

Epidemiology of antituberculosis drug resistance (the Global Project on Anti-tuberculosis Drug Resistance Surveillance): an updated analysis

Mohamed Abdel Aziz, Abigail Wright, Adalbert Laszlo, Aimé De Muynck, Françoise Portaels, Armand Van Deun, Charles Wells, Paul Nunn, Leopold Blanc, Mario Raviglione, for the WHO/International Union Against Tuberculosis And Lung Disease Global Project on Anti-tuberculosis Drug Resistance Surveillance*

Summary

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*Members listed at the end of the paper

Stop TB Department

(M A Aziz MD, A Wright MPH, A Laszlo PhD, P Nunn MD, L Blanc MD, M Raviglione MD), WHO, Geneva, Switzerland (Prof A De Muynck MD); Prince Léopold Tropical Institute, Antwerp, Belgium (Prof F Portaels PhD, A Van Deun MD); and Division of TB Elimination, Centers for Disease Control and Prevention, Atlanta, GA, USA (C Wells MD)

Correspondence to:

Dr Mario Raviglione, Stop TB Department, WHO, 20 avenue Appia, 1211, Geneva, Switzerland
raviglione@who.int

Background The burden of tuberculosis is compounded by drug-resistant forms of the disease. This study aimed to analyse data on antituberculosis drug resistance gathered by the WHO and International Union Against Tuberculosis and Lung Disease Global Project on Anti-tuberculosis Drug Resistance Surveillance.

Methods Data on drug susceptibility testing for four antituberculosis drugs—isoniazid, rifampicin, ethambutol, and streptomycin—were gathered in the third round of the Global Project (1999–2002) from surveys or ongoing surveillance in 79 countries or geographical settings. These data were combined with those from the first two rounds of the project and analyses were done. Countries that participated followed a standardised set of guidelines to ensure comparability both between and within countries.

Findings The median prevalence of resistance to any of the four antituberculosis drugs in new cases of tuberculosis identified in 76 countries or geographical settings was 10·2% (range 0·0–57·1). The median prevalence of multidrug resistance in new cases was 1·0% (range 0·0–14·2). Kazakhstan, Tomsk Oblast (Russia), Karakalpakstan (Uzbekistan), Estonia, Israel, the Chinese provinces Liaoning and Henan, Lithuania, and Latvia reported prevalence of multidrug resistance above 6·5%. Trend analysis showed a significant increase in the prevalence of multidrug resistance in new cases in Tomsk Oblast ($p < 0\cdot0001$). Hong Kong ($p = 0\cdot01$) and the USA ($p = 0\cdot0002$) reported significant decreasing trends in multidrug resistance in new cases of tuberculosis.

Interpretation Multidrug resistance represents a serious challenge for tuberculosis control in countries of the former Soviet Union and in some provinces of China. Gaps in coverage of the Global Project are substantial, and baseline information is urgently required from several countries with high tuberculosis burden to develop appropriate control interventions.

Introduction

Despite the recent progress of global control efforts, tuberculosis remains a major public-health burden in most developing countries. Current global estimates indicate that about a third of the world's population is infected with *Mycobacterium tuberculosis*, 8·7 million individuals develop the disease annually, and, in 2003, almost 2 million deaths occurred.¹ Tuberculosis control in some regions is jeopardised by the HIV epidemic.^{2–4} A third of the 40 million people living with HIV/AIDS are infected with *M tuberculosis*. In 2003, about 674 000 HIV-positive individuals developed tuberculosis,¹ which represents the main cause of death in such individuals.⁵

The emergence of drug-resistant strains occurs with the wide use and misuse of antimicrobials.⁶ Wild isolates of *M tuberculosis* that have never been exposed to antituberculosis drugs almost never show any resistance.^{7–14} Multidrug-resistant (MDR) tuberculosis—defined as resistance to at least isoniazid and rifampicin—represents a substantial challenge to tuberculosis control programmes, since the treatment of such cases is complex, more costly, and frequently

less successful than treatment of non-resistant strains. Cure rates in cases harbouring MDR strains range from 6% to 59%.¹⁵

In 1994, WHO, the International Union Against Tuberculosis and Lung Disease, and other partners launched the Global Project on Anti-tuberculosis Drug Resistance Surveillance.¹⁶ The aim of this project is to determine the prevalence, patterns, and trends of antituberculosis drug resistance around the world, ultimately to improve the performance of national tuberculosis control programmes through policy recommendations on patient management. The project measures in-vitro drug susceptibility to four of the six first-line antituberculosis drugs—ie, isoniazid, rifampicin, streptomycin, and ethambutol.¹⁷

Through its first two reports^{18,19} the project has provided a better understanding of the magnitude and distribution of antituberculosis drug resistance^{20,21} and has led to policy development for the treatment of MDR tuberculosis. The DOTS-Plus strategy for the use of second-line drugs in the management of patients who harbour drug-resistant strains, including MDR tuberculosis,^{22–24} was developed in 1999, followed by the

establishment of the Green Light Committee in 2000 to provide access to preferentially priced second-line drugs while ensuring rational use through mandatory programme review and monitoring. The culmination of these efforts has led to the development of WHO guidelines for the programmatic management of drug-resistant tuberculosis.²⁵

One of the most important contributions of the Global Project to tuberculosis control has been the strengthening of national tuberculosis reference laboratories through the guidance of supranational reference laboratories. A network of these laboratories was developed in 1994 to provide an international external laboratory quality assurance system for countries taking part in this project. Today there are 25 of these laboratories in six regions that assist over 100 national reference laboratories in culture and drug susceptibility testing for drug-resistance programmes. This network has resulted in more reliable epidemiological and laboratory data and, ultimately, better diagnostics for patients. However, poorly functioning laboratory networks have proven to be a formidable obstacle in the control of tuberculosis, especially in the expansion of surveillance and treatment of MDR tuberculosis, and must be placed high on the agenda over the next decade.

Periodic assessment of trends in antituberculosis drug resistance will help inform best control practices and assess the performance of national tuberculosis control programmes over time, thus informing necessary adjustments in the approach to control. The Global Project completed a third round of surveys and surveillance in 2002. The data gathered, combined with those from the previous two rounds, provide information on 109 countries or geographical settings worldwide—areas that represent almost 40% of notified smear-positive pulmonary cases of tuberculosis. The aim of this paper is to analyse the data gathered.

Methods

Data collection

Details of the methods of the Global Project have been described elsewhere.^{18–21} Briefly, surveys are done on the basis of three principles—the sample must be representative of the tuberculosis population in the area surveyed, the results of drug susceptibility testing must be quality controlled by a supranational reference laboratory, and data collection must differentiate between new and previously treated cases. Resistance in new and previously treated cases are proxy measures for primary and acquired resistance. New cases are defined as patients who have never been treated or treated for less than 1 month for tuberculosis. Previously treated cases are defined as patients who have been treated for tuberculosis for 1 month or more. The term combined cases does not differentiate treatment history and is used to determine prevalence of resistance in all cases in a population. All newly registered patients with sputum smear-positive

