

EXECUTIVE SUMMARY

Background and methods

This is the fourth report of the WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance. The three previous reports were published in 1997, 2000 and 2004 and included data from 35, 58 and 77 countries, respectively. This report includes drug susceptibility test (DST) results from 91,577 patients from 93 settings in 81 countries and 2 Special Administrative Regions (SARs) of China collected between 2002 and 2006, and representing over 35% of the global total of notified new smear-positive TB cases. It includes data from 33 countries that have never previously reported. New data are available from the following high TB burden countries¹: India, China, Russian Federation, Indonesia, Ethiopia, Philippines, Viet Nam, Tanzania, Thailand, and Myanmar. Between 1994 and 2007 a total of 138 settings in 114 countries and 2 SARs of China had reported data to the Global Project.

Trend data (three or more data points) are available from 48 countries. The majority of trend data are reported from low TB prevalence settings; however this report includes data from three Baltic countries and 2 Russian Oblasts. Trend data were also available from 6 countries conducting periodic or sentinel surveys (Cuba, Republic of Korea, Nepal, Peru, Thailand, and Uruguay).

For the first time, thirty six countries reported data on age and sex of cases by any resistance and multi-drug resistant TB² (MDR-TB). Seven countries reported data disaggregated by human immunodeficiency virus (HIV) status and drug resistance pattern. (Cuba, Donetsk Oblast, Ukraine, Honduras, Latvia, Spain, Tomsk Oblast of the Russian Federation, and Uruguay). Thirty four countries and two SARs of China reported data on second-line anti-TB drug resistance among patient isolates identified as MDR-TB. This report focuses on MDR-TB since these patients have significantly poorer outcomes than patients with drug susceptible TB.

¹ The 22 high TB burden countries (HBCs) account for approximately 80% of the estimated number of new TB cases (all forms) arising each year.

² Multi-drug resistant TB is defined as TB with resistance to isoniazid and rifampicin, the two most powerful first line drugs.

Data were included if they adhered to the principles of the global project which require accurate representation of the population under evaluation, and external quality assurance conducted by a Supranational Reference Laboratory (SRL). Although differentiation by treatment history is required for data interpretation, we included data from some countries where this was not possible. Data were obtained through routine or continuous surveillance of all TB cases (48 countries) or from specific surveys of sampled patients, as outlined in approved protocols (35 countries). Data were reported on a standard reporting form, either annually or at the completion of the survey. Data on resistance to second-line anti-TB drugs were included if drug susceptibility testing was conducted at a SRL or if the National Reference Laboratory (NRL) reporting was participating in a quality assurance programme for first-line anti-TB drugs. Currently there is no established system for international external quality assurance (EQA) for second-line anti-TB drugs.

The Supranational Reference Laboratory Network (SRLN) was formed in 1994 to ensure optimal performance of the laboratories participating in the Global Project. The network has expanded since 2004 and now includes 26 laboratories in six WHO regions and is coordinated by the Prince Léopold Institute of Tropical Medicine in Antwerp, Belgium. A panel of 30 pretested and coded isolates is exchanged annually within the network, and the 14th round of proficiency testing initiated in 2007 includes isolates with resistance to second-line anti-TB drugs. Results will be available later in 2008.

RESULTS

Magnitude of drug resistant TB

New cases

Data on new cases in this phase of the project were available for 72 countries and 2 SARs of China. DST results were available for 62 746 patients. The proportion of resistance to at least one antituberculosis drug (any resistance) ranged from 0% in two Western European countries to 56.3% in Baku, Azerbaijan. The proportion of MDR ranged from 0% in eight countries to 22.3% in Baku, Azerbaijan and 19.4% in the Republic of Moldova. Of the 20 settings surveyed with the highest proportion of MDR-TB among new cases in the history of the project, 14 are located in countries of the former Soviet Union and four are in China. Fifteen of the twenty settings with the highest prevalence of resistance ever recorded have been reported in the most recent phase of

the project, 2002-2007. New data from countries of the Eastern Mediterranean showed that MDR-TB among new cases was higher than previously estimated with the exception of Morocco and Lebanon which showed 0.5% and 1.1%, respectively. MDR-TB among new cases was 5.4%, and 2.9% in Jordan and Yemen, respectively. The Americas, Central Europe and Africa, reported the lowest proportions of MDR-TB; with the notable exceptions of Peru, Rwanda, and Guatemala, with 5.3%, 3.9%, and 3.0% MDR-TB among new cases respectively.

