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Anti-tuberculosis Drug Resistance in the World. Report no. 2: Prevalence and Trends

The WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance

World Health Organization

Department of Communicable Disease Surveillance and Response

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FOREWORD

ANTI-TUBERCULOSIS DRUG RESISTANCE IN THE WORLD

The present report of the global project on anti-tuberculosis drug resistance is much welcomed because it demonstrates that the joint efforts of the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) were successful. It gives the results of the survey conducted between 1996 and 1999, three years after the first survey, with the aim at collecting worldwide information on drug resistance of *Mycobacterium tuberculosis*. It was conducted in 58 different geographical settings. It is a great step forward compared with the information of the first survey collected from 35 geographical settings. A step of that size was possible only because of the excellent management of WHO and precise work,validated by numerous quality controls, of the microbiologists who participated in the survey. Without their intensive and meticulous work, the survey would not have been possible. It is therefore my duty and my pleasure to recognise their work and to congratulate them. Physicians also should be congratulated. They provided the key information on previous history of drug treatment that permits to classify the patients as new cases if they had no previous history of treatment; and as previously treated cases if they had previous history of treatment, in other words if they have failed to be cured after one or several episodes of therapy. The distinction is of crucial importance because it is well known for the last fifty years that failure to be cured is often associated with, if not caused by the selection of drug resistant mutants, high prevalence of drug resistance being the main characteristic of previously treated patients. Failing to identify those previously treated patients among all patients would result in confused information on drug resistance in a given setting. The collection of reliable clinical data is therefore essential for surveys on drug resistance. In addition, it is intimately linked with the sampling of the patients to be included in the survey. To prevent, or at least limit, the possible bias in sampling, two suggestions might be made: first, to collect prospectively and not retrospectively the clinical information; second, to enrol consecutive patients and not to enrol separately new cases and previously treated cases. Doing so would provide the proportion of previously treated patients among the tuberculosis patients, an essential indicator for the quality of the control programme in a given population. In the present report, the readers might be amazed by the decision to abandon the terms "primary" and "acquired" drug resistance. Two convincing reasons are given for such a decision. Despite the well accepted definition of primary drug resistance as resistance of a strain isolated from a patient who has never been treated with anti-tuberculosis drugs, we should recognise the extreme difficulty to ascertain the absence of previous treatment. Thus, the term "resistance among new cases of tuberculosis" has been preferred to primary resistance. This is not a revolutionary change but the choice of a more objective and less interpretative definition. More subtle is

the move from acquired resistance to "resistance among previously treated cases". Every one would agree that a patient who fails anti-tuberculosis therapy is likely to have acquired drug resistance. But how to be certain without performing drug susceptibility test on each initial isolate that the patient strain was fully susceptible at the initiation of treatment? Systematic drug susceptibility testing being neither recommended nor possible in a majority of settings, the initial susceptibility of the patient strain is usually unknown, and the resistance observed in case of treatment failure might be due to either "primary" or "acquired" resistance, or to a mixture of both. In order not to interpret the drug resistance found in a previously treated patient as resulting only from its previous treatment, the term "resistance in previously treated patients" has been chosen. Again, it is not a revolutionary choice but it leads to a more objective and less interpretative definition of drug resistance in previously treated patients. I will second both changes. I should say a few words on the real target of the survey, the worldwide prevalence of drug resistance but will limit my comments on the combined resistance to the two major anti-tuberculosis drugs, isoniazid and rifampicin, known as multidrug resistance or MDR. At first glance, the results of the second survey are satisfactory because no clear increase in the prevalence of MDR happened since the first survey: the median prevalence of MDR in strains isolated from new cases was 1.4% (range 0 to 14.4%) in the first survey and 1% (range 0 to 14.1%) in the second survey; and the median prevalence of MDR in strains isolated from previously treated cases was 13% (range 0 to 54%) in the first survey and 9.3% (range 0 to 48.2%) in the second survey. At more serious examination, the readers will notice that in a number of geographical settings, the prevalence of MDR strains is worrysome not only because it is high but also because it was high in the first survey and still high in the second survey, indicating that more preventive and curative interventions are needed in these settings. Although, on a median basis, the present prevalence of drug resistance is not alarming, several indicators are quite frightening and should be understood as telling us that the DOTS strategy should be implemented everywhere and at any cost, and the surveillance of drug resistance should not only continue but even extended.