	Duration (months) and type of project	Type of sample
Algeria, 2001	12, survey	Cluster
Botswana, 2002	8, survey	Cluster
Democratic Republic of the Congo, Kinshasa, 1999	NA, survey	All cases
South Africa, Eastern Cape province, 2002	12, survey	MSC
South Africa, Free State province, 2002	12, survey	MSC
South Africa, Gauteng province, 2002	12, survey	MSC
South Africa, Kwazulu-Natal province, 2002	12, survey	MSC
South Africa, Limpopo province, 2002	12, survey	MSC
South Africa, Mpumalanga, 2002	12, survey	MSC
South Africa, North West province, 2002	12, survey	MSC
South Africa, Western Cape province, 2002	12, survey	MSC
The Gambia, 2000	7, survey	All diagnostic centres
Zambia, 2000	14, survey	Cluster
Argentina, 1999	12, survey	Cluster
Canada, 2000	12, surveillance	All cases
Chile, 2001	6, survey	Cluster
Colombia, 2000	12, survey	Cluster
Cuba, 2000	12, surveillance	Sentinel
Ecuador, 2002	12, survey	All cases
El Salvador, 2001	12, survey	All cases
Honduras, 2002	14, survey	Cluster
Puerto Rico, 2001	12, surveillance	New cases only
USA, 2001	12, surveillance	All cases
Uruguay, 1999	NA, survey	Proportionate cluster
Venezuela, 1999	9, survey	Proportionate cluster
Egypt, 2002	12, survey	Proportionate cluster
Oman, 2001	12, surveillance	All cases
Qatar, 2001	12, surveillance	New cases only
Andorra, 2000	12, surveillance	All cases
Austria, 2000	12, surveillance	All cases
Belgium, 2000	12, surveillance	All cases
Bosnia Herzegovina, 2000	12, surveillance	All cases
Croatia, 2000	12, surveillance	All cases
Czech Republic, 2000	12, surveillance	All cases
Denmark, 2000	12, surveillance	All cases
Estonia, 2000	12, surveillance	All cases
Finland, 2000	12, surveillance	All cases
France, 15 regions, 2000	12, surveillance	Sentinel
Germany, 2000	12, surveillance	All cases
Iceland, 2000	12, surveillance	All cases
Ireland, 2000	12, surveillance	All cases
Israel, 2000	12, surveillance	All cases
Italy, 10 regions, 2000	12, surveillance	All cases
Kazakhstan, 2001	2, surveillance	All cases

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Latvia, 2000	12, survey	All cases
Lithuania, 2002	12, surveillance	All cases
Luxembourg, 2000	12, surveillance	All cases
Malta, 2000	12, surveillance	All cases
Netherlands, 2000	12, surveillance	All cases
Norway, 2000	12, surveillance	All cases
Poland, 2001	12, survey	All cases
Russia, Orel Oblast, 2002	12, surveillance	All cases
Russia, Tomsk Oblast, 2002	12, surveillance	All cases
Scotland, 2000	12, surveillance	All cases
Serbia and Montenegro, Belgrade, 2000	12, surveillance	All cases
Slovakia, 2000	12, surveillance	All cases
Slovenia, 2000	12, surveillance	All cases
Spain, Barcelona, 2001	12, surveillance	Cluster
Spain, Galicia, 2002	12, survey	All cases
Sweden, 2000	12, surveillance	All cases
Switzerland, 2000	12, surveillance	All cases
Turkmenistan, Dashoguz Velayat (Aral Sea Region), 2002	9, survey	All cases
UK (excluding Scotland), 2000	12, surveillance	All cases
Uzbekistan, Karakalpakstan (Aral Sea Region), 2002	7, survey	All cases
India, North Arcot, Tamil Nadu, 1999	3, survey	New cases only
India, Raichur, Karnataka, 1999	6, survey	New cases only
India, Wardha, Maharashtra, 2001	10, survey	New cases only
Nepal, 2001	10, survey	Cluster
Thailand, 2001	24, survey	Proportionate cluster
Australia, 2001	12, surveillance	All cases
Cambodia, 2001	7, survey	Proportionate cluster
China, Henan, 1999	12, survey	Proportionate cluster
China, Hong Kong, 2001	12, surveillance	All cases
China, Hubei, 1999	10, survey	Cluster
China, Liaoning, 1999	12, survey	Cluster
Japan, 1997	6, survey	Sentinel
Mongolia, 1999	7, survey	New cases only
New Zealand, 2001	12, surveillance	All cases
Singapore, 2001	12, surveillance	All cases

All surveys countrywide unless otherwise indicated. MSC=multistage stratified cluster. NA=not available.

Table 1: Countries or geographical settings studied in the third round of the Global Project

pulmonary tuberculosis were eligible for inclusion.^{16,17} In the context of surveys, sample sizes were determined on the basis of all new smear-positive cases notified in the previous year and the estimated proportion of rifampicin resistance in this population. In these settings, previously treated cases were included during the period of intake for new cases.²⁶ Therefore, samples of previously treated

cases in survey settings could be biased. One isolate was examined per case of tuberculosis. Culture on Löwenstein-Jensen medium and the proportion method for drug susceptibility testing were the most frequently used laboratory methods.²⁷ However, in some countries, cultures were done with Ogawa medium and drug susceptibility testing with the radiometric BACTEC 460 method;²⁸ the absolute concentration and resistance ratio methods were also used in some settings.^{27,29} Niacin production and nitrate reduction tests, together with paranitrobenzoic acid (500 mg/L)³⁰ and thiophene carboxylic acid hydrazide (2 mg/L) susceptibility tests,³¹ were used to identify species. Species other than *M tuberculosis* were excluded from analysis. Quality assurance was done by the supranational reference laboratories by sending a panel of isolates before the implementation of the survey and later by re-checking a percentage of isolates from patients included in the survey. HIV testing was not a mandatory component of these surveys.

The third round of the Global Project gathered data from surveys and on-going surveillance between 1999 and 2002 in 79 countries or geographical settings. Aggregate data reported from settings were entered into a database built with Microsoft Access software and to which all data from the first and second report were added.

Re-checking of patient treatment history through verification of medical records and patient re-interview was recommended to reduce the possibility of misclassification. All data were re-checked during the process of data entry and before the start of the analysis, and all data files and epidemiological profiles were returned to countries for verification.

Statistical analysis

Statistical analyses were done with EpiInfo version 6.04d and SPSS/Windows version 9.0. Arithmetic means, medians, and ranges were determined as summary statistics for new, previously treated, and combined cases. For settings that reported more than one data point, only the latest data point was used to estimate point prevalence. Trend analysis was done for geographical settings that reported more than two data points since the beginning of the project. The χ^2 test for trend was used on absolute numbers. European surveillance data reported for the years 1999 and 2000 were provided by EuroTB. Exact binomial confidence limits were calculated for all observed proportions of drug-resistant tuberculosis.

Role of the funding source

This project was financed by the US Agency for International Development. The Tuberculosis Coalition for Technical Assistance funded laboratory activities associated with the project. The sponsors of the study had no role in study design, data collection, data analysis, data