Previously treated cases

Data on previously treated cases were available for 66 countries and 2 SARs of China. In total, DST results were available for 12 977 patients. Resistance to at least one anti-tuberculosis drug (any resistance) ranged from 0% in three European countries to 85.9%, in Tashkent, Uzbekistan. The highest proportions of MDR were reported in Tashkent, Uzbekistan (60.0%), and Baku, Azerbaijan (55.8%). New data from Gujarat State, India, are the first reliable source of data on previously treated cases in India and show 17.2% MDR-TB among this group.

Unknown and combined cases

36 countries reported data on cases with unknown treatment history. In most countries this group of cases represented a small proportion of total cases; however, in nine countries, and one city in Spain, this was either the majority or the only group reported. Australia, Fiji, Guam, New Caledonia, Puerto Rico, Qatar, Solomon islands, Barcelona, Spain, and the USA.

Survey coverage and population weighted means

Based on available information from the duration of the Global Project, the most recent data available from 114 countries and 2 SARs of China was weighted by the population in areas surveyed, representing 2,509,545 TB cases, with the following results: Global population weighted proportion of resistance among new cases: any resistance 17.0% (95% CLs, 13.6-20.4), isoniazid resistance 10.3% (95% CLs, 8.4-12.1), and MDR 2.9% (95% CLs, 2.2-3.6). Global population weighted proportion of resistance among previously treated cases: any resistance 35.0% (95% CLs, 24.1-45.8), isoniazid resistance 27.7% (95% CLs, 18.7-36.7), MDR 15.3% (95% CLs, 9.6-21.1). Global population weighted proportion of resistance among all TB cases:

any resistance 20.0% (95% CLs, 16.1-23.9), isoniazid resistance 13.3% (95% CLs, 10.9-15.8), and MDR 5.3% (95% CLs, 3.9-6.6)³.

Global Estimates

Based on drug resistance information from 114 countries and 2 SARs of China reporting to this project, as well as 9 other epidemiological factors, the proportion of MDR among new, previously treated and combined cases was estimated for countries with no survey information available. The estimated proportion of MDR for all countries was then applied to estimated incident TB cases. It is estimated that 489,139 (95% CLs, 455,093-614,215) cases emerged in 2006, and the global proportion of resistance among all cases is 4.8% (95% CLs, 4.6-6.0). China, India, and the Russian Federation are estimated to carry the highest number of MDR cases. China and India carry approximately 50% of the global burden and the Russian Federation a further 7%.

Trends

Trends were evaluated in 47 countries with 3 or more data points. In low TB prevalence countries conducting continuous surveillance, trends were determined in the group of total cases reported. In countries conducting surveys, or where population of previously treated cases tested changed over time⁴, trends were determined in new cases only.

Notably in the US and Hong Kong significant reduction of the burden of MDR in the population continues. In both countries both TB notifications and MDR are declining, but MDR is declining at a faster rate. In most central and western European countries where TB, particularly drug resistant forms of TB, are imported, absolute numbers as well as proportions of MDR among all cases are relatively stable. Both Peru and the Republic of Korea are showing increases in MDR among new cases. Both countries showed steady declines in TB notification rates followed by recent leveling off. In countries of the former Soviet Union there are two scenarios. Two Baltic countries (Estonia, and Latvia) are showing a stable and flat trend in proportions of MDR among new cases, Lithuania shows a gradual and significant increase but at a slow rate.

³ Population figures are based on data reported in 2005.

All three countries are showing a decreasing TB notification rate (5 to 8% reduction per year). This is held in contrast to two Oblasts in the Russian Federation (Orel, and Tomsk) which are showing an increase in the proportion of MDR among new cases, as well as increases in absolute numbers. Notification rates are declining in both regions but at a slower rate than in the Baltic countries.