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SUMMARY

ANTI-TUBERCULOSIS DRUG RESISTANCE IN THE WORLD

BACKGROUND

In 1997, the World Health Organization (WHO), the International Union Against Tuberculosis and Lung Disease (IUATLD) and several partners worldwide released the first report of the Global Project on Anti-tuberculosis Drug Resistance Surveillance (DRS) (herein referred to as the "Global Project"). This report presented data from 35 geographical settings* (surveyed between 1994 and 1996) using standard epidemiological and laboratory guidelines. These data covered 16% of the World's notified tuberculosis (TB) cases.

The first report of the Global Project showed that drug-resistant *Mycobacterium tuberculosis* (*M. tuberculosis*) was present in all geographical settings surveyed and that multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least isoniazid (INH) and rifampicin (RMP), was a problem in certain settings. A prevalence of greater than 3% of MDR-TB among new cases was found in six geographical settings (Argentina, Dominican Republic, Estonia, Latvia, Côte d'Ivoire, and Ivanovo Oblast in the Russian Federation.

These findings prompted WHO to establish the DOTS-PLUS research initiative aiming to assess the feasibility and cost-effectiveness of programmatic interventions to manage patients with MDR-TB in middle- and low-income countries. The data from this initiative will be used to guide the design of comprehensive policy guidelines for the management of MDR-TB in settings with limited resources.

Trends in drug resistance could not be evaluated in the first phase of the Global Project, as only one data point from the 35 geographical settings surveyed was available. Thus, the need to expand surveillance to other geographical settings and to continue the monitoring of settings already covered for the assessment of trends of drug resistance was considered high priority.

This second report of the Global Project describes the progress of this international collaborative effort. This report contains data from 72 geographical settings involved in the Global Project between 1994 and 1999. These data are distributed as follows:

i) information collected in the period 1996–1999 on the prevalence of drug resistance from 58 geographical settings;
ii) trends on drug resistance from 28 geographical settings, 20 of which were originally included in the first report;
iii) data from 17 geographical settings on the levels of drug resistance according to place of birth;
iv) individual patient data from 11 geographical settings to assess determinants of drug resistance;
vi) ecological data from all 72 geographical settings that have participated in the Global Project since 1994.

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

EVOLUTION OF THE WHO/IUATLD GLOBAL PROJECT

The methods for surveillance of drug resistance focus around three major principles: 1) surveillance must be based on a sample of TB patients representative of all cases in the geographical setting under evaluation; 2) drug resistance must be clearly distinguished according to the type of patient (i.e., never treated, previously treated) in order to allow correct interpretation of resistance data; and 3) optimal laboratory performance must be attained using a quality assurance programme including an international exchange of strains of *M. tuberculosis*.

Methods have been revised according to the recommendations of members of the WHO/IUATLD Working Group on Anti-tuberculosis Drug Resistance Surveillance created in 1994. The terms "primary" and "acquired" drug resistance are no longer used in this report. The use of these terms for surveillance purposes was recommended in the WHO/IUATLD Guidelines for Surveillance of Drug Resistance in Tuberculosis. However, increasingly there were suggestions to abandon their use because of the difficulty to determine the exact nature of drug resistance. Acquired drug resistance was defined as the acquisition of resistance to anti-tuberculosis drugs by the organisms through selective multiplication of the spontaneously emerged resistant mutant fraction of the bacterial population as a result of inadequate chemotherapy. Primary drug resistance, on the other hand, develops in patients who become infected with a resistant strain without ever having been treated with anti-tuberculosis drugs. In daily practice, however, it is extremely difficult to assess the level of primary drug resistance. For example, patients may decide not to disclose prior treatment for different reasons, thus leading to a possible overestimation of primary resistance. Also, patients who fail anti-tuberculosis therapy may do so because their disease-causing strain was initially resistant and not because they "acquired" resistance during the course of treatment. In view of these issues, in this report the terms "primary" and "acquired drug resistance" have been abandoned. Instead, the terms "resistance among new cases" and "resistance among previously treated cases" are used. The term "new cases" refers to TB patients who have never received anti-tuberculosis drugs or received them for no more than one month of treatment. The term "previously treated cases" refers to patients who have received at least one month of anti-tuberculosis therapy in the past. Previously treated cases include relapses, treatment failures, patients returning after defaulting, and chronic cases. In order to prevent misclassification of previously treated cases as new cases, double-checking of the patients' histories, combined with a thorough review of their medical records, is essential.

The Global Network of Supranational Reference Laboratories (SRLs) now comprises 23 SRLs and 4 regional sub-networks (Africa, Asia, Europe, and Oceania) that include several national reference laboratories (NRLs). A new coordinating centre of the network was appointed in 1999 at The Prince Leopold Institute of Tropical Medicine, Antwerp, Belgium. Two new SRLs have been incorporated in the Global Network since 1997, the Instituto de Salud Publica of Chile and the Massachusetts State Laboratory in the United States of America.

