 1995. Importantly, DOT is not widely practised in Côte d'Ivoire as compared with Benin, Kenya, and Botswana.<sup>89–91</sup> While low prevalences of MDR-TB have been found in many African countries, surveillance of drug resistance must continue to be a priority in order to follow trends and take immediate actions. This is especially the case in countries where HIV prevalence is high and where the situation could change rapidly if HIV-associated MDR-TB outbreaks occur as they have in many developed countries.<sup>8–18</sup> In addition, the improvement and expansion of control activities should be promoted while limiting the availability of over-the-counter drugs. This is another measure to be considered to keep MDR-TB at very low prevalence levels.

The situation of drug-resistant TB in the Eastern Mediterranean Region appears to be heterogeneous. The survey in the Islamic Republic of Iran demonstrated high prevalences of MDR-TB and any RMP resistance. Several factors may explain this situation. First, as of 1997 the WHO/DOTS strategy in the Islamic Republic of Iran covered only 28% of the population.<sup>60</sup> Thus, the great majority of people did not have access to adequate TB control. Also, a substantial percentage of the MDR-TB cases detected in the survey were immigrants from neighbouring countries. When analysis was limited to the indigenous patients, the prevalence of MDR-TB decreased from 5% to 3.6%. However, MDR-TB was still relatively high among indigenous Iranians. It is necessary that control efforts in the Islamic Republic of Iran be expanded urgently to the rest of the country in order to prevent continued increases of MDR-TB. The data show that drug resistance is not a problem in Oman, nor is it in Casablanca, Morocco. It should be noted that both countries have good TB control, 100% DOTS coverage and close to 90% treatment success rate. In Morocco, the low prevalence detected in the largest metropolitan area where MDR-TB was suspected to be frequent suggests that Morocco may not have a MDR-TB problem. A country-wide survey is necessary to confirm these findings.

The situation of drug resistance in Europe is considered separately for Western Europe and Eastern Europe, since the countries in these sub-regions are dissimilar in terms of development. In Western Europe, MDR-TB is not a public health problem. While

Denmark and Germany showed increasing prevalences of any drug resistance among new cases, these are likely due to an increase in imported SM resistance. Data available from Denmark since 1991 confirm that resistance to RMP have remained very low.<sup>92</sup> The data presented in this report also showed no increases in any RMP and MDR-TB in Denmark in the period 1995–1998. The significance of an increase in imported SM resistance is clinically limited, as SM is not normally used now in Denmark.<sup>93</sup> In Germany, the increase of any drug resistance is difficult to evaluate, since only two data points were available. The data suggest, however, that the problem is likely to be associated with increases in SM and INH resistance. The availability of future data will clarify the magnitude of the problem. Regardless of increases in the prevalence of any drug resistance in Denmark and Germany, it is clear that MDR-TB is not a problem in these countries and in the rest of Western Europe. Of the 13 geographical settings that provided data for new TB cases, 11 had levels of 1% or less of MDR-TB. Countries that provided more than two data points did not report increase in the prevalence of MDR-TB among new and previously treated cases, nor in the combined prevalence of MDR-TB.

#### Drug-resistant TB in Western Europe

- The increase in the prevalence of any drug resistance (all types) in Denmark and Germany is due to an increase in SM resistance in the former, and probably also to an increase in SM and INH resistance in the latter
- MDR-TB in Western Europe is not a public health problem; of the 13 geographical settings that provided data for new TB cases, 11 had a prevalence of 1% or less of MDR-TB
- Continuous monitoring of drug-resistant TB in Western Europe is necessary in order to detect rising patterns

