EXECUTIVE SUMMARY THIRD GLOBAL REPORT

1. Background and methods

This is the third report of the WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance. The two previous reports were published in 1997 and 2001 and included data from 35 and 58 settings[a] respectively. The main conclusions of the two previous reports were that drug-resistant tuberculosis (TB) was present in all settings surveyed, multi-drug resistance (MDR) was identified in most settings, and that good TB control practices were associated with lower or decreasing levels of resistance. The goal of the third report is to expand knowledge of the prevalent patterns of resistance globally and explore trends in resistance over time.

This report includes new data from 77 settings or countries collected in the third phase of the project, between 1999 and 2002, representing 20% of the global total of new smear-positive TB cases. It includes 39 settings not previously included in the Global Project and reports trends for 46 settings.

Data were included if they adhered to the following principles: (1) the sample was representative of all TB cases in the setting under evaluation; (2) new patients were clearly distinguished from those with previous treatment[b]; and (3) optimal laboratory performance was assured and maintained through links with a supranational reference laboratory (SRL). Data were obtained through routine or continuous surveillance of all TB cases (38 settings) or from specific surveys of sampled patients, as outlined in approved protocols (39 settings). Data were reported on a standard reporting form, either annually or at the completion of the survey.

The Supranational Reference Laboratory Network (SRLN) was formed in 1994 to ensure optimal performance of the national reference laboratories participating in the Global Project. The network comprises 20 laboratories in five WHO regions and is coordinated by the Prince Leopold Institute of Tropical Medicine in Antwerp, Belgium. The coordinating centre ensures the quality of the SRLN by conducting annual proficiency testing, through the exchange of a panel of 30 pretested and coded strains with resistance to any of the following four first-line drugs – isoniazid (INH), streptomycin (SM), rifampicin (RMP) and ethambutol (EMB).

2. Results

2.1 MAGNITUDE AND TRENDS OF ANTI-TB DRUG RESISTANCE

New cases

Data on new cases were available for 75 settings. In total, 55 779 patients were surveyed. The prevalence of resistance to at least one antituberculosis drug (any resistance) ranged from 0% in some Western European countries to 57.1% in Kazakhstan (median = 10.2%). Median prevalences of resistance to specific drugs were as follows: SM, 6.3%; INH, 5.9%; RMP, 1.4%; and EMB, 0.8%. Prevalence of

[a] Setting is defined as a country or a subnational setting (i.e.province, district, oblast).

[b] There are three exceptions to this rule; Australia, Democratic Republic of Congo, Kinshasa, and Scotland reported only combined cases.

MDR ranged from 0% in eight countries to 14.2% in Kazakhstan (51/359) and Israel (36/253) (median = 1.1%). The highest prevalences of MDR were observed in Tomsk Oblast (Russian Federation) (13.7%), Karakalpakstan (Uzbekistan) (13.2%), Estonia (12.2%), Liaoning Province (China) (10.4%), Lithuania (9.4%), Latvia (9.3%), Henan Province (China) (7.8%), and Ecuador (6.6%)[a].

Increases in prevalence of resistance can be caused by poor or worsening TB control, immigration of patients from areas of higher resistance, outbreaks of drug-resistant disease and variations in surveillance methodologies. Trends in drug resistance in *new cases* were determined in 46 settings (20 with two data points and 26 with at least three). Significant increases in prevalence of *any resistance* were found in Botswana, New Zealand, Poland, and Tomsk Oblast, (Russian Federation). Cuba, Hong Kong SAR, and Thailand reported significant decreases over time. Tomsk Oblast, (Russian Federation), and Poland reported significantly increased prevalences of MDR. Decreasing trends in MDR were observed in Hong Kong SAR, Thailand, and the USA.

Previously treated cases

Data on previously treated cases were available for 66 settings. In total, 8405 patients were surveyed. The median prevalence of resistance to at least one drug (any resistance) was 18.4%, with the highest prevalence, 82.1%, in Kazakhstan (262/319). Median prevalences of resistance to specific drugs were as follows: INH, 14.4%; SM, 11.4%; RMP, 8.7%; and EMB, 3.5%. The median prevalence of MDR was 7.0%. The highest prevalences of MDR were reported in Oman (58.3%; 7/12) and Kazakhstan (56.4%; 180/319). Among countries of the former Soviet Union the median prevalence of resistance to the four drugs was 30%, compared with a median of 1.3% in all other settings. Given the small number of subjects tested in some settings, prevalence of resistance among previously treated cases should be interpreted with caution.