As the Global Project continues to grow, overall coverage cannot be estimated in a straightforward manner because of the changes in population and TB incidence. Also, several geographical settings have completed at least two surveys and others perform continuous surveillance. Whilst population and TB incidence do not change appreciably over short periods

of time, estimates of coverage should, however, be interpreted as gross ballpark figures that are subject to a certain degree of uncertainty. Coverage of the Global Project was calculated using notified TB cases and population figures for 1997. The last surveillance data point of each geographical setting was used, as was the specific population of the administrative units (states, provinces, oblasts) surveyed in large countries. As a result, the Global Project has covered geographical settings that account for approximately 33% of the world population and 28% of the reported TB cases worldwide. A total of 68 104 TB cases were examined for drug resistance in this phase (1996–1999) of the Global Project; the median number per setting was 661 [range = 41 (Northern Ireland)–12 675 (United States)].

MAIN FINDINGS

1. Magnitude of anti-tuberculosis drug resistance

New cases

Fifty-four geographical settings provided data on new TB cases. The prevalence of resistance to at least one anti-tuberculosis drug among new cases in this new phase of the Global Project ranged from 1.7% in Uruguay to 36.9% in Estonia (median = 10.7%). MDR–TB ranged from 0% in eight geographical settings to 14.1% in Estonia (median = 1%). High prevalences were observed in Henan Province (China) (10.8%), Latvia (9%), the Ivanovo (9%) and Tomsk Oblasts (6.5%) (Russian Federation), and the Islamic Republic of Iran (5%). Prevalences > 4% of any RMP resistance among new cases were found 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).

Trends from 24 settings showed a statistically significant increase ($p < 0.05$) in resistance to at least one drug in Estonia and Denmark. Germany, New Zealand and Peru also showed significantly higher proportions ($p < 0.05$) in any drug resistance in the more recent year of surveillance compared with previous years. A statistically significant increase in MDR-TB prevalence was observed only in Estonia, from 10.2% in 1994 to 14.1% in 1998 ($p = 0.02$). France (0.5% vs. 0%) and the United States (1.6% vs. 1.2%) reported significantly downward trends ($p < 0.05$) in MDR-TB prevalence. No significant differences were observed in Latvia and Ivanovo Oblast, although high prevalences (9%) were still found in the latest year of surveillance in both settings.

Previously treated cases

Forty-eight geographical settings provided data on previously treated cases. However, the total number of cases examined in individual settings varied from 2 in Finland to 994 in Poland (median = 64). Resistance to at least one drug ranged from 0% in Finland to 94% in Uruguay (median = 23.3%). The prevalence of MDR-TB among previously treated cases ranged from 0% in four geographical settings to 48.2% in the Islamic Republic of Iran (median = 9.3%). Trends from 20 settings showed that there was no statistically significant increase in the prevalence of any drug resistance. A statistically significant decrease ($p < 0.05$) in resistance to at least one drug was observed in Cuba, England & Wales, Peru

and the Republic of Korea. With regard to MDR-TB prevalence, Estonia showed a significant increase from 19.2% in 1994 to 37.8% in 1998 ($p = 0.04$), whereas significant decreases ($p < 0.005$) were observed in the Republic of Korea and Latvia.

All cases (combined)

Data on the combined prevalence of anti-tuberculosis drug resistance were available from 52 geographical settings. Prevalence of resistance to at least one drug ranged from 2.9% in New Caledonia to 40.8% in Estonia (median = 11.1%). MDR-TB ranged from 0% in Finland and New Caledonia to 18.1% in Estonia (median = 1.8%). Twelve geographical settings showed prevalences of MDR-TB exceeding 5%. Of the geographical settings that provided two or more data points, Germany (7.7% vs. 10.2%) and New Zealand (4.8% vs. 12%) reported statistically significant increases ($p < 0.001$) in any drug resistance in the most recent year for which surveillance data were available compared with the previous year. The Netherlands, on the other hand, reported a significant downward trend (14.1% vs. 11%, $p = 0.02$). A statistically significant increase in MDR-TB prevalence was observed in Ivanovo Oblast, from 7.3% in 1996 to 12.3% in 1998 ($p = 0.02$).