In Eastern Europe, drug-resistant TB continues to be a major problem especially in countries of the former Soviet Union. Estonia, Latvia, and two oblasts in the Russian Federation showed a high prevalence of any drug resistance, MDR-TB, any RMP resistance, and any INH resistance. Serious consideration must be given to rapid intervention. Analysis of trends did not show significant differences for some of these settings. However, the relatively high prevalences of MDR-TB and other patterns of resistance found, in the most recent year for which surveillance data were available, suggest a chronic public health problem that, if not contained rapidly, may be out of control in the coming years. In Estonia, data on trends suggest an epidemic. Estonia has not yet implemented efficient TB control country-wide and the use of second-line drugs is not yet well organized. This is likely to induce resistance to these drugs as well. Tomsk Oblast and Ivanovo Oblast in the Russian Federation also showed relatively high prevalence of MDR-TB and other patterns of drug resistance. The situation in Ivanovo Oblast looks unclear, as the rate of MDR-TB in new cases was high in the first year of surveillance, went down the following two years, and was up

again in the fourth year of surveillance. A similar situation was observed for previously treated cases. A proficiency-testing exercise conducted in 1998 by the SRL revealed 95% agreement for all drugs and 97% RMP specificity. Notwithstanding potential methodological problems, the prevalences in Ivanovo are of great concern and require close monitoring.<sup>94</sup> Although the DOTS strategy was implemented in Ivanovo Oblast in 1995, treatment completion rates remain unacceptably low, a problem perhaps confounded by the difficulties of providing care to an important fraction of the patient population (e.g. alcoholics, ex-prisoners, and chronic TB cases).

Data from other countries in Eastern Europe showed that drug-resistant TB, and specifically MDR-TB, are currently limited to former Soviet Union countries; therefore, the problem cannot be generalized to the whole of Eastern Europe. Data on trends from the Czech Republic confirmed that MDR-TB is not an increasing problem. Likewise, data from Poland, Slovenia, and Slovakia showed no MDR-TB. These countries have been able to implement well-organized DOTS control programmes (with the exception of Poland, the DOTS strategy covers more than 90% of the total population of Slovakia and Slovenia).<sup>60</sup> Nevertheless, surveillance of drug resistance should continue to be a priority in order to detect outbreaks. Also, surveillance should be urgently expanded to other areas of the Russian Federation, the Balkans, and the former Soviet Republics of Central Asia to have a clear view of the magnitude of the problem in these regions of the world.

#### Drug-resistant TB in Eastern Europe

- High MDR-TB prevalences in new cases continue to be reported from Estonia, Latvia and parts of the Russian Federation
- Countries with well-organized DOTS programmes (Poland, Slovenia and Slovakia) have very low (1% or less) prevalences of MDR-TB
- Surveillance for drug-resistant TB needs to be urgently expanded to the Balkans, other areas in the Russian Federation and the former Soviet Republics of Central Asia, to have a better picture of the situation in these regions

The situation of drug resistance in Asia is still unclear, although progress towards expanded surveillance has been made. The survey in Tamil Nadu State (India) showed 3.4% MDR-TB among new cases; this is a concern, although data on trends are needed to properly assess the magnitude of the problem. The scenario, however, is present for an increase of MDR-TB, since high prevalences of any INH resistance (15.4%) and any RMP resistance (4.4%) were detected. Data from a new survey carried out in selected districts of Delhi and in four Northern States could not be used in this report due to concerns about its quality. India is estimated to house the highest burden of TB in the world.<sup>95</sup> Thus, obtaining quality data on drug resistance in India is a high priority, and additional surveys are already underway.

In Thailand, MDR-TB was found to be low; however, high prevalences of any INH resistance (12.5%) and any RMP resistance (5.8%) were detected. Thus, further monitoring is

indicated. Preliminary data on trends from Nepal showed that drug-resistant TB is not increasing; this is likely to provide a further confirmation of the preventive effect of a sound TB control strategy.

