

ANTI - TUBERCULOSIS DRUG RESISTANCE

IN THE WORLD

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GLOBAL PROJECT
ON ANTI-TUBERCULOSIS
DRUG RESISTANCE SURVEILLANCE



WORLD HEALTH ORGANIZATION

ANTI-TUBERCULOSIS DRUG RESISTANCE IN THE WORLD

Fourth Global Report

The WHO/IUATLD Global Project on Anti-tuberculosis

Drug Resistance Surveillance

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The primary aim of this report is to share survey and surveillance data on drug resistance in TB. The data presented here are supplied largely by the programme managers who have led the work on surveys, but also heads of reference laboratories as well as principle investigators that may have been hired to assist the NTP with the study. We thank all of them, and their staff, for their contributions. The WHO/IUATLD Global Project is carried out with the financial backing of USAID and Eli Lilly and Company as part of the Lilly MDR-TB Partnership. Drug resistance surveys were supported financially by the The Dutch government, The Global Fund, Japan International Cooperation Agency (JICA), Kreditanstalt für Wiederaufbau (KfW Entwicklungsbank), National TB Programmes, United States Agency for International Development (USAID). The Supranational Reference Laboratory Network provided the external quality assurance as well as technical support to many of the countries reporting. Technical support for surveys was provided by CDC, JICA, KNCV, and WHO. Data for the European Region were collected and validated jointly with EuroTB (Paris), a European TB surveillance network funded by the European Commission.

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.

Chapter 1. INTRODUCTION

The fourth report of the WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance provides the latest data on the magnitude of drug resistance in 81 countries and 2 SARs of China collected between 2002 and 2007, as well as the most up to date trends from 47 countries collected over a thirteen year period.

The Global Project was initiated in 1994 in order to estimate the global burden of drug resistant TB worldwide using standardized methodologies so that data could be compared across and within regions. The Project was also begun to monitor trends in resistance, evaluate the performance of TB control programmes and to advise on drug regimens. The report is published every three years as most countries require between 12 and 18 months to complete a drug resistance survey.

Until 2000, very few NTPs globally were managing drug resistant TB cases in the public sector, and with the exception of high income countries and countries of the former Soviet Union diagnosis of drug resistance in TB was largely unavailable. Following the roll out and successful implementation of "DOTS-Plus" pilot projects for the management of drug resistant TB between 2000 and 2005, a new Stop TB Strategy was launched in 2006. The New Stop TB Strategy includes the diagnosis and the management of drug resistant TB. The launch of the Stop TB Strategy was followed by the Global Plan to Stop TB, 2006-2015 that provided targets for scale up and budgets required for the implementation of the strategy. Now, through the Global Fund and with the help of the Green Light Committee, most countries are initiating or scaling up the diagnosis and management of drug resistant TB. Until diagnosis of drug resistance is routine, surveys or surveillance systems will play an important role in determining the magnitude and trends in drug resistant TB.

In terms of the initial goals of the Global Project, considerable progress has been made in expanding coverage and estimating the global burden of MDR-TB as well as strengthening laboratories, but the Project has not met several of its initial goals suggesting that it may be time

to review some of the project methods. There are still major geographic gaps for which there is no information on the burden of drug resistant TB. Trend data from high burden countries are few. Adjustment of regimens is limited not by available data, but by the availability of new drugs. treatment. In addition, there is need for the monitoring of resistance to some of the key second-line anti-TB drugs and a better understanding of epidemiological relationship between drug resistance and HIV. Interim drug resistance surveillance guidelines were published in 2007, and a meeting planned in 2008 to review current methods in drug resistance surveillance will provide key input for a revision of these technical guidelines.

This report is based on the analysis of a quarter of a million isolates collected since 1994, in 114 countries and 2 SARs of China, representing one half of all notified TB cases. The report addresses the following areas:

The most recent profile of anti-tuberculosis drug resistance, looking at the latest data available for the period 2002-2007; Dynamics of anti-tuberculosis drug resistance over time, or trends; HIV and drug resistance; XDR-TB; The global means and distribution of resistance across and within regions, looking at the most recent data for each country or geographical setting surveyed since 1994; Estimates of the burden of MDR-TB by country and region; Results of proficiency testing of laboratories over time.

Chapter 2. METHODS

The Global Project methodology for surveillance of drug resistance was developed by a WHO/IUATLD working group in 1994, which published guidelines for surveillance of resistance in tuberculosis, in 1994, that were updated in 1997 and 2003[5]. Further interim guidelines have been published in 2007[6]. The methodology operates on three main principles: (1) the survey 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 treatment history of the patient (i.e. never treated or previously treated) in order to allow correct interpretation of the data; and (3) optimal laboratory performance of each participating laboratory must be attained through engaging in a quality assurance programme, including the international exchange of isolates of *M. tuberculosis*.

Definitions of drug resistance

DRUG RESISTANCE AMONG NEW CASES

Resistance among new cases is defined as the presence of resistant isolates of *M. tuberculosis* in patients who, in response to direct questioning, deny having had any prior anti-TB treatment (for as much as 1 month) and, in countries where adequate documentation is available, for whom there is no evidence of such a history. Drug resistance among new cases is used to evaluate recent transmission.

DRUG RESISTANCE AMONG PREVIOUSLY TREATED CASES

Resistance among previously treated cases is defined as the presence of resistant isolates of *M. tuberculosis* in patients who, in response to direct questioning, admit having been treated for tuberculosis for 1 month or more or, in countries where adequate documentation is available, in a patient for whom there is evidence of such a history. In previous reports resistance among previously treated patients was used as a proxy for acquired resistance; however, evidence shows that this patient category is comprised of patients who have acquired resistance, have been primarily infected with a resistant strain, subsequently and subsequently failed therapy, as well as patients who have been re-infected. Therefore resistance among previously treated cases is not a useful proxy for truly acquired resistance[7, 8].

COMBINED PROPORTION OF DRUG RESISTANCE

Combined proportion of drug resistance is the proportion of resistance in the population surveyed regardless of prior treatment. Despite the importance of the distinction between drug resistance among new and previously treated 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 the only group reported or represented the majority of all cases (Australia, Fiji, Guam, New Caledonia, Puerto Rico, Qatar, Solomon islands, Barcelona, Spain, and the USA).

Given the risk of misclassification due to reporting bias by patients or health staff, the combined proportion of anti-TB drug resistance represents a better approximation to the level of drug resistance in the community than the separate data for new and previously treated patients. Combined figures represent data collected on new and previously treated cases as well as all cases with an unknown treatment history.

EXTENSIVELY DRUG RESISTANT TB (XDR-TB)

XDR-TB is defined as TB with resistance to at least isoniazid and rifampicin as well further resistance to a fluoroquinolone and a second line injectable agent (amikacin, kanamycin, or capreomycin).

Survey areas and sampling strategies

New surveillance or survey projects presented in this report were carried out between 2002 and 2007, with the exception of two surveys in India carried out in the districts of Hoogli, West Bengal State, and Mayhurbhanj in Orissa State in 2001, and nationwide survey in Paraguay in 2001. Since 1999, the United Kingdom submits data to EuroTB in two ways – for England, Wales and Northern Ireland together, either with or without Scotland. In this report Scotland is included in data reported from the United Kingdom. Cuba, France, Italy, and Japan operate sentinel networks for surveillance. All, with the exception of Italy, can be considered nationally representative.

Trend data from Germany and from the United Kingdom are evaluated from 2001 because surveillance methods changed in that year. Final data from UR Tanzania and Madagascar were

not available at the time of analysis for this report, and results should be considered preliminary. Data from Senegal was still undergoing quality control of results.

Terminology

For the purposes of this report it is important to distinguish between surveys and surveillance. Surveillance, in this report, refers to either continuous or sentinel surveillance. Continuous surveillance is based on routine TB diagnosis including drug susceptibility testing provided to all TB cases in the coverage area, and thus reflects the entire TB population – smear-positive, smear-negative, extrapulmonary – regardless of treatment status. Sentinel surveillance of drug resistance, in the context of this report, comprises reporting of DST results from all TB cases from a (random or non-random) sample of sites. Sentinel surveillance reports annual data from the same sites with the exception of Japan which conducts sentinel surveys every three years.

Surveys are periodic, and reflect the population of registered pulmonary smear-positive cases. Depending on the area surveyed, a cluster sampling technique may be adopted, or all diagnostic units included. While some countries, such as Botswana, repeat surveys every 3–5 years, for the purposes of this report they are considered as repeated surveys and not surveillance.

Survey areas

In both survey and surveillance settings, the coverage area is usually the entire country, but in some cases sub national units are surveyed. Large countries, such as China, India, the Russian Federation, Brazil, Indonesia, and South Africa, tend to survey large administrative units (e.g. province, state, district, or oblast). Some countries have opted to limit surveys or surveillance to metropolitan areas, as in the case of Azerbaijan, Uzbekistan, and China. Several countries (e.g. Cuba, France, Italy, and Japan) conduct sentinel surveillance and some other countries have restricted surveys to sub national areas because of the remoteness of certain provinces or to avoid conflict areas. Data for Denmark do not include Greenland and the Faroe Islands.

Calculation of sample size

Calculation of sample size for surveys follows the principles outlined in the WHO/IUATLD Guidelines for the surveillance of resistance in tuberculosis[5]. Briefly, sample sizes are calculated on the basis of the number of new sputum smear-positive cases registered in the

previous year and the expected proportion of rifampicin (RMP) resistance in new TB cases based on previous studies or data available from the NTP. Separate sample sizes should be calculated for new cases and previously treated cases. However, the number of sputum-positive previously treated cases reported per year is usually small and, the intake period needed to achieve a statistically adequate sample size is long. Therefore, most countries have obtained an estimate of the drug resistance level among previously treated cases by including all previously treated cases who present at centres during the intake period. While this may not provide a statistically adequate sample size, it can nevertheless give a reasonable estimate of drug resistance among previously treated cases. Surveys in Gujarat, India, Baku, Azerbaijan, Armenia, and Georgia were designed with separate sample sizes for retreatment cases. In efforts to scale up diagnosis and treatment of MDR-TB many countries plan to expand routine culture and DST to all retreatment cases. Once fully implemented these data will provide routine estimates of drug resistance in these populations.

Sampling methods

Sampling strategies for monitoring of drug resistance include:

- countrywide, continuous surveillance of the population;
- surveys with sampling of all diagnostic centres during a specified period;
- surveys with randomly selected clusters of patients;
- surveys with cluster sampling proportional to the number of cases notified by the diagnostic centre.

Survey protocols

The quality of survey protocols has improved over the last ten years. The majority of protocols reviewed in this phase of the project were very complete and included detailed budgets, timelines, and plans for quality assurance at several levels. Most of the protocols reviewed were submitted through a local Ethics Review Board or the Ethics review board of a technical partner supporting the project.

Collection of data

Patient eligibility and registration

For surveys, all newly registered patients with smear-positive TB were eligible for inclusion, including children, and foreign-born persons. In surveillance settings, all TB patients were included. As in previous phases of the Global Project, HIV testing was not a mandatory component of these surveys; however, it has increasingly been incorporated in survey settings. Geographical settings that performed HIV testing as part of the survey were advised to follow international guidelines on counselling and confidentiality. This report includes data from 93 settings in 81 countries and 2 SARs of China. Survey data were reported from 35 countries or geographical settings and surveillance data from 48 countries or geographical settings.

Resistance to second-line anti-TB drugs

Thirty five countries and two special administrative regions reported data on second-line anti-TB drug resistance among confirmed MDR-TB isolates identified in routine surveillance or in surveys. A further five countries reported data on cohorts of known MDR-TB patients. Data from laboratory registers from South Africa are reported but not included in any analyses.

HIV

Eight settings in seven countries reported data on drug resistance stratified by HIV status: Cuba, Honduras, Latvia, the Russian Federation (Tomsk Oblast), Spain (Barcelona and Galicia), Ukraine (Donetsk Oblast) and Uruguay. Data were reported stratified by positive and unknown HIV status from Latvia and Galicia, Spain, and disaggregated by positive, negative and unknown HIV status from the remaining settings. Four countries were not able to discriminate between negative and unknown HIV status.

Age and Sex

Data on drug resistance stratified by sex and age groups was reported by 43 settings in 36 countries from all the six WHO Regions. Among these settings seven were able to report information for more than one year.

Accuracy of information on prior TB treatment

It was recommended that re-interview and double-checking of patient histories be undertaken in survey settings to reduce the possibility of misclassification of previously treated cases. The majority of countries cross-checked patient history collected in the survey with medical records, but fewer countries re-interviewed a percentage of patients.

Data management in individual countries

Since 1998, EuroTB, a project funded by the European Commission and based in Paris, France, has undertaken continuous collection and verification of drug resistance surveillance data in Western Europe and much of Central Europe. Since 2001, WHO and EuroTB have used a common collection form. All the data for Western Europe and much of that for Central Europe included in the present report were provided by EuroTB and conform to WHO/IUATLD Global Project standards. Other countries conducting surveillance have provided data either directly to WHO Headquarters or via WHO regional offices. All new data reported have been returned to countries for verification before publication. In this phase of the Global Project, a fourth version of WHO software, surveillance of drug resistance in tuberculosis (SDRTB 4.0), was used by many countries conducting surveys for data entry, management, and analysis of survey data.¹⁰ However, most countries conducting continuous surveillance of drug resistance in all TB cases use their own software. The Global Project requests that survey protocols include a description of methods used for the quality assurance of data collection, entry, and analysis.

Bacteriological methods

In survey settings, sputum smear microscopy using the Ziehl-Neelsen technique was used for diagnosis of TB and subsequent enrolment in the survey. In surveillance settings, a combination of smear and culture was used for initial diagnosis. The majority of laboratories used Löwenstein-Jensen (L-J) culture medium on which the specimen was inoculated after decontamination with sodium hydroxide (2-4%) or 1% cetyl-pyridium chloride (CPC). Some laboratories inoculated sodium hydroxide decontaminated specimen directly onto Ogawa medium without centrifugation. Labs in high income countries generally used liquid medium or

¹⁰ Brenner E. *Surveillance of drug resistance in tuberculosis software: SDRTB3*. Geneva, World Health Organization Geneva. 2000.

agar based medium. Identification of isolates was based on the niacin production test, the nitrate reduction test the para-nitrobenzoic (PNB) acid (500 mg/l) test[9], and the thiophene-2-carboxylic acid hydrazide (TCH) (2mg/l) resistance test[10]. Some countries also used molecular hybridization probes. Mycobacteria other than *M. tuberculosis* complex were excluded from the analysis.

Drug susceptibility tests were performed using the simplified variant of the indirect proportion method on L-J medium, the absolute concentration method, the resistance ratio method,[11, 12] or the radiometric Bactec 460 or MGIT 960 method.¹¹ The proportion method was most frequently used in all phases of the Global Project. Resistance was expressed as the percentage of colonies that grew on recommended critical concentrations of the drugs tested (i.e. 0.2 mg/l for isoniazid (INH), 2 mg/l for ethambutol (EMB), 4 mg/l for dihydrostreptomycin sulfate (STR) and 40 mg/l for rifampicin (RMP) when L-J medium is used). The criterion used for drug resistance was growth of 1% or more of the bacterial population on media containing the critical concentration of each drug. The results of the tests were recorded on standardized forms.

Proficiency testing and re-testing of a proportion of survey strains are two components of external¹² quality assurance of laboratories. Briefly, proficiency testing requires the exchange of a panel of 20 (or more) pretested isolates between the SRL and the NRL. Results of this round determine, in part, whether the performance of the laboratory is sufficiently high to conduct DST for the survey or whether additional training is necessary. For re testing of survey strains, the laboratory conducting the survey sends a percentage of both resistant and susceptible isolates to the SRL for checking. The percentage of isolates sent for checking is determined before the beginning of the survey. Adequate performance is defined as no more than one false-positive or false-negative result for rifampicin or isoniazid and no more than two for streptomycin or ethambutol. To date, the results of NRL proficiency testing have been evaluated by the corresponding SRL and interventions have been based on the judgement of the SRL. In several instances testing has been repeated to ensure acceptable performance and, in exceptional

¹¹ Siddiqi SH. *BACTEC 460TB system. Product and procedure manual, 1996.* Becton Dickinson and Company, 1996.

¹² In most cases, external quality control is international, as often the SRL is located outside of the country.

instances, surveys have been interrupted and data excluded because of significant discordance between the NRL and the SRL.

Susceptibility testing for second-line anti-TB drugs was performed using a range of methods and concentrations. Until 2007 there was limited international consensus on susceptibility testing for second-line anti-TB drugs. At the time of this report WHO had published policy recommendations for second line DST [13] and full technical guidelines are under development. External quality assurance for second-line anti-TB drugs was also not available during the time period of data collection. Starting in 2007 isolates with resistance to second-line anti-TB drugs have been included in the panels exchanged within the network of SRLs and extended to a few selected NRLs. Data on second line drug resistance were included if the country was participating in annual external quality assurance for first-line anti-TB drugs or if isolates were tested for second line resistance at a SRL. In general, countries conducting surveys sent MDR isolates to SRLs for retesting and for DST for second-line anti-TB drugs.

HIV testing

All countries with the exception of the Ukraine reported routine HIV testing information used for patient care. Information on methods used and quality assurance were not collected for this report. In Donetsk Oblast, Ukraine a locally produced HIV enzyme-linked immunosorbent assay (ELISA) test detecting HIV 1 and HIV 2 Ab (Diaprof Med, Kiev, Ukraine) was used for screening. All positive results were confirmed by the Genscreen Plus HIV Ag-Ab (Bio-Rad Laboratories, Steenvoorde, France).

Statistical procedures – data entry, checking and cleaning

With the exception of Western and Central European countries, all settings reported data and other information about survey and surveillance methods through a standard data collection form. The standard data collection form is used to compile aggregated survey results. Completed forms were collected and reviewed at all levels of WHO, by country offices, regional offices and at headquarters. All data in the form of annexed tables were returned to the country for a final review before publication. All data are entered into a Microsoft Access database.

Statistical analysis

Analysis was conducted on drug resistance data for new cases, previously treated cases, and combined proportions. The following patterns of drug resistance were highlighted: resistance to any TB drug, MDR-TB, and any resistance to isoniazid, rifampicin streptomycin , and ethambutol. XDR-TB was also highlighted where data were available. Descriptive statistics were calculated in Stata (version 9.0; StataCorp). Arithmetic means, medians and ranges were determined as summary statistics for new, previously treated, and combined cases, for individual drugs and pertinent combinations. For geographical settings reporting more than a single data point since the third report, only the latest data point was used for the estimation of point proportion. All tests of significance were two-tailed and the alpha-error was kept at the 0.05 level in all inference procedures. Ninety-five percent confidence intervals were calculated around the proportions and the means. Box plots were developed to illustrate the distribution of the data reported in WHO regions. Population weighted means from the last data point of all countries reporting to the project are calculated to reflect the mean proportion of resistance by region based on countries reporting data to the project. In the past unweighted medians were reported by regions, but as expansion of surveys takes place within countries and increasing numbers of low TB prevalence countries report data to the project, a population weighted mean was considered more valuable for estimating proportions of resistance (see below).

Global data using the last data point from all countries that have reported

For maps, means and Global Project coverage estimates the last data point from all settings ever reporting to the project were included. Global and regional means of resistance among new, previously treated, and all TB cases were weighted by new smear positive, retreatment, and all TB cases notified in the area surveyed in 2005[1], respectively. For surveys carried out on a sub national level (states, provinces, oblasts), information representing only the population surveyed is included where appropriate.

HIV, resistance to second-line anti-TB drugs, age and sex

If HIV, second line DST results, or age and sex data from a given setting was available from more than one survey and one year the information was combined for the analysis. Information from new and previously treated cases was also combined for analysis.

The association between HIV and drug resistant TB was evaluated through calculation of an odds ratio to compare proportion of drug resistance in HIV infected and uninfected patients. Statistical significance was tested using a Fisher's exact test.

For analysis of resistance to second-line anti-TB drugs the denominator used was MDR isolates tested for resistance to at least one fluoroquinolone and one injectable second-line anti-TB drug (required to define XDR-TB). XDR-TB and fluoroquinolone resistance are the two categories reported.

The association between MDRTB and the variables sex and age groups was studied in a multivariate logistic regression analysis. Statistical analyses were performed using Stata (version 9.0; StataCorp).

Dynamics of resistance over time

Analysis was conducted on proportion of drug resistance among new cases in survey settings among new and combined cases in settings conducting routine surveillance. Only countries and settings with three or more data points were included in this exercise. The following patterns of drug resistance were highlighted: any drug resistance, MDR, and any INH resistance. For settings that reported at least three data points, the trend was determined visually as ascending, descending, flat, indeterminate. The relative increase or decrease was expressed as a proportion. Statistical significance of trends was determined through a logistic regression.

Estimates

A total of 183 countries and 2 SARs of China that account for nearly 100% of the world's population were included in the present analysis, which used data from the most recent national surveys. For Brazil, Kenya, the Central African Republic, Sierra Leone, and Zimbabwe, the surveys covered most, but not quite all, of the respective countries. For China, India, Italy, Malaysia, Mexico, the Russian Federation, Spain, Turkmenistan, Uganda, Ukraine, and Uzbekistan, the surveys were sub national. For these countries, the proportion of MDR-TB cases was estimated as the mean of the results obtained from surveys conducted at the sub national level weighted by the population of patients with TB as described above. For countries for which data from repeated surveys were available, only the most recent data were included. MDR-TB

rates among new cases were available from 104 countries and 2 SARs of China. Among them 97 also reported data on MDR-TB rates among previously treated cases. A total of 10 countries reported data on combined cases only. The estimated number of new TB cases globally and by country was used to calculate the number of MDR-TB cases that occurred among new cases. To estimate the number of previously treated cases, for each country we multiplied the ratio of notified previously treated cases to notified new cases in 2006 by the total number of new cases estimated to have occurred in the same year, therefore the total number of estimated case includes estimated retreatment cases. Estimates were developed using a logistic regression model described in detail elsewhere[14].

Validity of the findings

Surveillance and survey data are prone to errors that may to some extent invalidate the findings. Those errors, or biases, may be related to the selection of subjects, the laboratory testing, the data-gathering or the data analysis. Where cases are sampled only for a short period or in a restricted geographical area, the sample may not be fully representative of the total eligible population. Selection bias may also occur when only a particular subgroup of TB patients is included in the sample.

Distinguishing accurately between new and previously treated cases is not always possible, as this depends on the patients' willingness to disclose a history of prior anti-TB treatment and on the training and motivation of the staff. For various reasons, patients may be unaware of their treatment antecedents, or prefer to conceal this information. Consequently, in some survey settings, a certain number of previously treated cases may have been misclassified as new cases. (Misclassification in the opposite direction is considered unlikely.) The impact of this misclassification may result in an overestimation of the resistance rates among new cases; it is difficult, however, to estimate the magnitude of this bias. It is important to mention that the proportion of resistance will be biased only if the correctly classified and misclassified TB patients have different risks for drug resistance.

Another bias, which is often not addressed in field studies, is the difference between the true prevalence and the observed or "test" prevalence. That difference depends on the magnitude of the true prevalence in the population, and the performance of the test under study conditions (i.e.

its sensitivity and specificity). In practice, no test is completely accurate. Therefore reported prevalence will either over- or underestimate the true prevalence in the population. In general, the sensitivity of specificity of isoniazid and rifampicin tends to be very high. It is more likely to find test errors in tests for ethambutol and streptomycin. This is particularly true for the evaluation of second-line anti-TB drugs where external quality assurance does not exist and resistance to these drugs is relatively rare.

Some settings reported a small number of resistant cases, and a few settings reported a small number of total cases examined. There were a number of possible reasons for these small denominators in various participating geographical settings, ranging from small absolute populations in some surveillance settings to feasibility problems in survey settings. This was particularly true for previously treated cases. The resulting reported prevalences thus lack stability and important variations are seen over time, though most of the variations are not statistically significant. Where there were serious doubts concerning the representativeness of the sample of previously treated cases, the data were not included in the final database.

It is also important to note that retreatment cases are a very heterogeneous group comprised of patients who have relapsed, defaulted, been treated in the private sector, failed treatment once or several times, and cases that have been re-infected. Thus, for optimal interpretation of survey results it is important to disaggregate patients by treatment history as accurately as possible. Very few settings have been able to do this due given the complexity of the interviews and the review of medical history required.

Chapter 3. RESULTS

PHASE 4 OF THE GLOBAL PROJECT 2002-2007

Phase 4 of the Global Project provides the most recent data on anti-TB drug resistance, from 93 geographical settings in 81 countries and 2 SARs of China. Of these, 33 provided national or sub national data that were never previously reported.

Subnational surveys, i.e. at the provincial, district, or city level, account for the discrepancy between the number of geographical settings and the number of countries. Eight countries had results for 20 sub national areas and two special administrative regions. Azerbaijan reported data from Baku city. China reported data from one province, one Autonomous Region two municipalities and two special administrative regions (SAR); Heilongjiang province, Inner Mongolia Autonomous Region, Beijing and Shanghai municipalities, and Hong Kong and Macao Special Administrative regions. India reported data from one state and three districts; Gujarat State, Ernakulam district within Kerala State, Hoogli district within West Bengal State, and Mayhurbhanj District within Orissa State. Indonesia reported data from Mimika district, in the Papua Province. The Russian Federation reported data from three of eighty-nine oblasts; Mary El, Orel, and Tomsk. Spain reported data from two regions and one city; Aragon, Galicia, and Barcelona. The Ukraine reported data from Donetsk Oblast, and Uzbekistan reported data from Tashkent city.

Types of data

The most recent anti-TB drug resistance profile contains data from 93 settings in 83 countries:

- 66 countries and 2 SARs of China provided information on drug resistance among new, previously treated and combined cases;
- 6 countries reported drug resistance information on new cases only; Andorra, Luxembourg, and Malta did not detect any previously treated cases.
- 36 countries reported 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

region in Spain, this represented the majority or the only group reported. Australia, Fiji, Guam, New Caledonia, Puerto Rico, Qatar, Solomon islands, Barcelona, Spain, and the USA

Drug resistance among new TB cases

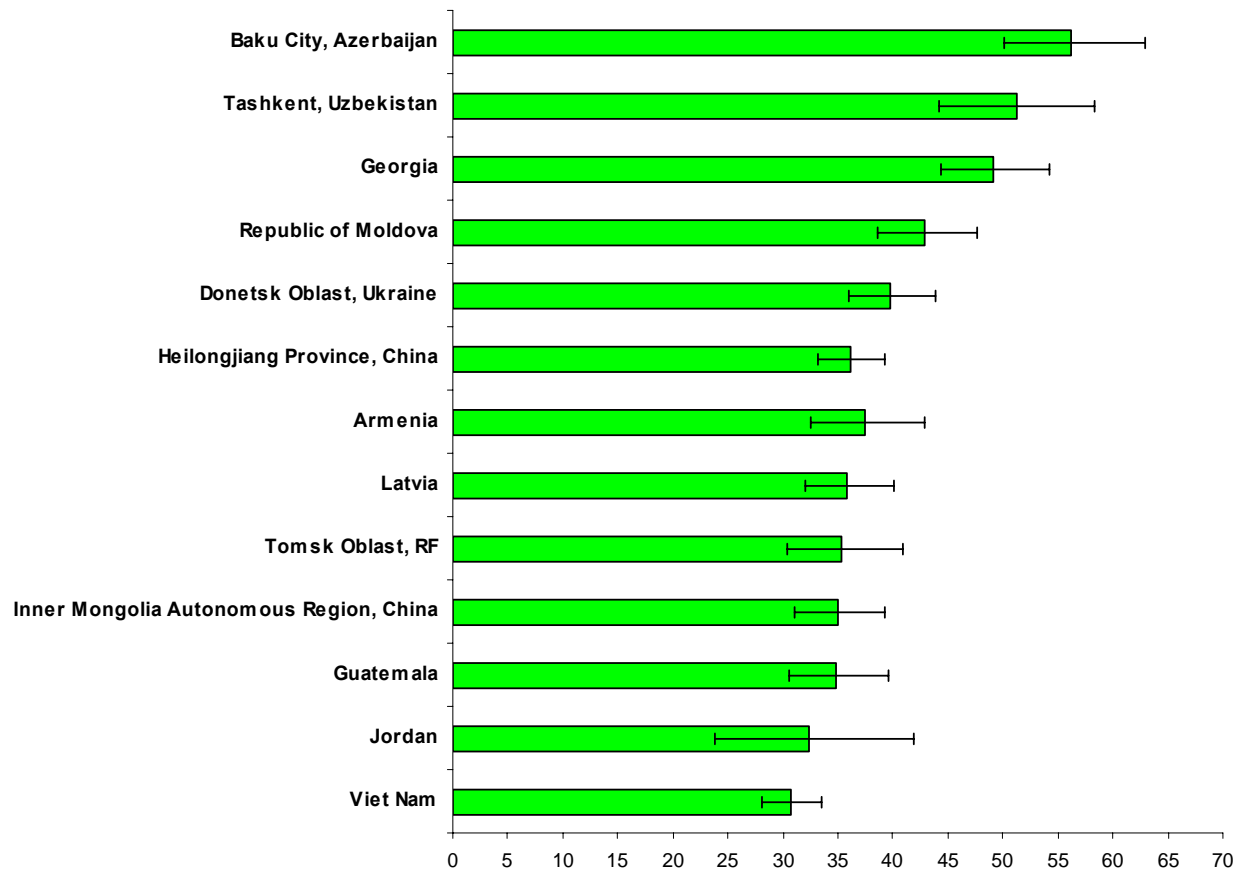
Full details of the proportion of drug resistance among new cases for the period 1994-2006 are given in Annex 1. This section of the report covers the latest data from countries reporting from 2002 to 2007. The median number of cases tested per setting in survey settings was 547 but ranged from 101 new cases in Mimika district in the Papua province of Indonesia to 1619 new cases in Viet Nam. The median number of new cases tested among the settings conducting surveillance was 485, and ranged from 7 cases in Iceland to 3379 in the United Kingdom.

Any resistance among new cases

Seventy two countries and 2 SARs of China provided data on the prevalence of any drug resistance among new cases of TB. The overall drug resistance ranged from 0% (Iceland¹³), 1.4% (95% CLs, 0.6-2.9) in Bosnia & Herzegovina and 1.5% (95% CLs, 0.6-2.9) in Sri Lanka to 49.2 (95% CLs, 44.4-54.3) in Georgia, 51.2 (95% CLs, 44.1-58.3) in Tashkent, Uzbekistan, and 56.3 (95% CLs, 50.2-62.9) in Baku City Azerbaijan, respectively. Thirteen settings reported prevalence of resistance to any drug 30% or higher. (Figure 1. Any resistance among new cases).

¹³ Iceland has been excluded from further analyses because no resistance was detected in the latest data reported.

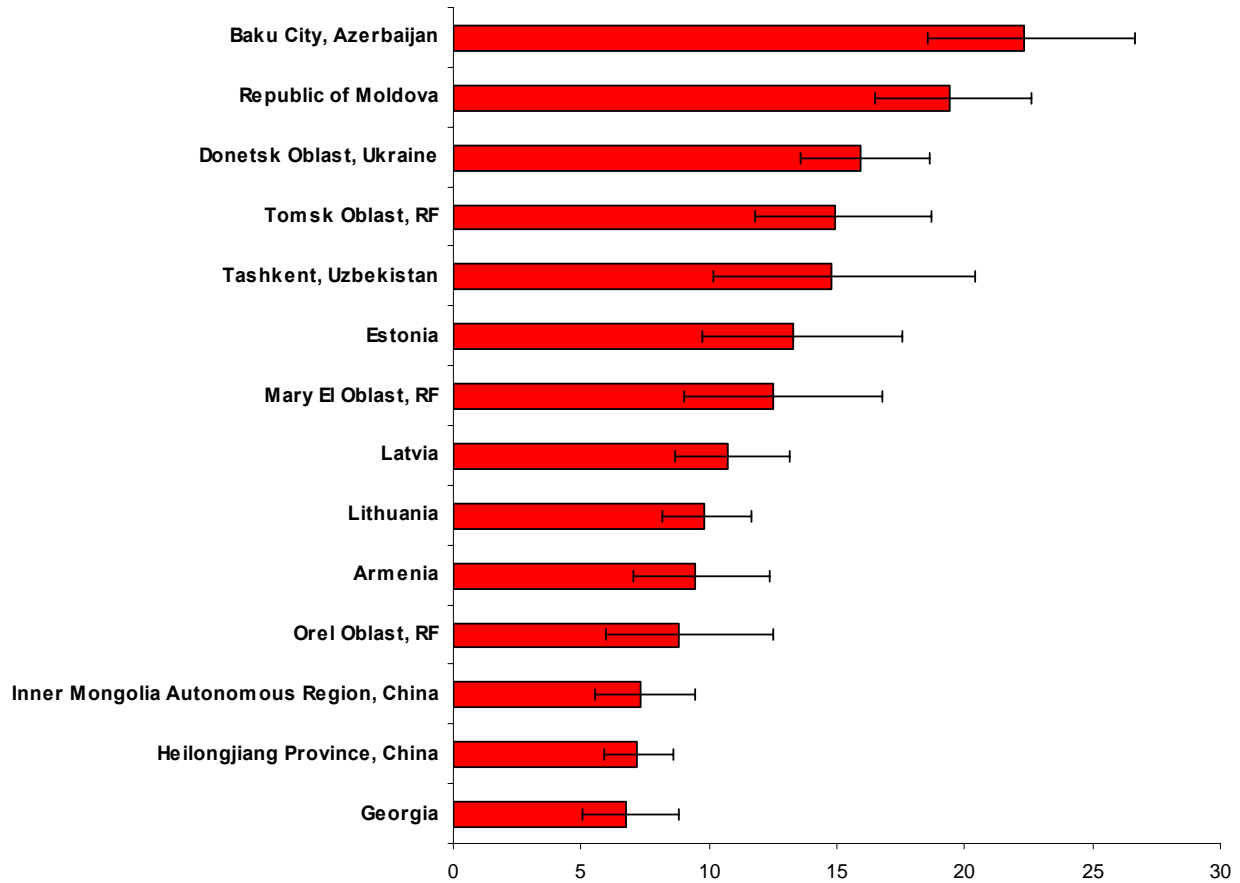
FIGURE 1: COUNTRIES/SETTINGS WITH PREVALENCE OF ANY RESISTANCE HIGHER THAN 30% AMONG NEW CASES, 2002–2007



MDR among new cases

Prevalence of MDR ranged from 0% (Andorra, Cuba, Luxembourg, Malta, Slovenia, Aragon, Spain, and Uruguay) to 19.4% (95% CLs, 16.5-22.6) in the Republic of Moldova, and 22.3% (95% CLs, 18.5-26.6) in Baku, Azerbaijan. Fourteen settings reported a prevalence of MDR among new cases higher than 5.0% (Figure 2).

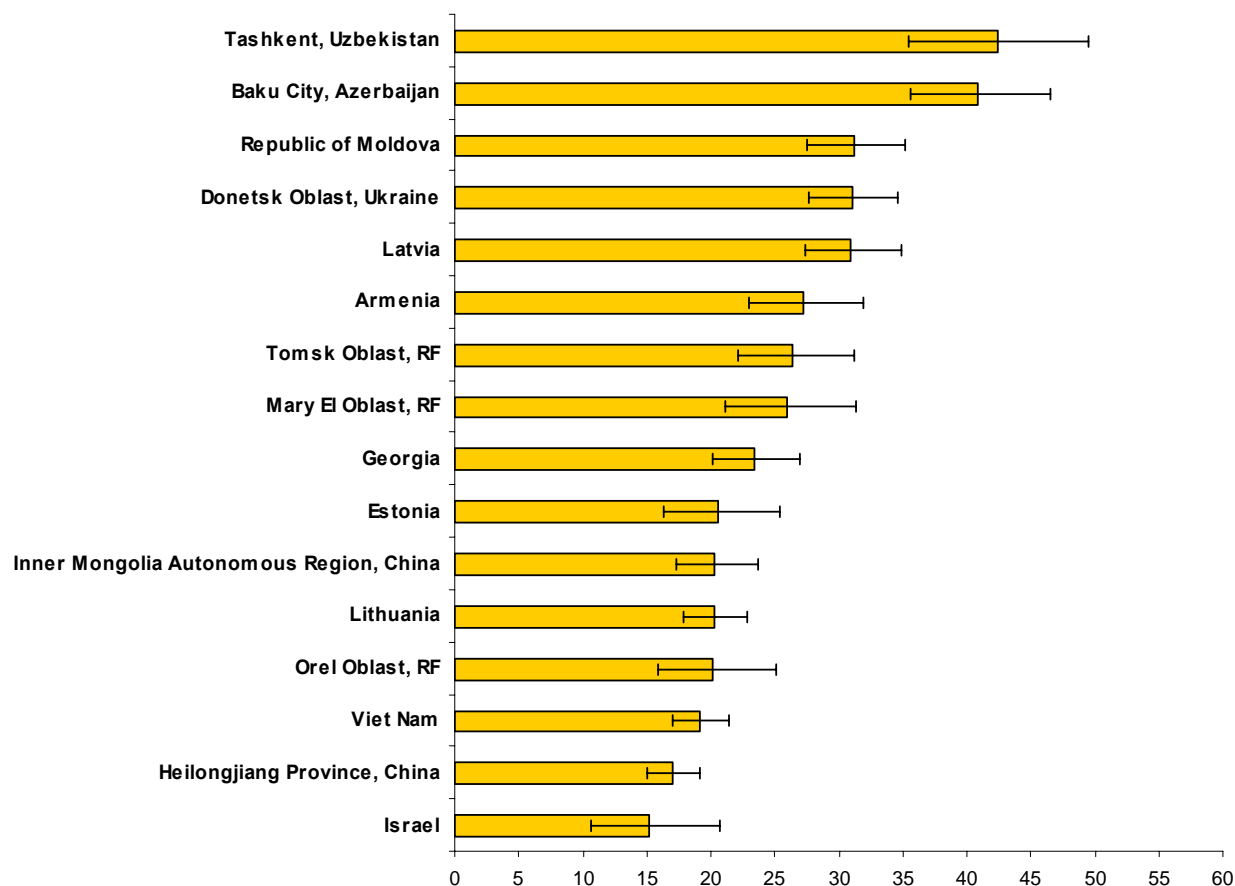
FIGURE 2: COUNTRIES/SETTINGS WITH MDR PREVALENCE HIGHER THAN 5.0% AMONG NEW CASES 2002-2007



Any isoniazid resistance among new cases

Prevalence of isoniazid resistance (INH) ranged from 0% in Malta and Iceland, 0.6% (95% CLs, 0.0-3.3) in Cuba and 0.7% (95% CLs, 0.2-1.9) in Sri Lanka to 42.4% (95% CLs, 35.5-49.5) in Tashkent, Uzbekistan, and 40.8% (95% CLs, 35.7-46.5) in Baku city, Azerbaijan. Sixteen settings reported a prevalence of isoniazid resistance 15% or higher among new cases (Figure 3).

FIGURE 3: PREVALENCE OF ANY RESISTANCE TO INH, AMONG NEW CASES, 2002-2007



Drug resistance among previously treated TB cases

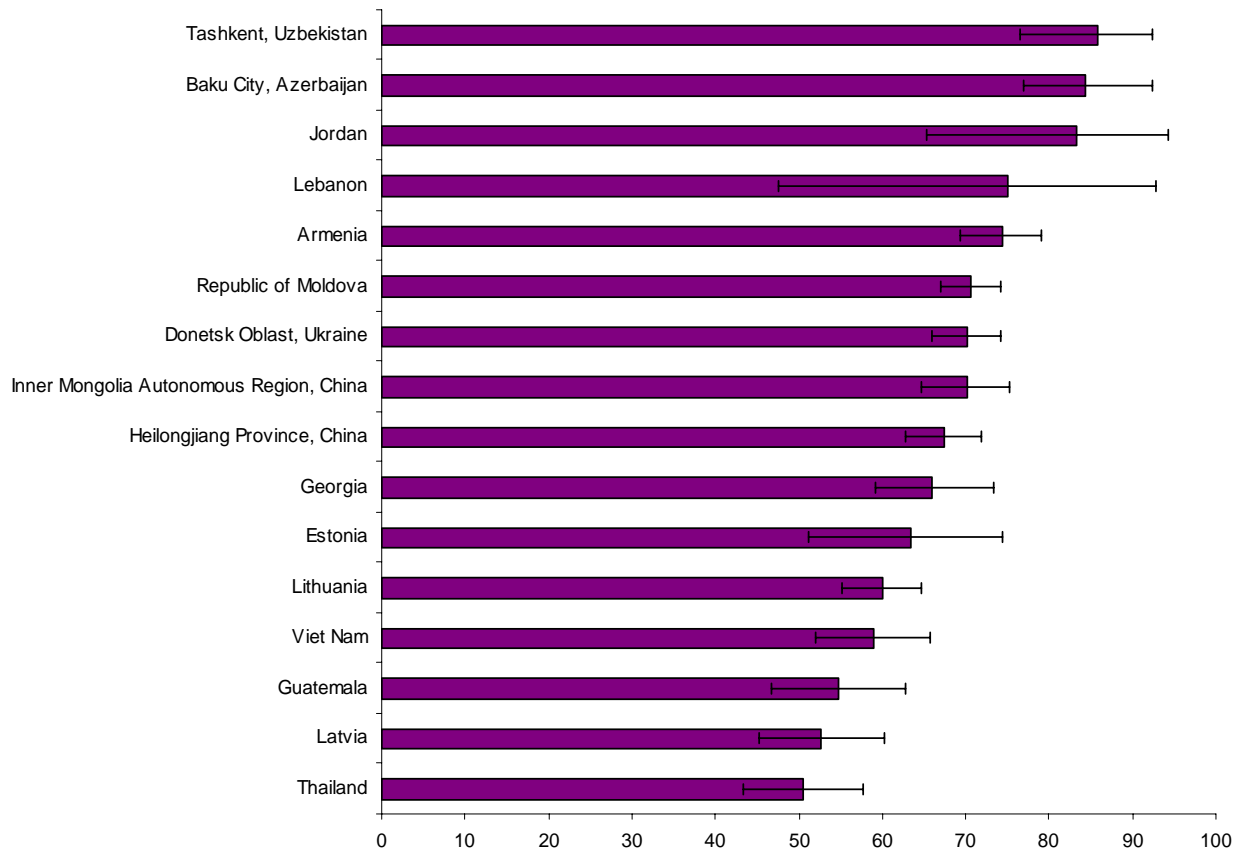
Data on the prevalence of drug resistance among previously treated cases were available for 66 countries and 2 SARs of China (Annex 2). The number of cases tested in settings conducting routine surveillance ranged from 1 (Iceland) to 522 (Poland) with a median of 58 cases per setting. The number of cases tested in settings conducting surveys ranged from 16 (Lebanon) to 1047 (Gujarat State, India) and 2054 cases in the Republic of Moldova¹⁴, with a median of 110¹⁵.