Extensively drug resistant TB (XDR-TB)⁵

Thirty five countries and two special administrative regions were able to report data on XDR-TB either through routine surveillance data or through drug resistance surveys. Quality assurance for laboratory testing was variable across countries reporting⁶. Twenty five countries reported routine surveillance data while ten countries reported from periodic surveys. Some countries reported data aggregated over a three year period, and other countries reported over a one year period. The numbers of MDR cases tested for the appropriate second-line anti-TB drugs are used as a denominator. In total, data were reported on 4 012 MDR-TB cases, and among those 301 or 7.0% XDR-TB cases were detected. Twenty five countries that reported were European; however three countries from the Americas and seven settings of the Western Pacific region also reported data. Survey data was available from two African countries, Rwanda and preliminary data from UR Tanzania, where no XDR-TB was found. No data were reported from the Eastern Mediterranean region or from the South East Asian region, although surveys including second-line anti-TB drug susceptibility testing are ongoing in both regions.

In general, absolute numbers of XDR-TB cases were low in Central and Western Europe, the Americas and in the Asian countries that reported data. The proportion of XDR-TB among MDR-TB in these settings varied from 0% in 11 countries to 30.0% in Japan. These countries have a relatively low MDR-TB burden, so this represents few absolute cases. A more significant problem lies in the countries of the former Soviet Union. Of the 9 countries that reported, approximately 10% of all MDR-TB cases were XDR ranging from 4.0% in Armenia to almost

⁴ Proportion of resistance among new cases is considered a more robust indicator of recent transmission. Additional information regarding the previous history of treatment is required to determine trends of resistance in this population.

⁵ Extensively drug resistant TB (XDR-TB) is defined as TB with resistance to at least isoniazid and rifampicin and resistance to a fluoroquinolone, and a second line injectable agent.

⁶ Previous data reported data from South Africa following a different methodology are included in the maps and discussions but not in the analysis.

24.0% in Estonia; however these proportions represent a much larger absolute number of cases. Recently released data from South Africa showed that of 996 or 5.6% of 17 615 MDR isolates collected from 2004 through October of 2007 were XDR-TB. Proportions varied across provinces with KwaZulu-Natal reporting 656 or 14% of 4701 MDR cases as XDR-TB. Selection and testing practices varied across the country and over time; however all isolates correspond to individual cases⁷. Since 2002 a total of 45 countries have reported at least one case globally. Several other countries are in the process of completing DST.

HIV and MDR

Of the seven countries that reported data on drug resistance stratified by HIV status, only Latvia and Donetsk Oblast, Ukraine reported large enough numbers to examine the relationship between the two epidemics. Any resistance and MDR were significantly associated with HIV in both Latvia and in Donetsk Oblast; however, HIV negative and HIV unknown were not distinguished in Latvia. From the data reported in Latvia the proportion of MDR among HIV positive cases was shown to be stable over time.

MDR-TB treatment programmes

By the end of 2007, 67 projects in 51 countries had been provided with second-line anti-TB drugs through the Green Light Committee for a cumulative total of over 30 000 MDR-TB patients. 23,256 cases of MDR-TB were notified in 2006 (8.7% of these cases were reported from GLC projects) representing less than 5% of the global number of MDR-TB cases estimated to have emerged in 2006. The average treatment success rate within GLC projects was 62%⁸ with Latvia reporting the best treatment success rate (69%). Globally, both the number of MDR-TB patients treated as well as the projected numbers for MDR-TB cases to be treated in 2007 and 2008, as reported by National TB Programmes (NTPs)[1], are far below targets set out by the Global XDR-TB Response Plan[2]

⁷ Data from a retrospective review of the National Health Laboratory Service of South Africa were presented at the IUATLD World Conference on Lung Health. 8-12 November 2007. Cape Town, South Africa.

⁸ Mirzayev F, Treatment outcomes from 9 projects approved by the Green Light Committee between 2000 and 2003. 38th World Conference on Lung Health. 8-12 November 2007. Cape Town, South Africa.

CONCLUSIONS

Magnitude of drug resistant TB

The population weighted mean of MDR-TB among all TB cases from the 114 countries and 2 SARs of China that have reported to the global project is 5.3% (95% CLs, 3.9-6.6), but ranges from 0% in some western European countries to over 35% in some countries of the former Soviet Union. In terms of proportion, the countries of the former Soviet Union are facing a serious and widespread epidemic where the population weighted average of countries reporting indicates that almost half of all TB cases are resistant to at least one drug and every fifth case of TB will have MDR-TB. MDR-TB cases in this region have more extensive resistance patterns including some of the highest proportions of XDR-TB.