China is the most populous country in the world and is estimated to house the second greatest incidence of TB worldwide.<sup>95</sup> Thus, a high prevalence of drug resistance would seriously hamper TB control efforts. Data were available from four provinces, two that implement the DOTS strategy for TB control through the IEDC project (Shandong and Guangdong), and two that do not (Henan and Zhejiang). A strikingly high prevalence of MDR-TB was found in Henan. Although in Zhejiang MDR-TB prevalence was not as high as in Henan, the findings are of concern. MDR-TB values of < 3% were observed in the two other provinces that implement the DOTS-based IEDC project. The survey conducted in Henan, the most populous province in China, has been questioned in the past. The data presented in this report were reviewed and revised (in particular, misclassified previously treated cases were properly categorized and laboratory results confirmed). The prevalence of MDR-TB among new cases decreased from 16% originally to 11%. Even though other methodological problems cannot be completely ruled out, there is an urgent need to implement sound TB control in the Henan province, before implementing any specific strategy for the management of MDR-TB. Data on treatment outcome in the cases enrolled in the Henan survey clearly suggest that TB control in this province is not currently well-organized nor effective. Only 47% of the new cases with drug-susceptible TB and 38% of those with drug-resistant TB converted to smear-negative at the end of treatment with first-line drugs.<sup>96</sup> The overall percentage of default was 37.5% (35% and 41% in drug-susceptible and drug-resistant cases respectively). From a public health point of view, any attempt to introduce second-line drugs to treat MDR-TB in a setting that is unable to guarantee acceptable cure rates in drug-susceptible TB cases may lead to disastrous consequences. Drug resistance to second-line drugs will likely emerge very rapidly, resulting in greater harm than benefit.

As shown by the data presented in this report, Guangdong and Shandong, two provinces that have been implementing sound TB control since 1992, enjoy relatively low prevalences of MDR-TB. This is reassuring, as these provinces have committed efforts to control TB within the DOTS-based IEDC project, have achieved high cure rates, and have decreased the number of cases for retreatment using proper case-management.<sup>26,97</sup> Nevertheless, more data points are needed to determine the tendency of drug resistance accurately in these and the other two provinces surveyed. While the success of Guangdong and Shandong is encouraging, the DOTS-based IEDC project covers only half of the Chinese population. Expansion to the rest of the country must be the highest priority. Surveillance of drug-resistant TB should be also expanded to the other DOTS-based IEDC provinces as well as those not covered by the project. The total magnitude of drug-resistant TB in China is not yet known. Upcoming data from Liaoning and Hubei Provinces under the umbrella of the Global Project will help to understand further this issue.

Trends from the Republic of Korea indicate that MDR-TB is not increasing. The Republic of Korea is another good example of efficient case-management of TB through a well-organized NTP that has been in place for many years.<sup>98</sup> The Republic of Korea uses also second-line drugs to treat MDR-TB.<sup>99</sup>

Expansion of DRS in Asia, mainly in large countries, should be a priority. While limited data are available from China and India, the magnitude of the problem is not yet well

known in the five countries with the greatest estimated incidence of TB worldwide: India, China, Indonesia, Bangladesh, and Pakistan.<sup>95</sup> Efforts are underway to expand/ launch DRS in these countries.

### MDR-TB in Asia

- Data from China show worrying prevalences of MDR-TB, especially in those areas where DOTS has not been implemented (Henan and Zhejiang Provinces)
- The limited amount of data from India shows a prevalence of MDR-TB that requires to be closely monitored and calls for expansion of surveillance
- Areas implementing sound TB control, including Thailand, Nepal, Republic of Korea and two provinces in China, enjoy relatively low MDR-TB prevalence
- Expansion of the DOTS strategy to cover the total population of China and India should be a high priority to prevent increases in drug-resistant TB
- Expansion of DRS in Asia, mainly in large countries, should be a priority. The magnitude of the problem is not yet well known in the five countries with the greatest estimated incidence of TB worldwide: India, China, Indonesia, Bangladesh, and Pakistan

In Oceania, New Zealand reported an increase in any drug resistance and any INH resistance in new cases. However, no increase was reported in MDR-TB and in any RMP resistance. In Australia, which provided combined drug resistance data, the increase in the combined prevalence of MDR-TB could be due to a high influx of immigrants from neighbouring high prevalence countries.<sup>100</sup>