	Total isolates tested	Any resistance	Resistance to isoniazid	Resistance to rifampicin	Resistance to ethambutol	Resistant to streptomycin	Multidrug resistance*
Algeria	518	32 (6.2%, 4.2-8.7)	16 (3.1%, 1.8-5.0)	6 (1.2%, 0.4-2.5)	0 (0%, 0.0-0.6)	27 (5.2%, 3.4-7.6)	6 (1.2%, 0.4-2.5)
Botswana	1182	123 (10.4%, 8.6-12.4)	53 (4.5%, 3.4-5.9)	24 (2.0%, 1.3-3.0)	15 (1.3%, 0.7-2.1)	82 (6.9%, 5.5-8.6)	10 (0.8%, 0.4-1.6)
South Africa							
Eastern Cape province	506	57 (11.3%, 8.5-14.6)	36 (7.1%, 5.0-9.8)	6 (1.2%, 0.4-2.6)	3 (0.6%, 0.1-1.7)	34 (6.7%, 4.7-9.4)	5 (1.0%, 0.3-2.3)
Free State province	454	39 (8.6%, 6.2-11.6)	29 (6.4%, 4.3-9.0)	11 (2.4%, 1.2-4.3)	3 (0.7%, 0.1-1.9)	18 (4.0%, 2.4-6.2)	8 (1.8%, 0.8-3.4)
Gauteng province	592	39 (6.6%, 4.7-9.0)	26 (4.4%, 2.9-6.4)	10 (1.7%, 0.8-3.1)	2 (0.3%, 0.0-1.2)	23 (3.9%, 2.5-5.8)	8 (1.4%, 0.6-2.7)
Kwazulu-Natal province	595	39 (6.6%, 4.7-9.0)	32 (5.4%, 3.7-7.6)	11 (1.8%, 0.9-3.3)	5 (0.8%, 0.3-2.0)	23 (3.9%, 2.5-5.8)	10 (1.7%, 0.8-3.1)
Limpopo province	451	32 (7.1%, 4.9-9.9)	25 (5.5%, 3.6-8.1)	11 (2.4%, 1.2-4.3)	10 (2.2%, 1.1-4.0)	18 (4.0%, 2.4-6.2)	11 (2.4%, 1.2-4.3)
Mpumalanga	702	66 (9.4%, 7.3-12.0)	49 (7.0%, 5.2-9.2)	22 (3.1%, 2.0-4.7)	7 (1.0%, 0.4-2.1)	29 (4.1%, 2.8-5.9)	18 (2.6%, 1.5-4.1)
North West province	631	51 (8.1%, 6.0-10.6)	37 (5.9%, 4.1-8.1)	17 (2.7%, 1.6-4.3)	8 (1.3%, 0.5-2.5)	28 (4.4%, 2.9-6.4)	14 (2.2%, 1.2-3.7)
Western Cape province	427	24 (5.6%, 3.6-8.2)	22 (5.2%, 3.3-7.7)	4 (0.9%, 0.3-2.4)	0 (0%, 0.0-0.7)	10 (2.3%, 1.1-4.3)	4 (0.9%, 0.3-2.4)
The Gambia	210	9 (4.3%, 2.0-8.0)	5 (2.4%, 0.8-5.5)	2 (1.0%, 0.1-3.4)	0 (0%, 0.0-1.4)	3 (1.4%, 0.3-4.1)	1 (0.5%, 0.0-2.6)
Zambia	445	51 (11.5%, 8.7-14.8)	28 (6.3%, 4.2-9.0)	8 (1.8%, 0.8-3.5)	9 (2.0%, 0.9-3.8)	24 (5.4%, 3.5-7.9)	8 (1.8%, 0.8-3.5)
Argentina	679	69 (10.2%, 7.9-12.9)	26 (3.8%, 2.5-5.6)	13 (1.9%, 1.0-3.3)	16 (2.4%, 1.3-3.8)	50 (7.4%, 5.5-9.7)	12 (1.8%, 0.9-3.1)
Canada	1244	106 (8.5%, 7.0-10.3)	84 (6.8%, 5.4-8.4)	11 (0.9%, 0.4-1.6)	13 (1.0%, 0.6-1.8)	43 (3.5%, 2.5-4.7)	9 (0.7%, 0.3-1.4)
Chile	867	91 (10.5%, 8.5-12.9)	39 (4.5%, 3.2-6.1)	7 (0.8%, 0.3-1.7)	2 (0.2%, 0.0-0.8)	78 (9.0%, 7.1-11.2)	6 (0.7%, 0.3-1.5)
Colombia	1087	169 (15.5%, 13.3-18.1)	103 (9.5%, 7.7-11.5)	18 (1.7%, 1.0-2.6)	9 (0.8%, 0.4-1.6)	125 (11.5%, 9.6-13.7)	16 (1.5%, 0.8-2.4)
Cuba	377	19 (5.0%, 3.1-7.8)	4 (1.1%, 0.3-2.7)	3 (0.8%, 0.2-2.3)	0 (0%, 0.0-0.8)	17 (4.5%, 2.6-7.1)	1 (0.3%, 0.0-1.5)
Ecuador	812	163 (20.1%, 17.1-23.4)	89 (11.0%, 8.8-13.5)	59 (7.3%, 5.5-9.4)	10 (1.2%, 0.6-2.3)	92 (11.3%, 9.1-13.9)	40 (4.9%, 3.5-6.7)
El Salvador	611	35 (5.7%, 4.0-8.0)	8 (1.3%, 0.6-2.6)	7 (1.1%, 0.5-2.4)	2 (0.3%, 0.0-1.2)	23 (3.8%, 2.4-5.6)	2 (0.3%, 0.0-1.2)
Honduras	169	29 (17.2%, 11.8-23.7)	11 (6.5%, 3.3-11.3)	4 (2.4%, 0.6-5.9)	2 (1.2%, 0.1-4.2)	25 (14.8%, 9.8-21.1)	3 (1.8%, 0.4-5.1)
Puerto Rico	100	12 (12.0%, 6.4-20.0)	8 (8.0%, 3.5-15.2)	3 (3.0%, 0.6-8.5)	1 (1.0%, 0.0-5.4)	8 (8.0%, 3.5-15.2)	2 (2.0%, 0.2-7.0)
USA	9751	1235 (12.7%, 12.0-13.4)	753 (7.7%, 7.2-8.3)	142 (1.5%, 1.2-1.7)	154 (1.6%, 1.3-1.8)	718 (7.4%, 6.8-7.9)	112 (1.1%, 0.9-1.4)
Uruguay	315	10 (3.2%, 1.5-5.8)	5 (1.6%, 0.5-3.7)	1 (0.3%, 0.0-1.8)	0 (0%, 0.0-0.9)	5 (1.6%, 0.5-3.7)	1 (0.3%, 0.0-1.8)
Venezuela	769	58 (7.5%, 5.7-9.8)	30 (3.9%, 2.6-5.6)	8 (1.0%, 0.4-2.0)	8 (1.0%, 0.4-2.0)	36 (4.7%, 3.3-6.5)	4 (0.5%, 0.1-1.3)
Egypt	632	193 (30.5%, 26.4-35.2)	62 (9.8%, 7.5-12.6)	44 (7.0%, 5.1-9.3)	18 (2.8%, 1.7-4.5)	149 (23.6%, 19.9-27.7)	14 (2.2%, 1.2-3.7)
Oman	171	9 (5.3%, 2.4-9.8)	7 (4.1%, 1.7-8.3)	1 (0.6%, 0.0-3.2)	0 (0%, 0.0-1.7)	2 (1.2%, 0.1-4.2)	0 (0%, 0.0-1.7)
Qatar	284	28 (9.9%, 6.7-13.9)	19 (6.7%, 4.1-10.3)	3 (1.1%, 0.2-3.1)	5 (1.8%, 0.6-4.1)	9 (3.2%, 1.5-5.9)	1 (0.4%, 0.0-1.9)
Andorra	3	0 (0%, 0.0-63.2)	0 (0%, 0.0-63.2)	0 (0%, 0.0-63.2)	0 (0%, 0.0-63.2)	0 (0%, 0.0-63.2)	0 (0%, 0.0-63.2)
Austria	694	31 (4.5%, 3.0-6.3)	20 (2.9%, 1.8-4.5)	5 (0.7%, 0.2-1.7)	1 (0.1%, 0.0-0.8)	18 (2.6%, 1.5-4.1)	3 (0.4%, 0.1-1.3)
Belgium	562	34 (6.0%, 4.2-8.5)	30 (5.3%, 3.6-7.6)	9 (1.6%, 0.7-3.0)	6 (1.1%, 0.4-2.3)	0 (0%, 0.0-0.5)	7 (1.2%, 0.5-2.6)
Bosnia Herzegovina	993	24 (2.4%, 1.5-3.6)	5 (0.5%, 0.2-1.2)	7 (0.7%, 0.3-1.5)	11 (1.1%, 0.6-2.0)	5 (0.5%, 0.2-1.2)	1 (0.1%, 0.0-0.6)
Croatia	780	14 (1.8%, 1.0-3.0)	8 (1.0%, 0.4-2.0)	1 (0.1%, 0.0-0.7)	0 (0%, 0.0-0.4)	7 (0.9%, 0.4-1.8)	1 (0.1%, 0.0-0.7)
Czech Republic	616	27 (4.4%, 2.9-6.4)	21 (3.4%, 2.1-5.2)	7 (1.1%, 0.5-2.3)	5 (0.8%, 0.3-1.9)	12 (1.9%, 1.0-3.4)	7 (1.1%, 0.5-2.3)
Denmark	392	47 (12.0%, 8.9-15.6)	29 (7.4%, 5.0-10.5)	2 (0.5%, 0.1-1.8)	3 (0.8%, 0.2-2.2)	34 (8.7%, 6.1-11.9)	1 (0.3%, 0.0-1.4)
Estonia	410	117 (28.5%, 24.2-33.2)	94 (22.9%, 18.9-27.3)	50 (12.2%, 9.2-15.8)	54 (13.2%, 10.1-16.8)	92 (22.4%, 18.5-26.8)	50 (12.2%, 9.2-15.8)
Finland	374	17 (4.5%, 2.7-7.2)	10 (2.7%, 1.3-4.9)	3 (0.8%, 0.2-2.3)	1 (0.3%, 0.0-1.5)	9 (2.4%, 1.1-4.5)	1 (0.3%, 0.0-1.5)
France	947	88 (9.3%, 7.5-11.4)	24 (2.5%, 1.6-3.8)	8 (0.8%, 0.4-1.7)	20 (2.1%, 1.3-3.3)	61 (6.4%, 4.9-8.3)	8 (0.8%, 0.4-1.7)
Germany	1561	106 (6.8%, 5.6-8.2)	61 (3.9%, 3.0-5.0)	16 (1.0%, 0.6-1.7)	16 (1.0%, 0.6-1.7)	66 (4.2%, 3.3-5.4)	12 (0.8%, 0.4-1.3)
Iceland	8	0 (0%, 0.0-31.2)	0 (0%, 0.0-31.2)	0 (0%, 0.0-31.2)	0 (0%, 0.0-31.2)	0 (0%, 0.0-31.2)	0 (0%, 0.0-31.2%)
Ireland	138	4 (2.9%, 0.8-7.3)	4 (2.9%, 0.8-7.3)	1 (0.7%, 0.0-4.0)	0 (0%, 0.0-2.1)	0 (0%, 0.0-2.1)	1 (0.7%, 0.0-4.0)
Israel	253	79 (31.2%, 25.6-37.3)	65 (25.7%, 20.4-31.5)	37 (14.6%, 10.5-19.6)	25 (9.9%, 6.5-14.2)	56 (22.1%, 17.2-27.8)	36 (14.2%, 10.2-19.2)
Italy	688	78 (11.3%, 9.0-14.1)	44 (6.4%, 4.6-8.6)	11 (1.6%, 0.8-2.9)	10 (1.5%, 0.7-2.7)	54 (7.8%, 5.9-10.2)	8 (1.2%, 0.5-2.3)
Kazakhstan	359	205 (57.1%, 51.8-62.3)	153 (42.6%, 37.4-47.9)	56 (15.6%, 12.0-19.8)	89 (24.8%, 20.4-29.6)	185 (51.5%, 46.2-56.8)	51 (14.2%, 10.8-18.3)
Latvia	897	284 (31.7%, 28.1-35.6)	260 (29.0%, 25.6-32.7)	83 (9.3%, 7.4-11.5)	56 (6.2%, 4.7-8.1)	219 (24.4%, 21.3-27.9)	83 (9.3%, 7.4-11.5)
Lithuania	819	239 (29.2%, 25.6-33.1)	208 (25.4%, 22.1-29.1)	80 (9.8%, 7.7-12.2)	60 (7.3%, 5.6-9.4)	178 (21.7%, 18.7-25.2)	77 (9.4%, 7.4-11.8)
Luxembourg	39	3 (7.7%, 1.6-20.9)	2 (5.1%, 0.6-17.3)	0 (0%, 0.0-7.4)	0 (0%, 0.0-7.4)	1 (2.6%, 0.1-13.5)	0 (0%, 0.0-7.4)
Malta	9	0 (0%, 0.0-28.3)	0 (0%, 0.0-28.3)	0 (0%, 0.0-28.3)	0 (0%, 0.0-28.3)	0 (0%, 0.0-28.3)	0 (0%, 0.0-28.3)
Netherlands	768	82 (10.7%, 8.5-13.3)	43 (5.6%, 4.1-7.5)	7 (0.9%, 0.4-1.9)	5 (0.7%, 0.2-1.5)	53 (6.9%, 5.2-9.0)	7 (0.9%, 0.4-1.9)
Norway	160	38 (23.8%, 17.4-31.1)	21 (13.1%, 8.3-19.4)	4 (2.5%, 0.7-6.3)	11 (6.9%, 3.5-12.0)	18 (11.3%, 6.8-17.2)	3 (1.9%, 0.4-5.4)