2. Relationship of drug resistance with TB control indicators

This analysis included data from the 72 geographical settings studied in the Global Project since the beginning in 1994. Response variables were the prevalence of any drug resistance and MDR-TB among new cases. Predictive factors included information on TB programme indicators and TB statistics. In univariate analysis with weighted logistic regression, the prevalence of any drug resistance was positively associated with the proportion of previously treated cases registered in the geographical setting ($t = 19.1$, $p < 0.05$) and inversely related to the proportion of cases under short-course chemotherapy (SCC) ($t = – 9.88$, $p < 0.05$). In multivariate analysis, the prevalence of any drug resistance was positively associated with the proportion of previously treated cases registered in the geographical setting, but inversely associated with the proportion of TB cases under short-course chemotherapy (SCC), the proportion of TB cases under directly observed therapy (DOT), and the gross national product (GNP) per capita income.

Variables strongly associated with MDR-TB in univariate analysis with weighted logistic regression were: a higher proportion of previously treated cases registered in the geographical setting ($t = 14.4$, $p < 0.05$), a lower proportion of treatment success achieved ($t = – 9.32$, $p < 0.05$), and a lower GNP per capita income ($t = – 12.7$, $p < 0.05$). In multivariate analysis, MDR-TB was also positively associated with the proportion of previously treated cases registered, but inversely associated with the proportion of TB cases under DOT, the proportion of treatment success achieved, the proportion of TB patients infected with HIV, and GNP per capita income.

3. Impact of migration on drug resistance

Seventeen geographical settings provided data on new TB cases. Significantly higher proportions ($p < 0.05$) of resistance to at least one drug were observed in the foreign-

born TB patients compared with indigenous patients in Canada, Denmark, Finland, Germany, the Islamic Republic of Iran, Netherlands, Sweden, England & Wales, and the United States. Nine geographical settings showed prevalences of MDR-TB below 1% in both indigenous and foreign-born. MDR-TB was significantly higher ($p < 0.05$) in the foreign-born compared with indigenous only in the Islamic Republic of Iran and the United States. Israel, Norway, and Puerto Rico also reported higher prevalences of MDR-TB in the foreign-born compared with indigenous, although the differences were not statistically significant.

4. Impact of age, HIV, and prior TB treatment on the magnitude of drug resistance

Individual data from new and previously treated cases from 11 geographical settings were evaluated. The lowest prevalences of any drug resistance and of MDR-TB were observed in the groups aged 0–14 and > 65 years. Patients > 65 years of age had a lower prevalence of resistance to RMP (1.0%) and ethambutol (EMB) (1.3%), compared to patients aged 35–44 years (3.9% and 2% respectively) and 15–24 years (3.1% and 1.6% respectively). Patients with any drug resistance (OR = 4.2, 95% CI: 3.7, 4.7; $p < 0.001$) and MDR-TB (OR = 10.5, 95% CI: 8.5, 12.9; $p < 0.001$) were more likely to have had prior TB treatment. Data on HIV status were available from a limited number of settings. Analysis showed that HIV seropositivity was associated only with MDR-TB. In multivariate analysis, prior treatment for TB was strongly associated with any drug resistance and MDR-TB. Having received TB drugs for a total period of time of 6–11 months (OR = 7.6, 95% CI: 2.6, 22.4; $p < 0.001$) or ≥12 months (OR = 13.7, 95% CI: 4.5, 41.6; $p < 0.001$) was positively associated with MDR-TB prevalence. The association between HIV positivity and MDR-TB did not hold when length of prior treatment was added to the model.

CONCLUSIONS

1. DRUG-RESISTANT TB varied widely across regions. MDR-TB among new cases is a severe problem in Estonia, Latvia, the Oblasts of Ivanovo and Tomsk in the Russian Federation, as well as in Henan Province, China, and the Islamic Republic of Iran. Other areas of concern were Zhejiang Province in China, Tamil Nadu State in India, and Mozambique. The finding of high prevalences of any RMP resistance among new cases in these settings suggests that MDR-TB may become a more significant problem in the future. The data also showed that MDR-TB prevalence has not significantly increased in geographical settings which are implementing sound TB control. However, some of these findings were based on limited data, usually only two data points. Therefore, these findings may not show the early emergence of new drug resistance. In areas where endogenous reactivation disease is the major contributor, rapid changes in the patterns of drug resistance should not be expected. On the other hand, where primary disease and exogenous re-infection are the major contributors to the burden of disease, changes in the patterns of drug resistance may be seen rapidly. The presence of drug-resistant TB in all geographical settings participating in the Global Project underlines the importance of expanding and strengthening TB control efforts worldwide. Containing and decreasing resistance at the lowest possible prevalence levels through

the implementation of sound TB control should be the goal of every country.

