FOREWORD

The release of this third report of the WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance marks the end of the first decade of activity. The three reports that have been produced are the result of unprecedented collaborative effort, and the Project itself serves as a model for surveillance, not only for tuberculosis (TB) but for many microbial diseases. Surveillance of resistance to anti-tuberculosis drugs is an essential component of a monitoring system. The benefits of surveillance are multiple: strengthening of laboratory networks, evaluation of programme performance, and the collection of data that inform appropriate therapeutic strategies. Most importantly, global surveillance identifies areas of high resistance and draws the attention of national health authorities to the need to reduce the individual or collective shortcomings that have created them.

This report makes two notable contributions to the discussion on surveillance: first, it addresses the importance of conducting surveillance on re-treatment cases, and second, it raises the issue of the role of the laboratory in TB control.

In the past, surveillance has focused on the prevalence of bacterial resistance among new patients – an extremely useful indicator for a TB programme. Prevalence of resistance among previously untreated patients reflects programme performance over a long period of time (the previous 10 years), and indicates the level of transmission within the community.

The prevalence of bacterial resistance among patients with a history of previous treatment has received less attention because surveillance of this population is a more complex process. Re-treatment patients are a heterogeneous group composed of chronic patients, those who have failed a course of treatment, those who have relapsed, and those who have returned after defaulting. In some settings, this population constitutes more than 40% of smear-positive cases. The association between drug resistance and re-treatment has been repeatedly demonstrated, both at the individual and the programme level; however, the prevalence of drug resistance varies greatly among subgroups of this population. Chronic cases and failures of a first treatment tend to be at greater risk of harbouring resistant and multidrug-resistant (MDR) bacilli. The other categories of patient (relapses and return after default) are more likely to have drug resistance than new cases, but are almost always at a lower risk for MDR than failures and chronic cases. This report therefore recommends that all subgroups of re-treatment cases be separately notified and their outcomes reported, and that surveillance of resistance be conducted on a representative sample of this population. This will make the comparison of resistance prevalence within and between countries more robust and will elucidate patterns of resistance among the subgroups, which will allow better definition of appropriate re-treatment strategies.

The second area I will touch on is that of the laboratory. It is clear that, while laboratory services are fundamental to TB control, they are often the weakest component of the system. High quality sputum smear microscopy, culture and drug susceptibility testing should be standard components of TB control everywhere, but unfortunately they are not. This lack of capacity in laboratories is already limiting the expansion of surveillance to settings that represent the most important gaps in our knowledge, and will undoubtedly adversely affect the ability of national TB programmes (NTPs) accurately to diagnose and treat MDR-TB.

It is now critical that we recognize the importance of the laboratory in the control of tuberculosis. National governments, health development agencies and partners must provide adequate financial and technical resources to radically improve diagnostic services in national TB laboratory networks.

We know from the experience of several countries, including my own, that the effective application of the internationally accepted DOTS strategy can prevent the emergence of drug resistance. Additionally, evidence is now emerging that the existing reservoir of resistant bacilli can be reduced through the supplementary application of DOTS-Plus, a strategy for the management of drug-resistant cases. Drug resistance surveillance, in conjunction with a functional laboratory network, must be expanded to help TB control programmes to identify problem areas for further support. After ten years, as this report points out, it is time to make surveillance a routine component of TB control. Only with improvement in laboratory capacity will this be possible.

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SUMMARY

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, multidrug 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 this 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 Léopold 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 isolates 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

[a] Setting is defined as a country or a subnational setting (i.e. province, district, or oblast).
[b] There are three exceptions; Australia, Democratic Republic of Congo, Kinshasa, and Scotland reported only combined cases.

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 MDR ranged from 0% in eight countries to 14.2% in Kazakhstan (51/359) and Israel (36/253)[c] (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%)[d].

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). A significant increase in the prevalence of *any resistance* was 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

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. The percentage of re-treatment cases in a national TB programme is an indicator of programme performance.

2.2 MDR-TB

We estimated the annual incidence of MDR cases in 69 settings included in this report.[e] For most Western and Central European countries, the estimated incidence

[c] Data reported from Israel in subsequent years show a considerably lower prevalence of MDR.
[d] Data from Ecuador included in the analysis are preliminary.
[e] Estimates were generated by applying prevalences determined in surveys to reported notification figures for the corresponding population and thus are dependent upon case-finding in the country and quality of recording and reporting of the national programme.

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 isolates representative of the most recent data from countries between 1994 and 2002 confirmed that, globally, more isolates 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[f] was the most prevalent pattern among previously treated cases and the proportions of isolates 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 monoresistance to either INH or SM is the main gateway 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 isolates 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.

2 The proportion of retreatment of all TB cases is an indicator of programme performance.[1,2] 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.

f HSRE = resistance to INH, SM, RMP, and EMB.

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[g] 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[h] and using the Green Light Committee[i] to ensure quality of second-line drugs and proper implementation and monitoring. Full adoption of DOTS is vital if the creation of MDR-TB cases is to be halted.

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.

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.

g Internationally adopted strategy to control tuberculosis.
h Strategy under development for the management of multi-drug resistant tuberculosis
i 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.

4 Rapid testing for rifampicin resistance may provide a useful proxy for MDR, 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. Information on anti-TB drug resistance is also needed from countries where no surveys have yet been conducted, particularly high-burden countries, such as Afghanistan, Bangladesh, Indonesia, United Republic of Tanzania, Pakistan 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 expand 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 emphasize 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, among 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.