¹⁴ The sample of previously treated cases included in the survey from the Republic of Moldova includes a large proportion of cases that had been on treatment for more than month but were not classified as retreatment cases in the TB register.

Any resistance among previously treated cases

There was no resistance reported in Iceland, Israel, and Norway where the number of previously treated cases was very small. In contrast, Baku, Azerbaijan and Tashkent, Uzbekistan showed tremendously high prevalences of any resistance – 84.4% (95% CLs, 76.9-92.4) and 85.9% (95% CLs, 76.6-92.5), respectively. In sixteen settings, prevalence of any resistance was reported as 50% or higher (Figure 4).

FIGURE 4: COUNTRIES/SETTINGS WITH A PREVALENCE OF ANY RESISTANCE HIGHER THAN 50% AMONG PREVIOUSLY TREATED CASES, 2002-2007

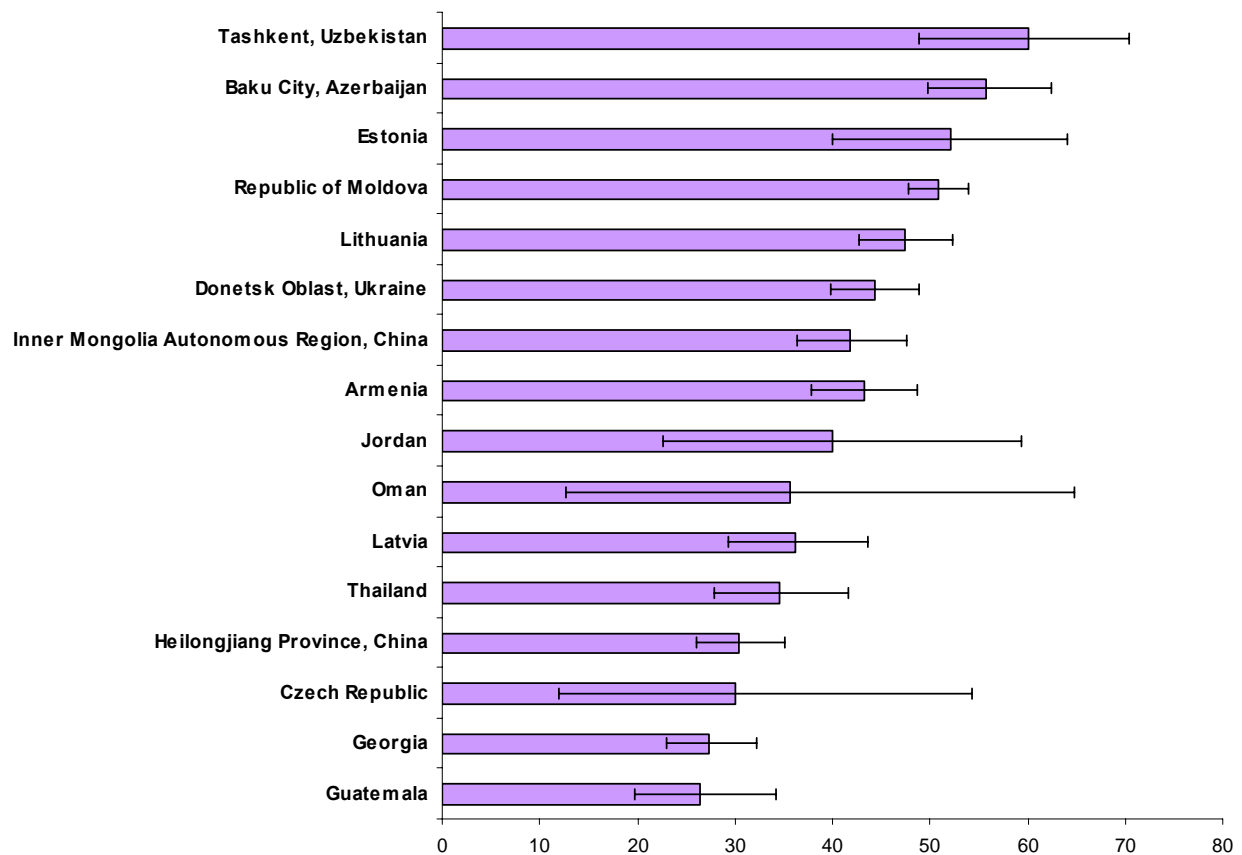


MDR among previously treated cases

No MDR was reported in Denmark, the Netherlands, New Zealand, Sri Lanka, or among the preliminary data reported from UR Tanzania. Estonia reported 52.1% (95%CLs, 39.9-64.1%) MDR-TB among previously treated cases, Baku, Azerbaijan, 55.8% (95% CLs, 49.7-62.4%) and

Tashkent, Uzbekistan reported 60.0% (95% CLs, 48.8-70.5) respectively. Lebanon reported 62.5% (95% CLs, 35.4-84.8), however only sixteen cases were included in the sample. The Russian Federation reported data on retreatment cases in Orel Oblast only. Sixteen settings reported MDR-TB 25% or higher among previously treated cases, (Figure 5).

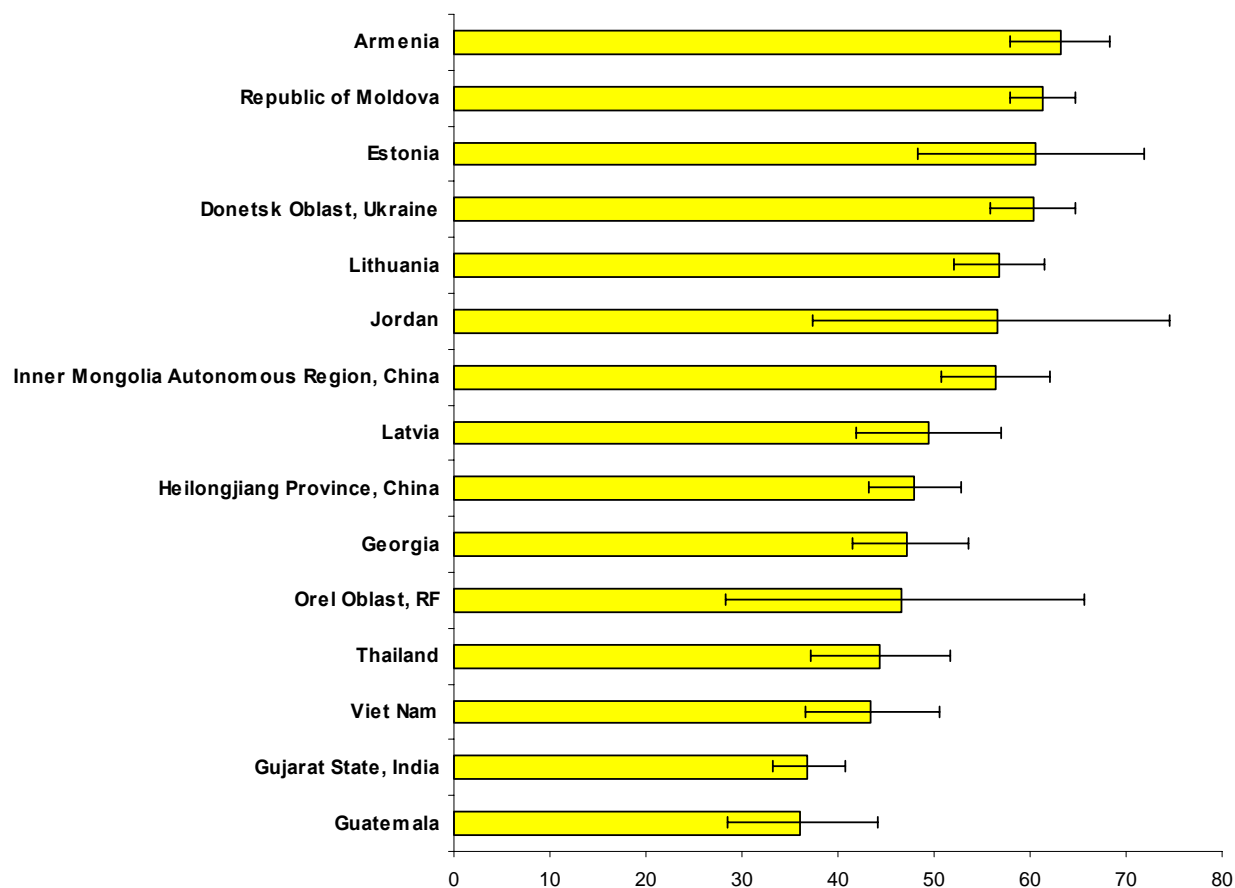
FIGURE 5: COUNTRIES/SETTINGS WITH PREVALENCE OF MDR HIGHER THAN 30% AMONG PREVIOUSLY TREATED CASES, 2002-2007



Any isoniazid resistance among previously treated cases

Prevalence of isoniazid resistance ranged from 0% in Iceland, Israel, and Norway, 3.8% (95% CLs, 1.0-9.5) in Singapore and 4.5% (95% CLs, 0.1-22.8) in Finland to 79.7% (95% CLs, 72.4-87.5) in Baku city, Azerbaijan, and 81.2 (95% CLs, 71.2-88.8) in Tashkent, Uzbekistan. Fifteen settings reported a prevalence of isoniazid resistance 30% or higher among previously treated cases (Figure 6).

FIGURE 6: PREVALENCE OF ANY RESISTANCE TO INH AMONG PREVIOUSLY TREATED CASES, 2002–2007



Drug resistance among all TB cases

Drug resistance among all TB cases is examined in detail in the trends section of this report for countries conducting routine surveillance, and all data are available in Annex 3. In the majority of survey settings the number of previously treated cases is small and does not reflect the proportion of retreatment cases within the TB programme, therefore when estimating proportions of resistance among combined cases proportions must be weighted by their population within the programme generating very wide confidence intervals. Therefore, the only proportion examined without distinguishing by treatment history is the proportion of non-MDR rifampicin resistance. Non-MDR rifampicin resistance is an important programmatic indicator that should be known if screening for MDR-TB on the basis of rifampicin testing alone. Because rifampicin resistance unaccompanied by isoniazid resistance is so rare it may also be good laboratory indicator. If non-

MDR-TB rifampicin resistance is greater than 3% this should be considered unusual and may suggest errors in either rifampicin or isoniazid testing. Of the 93 settings that reported, 80% reported less than 1% non-MDR rifampicin resistance. Only 3 settings reported non-MDR rifampicin resistance above 3%.

TABLE 1: PREVALENCE OF NON-MDR RIFAMPICIN RESISTANCE AMONG ALL TB CASES, 2002–2007¹⁶

0.00%	30 settings
0.1-1.0%	47 settings
1.1-3.0%	13 settings
	Donetsk Oblast, Ukraine
	Republic of Moldova
	Paraguay
	Armenia
	Beijing Municipality, China
	Romania
	Ernakulam district, Kerala State, India
	Tomsk Oblast, RF
	Guatemala
	Lebanon
	Ethiopia
	Shanghai Municipality, China
	Rep. Korea
>3.0%	3 settings
	Jordan
	Heilongjiang Province, China
	Inner Mongolia Autonomous Region, China

MDR among new and previously treated cases by region

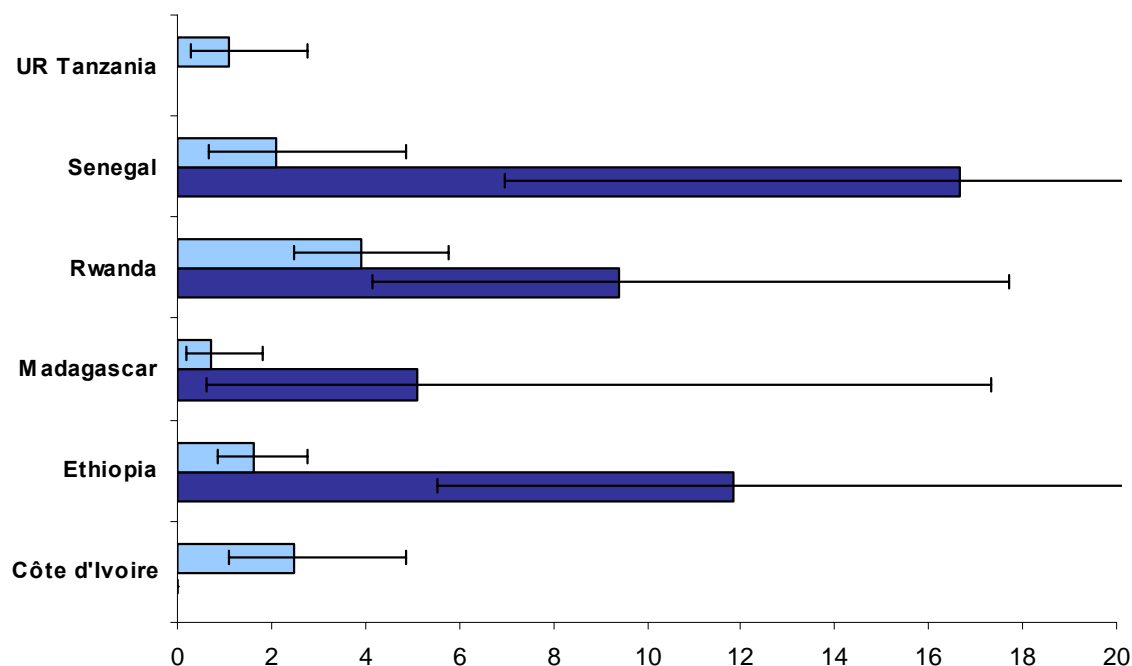
The African region

Six countries reported from the African region. The median sample size was 471 new cases and 46 previously treated cases. MDR among new cases ranged from 0.7% (95% CLs, 0.2-1.8) in Madagascar to 3.9% (95% CLs, 2.5-5.8) in Rwanda. Côte d'Ivoire did not survey previously

¹⁶ Data from countries and settings only reporting on new cases were also included in this analysis.

treated cases, and the preliminary data from UR Tanzania showed no MDR among previously treated cases¹⁷.

FIGURE 7: PREVALENCE OF MDR-TB AMONG NEW AND PREVIOUSLY TREATED CASES IN THE WHO AFRICAN REGION, 2002–2007



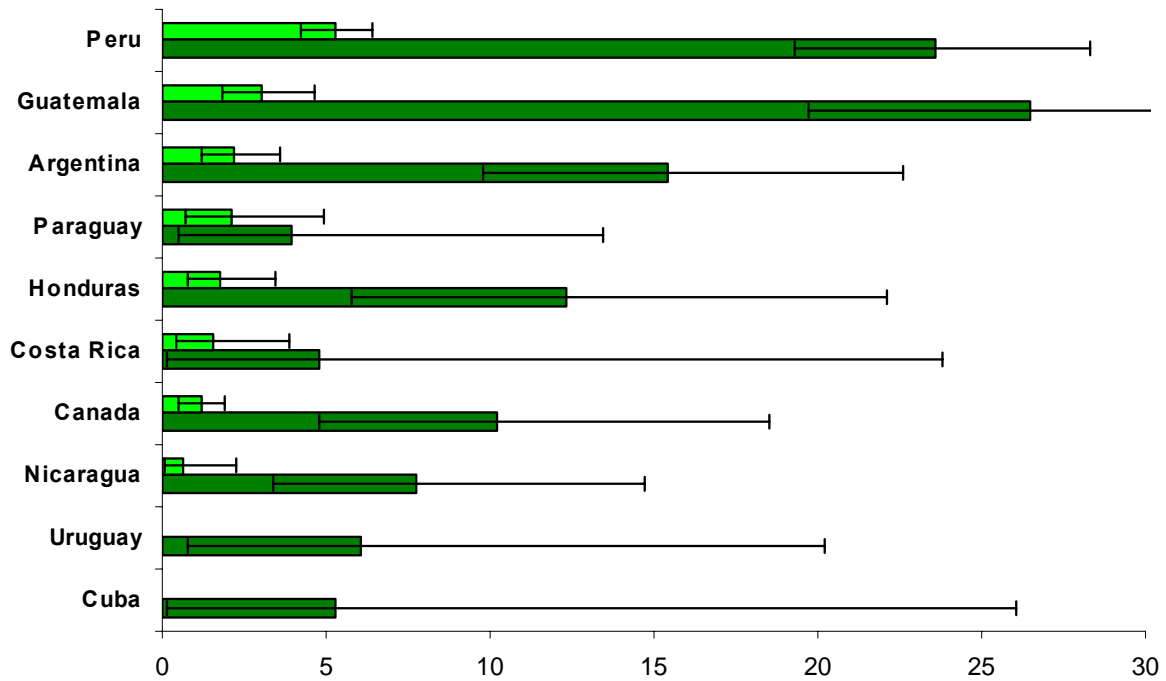
The Americas region

Eleven countries reported from the Americas region¹⁸. The median sample size was 335 for new cases and ranged from 169 new cases in Cuba to 1809 in Peru. The median sample size for previously treated cases was 80. No MDR was found among new cases in Cuba or Uruguay. Guatemala and Peru showed the highest proportion of MDR among new cases, 3.0 % (95% CLs, 1.8-4.6) and 5.3% (95% CLs, 4.2-6.4) respectively.

¹⁷ Data from Madagascar and UR Tanzania are preliminary and external quality assurance of laboratory testing was not complete at the time of this report.

¹⁸ The USA and Puerto Rico reported on combined cases only and are excluded from this analysis.

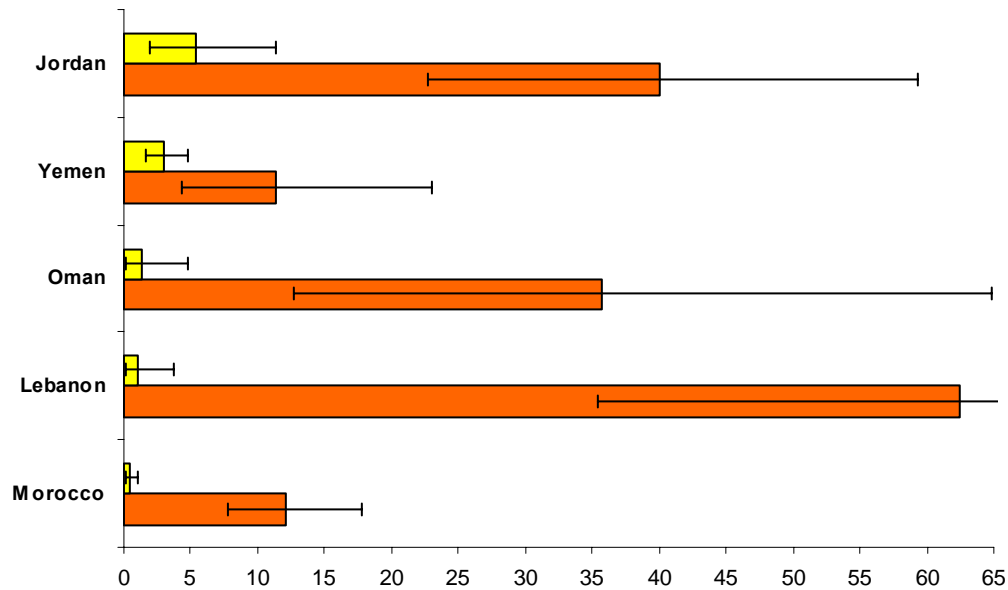
FIGURE 8: PREVALENCE OF MDR-TB AMONG NEW AND PREVIOUSLY TREATED CASES IN THE WHO AMERICAS REGION, 2002–2007



The Eastern Mediterranean region

Five countries reported from the Eastern Mediterranean region. The median sample size was 264 for new cases and ranged from 111 new cases in Jordan to 1049 in Morocco. The median sample size for previously treated cases was 42. MDR among new cases ranged from 0.5% (95% CLs, 0.2-1.1) in Morocco to 5.4 (95% CLs, 2.0-11.4), in Jordan.

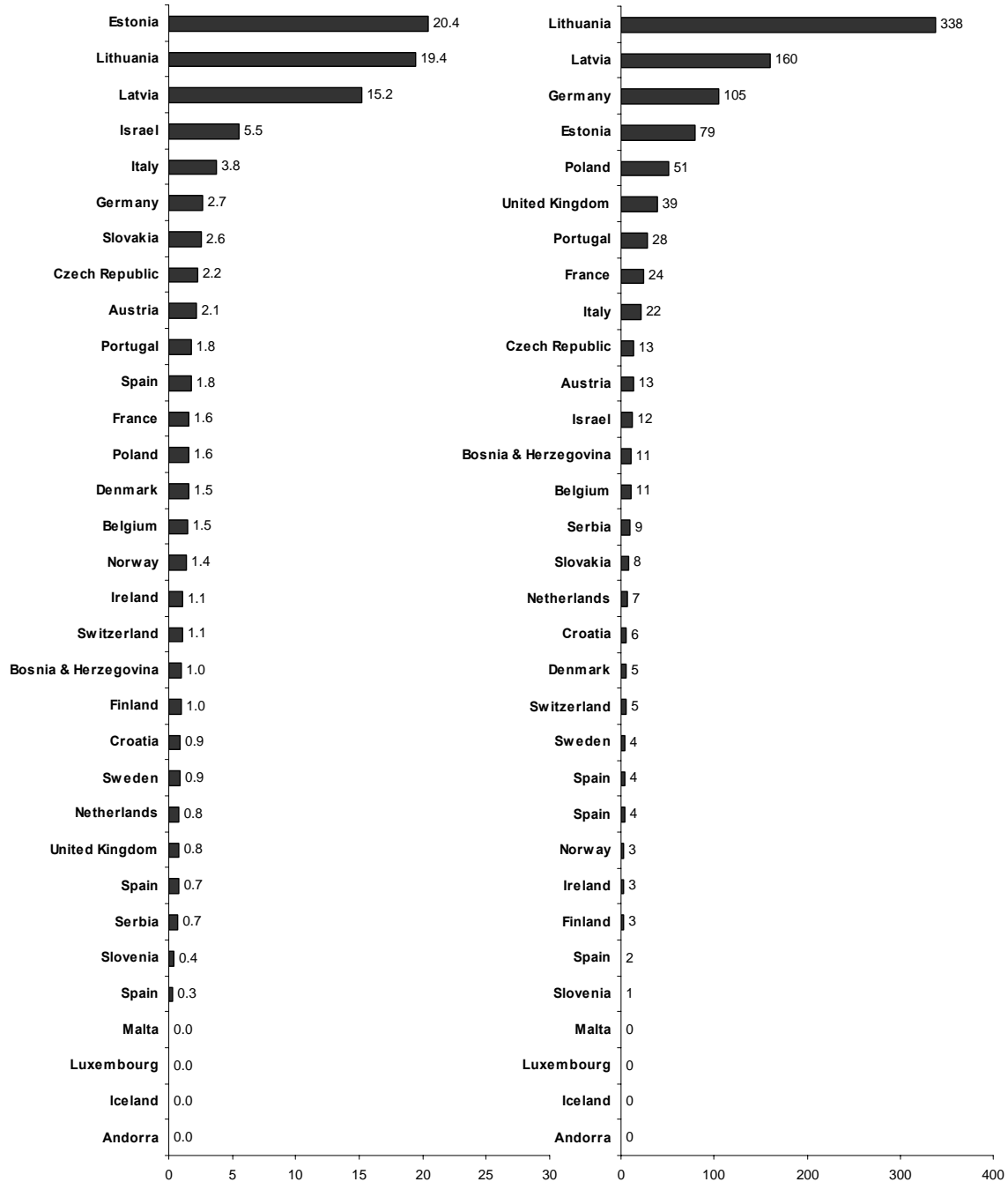
FIGURE 9: PREVALENCE OF MDR-TB AMONG NEW AND PREVIOUSLY TREATED CASES IN THE WHO EASTERN MEDITERRANEAN REGION, 2002–2007.



The European region

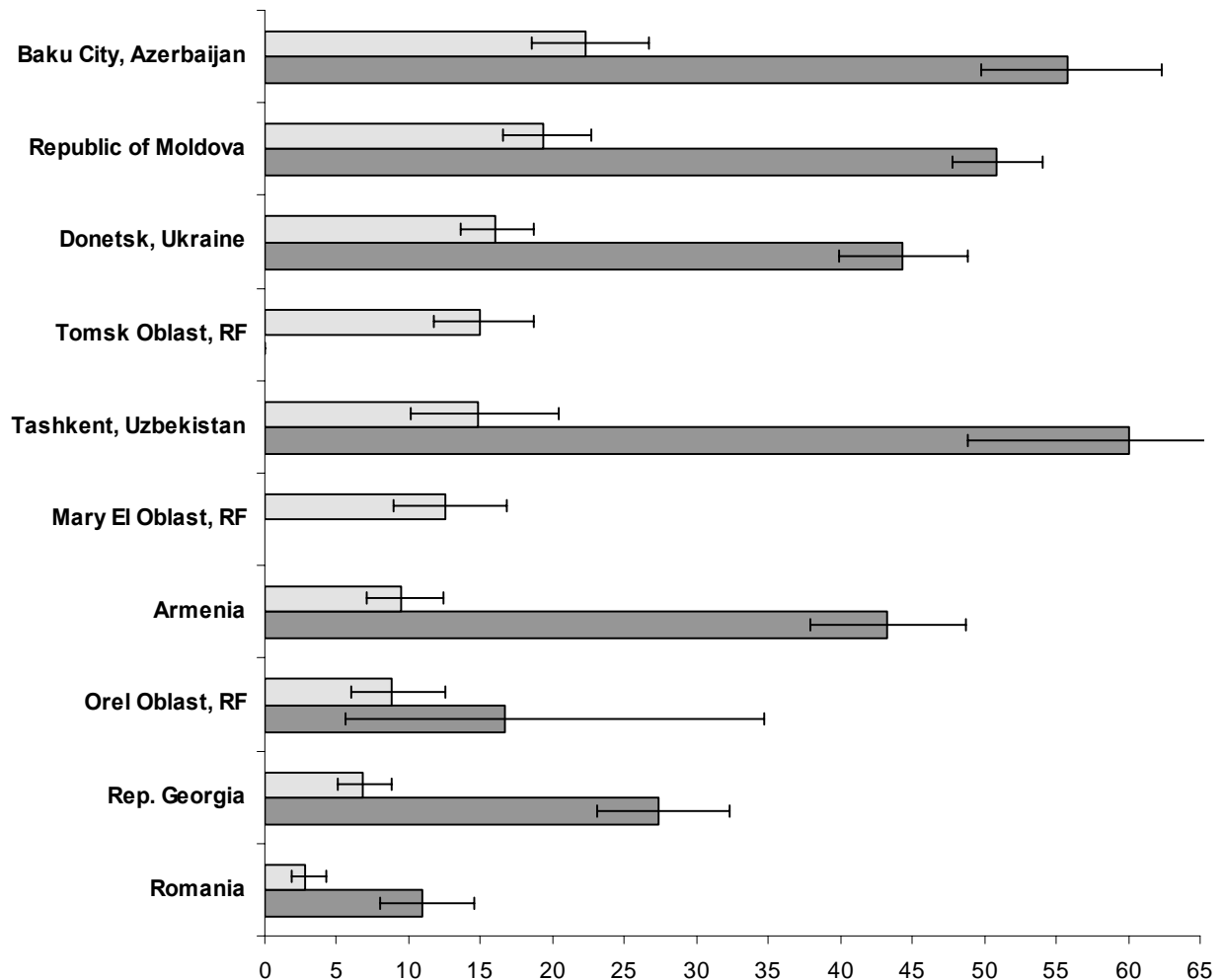
Thirty eight countries reported data from the European region. Of the 30 countries, including three settings in Spain, conducting routine nationwide surveillance the median of combined cases tested was 483, and ranged from 8 in Iceland to 4800 in the UK. Both absolute numbers and proportion of MDR-TB were highest in the Baltic countries.

FIGURE 10: TOTAL NUMBER OF MDR-TB CASES REPORTED IN EUROPEAN COUNTRIES AND SETTINGS CONDUCTING ROUTINE SURVEILLANCE. FIGURE X: PERCENTAGE OF MDR-TB AMONG ALL TB CASES REPORTED.



Of the eight countries conducting surveys or reporting sub national data, seven were countries of the former Soviet Union. The prevalence of MDR-TB among new cases ranged from 2.8% (95% CLs, 1.8-4.2) in Romania to 22.3% (95% CLs, 18.5-26.6) in Baku, Azerbaijan, 28.6%. Data on previously treated cases were not included from Mary El or Tomsk Oblasts of the Russian Federation.

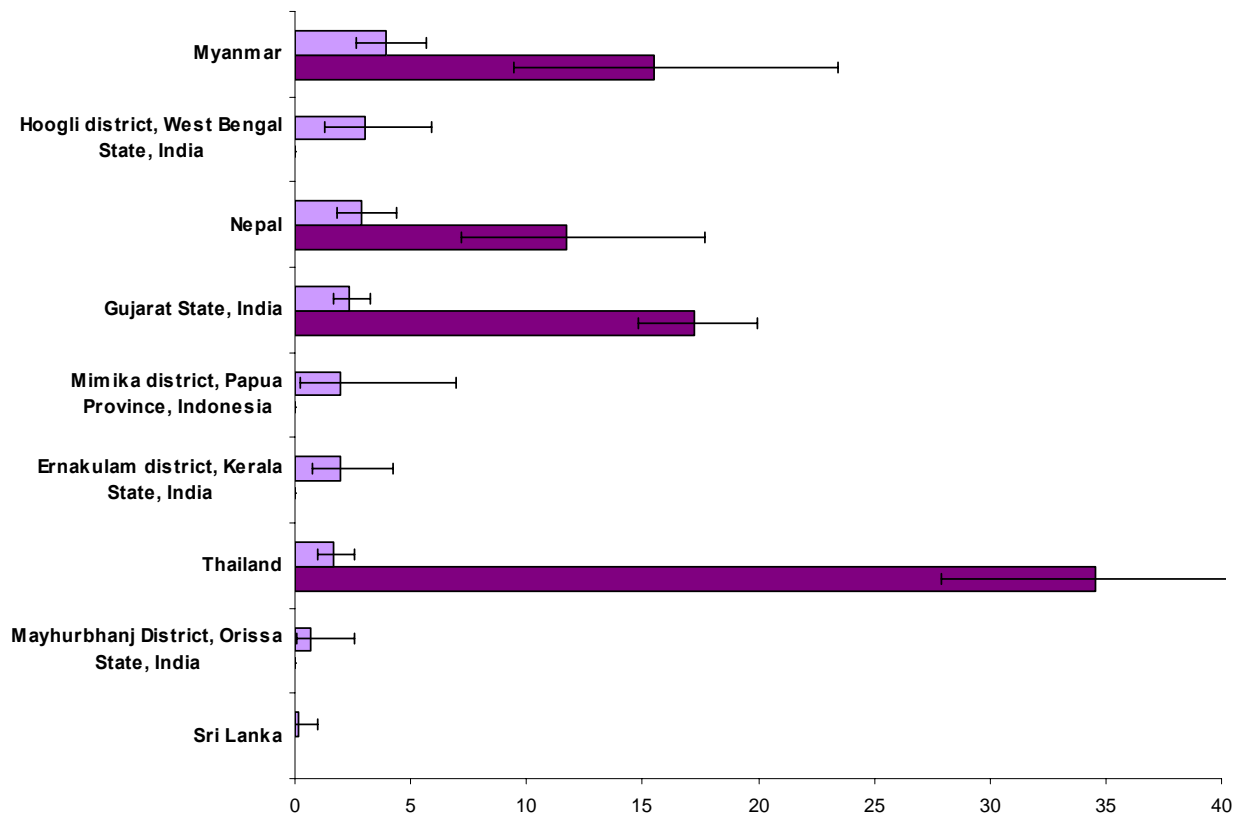
FIGURE 11: PREVALENCE OF MDR-TB AMONG NEW AND PREVIOUSLY TREATED CASES AMONG COUNTRIES/SETTINGS CONDUCTING SURVEYS IN THE WHO EUROPEAN REGION, 2002–2007.



The South East Asian region

Six countries reported data from the South East Asia region. Of the six countries, including four settings in India, the median number of new cases tested was 547, and ranged from 101 in Mimika district in the Papua province of Indonesia, to 1571 new cases tested in Gujarat, India. The median number of previously treated cases tested was 162. MDR-TB among new cases ranged from 0.2 % (95% CLs, 0.0-1.0) in Sri Lanka, and 0.7% (95% CLs, 0.1-2.5) in Mayhurbhanj District, Orissa State, India to 4.0% (95% CLs, 2.6-5.7) in Myanmar. India, Nepal and Myanmar showed similar proportions of resistance among retreatment cases. Sri Lanka, showed no resistance and Thailand showed 34.5% (95% CLs, 27.9-41.7) MDR among previously treated cases.

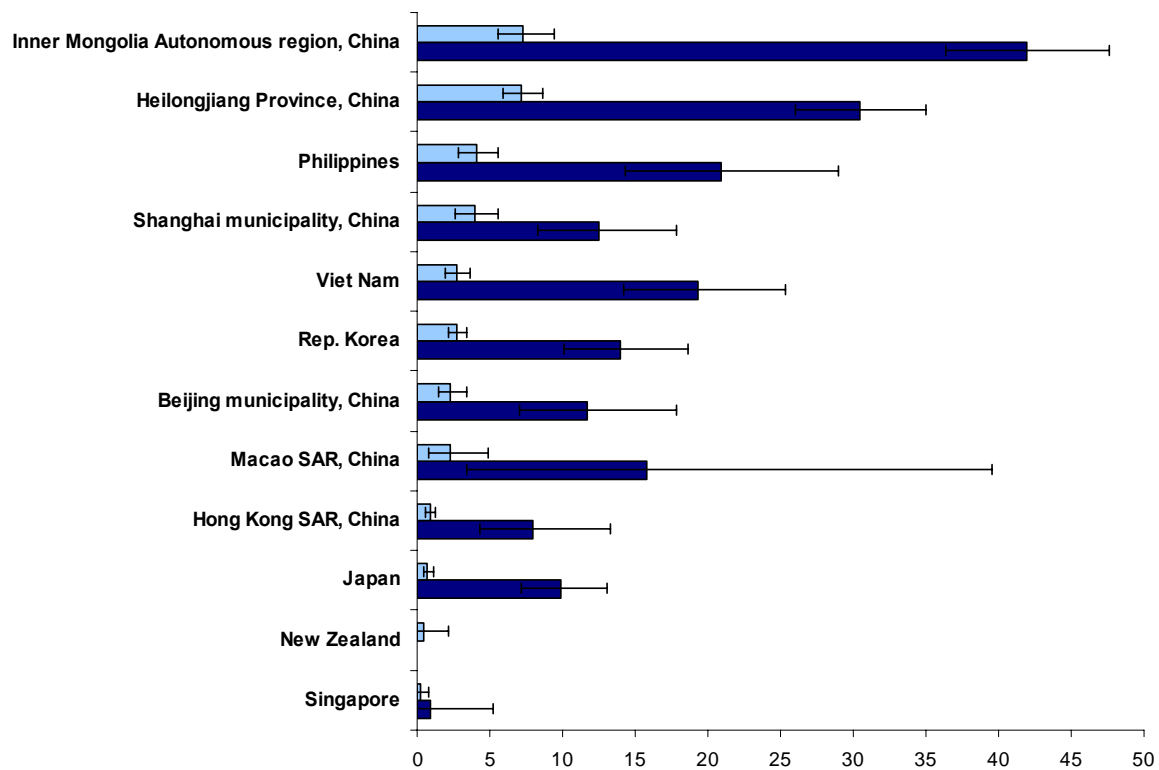
FIGURE 12: PREVALENCE OF MDR-TB AMONG NEW AND PREVIOUSLY TREATED CASES IN THE WHO SOUTH EAST ASIAN REGION, 2002–2007.



The Western Pacific region

Seven countries and two special administrative regions¹⁹ (Hong Kong and Macao, SAR, China) reported drug resistance data from the Western Pacific region. Of the six countries that reported data distinguished by treatment history, including four settings in mainland China, the median number of new cases tested was 1004, and ranged from 250 in New Zealand to 3271 in Hong Kong, SAR, both countries conduct routine surveillance of all TB cases. The median number of previously treated cases tested was 182. MDR-TB among new cases ranged from less than 1.0% in Hong Kong, SAR, Japan, New Zealand, and Singapore, to 7.2% (95% CLs, 5.9-8.6) and 7.3% (95% CLs, 5.6-9.4) in Heilongjiang, and Inner Mongolia Autonomous region of China.

FIGURE 13: PREVALENCE OF MDR-TB AMONG NEW AND PREVIOUSLY TREATED CASES IN THE WESTERN PACIFIC REGION, 2002–2007.



DRUG RESISTANT TB BY AGE AND SEX

Data on drug resistance stratified by sex and age groups was reported by 42 settings in 36 countries from all the 6 WHO Regions. Among these settings seven were able to report information for more than one year. MDR-TB among combined cases was found to be associated with male sex and with the younger age groups (25-44 years old) in most of the WHO regions.

DRUG RESISTANCE AND HIV

A total of 8 settings in seven countries reported data on drug resistance stratified by HIV status. The settings that reported are Cuba, Honduras, Latvia, Tomsk Oblast of the Russian Federation, Spain (Barcelona and Galicia), Ukraine (Donetsk Oblast) and Uruguay. Data were reported stratified by positive and unknown HIV status from Latvia and Galicia, Spain, and disaggregated by positive, negative and unknown HIV status from the remaining settings. The lack of differentiation between HIV unknown and HIV negative weakened the analysis. If data on drug resistance stratified by HIV status from a given setting was available from more than one survey and one year the information was combined for the analysis. Information from new and previously treated cases was also combined for analysis.

Due to the low number of HIV positive cases diagnosed with MDR-TB or with resistance to any TB drug in the majority of the settings was not sufficiently powerful to examine an association between HIV and drug resistant TB. The only two settings with large enough number of cases to be able to examine the relationship between the two epidemics were Latvia and Donetsk Oblast, Ukraine. HIV infection was significantly associated both to MDR-TB and any anti-TB drug resistance in both Latvia and in Donetsk Oblast, Ukraine. Table 2 presents the number and proportion of MDR and any resistance among patients with positive and unknown HIV status in Latvia from 2001 to 2005.

¹⁹ Australia, Guam, Fiji, New Caledonia, and the Solomon islands reported on combined cases only and are excluded from this analysis.

TABLE 2: PREVALENCE OF MDR-TB AND ANY RESISTANCE AMONG HIV POSITIVE TB CASES AND TB CASES WITH UNKNOWN HIV STATUS IN LATVIA, 2001–2005.

	MDR	Any resistance
DR in HIV unknown TB cases (%)	765/5,162 (14.8)	1,782/5,162 (34.5)
DR in HIV positive TB cases (%)	39/148 (26.4)	66/148 (44.6)
Odds Ratio (95% CL)	2.1 (1.4 to 3.0)	1.5 (1.1 to 2.1)
p value	< 0.01	< 0.05

In Donetsk Oblast, Ukraine, the drug resistance survey was linked to a TB/HIV survey. In this study, positive HIV status was found to be an independent predictor for MDR-TB, in addition to history of previous anti-TB treatment and history of imprisonment²⁰. Table 2 presents the number and proportion of MDR and any resistance among patients with positive and negative HIV status in Donetsk Oblast, Ukraine, in 2006.

²⁰ Lyepshina S. Association between multidrug-resistant tuberculosis and HIV status in the civilian and penitentiary sectors of Donetsk Oblast, Ukraine., 38th World Conference on Lung Health. 8-12 November, 2007, Cape Town, South Africa., Abstract Book

TABLE 3: PREVALENCE OF MDR-TB AND ANY RESISTANCE AMONG HIV POSITIVE AND HIV NEGATIVE TB CASES IN DONETSK OBLAST, UKRAINE, 2006.

	MDR	Any resistance
DR in HIV negative TB cases (%)	272/1,143 (23.8)	551/1,143 (48.2)
DR in HIV positive TB cases (%)	97/307 (31.6)	173/307 (56.4)
Odds Ratio (95% CL)	1.5 (1.1 to 2.0)	1.4 (1.1 to 1.8)
p value	< 0.01	< 0.05

XDR-TB

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. Twenty five countries and two special administrative regions reported routine surveillance data while ten countries reported from periodic surveys. Data on new and previously treated cases were combined and data from multiple years were also combined if available. The denominator used was MDR-TB cases tested for second-line anti-TB drugs that would allow the definition of XDR-TB. Data from the national lab registers in South Africa are included although these data are not considered nationally representative. A further five countries reported data from risk groups. Nineteen countries have reported at least one case since 2001, although no denominators are available. Four of these eighteen countries also reported surveillance data, but the XDR-TB case identified was not found during the years for which surveillance data are reported. A total of 45 countries and 1 special administrative region have identified at least one case of XDR-TB since 2002. Of the countries conducting routine surveillance; three countries and one oblast of the Russian Federation reported between 25 and 58 cases over a four year period representing between 6.6% (95% CLs, 4.5-9.2) of the MDR-TB burden in Tomsk, Oblast to 23.7% (95% CLs,

18.5-29.5) in Estonia. The United States reported seventeen cases over a six year period, representing 1.9% (95% CLs, 1.1-3.1) of MDR-TB cases tested for second-line anti-TB drugs during this period. Barcelona, Spain and the Czech Republic reported three and five cases respectively over a four year period, representing 8.1% (95% CLs, 1.7-21.9), and 20.0% (95% CLs, 6.8-40.7) of their MDR-TB cases. Eight countries conducting routine surveillance detected between one and two cases of XDR-TB over a four year period. Australia, France, Ireland, the Netherlands, Slovenia, Sweden reported one case, and Israel and Romania reported 2 cases during this time period. Aragon, Spain reported one case in 2005. Eight countries reported no XDR-TB cases over a four year period (Belgium, Croatia, Denmark, Norway, Poland, Switzerland, Singapore, and the United Kingdom). Canada, China, Macao, SAR, and Galicia, Spain, and New Zealand also reported no cases, but the reporting period was only one year. Of the countries conducting surveys; the proportion of XDR-TB among MDR-TB ranged from 0.0% in Rwanda and Tanzania to 12.8% (95% CLs, 9.8-16.3) or 55/431 in Baku, Azerbaijan, and 15.0% (95% CLs, 3.2-37.9), or 3/20 in Donetsk Oblast, Ukraine. Table 4: indicates the country, the source of the data, the number of MDR-TB cases tested, the years in which data were reported and the confidence intervals.