## 4.2 IMPACT OF MIGRATION ON THE DISTRIBUTION OF DRUG-RESISTANT TUBERCULOSIS

The effect of migration on the incidence of TB in a given country is of interest, as people migrating from one country to another may carry with them disease or infection. TB is not an exception to the rule; notification rates from Western Europe and other industrialized countries have shown higher rates of TB among the foreign-born than among indigenous.<sup>101,102</sup> The ratio of foreign-born to indigenous population's rates of TB in 1992 varied from 2.4 in Slovenia to 20.6 in the Netherlands.<sup>103</sup> This situation has not changed substantially: in 1997, rates of TB among foreign-born subjects were consistently higher than in indigenous subjects in nine Western European countries (twice as high in Slovenia to 42 times higher in Denmark).<sup>104</sup> Countries screening potential immigrants for TB usually do not allow the entrance of subjects with active disease. However, the majority of immigrants develop disease within two to five years after arrival, which limits the value of screening for active disease at entry.<sup>105</sup> Furthermore, infection with *M. tuberculosis* is not considered a criterion precluding immigration. It is therefore expected that migration from high to low incidence countries influences the TB morbidity in the latter, although the extent of such effect

has been estimated as minimal.<sup>106,107</sup>

In the case of drug-resistant TB, data are also available showing higher prevalence among the foreign-born than the indigenous.<sup>108–111</sup> The data presented in this report suggest that importation of drug-resistant *M. tuberculosis* into low TB incidence countries is a substantial problem. Among the indigenous population, drug-resistant TB was significantly lower than in the foreign-born population in most of the low incidence countries studied. It appears, however, that much of the importation is limited to drug-resistant strains other than MDR strains. Indeed, no statistically significant differences were found in the level of MDR-TB by country of birth in most low-incidence countries.

A high influx of persons with drug-resistant strains other than MDR-TB into low incidence countries may not have major impact on the TB control efforts of the host country. Many of these strains are resistant to SM, which most low incidence countries do not use routinely any longer.<sup>107</sup> However, if a continuous influx of immigrants from countries with high prevalence of MDR-TB is established, TB control efforts in the host country may be affected.<sup>30,107</sup> Fortunately, the percentages of MDR-TB among indigenous and foreign-born new TB cases were similar in most low incidence countries. Similar findings have been reported in the past.<sup>112</sup>

The most likely explanation for the similar percentages of MDR-TB among indigenous and foreign-born persons is that the majority of immigrants with MDR strains were originally from countries with low prevalence of MDR-TB.<sup>102</sup> As shown by the Global Project, only few of the countries surveyed report a MDR-TB prevalence exceeding 3%. If, on the other hand, immigrants are from countries with high prevalence of MDR-TB, such levels should be reflected in the foreign-born population, unless migration took place a long time before MDR-TB became a problem in the country of origin. This is the case of Israel where a high level of MDR-TB was observed among foreign-born cases in comparison to indigenous cases (9% vs. 2.5%). Eighty-four percent of the foreign-born subjects with MDR-TB were from countries of the former Soviet Union. As shown by the Global Project, these countries have very high prevalence of MDR-TB. A similar explanation has been offered in the case of the Islamic Republic of Iran, suggesting that most foreign-born patients are from countries with political turmoil, war and lack of proper TB control, and therefore bear a possibly high MDR-TB burden.

The lack of other important data including age, time at which immigration took place, country of origin, and background of the immigrants (e.g. refugees, asylum seekers) limits the extraction of in-depth conclusions on the above issue. Furthermore, it is impossible to rule out that some of the foreign-born people with TB acquired drug resistance in the host country.

Given the current movements of people worldwide, migration from high incidence countries to low TB incidence countries will continue and, likely, increase. War, political turmoil, poverty, and industrialization are some of the factors encouraging people to move to more prosperous and/or safer environments. Even though screening of immigrants for TB has limitations, a comprehensive approach should be used, including the best available case-management tools, along with proper social and culture-sensitive support for people with TB.<sup>102,113,114</sup>

One last point to emphasize is that data on drug-resistant TB from low incidence countries should be properly stratified according to place of origin. Otherwise, the interpre-

tation of the data may be difficult. It is therefore imperative that in future the Global Project institutionalizes and encourages the provision of drug-resistant TB data according to the place of origin.