2. SEVERAL GEOGRAPHICAL SETTINGS with good TB control programmes showed significant decreases in the prevalence of any drug resistance among previously treated cases. Assuming that case finding and cure rates are maintained at their highest levels, decreasing trends should continue. Nevertheless, drug resistance prevalence among previously treated cases should be interpreted with caution. In several settings, previously treated cases were only enrolled until the enrolment of new cases was completed. This issue may largely influence the size of the sample of previously treated cases, thus affecting the precision of the estimates. Indeed, in several settings involved in the Global Project, the samples of previously treated cases varied largely from one survey to another in the same area. On the other hand, a high prevalence of MDR-TB in a setting with small number of previously treated cases may reflect good TB control, because of a reduction in the number of non MDR-TB previously treated cases. Although the prevalence of MDR-TB may appear high, the absolute number of cases is actually low.
3. INCREASING THE USE OF DOT AND SCC, and decreasing the number of previously treated cases, is likely to prevent the emergence of drug resistance and MDR-TB, as suggested by the ecological analysis. Socio-economic improvement may also influence the course of drug-resistant TB through a decline in the incidence of TB, as was seen in Europe during the second half of the 19th century and the first half of the 20th century, before the introduction of chemotherapy. The multivariate models obtained suggest that other factors not measured or measurable in this study may influence the magnitude of drug-resistant TB.
4. IMPORTATION OF DRUG-RESISTANT *M.* TUBERCULOSIS into low TB incidence countries is a 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. However, most of the imported resistant strains are not MDR. This may suggest that the majority of immigrants with MDR strains were originally from countries with low prevalence of MDR-TB. A high influx of drug-resistant strains other than MDR-TB into low incidence countries should not have major impact on the TB control efforts of the host country. Many of these strains are likely to be resistant to streptomycin (SM), which has not been used by most low-incidence countries for many years. 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.
5. THE DATA PRESENTED IN THIS REPORT confirm that prior anti-tuberculosis therapy is a strong predictor of drug resistance. Rates of drug-resistant TB in subjects > 65 years of age may be due to a combination of reactivation of old infections and exogenous re-infection with new circulating strains. Resistance to EMB and RMP (both of which have been more recently introduced in TB programmes) in new TB cases were observed among all age groups, including subjects > 65 years of age, suggesting that recent exogenous infection with drug-resistant strains may occur in older patients. The lower prevalence of drug resistance and MDR-TB observed in younger age groups may also reflect recent decreases in the circulation of drug-resistant strains. However, to adequately assess this hypothesis, further serial surveys of individual countries will be needed.

RECOMMENDATIONS

1. SURVEILLANCE OF DRUG-RESISTANT TB should continue to be a priority in order to detect areas of emerging resistance in a timely fashion. Consistent, longitudinal data on drug resistance will help to quantify the magnitude of the problem and provide information on trends. It is therefore very important that countries make sustained efforts to implement continuous surveillance for drug-resistant TB. If continuous surveillance is not possible, surveys should be carried out at least every 3–5 years.
2. THE GLOBAL PROJECT SHOULD BE URGENTLY EXPANDED to cover the 22 countries that account for 80% of the incident cases of TB worldwide. While data are available from at least some areas in 11 of these countries, coverage needs to be expanded in order to define more precisely the magnitude of drug-resistant TB.
3. IN ORDER TO PREVENT DRUG-RESISTANT TB, countries should urgently implement and/or expand TB control under adequate structured programmes (i.e., political commitment in order to guarantee correct operation of the programme, constant supply of drugs, diagnosis based on bacteriological examination, proper recording and reporting of cases and treatment results, and finally use of SCC under DOT, at least during the initial intensive phase of treatment). The use of fixed-dose combination drugs of proven quality and bioavailability should also be considered as a means to prevent drug resistance.
4. TREATMENT REGIMENS with second-line drugs should be considered in settings where MDR-TB is relatively high (i.e., > 3% among new cases). However, it is essential that this recommendation be implemented only if TB control strategies consistent with international standards are also in place. From a public health point of view, attempts to introduce second-line drugs for MDR-TB in a setting that is unable to guarantee acceptable cure rates of drug-susceptible TB cases will most likely lead to disastrous consequences. Drug resistance to second-line drugs will emerge rapidly, resulting in greater harm than benefit.
5. PARTICULARLY IN LOW TB INCIDENCE COUNTRIES, where a substantial fraction of TB cases are foreign-born, drug-resistant TB should be properly stratified according to place of origin. Otherwise, trends cannot be interpreted. It is therefore imperative that in future the Global Project institutionalizes and encourages the collection of drug-resistant TB data according to place of origin of patients.