TABLE 4: COUNTRIES REPORTING DATA ON XDR-TB 2002-2007

Country	Source	Region	Year	Method	MDR	MDR tested	FLQ	FLQ%	lower CI	upper CI	XDR	XDR%	lower CI	upper CI
Representative survey or surveillance data														
Japan	Global Project, SRL Japan	WPR	2002	sentinel	60	55	21	38.2			17	30.9		
Estonia	EuroTB	EEUR	2003-2006	surveillance	248	245		0.0			58	23.7		
Latvia	Global Project	EEUR	2003-2006	surveillance	712	688		0.0			53	7.7		
Tomsk Oblast, RF	Global Project, SRL Boston, USA	EEUR	2003-2005	surveillance	468	458	33	7.2			30	6.6		
Lithuania	EuroTB	EEUR	2003-2006	surveillance	656	173		0.0			25	14.5		
USA	National Tuberculosis Surveillance System	AMR	2000-2006	surveillance	925	601	55	9.2			18	3.0		
Hong Kong SAR, China	Global Project, SRL Hong Kong, SAR	WPR	2005	surveillance	41	41	12	29.3			6	14.6		
Czech Republic	EuroTB	EUR	2003-2006	surveillance	38	25		0.0			5	20.0		
Spain, Barcelona	Global Project, SRL Spain	EUR	2002-2005	surveillance	43	37	4	10.8			3	8.1		
Romania	EuroTB	EUR	2003-2006	surveillance	50	44		0.0			2	4.5		
Israel	EuroTB	EUR	2003-2006	surveillance	45	44		0.0			2	4.5		
Ireland	EuroTB	EUR	2003-2006	surveillance	8	3		0.0			1	33.3		
Slovenia	EuroTB	EUR	2003-2007	surveillance	3	3		0.0			1	33.3		
Sweden	EuroTB	EUR	2003-2006	surveillance		18		0.0			1	5.6		
Netherlands	EuroTB	EUR	2003-2006	surveillance	34	33		0.0			1	3.0		
France	EuroTB	EUR	2003-2006	surveillance	152	149		0.0			1	0.7		
Australia	Global Project, SRLs Australia	WPR	2002-2005	surveillance	43	43	4	9.3			1	2.3		
Canada	Global Project	AMR	2005	surveillance	23	23	0	0.0			0	0.0		
UK	EuroTB	EUR	2003-2006	surveillance	174	62		0.0			0	0.0		
Belgium	EuroTB	EUR	2003-2006	surveillance	31	12		0.0			0	0.0		
Switzerland	EuroTB	EUR	2003-2006	surveillance	25	22		0.0			0	0.0		
Poland	EuroTB	EUR	2003-2006	surveillance	17	6		0.0			0	0.0		
Norway	EuroTB	EUR	2003-2006	surveillance	11	11		0.0			0	0.0		
Croatia	EuroTB	EUR	2003-2006	surveillance	5	1		0.0			0	0.0		
Denmark	EuroTB	EUR	2003-2006	surveillance	5	5		0.0			0	0.0		
Singapore	Global Project	WPR	2002-2005	surveillance	14	14	1	7.1			0	0.0		
Macao SAR, China	Global Project	WPR	2005	surveillance	9	9	1	11.1			0	0.0		
New Zealand	Global Project	WPR	2005	surveillance	4	4	2	50.0			0	0.0		
Spain, Galicia	Global Project	EUR	2006	surveillance	2	2	0	0.0			0	0.0		
Baku, Azerbaijan	Global Project, SRL Borstel, Germany	EEUR	2007	survey	431	431	125	29.0	24.8	33.5	55	12.8	9.8	16.3
Armenia	Global Project, SRL Borstel, Germany	EEUR	2007	survey	199	199	15	7.5	4.3	12.1	8	4.0	1.8	7.8
Donetsk, Ukraine	Global Project, SRL Gauting, Germany	EEUR	2006	survey	379	20	3	15.0	3.2	37.9	3	15.0	3.2	37.9
Georgia	Global Project, SRL Belgium	EEUR	2006	survey	105	70	3	4.3	0.9	12.0	3	4.3	0.9	12.0
Republic of Moldova	Global Project, SRL Borstel, Germany	EUR	2006	survey	203	47	11	23.4	12.3	38.0	3	6.4	1.3	17.5
Argentina	Global Project, SRL Argentina	AMR	2005	survey	36	36	3	8.3	1.8	22.5	2	5.6	0.7	18.7
Republic of Korea	Global Project	WPR	2004	survey	110	110	13	11.8	0.1	19.3	2	1.8	0.0	6.4
Spain, Aragon	Global Project	EUR	2005	survey	4	4	1	25.0	0.6	80.6	1	25.0	0.6	80.6
Rwanda	Global Project, SRL Belgium	AFR	2005	survey	32	32	3	9.4	2.0	25.0	0	0.0	0.0	8.9
UR Tanzania	Global Project, SRL Belgium	AFR	2007	survey	6	6	0	0.0	0.0	39.3	0	0.0	0.0	39.3
Routine laboratory data (non nationally representative)														
South Africa	National Health Laboratory System	AFR	2004-2007	retrospective review		17615		0.0	0.0	0.0	996	5.7	5.3	6.0
Risk groups and MDR-TB treatment programmes														
Philippines	Global Project, GLC program	WPR	2005-2006	Confirmed MDR for Tx	293	149	50.9	45.0	56.7		10	3.4	1.6	6.2
DR Congo, Kinshasa	Global Project, SRL Belgium	AFR	2006-2007	Selection of CatII failures	59	1	1.7	0.0	9.1		0	0.0	0.0	5.0
Burundi	Global Project, SRL Belgium	AFR	2006-2007	Selection of CatII failures	23	0	0.0	0.0	12.2		0	0.0	0.0	12.2
Myanmar	Global Project, SRL Belgium	SEAR	2007	Selection of CatII failures	43	4	9.3	2.6	22.1		0	0.0	0.0	6.7
Bangladesh	Global Project, Damien Foundation, SRL Belgium	SEAR	2003-2006	Retreatment	300	31	10.3	7.1	14.3		3	1.0	0.2	2.9
Countries reporting at least one case														
Brazil	(1)	AMR												
Chile	(1)	AMR												
Ecuador	(1)	AMR												
Germany	(1)	EUR												
Iran	(2)	EMR												
Italy	(3)	EUR												
Peru	(1)	AMR												
Portugal	(1)	EUR												
Vietnam	NTP report	WPR												
Mozambique	NTP report	AFR												
India	(4)	SEAR												
Thailand	NTP report	SEAR												
Mexico	(1)	SEAR												
UK*	(1)	EUR												
Poland*	NTP report	EUR												
Norway*	NTP report	EUR												
Canada*	NTP report	AMR												
Botswana	NTP report	AFR												
Nepal	NTP report	SEAR												

* one case reported outside of surveillance data reported to EuroTB

- Emergence of Mycobacterium tuberculosis with Extensive Resistance to Second-Line Drugs – Worldwide, 2000–2004. MMWR 2006;55:301-305
- Masjedi MR, Farnia P, Sorooch S, et al. Extensively drug-resistant tuberculosis: 2 years of surveillance in Iran. Clin Infect Dis 2006;43(7):841-7.
- Migliori GB, Ortmann J, Girardi E, et al. Extensively drug-resistant tuberculosis, Italy and Germany. Emerg Infect Dis 2007;13(5):780-2.
- Thomas A, Ramachandran R, Rehaman F, et al. Management of multi drug resistance tuberculosis in the field: Tuberculosis Research Centre experience. Indian J Tuberc 2007;54(3):117-24.

DATA REPORTED TO THE GLOBAL PROJECT 1994-2007 AND ESTIMATED GLOBAL AND REGIONAL MEANS OF RESISTANCE.

Since the start of the Global Project in 1994 data have been collected from 138 settings in 114 countries and 2 SARs of China worldwide. In order to estimate the global and regional means of resistance and to examine the distribution of resistance within a region we have included data since the beginning of the project and weighted them by the population they represent. Twenty countries reported data before the year 2000. Data from these 114 countries and 2 SARs of China represent 48% of the world's population and 46% of the total TB burden. Table 5: below describes global and regional population coverage. The population weighted means described in table 6 and shown in figures 14, 15, 16 and 17, correspond to these figures.

TABLE 5: POPULATION COVERAGE OF DRUG RESISTANCE DATA REPORTED TO WHO 1994-2007.

	Total population	Total TB cases	Total ss+ TB cases	Total retreatment TB cases	Number of countries
AFR	370,004,932 50%	908,305 72%	360,124 65%	106,025 84%	22
AMR	854,140,969 96%	222,731 93%	114,815 92%	21,725 96%	21
EMR	208,660,622 39%	58,023 22%	26,483 23%	1,581 14%	8
EEU	66,639,802 21%	99,990 29%	30,855 44%	23,241 31%	13
nonEEU	363,241,951 64%	46,408 55%	13,102 51%	3,694 44%	27
SEAR	318,224,322 19%	450,076 23%	176,448 21%	43,123 17%	6
WPR	929,999,840 53%	724,012 52%	391,784 58%	59,315 36%	19
Global	3,110,912,438 48%	2,509,545 46%	1,113,611 46%	258,704 39%	116 55%

TABLE 6: WEIGHTED MEAN OF RESISTANCE TO FIRST-LINE ANTI-TB DRUG BY TREATMENT HISTORY AND BY WHO REGION, 1994-2007.

Global	New	Previous	Combined	AFR	New	Previous	Combined	AMR	New	Previous	Combined
Countries	105	94	114	Countries	21	18	22	Countries	19	18	21
Settings	127	109	138	Settings	21	18	22	Settings	19	18	21
Any H	10.3 (8.4-12.1)	27.7 (18.7-36.7)	13.3 (10.9-15.8)	Any H	6.7 (5.2-8.1)	16.9 (8.8-25.0)	8.3 (6.8-9.9)	Any H	7.9 (5.6-10.3)	20.1 (9.4-30.7)	9.9 (7.0-12.9)
Any R	3.7 (2.8-4.5)	17.5 (11.1-23.9)	6.3 (4.7-7.8)	Any R	1.9 (1.2-2.6)	6.7 (4.4-9.0)	2.7 (1.6-3.8)	Any R	3.2 (1.0-5.4)	16.4 (4.5-28.2)	5.3 (2.2-8.3)
Any S	10.9 (8.0-13.7)	20.1 (12.2-28.0)	12.6 (9.3-16.0)	Any S	6.9 (2.2-11.6)	9.7 (6.3-13.2)	8.3 (2.6-14.1)	Any S	9.0 (3.1-14.9)	14.9 (2.8-27.1)	9.6 (3.5-15.6)
Any E	2.5 (1.7-3.2)	10.3 (5.0-15.6)	3.9 (2.6-5.2)	Any E	1.3 (0.6-2.0)	3.5 (1.8-5.1)	2.0 (0.9-3.0)	Any E	1.5 (0.2-2.8)	5.2 (0.0-10.8)	2.0 (0.2-3.9)
Any res.	17.0 (13.6-20.4)	35.0 (24.1-45.8)	20.0 (16.1-23.9)	Any res.	11.4 (6.4-16.5)	21.4 (12.5-30.3)	13.8 (8.0-19.5)	Any res.	14.9 (8.4-21.4)	28.1 (12.4-43.7)	16.7 (9.9-23.4)
MDR	2.9 (2.2-3.6)	15.3 (9.6-21.0)	5.3 (3.9-6.6)	MDR	1.5 (1.0-2.0)	5.8 (3.9-7.7)	2.2 (1.4-3.1)	MDR	2.2 (0.6-3.8)	13.2 (3.5-22.8)	4.0 (1.7-6.3)

EMR	New	Previous	Combined	EEUR	New	Previous	Combined	nonEUR	New	Previous	Combined
Countries	7	7	8	Countries	13	13	13	Countries	27	24	27
Settings	7	7	8	Settings	16	15	16	Settings	28	25	29
Any H	6.3 (2.5-10.1)	40.3 (19.8-60.8)	9.9 (3.2-16.7)	Any H	25.6 (9.5-41.8)	52.2 (30.4-74.0)	38.3 (18.9-57.6)	Any H	5.2 (4.0-6.4)	13.9 (11.0-16.8)	6.2 (5.2-7.2)
Any R	3.3 (0.0-7.3)	41.7 (18.3-65.1)	7.2 (0.0-15.1)	Any R	11.4 (5.6-17.1)	40.9 (13.8-68.0)	24.7 (10.1-39.2)	Any R	1.1 (0.7-1.5)	8.9 (6.8-11.0)	1.9 (1.4-2.3)
Any S	10.1 (0.8-19.5)	42.2 (21.7-62.8)	13.3 (1.5-25.1)	Any S	28.8 (8.5-49.0)	52.6 (20.7-84.6)	40.7 (15.7-65.6)	Any S	4.0 (1.9-6.0)	9.7 (5.6-13.8)	4.4 (2.1-6.7)
Any E	1.9 (0.0-4.5)	26.2 (12.0-40.3)	4.2 (0.0-9.2)	Any E	10.4 (0.9-20.0)	31.2 (6.7-55.8)	19.7 (3.7-35.7)	Any E	0.7 (0.3-1.1)	3.9 (2.0-5.8)	1.0 (0.5-1.6)
Any res.	13.7 (1.3-26.1)	54.4 (26.5-82.3)	17.6 (2.3-33.0)	Any res.	35.8 (15.8-55.7)	62.8 (35.6-90.1)	48.8 (25.3-72.2)	Any res.	7.9 (5.9-10.0)	17.8 (14.4-21.3)	8.9 (7.2-10.7)
MDR	2.0 (0.0-4.3)	35.3 (16.4-54.3)	5.4 (0.5-10.4)	MDR	10.0 (3.8-16.1)	37.7 (12.3-63.0)	22.6 (8.6-36.6)	MDR	0.9 (0.5-1.2)	7.7 (5.7-9.8)	1.5 (1.1-2.0)

SEAR	New	Previous	Combined	WPR	New	Previous	Combined
Countries	6	5	6	Countries	12	9	17
Settings	13	6	14	Settings	23	20	28
Any H	10.3 (6.9-13.7)	36.8 (26.7-47.0)	15.7 (10.5-20.9)	Any H	13.3 (10.6-16.0)	34.9 (28.3-41.4)	16.5 (13.3-19.6)
Any R	3.4 (2.4-4.4)	19.3 (14.1-24.5)	6.9 (4.8-9.0)	Any R	5.0 (3.4-6.6)	26.6 (20.2-32.9)	8.3 (5.7-11.0)
Any S	8.9 (5.9-11.8)	21.7 (13.3-30.2)	11.7 (7.5-16.0)	Any S	14.6 (10.2-19.0)	26.3 (17.2-35.4)	16.2 (11.0-21.2)
Any E	3.0 (0.7-5.4)	13.8 (0.3-27.3)	4.7 (2.2-7.2)	Any E	3.0 (2.0-4.0)	13.8 (10.2-17.3)	4.5 (3.3-5.8)
Any res.	15.8 (11.6-20.0)	42.3 (32.3-52.3)	20.8 (14.2-27.4)	Any res.	22.0 (17.3-26.8)	46.5 (37.7-55.2)	25.3 (19.9-30.7)
MDR	2.8 (1.9-3.6)	18.8 (13.3-24.3)	6.3 (4.2-8.4)	MDR	3.9 (2.6-5.2)	21.6 (16.8-26.4)	6.7 (4.6-8.8)

95% CLs are given between brackets

The weighted mean of resistance to individual drugs varied across WHO regions with the proportion of resistance to every drug, as well as MDR-TB, highest in Eastern Europe and lowest in Africa and Western and Central Europe. The global weighted mean of MDR was 2.9% (95% CLs, 2.2-3.6) among new cases, 15.3% (95% CLs, 9.6-21.0) among previously treated cases and 5.3%(95% CLs, 3.9-6.7) among all TB cases.

Table 6: The relationship between resistance to specific drugs across regions and by history of previous treatment was similar with the highest proportions of resistance to isoniazid and streptomycin followed by rifampicin and ethambutol. This was true for all regions without

regard to treatment history with the exception of previously treated cases in the Eastern Mediterranean region where rifampicin resistance was higher than isoniazid resistance. Figures 18, 19, and 20 shows the distribution of proportions of MDR-TB, any resistance, and isoniazid resistance among combined cases within region .

FIGURE 14: WEIGHTED MEAN OF RESISTANCE TO SPECIFIC DRUGS AMONG NEW CASES, BY WHO REGION, 1994-2007

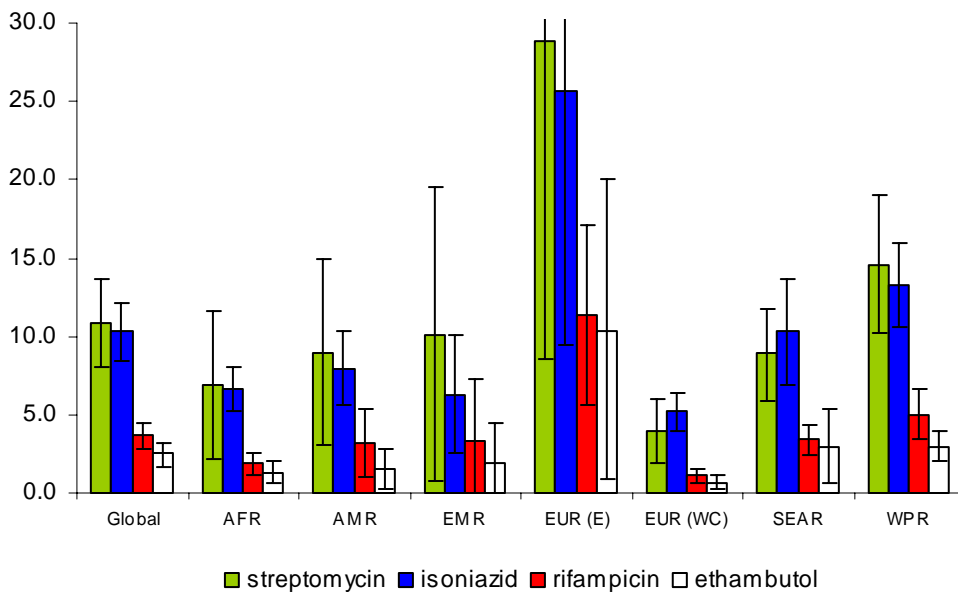


FIGURE 15: WEIGHTED MEAN OF RESISTANCE TO SPECIFIC DRUGS AMONG PREVIOUSLY TREATED CASES, BY WHO REGION, 1994-2007

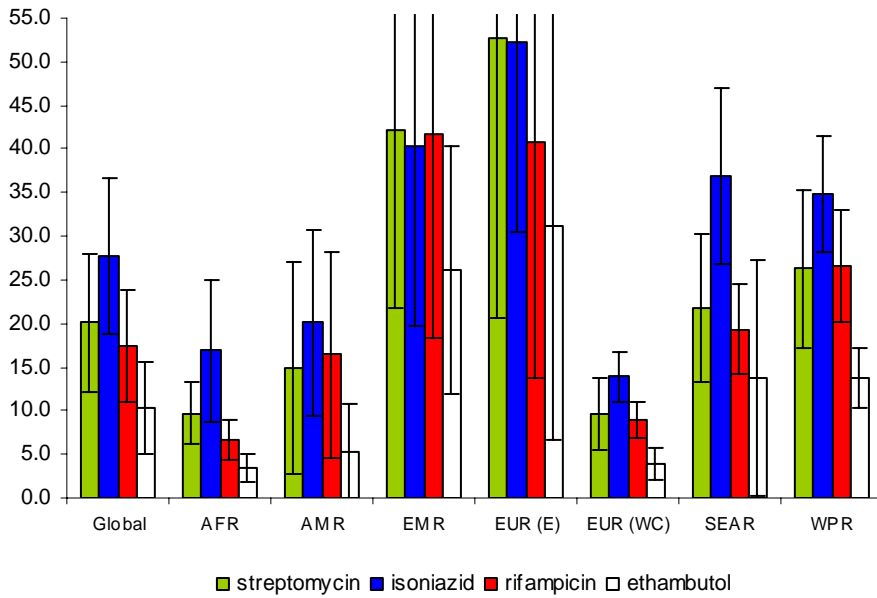


FIGURE 16: WEIGHTED MEAN OF RESISTANCE TO SPECIFIC DRUGS AMONG ALL TB CASES TREATED CASES, BY WHO REGION, 1994-2007

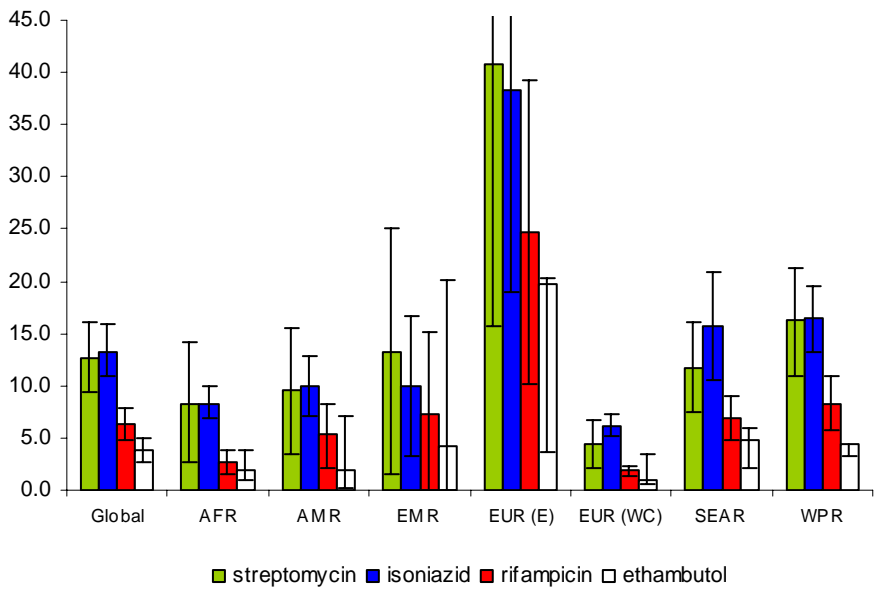
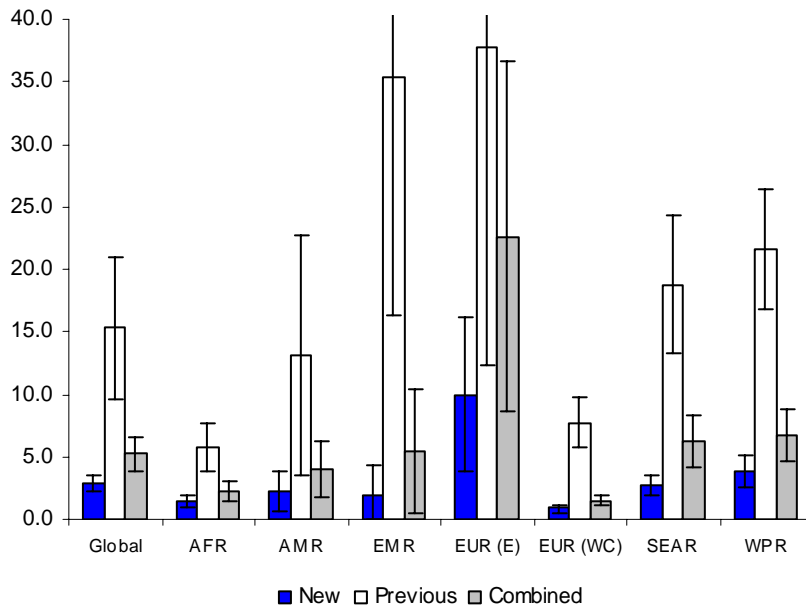


FIGURE 17: WEIGHTED MEAN OF MDR-TB AMONG NEW, PREVIOUS TREATED AND COMBINED TB CASES BY WHO REGION, 1994-2007



A box plot is one way of graphically depicting groups of numerical data through their five-number summaries (the smallest observation, lower quartile (Q1), median, upper quartile (Q3), and largest observation). A box plot also indicates which observations, if any, might be considered outliers. Outliers may present valuable information about epidemiological clues or data validity. Box plots are able to visually show different types of populations, without making any assumptions of the underlying statistical distribution. The spacings between the different parts of the box help indicate variance, skewness and identify outliers. Figure 18 shows the distribution of MDR within regions. The widest distribution in the Eastern European region, while the narrowest distribution is found in central and western Europe and the African region. Box plots in figures 19 and 20, showing the distribution of any resistance and isoniazid resistance also show the widest distribution in the Eastern European region; and the narrowest distribution found in Central and Western Europe and in Africa, although not as narrow as the distribution of MDR-TB.

FIGURE 18: BOX PLOT DISTRIBUTION OF MDR-TB AMONG COMBINED TB CASES BY WHO REGION, 1994-2007

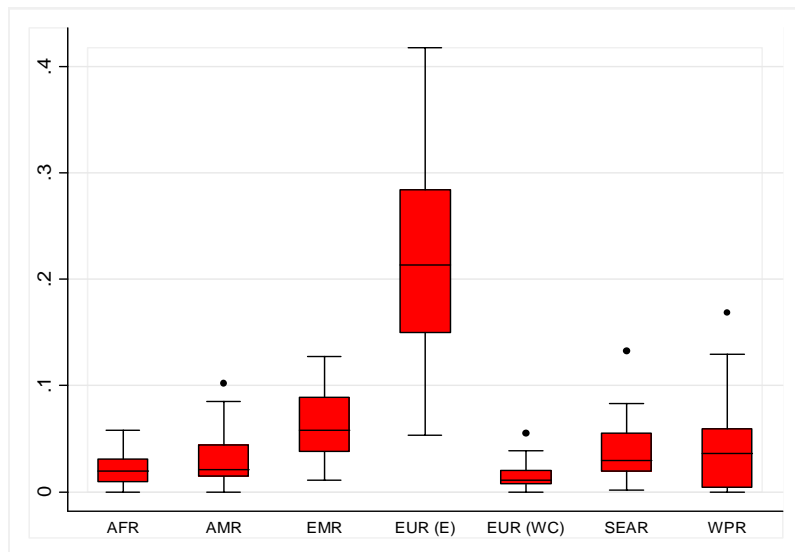


FIGURE 19: BOX PLOT DISTRIBUTION OF ANY RESISTANCE AMONG COMBINED TB CASES BY WHO REGION, 1994-2007

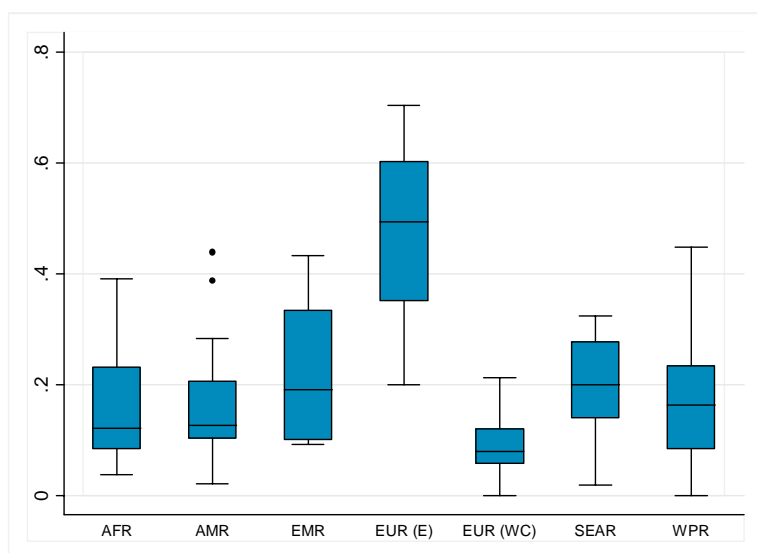
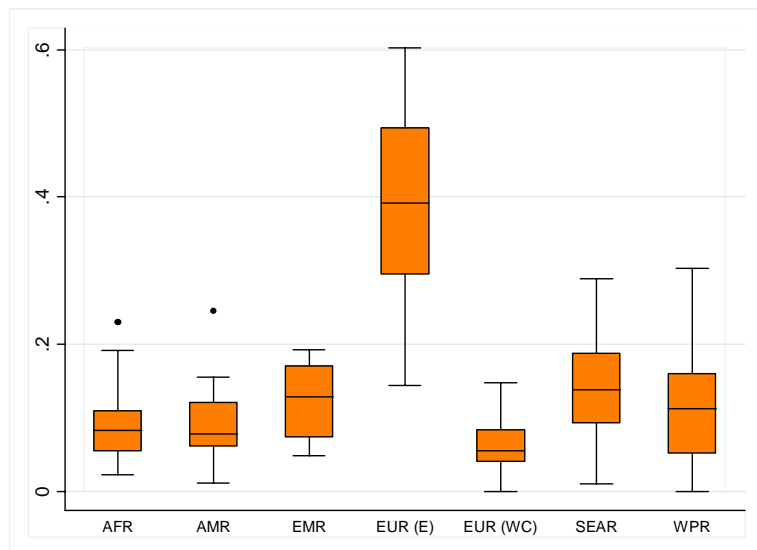


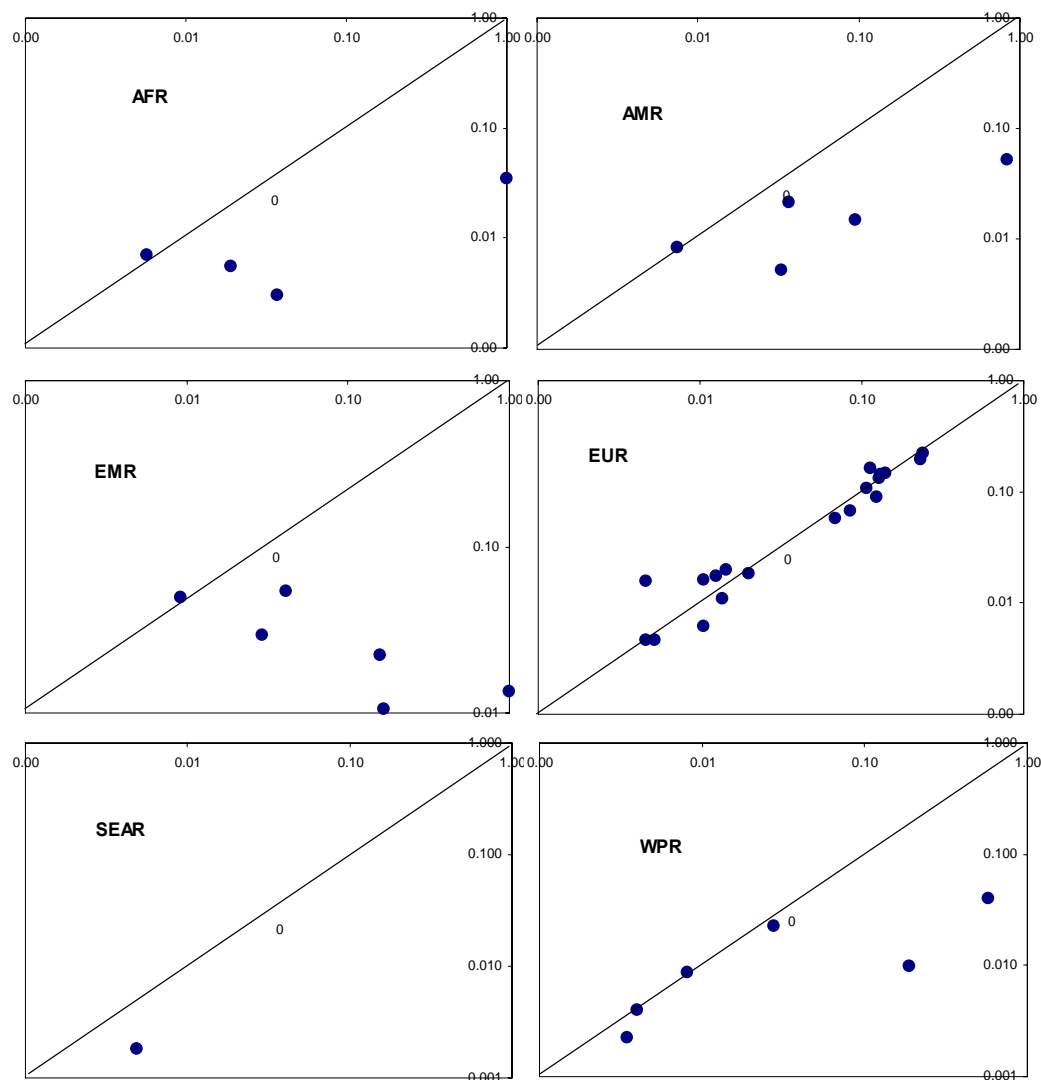
FIGURE 20: BOX PLOT DISTRIBUTION OF ANY RESISTANCE TO INH AMONG COMBINED TB CASES BY WHO REGION, 1994-2007



Correlation between MDR cases in national registers and survey data

The proportion of MDR-TB reported in national registers of cases receiving DST were compared to the proportion of MDR estimated through surveys. This was done to examine whether routine data can be used to estimate the proportion of MDR-TB in the population. The only WHO region that was significantly correlated was the European region suggesting that estimations of MDR-TB are either based on routine data already, or can be in the future. Other regions are not routinely testing for MDR-TB, and in these regions surveys will continue to play an important role in estimating the MDR-TB burden.

FIGURE 21: CORRELATION OF DRUG RESISTANCE SURVEY DATA WITH ROUTINE NOTIFICATION OF MDR-TB.



DYNAMICS OF DRUG RESISTANCE OVER TIME (1994-2007)

The Global Project has collected data from 114 countries and 2 SARs of China. The following analysis includes data from all global reports, as well as data provided between the publication of reports. It thus reflects both published and previously unpublished data. This analysis is limited to countries reporting three data points or more. Trend information on MDR-TB and resistance to any drug are available for countries reporting more than one year of information in Annexes 6 and 7. Fifty countries have reported three or more years of data, eight countries have reported on two years and fifty eight countries have reported baseline data only. In countries conducting surveillance on all TB cases trends are reported on both new and combined cases. In settings

conducting surveys trends are reported on new cases only. Proportions of MDR-TB, isoniazid resistance, and any resistance were examined.

TABLE 7: DATA POINTS AVAILABLE FOR TREND ANALYSIS BY WHO REGION, 1994-2007

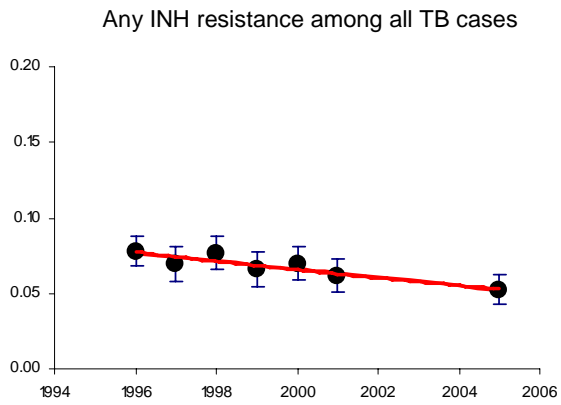
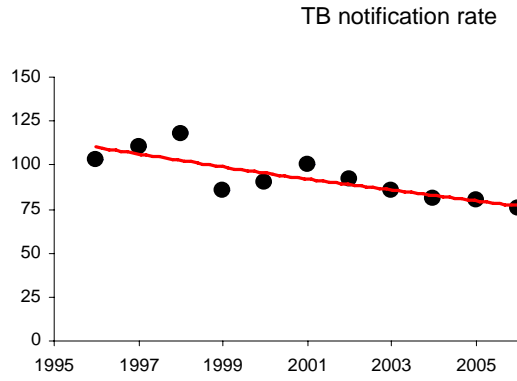
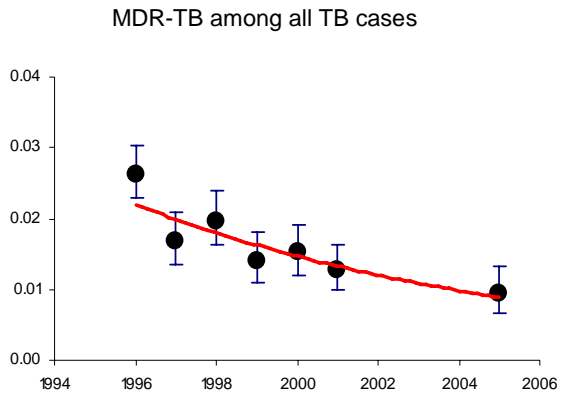
WHO region	Number of data points			Total
	1	2	≥3	
Africa	19	2	1	22
Americas	12	3	6	21
Eastern Mediterranean	6	0	2	8
Europe	9	1	30	40
South East Asia	4	0	2	6
Western Pacific	8	2	9	19
	58	8	50	116

Numbers and proportions of any resistant and MDR-TB for new and combined cases for all settings reporting two data points or more are available in annexes 6 and 7.

Declining trends in resistance

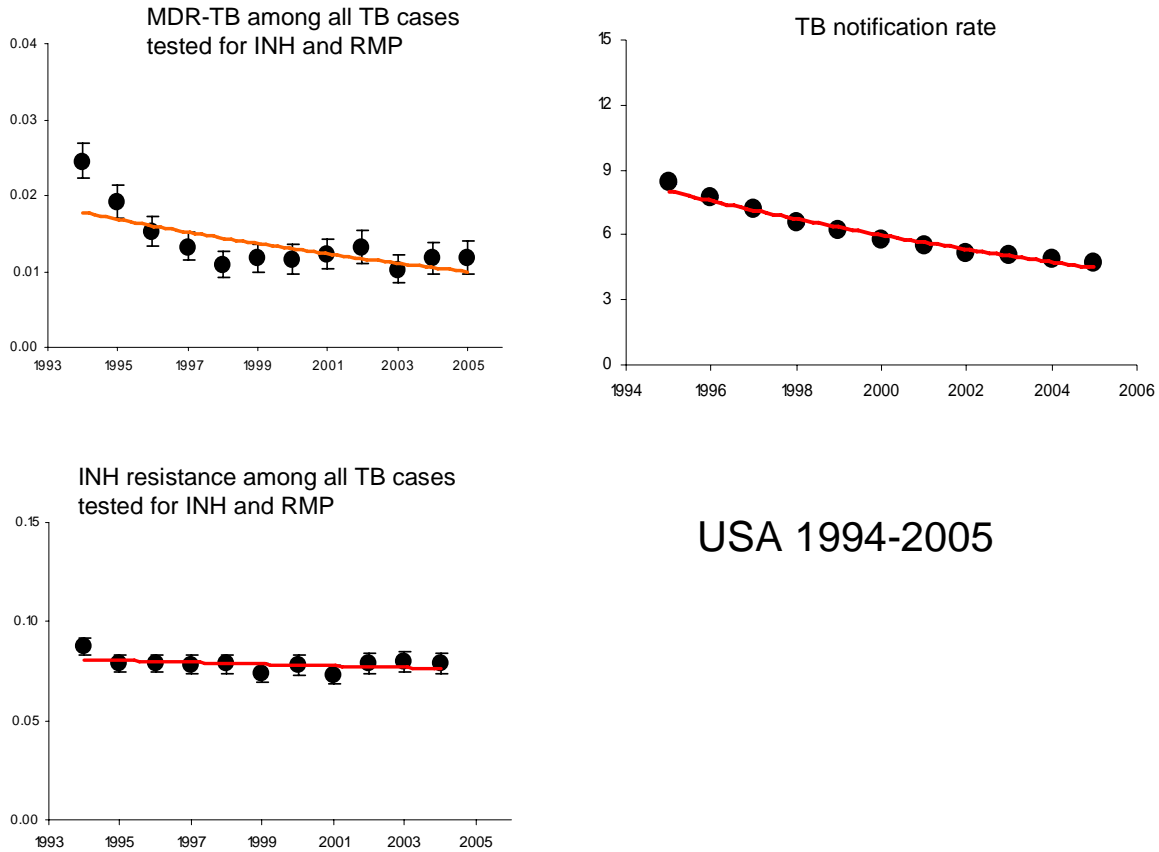
The USA and Hong Kong, SAR, China reported significant decreasing trends MDR-TB among all TB cases. Hong Kong, SAR, China also showed significant decreases in any resistance among all cases and isoniazid resistance and MDR-TB among new cases. Both countries report declining TB notifications. Denmark showed significant declines in any drug resistance in both new and combined TB cases. Puerto Rico showed declining trends in any resistance and MDR-TB among combined cases. Singapore showed a significant decrease in prevalence of MDR-TB among all TB cases; however numbers were very small.

FIGURE 22: HONG KONG, SAR, CHINA 1994-2005



Hong Kong, SAR 1995-2005

FIGURE 23: USA, 1994-2005



Stable trends in resistance

Several countries are showing either stable proportion of resistance over time or stable absolute numbers of cases. Many low TB prevalence countries may show fluctuating trends in prevalence of resistance because their overall burden of TB is low; however most of these countries report small absolute numbers of MDR-TB per year, figure 24.

Countries of the Baltic region (Estonia, Latvia, and Lithuania) are showing relatively stable trends in MDR-TB among new cases, with a slow but significant increase in MDR-TB among new cases in Lithuania. The proportion of resistance remains high in these countries, ranging from 9.8% (CLs, 8.2-11.7) in Lithuania to 13.2% (CLs, 9.7-17.5) in Estonia. These trends in MDR-TB are coupled with declining TB notification rates in all three countries. Estonia has

shown the most rapid decline at about 8% per year, where the TB notification rate has declined from 59 to 31 per 100 000 between 1998 and 2006. Latvia has shown a decline of about 6% per year, from 91 TB cases per 100 000 in 1998 to 56 cases in 2006. The notification rate in Lithuania has declined at a slower rate of just under 5.0% per year, from 79 per 100 000 in 1999 to 56 per 100 000 in 2006.