### 4.3 TUBERCULOSIS CONTROL AND DRUG RESISTANCE

The analysis of drug resistance and TB control suggested that several factors were likely to influence the course of drug resistance. Not surprisingly, any drug resistance and MDR-TB were significantly associated with the proportion of previously treated cases registered in a given setting. Previously treated cases, including chronics, are the richest source of drug-resistant bacilli in the community.<sup>79, 115</sup> They are also an important source of infection, since their infectiousness is usually longer than that of new cases.<sup>116</sup> Thus, settings with a very high pool of previously treated cases are expected to have a high number of resistant strains circulating in the community and, therefore, high prevalence of drug resistance among both previously treated and new cases. This is likely the case in countries that were part of the former Soviet Union where high prevalence of chronic cases co-exists with high prevalence of drug resistance. In contrast, settings that have been able to decrease the number of previously treated cases over the years, due to sound TB control, have also reported a parallel decrease in the prevalence of any drug resistance.<sup>79, 117</sup> This effect is not entirely observed in the prevalence of MDR-TB, since the reduction in the number of previously treated cases is predominantly at expense of the non-MDR-TB cases. However, the absolute number of MDR-TB cases is usually small and should not constitute a public health threat, assuming the TB control programmes keep achieving high cure rates in new cases.

The administration of SCC under DOT is the cornerstone of curing new cases, and thus to reduce rapidly the pool of previously treated cases. In this analysis the use of SCC and DOT was inversely associated with the prevalence of any drug resistance. Use of DOT was also inversely associated with MDR-TB. It is well known that standardization and use of mass chemotherapy increase the proportion of TB patients cured; however, this rise is not as high as when DOT is part of the package.<sup>118, 119</sup> Furthermore, if SCC is ineffectively used, an increase in the pool of infectious cases, and often drug resistance, is likely to take place.<sup>120</sup> Thus, the key factor to achieve high cure rates and to reduce the likelihood of drug resistance is compliance through direct observation. By using DOT, Benin and Botswana have been able to achieve high cure rates of new cases and maintain low prevalence of drug resistance.<sup>89, 91</sup> Evidence from New York City and Tarrant County, Texas, showed that, after the implementation of universal DOT, the rates of drug resistance declined significantly in new and previously treated cases, despite a high proportion of intravenous drug use and homelessness.<sup>83, 121</sup>

The argument that the generation of MDR-TB is associated with the time of introduction of RMP into the treatment regimens for TB,<sup>1</sup> although sequentially logical, is probably confounded by the quality and effectiveness of programmes for the management of TB. This was demonstrated in New York City where the failure to follow the basics of TB control, compounded with the use of rifampicin-containing regimens, led to lower cure rates than in resource-limited countries, followed by a significant increase in the rate of MDR-TB.<sup>122</sup> Thus, if TB control is not properly executed under adequate conditions (i.e. political will to guarantee correct operations of the programme, constant supply of drugs, diagnosis based on bacteriological examination, proper recording and reporting of cases and treatment results,

and DOT at least during the initial intensive phase), the use of RMP will be closely associated with the generation of MDR-TB.

This analysis also showed an inverse association between GNP per capita and the prevalence of drug resistance and MDR-TB. For a long time it has been suggested that, in addition to mass Bacille Calmette-Guérin (BCG) vaccination, case-finding and treatment, the improvement of the socioeconomic conditions and hygiene is one of the strongest factors influencing favourably the course of the TB epidemic in a community.<sup>123</sup> The best example of the impact of economic prosperity on the incidence of TB was observed in Europe, where the disease started to decline during the second half of the 19<sup>th</sup> century, long before the introduction of chemotherapy. In particular, the annual risk of infection declined by 4%–5% each year.<sup>124</sup> With the introduction of chemotherapy this reduction increased to 10%–14% each year. Since TB is associated with poverty,<sup>125–128</sup> improvements in the wealth of people should lead to a reduction in the incidence of active disease and, logically, in the incidence of drug resistance. This was in part the explanation for the decline of TB in the industrialized world before the advent of chemotherapy. Improvement in size and ventilation of living spaces with the increase in wealth led to a reduction of crowding and, therefore, to a reduction in the number of individuals intensively exposed to *M. tuberculosis*.