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Poland	3037	186 (6.1%, 5.3-7.1)	125 (4.1%, 3.4-4.9)	44 (1.4%, 1.1-1.9)	19 (0.6%, 0.4-1.0)	103 (3.4%, 2.8-4.1)	35 (1.2%, 0.8-1.6)
Russia							
Orel Oblast	379	80 (21.1%, 17.1-25.6)	68 (17.9%, 14.2-22.2)	10 (2.6%, 1.3-4.8)	18 (4.7%, 2.8-7.4)	72 (19.0%, 15.2-23.3)	10 (2.6%, 1.3-4.8)
Tomsk Oblast	533	199 (37.3%, 32.3-42.9)	155 (29.1%, 24.7-34.0)	76 (14.3%, 11.2-17.8)	23 (4.3%, 2.7-6.5)	182 (34.1%, 29.4-39.5)	73 (13.7%, 10.7-17.2)
Serbia and Montenegro	249	14 (5.6%, 3.1-9.3)	4 (1.6%, 0.4-4.1)	5 (2.0%, 0.7-4.6)	2 (0.8%, 0.1-2.9)	6 (2.4%, 0.9-5.2)	1 (0.4%, 0.0-2.2)
Slovakia	465	19 (4.15%, 2.5-6.3)	15 (3.2%, 1.8-5.3)	7 (1.5%, 0.6-3.1)	1 (0.2%, 0.0-1.2)	6 (1.3%, 0.5-2.8)	5 (1.1%, 0.4-2.5)
Slovenia	282	7 (2.5%, 1.0-5.0)	6 (2.1%, 0.8-4.6)	0 (0%, 0.0-1.1)	0 (0%, 0.0-1.1)	3 (1.1%, 0.2-3.1)	0 (0%, 0.0-1.1)
Spain							
Barcelona	133	14 (10.5%, 5.9-17.0)	8 (6.0%, 2.6-11.5)	2 (1.5%, 0.2-5.3)	0 (0%, 0.0-2.2)	9 (6.8%, 3.1-12.5)	1 (0.8%, 0.0-4.1)
Galicia	360	42 (11.7%, 8.5-15.4)	16 (4.4%, 2.6-7.1)	5 (1.4%, 0.5-3.2)	8 (2.2%, 1.0-4.3)	26 (7.2%, 4.8-10.4)	5 (1.4%, 0.5-3.2)
Sweden	344	36 (10.5%, 7.4-14.2)	35 (10.2%, 7.2-13.9)	4 (1.2%, 0.3-3.0)	2 (0.6%, 0.1-2.1)	8 (2.3%, 1.0-4.5)	4 (1.2%, 0.3-3.0)
Switzerland	330	18 (5.5%, 3.3-8.5)	18 (5.5%, 3.3-8.5)	0 (0%, 0.0-0.9)	0 (0%, 0.0-0.9)	0 (0%, 0.0-0.9)	0 (0%, 0.0-0.9)
Turkmenistan	105	32 (30.5%, 21.9-40.2)	16 (15.2%, 9.0-23.6)	4 (3.8%, 1.0-9.5)	2 (1.9%, 0.2-6.7)	26 (24.8%, 16.9-34.1)	4 (3.8%, 1.0-9.5)
UK (excluding Scotland)	2312	195 (8.4%, 7.3-9.7)	139 (6.0%, 5.1-7.1)	28 (1.2%, 0.8-1.8)	11 (0.5%, 0.2-0.9)	84 (3.6%, 2.9-4.5)	21 (0.9%, 0.6-1.4)
Uzbekistan	106	51 (48.1%, 38.3-58.0)	39 (36.8%, 27.6-46.7)	14 (13.2%, 7.4-21.2)	16 (15.1%, 8.9-23.4)	47 (44.3%, 34.7-54.3)	14 (13.2%, 7.4-21.2)
India							
North Arcot, Tamil Nadu	282	78 (27.7%, 22.5-33.3)	66 (23.4%, 18.6-28.8)	8 (2.8%, 1.2-5.5)	13 (4.6%, 2.5-7.8)	35 (12.4%, 8.8-16.8)	8 (2.8%, 1.2-5.5)
Raichur, Karnataka	278	61 (21.9%, 17.2-27.3)	52 (18.7%, 14.3-23.8)	7 (2.5%, 1.0-5.1)	9 (3.2%, 1.5-6.1)	20 (7.2%, 4.4-10.9)	7 (2.5%, 1.0-5.1)
Wardha, Maharashtra	197	39 (19.8%, 14.5-26.1)	30 (15.2%, 10.5-21.0)	1 (0.5%, 0.0-2.8)	2 (1.0%, 0.1-3.6)	15 (7.6%, 4.3-12.2)	1 (0.5%, 0.0-2.8)
Nepal	755	83 (11.0%, 8.8-13.6)	41 (5.4%, 3.9-7.4)	13 (1.7%, 0.9-2.9)	7 (0.9%, 0.4-1.9)	67 (8.9%, 6.9-11.3)	10 (1.3%, 0.6-2.4)
Thailand	1505	223 (14.8%, 12.9-16.9)	143 (9.5%, 8.0-11.2)	21 (1.4%, 0.9-2.1)	17 (1.1%, 0.7-1.8)	124 (8.2%, 6.9-9.8)	14 (0.9%, 0.5-1.6)
Cambodia	638	66 (10.3%, 8.0-13.2)	41 (6.4%, 4.6-8.7)	4 (0.6%, 0.2-1.6)	1 (0.2%, 0.0-0.9)	32 (5.0%, 3.4-7.1)	0 (0%, 0.0-0.5)
China							
Henan	1222	364 (29.8%, 26.8-33.0)	208 (17.0%, 14.8-19.5)	117 (9.6%, 7.9-11.5)	53 (4.3%, 3.2-5.7)	271 (22.2%, 19.6-25.0)	95 (7.8%, 6.3-9.5)
Hong Kong	3470	355 (10.2%, 9.2-11.4)	191 (5.5%, 4.8-6.3)	33 (1.0%, 0.7-1.3)	19 (0.5%, 0.3-0.9)	260 (7.5%, 6.6-8.5)	27 (0.8%, 0.5-1.1)
Hubei	859	150 (17.5%, 14.8-20.5)	83 (9.7%, 7.7-12.0)	33 (3.8%, 2.6-5.4)	5 (0.6%, 0.2-1.4)	98 (11.4%, 9.3-13.9)	18 (2.1%, 1.2-3.3)
Liaoning	818	344 (42.1%, 37.7-46.7)	207 (25.3%, 22.0-29.0)	93 (11.4%, 9.2-13.9)	31 (3.8%, 2.6-5.4)	279 (34.1%, 30.2-38.4)	85 (10.4%, 8.3-12.8)
Japan	1374	141 (10.3%, 8.6-12.1)	61 (4.4%, 3.4-5.7)	19 (1.4%, 0.8-2.2)	6 (0.4%, 0.2-1.0)	103 (7.5%, 6.1-9.1)	12 (0.9%, 0.5-1.5)
Mongolia	405	119 (29.4%, 25.0-34.1)	62 (15.3%, 11.9-19.2)	5 (1.2%, 0.4-2.9)	7 (1.7%, 0.7-3.5)	98 (24.2%, 20.1-28.7)	4 (1.0%, 0.3-2.5)
New Zealand	272	31 (11.4%, 7.9-15.8)	17 (6.3%, 3.7-9.8)	1 (0.4%, 0.0-2.0)	2 (0.7%, 0.1-2.6)	17 (6.3%, 3.7-9.8)	0 (0%, 0.0-1.1)
Singapore	823	41 (5.0%, 3.6-6.8)	27 (3.3%, 2.2-4.8)	5 (0.6%, 0.2-1.4)	6 (0.7%, 0.3-1.6)	25 (3.0%, 2.0-4.5)	4 (0.5%, 0.1-1.2)