FIGURE 24: ABSOLUTE NUMBERS AND PROPORTIONS OF MDR-TB AMONG LOW TB PREVALENCE COUNTRIES, 1994-2007

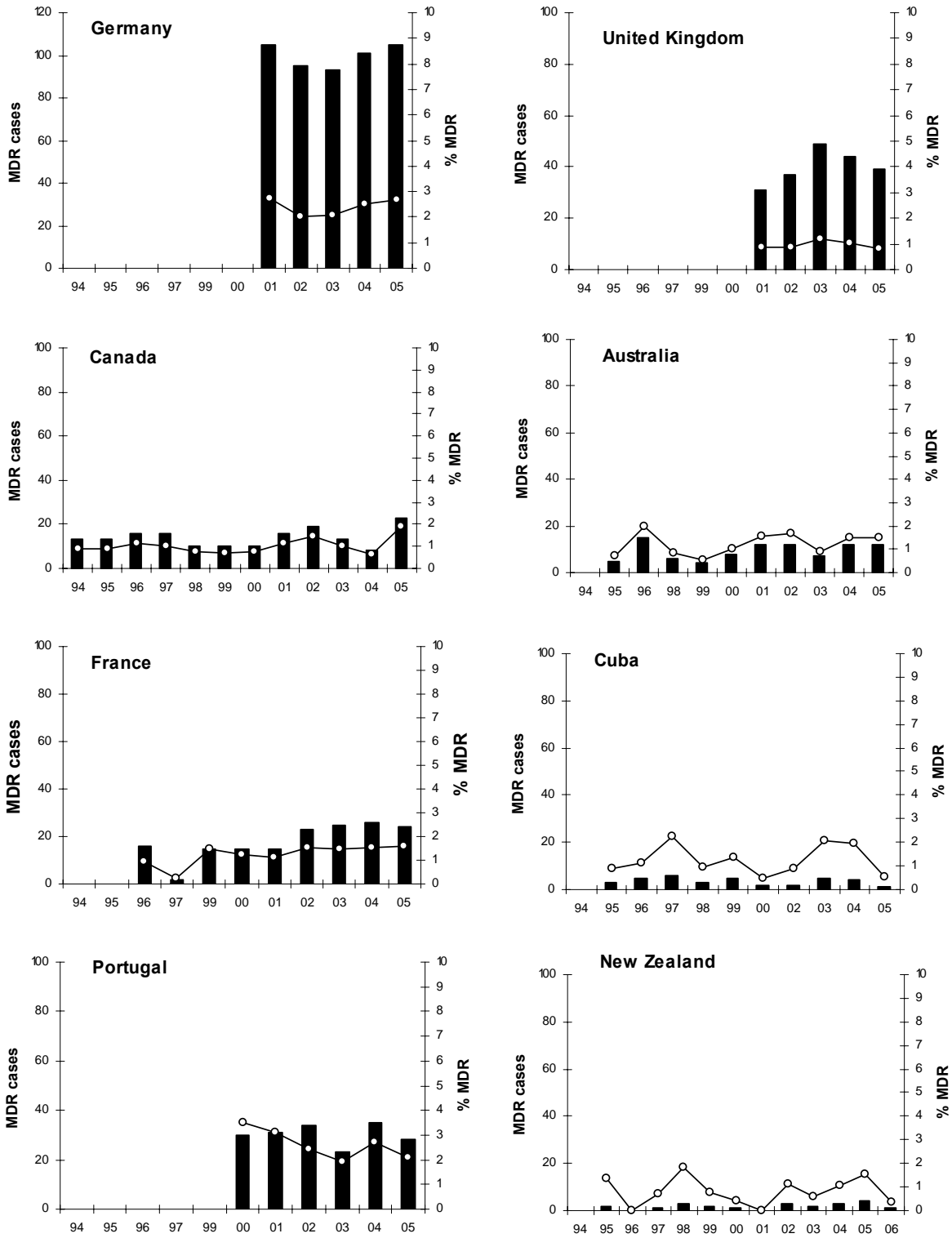
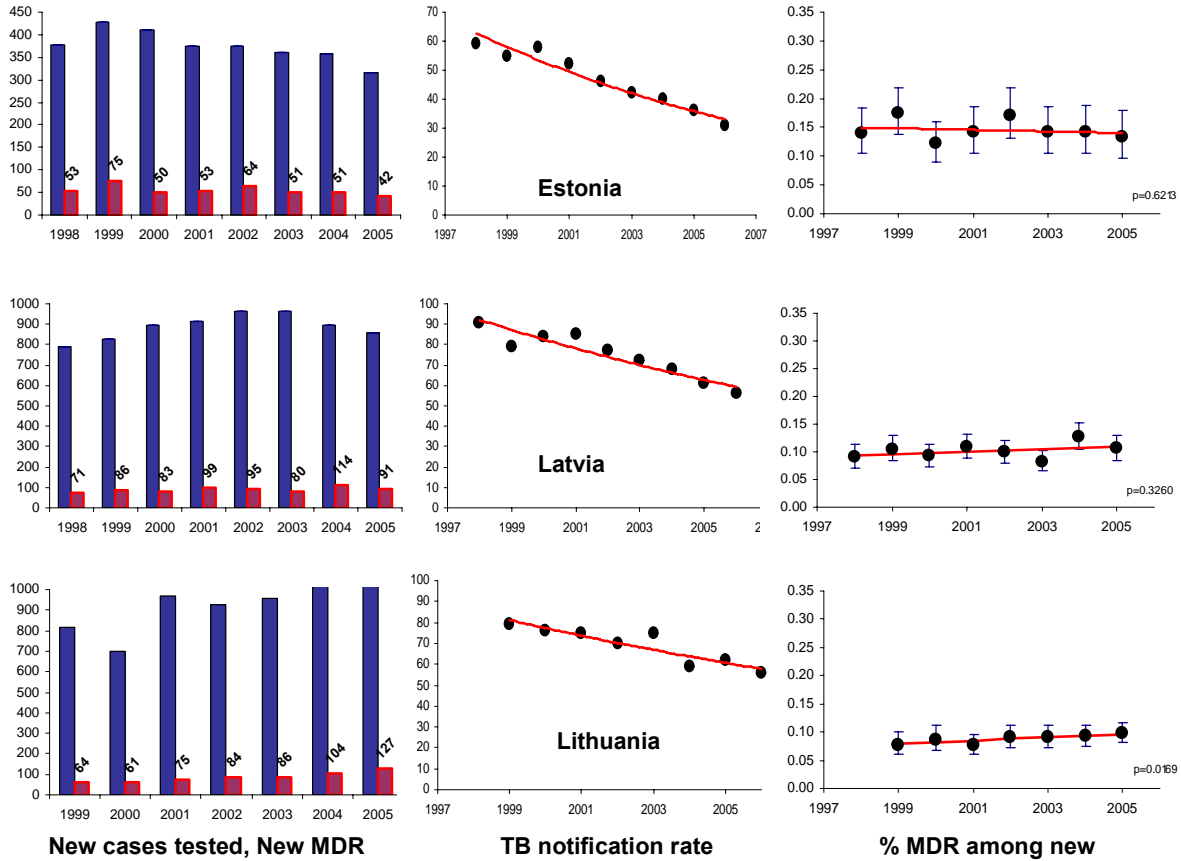


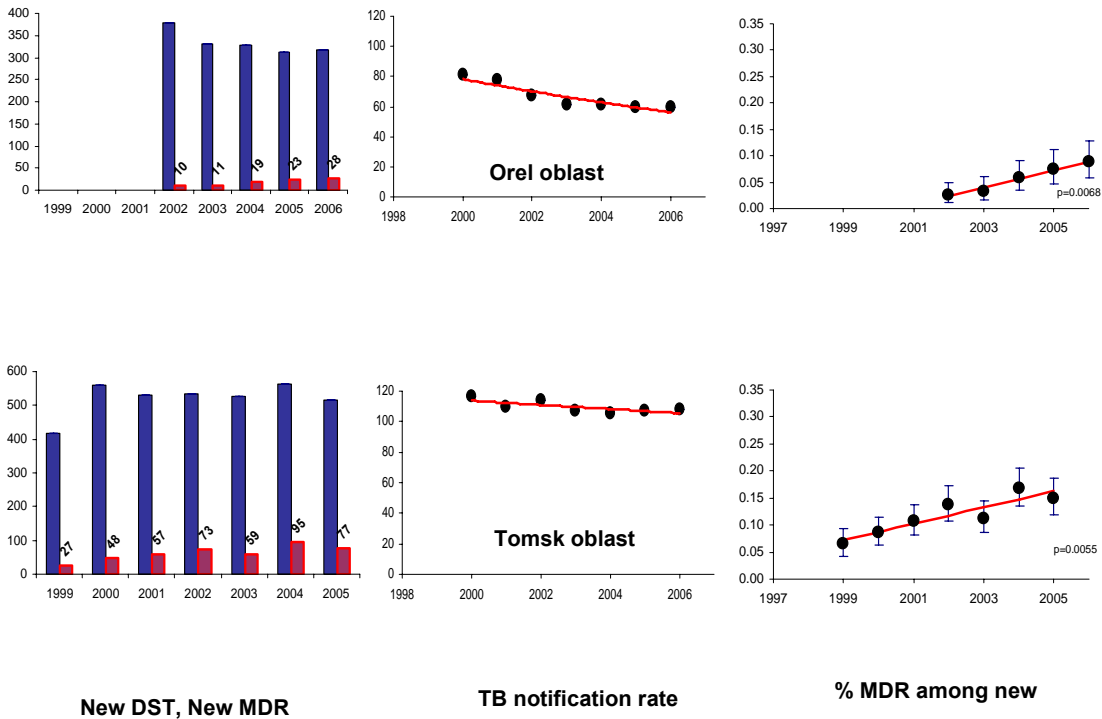
FIGURE 25: ABSOLUTE NUMBERS AND PROPORTIONS OF MDR-TB AMONG NEW TB CASES IN THE BALTIC COUNTRIES, 1997-2007



Increasing trends in resistance

In contrast, to the stable proportions of MDR reported among new cases in the Baltic countries, data reported to the global project from Orel and Tomsk Oblasts of the Russian Federation indicate statistically significant increases in the proportion of MDR among new TB cases as well as increases in absolute numbers of cases. Both regions showed increases in isoniazid resistance though neither were statistically significant. Both regions are showing a slowly declining TB notification rate. In Orel Oblast the TB notification rate has declined from 81 to 59 per 100 000 between 2000 and 2006, over 3% per year. Tomsk Oblast showed a steady decline by 1.3% per year from 117 to 108 per 100 000 between 2000 and 2006. During this same time period TB notification rates for the whole of the Russian Federation have remained stable.

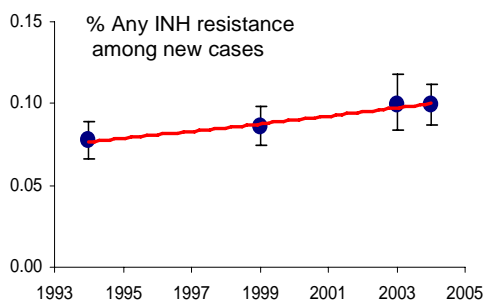
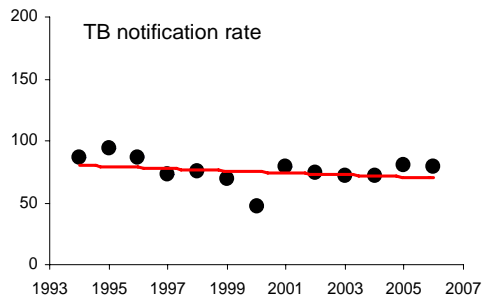
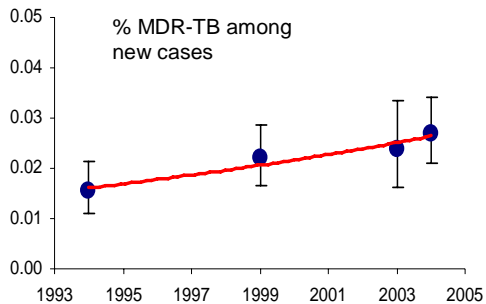
FIGURE 26: ABSOLUTE NUMBERS AND PROPORTIONS OF MDR-TB AMONG NEW TB CASES IN OBLASTS OF THE RUSSIAN FEDERATION, 1997-2007



The Republic of Korea and Peru have shown increasing trends in MDR-TB, Any resistance and isoniazid resistance among new cases. Note that in Peru and the Republic of Korea data from three and four periodic surveys have been reported respectively and confidence intervals are wide, but nevertheless increases in isoniazid and any resistance were found to be statistically significant in both settings²¹. The increase in MDR-TB was statistically significant in the Republic of Korea. The Republic of Korea has shown a steadily declining TB notification rate from 1994 until 2003. From 2004 the TB notification rate has increased slowly; however this is likely due to expansion of the national surveillance system into the private sector. Similarly in Peru the notification rate dropped from 172 per 100 000 in 1996 to 117 in 2003. From 2004 through 2006 the notification rate has stayed between 123 and 124 per 100 000.

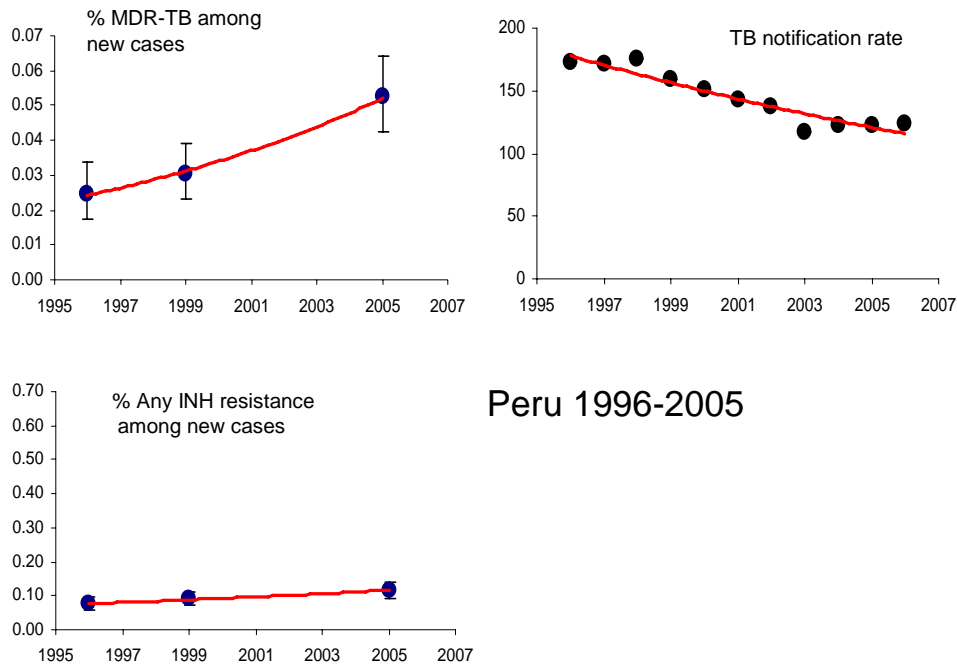
²¹ At the time of this report Peru had not completed rechecking of laboratory results.

FIGURE 27: THE REPUBLIC OF KOREA, 1996-2005



The Republic of Korea
1994-2005

FIGURE 28: PERU, 1996-2005



GLOBAL ESTIMATES OF MDR-TB

Based on drug resistance data reported from 114 countries and 2 SARs of China, we used a model to estimate the proportion of MDR-TB among new, previously treated, and combined TB cases for a further 69 countries and to develop a global estimated burden of incident MDR-TB cases.

New cases

The total number of MDR-TB cases estimated to have occurred in 2006 among newly diagnosed TB cases was 285,718 (95% CLs, 256,072-399,224), or 3.1% (95% CLs, 2.9-4.3) of the total number of new TB cases estimated in 2006 in the 175 countries (9,123,922). The numbers and proportions of MDR-TB among new cases by country are given in annex 8.

Previously treated cases

The total number of MDR-TB cases among previously treated cases was estimated to be 203,230 (95% CLs, 172,935-242,177) or 19.3% (95% CLs, 18.2-21.3) of the estimated number of

previously treated cases in 2006 in the 175 countries (1,052,145). Annex 9 gives the numbers and proportions of MDR-TB among previously treated cases by country.

Total cases

The global estimated number of incident MDR-TB cases in 2006 is 489,139 (95% CLs, 455,093-614,215) which is 4.8% (95% CLs, 4.6-6.0) of the total number of estimated incident TB cases in 2006 in 185 countries (10,229,315)²². Two high TB burden countries, China and India, are estimated to have 240,680 cases (95% CLs, 177,608-307,286) which together account for 50% of all estimated incident cases of MDR-TB. The distribution of all MDR-TB cases by country can be found in annex 10. The numbers and proportions of MDR-TB among new, previously treated, and all TB cases by epidemiological region can be found in annex 11.

Table 8. ESTIMATED NUMBERS AND PROPORTIONS OF MDR-TB AMONG ALL TB CASES BY EPIDEMIOLOGICAL REGION²³.

Regions	No. of All TB cases	No. of MDR TB cases		% MDR TB	Low 95% CL	High 95% CL
		Low 95% CL	High 95% CL			
Established Market Economies	105,795	1,317	1,147	1.2	1.1	1.5
Central Europe	50,502	1,201	623	2.4	1.3	7.2
Eastern Europe	416,316	80,057	71,893	19.2	18.0	22.2
Latin America	349,278	12,070	10,523	3.5	3.0	4.4
Eastern Mediterranean Region	601,225	25,475	15,737	4.2	2.6	11.9
Africa low HIV incidence	375,801	8,415	6,889	2.2	1.9	5.0
Africa high HIV incidence	2,656,422	58,296	48,718	2.2	1.9	4.5
South-east Asia	3,464,313	149,615	114,780	4.3	3.5	6.2
Western Pacific Region	2,173,333	152,694	119,886	7.0	6.1	8.1
Surveyed countries	7,953,603	408,325	361,264	5.1	4.7	5.7
Non surveyed countries	2,239,383	80,814	71,684	3.6	3.2	8.4
All countries (n=185)	10,192,986	489,139	455,093	4.8	4.6	6.0

²³ The number of all estimated TB cases, includes estimated retreatment cases.

THE SUPRANATIONAL LABORATORY NETWORK

Performance, as measured by average sensitivity, specificity, efficiency and reproducibility of proficiency testing results, of the Supranational Laboratory Network has been consistently good over the last five years. On average, specificity, sensitivity, efficiency and reproducibility have stayed between 98-100% for isoniazid, and between 98-100% for rifampicin resistance with the exception of round 12 where the average specificity was 97%. Performance for ethambutol and streptomycin testing was generally lower. The average sensitivity for ethambutol ranged from 92-96%. Specificity, efficiency and reproducibility generally stayed between 96-98%, except for round 12 where the average reproducibility was 95%. Sensitivity, specificity, efficiency and reproducibility for streptomycin testing generally stayed between 95-98% with the exception of sensitivity in round 12 which was 92%. Network averages are shown in Table 9. Network averages, while important to consider when looking at the overall performance of the network, disguises variation within the network by round. Table 10 shows the variation within the network for the 13th round of proficiency testing; however, in previous rounds at least one or two labs per round showed sub-optimal performance. It is also important to note that because results are determined judicially that strains with less than 80% concordance within the network are excluded from standard evaluation, however these strains have been examined in subsequent studies to determine the reason for borderline results. In rounds 9, 10, 11, 12 and 13, there were nine, nine, seven, twelve and three strains excluded respectively, or approximately 7% (40/600) of the total strains tested.

Table 9: AVERAGE PERFORMANCE OF .SRL NETWORK LABORATORIES OVER FIVE ROUNDS OF PROFICIENCY TESTING.

	# LABS	isoniazid	rifampicin	ethambutol	streptomycin
SENSITIVITY					
2002 round 9	20	99	100	95	96
2003 round 10	21	100	99	92	97
2004 round 11	23	100	100	96	99
2005 round 12	26	99	98	95	92
2006 round 13	26	100	100	93	98
SPECIFICITY					
2002 round 9	20	99	99	98	97
2003 round 10	21	99	98	99	98
2004 round 11	23	100	100	97	99
2005 round 12	26	98	97	97	95
2006 round 13	26	100	100	98	97
EFFICIENCY					
2002 round 9	20	99	100	96	96
2003 round 10	21	99	99	97	98
2004 round 11	23	100	100	97	99
2005 round 12	26	98	98	97	94
2006 round 13	26	100	100	97	98
REPRODUCIBILITY					
2002 round 9	20	100	100	96	98
2003 round 10	21	99	98	99	98
2004 round 11	23	99	100	97	100
2005 round 12	26	100	98	95	98
2006 round 13	26	100	100	96	97

Table 10. PROFICIENCY TESTING ROUND 13 WITHIN THE SUPRANATIONAL LABORATORY NETWORK.

SUMMARY STATISTICS, DISCORDANT STRAINS EXCLUDED

Round 13

Total participating labs: 26

<u>Method used:</u>	<u>No. of labs</u>
1* Proportion method LJ	14
2* Proportion method agar	3
3* Bactec 460	3
4* Resistance ratio	1
5* Absolute conc.	2
6* MGIT	3

JUDICIAL RESULTS ONLY

ISONIAZID

	No. of labs with results in the range of					Average score
	100%	95-99%	90-94%	80-89%	<80%	
SENSITIVITY	26	0	0	0	0	100%
SPECIFICITY	26	0	0	0	0	100%
PREDICTIVE VALUE RESISTANT	26	0	0	0	0	100%
PREDICTIVE VALUE SUSCEPTIBLE	26	0	0	0	0	100%
EFFICIENCY	26	0	0	0	0	100%
REPRODUCIBILITY	26	0	0	0	0	100%

RIFAMPICIN

	No. of labs with results in the range of					Average score
	100%	95-99%	90-94%	80-89%	<80%	
SENSITIVITY	26	0	0	0	0	100%
SPECIFICITY	24	0	2	0	0	100%
PREDICTIVE VALUE RESISTANT	24	0	2	0	0	99%
PREDICTIVE VALUE SUSCEPTIBLE	26	0	0	0	0	100%
EFFICIENCY	24	2	0	0	0	100%
REPRODUCIBILITY	25	0	1	0	0	100%

STREPTOMYCIN

	No. of labs with results in the range of					Average score
	100%	95-99%	90-94%	80-89%	<80%	
SENSITIVITY	21	0	4	1	0	98%
SPECIFICITY	20	0	4	0	2	97%
PREDICTIVE VALUE RESISTANT	20	0	4	0	2	96%
PREDICTIVE VALUE SUSCEPTIBLE	21	0	5	0	0	99%
EFFICIENCY	15	9	0	2	0	98%
REPRODUCIBILITY	20	0	5	0	1	97%

ETHAMBUTOL

	No. of labs with results in the range of					Average score
	100%	95-99%	90-94%	80-89%	<80%	
SENSITIVITY	18	0	0	5	3	93%
SPECIFICITY	20	5	0	1	0	98%
PREDICTIVE VALUE RESISTANT	20	0	0	5	1	96%
PREDICTIVE VALUE SUSCEPTIBLE	18	5	2	1	0	97%
EFFICIENCY	14	6	4	2	0	97%
REPRODUCIBILITY	17	0	8	0	1	96%

Table 11. LINKS WITHIN THE SUPRANATIONAL LABORATORY NETWORK

Country	WHO region	Laboratory	Routine
Algeria	AFR	Laboratoire de la Tuberculose, Institut Pasteur d'Algérie, Alger, Algeria	Benin, Jordan, Syria Mauritania, Morocco
Argentina	AMR	Mycobacteria Laboratory, National Institute of Infectious Diseases ANLIS "Dr Carlos G. Malbran," Buenos Aires, Argentina	Brazil, Cuba, Paraguay Uruguay, Venezuela
Australia	WPR	Mycobacterium Reference Laboratory, Institute of Medical and Veterinary Science, Adelaide, Australia	Indonesia
Australia	WPR	Queensland Mycobacterium Reference Laboratory, Brisbane, Australia	Eritrea, New Zealand, Kenya
Belgium	EUR	Département de Microbiologie, Unité de Mycobactériologie Institut de Médecine Tropicale, Antwerp, Belgium	Bangladesh, Benin, Brazil, Burundi, Cameroon, DR Congo Rwanda, Senegal, Slovakia, Sudan, Tanzania, Zimbabwe
Chile	AMR	Instituto de Salud Publica de Chile, Santiago, Chile	Bolivia, Colombia, Dominican Republic, Ecuador, Peru
Czech Republic	EUR	National Institute of Public Health, Prague, Czech Republic	Slovakia
Egypt	EMR	Central Health Laboratory, Ministry of Health and Population, Cairo, Egypt	Jordan, Libya, Pakistan, Sudan, Syria, Yemen
France	EUR	Institut Pasteur, Centre National de Références des Mycobactéries, Paris, France	Côte d'Ivoire, Central African Republic, Guinea Lebanon, New Caledonia
Germany	EUR	Kuratorium Tuberkulose in der Welt e.V., IML (Institut für Mikrobiologie und Laboratoriumsdiagnostik) Gauting, Germany	Bhutan, Nepal, Tajikistan, Ukraine (Donetsk), Uzbekistan
Germany	EUR	National Reference Center for Mycobacteria, Borstel, Germany	Austria, Armenia, Azerbaijan, Bosnia and Herzegovina, Croatia, Cyprus, Kazakhstan, Kyrgyzstan, Moldova, Nukus region (UZB and TKM), Serbia, Slovenia
China, Hong Kong SAR,	WPR	TB Reference Laboratory Department of Health, SAR Hong Kong, China	Provincial surveys China Nationwide survey China
India	SEAR	TB Research Centre (TRC), Indian Council of Medical Research, Chennai, India	Provincial surveys India, DPR Korea, Maldives, Sri Lanka
Italy	EUR	Istituto Superiore di Sanità Dipartimento di Malattie Infettive, Parassitarie e Immunomediate, Rome, Italy and Laboratory of Bacteriology & Medical Mycology and San Raffaele del Monte Tabor Foundation (hSR), Milan, Italy	Albania, Bahrain, Bulgaria, Burkina Faso, Kosovo, Mozambique, Nigeria, Oman, Turkey, TFYR Macedonia, Qatar
Japan	WPR	Research Institute of Tuberculosis Japan Anti-Tuberculosis Association, Tokyo, Japan	Cambodia, Mongolia, Philippines Singapore, Yemen
Korea	WPR	Korean Institute of Tuberculosis, Seoul, Korea	Philippines
Mexico	AMR	Departamento de Micobacterias Instituto de Diagnostico y Referencia Epidemiologicos (INDRE), Mexico	Belize, Costa Rica, El Salvador, Guatemala, Nicaragua, Panama
Netherlands	EUR	National Institute of Public Health and the Environment (RIVM), Bilthoven, Netherlands	Ethiopia, Poland, Viet Nam
Portugal	EUR	Centro de Tuberculose e Micobacterias (CTM) Instituto Nacional de Saude, Porto, Portugal	
South Africa	AFR	The Medical Research Council, TB Research Lead Programme Operational and Policy Research, Pretoria, South Africa	Lesotho, Malawi, Namibia, Zambia, Zimbabwe
Spain	EUR	Servicio de Microbiologia, Hospital Universitario, Vall d'Hebron, Barcelona, Spain	Provincial surveys Spain
Sweden	EUR	Swedish Institute for Infectious Disease Control (SIDC), Solna, Sweden	Belarus, Estonia, Denmark, Finland Iceland, Islamic Republic of Iran Latvia, Lithuania, Norway, Romania
Thailand	SEA	National TB Reference Laboratory Center Tuberculosis Cluster, Bangkok, Thailand	Bangladesh, Indonesia, Myanmar
United Kingdom of Great Britain and Northern Ireland	EUR	Health Protection Agency, National Mycobacterium Reference Unit Department of Infectious Diseases, United Kingdom	Belgium, France, Hungary Ireland, Israel, Malta, Samara Oblast, Russian Federation Switzerland, The Gambia, Seychelles
United States of America	AMR	Centers for Disease Control and Prevention, Mycobacteriology/ Tuberculosis Laboratory, Georgia, USA	Botswana, CAREC, Guyana, Haiti, Orel Oblast, Russian Federation, Mexico, Puerto Rico Surinam
United States of America	AMR	Massachusetts State Laboratory, Massachusetts, USA	Peru, Tomsk Oblast, Russian Federation

Chapter 4. DISCUSSION

Overview

From 1994 through 2007, the Global Project has collected data from areas representing almost 50% of the world's TB cases. While coverage of the project is increasing on the whole, with notable expansion in both high TB burden countries and countries with high MDR-TB prevalence, coverage varies widely. The number of countries submitting survey protocols through national ethics committees has increased as well as the attention to quality assurance of patient classification, laboratory results, and data entry.

The areas represented in this project are those with at least the minimum requirements to conduct drug resistance surveys. Laboratory capacity remains the largest obstacle, but other operational components required to conduct surveys also strain the capacity of most 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 and treatment are not already an established component of routine care. DST to second-line anti-TB drugs is not available in most countries. Newly available policy guidance will assist in developing capacity; however SRLs will continue to play a very important role in providing second line testing of selected isolates.

The primary success of the project has been its ability to collect comparative baseline data on resistance to first-line anti-TB drugs from areas representing half of the world's TB population, as well as the strengthening of laboratories through the Supranational Laboratory Network. However the project, by in large, has not achieved its primary objective to measure trends in drug resistance in high burden countries. As part of the Global Plan to Stop TB, 2006-2015 all countries are committed to scaling up diagnostic networks, but as shown by the poor correlation of survey data to routine reporting of MDR-TB in most regions, it is clear that until culture and drug susceptibility testing are the standard of diagnosis everywhere surveys will continue to be important to monitor resistance. However, based on observed operational difficulties in the implementation of repeated surveys it may be time to re evaluate the survey methods we are using, as well as coordinate supplementary research to answer the epidemiological questions that routine drug resistance surveillance can not.

Survey methods

There are operational, technical, and methodological barriers to the implementation and repetition of drug resistance surveys in most high burden countries. The foremost operational barrier is the laboratory capacity. In addition to the laboratory, considerable human resources to interview and verify patient classification are required, as well as extensive national and international transport networks required to ship sputum specimens, cultures, and *M. tuberculosis* isolates within and across national borders. Some desirable components of surveys such as, larger sample sizes, better differentiation of sub-categories of previously treated cases, HIV testing, and DST to second line drugs come at great additional expense and workload to the NTP. For this reason surveys tend to be repeated infrequently.

Current survey methods are based on smear positive cases. This is done for operational reasons because smear positive cases are more likely to result in a positive culture required for drug susceptibility testing. Inclusion of smear negative TB cases may increase survey sample sizes by up to ten times. Currently there is no evidence to suggest that smear negative cases may have different proportions of resistance than smear positive cases, however HIV co infected TB cases are more frequently smear negative and so exclusion of smear negative cases from surveys may underestimate the proportion of resistance in HIV co infected populations. Current survey methods are based on patients notified in the public sector, and do not attempt to evaluate prevalent cases, chronic populations of patients, or patients in the private sector. There are significant operational difficulties with designing such surveys within the context of routine programmes, and the resulting information may not warrant the expense required. Additional research may be useful to explore the prevalence of drug resistance in these three populations.

Another limitation of current methodology has been the ability to determine true acquired resistance. Previous reports have suggested that resistance among previously treated cases may be a useful proxy for acquired resistance. Previously treated cases are a heterogeneous group that may also represent cases that were primarily infected with a resistant strain, failed therapy, and acquired further resistance. Additional evidence suggests that previously treated cases also may include patients re-infected with resistant isolates [7, 8, 15]. Without the ability to conduct repeat drug susceptibility testing and without the use of molecular tools it is very difficult to determine

true acquired resistance. Risk factors for acquisition of resistance, particularly in HIV co infected populations, warrant further research.

If surveillance coverage and determination of trends is to be scaled up in high burden countries we need to simplify the process of surveys for NTPs. A study is currently ongoing in Tanzania to validate rapid molecular methods against phenotypic methods in the context of drug resistance surveys and assess feasibility. Because current knowledge regarding mutations causing resistance is incomplete, the use of molecular methods alone would limit the amount of information obtained to one or two drugs. However, a substantial advantage would be the reduced lab capacity required and the transportation of non infectious material. Laboratory testing could be carried out within or outside of the country.

When considering the number of drugs tested in routine surveys it is important to keep in mind that presently the ability to adjust regimens for TB treatment is limited in most countries and the majority of countries provide four primary regimens; category I for smear positive cases, category III for smear negative cases, category II for retreatment cases, and category IV for MDR-TB cases. In programmatic terms surveillance of rifampicin resistance, isoniazid resistance (MDR-TB) and XDR-TB are the most critical trends to follow.

If rapid rifampicin and isoniazid testing could be used in the context of surveillance (and where MDR-TB treatment programmes exist), patients identified with MDR-TB could be rapidly enrolled into a treatment programme and further culture and drug susceptibility testing could be undertaken to determine resistance to second line drugs. Another option where phenotypic methods are used, could be to add a fluoroquinolone and one or two second line injectable agents to the panel of drugs tested, or replace streptomycin and ethambutol with a fluoroquinolone and an injectable agent. One option to enable better assessment of trends in drug resistance over time might be to keep population based clusters open throughout the year. Patients would be classified by treatment history on a routine basis. Sputum samples or smears could be transported to the NRL for a period of time each year, or a determined number of cases per month where molecular testing for rifampicin or rifampicin and isoniazid could be conducted. If a point of care test were available, then this could simplify the process even further. All cases with rifampicin resistance would be further screened for resistance to second line drugs and enrolled on treatment. These

sites could also develop capacity for programmatic management and be used for screening all treatment failure cases and cases classified as high risk for drug resistance as outlined in the Global Plan to Stop TB, 2006-2015.

It is important to distinguish population based surveys used for epidemiological purposes, and surveys used for programmatic reasons, and studies designed to answer research questions. In addition to epidemiological surveys, many countries are conducting two types of surveys to answer relevant programmatic questions. Many countries are determining the proportion of category I and category II failure cases that have MDR-TB in order to develop a case finding strategy for MDR-TB cases. Many countries are also conducting second line DST on risk groups, such as chronic cases, and known MDR-TB cases, in order to examine the extent of second-line anti-TB drug resistance in these populations but also to inform MDR-TB treatment regimens, where regimens are standardized. Transmission dynamics and acquisition of resistance are areas that undoubtedly require further research, but are difficult to answer in the context of routine surveillance in most settings. A subgroup on research for MDR-TB has recently been set up with the Stop TB Working group on MDR-TB and it may play a key role in protocol development as well as coordination and implementation of global research studies.

There are several possibilities for improving current surveillance mechanisms, utilizing both new molecular tools, as well as modified survey methods. A meeting coordinated by WHO is planned to take place in 2008 in order to evaluate current methods and develop recommendations for revisions of the current surveillance strategies.

Magnitude and trends

Survey data indicate that proportions of resistance to any TB drug as well as MDR are lowest in Western and Central Europe, followed by African countries and then the Americas. The Eastern Mediterranean and South East Asian region show moderate proportions of resistance, followed by the Western Pacific region. Eastern Europe continues to report the highest proportions of resistance globally and for all first line drugs. There are important variations within regions, particularly in the Eastern Mediterranean and the Western Pacific regions, as well as Europe when the Western, Central and Eastern Europe are grouped together. Western and Central

Europe show little variation in resistance across the region. All WHO regions have reported outliers.

Trends are showing that a range of scenarios exist. Rapid decreases in MDR-TB are reported from Hong Kong, SAR, China and the United States. Thailand, limited data from Viet Nam, as well as three Baltic countries and many low TB prevalence countries are showing stable trends in MDR-TB. The Republic of Korea as well as Peru have shown increases in MDR-TB as well as a slowing in the decline in the TB notification rates. In Peru, supporting data suggest weaknesses in TB control. In Korea, the slowing in the decline of the notification rate has been attributed to an expanding surveillance system that reaches the private sector. Meanwhile, case detection, and success rates remain high, and the burden of TB is shifting to the older population, which is inconsistent with the recent increase in MDR-TB among new TB cases. The two oblasts in the Russian Federation are showing increases in the proportion of MDR-TB among new cases at a very rapid rate, while the TB notification rate in these regions is falling slowly. Although the global burden of MDR-TB can be estimated, it is not possible to estimate global trends in MDR-TB, because of the few trends available from high burden countries.

The data reflect TB programmes at various stages of implementation; thus trends must be interpreted in the context of additional relevant programme indicators. Programme improvement can affect the prevalence of resistance in several ways. A better programme can result in the reduction of the overall number of cases, particularly re-treated cases; however, difficult (resistant) cases may persist. Thus, in some instances an increase in MDR proportion in a population may reflect a stable number of MDR cases but a decrease in the overall re-treatment population. Or it may be the result of successful treatment of susceptible cases, with insufficient case management of MDR-TB cases. It is also possible that, as diagnostic systems improve, coverage and reporting of culture and DST may result in increases in reported case numbers. Improvement in laboratory proficiency, particularly the sensitivity and specificity of drug susceptibility testing, may also affect the observed prevalence of resistance. The scenarios outlined above highlight the importance of evaluating trends in prevalence of drug resistance within the context of relevant programme developments.

XDR-TB

XDR-TB is more expensive and difficult to treat than MDR-TB and outcomes for patients are much worse[16, 17], therefore understanding the magnitude and distribution of XDR-TB is important.

Data included in this report are the first representative information available on XDR-TB, however there are several limitations. The first is the insufficient quality assurance of drug susceptibility testing for second-line drugs. A number of settings reported results that were tested by a SRL, but this was not the case for the majority of settings. The second limitation is that second-line drug susceptibility testing is not available in most countries. The cost of shipping of isolates and the cost of second line testing is significant. Therefore, in most settings only MDR-TB isolates were tested for resistance to second-line drugs. Even in countries where second-line drug susceptibility testing is routinely conducted, usually only isolates with MDR-TB or other extensive resistance patterns will receive DST to selected second-line drugs, which limits our understanding of the emergence of second line resistance to all but the highest risk cases, this may be particularly relevant for fluoroquinolones which are widely used and an important component of second-line anti-TB therapy.

Using MDR-TB cases tested for second-line drugs as a denominator is problematic in survey settings where the number of MDR-TB cases detected in the nationwide survey sample may be small and may not reflect the true proportion of XDR-TB among all MDR-TB cases. Alternatively examining cases in MDR-TB treatment programmes may also be biased towards chronic cases and may overestimate the proportion of XDR-TB among all MDR-TB cases.

The current recommendation in the context of surveys is to conduct second-line DST on the sample MDR-TB cases detected in the survey, and to conduct separate programmatically relevant surveys within MDR-TB treatment programmes or of risk groups such as treatment failures.

Despite limitations in the quality assurance of laboratory testing, data from this report indicate that XDR-TB is widespread with 45 countries having reported at least one case. The majority of countries that reported were low TB burden countries, and reported very few cases, and therefore

do not give an indication of global magnitude. Japan, and the Republic of Korea in a previous study, have shown a high proportion of XDR-TB among MDR, however these countries have a small underlying population of MDR-TB cases. The sentinel system in Japan is hospital based and previous data reported from Korea based on the national laboratory register representing 70% of cases in the country, may be biased towards the most ill patients and may be overestimating the proportion of all MDR-TB cases that are XDR-TB. Data from a nationwide survey in Korea, examining 110 MDR-TB patients showed a significantly lower prevalence of XDR-TB among MDR-TB cases. Data on second line drug resistance are currently unavailable from China, although there are plans to conduct second line DST on MDR-TB cases detected in an ongoing nationwide survey. Second line DST from the nationwide survey in the Philippines was not completed at the time of this publication; however, the resistance to fluoroquinolones in the MDR-TB patients under treatment (50%) suggests further investigation is required. Although the numbers are small, most of the data available from African countries reveal a low proportion of XDR-TB among MDR-TB cases, although numbers are small. South Africa is the outlier in the region. Although a moderate proportion of XDR-TB was reported, and there are known biases related to the selection of cases for testing²⁴, this constitutes a large burden of cases, the majority being HIV infected. No countries from the Eastern Mediterranean region have yet reported representative data on second-line drug resistance although studies are planned and Morocco is having all MDR-TB isolates from the nationwide survey further tested. India has conducted second-line DST in surveys in both Gujarat and Maharashtra, but data are not yet available. Myanmar is surveying risk populations, but currently showing low proportions of second-line drug resistance. Quinolones are widely available in this region and therefore determining the extent of resistance to this class of drug is a priority as well as establishing cross resistance between early and later generations of quinolones.

The high proportion of XDR-TB among MDR-TB, ranging from 4.0% to over 20% as well as the large underlying burden of MDR-TB suggests a significant problem within the countries of the former Soviet Union where drug resistance is widespread. Second-line drugs are locally

²⁴ 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.

available in most of the countries of the former Soviet Union and have been widely used for a long period of time.

These data highlight the need to strengthen global capacity for both diagnosis and surveillance of resistance to second-line drugs if the true magnitude and distribution of XDR-TB are to be understood.

DRUG RESISTANCE AND HIV

There is a well documented association between TB and human immunodeficiency virus (HIV), and although outbreaks of drug resistant forms of tuberculosis among HIV infected patients have been widely documented in nosocomial and other congregate settings[18, 19], little information is available about the association of HIV and drug resistant TB on a population level.[20-22] The primary reason for the lack of information is that HIV and anti-TB drug susceptibility testing have not been sufficiently accessible for joint surveys under routine conditions. The scale up of HIV testing has opened up possibilities for joint surveys; however, in this report only seven countries were able to provide drug susceptibility testing information disaggregated by HIV status. In the majority of high TB burden settings either drug resistant TB or HIV, or both are rare, and thus routine surveys may not capture a large enough number of either drug resistant TB patients or HIV infected patients to examine an association with sufficient statistical power[3]. In order to examine the association on a population level it may be necessary to sample both HIV infected and uninfected TB patients separately.

There are two main reasons why drug resistant-TB may be associated with HIV and drug resistant TB. Acquired rifamycin resistance has been associated with HIV infection among TB patients under treatment and anti-TB drug malabsorption has been documented in patient cohorts in settings of high HIV prevalence. In addition, HIV infected patients and drug resistant TB patients may have similar risk factors such as history of hospitalization. It is also possible although no data have shown that HIV infected patients may be more susceptible to infection once exposed. The epidemiological impact of HIV on the epidemic of drug resistant TB is not known, and may depend on several factors. HIV infected TB cases are more likely to be smear negative, and delayed diagnosis of drug resistance as well as unavailability of treatment have led to high death rates in people living with HIV. Both of these factors may suggest a lower rate of

transmission. However, HIV infected cases progress rapidly to disease, and in settings where MDR-TB is prevalent, either in the general population, or in the local population such as a hospital or a district, this may lead to rapid development of a pool of drug resistant TB patients, or an outbreak.

The data reported from the majority of countries were not strong enough to examine an association between HIV and drug resistance. However, the data available from Donetsk Oblast, Ukraine, and Latvia indicated a significant association between HIV and MDR-TB. Additional information on risk factors including history of hospitalization or imprisonment were not available for this analysis, so the specific reasons for the association are not known. Both countries have a high underlying prevalence of MDR-TB, as well as an emerging HIV epidemic, that initially was concentrated among risk groups, but has now become more generalized. Despite some of the weakness in these data and subsequent analysis, the association between HIV and MDR-TB is concerning particularly given the implications for the clinical management of these patients. As both countries have well developed diagnostic infrastructure continued monitoring of the epidemic over time will be crucial in order to gain a better understanding of how HIV may impact the epidemiology of drug resistance in the region.

Rapid progression to death in HIV-infected MDR-TB patients in both outbreaks and treatment cohorts has been widely documented[18, 23]. Anti-retroviral treatment for HIV does appear to benefit co-infected MDR-TB patients; however, co-management of treatment for both diseases is very complicated. Currently, most TB control programmes in high burden countries do not have the diagnostic infrastructure to either detect an outbreak nor the programmatic capacity to manage an outbreak. Given the impact on mortality, outbreaks should be avoided at all cost. The development of infection control measures in congregate settings as well as diagnostic screening tools to rapidly identify drug resistant TB are a priority, for all countries, but particularly for those with high prevalence of HIV or MDR-TB.

From a global perspective, routine diagnosis of both HIV and drug resistant TB should be scaled up for patient benefit. Better surveillance data may help in developing an understanding of the relationship between these epidemics; however, additional studies should be undertaken in several settings in order to answer the questions surveys cannot.