#### 4.4 EFFECT OF AGE, HIV, AND PRIOR ANTI-TUBERCULOSIS THERAPY

The analysis of individual patient data from 11 countries showed that prior treatment for TB is a strong predictor of drug resistance, in particular of MDR-TB. Drug-resistant TB and MDR-TB were significantly associated with an overall prior treatment period of  $\geq 12$  months and  $\geq 6$  months respectively, compared with a treatment period of three months or less. This association may be due to initial infection with drug-resistant strains, with prolonged therapy being the result, rather than the cause, of MDR-TB. It is also possible, however, that those who had a longer treatment history may have received non-standard regimens or interrupted treatment. It has been suggested that selection of resistant mutants takes place after several regimens have been administered, in which several cycles of killing (when drugs are taken) and re-growth (when drug-taking stops) of resistant strains occur.<sup>129,130</sup> As the cycles repeat, there is an increased selection favouring the resistant strains relative to the susceptible ones. This cyclic process creates an imbalance, causing resistance to one drug and later to other drugs, e.g. MDR. The finding—that those treated for 1–3 months had lower levels of drug resistance than those treated for longer periods without achieving cure—would support the possibility that inappropriate or interrupted treatment may have played a role in the higher overall resistance and MDR-TB rates observed in the latter cases.

The data presented in this report also suggest that HIV infection is not an independent risk factor for drug resistance, nor is it for MDR-TB. While some of the available data are contradictory, evidence from different settings suggests that HIV-infected TB patients are no more likely to develop drug resistance than HIV-negative TB patients.<sup>131–133</sup> Nevertheless, when TB patients are not adequately treated and levels of acquired resistance are elevated, co-existence of HIV could be responsible for the rapid spread of primary drug-resistant TB. This was likely the case in some areas of the United States and elsewhere, where TB, HIV, and inadequate treatment programmes were present,<sup>122,134</sup> often in settings of nosocomial transmission.<sup>135,136</sup>

Drug resistance was lower in the youngest and the oldest age groups. The lower prevalence of drug resistance and MDR-TB observed in the younger age groups may reflect recent decreases in circulating drug-resistant strains. However, to assess this hypothesis adequately, serial surveys of individual countries will be needed. Resistance to EMB and RMP in new TB cases, both of which have been more recently introduced in TB programmes, was observed among all age groups, including subjects > 65 years of age, suggesting recent infection with drug-resistant strains even in older patients.<sup>137</sup>

These data are subject to several limitations. First, it was not possible to evaluate other factors known to be associated with drug-resistant TB, such as history of imprisonment and prior hospitalization.<sup>138,139</sup> Secondly, the data from each geographical setting may have limited comparability as a result of differences in country-specific TB epidemiology. HIV testing was not included as part of the methodology for the drug resistance surveys. Thus, the HIV results presented here are not representative of each setting since they are based on the reporting of the participant subjects and/or record review. A third limitation is that possible misclassification of new and previously treated cases may have occurred. It is well known that patients may not reveal their previous TB treatment history.<sup>140-142</sup> Thus, although a history of prior treatment was obtained from both the patients themselves and their medical charts when available, an overestimation of resistance among new cases may be present. Similarly, errors in reporting episodes and duration of TB treatment may also have occurred.

In summary, this analysis showed that prior but ineffective treatment for TB is a strong predictor of drug resistance. This study also suggests that age-specific rates of drug-resistant TB may be due to a combination of reactivation of old infections and re-infection with new circulating strains. Restriction-fragment length polymorphism (RFLP) studies, comparing susceptible and resistant strains at different ages, may further elucidate this issue.

#### 4.5 LABORATORY ISSUES

The network of SRLs started in 1994 with the first round of DST proficiency testing.<sup>47</sup> The data presented in this report suggest that performance of the network has improved substantially through the years. This progress has been particularly evident for EMB and SM sensitivity, which was very low in the first rounds of proficiency testing. In 1998 sensitivity for these two drugs was higher than 95%. This indeed reflects the enhanced efforts made by the SRLs to improve their individual performance.