*Resistance to at least isoniazid and rifampicin. Data are number of positive isolates (%; 95% CI).

Table 2: Prevalence of drug resistance in new cases in 76 countries or settings, 1999–2002

interpretation, or writing of the report. The corresponding author had access to all data in the study and had final responsibility for the decision to submit for publication.

Results

The third round of the Global Project included data from 79 countries and geographical settings (table 1).²⁶ 66 of these countries or settings provided information on drug resistance in new, previously treated, and combined cases. 10 countries or settings reported drug susceptibility results from new cases only, and Kinshasa (Democratic Republic of the Congo), Scotland, and Australia reported data without differentiating treatment history. The median number of new cases tested per survey setting was 512 (range 3–9751). The median number of previously treated cases tested was 107 (range 1–668).

Drug susceptibility data were analysed for 57584 new cases in 76 countries or geographical settings (table 2). The prevalence of any resistance to the first-line drugs

tested ranged from 0% (Andorra, Iceland, and Malta) to 57% (Kazakhstan), with a median value of 10.2%. The prevalence of resistance to specific drugs in new cases was high for streptomycin (median 6.3%) and isoniazid (5.9%), and lower for rifampicin (1.4%) and ethambutol (0.8%). The median prevalence of multidrug resistance in the surveyed countries was 1.1%. Nine countries reported no multidrug resistance in new cases, whereas the highest prevalence of such resistance was reported from Kazakhstan and Israel (however, data from Israel in 2001 and 2002 show a substantial decrease in multidrug resistance) followed by Tomsk Oblast (Russia), Karakalpakstan (Uzbekistan), Estonia, Liaoning province (China), Lithuania, Latvia, and Henan province (China), with a prevalence of multidrug resistance of 7.8%.