Drug resistance trends in previously treated cases were determined in 43 settings (19 with two data points and 24 with at least three data points). Significant increases in the prevalence of *any resistance* were observed in Botswana. Cuba, Switzerland, and the USA showed significant decreases. The prevalence of MDR significantly increased in Estonia, Lithuania, and Tomsk Oblast (Russian Federation). Decreasing trends were significant in Slovakia, and the USA.

Association of drug resistance with the quality of TB control

The percentage of re-treatment cases in a national TB programme is an indicator of programme performance. Multivariate analysis showed the proportion of cases being re-treated among the total number of cases was significantly associated with both MDR and any drug resistance.

[a] Data from Ecuador included in the analysis are preliminary.

2.2 THE BURDEN OF MDR-TB

We estimated the annual incidence of MDR cases in 69 settings included in this report[a]. For most Western and Central European countries, the estimated incidence was fewer than 10 cases each. Estonia, Latvia, Lithuania and two oblasts in the Russian Federation were estimated to have between 99 and 248 MDR cases. For Henan and Hubei Provinces of China, the figure was more than 1000 cases each, and for Kazakhstan and South Africa, more than 3000. In order to analyse the burden of MDR in a given setting, prevalence in new and re-treatment cases should be linked with relevant programme information, such as proportion and categories of re-treatment among all cases, as well as absolute case numbers.

Rifampicin resistance was evaluated as a predictor of MDR-TB, in order to explore the relevance of rapid rifampicin resistance testing to identify cases likely to have MDR-TB. This would allow the rapid initiation of infection control measures and effective treatment. The positive predictive value (PPV), a function of the sensitivity and specificity of RMP resistance testing and the prevalence of MDR and non-MDR rifampicin resistance, was highest among previously treated cases in settings with high MDR prevalence and low non-MDR rifampicin resistance.

2.3 PATTERNS AND AMPLIFICATION 1994–2002

Analysis of almost 90 000 strains representative of the most recent data from countries between 1994 and 2002 confirmed that, globally, more strains were resistant to INH than to any other drug (range 0–42%). In general, INH and SM resistance were more prevalent than RMP or EMB resistance. HSRE[b] was the most prevalent pattern among previously treated cases and the proportions of strains resistant to three or four drugs were significantly greater among this group than among new cases. This relationship holds globally as well as regionally and suggests amplification of resistance. It appears that INH and SM monoresistance are the main gateways to acquisition of additional resistance

3. Conclusions

3.1 SCALE OF THE EPIDEMIC OF DRUG-RESISTANT TB

1. Drug-resistant TB was found among TB patients surveyed in 74 of 77 settings between 1999 and 2002. As in the two previous surveys, drug-resistant TB, including multidrug-resistant TB, was found in all regions of the world. The prevalence of MDR-TB was exceptionally high in almost all former Soviet Union countries surveyed, including Estonia, Kazakhstan, Latvia, Lithuania, the Russian Federation, and Uzbekistan. Proportions of strains resistant to three or four drugs were also significantly higher in this region. High prevalences of MDR-TB were also found among new cases in China (Henan and Liaoning provinces), Ecuador and Israel. Central Europe and Africa, in contrast, reported the lowest median levels of drug resistance.

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[a] Estimates were generated by applying prevalences determined in surveys to reported notification figures for the corresponding population.

[b] HSRE = resistance to INH, SM, RMP, and EMB.

2. The percentage of re-treatment cases in a national TB programme is an indicator of programme performance. As in previous phases of the Global Project, a link was found between poor programme performance, or insufficient coverage of a good programme, and drug resistance. Previously treated cases, worldwide, are not only more likely to be drug-resistant, but also to have resistance to more drugs than untreated patients.

3. Significant increases in prevalence of any resistance and MDR were detected in a number of settings. Increases in MDR-TB are especially worrying, since such cases are significantly more difficult to treat, and mortality is higher than for drug-susceptible cases. Increases in prevalence of any resistance may reflect an environment that favours the acquisition of additional resistance and can lead to future increases in MDR.