Global Estimates

It is estimated that 489,139 (95% CLs, 455,093-614,215) cases emerged in 2006, and the global proportion of resistance among all incident TB cases was 4.8% (95% CLs, 4.6-6.0). China and India are estimated to carry 50% of the global burden, with the Russian Federation carrying a further 7%. The difference between the estimated number of cases as well as proportions published in 2004 and those published in this report can be accounted for, both by revisions in underlying estimations of TB incidence as well as more recent survey and surveillance data. In this report, as in previous publications, we have estimated the incidence and not the prevalence of MDR-TB. An estimate of prevalence can be made by multiplying incidence by the average duration of the disease. The duration of MDR-TB is not known, and likely variable depending on diagnostics, treatment available, and HIV co infection; however, it is expected to be longer than 1.75 years, the current estimated duration for an episode of drug susceptible TB. Duration, in general, is expected to be longer because most patients will receive some treatment, which may not lead to cure, but rather contribute to prolongation of disease. A modelling exercise estimated MDR-TB prevalence to be three times the annual MDR-TB incidence[[24]. If we assume that the duration of the disease is between 2 and 3 years, the global prevalence of MDR-TB would range from 1,000,000 to 1,500,000 cases.

SRLN

The SRLN currently comprises 26 laboratories in six regions that provide a wide range of support to over 150 laboratories worldwide. The network has completed thirteen rounds of proficiency testing since 1994; and cumulative results indicate an overall high performance of the network. It is important to note that while overall performance of the network is good, annually one to two laboratories within the network will show sub optimal performance. This indicates the difficulty of executing high quality drug susceptibility testing year after year, and also highlights the important of internal quality assurance.

Results are determined judicially, therefore it is important to note that through the course of thirteen rounds of proficiency testing, "borderline" strains have been encountered, where up to half the network has found these strains to be susceptible and the other half of the network have found them to be resistant. Since round 9, care has been taken to exclude such strains from

panels by thorough pre-testing however, this has not always been possible. Therefore, strains with less than 80% concordance within the network have been excluded from overall performance measures in order not to distort judicial results. Over a five years period 40/600 strains, or approximately 7% of strains included in annual panels have been excluded. Although it is acknowledged by the network that these strains are present in routine care of TB patients, it was decided to examine them outside of annual proficiency testing in order to determine the reasons for the results, but also to ensure reliable evaluation of national and other reference laboratories that subsequently receive these panels. The study on borderline strains has been useful to confirm that the most important factor explaining the variation of the results of panel testing is the strain selection. Results of the borderline study are not yet published. Currently there is no established gold standard to replace the judicial system. One possible solution would be a definition of "intermediary" resistant results; however, this would require testing at two concentrations. Many high income countries will test drugs, at least isoniazid, at two concentrations. However, this is not the case in most low income countries.

While DST for first-line anti-TB drugs has been thoroughly studied and consensus reached on appropriate methodologies, surveys on current practices for second-line DST in the SRLN as well as some multi-centre studies have indicated a range of methods, critical concentrations of drugs, and critical proportions of resistance used in the drug susceptibility testing. To date no study has systematically evaluated all available methods for testing, established critical concentrations for all available second line drugs, nor evaluated a large number of clinical isolates for microbiological and clinical end-points. Despite the absence of this critical information, there was a clear and urgent need to provide guidance to countries engaging in MDR-TB treatment programmes, and to develop mechanisms for external quality assurance of DST for second-line drugs.

In July 2007 guidance was developed[13] for the selection of and testing for second line drugs. Based on all available evidence or expert consensus where no evidence was available, a hierarchy was developed recommending drug susceptibility testing based on both clinical relevance as well as reliability of the test available. Rifampicin and isoniazid are prioritized, followed by ethambutol, streptomycin and pyrazinamide, and then the second-line injectables (amikacin, kanamycin, and capreomycin) and fluoroquinolones. The policy guidance is available

and full technical guidelines for the drug susceptibility testing of second line drugs will be available in March 2008. At the same time, the SRLN began to include isolates with second-line drug resistance into the fourteenth round of proficiency testing for the SRLN and selected NRLs. Results of this first exercise will be available in mid-2008.

It is widely acknowledged that newer, rapid phenotypic and genotypic DST methods hold considerable promise for the rapid diagnosis of MDR-TB as well as opportunities for scaling up surveillance of resistance, discussed previously. While several of these tests are in a validation stage, many countries are already using some these methods to identify MDR-TB patients. Currently, tests for rapid identification of second-line drug resistance are not yet available.

The SRLN continues to play a critical role in capacity strengthening of laboratories worldwide and provides the backbone for surveillance activities. The Network is still largely supported by host governments; however, an increasing number of countries are obtaining funding for services provided by the SRLN through Global Fund grants. Inadequate laboratory capacity now presents one of the greatest obstacles to achieving the targets set out in the Stop TB Global Plan. The Subgroup on Laboratory Capacity Strengthening has become a more substantive movement, and renamed the Global Laboratory Initiative with a secretariat based at WHO and engaging funding agencies and all technical partners. Since 2007, the SRLN has been fully integrated into this initiative. The main priority for the SRLN is expansion within regions in order to fulfill the demand for reference laboratories and obtaining sustainable financing to continue to deliver services to countries requiring assistance. All WHO regions are committed to expansion and most have identified laboratories to be evaluated for integration into the SRLN.

WHO REGIONS

AFRICAN REGION

In the African region six countries have reported data since 2002, Côte d'Ivoire, Ethiopia, Madagascar, Rwanda, Senegal, and UR Tanzania. Data from UR Tanzania and Madagascar are considered preliminary. Rwanda was the outlier, reporting 3.9% (95% CLs, 2.5-5.8) MDR among new cases. Senegal reported 2.1% (95% CLs, 0.7-4.9) among new cases, but all other countries reported less than 2.0% MDR-TB. Since 1994, 22 of 46 African countries have reported drug resistance data from areas representing 72% of all TB cases in the region. The population weighted mean of MDR-TB based on countries reporting in the region is 1.5% (95% CLs, 1.0-2.0) among new cases, 5.8% among previously treated cases (95% CLs, 3.9-7.7), and 2.2% (95% CLs, 1.4-3.1) among combined cases. The variation in resistance among countries within the region is relatively narrow; however, roughly half of the data points used to look at the distribution are at least five years old. It is possible that current survey methodology, which is based on smear positive cases, may under represent HIV co infected TB cases who are more likely to be smear negative. In addition, transmission dynamics of drug resistant TB in a heavily HIV infected population are not well understood. These and other factors, described in detail in the HIV and MDR section of this report, make estimation of the true burden of MDR-TB difficult in high HIV prevalence settings. With the exception of Botswana, Mozambique, and South Africa, HIV testing has not been a component of drug resistance surveys. However, as routine HIV testing rapidly scales up in the region, from 11% of TB cases tested in 2005 to 22% in 2006, HIV information will become a more routine component of anti-TB drug resistance surveys. Based on available information it is estimated that there were 66,711 (95% CLs, 55,606-137,263) incident MDR-TB cases in the region in 2006, with almost 90% of these cases emerging in high HIV prevalent settings.

The African region has the fewest settings for which trends can be identified. Only Botswana, Sierra Leone, Côte d'Ivoire, and Mpumalanga Province, South Africa, have carried out repeat surveys. In the surveys reported previously Botswana showed a significant increase in drug resistance among new cases, and an increase, though not significant, in the proportion of MDR-TB cases. A fourth survey is under way in Botswana, which will be very important to understand the trends in drug resistance in this country, and other countries where HIV is prevalent. Côte

d'Ivoire showed a decrease in the proportion of MDR-TB cases between surveys but an increase in resistance to streptomycin and ethambutol, and an increase in isoniazid monoresistance. Survey methods remained the same between the surveys, and most of the MDR-TB cases captured in the first survey had an identical resistance pattern suggesting that a cluster of cases may have been included. Further surveys are required to interpret trends in Côte d'Ivoire.

The low median proportions of drug resistance and limited trend data may underestimate the importance of drug resistant TB in high HIV prevalence settings. A large outbreak of XDR-TB, in an HIV infected population in the province of KwaZulu-Natal, South Africa was associated with extremely high mortality[25] and highlighted the vulnerability of TB patients co-infected with HIV. Detection of this outbreak was only possible because of the extensive laboratory infrastructure available in the country. It is likely that similar outbreaks of drug resistance with associated high mortality are taking place in other countries, but currently going undetected due to insufficient laboratory capacity.

Botswana, Mauritania and Mozambique, have nationwide surveys under way and Angola, Burundi, Lesotho, Malawi, Namibia, South Africa, Uganda, and Zambia have plans to initiate nationwide surveys over the next year. Nigeria and DR Congo, plan to begin a survey covering selected districts in their respective countries in 2008. All protocols stipulate second-line drug susceptibility testing for MDR-TB isolates, and the majority of surveys are being financed through Global Fund grants. Currently, Botswana and Swaziland are undertaking surveys of high risk populations to examine the extent of first and second-line drug resistance; results should be available in early 2008. DR Congo, Burundi and Rwanda[26-28], with the assistance of a SRL, are routinely examining second line resistance among treatment failure cases and thus far have detected limited second line resistance; however, samples are relatively small. Mozambique, Malawi, Zambia, and Zimbabwe all have plans to conduct similar studies. South Africa has recently conducted a review of their laboratory database and found that 996 or 5.6% of 17 615 MDR isolates collected over a four year period 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 cases²⁵. UR Tanzania, with the support of a SRL, is evaluating the use of rapid rifampicin testing for the purposes of surveillance. Data from this project will be available in early 2008, and if shown to be comparable with phenotypic testing may be a useful tool in the expansion of survey coverage in the region as well as trend analysis.

The most critical factor in addressing drug resistance in African countries is the lack of laboratory infrastructure and transport networks that can provide rapid diagnosis. The Global Plan to Stop TB 2006-2015 stipulates expansion of culture and DST to all retreatment cases and to 90% of new cases that are at high risk of MDR-TB (i.e. contacts and treatment failures at 3 months). Most countries in the region are far from reaching this target. In 2006 it was reported 9% of retreatment cases received DST in the African region. Most countries have, at most, one laboratory able to conduct culture and drug susceptibility testing in the public sector, let alone DST for second line drugs. There are two SRLs in the region, one in Algeria and one in South Africa; however the National Health Laboratory service of South Africa as well as laboratories outside the region are playing an important role in providing quality assurance, as well as DST for second line drugs. There are plans to upgrade national lab networks in most countries and the identification and upgrade of at least three SRLs are planned for the region over the coming two years. Reviews of existing laboratories have already begun. Pilot projects led by the Foundation for Innovative New Diagnostics (FIND) and other partners are paving the way for the integration of new and more rapid diagnostics in the region, and funding from the U.S. President's Plan for Emergency AIDS relief (PEPFAR) and the Global Fund are filling critical gaps. However, if labs are to scale up rapidly coordination of funding and technical agencies will be critical, as well as concerted efforts to address the widespread constraints in human resource capacity in the region.

Currently, Burkina Faso, DR Congo, Guinea, Kenya, Lesotho, Malawi, Rwanda and Uganda have approved GLC projects. Mozambique has submitted an application which is under review. Benin, Ethiopia, Mali, Namibia, UR Tanzania and Zambia have Global Fund approved grants for the management of MDR-TB and have plans to apply to the GLC in 2008.

²⁵ 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.

REGION OF THE AMERICAS

In the Americas region eleven countries have reported data since 2002, including never previously reported data from Costa Rica, Honduras, Guatemala (final data), and Paraguay. Since 1994 twenty one countries have reported drug resistance data from areas representing 93% of all TB cases in the region, but covering 48% of the countries. The population weighted mean of MDR-TB based on all countries that have reported in the Americas is 2.2% (95% CLs, 0.6-3.8) among new cases, 13.2% (95% CLs, 3.5-22.8) among previously treated cases, and 4.0% (95% CLs, 1.7-6.3) among combined cases.

To a great extent, as found in previous reports, the prevalence of MDR is low in the region as a whole; however, there are important outliers. In this report Guatemala reported 3.0% (95% CLs, 1.8-4.6), and Peru showed 5.3% (95% CLs, 4.2-6.4) among new TB cases. In the last report, though in the same reporting period (2002), Ecuador showed 4.9% (95% CLs, 3.5-6.7) MDR-TB among new cases.

In North America, Canada has shown low proportions of resistance and relatively steady trends in resistance among both new and previously treated cases. TB case notification has decreased since 1997 and in 2005, 23 MDR-TB cases were identified. The USA has shown decreases in overall TB notifications as well as overall numbers of MDR-TB cases since 1995. The US reported significant decreases in MDR among all TB cases. A total of 124 MDR-TB cases were recorded in 2005.

Argentina showed a slight, but not statistically significant, increase in MDR-TB among new cases from 1.8% (95% CLs, 0.9-3.0) in 1999 to 2.2 (95% CLs, 1.2-3.6) in 2005, and the TB notification rate has steadily decreased over the past decade. Uruguay showed a decrease in resistance to any drug, but this was not significant. The prevalence of any resistance remains low in this country at 2.1% (95% CLs, 0.8-4.3) among new TB cases. Cuba continues to show low prevalence of resistance in the population with MDR never reaching much above 2.0% among all TB patients. Cuba was one of the few countries able to report on DST results disaggregated both by HIV status, sub category of retreatment, and prison status[29]. Peru reported increases in any resistance, isoniazid resistance and MDR-TB among new cases, though only the increase in

any resistance and isoniazid resistance were significant. MDR increased from 2.4% (95% CLs, 1.7-3.4) in 1996, to 5.3% (95% CLs, 4.2-6.4) in 2006. Peru showed a yearly reduction in the TB notification rate between 1994 and 2002 of approximately 4 to 6%; however, since 2003 the notification rate has slightly increased between 123 and 124 per 100 000. The recent rise in the notification rate and the increase in drug resistance may likely be due weakness in management of TB cases (both new and MDR-TB) in previous years as well as weakness in the entire health system, particularly in the years 2003 and 2004. The GLC approved project has operated primarily in Lima until expanded nationally as recently as 2006.

Currently a nationwide drug resistance survey, by state, is under way in Brazil and includes HIV testing. A repeat survey in the Dominican Republic is also ongoing and will help better establish the prevalence of MDR-TB, which was shown to be 6.6% among new TB cases in the first survey over a decade ago. Mexico has started a nationwide survey in which HIV testing will be incorporated. Panama also has plans for a nationwide survey. All surveys have plans to test MDR-TB isolates for second line drug resistance at a SRL.

Currently there are five SRLs in the Americas region with plans to expand the network to one or two additional labs over the next two years. This network provides annual proficiency testing panels to almost all NRLs in the region. In addition to plans in many countries to upgrade laboratory networks, there is increased demand for development of second line testing capacity.

It is estimated that there were 12,070 (95% CLs, 10,523-15, 526) incident MDR-TB cases in Latin America in 2006. Peru is estimated to have 3,972 (95% CLs, 2,842-5,1892) incident cases, while Ecuador and Brazil are estimated to have 1,483 (95% CLs, 1,034-1,998) and 1,464 (95% CLs, 945-2,077) respectively. The Americas regions has the largest number of GLC approved projects with programmes in Belize, Bolivia, Costa Rica, Dominican Republic, Ecuador, Guatemala, Honduras, Haiti, Mexico, Nicaragua, Peru (nationwide), Paraguay, El Salvador, Uruguay. Though not GLC approved, MDR-TB management is fully integrated in Brazil and the laboratory network able to conduct culture and drug susceptibility testing is extensive. Treatment success of MDR-TB patients reported from Brazil was 60% for the 2003 cohort.

EASTERN MEDITERRANEAN REGION

The Eastern Mediterranean region has made strong progress in survey coverage since 2002, reporting data from six countries, including never previously reported data from Lebanon, Jordan, nationwide survey data from Morocco, and Yemen. Since 1994 eight countries have reported drug resistance data from areas representing 22% of all TB cases in the region, but covering 36% of the countries in the region. The population weighted mean of MDR-TB based on all countries that have reported in the Eastern Mediterranean region is 2.0% (95% CLs, 0.0-4.3) among new cases, 35.3% (95% CLs, 16.4-54.3) among previously treated cases, and 5.4% (95% CLs, 0.5-10.4) among combined cases. Based on available information it is estimated that there were 25,475 (95% CLs, 15,737-73,132) incident MDR-TB cases in the region in 2006, with almost 60% of these cases estimated to be in Pakistan.

Lebanon, Morocco, and Oman reported low proportions of MDR among new cases from 0.5% (95% CLs, 0.2-1.1) in Morocco to 1.3% (95% CLs, 0.2-4.7) in Oman. Yemen reported a higher proportion of resistance, 2.9% (95% CLs, 1.6-4.9) and Jordan reported 5.4% (95% CLs, 2.0-11.4) MDR among new cases. Jordan, Lebanon, and Oman reported very high proportions of resistance among retreated cases, though sample sizes were small and the confidence intervals were wide. The high proportions of resistance found in Jordan are similar to what was reported from the Islamic Republic of Iran in 1998. Jordan reports high success rates and low proportions of retreatment cases suggesting that further evaluation should be done in order to confirm the high proportion of MDR-TB found among new cases.

Trends are available only for the Gulf States of Oman and Qatar, both with small numbers of total cases and low to moderate levels of resistance, much of which is imported. Trends are difficult to interpret because of the small numbers of cases, though drug resistance does not appear to be a problem in either of these countries. The extent of second line drug resistance is not known in the region. The only available data have been reported from Iran, which showed the existence of XDR-TB, but denominators were not available. Morocco plans to have MDR-TB isolates collected from its nationwide survey tested for second line drug resistance.

The primary limiting factor to expanding survey coverage in the region is the high number of countries currently addressing conflict situations. In many of these countries basic health

services must be prioritized over expansion of surveillance. The second limiting factor is the poor laboratory infrastructure in many countries. Currently there is only one SRL in the region, but one candidate SRL has been nominated and is undergoing evaluation, and there are plans for identification of another candidate in the region in the next year.

Pakistan has widely expanded external quality assurance of microscopy laboratories and is in the process of identifying a national reference laboratory which is a pre-requisite for nationwide survey as well desirable for the successful implementation of a MDR-TB treatment programme under the NTP. The Islamic Republic of Iran has been planning a second nationwide survey for several years; however, to date the survey has not taken place. The Libyan Arab Jamahiriya, Saudi Arabia, and Somalia will start preparation for drug resistance surveys in 2008. Sudan has recently begun a survey.

Currently, Egypt, Jordan, Lebanon, the Syrian Arab Republic, and Tunisia, have approved GLC projects. However; Djibouti, Egypt, Iraq, Morocco, and Sudan have Global Fund approved grants for MDR-TB management which will result in GLC applications shortly.

EUROPEAN REGION

In the European region thirty-eight countries have reported data since 2002, including never previously reported data from Armenia, Baku, Azerbaijan, Donetsk Oblast within Ukraine, Georgia, the Republic of Moldova, Tashkent, Uzbekistan and three Oblasts in the Russian Federation. Since 1994, 40 countries have reported drug resistance data from areas representing 35% of all TB cases in the region (31% of the cases in Eastern European countries, and 55% of the cases in Central and Western European countries). The population weighted mean of MDR-TB based on all countries that have reported in Central and Western Europe is .9% (95% CLs, 0.5-1.2) among new cases, 7.7% (95% CLs, 5.7-9.8) among previously treated cases, and 1.5% (95% CLs, 1.1-2.0) among combined cases. The proportion of MDR-TB was significantly higher in the Eastern European and Central Asian countries with the following population weighted means; 10.0% MDR-TB (95% CLs, 3.8-16.1) among new cases, 37.7% (95% CLs, 12.3-63.0) among previously treated cases, and 22.6% (95% CLs, 8.6-36.6) among combined cases.

Based on the important differences in epidemiology, Western and Central Europe are discussed separately from Eastern Europe and Central Asia. Most Western and Central European countries are reporting routine surveillance data. Both proportions and absolute numbers of drug resistant cases remain low in most of Western and Central Europe. Germany reports the highest number of MDR cases, recording approximately 100 cases per year. Most of the drug resistant cases recorded are imported cases. Israel is an outlier, presenting the highest levels of resistance to all drugs. However, the situation of this country is unique, because of the high levels of immigration from areas of the former Soviet Union. Between 80% and 85% of TB patients in Israel are foreign-born, mainly from Ethiopia and countries of the former Soviet Union. Therefore, most MDR-TB cases in the country were likely to have been infected abroad before immigrating to Israel²⁶. A 1994 survey in Romania showed 2.4% MDR-TB among new cases, and 5.4% among all TB cases. Given the burden of TB the country the absolute number of incident cases estimated in 2006 was 1,546 (95% CLs, 1,047-2,138). Turkey has never carried out a nationwide survey, although there are plans to do so. The number of cases estimated to have emerged in 2006 is 889 (95% CLs, 284-3,320). Importantly, almost all countries in Western and Central Europe are now linked to a SRL and are participating in annual external quality assurance for drug susceptibility testing.

Eastern Europe

Since the beginning of this project countries of Eastern Europe and Central Asia have reported the highest proportions of resistance to anti-TB drugs. It has been speculated that one of the most important factors in the resurgence of tuberculosis in the region and the emergence of the drug resistance epidemic was the disintegration of the Union of Soviet Socialist Republics in 1991 and the economic crisis that followed. This crisis resulted in interruptions in drug supply and overall deterioration of the health sector which also had an impact on transmission of infection and susceptibility to disease. The lack of standardized treatment regimens in many countries also likely contributed to the development of drug resistance and there is extensive documentation of spread of drug resistance throughout the prison sector. In this report, data reported from the Georgia showed the lowest proportion of resistance in region at 6.8% (95% CLs, 5.1-8.8) among

²⁶ Chemtob D. Multi and extensive drug-resistant tuberculosis burden in Israel, a country with immigration from high endemic areas. 4th Congress of the IUATLD, European Region, Riga, Latvia, June 2007, pp. 19.

new cases and has continued to use the systems developed for the survey to improve its routine surveillance system.. Baku, Azerbaijan, as well as data from the Republic of Moldova showed proportions of MDR-TB 20.0% and higher among new cases. Data from several of the countries surveyed showed that between 4.0%,(Armenia) and 23.7% (Estonia) of MDR-TB cases were XDR-TB. Donetsk Oblast, Ukraine conducted a joint drug resistance and HIV survey among TB patients which showed a significant association between drug resistance and HIV. Currently it is estimated that 80,057 (95% CLs, 71,893-97,623) MDR-TB cases emerged in Eastern Europe and Central Asia in 2006.

Though most countries in the region conduct routine culture and drug susceptibility testing on all, or at least the majority of TB cases notified, practices do not follow the criteria required for inclusion in this report. These countries are not participating in annual quality assurance of laboratory results, patients may not be classified according to treatment history, and culture and DST coverage may not be sufficiently high. Nevertheless, the notification of MDR-TB cases collected through annual reporting to WHO correlate well with survey data collected from the region which indicates that relying on routine data collection for surveillance of drug resistance will be possible in the future. In the meantime surveys are important to estimate the burden of MDR-TB in these countries.

At this point in time robust trend information is only available from the Baltic countries and two Oblasts in the Russian Federation. Trends in MDR-TB among new cases in the Baltic countries appear to be relatively stable between 9.8% in Lithuania and 13.2% in Estonia with a slow decrease indicated in Estonia and slow but significant increase in MDR-TB in Lithuania. The TB notification rate is falling by between 5.0% (Lithuania) to 8.0% (Estonia) per year. Treatment success of new smear positive case over the same period has been relatively stable around 70 to 74%, but falling slightly in Lithuania from 74 to 70% over the last four years. DOTS was initiated in 1996, 1998, and 2000 in Latvia, Lithuania, and Estonia respectively, and "DOTS-Plus" or treatment of drug resistant TB according to internationally accepted standards was initiated in 1998, 2002, and 2005 in Latvia, Estonia and Lithuania. Success rates for patients with MDR-TB in 2003 were highest in Latvia at 69%, but quite low in Lithuania at around 36%.

The TB scenario in the Baltics, especially in Latvia and Estonia, likely reflects improved TB control over the past ten years including better management of MDR-TB with more rapid diagnosis and infection control (particularly in hospitals). Economic growth and investment in health has also very likely contributed to the decline in TB over this period. Absolute numbers of chronic cases and defaulters have steadily declined in the years 2003 through 2006[30, 31].

All three countries struggle with social issues among TB patients, such as alcohol and drug abuse as well as homelessness. This has been identified as a limiting factor in reduction of default and failure rates. Social support must continue to be a key aspect in reduction of poor treatment outcomes. Reduction in the proportion of MDR, if sustained in the Baltic countries, particularly Latvia and Estonia may provide an important model for other countries in the region that struggle with MDR-TB epidemics.

The scenario in the Russian Federation differs from the picture indicated in the Baltic countries. TB notification rates for the whole of the Russian Federation have been relatively stable from 1997, (81/100 000) through 2006 (87/100 000), data from selected Oblasts where TB control has been well implemented are showing declines in TB. In Orel Oblast the TB notification rate has declined by over 3% per year for the last six years. Tomsk Oblast, showed a steady decline in TB notification rate by 1.3% over the same period.

Trend data are currently available from two Oblasts in the Russian Federation (Tomsk, and Orel). The data from these regions are considered reliable because culture and drug susceptibility testing has been provided to 85-100% of the new TB cases over this time period, new and previously treated cases are reliably differentiated, and there is evidence of good laboratory performance over the period of data collection.

In addition, an exercise was undertaken to examine quarterly data from ten oblasts with the view to use routine data as a basis for surveillance of drug resistance. Based on a validation exercise to determine the population coverage of culture and DST as well as other quality indicators and combined with external quality assurance results from the laboratory, data on new cases in the civilian sector from Mary El Oblast were also included in this report. Data are representative only for the populations covered and cannot be extrapolated to the whole of the country. The

exercise showed that the national reporting system and lab registers correlate very well for new cases, therefore, as quality assured diagnostic coverage of the population expands; routine data from additional regions in Russian Federation could be included in future reports²⁷.

While overall notifications of TB in Orel and Tomsk Oblasts are declining, the trends in drug resistance are showing important increases in the proportion ranging from an average 13.0% per year increase in Tomsk to 32.0% increase per year in Orel. Absolute numbers of new TB cases with MDR are also increasing. Both regions have strong and improving TB control programs, as well as GLC approved MDR-TB management programmes. It is possible that while susceptible cases are being successfully treated, a sufficient reduction in MDR-TB cases has not been achieved leaving drug resistant cases as an increasing reservoir of TB transmission. Data reported do not allow disaggregation of cases by place of origin or previous history of hospitalization or imprisonment both of which may have an impact on trends in resistance in these oblasts. Supporting the trend data reported from these oblasts, is a report jointly published in 2006 by the Russian Ministry of Health and WHO²⁸ which indicated an increase in MDR-TB both in proportion and absolute numbers of cases and highlighted the variation in proportions of resistance across oblasts indicating that up to 20% of new TB cases in Samara Oblast[32-34] may have MDR-TB. According to this report approximately 40% of TB patients in the Russian Federation were categorized as chronic cases in the national register. Although some of the increase in numbers of MDR-TB cases in the national system may be due to better laboratory detection, it is likely that this does not explain the size of the increase. The enormous pool of chronic cases constitutes an important reservoir of transmission of MDR.

Over the past several years the Russian Federation has made important progress in addressing TB including the implementation of World Bank and Global Fund projects. The revised TB control strategy is being implemented in 85 of 88 regions and new TB treatment standards and forms have been introduced. Currently 14 of 89 regions have approved GLC applications (and

²⁷ According to official statistics, the prevalence of MDR-TB among new cases in the Russian Federation is 9.4%. These data do not currently conform to global project methodology and therefore have not been included in this report.

²⁸ Tuberculosis in the Russian Federation, 2006. An analytical review of the main tuberculosis statistical indicators used in the Russian Federation, (Ministry of Health and Social Development of RF/FPHI/RIPP/CTRI/FSIN/WHO), Moscow, 2007. P.126

many more are in the pipeline). The country forecasts 3,200 MDR-TB will be enrolled on MDR-TB treatment by 2008, as well as the designation of five Federal centres of excellence for the treatment of MDR-TB in the civilian sector, and 8 in the penal system. The strengthening and upgrading of laboratory services have been prioritized and 120 laboratories have been enrolled in external quality assurance programmes. Despite the current momentum, the epidemiological picture available from the Russian Federation suggests extraordinary measures to accelerate and strengthen the implementation of the Stop TB strategy will be necessary if MDR-TB is to be reduced in the population.

Commitment to TB control varies across the region, but in general progress has been made. A regional laboratory task force has been developed to improve laboratory networks through newly developed accreditation procedures, development of guidance on laboratory bio safety and infection control, identification of additional SRLs specifically to serve this region, as well as expansion of quality assurance practices and integration of new tools. Currently, all countries in this sub region are linked to a SRL with the exception of Turkmenistan, and Bulgaria. Despite progress, further efforts are needed to accelerate the roll out of GLC approved programmes to treat the large burden of MDR-TB cases, as well as better supply and management of good quality second-line anti-TB drugs, improved infection control, and continued improvement in rapid detection of resistant cases.

Belarus, Bulgaria, Tajikistan, Turkmenistan are priority countries for drug resistance surveys, Kazakhstan is repeating a nationwide survey, Kyrgyzstan is starting with a survey of Bishkek, and Uzbekistan is planning an nationwide survey following the survey in Tashkent. MDR-TB treatment through the GLC mechanism is expanding with thirteen countries (including 14 regions in Russia) currently approved by the GLC. Partners are willing and coordinated to improve community involvement and links to prisons, but additional investment will be needed to scale up and meet the targets outlines in the Global Plan.

SOUTH-EAST ASIAN REGION

In the South East Asian region six countries reported data since 2002; India, Indonesia, Myanmar, Nepal, Sri Lanka, and Thailand. India reported data from three districts and one state and Indonesia reported data from one district. Of the countries reporting, Mayhurbhanj district in

Orissa State[35], India, Sri Lanka, and Thailand reported less than 2.0% MDR-TB among new cases. Ernakulam district in Kerala State[36], Hoogli district in West Bengal State[35], and Gujarat State, India as well as Mimika district, of Papua province in Indonesia and Nepal reported between 2.0-3.0% MDR-TB among new cases. Myanmar was the outlier, reporting 3.9% (95% CLs, 2.6-5.7) MDR among new cases. Since 1994 six of eleven countries have reported drug resistance data from areas representing 23% of all TB cases in the region, but covering 55% of the countries in the region. The population weighted mean of MDR-TB based on all countries that have reported in the South East Asian region is 2.8% (95% CLs, 1.9-3.6) among new cases, 18.8% (95% CLs, 13.3-24.3) among previously treated cases, and 6.3% (95% CLs, 4.2-8.4) among combined cases. Based on available information it is estimated that there were 149,615 (95% CLs, 114,780-217,921) incident MDR-TB cases in the region in 2006, with 74% of these cases estimated to be in India.

Based on results from a nationwide survey in Myanmar[37] showing 3.9% (95% CLs, 2.6-5.7) MDR-TB among new cases and 15.5% (95% CLs, 9.5-23.4) among retreatment cases it is estimated that there were 4,251 (95% CLs, 2,648-6,187) incident MDR-TB cases in Myanmar in 2006. Myanmar has made good progress in TB control with case detection is reaching 61% and treatment success reaching 86% and the proportion of retreatment cases comprises approximately 5% of the notified cases. Despite resource constraints Myanmar is moving quickly towards implementing management of MDR-TB under the NTP. Currently, there are only two laboratories in the public sector providing culture and only one of these conducts DST; however, plans are under way to extend DST capacity to the second laboratory. A second drug resistance survey is ongoing as well as a survey of category II failure cases and chronics in order to determine the extent of second line drug resistance in this population and to inform the development of a treatment regimen. A GLC application has been approved.

The results from the recent survey in Gujarat State in India show low to moderate levels of MDR-TB among new TB cases 2.4% (95% CLs, 1.7-3.2), and 17.2% (95% CLs, 14.8-19.9) among retreatment cases. However, India reports that retreatment cases comprise 13.7% of notified cases in the country, suggesting a considerable burden of MDR-TB in this population. It is widely thought, though little documented, that a large number of registered retreatment cases are reporting from the private sector. In general, the TB control programme is performing well.

The Revised National TB Control Programme has achieved population coverage of DOTS in all districts in the country in 2006; case detection is about 61% and treatment success at 86%. However plans for scaling up 24 inter-regional laboratories capable of culture and DST, attached to 24 MDR-TB management sites capable of managing some 5000 cases per year are behind schedule. Currently most MDR-TB is managed in an unregulated private sector with access to second line drugs that are manufactured locally and of variable quality. XDR-TB has been reported in the country[38] and results of second line testing from the state wide survey in Gujarat and a survey nearly completed in Maharashtra will provide further evidence as to the extent of second line resistance in the country.

A GLC application has been approved for two sites in the states of Andhra Pradesh, and Haryana. Laboratory capacity is seen as the biggest bottleneck in the country's ability to respond to MDR TB. There is consensus that the private sector, including private laboratories and medical colleges, must be more involved, but accreditation under the public system as well as formal linkages may take time. The concern is that unless MDR-TB management develops rapidly in the public sector an increasing number of MDR-TB cases will be managed by the unregulated private sector.

The data available from Mimika district of Papua province in Indonesia[39] show moderate levels of resistance; however the sample for this survey was small and represented a very small proportion of the population. Soon to be available data from a drug resistance survey in central Java should provide a better estimate of drug resistance in Indonesia. A survey of treatment failure cases is also under way to determine the extent of second line resistance in this population. Case detection is just under the target of 70% and cure rates in the country are very high. Indonesia, like Myanmar and India is struggling with the upgrade, expansion and quality assurance of its laboratory network. A GLC application has been approved, but patients have not yet been enrolled.

The new survey data available from Sri Lanka are showing exceptionally low proportions of resistance. While these data have not yet been fully quality assured, other programmatic indicators support this estimate. All treatment failures cases receive culture and DST and identified MDR-TB cases are managed by the public sector. Sri Lanka is the only country in the

region routinely reporting MDR-TB cases. The success rate among MDR-TB cases is not known, but the country has plans to submit an application to the GLC.

Nepal and Thailand are the only two countries reporting trend data in this report. The proportion of MDR-TB among new cases in Nepal has fluctuated from a little over 1.0% to 3.0% in the four surveys that have been conducted since 1996 making trends difficult to interpret. The current estimate is 2.9% (95% CLs, 1.8-4.3) among new cases and 11.7% (95% CLs, 7.2-17.7) among retreatment cases. Nepal has had a well functioning TB control programme for over a decade and both case detection and treatment success remain high. Nepal has proven to be the leader in MDR-TB control in the region establishing the first MDR-TB control programme in the public sector and expanding it's coverage to 100% of the country by the end of 2006. Currently there is one MDR-TB treatment centre and at least three to four sub-centres in all the five regions of the country. Cure rates among registered MDR-TB cases for whom treatment outcomes are available are 75%. Like other countries in the region the ability to expand MDR-TB services has been limited by laboratory capacity however there are plans in place to expand the culture network.

Thailand has also reported data from three surveys showing stable trends in resistance with MDR-TB just under 2.0% among new TB cases. Data from a separate surveillance network with roughly the same population coverage are showing similar proportions of resistance in the population, however data from border regions with Myanmar are showing higher proportions of resistance²⁹. Unlike the other countries in the region Thailand has an extensive and well developed laboratory network. Due the decentralized nature of laboratory services and an abundance of private sector laboratories maintaining a high level of performance is one of the major challenges of the NTP. The Thai NRL currently serves as a SRL for the region and is one of a few labs in the region able to perform second line DST. Currently MDR-TB patients are managed in the public sector, but practices do not conform to international guidelines.

²⁹ Personal communication with Somsak and Dhanida Reinthong of the National Reference Laboratory, Bangkok, Thailand.

Although survey data are not included in this report Bangladesh, the Damien Foundation has been monitoring drug resistance in a rural population of the country for the past ten years and levels of drug resistance appear to be low[40] A NRL has recently been recognized and upgraded and there are plans to conduct a nationwide survey in the coming year. A GLC application has been approved. DPR Korea has developed plans to improve capacity of the NRL in order to conduct culture and drug susceptibility testing. The primary obstacle to achieve this goal is the lack of sustainable funding for the development and operation of the laboratory. DPR Korea reports that retreatment cases comprise 18% of notified cases in the country, suggesting a considerable burden of MDR-TB in this population indicating that drug resistance may be higher than other countries in the region. 3,472 (95% CLs, 1,136-11,248) MDR-TB cases, were estimated to have emerged in 2006 in DPR Korea or 6.8% of all cases (95% CLs, 2.3-21.7). Additional assistance will be required to upgrade the NRL and to measure the burden of resistance in this country.

The South East Asia region is home to four high burden countries. Though resistance in the region is moderate the overall burden of MDR-TB is considerable. Important progress has been made throughout the region in initiating plans for MDR-TB treatment and almost all countries in the region have GLC applications approved or in the pipeline. However, with the exception of Thailand all countries have identified laboratory capacity as their primary bottleneck to scaling up diagnosis and treatment to reach the targets outlines in the Global Plan to Stop TB, 2006-2015. In addition many countries in the region have growing private sectors that are currently managing most of the MDR-TB cases in the region, and second line drugs are widely available through the private sector. Coordinated efforts on behalf of NTPs as well as partners will be required in order to solve the laboratory capacity shortage in the region.

WESTERN PACIFIC REGION

In the Western Pacific region fourteen countries and two special administrative regions reported data since 2002, including data from one provinces, one special administrative region, and two municipalities in China, the Philippines, and Viet Nam. Of the countries reporting, Fiji, Guam, New Caledonia, New Zealand, the Northern Mariana Islands, Singapore, Solomon Islands, Vanuatu, reported the fewest cases, between 0 and 3 cases of MDR-TB per year. Australia reported 12 cases in 2005 and Macao SAR, China reported 9 cases of MDR-TB. Hong Kong,

SAR, China reported 41 MDR-TB cases in 2005 among all cases or 1.2% (95% CLs, 0.9-1.6) and Japan, through its sentinel survey reported that 1.9% (95% CLs, 1.5-2.5) of all notified cases were MDR-TB. China, the Philippines and Viet Nam reported higher proportions of resistance.

Since 1994 nineteen countries have reported drug resistance data from areas representing 52% of all TB cases in the region, but covering 53% of the countries in the region. The population weighted mean of MDR-TB based on all countries that have reported in the Western Pacific region is 3.9% (95% CLs, 2.6-5.2) among new cases, 21.6% (95% CLs, 16.8-26.4) among previously treated cases, and 6.7% (95% CLs, 4.6-8.8) among combined cases. Based on available information it is estimated that there were 152,694 (95% CLs, 119,886-188,014) incident MDR-TB cases in the region in 2006, with almost 85% of these cases estimated to be in China.

Viet Nam reported 2.7% (95% CLs, 2.0-3.6) MDR-TB among new cases in their 2006 survey, and 2.3% (95% CLs, 1.3-3.9) in a survey carried out a decade ago, which suggests that MDR-TB has not significantly increased among new cases over this time period. Any resistance was shown to have decreased, though not significantly. There were no results for retreatment cases in the first survey, and the 2006 survey shows a considerable proportion of MDR-TB among previously treated cases, 19.3% (95% CLs, 14.2-25.4). A survey in southern Viet Nam in 2001 also showed that any drug resistance had actually decreased since 1996 and there had been no increase in MDR-TB[41].

The Philippines conducted its first nationwide survey in 2004 and showed 4.0% (95% CLs, 2.9-5.5) MDR-TB among new cases and 20.9% (95% CLs, 14.3-29.0) among previously treated cases. MDR-TB isolates from this survey are being further tested to second line drugs at the SRL. Given the underlying high TB burden it is estimated that there were 11,848 (95% CLs, 7,428-17,106) incident MDR-TB in 2006. TB notifications in the country are stable and treatment success is high. Importantly, the Philippines have had a long running GLC approved programme for the management of MDR-TB patients that is now expanding. Treatment success

in this programme is high at 73% in the 2003 cohort. Based on data from the GLC programme³⁰, 50.0% of the MDR-TB patients enrolled in the GLC programme were resistant to a fluoroquinolone, and 3.4% (95% CLs, 1.6-6.1) were XDR-TB. The high proportion of resistance to quinolones among MDR-TB cases is concerning and should be monitored in subsequent surveys.

Since 1994 China has reported data on eight of 31 provinces, two major municipalities, and two special administrative regions. Several other provincial surveys are under way as well as a nationwide drug resistance survey that is due to be completed in 2008.

Data from surveys in Heilongjiang Province, Inner Mongolia Autonomous Region, and Beijing and Shanghai municipalities are included in this report. These data support finding from previous surveys in other provinces. Heilongjiang Province, and Inner Mongolia Autonomous Region showed 7.2% (95% CLs, 5.9-8.6), and 7.3% (95% CLs, 5.6-9.4) MDR-TB among new cases respectively. These proportions are similar to those reported from Liaoning province, also in North Eastern China. Beijing and Shanghai reported lower proportions of resistance; 2.3% (95% CLs, 1.5-3.4), and 3.9% (95% CLs, 2.6-5.6) respectively. This is one of the first reports of lower proportions of drug resistance in urban settings. A nationwide survey, based on a random selection of 70 clusters, representing counties or districts, is scheduled to complete in 2008. Surveys in Chongqing, Hunan, and Xinjiang, provinces will be finalized shortly. Despite reaching the global targets for case detection and cure, China has proportions of resistance that are among the highest in the world, only second to rates found in countries of the former Soviet Union. The plan for expansion of MDR-TB treatment under the NTP includes the launch pilot projects in 31 prefectures in six provinces with plans to enroll 5,000 MDR-TB patients by 2009 and scale up to 50 prefectures in ten additional provinces, treating 10,000 MDR-TB patients by 2011. Though MDR-TB management guidelines, in line with international standards, have been published and a GLC application has been approved China, is not on target to meet this goal.

³⁰ Drug susceptibility testing data were reported from a local laboratory currently conducting external quality assurance for first line drugs, but second line results have not be rechecked by a Supranational Laboratory.

The extent of resistance to second line drugs is currently unknown; however the NRL is developing capacity to conduct second line testing and MDR-TB isolates from the nationwide survey will be evaluated. China has spent considerable time expanding quality assurance for smear microscopy in the country and now has plans to upgrade culture and DST laboratories as well as expand quality assurance for drug susceptibility testing.