Following countries of the former Soviet Union, provinces in China reported the highest proportions of resistance, while Western Europe, followed by countries in Africa, reported the lowest proportions of MDR-TB. It is important to note at least one country in all six WHO regions has reported >3.0% MDR-TB among new cases.

Based on the most recent survey data from 114 countries and 2 SARs of China as well as 9 other epidemiological factors we estimated the burden of incident MDR-TB for a further 69 countries to develop a global estimate and to better establish the incident global burden of MDR-TB cases. We estimate that 489,139 (95% CLs, 455,093-614,215) MDR-TB cases emerged in 2006, and the global proportion of resistance among all TB cases is 4.6% (95% CLs, 4.6-6.0). China and India are estimated to carry 50% of the global burden of cases, and the Russian Federation is estimated to carry a further 7%.

Data from surveys in ten of 31 provinces in China over a ten year period indicate that drug resistance is widespread and in terms of proportion ranked second to countries of the former Soviet Union, but China has the highest burden of cases in the world. It is estimated that 130,548 (97,633-164,900) MDR-TB cases emerged in 2006 or over 25% of the global burden. The high proportion of drug-resistant TB among new cases in China suggests a concerning level of transmission of drug-resistant strains. It is estimated that over 1 in 10 cases of MDR TB that

emerged in 2006 globally occurred in patients in China without a history of prior anti-TB treatment. Now that China has reached the global targets for case detection and treatment success the rapid implementation of services for the diagnosis and treatment of MDR-TB is necessary to ensure success of the TB control programme and control transmission of drug-resistant strains. Careful monitoring of the trends of resistance in China should remain a priority.

Data from nine sites in India show that drug resistance among new cases is relatively low; however, new data from Gujarat indicate that 17.2% MDR among retreatment cases is higher than previously anticipated and it is estimated that 110,132 (79,975-142,386) MDR-TB cases emerged in India in 2006, representing over 20% of the global burden. Although plans have been developed for management of 5000 MDR-TB cases annually by 2010, insufficient laboratory capacity is seen as the primary limitation in implementation of these plans.

Trends

The available trend data show a range of scenarios. The majority of low TB burden countries reporting surveillance data showed stable proportions of resistance as well as absolute numbers of cases. Trends in resistance in Hong Kong represent the best case scenario where MDR-TB is falling faster than TB. Countries such as Peru and the Republic of Korea showed increasing proportions in MDR-TB. Although both countries have shown a decline in overall TB notifications, the decline has slowed in recent years. In Peru this may reflect weakening in basic TB control including management of MDR-TB. The Republic of Korea has recently integrated the private sector into a national surveillance network which may explain the recent leveling of the TB notification rate. The reason for the increase in proportion of MDR-TB among new cases is not yet clear.

The most important findings of this report however, are the trend data reported from the Baltic countries and the Russian Federation where the MDR-TB epidemic is widespread. The Baltic countries are showing a decline in TB notification rates with the proportion of MDR-TB held relatively stable. The Baltic countries likely represent the best scenario for this region. The surveyed oblasts of the Russian Federation show a different picture where TB notifications are falling but at a much slower rate, and where the proportion as well as absolute numbers of MDR-TB are significantly increasing, especially among new cases. The declining notifications in these

oblasts of the Russian Federation suggest that TB control is improving and susceptible TB cases are being successfully treated, but it is likely that a large pool of chronic cases continues to fuel the epidemic, reflected in the growing proportion of MDR-TB cases. The two oblasts that reported are some of the best performing regions in the country. Commitment to TB control seen in recent years, including new legislation updating the TB strategy, and the nationwide implementation of TB control activities, including management of MDR-TB cases and the upgrade of diagnostic services financed by the Global Fund and the World Bank, indicates positive momentum, but efforts will have to be accelerated to impact what appears to be a growing epidemic of drug resistant TB.