4. Between 1994 and 2002, the Global Project surveyed areas representing over one-third of notified TB cases worldwide. However, enormous gaps still exist in many crucial areas, especially countries with a large TB burden or where available data strongly suggest that there may be a much larger problem, particularly China, India, and countries of the former Soviet Union.

5. The ability to conduct a drug resistance survey is indicative of a reasonable level of capacity of the TB control services, most importantly the laboratory service. Thus it is likely that TB control in some unsurveyed areas is worse than in those surveyed.

4. Recommendations

4.1 MANAGEMENT OF TB CONTROL

1. The findings of this phase of the Global Project emphasize the importance of strengthening TB control worldwide, by expanding DOTS[a] in order to prevent the emergence of further drug resistance. Existing cases need to be managed by national programmes, regardless of prevalence, through application of the DOTS-Plus strategy[a] and using the Green Light Committee[b] to ensure quality of second-line drugs and proper implementation and monitoring. Full adoption of DOTS is vital for stopping the creation of MDR-TB cases.

2. In light of the high frequency of resistance to three or four drugs in previously treated patients, the WHO Category II regimen for re-treatment should be re-evaluated in some settings and the re-treatment guidelines should be revised if necessary. A re-evaluation should also be conducted of the efficacy of both Category I and III regimens, in which INH is recommended in the continuation phase, in settings with a high prevalence of isoniazid resistance.

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[a] Internationally adopted strategy to control tuberculosis.
[b] Strategy under development for the management of multi-drug resistant tuberculosis
[c] The Green Light Committee reviews project applications for DOTS Plus pilot projects. Projects accepted by the GLC are then granted access to preferentially priced second-line drugs.

3. Standardized annual recording and reporting on all categories of re-treatment – relapse, failure and return after default – should be mandatory. Accurate reporting on this population will help in monitoring programme performance and developing re-treatment strategies, and provide the required information for survey sampling.

4. Rapid testing for rifampicin resistance may provide a useful proxy for MDR testing, but only in situations of high MDR prevalence (with little or no non-MDR rifampicin resistance). Early identification of these patients would permit rapid isolation and initiation of appropriate treatment, thus avoiding acquisition of additional resistance, until results of further drug susceptibility testing (DST) are available.

4.2 SURVEILLANCE OF DRUG RESISTANCE

1. Information on drug resistance is urgently needed from unsurveyed areas of China, India, and the former Soviet Union, in the light of the prevalence of resistance detected in those countries to date and given the high rate of DOTS expansion currently under way or planned in those countries. Information on anti-TB drug resistance is also needed from countries where no surveys have yet been conducted, particularly high-burden countries, such as Bangladesh, Indonesia, and Nigeria. Drug resistance surveillance should be seen as an essential component of TB control programmes in these settings.

2. Continuous drug resistance surveillance, culture and drug susceptibility testing of every TB patient are desirable wherever resources permit. Where this is not feasible but there is survey capacity, periodic surveys with separate sampling of new and re-treatment cases should be undertaken. The different types of re-treatment cases should be identified, namely relapse, failure and return after default. This is essential for the planning of a treatment programme for those with known or suspected drug resistance (DOTS Plus).

3. In order to enable expansion of drug resistance surveillance, national governments and international partners need to invest, in a coordinated way, in the evaluation and strengthening of national laboratories. The Laboratory Strengthening Subgroup of the DOTS Expansion Working Group is well placed to assist in this task.

4. A comprehensive approach to drug resistance surveillance is necessary to accurately evaluate the course of drug resistance, particularly in settings with high MDR prevalence. Data collection from drug resistance surveillance and DOTS Plus projects, as well as routine collection of notifications and outcomes, should be linked in order to allow interventions to be evaluated.

5. The high proportions of resistance to three and four drugs among cases that have been previously treated emphasizes the importance of developing new anti-TB drugs.

6. This report has raised some key questions regarding drug resistance that cannot be answered through routine surveillance. Operational research should be carried out to determine, amongst other things, the impact of HIV on the transmission of MDR-TB in certain settings, the impact of amplification of resistance at both the individual and population level, and the impact of private sector treatment policies on drug resistance. Financial support from the international community will be essential for such research.