Trends are available from Hong Kong, SAR, China and the Republic of Korea. Trends in resistance to any drug, isoniazid, and MDR-TB continue to decline in Hong Kong, SAR, China[42] at a faster rate than TB. The TB notification rate has decreased from 103 per 100,000 in 1996 to 81 per 100,000 in 2005. The Republic of Korea has conducted four nationwide surveys. The surveys have shown a gradual but significant increase in MDR-TB[43], any resistance and isoniazid resistance among new cases. The TB notification rate has declined since 1994, but been relatively stable for the past three years. The slowing in the decline in the overall TB notification rate likely reflects the expansion of the routine registration of TB patients from the private sector. The TB notification rate in the public sector alone continued to show a decline for those same years. The last two drug resistance surveys were carried out one year apart so future surveys will be important to better understand if this is a true increase in population prevalence. The Korean Institute of Tuberculosis (KIT) which is National Reference Laboratory as well as a Supranational Reference Laboratory, conducts nearly 70% of culture and DST in the country for both the public and private sectors. Data reported in the CDC Morbidity and Mortality Weekly Report[44] showing results of a global survey of Supranational Laboratories showed that 15.4% of MDR-TB cases in Korea were XDR-TB. Because these data were biased towards hospitalized patients in the private sector it is likely that it overestimated the proportion of both MDR-TB among total isolates tested as well as MDR cases that are XDR-TB. Data from the nationwide survey showed that only 1.8% of MDR-TB cases detected in the survey had XDR-TB. Therefore, if culture and DST coverage are not complete, routine laboratory investigations may be biased towards chronic cases and treatment failure.

Currently, information on resistance to second line drugs is limited. Australia, Hong Kong and Macao, SAR, Japan, and the Republic of Korea are able to report data on second line drug resistance routinely. The Philippines has been able to report data on a GLC cohort and Viet Nam has identified one case. Thus, far the data are difficult to interpret. The proportion of XDR-TB

among MDR-TB was highest in Japan, 30.9% (95% CLs, 19.1-44.9), and Hong Kong, SAR, 14.6 (95% CLs, 13.7-16.1) respectively. Where absolute numbers of MDR-TB are low, XDR-TB may not represent a significant obstacle for TB control. However, in high burden countries where second line drugs are widely available such as China and the Philippines, further assessment of resistance to second line drugs will be a critical component of designing the strategy for the management of MDR-TB.

Currently, Cambodia, China, Micronesia, Mongolia, the Philippines, Samoa, and Viet Nam have GLC approved programmes.

Similar to the South East Asian region the Western Pacific is also faced with limited capacity for culture and drug susceptibility testing. China, Vietnam, and the Republic of Korea have extensive culture networks in the public sector, but only China has a significant number of laboratories able to conduct drug susceptibility testing. Quality assurance of DST as well as links with the private sector may also prove critical in this region in order to build the capacity necessary for the scale up outlined in the Global Plan. The Western Pacific region currently has five very active SRLs and has plans to add one more over the next year.

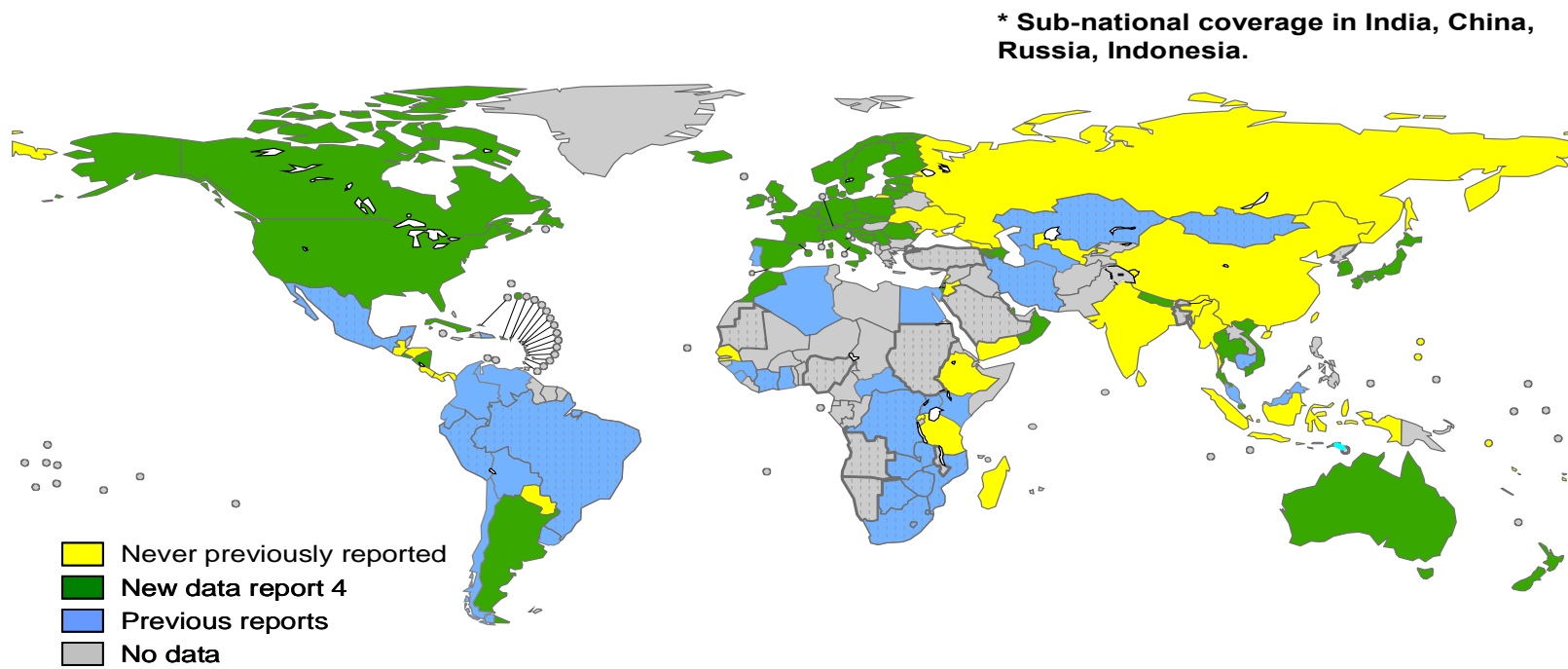
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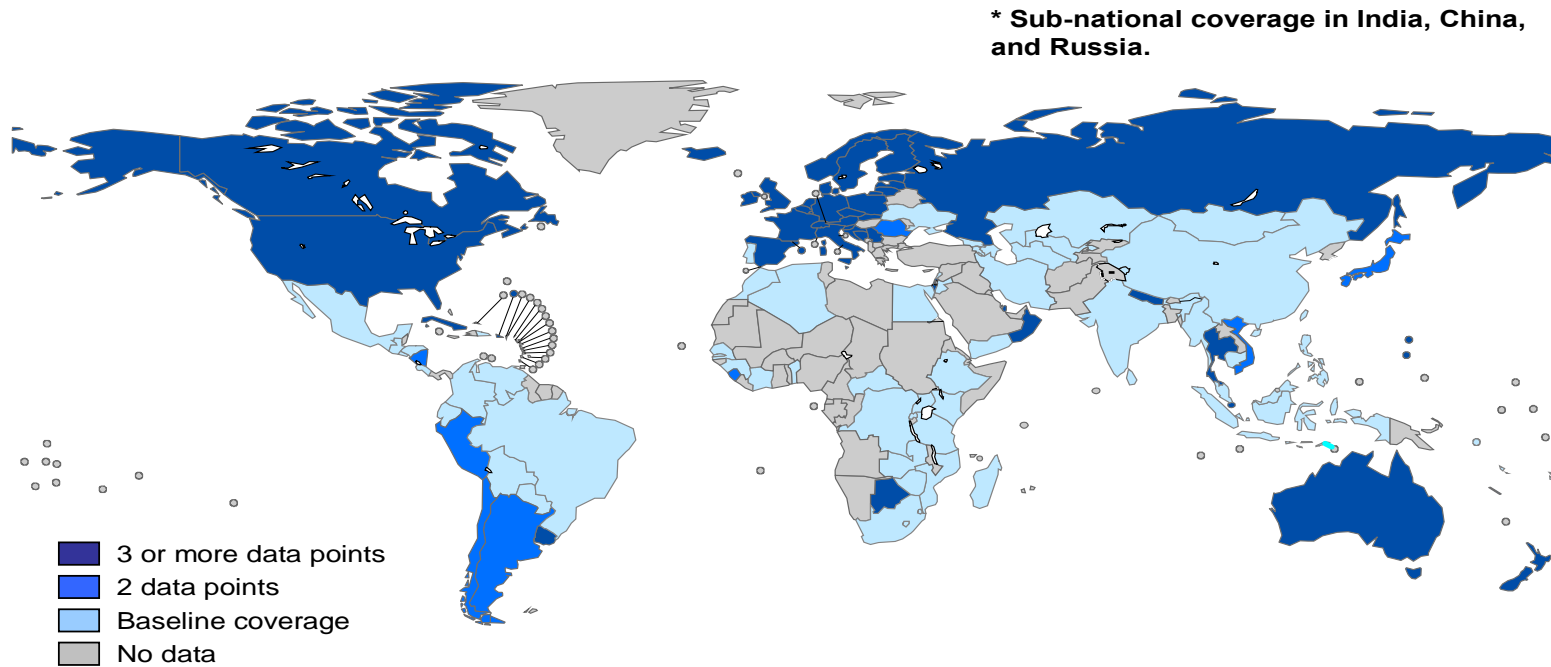
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Map 1: Global Project coverage 1994-2007



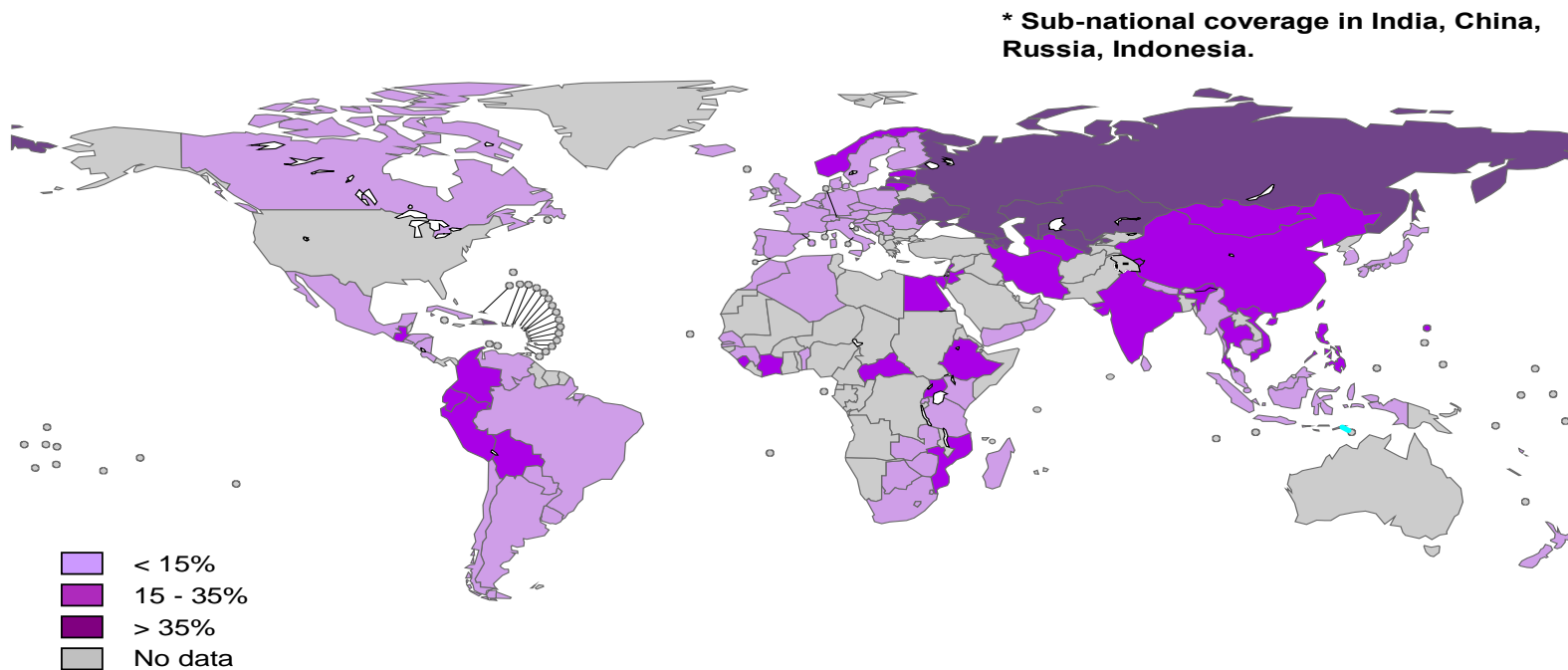
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Map 2: Available trends 1994-2007



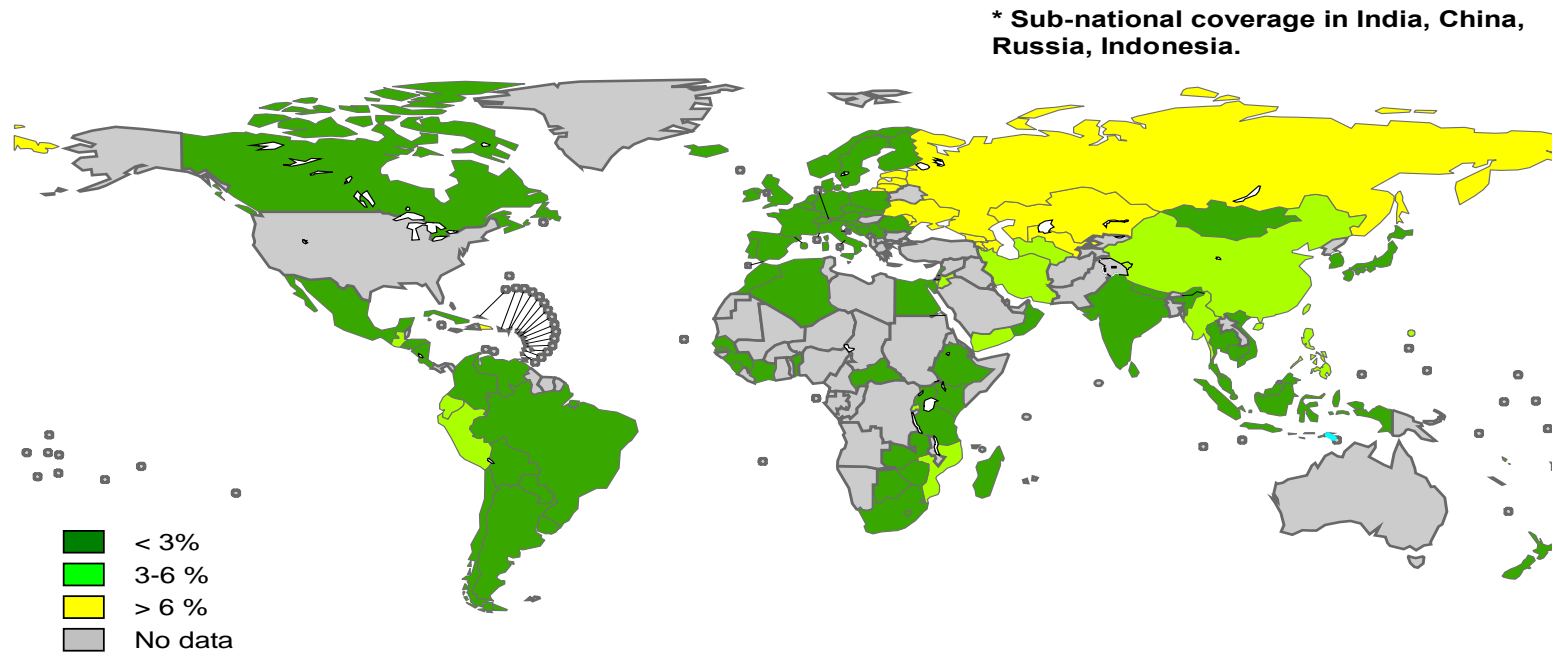
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Map 3. Any resistance among new cases 1994-



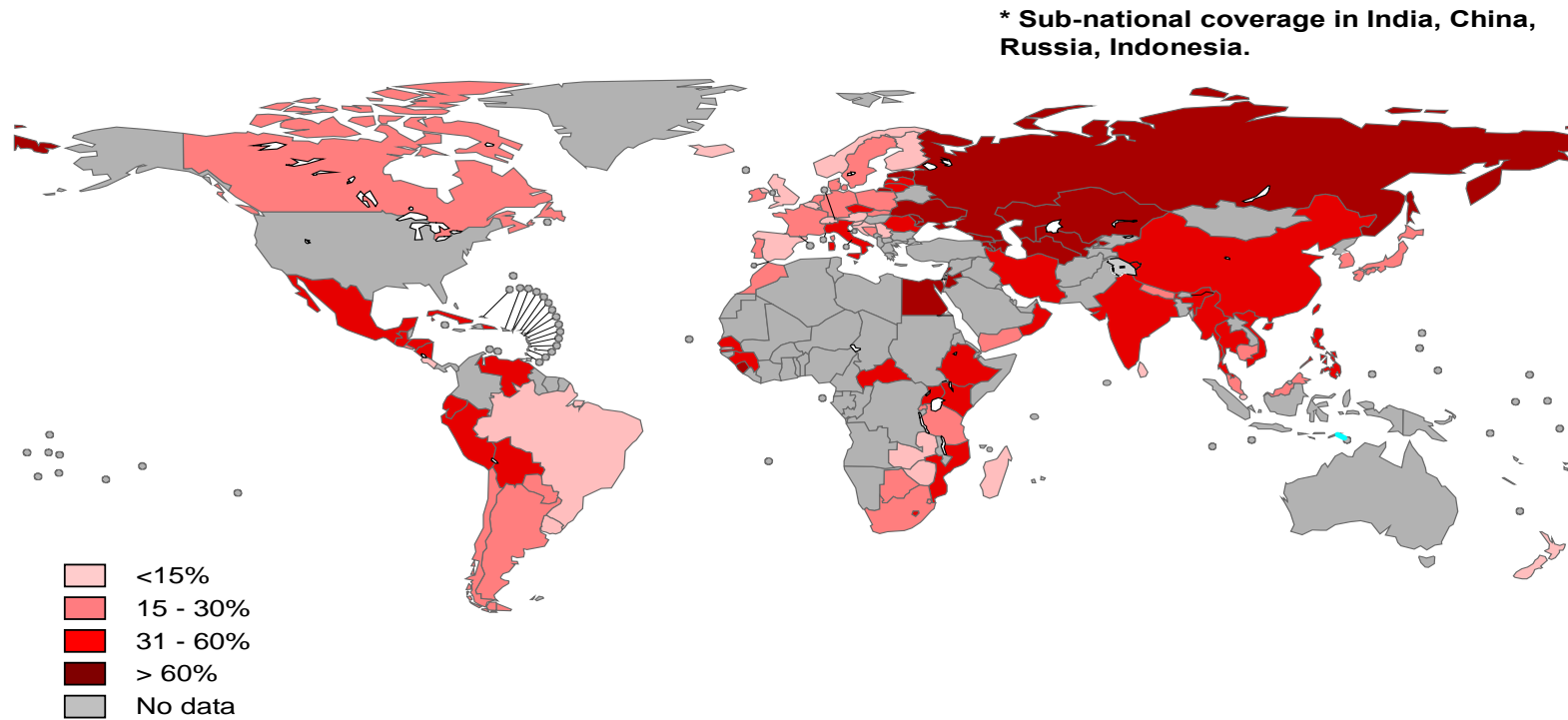
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Map 4: MDR-TB among new TB cases 1994-2007



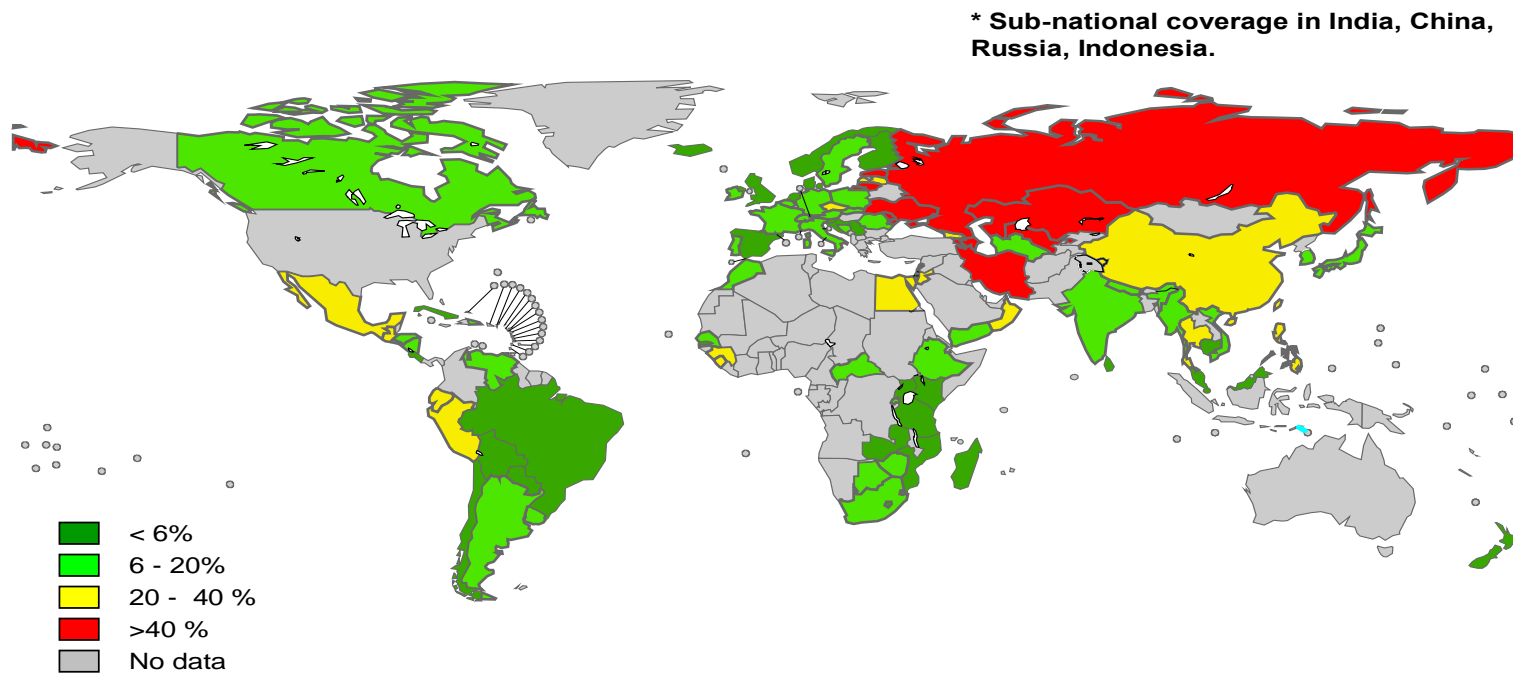
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Map 5: Any resistance among previously treated TB cases 1994-2007



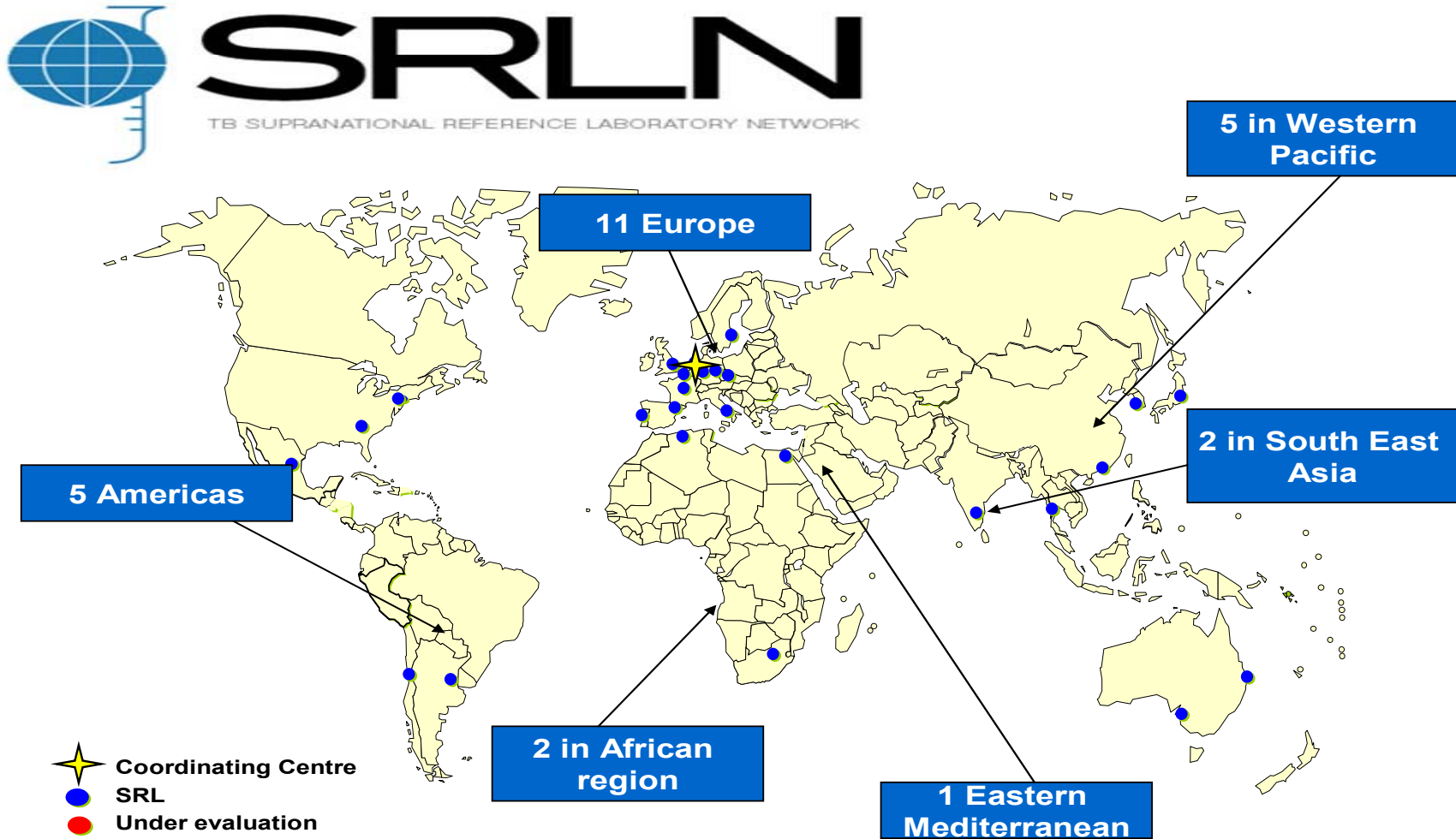
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Map 6: MDR-TB among previously treated TB cases 1994-2007



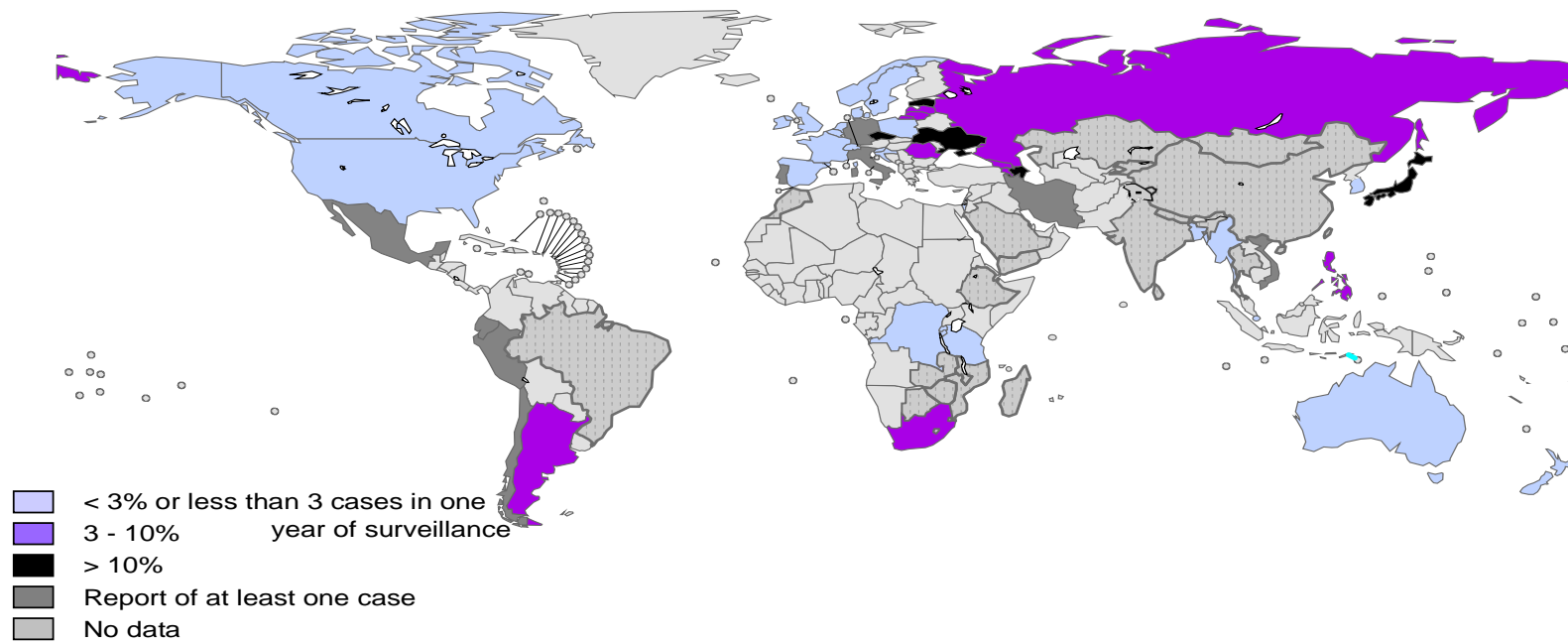
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Map 7: The Supranational Laboratory Network



Map 8: XDR-TB

* Sub-national averages applied to Russia



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Annex 1. Notified prevalence of resistance to specific drugs among new TB cases tested for resistance to at least INH and RIF (1)

Region	Country	Sub-national	Year	Method	Patients tested	Susceptible		Any resistance		Any H		Any R		Any E		Any S		Mono		Mono H		Mono R		Mono E		Mono S		MDR		HR		HRE		HRS		HRES		Poly		HE		HS		HES		RE		RS		RES		ES			
						%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%						
AFR	Algeria	Countrywide	2001	Survey	518	486	93.8	32	6.2	16	3.1	6	1.2	0	0.0	27	5.2	21	4.1	5	1.0	0	0.0	0	0.0	16	3.1	6	1.2	0	0.0	0	0.0	6	1.2	0	0.0	5	1.0	0	0.0	5	1.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
AFR	Benin	Countrywide	1997	Survey	333	305	91.6	28	8.4	18	5.4	1	0.3	2	0.6	16	4.8	20	6.0	11	3.3	0	0.0	0	0.0	9	2.7	1	0.3	0	0.0	1	0.3	0	0.0	0	0.0	7	2.1	0	0.0	6	1.8	0	0.0	0	0.0	0	0.0	0	0.0				
AFR	Botswana	Countrywide	2002	Survey	1182	1,059	89.6	123	10.4	53	4.5	24	2.0	15	1.3	82	6.9	86	7.3	22	1.9	10	0.8	2	0.2	52	4.4	10	0.8	3	0.3	2	0.2	3	0.3	2	0.2	27	2.3	2	0.2	15	1.3	4	0.3	0	0.0	3	0.3	1	0.1	2	0.2		
AFR	Central African Republic	Bangui	1998	Survey	464	388	83.6	76	16.4	44	9.5	6	1.3	11	2.4	51	11.0	50	10.8	19	4.1	1	0.2	0	0.0	30	6.5	5	1.1	2	0.4	2	0.4	0	0.0	1	0.2	21	4.5	1	0.2	13	2.8	6	1.3	0	0.0	0	0.0	0	0.0	0	0.0		
AFR	Côte d'Ivoire	Countrywide	2006	Survey	320	244	76.3	76	23.8	39	12.2	10	3.1	22	6.9	32	10.0	53	16.6	23	7.2	0	0.0	13	4.1	17	5.3	8	2.5	4	1.3	1	0.3	3	0.9	0	0.0	15	4.7	3	0.9	5	1.6	0	0.0	0	0.0	2	0.6	0	0.0	5	1.6		
AFR	DR Congo	Kinshasa	1999	Survey	combined only																																																		
AFR	Ethiopia	Countrywide	2005	Survey	804	588	73.1	216	26.9	62	7.7	22	2.7	19	2.4	187	23.3	165	20.5	16	2.0	8	1.0	1	0.1	140	17.4	13	1.6	3	0.4	0	0.0	1	0.1	9	1.1	38	4.7	1	0.1	28	3.5	4	0.5	0	0.0	1	0.1	0	0.0	4	0.5		
AFR	Gambia	Countrywide	2000	Survey	210	201	95.7	9	4.3	5	2.4	2	1.0	0	0.0	3	1.4	8	3.8	4	1.9	1	0.5	0	0.0	3	1.4	1	0.5	1	0.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
AFR	Guinea	Sentinel sites	1998	Survey	539	460	85.3	79	14.7	50	9.3	4	0.7	3	0.6	51	9.5	53	9.8	24	4.5	1	0.2	0	0.0	28	5.2	3	0.6	1	0.2	0	0.0	2	0.4	0	0.0	23	4.3	2	0.4	20	3.7	1	0.2	0	0.0	0	0.0	0	0.0	0	0.0		
AFR	Kenya	Nearly Countrywide	1995	Survey	445	417	93.7	28	6.3	28	6.3	0	0.0	0	0.0	4	0.9	24	5.4	24	5.4	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	4	0.9	0	0.0	4	0.9	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
AFR	Lesotho	Countrywide	1995	Survey	330	301	91.2	29	8.8	26	7.9	3	0.9	0	0.0	10	3.0	20	6.1	17	5.2	0	0.0	0	0.0	3	0.9	3	0.9	2	0.6	0	0.0	1	0.3	0	0.0	6	1.8	0	0.0	6	1.8	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
AFR	Madagascar (2)	Countrywide	1997	Survey	810	759	93.7	51	6.3	37	4.6	4	0.5	4	0.5	26	3.2	42	5.2	28	3.5	0	0.0	0	0.0	20	2.5	4	0.5	1	0.1	1	0.1	0	0.0	2	0.2	5	0.6	1	0.1	4	0.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
AFR	Mozambique	Countrywide	2009	Survey	1028	814	79.2	214	20.8	170	16.5	54	5.3	5	0.5	108	10.5	125	12.2	81	7.9	18	1.8	0	0.0	26	2.5	36	3.5	7	0.7	0	0.0	24	2.3	5	0.5	53	5.2	0	0.0	53	5.2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
AFR	Rwanda	Countrywide	2005	Survey	616	552	89.6	64	10.4	38	6.2	24	3.9	32	5.2	46	7.5	33	5.4	7	1.1	0	0.0	1	0.1	16	2.6	24	3.9	1	0.2	0	0.0	3	0.3	21	3.4	7	1.1	0	0.0	6	1.0	1	0.2	0	0.0	0	0.0	0	0.0	0	0.0		
AFR	Senegal	Countrywide	2006	Survey	237	212	89.5	25	10.5	10	4.2	5	2.1	8	3.4	18	7.6	18	7.6	3	1.3	0	0.0	0	0.0	1.3	12	5.1	5	2.1	0	0.0	1	0.4	1	0.4	3	1.3	2	0.8	0	0.0	1	0.4	0	0.0	0	0.0	0	0.0	0	0.0			
AFR	Sierra Leone	Nearly Countrywide	1997	Survey	117	88	75.2	29	24.8	12	10.3	1	0.9	0	0.0	25	21.4	21	17.9	4	3.4	0	0.0	0	0.0	17	14.5	1	0.9	0	0.0	0	0.0	1	0.9	0	0.0	7	6.0	0	0.0	7	6.0	0	0.0	0	0.0	0	0.0	0	0.0				
AFR	South Africa	Countrywide	2002	Survey	4243	3,906	92.1	337	7.9	249	5.9	91	2.1	38	0.9	178	4.2	197	4.6	109	2.6	14	0.3	0	0.0	74	1.7	77	1.8	21	0.5	10	0.2	26	0.6	20	0.5	63	1.5	5	0.1	55	1.3	3	0.1	0	0.0	0	0.0	0	0.0	0	0.0		
AFR	Swaziland	Countrywide	1995	Survey	334	295	88.3	39	11.7	30	9.0	3	0.9	3	0.9	24	7.2	22	6.6	13	3.9	0	0.0	1	0.3	8	2.4	3	0.9	0	0.0	1	0.3	2	0.6	0	0.0	14	4.2	0	0.0	13	3.9	1	0.3	0	0.0	0	0.0	0	0.0	0	0.0		
AFR	Uganda	3 GLRA Zones *	1997	Survey	374	300	80.2	74	19.8	25	6.7	3	0.8	23	6.1	50	13.4	48	12.8	12	3.2	1	0.3	9	2.4	26	7.0	2	0.5	1	0.3	1	0.3	0	0.0	0	0.0	24	6.4	0	0.0	11	2.9	0	0.0	0	0.0	0	0.0	0	0.0	13	3.5		
AFR	UR Tanzania (2)	Countrywide	2007	Survey	369	346	93.8	23	6.2	16	4.3	4	1.1	3	0.8	13	3.5	15	4.1	8	2.2	0	0.0	0	0.0	7	1.9	4	1.1	0	0.0	1	0.3	2	0.5	1	0.3	4	1.1	1	0.3	3	0.8	0	0.0	0	0.0	0	0.0	0	0.0				
AFR	Zambia	Countrywide	2000	Survey	445	394	88.5	51	11.5	28	6.3	8	1.8	9	2.0	24	5.4	38	8.5	15	3.4	0	0.0	3	0.7	20	4.5	8	1.8	4	0.9	3	0.7	0	0.0	1	0.2	5	1.1	2	0.4	3	0.7	0	0.0	0	0.0	0	0.0	0	0.0				
AFR	Zimbabwe	Nearly Countrywide	1995	Survey	676	654	96.7	22	3.3	22	3.3	13	1.9	4	0.6	5	0.7	9	1.3	9	1.3	0	0.0	0	0.0	13	1.9	8	1.2	0	0.0	1	0.1	4	0.6	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0				
AMR	Argentina	Countrywide	2005	Survey	683	615	90.0	68	10.0	39	5.7	6	0.9	4	0.6	44	6.4	43	6.3	14	2.0	1	0.1	1	0.1	27	4.0	15	2.2	7	1.0	1	0.1	5	0.7	2	0.3	10	1.5	0	0.0	10	1.5	0	0.0	0	0.0	0	0.0	0	0.0				
AMR	Bolivia	Countrywide	1998	Survey	498	371	74.5	127	25.5	51	10.2	30	6.0	25	5.0	49	9.8	100	20.1	34	6.8	14	2.8	18	3.6	34	6.8	8	1.2	5	1.0	0	0.0	1	0.2	0	0.0	21	4.2	2	0.4	9	1.8	0	0.0	5	1.0	0	0.0	0	0.0				
AMR	Brazil	Nearly Countrywide	1996	Survey	2095	1,915	91.4	180	8.6	124	5.9	23	1.1	3	0.1	76	3.6	135	6.4	79	3.8	4	0.2	2	0.1	50	2.4	19	0.9	18	0.9	0	0.0	1	0.0	0	0.0	26	1.2	1	0.0	25	1.2	0	0.0	0	0.0	0	0.0	0	0.0				
AMR	Canada	Countrywide	2005	Surveillance	1087	957	88.0	130	12.0	89	8.2	15	1.4	15	1.4	62	5.7	98	9.0	57	5.2	2	0.2	5	0.5	34	3.1	13	1.2	2	0.2	1	0.1	5	0.5	5	0.5	19	1.7	1	0.1	15	1.4	3	0.3	0	0.0	0	0.0	0	0.0				
AMR	Chile	Countrywide	2001	Survey	867	776	89.5	91	10.5	39	4.5	7	0.8	2	0.2	78																																							