Despite the above improvement in global performance, a few SRLs are still performing at sub-standard levels because of a lower specificity for all the four drugs tested. Lower specificity may result in an overestimation of the prevalence of drug resistance. Sub-standard performance has negative implications, since it may cause the blaming of programmes because of artificially high levels of drug resistance. SRLs are confidentially informed of their results, and are encouraged to discuss their findings with the coordinator of the network in order to improve their performance. However, this approach has not been entirely successful. Thus, to achieve the highest level of performance, SRLs should be subject to more stringent criteria to continue assisting geographical settings for DRS. It is therefore proposed that SRLs, that show sensitivity or specificity below the lower limit of the 95% confidence intervals of the overall mean of the network in two consecutive rounds

of proficiency testing, should be excluded from the network. This criterion should also apply to laboratories within sub-networks. So far the Global Project has penalized only NRLs with sub-standard performance by not releasing their data unless they are re-tested. Indeed, in this phase of the Global Project a few NRLs were asked to send all the strains to their respective SRLs for re-testing because of poor performance.

The network of SRLs is one of the most valuable tools of the Global Project for the proper assessment of drug-resistant TB. The findings of high prevalence drug resistance in a given geographical setting serviced by a SRL are expected to lead to action to prevent and contain this problem. Thus, it is important that the SRLs' network maintains the highest level of performance.

#### 4.6 LIMITATIONS OF THE GLOBAL PROJECT (1996–1999)

The Global Project has expanded extensively and has overcome many of the limitations experienced in its first three years.<sup>1,2</sup> More information is now available on the magnitude of the problem of drug resistance. The network of SRLs has developed into successful sub-networks bringing together more than 100 laboratories worldwide. Notwithstanding these successes, there are still limitations to address. First, more information on the magnitude of drug-resistant TB is needed from countries that have the greatest incidence of disease.<sup>95</sup> Of the 22 high-burden countries (responsible for 80% of all estimated incident cases), data are available only from 11. Furthermore, in countries such as China, India, the Russian Federation, and South Africa these data are limited to a small number of states, provinces, or oblasts, and may not be representative of the general situation of drug-resistant TB. It is therefore necessary to expand surveillance efforts in these countries in order to estimate the true extent of the problem. Drug resistance surveys are underway in Indonesia, Nigeria, and Uganda. Thus, more data should be available in the near future. Other high-burden countries such as Bangladesh, Cambodia, Myanmar, Philippines and South Africa are also planning to assess the magnitude of anti-tuberculosis drug resistance.

Methodological limitations found in some of the DRS projects were due to misclassification of previously treated cases as new cases, and to selection bias. Misclassification of patients will erroneously inflate the proportion of drug resistance among new cases. This was the case of the 1996 survey in Henan where, after revising the data, the proportion of MDR-TB decreased from 16% to 11%.<sup>143</sup> Countries are, therefore, encouraged to conduct verification and thorough evaluation of medical records and charts to prevent misclassification of previously treated cases as new cases. On the other hand, bias in sample selection will also produce wrong estimates. Likewise, an in-depth review of the study carried out in Delhi and the four Northern States in India by an independent panel, revealed that sampling was biased to referral centres only. There was also misclassification of patients, and laboratory procedures were not validated. Trends from Latvia suggest that methodological problems affected the survey carried out in 1996. The prevalence of several patterns of drug resistance observed before and after the survey carried out in 1996 was much lower than those found in this survey.<sup>144</sup> Laboratory limitations were found in other projects; thus, all the strains had to be re-tested in part or in total at the SRL.

Trends were only available for two years in several of the countries that provided these data. While two data points are informative and may suggest where the trend of drug resistance is heading, these data are not the most suitable for trend assessment. At least

three data points are needed to properly evaluate tendencies. Furthermore, many of the national laboratories have changed DST methods or improved their laboratory services over time, further complicating the interpretation of trends. Over the coming years, the Global Project should be able to perform a thorough evaluation of trends in drug-resistant TB.

Finally, there were four countries that did not provide data differentiated by new and previously treated cases: Australia, Belgium, the Netherlands, and Israel. Fortunately, these countries do continuous surveillance in all TB cases. Unless continuous surveillance is done in all TB cases, the interpretation of combined data from surveys that do not differentiate between new and previously treated cases may be inappropriate. The proportion of previously treated cases among all TB cases registered for treatment in most countries is usually much lower than that of new cases. Thus, presenting only combined prevalence without knowing the contribution of new and previously treated cases to the sample may not reflect the true situation of drug resistance.