Trends in resistance in new cases were analysed for 20 countries with two data points and 26 countries that provided at least three data points since 1994 (table 3).

	Year									p value*
	1994	1995	1996	1997	1998	1999	2000	2001	2002	
Resistance to any drug										
Barcelona, Spain	21/219 (9.6%)	..	11/315 (3.5%)	8/128 (6.3%)	12/135 (8.9%)	14/133 (10.5%)	..	NS
Botswana	15/407 (3.7%)	40/638 (6.3%)	123/1182 (10.4%)	<0.0001
Canada	140/1424 (9.8%)	119/1270 (9.4%)	126/1328 (9.5%)	106/1244 (8.5%)	NS
Cuba	..	63/763 (8.3%)	13/284 (4.6%)	..	19/377 (5.0%)	0.017
Czech Republic	..	4/199 (2.0%)	17/628 (2.7%)	27/616 (4.4%)	NS
Denmark	54/412 (13.1%)	60/392 (15.3%)	47/392 (12.0%)	NS
Estonia	75/266 (28.2%)	139/377 (36.9%)	143/428 (33.4%)	117/410 (28.5%)	NS
Finland	20/410 (4.9%)	..	8/371 (2.2%)	17/374 (4.5%)	NS
France	..	123/1491 (8.2%)	..	73/787 (9.3%)	..	84/910 (9.2%)	88/947 (9.3%)	NS
Germany	90/1556 (5.8%)	137/1515 (9.0%)	132/1930 (6.8%)	106/1561 (6.8%)	NS
Hong Kong	541/4424 (12.2%)	406/3432 (11.8%)	450/3753 (12.0%)	442/3460 (12.8%)	400/3479 (11.5%)	355/3470 (10.2%)	..	0.023
Latvia	118/347 (34.0%)	..	236/789 (29.9%)	254/825 (30.8%)	284/897 (31.7%)	NS
Lithuania	230/819 (28.1%)	194/701 (27.7%)	..	239/819 (29.2%)	NS
Nepal	77/787 (9.8%)	89/668 (13.3%)	..	83/755 (11.0%)	..	NS
Netherlands	107/1042 (10.3%)	79/899 (8.8%)	82/768 (10.7%)	NS
New Zealand	..	8/144 (5.6%)	6/136 (4.4%)	16/123 (13.0%)	20/155 (12.9%)	19/228 (8.3%)	31/231 (13.4%)	31/272 (11.4%)	..	0.015
Norway	15/138 (10.9%)	23/144 (16.0%)	38/160 (23.8%)	0.006
Oman	6/138 (4.5%)	15/173 (8.7%)	9/171 (5.3%)	..	NS
Puerto Rico	37/369 (10.0%)	18/160 (11.3%)	12/126 (9.5%)	12/166 (7.2%)	11/135 (8.1%)	12/100 (12.0%)	..	NS
Slovakia	16/589 (2.7%)	13/456 (2.9%)	19/465 (4.1%)	NS
Slovenia	7/290 (2.4%)	..	9/304 (3.0%)	7/282 (2.5%)	NS
Sweden	28/356 (7.9%)	..	44/377 (11.7%)	36/344 (10.5%)	NS
Switzerland	10/322 (3.1%)	..	26/428 (6.1%)	18/330 (5.5%)	NS
Tomsk Oblast, Russia	21/417 (29.0%)	198/561 (35.3%)	196/532 (36.8%)	199/533 (37.3%)	0.005
UK (excluding Scotland)†	..	191/2801 (6.8%)	..	221/3094 (7.1%)	..	186/2138 (8.7%)	195/2312 (8.4%)	NS
USA	..	1657/13 511 (12.3%)	..	1445/12 063 (12.0%)	1404/11 445 (12.3%)	1256/10 833 (11.6%)	1290/10 184 (12.7%)	1235/9751 (12.7%)	..	NS
Multidrug resistance										
Barcelona, Spain	..	1/218 (0.5%)	..	1/315 (0.3%)	..	0/128 (0%)	3/135 (2.2%)	1/133 (0.8%)
Botswana	1/407 (0.2%)	3/638 (0.5%)	10/1182 (0.8%)	NS
Canada	12/1424 (0.8%)	7/1270 (0.6%)	8/1328 (0.6%)	9/1244 (0.7%)	NS
Cuba	..	5/763 (0.7%)	0/284 (0%)	..	1/377 (0.3%)
Czech Republic	..	2/199 (1.0%)	2/628 (0.3%)	7/616 (1.1%)	NS
Denmark	2/412 (0.5%)	0/392 (0%)	1/392 (0.3%)
Estonia	27/266 (10.2%)	53/377 (14.1%)	75/428 (17.5%)	50/410 (12.2%)	NS
Finland	0/410 (0%)	..	0/371 (0%)	1/374 (0.3%)
France	8/1491 (0.5%)	0/787 (0%)	..	6/910 (0.7%)	8/947 (0.8%)

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Germany	8/1556 (0.5%)	15/1515 (1.0%)	16/1930 (0.8%)	12/1561 (0.8%)	NS
Hong Kong	62/4424 (1.4%)	39/3832 (1.1%)	49/3753 (1.3%)	35/3460 (1.0%)	37/3479 (1.1%)	27/3470 (0.8%)	..	0.01
Latvia	50/347 (14.4%)	..	71/789 (9.0%)	86/825 (10.4%)	83/897 (9.3%)	0.032
Lithuania	64/819 (7.8%)	61/701 (8.7%)	..	77/819 (9.4%)	NS
Nepal	9/787 (1.1%)	25/668 (3.7%)	..	10/755 (1.3%)	..	NS
Netherlands	6/1042 (0.6%)	4/899 (0.4%)	7/768 (0.9%)	NS
New Zealand	..	2/144 (1.4%)	0/136 (0%)	1/123 (0.8%)	2/155 (1.3%)	2/228 (0.9%)	1/231 (0.4%)	0/272 (0%)
Norway	3/138 (2.2%)	3/144 (2.1%)	3/160 (1.9%)	NS
Oman	1/138 (0.8%)	..	6/173 (3.5%)	0/171 (0%)
Puerto Rico	7/369 (1.9%)	4/160 (2.5%)	2/126 (1.6%)	0/166 (0%)	0/135 (0%)	2/100 (2.0%)
Slovakia	2/589 (0.3%)	3/456 (0.7%)	5/465 (1.1%)	NS
Slovenia	2/290 (0.7%)	..	0/304 (0%)	0/282 (0%)
Sweden	2/356 (0.6%)	..	3/377 (0.8%)	4/344 (1.2%)	NS
Switzerland	0/322 (0%)	..	3/428 (0.7%)	0/330 (0%)
Tomsk Oblast, Russia	27/417 (6.5%)	..	48/561 (8.6%)	57/532 (10.7%)	73/533 (13.7%)	0.005
UK (excluding Scotland)†	..	30/2801 (1.1%)	..	24/3094 (0.8%)	..	10/2138 (0.5%)	21/2312 (0.9%)
USA	..	222/13 511 (1.6%)	..	146/12 063 (1.2%)	125/11 445 (1.1%)	120/10 833 (1.1%)	118/10 184 (1.2%)	112/9751 (1.1%)	..	0.0002

..=no data. NS=not significant. Data are number of resistant isolates/total number of isolates (%). *P values for χ^2 for trend. †Data from England, Wales, and Northern Ireland reported before 1999 cannot be compared with data reported after 1999 because of changes in surveillance methodologies.