Annex 4. Survey methods 1994-2007

Region	Country	Sub-national	Year	Report	Population in area surveyed	TB patients notified in area surveyed	sm+ TB patients notified in area surveyed	Patients tested	Method	Survey duration (months)	Medical record/ TB register cross check	Patient interview	Re-interview	Sample target complete	Software
AFR	Algeria	Countrywide	2001	3	32,853,798	21,501	8,654	713	Proportionate cluster	12		Structured questionnaire		Yes	
AFR	Benin	Countrywide	1997	1	8,438,853	3,457	2,739	337	Proportionate cluster	24			No	Yes	
AFR	Botswana	Countrywide	2002	3	1,764,926	10,104	3,170	548	100% diagnostic units	8		Structured questionnaire	No	Yes	
AFR	Central African Republic	Bangui	1998	2	620,000	3,338	2,153	291	100% diagnostic units	3			No	Yes	
AFR	Côte d'Ivoire	Countrywide	2006	4	18,153,867	20,026	12,496	980	Proportionate cluster			Structured questionnaire		Yes	
AFR	DR Congo	Kinshasa	1999	3		18,207	10,710	1,338	Proportionate cluster			Structured questionnaire	No		
AFR	Ethiopia	Countrywide	2005	4	77,430,702	125,135	38,525	3,119	Proportionate cluster	12		Structured questionnaire		Slightly under target	
AFR	Gambia	Countrywide	2000	3	1,517,079	2,120	1,127	166	100% diagnostic units	7			No	Yes	
AFR	Guinea	Sentinel sites	1998	2	7,164,893	7,000	3,362	120	Random cluster	10			No	Yes	
AFR	Kenya	Nearly Countrywide	1995	1	34,255,722	108,401	40,389	8,975	Proportionate cluster	5			No		
AFR	Lesotho	Countrywide	1995	1	1,794,769	11,404	4,280	1,041	Proportionate cluster	18			No	Yes	
AFR	Madagascar	Countrywide	2007	4	18,605,921	19,475	13,056	1,498	Proportionate cluster	23	Yes	Structured questionnaire	Yes	Yes	Epi Info
AFR	Mozambique	Countrywide	1999	2	19,792,295	33,718	17,877	1,886	Proportionate cluster	9		Structured questionnaire	No	Yes	
AFR	Rwanda	Countrywide	2005	4	9,037,690	7,680	4,166	831	100% diagnostic units	4	Yes	Structured questionnaire	Yes	Yes	SPSS
AFR	Senegal	Countrywide	2006	4	11,658,172	10,120	6,722	920	Proportionate cluster	16	Yes	Structured questionnaire	Yes	Yes	SDRTB4
AFR	Sierra Leone	Nearly Countrywide	1997	2	5,525,478	6,930	4,370	330	Random cluster	6			No	Yes	
AFR	South Africa	Countrywide	2002	3	47,431,829	302,467	125,460	60,588	Proportionate cluster	12		Structured questionnaire	No	Yes	
AFR	Swaziland	Countrywide	1995	1	1,032,438	8,864	2,187	470	Proportionate cluster	18			No	Yes	
AFR	Uganda	3 GLRA Zones *	1997	2	9,919,700	16,000	5,405	5,405	Proportionate cluster	18			No	Yes	
AFR	UR Tanzania	Countrywide	2007	4	38,328,809	64,200	25,264	5,032	Proportionate cluster	16		Structured questionnaire	Yes	Unfinished	MS Excel and Epi Info
AFR	Zambia	Countrywide	2000	3	11,668,457	53,267	14,857	5,496	Proportionate cluster	14		Structured questionnaire	No	Yes	
AFR	Zimbabwe	Nearly Countrywide	1995	1	13,009,534	54,891	13,155	5,941	All diagnostic centers	30		Structured questionnaire	No	Yes	
AMR	Argentina	Countrywide	2005	4	38,747,148	11,242	4,709	809	Proportionate cluster	12	Yes	Structured questionnaire	Yes	Slightly under target	SDRTB4 Epi Info
AMR	Bolivia	Countrywide	1996	1	9,182,015	9,973	6,278	772	Proportionate cluster	11			No	Yes	
AMR	Brazil	Nearly Countrywide	1996	1	186,404,913	87,223	42,093	9,637	Proportionate cluster	14					
AMR	Canada	Countrywide	2005	4	32,268,243	1,616	433	103	All bacteriologically confirmed cases (100%)	12	Yes	Routine	Yes	Yes	Oracle and MS Access
AMR	Chile	Countrywide	2001	3	16,295,102	2,225	1,186	232	Proportionate cluster	6		Structured questionnaire	No	Yes	
AMR	Colombia	Countrywide	2000	3	45,600,244	10,360	6,870	443	Proportionate cluster	12			No	Yes	
AMR	Costa Rica	Countrywide	2006	4	4,327,228	560	330	45	100% diagnostic units	16	Yes	Structured questionnaire	Yes	No	SDRTB4
AMR	Cuba	Countrywide	2005	4	11,269,400	781	467	49	Proportionate cluster	12	Yes	Routine	Yes	Yes	MS Excel
AMR	Dominican Republic	Countrywide	1995	1	8,894,907	5,312	2,949	729	Proportionate cluster	21			No	Yes	
AMR	Ecuador	Countrywide	2002	3	13,228,423	4,808	3,048	795	100% diagnostic units	18		Structured questionnaire	No	Yes	
AMR	El Salvador	Countrywide	2001	3	6,880,951	1,830	1,059	114	100% diagnostic units	12		Structured questionnaire		Yes	
AMR	Guatemala	Countrywide	2002	4	12,599,059	3,861	2,420	159	Proportionate cluster	10		Structured questionnaire	Yes	Yes	MS Excel
AMR	Honduras	Countrywide	2004	3	7,204,723	3,333	2,069	181	Proportionate cluster	30	Yes	Structured questionnaire	Yes	Yes	SDRTB4
AMR	Mexico	Baja California, Sinaloa, Oaxaca	1997	2	94,732,320	19,932	11,997	2,026	100% diagnostic units	7			No		
AMR	Nicaragua	Countrywide	2006	4		-	-	-	Proportionate cluster	17	Yes	Structured questionnaire	Yes	Yes	SDRTB4 and Epi Info
AMR	Paraguay	Countrywide	2001	4	6,158,259	2,348	1,260	273	Proportionate cluster			Structured questionnaire		Yes	
AMR	Peru	Countrywide	2006	4	27,968,244	35,541	18,490	4,989	Proportionate cluster	8	Yes	Structured questionnaire	Yes	Yes	SDRTB4 National surveillance system
AMR	Puerto Rico	Countrywide	2005	4	3,954,584	113	60	-	All bacteriologically confirmed cases (100%)	12	No	Not collected at National level	No	NA	TIMS and SAS
AMR	Uruguay	Countrywide	2005	4	3,463,197	626	355	19	Structured questionnaire	12		Structured questionnaire		Yes	
AMR	USA	Countrywide	2005	4	298,212,895	14,097	5,089	-	All bacteriologically confirmed cases (100%)	12		Not collected at National level	No	NA	TIMS and SAS
AMR	Venezuela	Countrywide	1999	3	26,749,114	6,950	3,653	350	Proportionate cluster	9		Structured questionnaire	No	Yes	
EMR	Egypt	Countrywide	2002	3	74,032,884	11,735	5,217	738	Proportionate cluster	12		Structured questionnaire	No	Yes	
EMR	Iran	Countrywide	1998	2	69,515,206	9,608	4,686	474	Random cluster	18			No	Yes	
EMR	Jordan	Countrywide	2004	4	5,702,776	371	86	10	100% diagnostic units	12	Yes	Structured questionnaire	Yes	Yes	MS Excel
EMR	Lebanon	Countrywide	2003	4	3,576,818	391	131	4	100% diagnostic units	22	Yes	Structured questionnaire	Yes	Yes	MS Excel
EMR	Morocco	Countrywide	2006	4	31,478,460	26,269	12,757		Proportionate cluster	22	Yes	Structured questionnaire	Yes	Yes	Epi Info

Region	Country	Sub-national	Year	Report	Population in area surveyed	TB patients notified in area surveyed	sm+ TB patients notified in area surveyed	Patients tested	Method	Survey duration (months)	Medical record/ TB register cross check	Patient interview	Re-interview	Sample target complete	Software
EMR	Oman	Countrywide	2006	4	2,566,981	261	131	4	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EMR	Qatar	Countrywide	2006	4	812,842	325	96	-	All bacteriologically confirmed cases (100%)	12	Yes	Routine		NA	
EMR	Yemen	Countrywide	2004	4	20,974,655	9,063	3,379	351	100% diagnostic units	12		Structured questionnaire			MS Excel
EUR	Andorra	Countrywide	2005	4	67,151	10	5	-	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EUR	Armenia	Countrywide	2007	4	3,016,312	2,322	581	327	100% diagnostic units	13	Yes	Structured questionnaire	Yes	Yes	
EUR	Austria	Countrywide	2005	4	8,189,444	954	234	26	All bacteriologically confirmed cases (100%)	12		Routine		NA	SDRTB4
EUR	Azerbaijan	Baku City	2007	4	1,827,500	3,960	781	-	100% diagnostic units	11	Yes	Structured questionnaire	Yes	Yes	
EUR	Belgium	Countrywide	2005	4	10,419,049	1,144	380	68	All bacteriologically confirmed cases (100%)	12		Routine		NA	SDRTB4 and MS Excel
EUR	Bosnia & Herzegovina	Countrywide	2005	4	3,907,074	2,160	640	156	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EUR	Croatia	Countrywide	2005	4	4,531,338	1,144	372	94	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EUR	Czech Republic	Countrywide	2005	4	10,219,603	1,007	308	34	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EUR	Denmark	Countrywide	2005	4	5,430,590	424	129	29	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EUR	Estonia	Countrywide	2005	4	1,329,697	519	162	94	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EUR	Finland	Countrywide	2005	4	5,249,060	361	130	22	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EUR	France	Countrywide	2005	4	60,495,537	5,374	1,941	371	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EUR	Georgia	Countrywide	2006	4	4,474,404	6,448	1,509	2,152	100% diagnostic units	12	Yes	Structured questionnaire	Yes	Yes	
EUR	Germany	Countrywide	2005	4	82,689,210	6,045	1,379	493	All bacteriologically confirmed cases (100%)	12		Routine		NA	SDRTB3
EUR	Iceland	Countrywide	2005	4	294,561	11	2	1	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EUR	Ireland	Countrywide	2005	4	4,147,901	461	130	40	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EUR	Israel	Countrywide	2005	4	6,724,564	406	98	7	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EUR	Italy	Half of the country	2005	4				-	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EUR	Kazakhstan	Countrywide	2001	3	14,825,105	31,187	6,911	8,884	100% diagnostic units	2		Structured questionnaire	No	Yes	
EUR	Latvia	Countrywide	2005	4	2,306,988	1,443	536	205	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EUR	Lithuania	Countrywide	2005	4	3,431,033	2,574	964	460	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EUR	Luxembourg	Countrywide	2005	4	464,904	37	14	-	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EUR	Malta	Countrywide	2005	4	401,630	23	5	1	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EUR	Netherlands	Countrywide	2005	4	16,299,173	1,157	237	44	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EUR	Norway	Countrywide	2005	4	4,620,275	290	48	14	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EUR	Poland	Countrywide	2004	4	38,529,562	9,280	2,823	1,077	100% diagnostic units	12	Yes	Routine		Yes	
EUR	Portugal	Countrywide	2005	4	10,494,502	3,536	1,302	350							
EUR	Republic of Moldova	Countrywide	2006	4	4,205,747	6,278	1,696	1,777	100% diagnostic units	12	Yes	Routine	Yes	Yes	
EUR	Romania	Countrywide	2004	4	21,711,472	29,347	10,801	6,938	100% diagnostic units	12		Structured questionnaire		Yes	
EUR	Russian Federation	Ivanovo Oblast	2002	3	1,114,925	1,363	684		All bacteriologically confirmed cases (100%)	12			No	NA	
EUR	Russian Federation	Orel Oblast	2006	4	842,351	486	286	-	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EUR	Russian Federation	Mary El oblast	2006	4	716,850	588	480	-	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EUR	Russian Federation	Tomsk Oblast	2005	4	1,036,500	990	968	215	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EUR	Serbia	Countrywide	2005	4				-	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EUR	Slovakia	Countrywide	2005	4	5,400,908	760	162	108	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EUR	Slovenia	Countrywide	2005	4	1,966,814	278	109	29	All bacteriologically confirmed cases (100%)	12		Routine		NA	MS Excel
EUR	Spain	Galicia	2005	4	2,750,985	1,053	361	96	All bacteriologically confirmed cases (100%)	12	Yes	Structured questionnaire	Yes	NA	MS Access
EUR	Spain	Aragon	2005	4	1,230,090	255	121	26	All bacteriologically confirmed cases (100%)	12	Yes	Structured questionnaire	No	NA	
EUR	Spain	Barcelona	2005	4	2,736,589	410	109	-	All bacteriologically confirmed cases (100%)	12		Structured questionnaire	Yes	NA	
EUR	Sweden	Countrywide	2005	4	9,041,262	569	134	30	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EUR	Switzerland	Countrywide	2005	4	7,252,331	626	108	118	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EUR	Turkmenistan	Dashoguz Velayat (Aral Sea Region)	2002	3	1,141,900	1,300	366	425	100% diagnostic units	9			No	Yes	
EUR	Ukraine	Donetsk	2006	4	4,659,018	6,346	1,283	1,764	100% diagnostic units	12	Yes	Structured questionnaire	Yes	Yes (civilian only)	
EUR	United Kingdom	Countrywide	2005	4	59,667,844	8,633	1,821	460	All bacteriologically confirmed cases (100%)	12		Routine		NA	
EUR	Uzbekistan	Tashkent	2005	4		4,839	2,847	-	100% diagnostic units	12		Structured questionnaire		Yes	
SEAR	India	Mayhurbhanj District, Orissa State	2001	4	2,400,000	4,412	2,130	155	100% diagnostic units	9	Yes	Structured questionnaire	Yes	Slightly under target	
SEAR	India	Wardha District, Maharashtra State	2001	3	1,300,000	1,826	726	183	100% diagnostic units	10		Structured questionnaire	No	Yes	MS Excel and SPSS

Region	Country	Sub-national	Year	Report	Population in area surveyed	TB patients notified in area surveyed	sm+ TB patients notified in area surveyed	Patients tested	Method	Survey duration (months)	Medical record/ TB register cross check	Patient interview	Re-interview	Sample target complete	Software
SEAR	India	Delhi State	1995	1	16,000,000	45,717	12,703	6,008	100% diagnostic units	6		Structured questionnaire	No	Yes	
SEAR	India	Raichur District, Karnataka State	1999	3	1,800,000	3,047	1,289	492	100% diagnostic units	6		Structured questionnaire	No	Yes	
SEAR	India	North Arcot District, Tamil Nadu State	1999	3	5,664,823	5,600	2,000	952	100% diagnostic units	3		Structured questionnaire	No	Yes	
SEAR	India	Emakulam district, Kerala State	2004	4	3,200,000	2,598	1,117	262	100% diagnostic units	4	Yes	Structured questionnaire	Yes	Yes	
SEAR	India	Gujarat State	2006	4	54,900,000	77,087	30,289	15,986	Proportionate cluster	10	Yes	Structured questionnaire	Yes	Yes	
SEAR	India	Tamil Nadu State	1997	2	64,800,000	92,725	37,254	7,602	Proportionate cluster	2		Structured questionnaire	No	Yes	
SEAR	India	Hoogli district, West Bengal State	2001	4	5,400,000	6,996	2,958	608	100% diagnostic units	11	Yes	Structured questionnaire	Yes	Slightly under target	MS Excel, Access, and STATA
SEAR	Indonesia	Mimika district, Papua Province	2004	4	131,715	410	194	-	100% diagnostic units	10	Yes	Structured questionnaire	Yes	Yes	Epi Info
SEAR	Myanmar	Countrywide	2003	4	50,519,492	107,991	36,541	5,597	Proportionate cluster	11	Yes	Structured questionnaire	Yes	Yes	SDRTB and MS Access
SEAR	Nepal	Countrywide	2007	4	27,132,629	34,077	14,617	2,973	Proportionate cluster	12	Yes	Structured questionnaire	Yes	Yes	
SEAR	Sri Lanka	Countrywide	2006	4	20,742,905	9,695	4,868	510	All bacteriologically confirmed cases (100%)	12		Structured questionnaire	Yes	Yes	SDRTB4
SEAR	Thailand	Countrywide	2006	4	64,232,758	57,895	29,762	1,795	Proportionate cluster	19	Yes	Structured questionnaire	Yes	Yes	
WPR	Australia	Countrywide	2005	4	20,155,129	1,072	244	31	All bacteriologically confirmed cases (100%)	12			No	NA	
WPR	Cambodia	Countrywide	2001	3	14,071,014	36,123	21,001	1,306	Proportionate cluster	7	Yes	Structured questionnaire	No	Yes	
WPR	China	Guandong Province	1999	2	88,890,000	54,609	32,268	7,645	Proportionate cluster	12		Structured questionnaire	Yes	Yes	MS Excel
WPR	China	Beijing Municipality	2004	4	15,380,000	2,866	1,015	433	100% diagnostic units	12	Yes	Structured questionnaire	Yes	Yes	
WPR	China	Shandong Province	1997	2	92,840,000	38,880	30,234	5,443	Proportionate cluster	12		Structured questionnaire		Yes	
WPR	China	Henan Province	2001	3	97,170,000	80,827	42,075	1,201	Proportionate cluster	12		Structured questionnaire		Yes	
WPR	China	Liaoning Province	1999	3	42,280,000	23,390	12,013	1,465	Proportionate cluster	12		Structured questionnaire		Yes	
WPR	China	Heilongjiang Province	2005	4	38,160,000	37,925	19,214	4,630	Proportionate cluster	12	No	Structured questionnaire	Yes	Yes	SDRTB4
WPR	China	Hubei Province	1999	3	60,310,000	51,109	33,218	5,868	Proportionate cluster	10		Structured questionnaire		Yes	
WPR	China	Zhejiang Province	1999	2	47,200,000	37,568	14,658	5,259	Proportionate cluster	12		Structured questionnaire		Yes	SDRTB4
WPR	China	Shanghai Municipality	2005	4	17,780,000	7,224	3,123	942	100% diagnostic units	12		Structured questionnaire	Yes	Yes	
WPR	China	Inner Mongolia Autonomous region	2002	4	23,850,000	20,478	11,574	3,204	Proportionate cluster	13		Structured questionnaire	Yes	Yes	Visual Foxpro and MS Excel
WPR	China, Hong Kong SAR	Hong Kong	2005	4				-	All bacteriologically confirmed cases (100%)	12		Routine	Yes	NA	MS Access
WPR	China, Macao SAR	Macao	2005	4	460,162	415	136	31	All bacteriologically confirmed cases (100%)	12		Routine		NA	
WPR	Fiji	Countrywide	2006	4				-	Random cluster	12					
WPR	Guam	Countrywide	2002	4				-	Random cluster						MS Excel
WPR	Japan	Countrywide	2002	4	128,084,652	28,319	10,931	1,992	100% diagnostic units	11	Yes	Routine	Yes	Yes	
WPR	Malaysia	Peninsular Malaysia	1997	2	16,489,355	16,066	8,446	983	Proportionate cluster	17			No	Yes	
WPR	Mongolia	Countrywide	1999	3	2,646,487	4,743	1,868	341	100% diagnostic units	7		Structured questionnaire	No	Yes	
WPR	New Caledonia	Countrywide	2005	4				-	Random cluster					Yes	SAS
WPR	New Zealand	Countrywide	2006	4	4,027,947	355	140	19	All bacteriologically confirmed cases (100%)	12	Yes	Routine	Yes	NA	
WPR	Northern Mariana Is	Countrywide	2006	4				-	All bacteriologically confirmed cases (100%)	12	Yes				
WPR	Philippines	Countrywide	2004	4	83,054,478	137,100	81,647	3,957	Proportionate cluster	12		Structured questionnaire		Yes	
WPR	Rep. Korea	Countrywide	2004	4	47,816,936	46,969	11,638	7,098	Proportionate cluster			Routine			National Surveillance system
WPR	Singapore	Countrywide	2005	4	4,325,539	1,469	552	153	All bacteriologically confirmed cases (100%)	12		Routine	Yes	NA	
WPR	Solomon Islands	Countrywide	2004	4	477,742	397	169	5	Random cluster						
WPR	Vanuatu	Countrywide	2006	4	211,367	81	35	8	Random cluster					Yes	
WPR	Viet Nam	Countrywide	2006	4	84,238,231	95,970	55,570	7,301	Proportionate cluster			Structured questionnaire			

Annex 5. Laboratory methods 1994-2007

Region	Country	Sub-national	Year	Supranational Laboratory	Culture method	DST method	Number of culture labs used in survey	Number of DST labs used in survey	H	R	E	S	PZA	Km	Ank	Cap	Cip	Off	% agreement H	% agreement R	Rechecking			
AFR	Algeria	Countrywide	2001	Laboratoire de la Tuberculose, Institut Pasteur d'Algérie, Alger, ALGERIA	Löwenstein-Jensen	Proportion method	1	1													Yes			
AFR	Benin	Countrywide	1997	Laboratoire de la Tuberculose, Institut Pasteur d'Algérie, Alger, ALGERIA	Löwenstein-Jensen	Proportion method															Yes			
AFR	Botswana	Countrywide	2002	Centers for Disease Control and Prevention, Mycobacteriology/ Tuberculosis Laboratory, Georgia, USA	BACTEC 460	Resistance ratio method																		
AFR	Central African Republic	Bangui	1998	Institut Pasteur, Centre National de Référence des Mycobactéries, Paris, FRANCE	Löwenstein-Jensen	Proportion method																		
AFR	Côte d'Ivoire	Countrywide	2006	Institut Pasteur, Centre National de Référence des Mycobactéries, Paris, FRANCE		Proportion method															Yes			
AFR	DR Congo	Kinshasa	1999	Département de Microbiologie/Unité de Mycobactériologie/Institut de Médecine Tropicale, Antwerp, BELGIUM																	Yes			
AFR	Ethiopia	Countrywide	2005	National Institute of Public Health and the Environment (RIVM), Bilthoven, NETHERLANDS	Löwenstein-Jensen	Proportion method	1	1													Yes			
AFR	Gambia	Countrywide	2000	Health Protection Agency, National Mycobacterium Reference Unit, Department of Infectious Diseases, UNITED KINGDOM	Löwenstein-Jensen and BACTEC 460	Resistance ratio method	1	1													Yes			
AFR	Guinea	Sentinel sites	1998	Institut Pasteur, Centre National de Référence des Mycobactéries, Paris, FRANCE	Löwenstein-Jensen	Proportion method															Yes			
AFR	Kenya	Nearby Countrywide	1995	Health Protection Agency, National Mycobacterium Reference Unit, Department of Infectious Diseases, UNITED KINGDOM	Löwenstein-Jensen	Resistance ratio method																		
AFR	Lesotho	Countrywide	1995	The Medical Research Council, TB Research Lead Programme, Pretoria, SOUTH AFRICA	Löwenstein-Jensen	Proportion method																		
AFR	Madagascar	Countrywide	2007	Health Protection Agency, National Mycobacterium Reference Unit, Department of Infectious Diseases, UNITED KINGDOM	Löwenstein-Jensen	Proportion method	1	1	0.1	40.0	2.0	4.0									Yes			
AFR	Mozambique	Countrywide	1999	Swedish Institute for Infectious Disease Control (SIDC), Solna, SWEDEN	Löwenstein-Jensen	Proportion method																		
AFR	Rwanda	Countrywide	2005	Département de Microbiologie/Unité de Mycobactériologie/Institut de Médecine Tropicale, Antwerp, BELGIUM	Various	Proportion method	1	1	0.2	40.0	2.0	4.0		6	10	2	100	100			Yes			
AFR	Senegal	Countrywide	2006	Département de Microbiologie/Unité de Mycobactériologie/Institut de Médecine Tropicale, Antwerp, BELGIUM	Löwenstein-Jensen	Proportion method	1	1	0.2	40.0	2.0	4.0									Yes			
AFR	Sierra Leone	Nearby Countrywide	1997	Armauer Hansen Institut, Würzburg, GERMANY	Löwenstein-Jensen	Proportion method															Yes			
AFR	South Africa	Countrywide	2002	The Medical Research Council, TB Research Lead Programme, Pretoria, SOUTH AFRICA	Löwenstein-Jensen	Proportion method															NA			
AFR	Swaziland	Countrywide	1995	The Medical Research Council, TB Research Lead Programme, Pretoria, SOUTH AFRICA	Löwenstein-Jensen	Proportion method																		
AFR	Uganda	3 GLRA Zones *	1997	Armauer Hansen Institut, Würzburg, Germany	Löwenstein-Jensen	Proportion method															Yes			
AFR	UR Tanzania	Countrywide	2007	Département de Microbiologie/Unité de Mycobactériologie/Institut de Médecine Tropicale, Antwerp, BELGIUM	Löwenstein-Jensen	Proportion method	1	1	1.0	40.0	2.0	5.0						100	100		Yes			
AFR	Zambia	Countrywide	2000	The Medical Research Council, TB Research Lead Programme, Pretoria, SOUTH AFRICA	Löwenstein-Jensen	Proportion method																		
AFR	Zimbabwe	Nearby Countrywide	1995	National Reference Center for Mycobacteria, Borstel, GERMANY	Löwenstein-Jensen	Various																		
AMR	Argentina	Countrywide	2005	Mycobacteria Laboratory, National Institute of Infectious Diseases, ANLIS "Dr Carlos G. Malbran," Buenos Aires, ARGENTINA	Löwenstein-Jensen and BACTEC 460	Proportion method	45	8	0.2	40.0	2.0	4.0	100	20	MIC	40	MIC	2	100	100	Yes			
AMR	Bolivia	Countrywide	1996	Mycobacteria Laboratory, National Institute of Infectious Diseases, ANLIS "Dr Carlos G. Malbran," Buenos Aires, ARGENTINA	Löwenstein-Jensen	Proportion method															Yes			
AMR	Brazil	Nearby Countrywide	1996	Mycobacteria Laboratory, National Institute of Infectious Diseases, ANLIS "Dr Carlos G. Malbran," Buenos Aires, ARGENTINA	Löwenstein-Jensen	Proportion method																		
AMR	Canada	Countrywide	2005	Centers for Disease Control and Prevention, Mycobacteriology/ Tuberculosis Laboratory, Georgia, USA	Various	Proportion method	10	10	0.1	2.0	2.5	2.0	100.0	5.0	1.0	1.3	2	100	100		NA			
AMR	Chile	Countrywide	2001	Instituto de Salud Publica de Chile, Santiago, CHILE	Löwenstein-Jensen	Proportion method															NA			
AMR	Colombia	Countrywide	2000	Instituto de Salud Publica de Chile, Santiago, CHILE	Ogawa	Proportion method															Yes			
AMR	Costa Rica	Countrywide	2006	Departamento de Micobacterias, Instituto de Diagnostico y, Referencia Epidemiologicos (INDRE), MEXICO	Löwenstein-Jensen	Proportion method	1	1	0.2	40.0	2.0	4.0						96	96		Yes			
AMR	Cuba	Countrywide	2005	Mycobacteria Laboratory, National Institute of Infectious Diseases, ANLIS "Dr Carlos G. Malbran," Buenos Aires, ARGENTINA	Löwenstein-Jensen	Proportion method	46	1	0.2	40.0	2.0	4.0						100	100		NA			
AMR	Dominican Republic	Countrywide	1995	Laboratory Centre for Disease Control, Ottawa, CANADA (historical)	Löwenstein-Jensen	Proportion method															Yes			
AMR	Ecuador	Countrywide	2002	Instituto de Salud Publica de Chile, Santiago, CHILE	Löwenstein-Jensen	Proportion method															Yes			
AMR	El Salvador	Countrywide	2001	Instituto de Salud Publica de Chile, Santiago, CHILE	Löwenstein-Jensen	Proportion method															Yes			
AMR	Guatemala	Countrywide	2002	Instituto de Salud Publica de Chile, Santiago, CHILE	Löwenstein-Jensen	Proportion method	8	1	0.2	40.0	2.0	4.0								99	100			
AMR	Honduras	Countrywide	2004	Instituto de Salud Publica de Chile, Santiago, CHILE	Löwenstein-Jensen	Proportion method	4	1	0.2	40.0	2.0	4.0									96	100		
AMR	Mexico	Baja California, Sinaloa, Oaxaca	1997	Centers for Disease Control and Prevention, Mycobacteriology/ Tuberculosis Laboratory, Georgia, USA	Löwenstein-Jensen	Proportion method																		
AMR	Nicaragua	Countrywide	2006	Instituto de Salud Publica de Chile, Santiago, CHILE	Löwenstein-Jensen	Proportion method	2	1	0.2	40.0	2.0	4.0									100	90		
AMR	Paraguay	Countrywide	2001	Mycobacteria Laboratory, National Institute of Infectious Diseases, ANLIS "Dr Carlos G. Malbran," Buenos Aires, ARGENTINA	Löwenstein-Jensen	Proportion method																		
AMR	Peru	Countrywide	2006	Instituto de Salud Publica de Chile, Santiago, CHILE	Ogawa	Proportion method			0.2	40.0	0.2	4.0									100	100		
AMR	Puerto Rico	Countrywide	2005	Centers for Disease Control and Prevention, Mycobacteriology/ Tuberculosis Laboratory, Georgia, USA	Various	Proportion method								5	4	10	2				NA			
AMR	Uruguay	Countrywide	2005	Mycobacteria Laboratory, National Institute of Infectious Diseases, ANLIS "Dr Carlos G. Malbran," Buenos Aires, ARGENTINA	Löwenstein-Jensen	Proportion method	1	1	0.2	40.0	2.0	4.0									100	100		
AMR	USA	Countrywide	2005	Centers for Disease Control and Prevention, Mycobacteriology/ Tuberculosis Laboratory, Georgia, USA	Various	Proportion method								5	4	10	2				NA			
AMR	Venezuela	Countrywide	1999	Instituto de Salud Publica de Chile, Santiago, CHILE	Löwenstein-Jensen	Proportion method																		
EMR	Egypt	Countrywide	2002	Laboratoire de la Tuberculose, Institut Pasteur d'Algérie, Alger, ALGERIA	Löwenstein-Jensen	Proportion method																		
EMR	Iran	Countrywide	1998	Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, Tokyo, JAPAN	Löwenstein-Jensen	Proportion method															No			
EMR	Jordan	Countrywide	2004	Laboratoire de la Tuberculose, Institut Pasteur d'Algérie, Alger, ALGERIA		Proportion method	1	1	0.2	40.0	2.0	4.0									73	93		
EMR	Lebanon	Countrywide	2003	Institut Pasteur, Centre National de Référence des Mycobactéries, Paris, FRANCE	Various	Proportion method	1	1	0.1	2.0	2.5	2.0									100	100		
EMR	Morocco	Countrywide	2006	Laboratoire de la Tuberculose, Institut Pasteur d'Algérie, Alger, ALGERIA	Löwenstein-Jensen	Proportion method	12	1	0.2	40.0	2.0	4.0	0.2									100	100	
EMR	Oman	Countrywide	2006	Laboratory of Bacteriology & Medical Mycology and San Raffaele del Monte Tabor Foundation (hSR), Milan, ITALY		Proportion method	10	1														NA		
EMR	Qatar	Countrywide	2006	Laboratory of Bacteriology & Medical Mycology and San Raffaele del Monte Tabor Foundation (hSR), Milan, ITALY		Proportion method	1	1														100	100	
EMR	Yemen	Countrywide	2004	Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, Tokyo, JAPAN		Proportion method	4	1														Yes		
EUR	Andorra	Countrywide	2005			Proportion method	1	0														NA		
EUR	Armenia	Countrywide	2007	National Reference Center for Mycobacteria, Borstel, GERMANY	Löwenstein-Jensen or Middlebrook	Proportion method	1	1														100	100	
EUR	Austria	Countrywide	2005	National Reference Center for Mycobacteria, Borstel, GERMANY		Proportion method	11	9														100	100	
EUR	Azerbaijan	Baku City	2007	National Reference Center for Mycobacteria, Borstel, GERMANY		Proportion method	1	1															Yes	
EUR	Belgium	Countrywide	2005	Health Protection Agency, National Mycobacterium Reference Unit, Department of Infectious Diseases, UNITED KINGDOM		Proportion method	155	25														100	100	
EUR	Bosnia & Herzegovina	Countrywide	2005	National Reference Center for Mycobacteria, Borstel, GERMANY		Proportion method	8	8															NA	
EUR	Croatia	Countrywide	2005	National Reference Center for Mycobacteria, Borstel, GERMANY		Proportion method	15	8															NA	
EUR	Czech Republic	Countrywide	2005	National Institute of Public Health, Prague, CZECH REPUBLIC		Proportion method	45	14														100	100	
EUR	Denmark	Countrywide	2005	Swedish Institute for Infectious Disease Control (SIDC), Solna, SWEDEN		Proportion method	1	1															95	100
EUR	Estonia	Countrywide	2005	Swedish Institute for Infectious Disease Control (SIDC), Solna, SWEDEN		Absolute concentration method	3	2															90	95
EUR	Finland	Countrywide	2005	Swedish Institute for Infectious Disease Control (SIDC), Solna, SWEDEN		Proportion method	15	2															100	90
EUR	France	Countrywide	2005	Health Protection Agency, National Mycobacterium Reference Unit, Department of Infectious Diseases, UNITED KINGDOM		Proportion method	310	110															100	100
EUR	Georgia	Countrywide	2006	Département de Microbiologie/Unité de Mycobactériologie/Institut de Médecine Tropicale, Antwerp, Belgium	Löwenstein-Jensen	Absolute concentration method	1	1	0.2	40.0	2.0	4.0											100	100
EUR	Germany	Countrywide	2005	National Reference Center for Mycobacteria, Borstel, GERMANY		Proportion method	200	63																NA
EUR	Iceland	Countrywide	2005	Swedish Institute for Infectious Disease Control (SIDC), Solna, SWEDEN	Various	Proportion method	1	0																NA
EUR	Ireland	Countrywide	2005	Health Protection Agency, National Mycobacterium Reference Unit, Department of Infectious Diseases, UNITED KINGDOM		Proportion method	13	4															100	100
EUR	Israel	Countrywide	2005	Health Protection Agency, National Mycobacterium Reference Unit, Department of Infectious Diseases, UNITED KINGDOM		Proportion method	19	2															100	100

Region	Country	Sub-national	Year	Supranational Laboratory	Culture method	DST method	Number of culture labs used in survey	Number of DST labs used in survey	H	R	E	S	PZA	Km	Amk	Cap	Clp	Ofi	% agreement H	% agreement R	Rechecking														
EUR	Italy	Half of the country	2005	Istituto Superiore di Sanità Dipartimento di Malattie infettive, Parassitarie e Immunomediate, Rome, ITALY		Proportion method	9	1											100	100	NA														
EUR	Kazakhstan	Countrywide	2001	Laboratory of Bacteriology & Medical Mycology and San Raffaele del Monte Tabor Foundation (nSR), Milan, ITALY	Löwenstein-Jensen	Absolute concentration method													100	100	Yes														
EUR	Latvia	Countrywide	2005	National Reference Center for Mycobacteria, Borstel, GERMANY		Absolute concentration method	9	1											95	100	NA														
EUR	Lithuania	Countrywide	2005	Swedish Institute for Infectious Disease Control (SIDC), Solna, SWEDEN		Absolute concentration method	5	5											100	95	NA														
EUR	Luxembourg	Countrywide	2005	Swedish Institute for Infectious Disease Control (SIDC), Solna, SWEDEN		Proportion method	1	1													NA														
EUR	Malta	Countrywide	2005	Health Protection Agency, National Mycobacterium Reference Unit, Department of Infectious Diseases, UNITED KINGDOM		Proportion method	1	1													NA														
EUR	Netherlands	Countrywide	2005	National Institute of Public Health and the Environment (RIVM), Bilthoven, NETHERLANDS			43	15													NA														
EUR	Norway	Countrywide	2005	Swedish Institute for Infectious Disease Control (SIDC), Solna, SWEDEN		Proportion method	13	3													NA														
EUR	Poland	Countrywide	2004	National Institute of Public Health and the Environment (RIVM), Bilthoven, NETHERLANDS			72	72													NA														
EUR	Portugal	Countrywide	2005																		NA														
EUR	Republic of Moldova	Countrywide	2006	National Reference Center for Mycobacteria, Borstel, GERMANY	Löwenstein-Jensen	Absolute concentration method	4	4	1.0	40.0	2.0	5.0	30.0	30.0	2.0	2.0	95	95			Yes														
EUR	Romania	Countrywide	2004	Swedish Institute for Infectious Disease Control (SIDC), Solna, SWEDEN			110	65													Yes														
EUR	Russian Federation	Ivanovo Oblast	2002		Löwenstein-Jensen	Proportion method															NA														
EUR	Russian Federation	Orel Oblast	2006	Swedish Institute for Infectious Disease Control (SIDC), Solna, SWEDEN		Absolute concentration method															95	NA													
EUR	Russian Federation	Mary El oblast	2006	Swedish Institute for Infectious Disease Control (SIDC), Solna, SWEDEN		Absolute concentration method																NA													
EUR	Russian Federation	Toms Oblast	2005	Massachusetts State Laboratory, Massachusetts, USA		Absolute concentration method																95	Yes												
EUR	Serbia	Countrywide	2005	National Reference Center for Mycobacteria, Borstel, GERMANY		Proportion method	45	10														NA													
EUR	Slovakia	Countrywide	2005	National Reference Center for Mycobacteria, Borstel, GERMANY		Proportion method	14	6														90	90	NA											
EUR	Slovenia	Countrywide	2005	National Reference Center for Mycobacteria, Borstel, GERMANY		Proportion method	5	1															100	100	NA										
EUR	Spain	Galicia	2005	Servicio de Microbiología Hospital Universitaria, Vall d'Hebron, Barcelona, SPAIN	Various	Proportion method	13	1	0.1	1.0	5.0	1.0	100 ug/ml	5	1	1.25	2	100	100			NA													
EUR	Spain	Aragon	2005	Servicio de Microbiología Hospital Universitaria, Vall d'Hebron, Barcelona, SPAIN	Various	Proportion method	7	7	1	1	5.0	1	100										100	100	Yes										
EUR	Spain	Barcelona	2005	Servicio de Microbiología Hospital Universitaria, Vall d'Hebron, Barcelona, SPAIN	Various	Proportion method	3	3																100	100	NA									
EUR	Sweden	Countrywide	2005	Swedish Institute for Infectious Disease Control (SIDC), Solna, SWEDEN		Proportion method	5	5																	100	100	NA								
EUR	Switzerland	Countrywide	2005	Health Protection Agency, National Mycobacterium Reference Unit, Department of Infectious Diseases, UNITED KINGDOM		Proportion method	28	28																		100	100	NA							
EUR	Turkmenistan	Dashoguz Velayat (Aral Sea Region)	2002	National Reference Center for Mycobacteria, Borstel, GERMANY	Löwenstein-Jensen	Absolute concentration method																					Yes								
EUR	Ukraine	Donetsk	2006	Kuratorium Tuberkulose in der Welt e.V./IML (Institut für Mikrobiologie und Laboratoriumsdiagnostik) Gauting, GERMANY	Löwenstein-Jensen, Finn-2	Absolute concentration method	14	1	1	40.0	2.0	10.0															Yes								
EUR	United Kingdom	Countrywide	2005	Health Protection Agency, National Mycobacterium Reference Unit, Department of Infectious Diseases, UNITED KINGDOM		Resistance ratio method	268	10																			NA								
EUR	Uzbekistan	Tashkent	2005	Kuratorium Tuberkulose in der Welt e.V./IML (Institut für Mikrobiologie und Laboratoriumsdiagnostik) Gauting, GERMANY		Absolute concentration method	1	1																				Yes							
SEAR	India	Mayhurbhanj District, Orissa State	2001	TB Research Centre (TRC), Indian Council of Medical Research, Chennai, INDIA	Löwenstein-Jensen	Proportion method	1	1	0.2	40.0	2.0	4.0																100	100	NA					
SEAR	India	Wardha District, Maharashtra State	2001	TB Research Centre (TRC), Indian Council of Medical Research, Chennai, INDIA	Löwenstein-Jensen	Proportion method																							NA						
SEAR	India	Delhi State	1995	Queensland Mycobacterium Reference Laboratory, Brisbane, AUSTRALIA	Löwenstein-Jensen	Proportion method																							NA						
SEAR	India	Raichur District, Karnataka State	1999	TB Research Centre (TRC), Indian Council of Medical Research, Chennai, INDIA	Löwenstein-Jensen	Proportion method																							NA						
SEAR	India	North Arcot District, Tamil Nadu State	1999	TB Research Centre (TRC), Indian Council of Medical Research, Chennai, INDIA	Löwenstein-Jensen	Proportion method																							NA						
SEAR	India	Ernakulam district, Kerala State	2004	TB Research Centre (TRC), Indian Council of Medical Research, Chennai, INDIA	Löwenstein-Jensen	Proportion method	1	1	0.2	40.0	2.0	4.0																	100	100	NA				
SEAR	India	Gujarat State	2006	TB Research Centre (TRC), Indian Council of Medical Research, Chennai, INDIA	Löwenstein-Jensen	Proportion method	1	1	0.2	40.0	2.0	4.0																		NA					
SEAR	India	Tamil Nadu State	1997	Queensland Mycobacterium Reference Laboratory, Brisbane, AUSTRALIA	Löwenstein-Jensen	Resistance ratio method																								NA					
SEAR	India	Hoogli district, West Bengal State	2001	TB Research Centre (TRC), Indian Council of Medical Research, Chennai, INDIA	Löwenstein-Jensen	Proportion method	1	1	0.2	40.0	2.0	4.0																		100	100	NA			
SEAR	Indonesia	Mimika district, Papua Province	2004	Mycobacterium Reference Laboratory, Institute of Medical and Veterinary Science, Adelaide, AUSTRALIA	BACTEC 460	Proportion method	1	1	0.1, 0.4	2.0	2.5	2.0	100		1.0	2.5	1.0													100	100	Yes			
SEAR	Myanmar	Countrywide	2003	TB Research Centre (TRC), Indian Council of Medical Research, Chennai, INDIA	Löwenstein-Jensen and Ogawa	Proportion method	1	1	0.2	40.0	2.0	4.0																		100	95	Yes			
SEAR	Nepal	Countrywide	2007	Kuratorium Tuberkulose in der Welt e.V./IML (Institut für Mikrobiologie und Laboratoriumsdiagnostik) Gauting, GERMANY		Proportion method	1	1	0.2	40.0	2.0	4.0																			Yes				
SEAR	Sri Lanka	Countrywide	2006	TB Research Centre (TRC), Indian Council of Medical Research, Chennai, INDIA		Proportion method	1	1																							Planned				
SEAR	Thailand	Countrywide	2006	Département de Microbiologie/Unité de Mycobactériologie/Institut de Médecine Tropicale, Antwerp, BELGIUM	Löwenstein-Jensen	Proportion method	8	1	0.2	40.0	2.0	4.0																			97	100	NA		
WPR	Australia	Countrywide	2005	Mycobacterium Reference Laboratory, Institute of Medical and Veterinary Science, Adelaide, AUSTRALIA	Various	Proportion method	60	5																							NA				
WPR	Cambodia	Countrywide	2001	Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, Tokyo, JAPAN	Various	Proportion method																									Yes				
WPR	China	Guandong Province	1999	Korean Institute of Tuberculosis, Seoul, REPUBLIC OF KOREA	Löwenstein-Jensen	Proportion method	40	1																							No				
WPR	China	Beijing Municipality	2004	TB Reference Laboratory Department of Health, SAR Hong Kong, CHINA	Löwenstein-Jensen	Proportion method	18	1	0.2	40.0	2.0	4.0																			100	100	No		
WPR	China	Shandong Province	1997	Korean Institute of Tuberculosis, Seoul, REPUBLIC OF KOREA	Löwenstein-Jensen	Proportion method	30	1																								No			
WPR	China	Henan Province	2001	Korean Institute of Tuberculosis, Seoul, REPUBLIC OF KOREA	Löwenstein-Jensen	Proportion method	30	1																								No			
WPR	China	Liaoning Province	1999	Korean Institute of Tuberculosis, Seoul, REPUBLIC OF KOREA	Löwenstein-Jensen	Proportion method	30	1																								No			
WPR	China	Heilongjiang Province	2005	TB Reference Laboratory Department of Health, SAR Hong Kong, CHINA	Löwenstein-Jensen	Proportion method	30	1	0.2	40.0	2.0	4.0																				100	93	No	
WPR	China	Hubei Province	1999	Korean Institute of Tuberculosis, Seoul, REPUBLIC OF KOREA	Löwenstein-Jensen	Proportion method	30	1																								No			
WPR	China	Zhejiang Province	1999	Korean Institute of Tuberculosis, Seoul, REPUBLIC OF KOREA	Löwenstein-Jensen	Proportion method	30	1																								No			
WPR	China	Shanghai Municipality	2005	TB Reference Laboratory Department of Health, SAR Hong Kong, CHINA	Löwenstein-Jensen	Proportion method	19	1	0.2	40.0	2.0	4.0																				93	97	No	
WPR	China	Inner Mongolia Autonomous region	2002	TB Reference Laboratory Department of Health, SAR Hong Kong, CHINA	Löwenstein-Jensen	Proportion method	30	1	0.2	40.0	2.0	4.0																					93	97	No
WPR	China, Hong Kong SAR	Hong Kong	2005	TB Reference Laboratory Department of Health, SAR Hong Kong, CHINA	Löwenstein-Jensen	Absolute concentration method	1	1	0.2	32.0	2.8	16.0	50.0	16.0	8.0	32.0	2.4	100	100													NA			
WPR	China, Macao SAR	Macao	2005	TB Reference Laboratory Department of Health, SAR Hong Kong, CHINA	Löwenstein-Jensen and Bacti/ALERT MP	1% Proportion Method-Bactec MGIT 960	1	1	0.1	1.0	5.0	1.0																				NA			
WPR	Fiji	Countrywide	2006	Queensland Mycobacterium Reference Laboratory, Brisbane, AUSTRALIA																												NA			
WPR	Guam	Countrywide	2002																													NA			
WPR	Japan	Countrywide	2002	Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, Tokyo, JAPAN	MGIT and Ogawa	Proportion method			0.2, 1.0	40.0	2.5	10.0	100	20																		100	100	NA	
WPR	Malaysia	Peninsular Malaysia	1997	Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, Tokyo, JAPAN	Ogawa</																														