XDR-TB

XDR-TB is more expensive and difficult to treat than MDR-TB and outcomes for patients are much worse⁹, therefore understanding the magnitude and distribution of XDR-TB is important. Despite limitations in the quality assurance applied to laboratory testing, data from this report indicate that XDR-TB is widespread with 45 countries having reported at least one case. The high proportion of XDR-TB among MDR-TB as well as the large overall burden suggests a significant problem within the countries of the former Soviet Union. Japan, and the Republic of Korea in a previous study, have also shown a high proportion of XDR-TB among MDR. South Africa reported a moderate proportion of XDR-TB among MDR-TB cases; however, the underlying burden of MDR-TB is considerable and 44% of TB patients are estimated to be co infected with HIV. Few representative data from Africa are available with the exception of Rwanda and preliminary data from Tanzania, which showed no XDR-TB and very little second line resistance among MDR-TB cases suggesting that second-line anti-TB drugs have not been widely used in these two countries; however, risk populations should continue to be monitored. XDR-TB is likely to emerge where second-line anti-TB drugs are widely and inappropriately used; however transmission is not limited to these settings. Data were largely reported from high income countries or with the assistance of a Supranational Laboratory, indicating that countries require strengthened capacity to monitor second line resistance if we are to develop an accurate understanding of the global magnitude and distribution.

⁹ Personal communication Vaira Leimane, National TB Programme, Latvia.

MDR and HIV

Despite the expansion of HIV testing and treatment globally, only seven countries were able to report drug resistance data disaggregated by HIV status. The two countries with the most robust data both showed a significant association between HIV and MDR-TB. Both of these countries are situated in the former Soviet Union where diagnostic networks for both TB and HIV are relatively well developed. This population level association is a great concern for countries without accessible diagnostic networks in place, indicating that HIV infected patients will not receive appropriate therapy quickly enough to avert mortality. It is important to note other supporting evidence suggests that the association between HIV and MDR-TB may be more closely related to environmental factors such as transmission in congregate settings rather than biological factors[3]. Though this requires further investigation, it indicates that improving infection control in congregate settings including health care facilities and prisons may be one of the most critical components in addressing dual infection. The development of laboratory networks to provide rapid diagnosis of resistance using molecular methods, particularly for HIV infected patients, is of utmost importance.

Coverage and Methods

Survey coverage continues to expand with data from several additional high burden countries and the reliability of surveillance data continues to improve; however, major gaps exist in populations covered and epidemiological questions answered. Laboratory capacity remains the largest obstacle, but other survey components also strain the capacity of most National TB programmes (NTPs), resulting most importantly in the inability to determine trends in most high burden countries. HIV testing continues to scale up, but has proven difficult to incorporate where testing is not already a component of routine care. Second line testing is not available in most countries. Newly available policy guidance will assist in the development of this capacity in countries. However, SRLs will continue to play a very important role in providing this service in the meantime. As part of the Global Plan to Stop TB all countries are committed to scaling up

diagnostic networks, but until culture and drug susceptibility testing are the standard of diagnosis everywhere surveys will continue to be important to monitor resistance. Currently molecular methods are being piloted in order to expand coverage and increase trends, but new survey methods, such as continuous sentinel surveillance, must also be considered. Special studies must supplement surveys in order to answer the questions about risk factors for acquisition and transmission dynamics of drug resistance that routine surveillance can not.

TB Control and drug resistant TB [4]

Preventing the development of drug resistant TB should continue to be the top priority for all countries; however, managing the MDR-TB cases that emerge is part of the Stop TB strategy and should be a component of all TB programmes, however, for countries facing high proportions of drug resistance, high burden countries carrying the largest absolute burden of MDR-TB, and countries with a population heavily co infected with HIV, developing rapid detection and management of drug resistant cases is of great urgency. Although by 2006, basic TB control has expanded to 184 countries globally, the targets for number of MDR-TB cases detected and treated have not been reached, and the latest information reported indicates that at the current pace few countries will reach the targets outlined in the Global Plan to Stop TB.

If targets are to be achieved coordinated global efforts will be required to roll out the full package of TB services as outlined by the Stop TB Strategy to prevent the further emergence of MDR-TB. The enhancement of infection control measures to prevent transmission, the expansion of high quality diagnostic services for timely detection of cases, and community involvement to improve adherence are three priority areas that need more attention, but perhaps most importantly, the development of treatment programmes into which patients can be enrolled and treated successfully is the most fundamental.

In the two countries with the highest TB burden, China and India, 8% and 5% of TB cases are estimated to have MDR-TB and will likely not respond to treatment they currently receive. In countries of Eastern Europe 1 in 5 cases will have MDR-TB, signaling that new drugs are urgently needed. The current pipeline is inadequate to respond to the pressing need.