Table 3: Trends in resistance in new cases in 26 countries or settings

Significant increases in the prevalence of resistance to any drug were noted in Botswana ($p < 0.0001$), New Zealand ($p = 0.015$), and Tomsk Oblast ($p = 0.005$), whereas significant decreases were reported in Cuba ($p = 0.017$) and Hong Kong ($p = 0.023$). A significant increase in the prevalence of multidrug resistance in new cases were recorded in Tomsk Oblast ($p < 0.0001$; table 3). Significant decreasing trends in multidrug resistance were reported in Hong Kong ($p = 0.01$) and the USA ($p = 0.0002$).

Drug susceptibility data were analysed from 8902 previously treated cases from 66 countries or geographical settings (table 4). The median prevalence of any resistance was 18.6%. Several countries reported a prevalence of 0% (The Gambia, Luxembourg, Iceland, and Malta); Kazakhstan had the highest prevalence. The median prevalence of multidrug resistance in previously treated cases was 6.9%, with the highest prevalences reported in Oman and Kazakhstan. However, in Oman, only 12 previously treated cases were reported.

Trends for previously treated cases were determined for 43 countries or settings (table 5). 19 of these settings provided two data points, whereas 24 provided at least three data points since 1994. Botswana showed a substantial increase in prevalence of any resistance, whereas significant decreases were reported in Cuba ($p < 0.0001$), Switzerland ($p = 0.006$), and the USA ($p < 0.0001$). Significantly increasing trends in multidrug

resistance in previously treated cases were reported from Estonia ($p < 0.0001$), Lithuania ($p = 0.007$), and Tomsk Oblast ($p = 0.0002$); decreasing trends were noted in Slovakia ($p = 0.009$) and the USA ($p = 0.01$; table 5).

Discussion

Data from the third round of the Global Project, gathered between 1999 to 2002, show that antituberculosis drug resistance has been identified in virtually all countries surveyed, reaching especially high levels in areas of the former Soviet Union and some provinces in China. The high prevalence of multidrug resistance reported from the expanding number of provinces surveyed in China and Russia is indicative of a larger epidemic than previously suspected. Also of note is that geographical areas with a high prevalence of multidrug resistance have a history of poor tuberculosis control and widespread and uncontrolled use of antituberculosis agents. Many of these settings have, over the past several years, put into place internationally recommended tuberculosis control measures, based on the DOTS strategy, and are in the process of developing appropriate plans for the management of MDR-tuberculosis cases with regimens that use second-line drugs. Until programmes can offer effective diagnosis and treatment for drug-resistant cases, drug resistance will probably be exacerbated, mortality will remain high, and ultimately efforts to control tuberculosis in these countries will be seriously jeopardised.