Annex 8: Estimates of MDR-TB among new cases

Country	No. of New TB cases	No. of MDR cases	Low 95%	High 95%	% MDR TB	Low 95%	High 95%
			CL	CL		CL	CL
Afghanistan	42,078	1,415	201	7,885	3.4	0.5	18.3
Albania	598	9	1	60	1.5	0.3	10.0
Algeria	18,699	217	60	437	1.2	0.4	2.5
Andorra	14	0	0	4	0.0	0.0	28.3
Angola	47,231	930	149	5,962	2.0	0.3	12.1
Antigua & Barbuda	5	0	0	0	1.3	0.2	8.2
Argentina	15,231	335	154	563	2.2	1.2	3.6
Armenia	2,236	211	125	310	9.4	7.1	12.2
Austria	1,046	20	8	36	1.9	1.0	3.4
Azerbaijan	6,660	1,487	926	2,090	22.3	18.9	26.0
Bahamas	126	1	0	10	1.2	0.2	7.6
Bahrain	304	7	1	41	2.2	0.3	12.9
Bangladesh	350,641	12,562	1,829	70,022	3.6	0.6	19.4
Belarus	5,989	695	115	2,906	11.6	2.0	46.9
Belgium	1,389	17	5	32	1.2	0.5	2.4
Belize	137	2	0	13	1.5	0.2	9.6
Benin	7,878	24	0	83	0.3	0.0	1.7
Bhutan	621	20	3	108	3.2	0.5	17.3
Bolivia	18,562	224	61	455	1.2	0.4	2.6
Bosnia & Herzegovina	2,005	8	2	17	0.4	0.1	1.0
Botswana	10,230	87	33	159	0.8	0.4	1.6
Brazil	93,933	852	414	1,401	0.9	0.5	1.4
Brunei Darussalam	317	7	1	44	2.3	0.4	13.4
Bulgaria	3,101	332	53	1,454	10.7	1.8	44.7
Burkina Faso	35,678	732	117	4,593	2.1	0.3	12.6
Burundi	30,052	722	114	4,479	2.4	0.4	14.5
Cambodia	70,949	0	0	332	0.0	0.0	0.5
Cameroon	34,905	601	93	3,863	1.7	0.3	10.8
Canada	1,678	14	5	27	0.8	0.4	1.7
Cape Verde	873	14	2	92	1.6	0.3	10.2
Central African Republic	14,744	159	32	338	1.1	0.4	2.5
Chad	31,329	641	95	4,251	2.0	0.3	13.0
Chile	2,417	17	5	34	0.7	0.3	1.5
China	1,311,184	65,853	41,883	90,663	5.0	4.6	5.5
China, Hong Kong SAR	4,433	38	21	59	0.9	0.6	1.2
China, Macao SAR	283	6	2	13	2.3	0.8	4.9
Colombia	20,514	302	144	509	1.5	0.8	2.4
Comoros	358	7	1	44	1.8	0.3	11.9
Congo	14,901	256	40	1,657	1.7	0.3	11.0
Costa Rica	620	9	2	21	1.5	0.4	3.8
Côte d'Ivoire	79,686	1,992	709	3,775	2.5	1.1	4.9
Croatia	1,832	9	0	23	0.5	0.1	1.5
Cuba	1,018	0	0	18	0.0	0.0	1.8
Cyprus	42	0	0	3	1.1	0.2	7.5
Czech Republic	1,007	13	4	24	1.2	0.5	2.5
Denmark	444	7	2	15	1.6	0.5	3.8
Djibouti	6,622	220	32	1,185	3.3	0.5	17.7
Dominica	11	0	0	1	1.5	0.2	9.7
Dominican Republic	8,534	563	290	913	6.6	4.1	10.0
DPR Korea	42,147	1,538	233	8,450	3.7	0.6	19.5
DR Congo	237,985	5,657	878	34,850	2.4	0.4	14.8
Ecuador	16,958	835	477	1,266	4.9	3.5	6.6
Egypt	17,821	395	177	682	2.2	1.2	3.7
El Salvador	3,385	11	0	30	0.3	0.0	1.2
Eritrea	4,402	99	16	628	2.3	0.4	14.2
Estonia	519	69	40	104	13.3	9.7	17.5
Ethiopia	306,990	4,964	2,135	8,697	1.6	0.9	2.7
Finland	287	3	0	8	1.0	0.1	3.6
France	8,630	94	43	162	1.1	0.6	1.8
French Polynesia	68	1	0	9	2.1	0.3	12.5
Gabon	4,635	63	10	421	1.4	0.2	9.0
Gambia	4,278	20	0	72	0.5	0.0	2.6
Georgia	3,834	259	153	383	6.8	5.1	8.7

Country	No. of New TB cases	No. of MDR cases	Low 95%	High 95%	% MDR TB	Low 95%	High 95%
			CL	CL		CL	CL
Germany	5,370	99	58	146	1.8	1.4	2.4
Ghana	46,693	898	143	5,534	1.9	0.3	12.0
Greece	2,009	22	3	149	1.1	0.2	7.4
Guatemala	10,277	308	155	503	3.0	1.8	4.6
Guinea	24,321	135	0	328	0.6	0.1	1.6
Guinea-Bissau	3,602	81	13	528	2.3	0.4	14.0
Guyana	1,215	21	3	140	1.7	0.3	11.2
Haiti	28,289	537	86	3,520	1.9	0.3	12.0
Honduras	5,322	93	33	176	1.8	0.8	3.4
Hungary	1,904	25	4	169	1.3	0.2	8.7
Iceland	13	0	0	4	0.0	0.0	34.8
India	1,932,852	54,806	33,723	78,291	2.8	2.3	3.4
Indonesia	534,439	10,583	0	28,811	2.0	0.2	7.0
Iran	15,678	777	428	1,204	5.0	3.4	6.9
Iraq	15,968	478	68	2,729	3.0	0.5	16.6
Ireland	555	3	0	10	0.5	0.0	2.8
Israel	521	30	13	52	5.7	3.0	9.7
Italy	4,393	72	25	137	1.6	0.7	3.2
Jamaica	197	3	0	19	1.4	0.2	9.1
Japan	28,330	199	99	328	0.7	0.4	1.1
Jordan	306	17	5	33	5.4	2.0	11.4
Kazakhstan	19,961	2,836	1,681	4,158	14.2	10.8	18.3
Kenya	132,578	0	0	890	0.0	0.0	0.7
Kiribati	348	11	2	61	3.2	0.5	17.6
Kuwait	667	13	2	79	1.9	0.3	11.5
Kyrgyzstan	6,454	949	154	3,580	14.7	2.6	53.4
Lao PDR	8,779	322	46	1,791	3.7	0.6	19.9
Latvia	1,312	141	87	201	10.8	8.8	13.0
Lebanon	452	5	0	13	1.1	0.1	3.8
Lesotho	12,670	115	0	278	0.9	0.2	2.6
Libyan Arab Jamahiriya	1,062	28	4	159	2.6	0.4	14.4
Lithuania	2,102	206	128	292	9.8	8.3	11.6
Luxembourg	57	0	0	5	0.0	0.0	8.0
Madagascar	47,469	234	45	517	0.5	0.1	1.3
Malawi	51,172	1,203	195	7,455	2.4	0.4	14.7
Malaysia	26,877	27	0	96	0.1	0.0	0.6
Maldives	136	4	1	21	2.9	0.4	15.6
Mali	33,460	680	108	4,413	2.0	0.3	12.7
Malta	25	0	0	6	0.0	0.0	25.9
Marshall Islands	127	4	1	21	2.9	0.4	16.1
Mauritius	284	4	1	25	1.3	0.2	8.7
Mexico	22,473	538	187	1,018	2.4	1.0	4.7
Micronesia	112	3	0	19	3.0	0.4	16.4
Mongolia	4,893	48	9	107	1.0	0.3	2.5
Morocco	28,776	137	28	288	0.5	0.2	1.1
Mozambique	92,971	3,256	1,829	5,018	3.5	2.5	4.8
Myanmar	82,687	3,271	1,797	5,065	4.0	2.7	5.6
Namibia	15,723	241	38	1,536	1.5	0.3	9.8
Nepal	48,772	1,401	736	2,239	2.9	1.8	4.3
Netherlands	1,249	9	2	18	0.7	0.2	1.6
New Zealand	352	1	0	5	0.4	0.0	2.2
Nicaragua	3,203	20	0	54	0.6	0.1	2.2
Niger	23,845	519	82	3,207	2.2	0.4	13.1
Nigeria	450,527	8,559	1,319	55,698	1.9	0.3	11.9
Norway	263	4	0	10	1.6	0.3	4.5
Oman	336	4	0	12	1.3	0.2	4.7
Pakistan	291,743	9,880	1,454	53,653	3.4	0.5	18.4
Palau	10	0	0	1	2.4	0.4	13.9
Panama	1,463	21	3	135	1.4	0.2	9.3
Papua New Guinea	15,473	563	82	3,142	3.6	0.6	20.0
Paraguay	4,267	91	19	193	2.1	0.7	4.9
Peru	44,815	2,353	1,446	3,375	5.3	4.3	6.4
Philippines	247,740	10,012	5,676	15,135	4.0	2.9	5.5
Poland	9,462	28	9	54	0.3	0.1	0.6
Portugal	3,382	29	12	50	0.9	0.4	1.5

Country	No. of New TB cases	No. of MDR cases	Low 95%	High 95%	% MDR TB	Low 95%	High 95%
			CL	CL		CL	CL
Rep. Korea	42,359	1,141	686	1,655	2.7	2.1	3.4
Republic of Moldova	5,551	1,077	684	1,504	19.4	16.7	22.3
Romania	27,533	778	416	1,242	2.8	1.8	4.2
Russian Federation	152,797	19,845	12,376	27,566	13.0	11.3	14.8
Rwanda	37,644	1,467	768	2,324	3.9	2.5	5.7
Saint Lucia	28	0	0	3	1.5	0.2	9.4
Samoa	36	1	0	6	3.0	0.5	16.8
Saudi Arabia	10,631	232	33	1,362	2.2	0.3	12.6
Senegal	32,638	689	141	1,452	2.1	0.7	4.9
Serbia	3,183	11	2	26	0.4	0.1	0.9
Seychelles	28	0	0	3	1.3	0.2	8.9
Sierra Leone	29,690	254	0	886	0.9	0.0	4.7
Singapore	1,128	3	0	7	0.2	0.0	0.8
Slovakia	829	13	3	30	1.6	0.4	4.1
Slovenia	261	0	0	4	0.0	0.0	1.4
Somalia	18,444	328	52	2,118	1.8	0.3	11.2
South Africa	453,929	8,238	4,952	11,848	1.8	1.4	2.3
Spain	13,180	17	0	62	0.1	0.0	0.7
Sri Lanka	11,620	21	0	75	0.2	0.0	1.0
St Vincent & Grenadines	35	1	0	4	1.7	0.3	10.8
Sudan	91,331	1,696	265	10,681	1.9	0.3	11.7
Swaziland	13,097	118	0	281	0.9	0.2	2.6
Sweden	549	3	0	7	0.5	0.1	1.7
Switzerland	500	3	0	8	0.6	0.1	2.2
Syrian Arab Republic	6,251	192	27	1,050	3.1	0.5	16.6
Tajikistan	13,532	2,164	359	7,855	16.0	2.8	55.1
TFYR Macedonia	596	9	1	61	1.6	0.3	9.9
Thailand	90,252	1,491	752	2,423	1.7	1.0	2.6
Timor-Leste	6,187	211	31	1,186	3.4	0.5	18.7
Togo	24,922	506	79	3,295	2.0	0.3	12.8
Tonga	24	1	0	4	3.1	0.5	17.4
Tunisia	2,520	68	10	382	2.7	0.4	15.0
Turkey	21,752	303	48	2,026	1.4	0.2	9.0
Turkmenistan	3,175	121	24	269	3.8	1.0	9.5
Uganda	106,037	567	0	1,547	0.5	0.1	1.9
Ukraine	49,308	7,866	4,948	11,029	16.0	13.7	18.4
United Arab Emirates	681	16	2	91	2.3	0.4	12.9
United Kingdom	9,358	63	33	101	0.7	0.4	1.0
UR Tanzania	123,140	1,335	256	2,997	1.1	0.3	2.8
Uruguay	910	0	0	8	0.0	0.0	0.9
Uzbekistan	32,778	4,844	2,707	7,477	14.8	10.2	20.4
Venezuela	11,271	59	11	130	0.5	0.1	1.3
Viet Nam	148,918	4,047	2,341	6,056	2.7	2.0	3.6
West Bank and Gaza Strip	790	25	4	137	3.1	0.5	17.4
Yemen	16,985	500	234	850	2.9	1.7	4.8
Zambia	64,632	1,162	388	2,199	1.8	0.8	3.5
Zimbabwe	85,015	1,635	722	2,828	1.9	1.0	3.3

Annex 9: Estimates of MDR-TB among previously treated cases

Country	No. of Previously treated TB cases	No. of MDR cases	Low 95%		% MDR TB	High 95%	
			CL	CL		CL	CL
Afghanistan	1,957	724	159	1,619	37.0	8.7	76.2
Albania	45	5	1	18	10.3	2.0	39.5
Algeria	617	60	11	242	9.8	1.9	37.7
Andorra	1	0	0	1	10.4	2.1	40.5
Angola	5,463	735	142	2,643	13.5	2.6	46.5
Antigua & Barbuda	0	0	0	0	10.6	2.1	40.7
Argentina	829	128	67	206	15.4	9.8	22.6
Armenia	394	170	109	235	43.2	37.9	48.7
Austria	22	3	0	7	12.5	1.6	38.3
Azerbaijan	1,631	910	588	1,245	55.8	51.5	60.0
Bahamas	13	1	0	5	9.4	1.9	37.6
Bahrain	12	4	1	10	36.5	8.8	75.0
Bangladesh	10,492	2,022	407	6,266	19.3	4.2	57.8
Belarus	997	401	95	847	40.2	10.2	78.4
Belgium	112	8	0	19	7.3	1.5	19.9
Belize	16	2	0	6	9.8	2.0	39.0
Benin	719	66	12	269	9.2	1.8	37.2
Bhutan	41	8	2	25	19.9	4.3	58.6
Bolivia	1,514	71	15	147	4.7	1.5	10.6
Bosnia & Herzegovina	134	9	3	17	6.6	2.7	13.1
Botswana	428	44	18	79	10.4	5.3	17.8
Brazil	11,287	612	355	921	5.4	4.0	7.2
Brunei Darussalam	20	4	1	12	19.5	4.3	57.4
Bulgaria	316	119	28	262	37.8	9.2	76.6
Burkina Faso	4,566	439	80	1,852	9.6	1.8	38.4
Burundi	1,042	94	17	384	9.0	1.8	36.2
Cambodia	2,956	92	0	221	3.1	0.6	8.9
Cameroon	2,182	185	32	757	8.5	1.6	34.6
Canada	150	11	3	22	7.5	2.8	15.6
Cape Verde	83	8	2	33	10.2	2.0	39.0
Central African Republic	1,409	256	79	487	18.2	7.0	35.5
Chad	1,731	167	31	676	9.6	1.9	38.5
Chile	182	7	3	12	3.8	1.9	6.7
China	252,863	64,694	41,304	88,232	25.6	23.7	27.5
China, Hong Kong SAR	540	43	19	75	8.0	4.3	13.3
China, Macao SAR	27	4	0	10	15.8	3.4	39.6
Colombia	825	80	15	334	9.7	1.9	38.9
Comoros	23	2	0	9	10.1	1.9	39.2
Congo	733	64	12	268	8.8	1.7	36.1
Costa Rica	53	3	0	9	4.8	0.1	23.8
Côte d'Ivoire	4,761	411	76	1,722	8.6	1.7	35.2
Croatia	189	9	0	22	4.9	1.0	13.7
Cuba	70	4	0	13	5.3	0.1	26.0
Cyprus	1	0	0	0	9.6	1.9	37.7
Czech Republic	34	10	3	19	30.0	11.9	54.3
Denmark	46	0	0	7	0.0	0.0	15.3
Djibouti	648	229	51	526	35.4	8.8	74.5
Dominica	1	0	0	0	10.6	2.1	40.3
Dominican Republic	1,204	237	126	372	19.7	12.9	28.0
DPR Korea	8,634	1,933	391	5,611	22.4	4.8	61.4
DR Congo	15,195	1,387	268	5,594	9.1	1.9	36.1
Ecuador	2,661	647	380	955	24.3	18.3	31.2
Egypt	1,483	567	358	800	38.2	31.8	45.1
El Salvador	298	21	6	41	7.0	2.9	13.9
Eritrea	284	27	5	113	9.7	1.9	38.1
Estonia	114	59	36	86	52.1	39.9	64.1
Ethiopia	7,271	861	342	1,576	11.8	5.6	21.3
Finland	19	1	0	3	4.5	0.1	22.8
France	625	45	16	83	7.1	3.1	13.6
French Polynesia	8	2	0	5	18.8	3.9	57.5
Gabon	426	35	6	147	8.2	1.5	33.2
Gambia	248	0	0	45	0.0	0.0	18.1
Georgia	1,435	393	247	551	27.4	23.6	31.4

Country	No. of Previously treated TB cases		Low 95%	High 95%	% MDR TB	Low 95%	High 95%
	No. of MDR cases		CL	CL		CL	CL
Germany	456	56	32	87	12.4	8.5	17.1
Ghana	2,094	192	34	770	9.2	1.7	36.3
Greece	218	22	4	91	10.3	2.1	40.1
Guatemala	471	125	74	185	26.5	19.7	34.1
Guinea	1,648	464	193	806	28.1	13.7	46.7
Guinea-Bissau	282	27	5	112	9.7	2.0	38.3
Guyana	110	10	2	44	9.4	1.9	38.1
Haiti	638	57	10	237	9.0	1.7	36.0
Honduras	304	37	15	69	12.3	5.8	22.1
Hungary	386	45	8	172	11.6	2.3	42.5
Iceland	1	0	0	1	0.0	0.0	95.0
India	321,200	55,326	34,714	77,769	17.2	15.0	19.7
Indonesia	8,264	1,559	315	4,898	18.9	4.2	56.6
Iran	833	402	236	593	48.2	34.7	62.0
Iraq	1,295	492	112	1,074	38.0	9.5	77.0
Ireland	28	3	0	10	10.0	0.3	44.5
Israel	4	0	0	3	0.0	0.0	63.2
Italy	256	45	21	76	17.7	10.0	27.9
Jamaica	11	1	0	4	8.1	1.6	34.1
Japan	1,253	123	70	186	9.8	7.1	13.1
Jordan	8	3	2	5	40.0	22.7	59.4
Kazakhstan	6,686	3,773	2,388	5,225	56.4	50.8	61.9
Kenya	13,012	0	0	820	0.0	0.0	6.3
Kiribati	5	1	0	3	18.9	4.0	56.9
Kuwait	9	3	1	7	36.5	8.8	75.7
Kyrgyzstan	1,048	419	99	872	40.0	9.9	78.2
Lao PDR	393	76	16	241	19.4	4.0	58.1
Latvia	211	77	47	108	36.3	29.3	43.7
Lebanon	10	6	3	10	62.5	35.4	84.8
Lesotho	1,859	105	0	246	5.7	1.2	15.7
Libyan Arab Jamahiriya	14	5	1	12	38.7	9.7	77.3
Lithuania	461	219	139	301	47.5	42.8	52.3
Luxembourg	3	0	0	1	9.8	2.0	39.0
Madagascar	3,921	154	0	421	3.9	0.5	13.5
Malawi	2,829	160	28	786	5.6	1.1	25.9
Malaysia	1,707	0	0	291	0.0	0.0	17.1
Maldives	7	1	0	4	19.3	4.1	57.3
Mali	768	76	14	301	9.9	2.0	38.2
Malta	1	0	0	1	9.8	1.9	38.5
Marshall Islands	8	2	0	5	21.3	4.7	60.8
Mauritius	10	1	0	4	9.5	1.9	37.5
Mexico	4,640	1,041	571	1,612	22.4	14.9	31.5
Micronesia	13	3	1	8	21.0	4.6	60.5
Mongolia	332	68	13	204	20.5	4.3	59.6
Morocco	1,101	134	70	214	12.2	7.8	17.8
Mozambique	4,975	163	31	356	3.3	0.9	8.2
Myanmar	6,312	979	499	1,573	15.5	9.5	23.4
Namibia	1,432	101	18	457	7.1	1.3	30.0
Nepal	4,439	521	260	848	11.7	7.2	17.7
Netherlands	46	2	0	5	3.3	0.1	17.2
New Zealand	21	0	0	4	0.0	0.0	17.1
Nicaragua	403	31	11	58	7.8	3.4	14.7
Niger	2,260	231	43	914	10.2	2.1	38.9
Nigeria	28,209	2,612	456	11,193	9.3	1.7	36.9
Norway	16	0	0	5	0.0	0.0	31.2
Oman	5	2	1	3	35.7	12.8	64.9
Pakistan	14,675	5,353	1,136	11,803	36.5	8.7	75.3
Palau	2	0	0	1	20.3	4.5	59.8
Panama	252	26	5	102	10.2	2.0	39.6
Papua New Guinea	1,804	352	66	1,082	19.5	4.1	58.6
Paraguay	452	18	0	48	3.9	0.5	13.5
Peru	6,855	1,619	996	2,321	23.6	19.3	28.3
Philippines	8,771	1,836	1,007	2,810	20.9	14.3	29.0
Poland	1,198	99	56	148	8.2	6.0	10.9
Portugal	380	35	17	59	9.3	5.4	14.7

Country	No. of Previously treated TB cases	No. of MDR cases	Low 95%	High 95%	% MDR TB	Low 95%	High 95%
			CL	CL		CL	CL
Rep. Korea	7,471	1,048	605	1,559	14.0	10.2	18.7
Republic of Moldova	1,886	959	611	1,298	50.8	48.6	53.0
Romania	6,985	768	440	1,158	11.0	8.0	14.6
Russian Federation	33,283	16,192	10,265	22,900	48.6	41.2	56.1
Rwanda	2,719	256	91	473	9.4	4.2	17.7
Saint Lucia	4	0	0	2	11.1	2.2	42.1
Samoa	5	1	0	3	21.1	4.6	60.4
Saudi Arabia	393	143	33	320	36.4	8.5	75.9
Senegal	3,723	621	214	1,182	16.7	7.0	31.4
Serbia	351	15	3	30	4.1	1.4	9.4
Seychelles	2	0	0	1	11.5	2.3	42.8
Sierra Leone	1,204	278	0	605	23.1	5.0	53.8
Singapore	149	1	0	5	1.0	0.0	5.2
Slovakia	113	8	2	18	7.1	2.0	17.3
Slovenia	17	1	0	2	3.6	0.1	18.3
Somalia	859	84	16	330	9.8	1.9	38.3
South Africa	86,642	5,796	3,542	8,303	6.7	5.5	8.1
Spain	715	30	6	69	4.3	1.2	10.5
Sri Lanka	610	0	0	53	0.0	0.0	8.7
St Vincent & Grenadines	4	1	0	2	14.7	3.0	49.5
Sudan	6,972	681	120	2,736	9.8	1.9	37.5
Swaziland	1,438	131	27	282	9.1	2.5	21.7
Sweden	12	1	0	4	11.8	1.5	36.4
Switzerland	50	3	0	9	6.7	0.8	22.1
Syrian Arab Republic	259	95	23	209	36.8	9.1	76.0
Tajikistan	2,454	1,040	254	2,127	42.4	11.0	80.1
TFYR Macedonia	84	10	2	37	11.4	2.3	42.3
Thailand	3,887	1,342	839	1,916	34.5	27.9	41.7
Timor-Leste	73	14	3	43	18.8	3.9	55.7
Togo	1,781	162	28	665	9.1	1.7	36.8
Tonga	2	0	0	1	20.3	4.3	59.1
Tunisia	43	16	4	35	36.1	8.8	74.9
Turkey	5,520	586	108	2,428	10.6	2.1	41.5
Turkmenistan	715	131	65	211	18.4	11.3	27.5
Uganda	6,061	269	0	713	4.4	0.5	15.1
Ukraine	12,549	5,563	3,547	7,697	44.3	39.9	48.8
United Arab Emirates	32	12	3	26	36.7	8.9	75.4
United Kingdom	418	11	3	21	2.6	1.0	5.2
UR Tanzania	9,932	0	0	589	0.0	0.0	5.9
Uruguay	76	5	0	12	6.1	0.7	20.2
Uzbekistan	8,309	4,985	3,094	7,059	60.0	48.8	70.5
Venezuela	683	92	44	157	13.5	7.6	21.6
Viet Nam	12,287	2,374	1,378	3,535	19.3	14.2	25.4
West Bank and Gaza Strip	30	11	3	25	36.8	10.2	77.1
Yemen	648	73	22	145	11.3	4.3	23.0
Zambia	7,394	168	0	586	2.3	0.1	12.0
Zimbabwe	9,906	826	0	1,966	8.3	1.8	22.5

Annex 10: Estimates of MDR-TB among all TB cases

Country	No. of All TB cases	No. of MDR cases	Low 95%	High 95%	% MDR TB	Low 95%	High 95%
			CL	CL		CL	CL
Afghanistan	44,035	2,139	671	8,802	4.9	1.6	19.5
Albania	643	14	4	67	2.1	0.7	10.3
Algeria	19,316	277	105	561	1.4	0.6	2.8
Andorra	15	0	0	0	0.7	0.1	3.4
Angola	52,694	1,665	547	7,144	3.2	1.1	13.1
Antigua & Barbuda	5	0	0	0	1.3	0.7	9.1
Argentina	16,060	463	267	699	2.9	1.8	4.1
Armenia	2,630	381	273	501	14.5	11.6	18.0
Australia	1,414	21	11	36	1.5	0.8	2.6
Austria	1,068	23	10	39	2.1	1.0	3.4
Azerbaijan	8,291	2,397	1,744	3,074	28.9	25.1	33.2
Bahamas	139	3	1	12	1.9	0.7	8.5
Bahrain	316	11	4	43	3.5	1.1	13.4
Bangladesh	361,133	14,583	3,566	72,744	4.0	1.0	19.3
Belarus	6,986	1,096	371	3,272	15.7	5.4	46.5
Belgium	1,501	25	10	43	1.6	0.7	2.8
Belize	153	4	1	15	2.3	0.8	10.2
Benin	8,597	90	18	304	1.0	0.2	3.7
Bhutan	662	28	8	119	4.2	1.3	17.5
Bolivia	20,076	294	117	526	1.5	0.6	2.5
Bosnia & Herzegovina	2,139	17	7	29	0.8	0.3	1.4
Botswana	10,658	131	69	206	1.2	0.7	1.9
Brazil	105,220	1,464	945	2,077	1.4	1.0	1.9
Brunei Darussalam	337	11	3	47	3.3	1.1	13.8
Bulgaria	3,417	451	143	1,563	13.2	4.2	44.1
Burkina Faso	40,244	1,170	369	5,402	2.9	1.0	13.1
Burundi	31,094	815	199	4,725	2.6	0.7	15.1
Cambodia	73,905	92	0	221	0.1	0.0	0.3
Cameroon	37,087	786	227	4,036	2.1	0.6	11.0
Canada	1,828	25	12	42	1.4	0.7	2.3
Cape Verde	956	22	7	102	2.3	0.8	10.7
Central African Republic	16,153	415	188	703	2.6	1.2	4.5
Chad	33,060	807	230	4,297	2.4	0.7	13.3
Chile	2,599	24	10	42	0.9	0.4	1.5
China	1,564,047	130,548	97,633	164,900	8.3	7.0	10.2
China, Hong Kong SAR	4,973	81	51	117	1.6	1.1	2.4
China, Macao SAR	310	11	4	19	3.4	1.4	6.1
Colombia	21,339	382	202	690	1.8	1.1	3.2
Comoros	381	9	3	45	2.3	0.7	11.9
Congo	15,634	321	90	1,737	2.1	0.6	11.0
Costa Rica	673	12	2	25	1.8	0.4	3.5
Côte d'Ivoire	84,447	2,403	1,033	4,574	2.8	1.3	5.2
Croatia	2,021	19	5	36	0.9	0.3	1.8
Cuba	1,088	4	0	13	0.3	0.0	1.2
Cyprus	43	1	0	3	1.3	0.4	7.6
Czech Republic	1,041	23	11	37	2.2	1.1	3.6
Denmark	490	7	1	15	1.5	0.3	2.9
Djibouti	7,270	449	150	1,489	6.2	2.1	20.1
Dominica	12	0	0	1	2.2	0.8	10.2
Dominican Republic	9,738	800	496	1,162	8.2	5.7	11.1
DPR Korea	50,781	3,472	1,136	11,248	6.8	2.3	21.4
DR Congo	253,180	7,044	2,030	36,534	2.8	0.8	14.5
Ecuador	19,619	1,483	1,034	1,998	7.6	5.8	9.8
Egypt	19,304	962	646	1,315	5.0	3.4	7.0
El Salvador	3,683	32	12	58	0.9	0.3	1.6
Eritrea	4,686	127	36	681	2.7	0.8	14.1
Estonia	633	128	91	172	20.3	15.9	25.7
Ethiopia	314,261	5,825	2,992	9,689	1.9	1.0	2.8
Fiji	186	0	0	17	0.0	0.0	9.3
Finland	306	4	0	9	1.2	0.0	2.8
France	9,255	138	76	214	1.5	0.9	2.2
French Polynesia	76	3	1	10	3.9	1.3	13.6
Gabon	5,061	98	31	460	1.9	0.6	9.1

Country	No. of All TB cases	No. of MDR cases	Low 95%	High 95%	% MDR TB	Low 95%	High 95%
			CL	CL		CL	CL
Gambia	4,526	20	0	72	0.5	0.0	1.4
Georgia	5,269	652	467	847	12.4	9.9	15.4
Germany	5,826	155	107	210	2.7	2.1	3.5
Ghana	48,787	1,090	288	6,169	2.2	0.6	12.1
Greece	2,227	45	15	186	2.0	0.7	8.5
Guam	69	3	0	10	4.3	0.5	14.5
Guatemala	10,748	432	269	633	4.0	2.7	5.5
Guinea	25,969	599	287	978	2.3	1.1	4.1
Guinea-Bissau	3,884	109	32	545	2.8	0.8	13.9
Guyana	1,325	31	10	152	2.4	0.8	11.3
Haiti	28,927	594	139	3,515	2.1	0.5	11.9
Honduras	5,626	131	63	218	2.3	1.2	3.6
Hungary	2,290	69	23	258	3.0	1.0	11.1
Iceland	14	0	0	0	0.0	0.0	0.0
India	2,254,052	110,132	79,975	142,386	4.9	3.9	6.2
Indonesia	542,703	12,142	753	30,388	2.2	0.1	5.3
Iran	16,511	1,178	788	1,642	7.1	5.3	9.5
Iraq	17,263	969	334	3,246	5.6	2.0	18.6
Ireland	583	6	0	15	1.0	0.0	2.5
Israel	525	30	13	52	5.6	2.8	8.9
Italy	4,649	118	62	188	2.5	1.4	3.9
Jamaica	208	4	1	20	1.8	0.5	9.4
Japan	29,583	322	206	462	1.1	0.7	1.5
Jordan	314	20	8	36	6.3	2.6	10.8
Kazakhstan	26,647	6,608	4,806	8,534	24.8	20.0	30.4
Kenya	145,590	0	0	0	0.0	0.0	0.0
Kiribati	353	12	2	66	3.4	0.7	18.1
Kuwait	676	16	4	79	2.4	0.7	11.6
Kyrgyzstan	7,502	1,368	443	4,026	18.2	6.2	51.5
Lao PDR	9,172	398	106	1,837	4.3	1.2	19.8
Latvia	1,523	218	156	284	14.3	11.9	17.3
Lebanon	462	11	5	20	2.4	1.0	4.3
Lesotho	14,529	220	66	427	1.5	0.5	2.9
Libyan Arab Jamahiriya	1,076	33	8	166	3.1	0.8	15.2
Lithuania	2,563	425	313	545	16.6	13.6	20.5
Luxembourg	60	0	0	1	0.5	0.1	2.3
Madagascar	51,390	388	104	740	0.8	0.2	1.5
Malawi	54,001	1,362	341	7,663	2.5	0.7	14.4
Malaysia	28,584	27	0	95	0.1	0.0	0.3
Maldives	143	5	2	24	3.7	1.1	16.4
Mali	34,228	756	177	4,363	2.2	0.5	12.8
Malta	26	0	0	1	0.4	0.1	2.3
Marshall Islands	135	5	2	24	4.0	1.3	16.7
Mauritius	294	5	1	26	1.6	0.5	8.6
Mexico	27,113	1,579	960	2,301	5.8	3.6	8.7
Micronesia	125	6	2	22	4.8	1.7	17.7
Mongolia	5,225	116	42	263	2.2	0.8	5.3
Morocco	29,877	271	141	446	0.9	0.5	1.5
Mozambique	97,946	3,419	1,987	5,168	3.5	2.5	4.6
Myanmar	88,999	4,251	2,648	6,187	4.8	3.4	6.3
Namibia	17,155	342	103	1,716	2.0	0.6	9.8
Nepal	53,211	1,921	1,195	2,822	3.6	2.4	4.9
Netherlands	1,295	10	3	21	0.8	0.3	1.5
New Caledonia	74	0	0	39	0.0	0.0	52.2
New Zealand	373	1	0	5	0.4	0.0	1.1
Nicaragua	3,606	51	19	93	1.4	0.5	2.6
Niger	26,105	750	233	3,667	2.9	0.9	13.5
Nigeria	478,736	11,171	3,254	58,081	2.3	0.7	12.0
Northern Mariana Is	66	3	0	0	4.5	0.0	0.0
Norway	279	4	0	10	1.5	0.0	3.4
Oman	341	6	1	14	1.8	0.3	4.0
Pakistan	306,418	15,233	4,752	59,884	5.0	1.6	19.4
Palau	12	1	0	2	5.4	1.7	16.5
Panama	1,715	47	16	188	2.7	0.9	11.0
Papua New Guinea	17,277	915	285	3,560	5.3	1.7	20.1

Country	No. of All TB cases	No. of MDR cases	Low 95%	High 95%	% MDR TB	Low 95%	High 95%
			CL	CL		CL	CL
Paraguay	4,719	109	34	212	2.3	0.8	4.2
Peru	51,670	3,972	2,842	5,192	7.7	6.3	9.4
Philippines	256,511	11,848	7,428	17,106	4.6	3.4	5.9
Poland	10,660	127	81	181	1.2	0.8	1.8
Portugal	3,762	64	38	96	1.7	1.1	2.5
Puerto Rico	206	0	0	0	0.0	0.0	0.0
Qatar	493	5	1	15	1.1	0.2	3.1
Rep. Korea	49,830	2,189	1,541	2,914	4.4	3.4	5.7
Republic of Moldova	7,437	2,035	1,504	2,581	27.4	23.8	31.4
Romania	34,518	1,546	1,047	2,138	4.5	3.3	5.9
Russian Federation	186,080	36,037	28,992	50,258	19.4	17.1	24.6
Rwanda	40,363	1,723	1,000	2,617	4.3	2.8	5.8
Saint Lucia	32	1	0	4	2.7	0.9	11.1
Samoa	41	2	1	8	5.2	1.8	18.6
Saudi Arabia	11,024	375	124	1,540	3.4	1.1	13.6
Senegal	36,361	1,309	587	2,225	3.6	1.6	6.0
Serbia	3,534	26	10	47	0.7	0.3	1.3
Seychelles	30	1	0	3	2.0	0.6	9.2
Sierra Leone	30,894	532	81	1,228	1.7	0.3	3.9
Singapore	1,277	4	0	9	0.3	0.0	0.7
Slovakia	942	21	7	40	2.3	0.8	4.1
Slovenia	278	1	0	2	0.2	0.0	0.8
Solomon Islands	664	0	0	29	0.0	0.0	4.3
Somalia	19,303	412	113	2,229	2.1	0.6	11.3
South Africa	540,571	14,034	10,019	18,409	2.6	2.1	3.2
Spain	13,895	48	8	102	0.3	0.1	0.7
Sri Lanka	12,230	21	0	75	0.2	0.0	0.5
St Vincent & Grenadines	39	1	0	5	3.1	1.1	12.2
Sudan	98,303	2,377	752	12,040	2.4	0.8	11.9
Swaziland	14,535	248	79	462	1.7	0.5	3.2
Sweden	561	4	1	9	0.7	0.1	1.6
Switzerland	550	6	1	14	1.2	0.3	2.5
Syrian Arab Republic	6,510	287	90	1,195	4.4	1.4	17.8
Tajikistan	15,986	3,204	1,072	8,916	20.0	6.8	53.9
TFYR Macedonia	680	19	6	79	2.8	0.9	11.4
Thailand	94,139	2,834	1,920	3,926	3.0	2.1	4.2
Timor-Leste	6,260	225	46	1,192	3.6	0.7	18.5
Togo	26,703	667	190	3,449	2.5	0.7	12.6
Tonga	26	1	0	5	4.5	1.4	17.6
Tunisia	2,563	84	22	413	3.3	0.9	15.7
Turkey	27,272	889	284	3,320	3.3	1.1	12.3
Turkmenistan	3,890	252	125	411	6.5	3.3	10.2
Uganda	112,098	836	120	1,858	0.7	0.1	1.6
Ukraine	61,857	13,429	9,810	17,150	21.7	18.8	25.1
United Arab Emirates	713	27	9	104	3.8	1.3	14.2
United Kingdom	9,776	74	42	113	0.8	0.5	1.0
UR Tanzania	133,072	1,335	240	2,942	1.0	0.2	2.0
Uruguay	986	5	0	13	0.5	0.0	1.4
USA	13,616	159	133	190	1.2	1.0	1.4
Uzbekistan	41,087	9,829	6,891	13,073	23.9	18.4	30.3
Vanuatu	130	0	0	0	0.0	0.0	0.0
Venezuela	11,954	151	76	244	1.3	0.6	2.1
Viet Nam	161,205	6,421	4,402	8,760	4.0	3.0	5.1
West Bank and Gaza Strip	820	36	11	151	4.3	1.4	18.2
Yemen	17,633	573	299	923	3.2	1.9	4.8
Zambia	72,026	1,330	494	2,442	1.8	0.8	3.1
Zimbabwe	94,921	2,460	1,190	4,053	2.6	1.4	4.1

Annex 11: Estimates of MDR-TB by epidemiological region

Regions	No. of MDR TB					% MDR TB	Low 95% CL	High 95% CL
	No. of New TB cases	cases	Low 95% CL	High 95% CL	cases			
Established Market Economies	85,729	724	573	942		0.8	0.7	1.1
Central Europe	42,464	416	166	2,170		1.0	0.4	5.0
Eastern Europe	336,842	43,878	35,881	54,877		13.0	11.8	15.3
Latin America	315,216	7,196	5,850	10,360		2.3	1.9	3.3
Eastern Mediterranean Region	569,446	16,430	8,137	64,077		2.9	1.5	11.1
Africa low HIV incidence	350,671	5,311	3,705	14,948		1.5	1.1	4.3
Africa high HIV incidence	2,440,270	43,767	33,907	102,418		1.8	1.4	4.2
South-east Asia	3,100,354	85,908	58,085	148,884		2.8	2.1	4.7
Western Pacific Region	1,882,930	82,087	57,531	107,804		4.4	3.9	4.8
Surveyed countries (n=105)	7,029,716	228,367	190,128	267,943		3.2	2.9	3.6
Non surveyed countries (n=70)	2,094,206	57,351	45,599	164,828		2.7	2.2	7.7
All countries (n=175)	9,123,922	285,718	256,072	399,224		3.1	2.9	4.3

Regions	No. of Previously treated TB cases	No. of MDR TB			% MDR TB	Low 95% CL	High 95% CL
		cases	Low 95% CL	High 95% CL			
Established Market Economies	5,036	413	330	528	8.2	6.8	10.2
Central Europe	8,038	785	303	2,625	9.8	3.9	31.3
Eastern Europe	79,474	36,179	29,216	43,769	45.5	41.8	49.4
Latin America	33,856	4,873	4,001	5,937	14.4	12.4	16.9
Eastern Mediterranean Region	31,286	9,040	4,733	15,901	28.9	15.5	48.9
Africa low HIV incidence	25,130	3,105	2,169	5,527	12.4	8.9	21.4
Africa high HIV incidence	216,152	14,528	11,004	24,886	6.7	5.4	11.4
South-east Asia	363,959	63,707	43,416	87,495	17.5	15.4	20.2
Western Pacific Region	289,214	70,601	47,134	94,543	24.4	22.7	26.1
Surveyed countries (n=96)	906,968	179,767	146,915	212,012	19.8	18.4	21.3
Non surveyed countries (n=79)	145,177	23,463	19,117	39,326	16.2	13.1	26.3
All countries (n=175)	1,052,145	203,230	172,935	242,177	19.3	18.2	21.3

Regions	No. of MDR TB					Low 95% CL	High 95% CL
	No. of All TB cases	cases	Low 95% CL	High 95% CL	% MDR TB		
Established Market Economies	105,795	1,317	1,147	1,557	1.2	1.1	1.5
Central Europe	50,502	1,201	623	3,694	2.4	1.3	7.2
Eastern Europe	416,316	80,057	71,893	97,623	19.2	18.0	22.2
Latin America	349,278	12,070	10,523	15,526	3.5	3.0	4.4
Eastern Mediterranean Region	601,225	25,475	15,737	73,132	4.2	2.6	11.9
Africa low HIV incidence	375,801	8,415	6,889	18,758	2.2	1.9	5.0
Africa high HIV incidence	2,656,422	58,296	48,718	118,506	2.2	1.9	4.5
South-east Asia	3,464,313	149,615	114,780	217,921	4.3	3.5	6.2
Western Pacific Region	2,173,333	152,694	119,886	188,014	7.0	6.1	8.1
Surveyed countries	7,953,603	408,325	361,264	464,069	5.1	4.7	5.7
Non surveyed countries	2,239,383	80,814	71,684	188,605	3.6	3.2	8.4
All countries (n=185)	10,192,986	489,139	455,093	614,215	4.8	4.6	6.0