	Total isolates tested	Any resistance	Resistance to isoniazid	Resistance to rifampicin	Resistance to ethambutol	Resistance to streptomycin	Multidrug resistance*
Botswana	106	23 (21.7%, 14.3–30.8)	15 (14.2%, 8.1–22.3)	13 (12.3%, 6.7–20.1)	9 (8.5%, 4.0–15.5)	17 (16.0%, 9.6–24.4)	11 (10.4%, 5.3–17.8)
South Africa							
Eastern Cape province	283	50 (17.7%, 13.4–22.6)	38 (13.4%, 9.7–18.0)	22 (7.8%, 4.9–11.5)	4 (1.4%, 0.4–3.6)	25 (8.8%, 5.8–12.8)	21 (7.4%, 4.7–11.1)
Free State province	174	16 (9.2%, 5.3–14.5)	12 (6.9%, 3.6–11.7)	5 (2.9%, 0.9–6.6)	1 (0.6%, 0.0–3.2)	5 (2.9%, 0.9–6.6)	3 (1.7%, 0.4–5.0)
Gauteng province	165	21 (12.7%, 8.1–18.8)	16 (9.7%, 5.6–15.3)	10 (6.1%, 2.9–10.9)	8 (4.8%, 2.1–9.3)	13 (7.9%, 4.3–13.1)	9 (5.5%, 2.5–10.1)
Kwazulu-Natal province	207	38 (18.4%, 13.3–24.3)	30 (14.5%, 10.0–20.0)	18 (8.7%, 5.2–13.4)	5 (2.4%, 0.8–5.5)	22 (10.6%, 6.8–15.6)	16 (7.7%, 4.5–12.2)
Limpopo province	88	15 (17.0%, 9.9–26.6)	11 (12.5%, 6.4–21.3)	9 (10.2%, 4.8–18.5)	2 (2.3%, 0.3–8.0)	3 (3.4%, 0.7–9.6)	6 (6.8%, 2.5–14.3)
Mpumalanga	175	41 (23.4%, 17.4–30.4)	33 (18.9%, 13.4–25.5)	28 (16.0%, 10.9–22.3)	16 (9.1%, 5.3–14.4)	25 (14.3%, 9.5–20.4)	24 (13.7%, 9.0–19.7)
North West province	188	36 (19.1%, 13.8–25.5)	21 (11.2%, 7.0–16.6)	18 (9.6%, 5.8–14.7)	2 (1.1%, 0.1–3.8)	23 (12.2%, 7.9–17.8)	13 (6.9%, 3.7–11.5)
Western Cape province	228	18 (7.9%, 4.7–12.2)	15 (6.6%, 3.7–10.6)	9 (3.9%, 1.8–7.4)	3 (1.3%, 0.3–3.8)	8 (3.5%, 1.5–6.8)	9 (3.9%, 1.8–7.4)
The Gambia	15	0 (0%, 0.0–18.1)	0 (0%, 0.0–18.1)	0 (0%, 0.0–18.1)	0 (0%, 0.0–18.1)	0 (0%, 0.0–18.1)	0 (0%, 0.0–18.1)
Zambia	44	7 (15.9%, 6.6–30.1)	3 (6.8%, 1.4–18.7)	1 (2.3%, 0.1–12.0)	1 (2.3%, 0.1–12.0)	2 (4.5%, 0.6–15.5)	1 (2.3%, 0.1–12.0)
Argentina	149	34 (22.8%, 16.3–30.4)	24 (16.1%, 10.6–23.0)	15 (10.1%, 5.7–16.1)	10 (6.7%, 3.3–12.0)	24 (16.1%, 10.6–23.0)	14 (9.4%, 5.2–15.3)
Canada	119	20 (16.8%, 10.6–24.8)	15 (12.6%, 7.2–19.9)	5 (4.2%, 1.4–9.5)	4 (3.4%, 0.9–8.4)	8 (6.7%, 2.9–12.8)	4 (3.4%, 0.9–8.4)
Chile	291	60 (20.6%, 16.1–25.7)	50 (17.2%, 13.0–22.0)	17 (5.8%, 3.4–9.2)	10 (3.4%, 1.7–6.2)	52 (17.9%, 13.6–22.8)	11 (3.8%, 1.9–6.7)
Cuba	38	6 (15.8%, 6.0–31.3)	3 (7.9%, 1.7–21.4)	1 (2.6%, 0.1–13.8)	1 (2.6%, 0.1–13.8)	6 (15.8%, 6.0–31.3)	1 (2.6%, 0.1–13.8)
Ecuador	185	81 (43.8%, 36.5–51.3)	56 (30.3%, 23.7–37.4)	62 (33.5%, 26.8–40.8)	10 (5.4%, 2.6–9.7)	38 (20.5%, 15.0–27.1)	45 (24.3%, 18.3–31.2)
El Salvador	100	22 (22.0%, 14.3–31.4)	12 (12.0%, 6.4–20.0)	13 (13.0%, 7.1–21.2)	3 (3.0%, 0.6–8.5)	9 (9.0%, 4.2–16.4)	7 (7.0%, 2.9–13.9)
Honduras	29	12 (41.4%, 23.5–61.1)	5 (17.2%, 5.8–35.8)	5 (17.2%, 5.8–35.8)	1 (3.4%, 0.1–17.8)	8 (27.6%, 12.7–47.2)	2 (6.9%, 0.8–22.8)
USA	537	101 (18.8%, 15.3–22.9)	75 (14.0%, 11.0–17.5)	35 (6.5%, 4.5–9.1)	19 (3.5%, 2.1–5.5)	46 (8.6%, 6.3–11.4)	28 (5.2%, 3.5–7.5)
Venezuela	104	32 (30.8%, 22.1–40.6)	24 (23.1%, 15.4–32.4)	19 (18.3%, 11.4–27.1)	8 (7.7%, 3.4–14.6)	16 (15.4%, 9.1–23.8)	14 (13.5%, 7.6–21.6)
Egypt	217	148 (68.2%, 61.6–74.3)	101 (46.5%, 39.8–53.4)	110 (50.7%, 43.8–57.5)	67 (30.9%, 24.8–37.5)	117 (53.9%, 47.0–60.7)	83 (38.2%, 31.8–45.1)
Oman	12	7 (58.3%, 27.7–84.8)	7 (58.3%, 27.7–84.8)	7 (58.3%, 27.7–84.8)	3 (25.0%, 5.5–57.2)	7 (58.3%, 27.7–84.8)	7 (58.3%, 27.7–84.8)
Austria	67	6 (9.0%, 3.4–18.5)	2 (3.0%, 0.4–10.4)	1 (1.5%, 0.0–8.0)	0 (0%, 0.0–4.4)	5 (7.5%, 2.5–16.6)	1 (1.5%, 0.0–8.0)
Belgium	78	11 (14.1%, 7.3–23.8)	10 (12.8%, 6.3–22.3)	5 (6.4%, 2.1–14.3)	4 (5.1%, 1.4–12.6)	0 (0%, 0.0–3.8)	4 (5.1%, 1.4–12.6)
Bosnia Herzegovina	153	20 (13.1%, 8.2–19.5)	5 (3.3%, 1.1–7.5)	9 (5.9%, 2.7–10.9)	10 (6.5%, 3.2–11.7)	8 (5.2%, 2.3–10.0)	3 (2.0%, 0.4–5.6)
Croatia	99	6 (6.1%, 2.3–12.7)	4 (4.0%, 1.1–10.0)	3 (3.0%, 0.6–8.6)	1 (1.0%, 0.0–5.5)	1 (1.0%, 0.0–5.5)	1 (1.0%, 0.0–5.5)
Czech Republic	22	3 (13.6%, 2.9–34.9)	2 (9.1%, 1.1–29.2)	3 (13.6%, 2.9–34.9)	1 (4.5%, 0.1–22.8)	1 (4.5%, 0.1–22.8)	2 (9.1%, 1.1–29.2)
Denmark	33	9 (27.3%, 13.3–45.5)	8 (24.2%, 11.1–42.3)	1 (3.0%, 0.1–15.8)	1 (3.0%, 0.1–15.8)	8 (24.2%, 11.1–42.3)	1 (3.0%, 0.1–15.8)
Estonia	117	68 (58.1%, 48.6–67.2)	64 (54.7%, 45.2–63.9)	53 (45.3%, 36.1–54.8)	49 (41.9%, 32.8–51.4)	57 (48.7%, 39.4–58.1)	53 (45.3%, 36.1–54.8)
Finland	29	4 (13.8%, 3.9–31.7)	4 (13.8%, 3.9–31.7)	1 (3.4%, 0.1–17.8)	0 (0%, 0.0–9.8)	0 (0%, 0.0–9.8)	1 (3.4%, 0.1–17.8)
France	82	23 (28.0%, 18.7–39.1)	15 (18.3%, 10.6–28.4)	9 (11.0%, 5.1–19.8)	2 (2.4%, 0.3–8.5)	13 (15.9%, 8.7–25.6)	7 (8.5%, 3.5–16.8)
Germany	236	43 (18.2%, 13.5–23.7)	37 (15.7%, 11.3–21.0)	15 (6.4%, 3.6–10.3)	11 (4.7%, 2.3–8.2)	29 (12.3%, 8.4–17.2)	14 (5.9%, 3.3–9.8)
Iceland	1	0 (0%, 0.0–95.0)	0 (0%, 0.0–95.0)	0 (0%, 0.0–95.0)	0 (0%, 0.0–95.0)	0 (0%, 0.0–95.0)	0 (0%, 0.0–95.0)
Ireland	26	2 (7.7%, 0.9–25.1)	1 (3.8%, 0.1–19.6)	1 (3.8%, 0.1–19.6)	0 (0%, 0.0–10.9)	1 (3.8%, 0.1–19.6)	1 (3.8%, 0.1–19.6)
Israel	24	10 (41.7%, 22.1–63.4)	9 (37.5%, 18.8–59.4)	5 (20.8%, 7.1–42.2)	2 (8.3%, 1.0–27.0)	7 (29.2%, 12.6–51.1)	5 (20.8%, 7.1–42.2)
Italy	108	51 (47.2%, 37.5–57.1)	39 (36.1%, 27.1–45.9)	32 (29.6%, 21.2–39.2)	12 (11.1%, 5.9–18.6)	25 (23.1%, 15.6–32.2)	26 (24.1%, 16.4–33.3)
Kazakhstan	319	262 (82.1%, 77.5–86.2)	216 (67.7%, 62.3–72.8)	196 (61.4%, 55.9–66.8)	173 (54.2%, 48.6–59.8)	246 (77.1%, 72.1–81.6)	180 (56.4%, 50.8–61.9)
Latvia	247	94 (38.1%, 32.0–44.4)	87 (35.2%, 29.3–41.5)	67 (27.1%, 21.7–33.1)	37 (15.0%, 10.8–20.1)	81 (32.8%, 27.0–39.0)	67 (27.1%, 21.7–33.1)
Lithuania	321	218 (67.9%, 62.5–73.0)	210 (65.4%, 59.9–70.6)	171 (53.3%, 47.6–58.8)	122 (38.0%, 32.7–43.6)	188 (58.6%, 53.0–64.0)	171 (53.3%, 47.6–58.8)
Luxembourg	5	0 (0%, 0.0–45.1)	0 (0%, 0.0–45.1)	0 (0%, 0.0–45.1)	0 (0%, 0.0–45.1)	0 (0%, 0.0–45.1)	0 (0%, 0.0–45.1)
Malta	1	0 (0%, 0.0–95.0)	0 (0%, 0.0–95.0)	0 (0%, 0.0–95.0)	0 (0%, 0.0–95.0)	0 (0%, 0.0–95.0)	0 (0%, 0.0–95.0)
Netherlands	95	8 (8.4%, 3.7–15.9)	8 (8.4%, 3.7–15.9)	1 (1.1%, 0.0–5.7)	2 (2.1%, 0.3–7.4)	4 (4.2%, 1.2–10.4)	1 (1.1%, 0.0–5.7)
Norway	10	1 (10%, 0.3–44.5)	0 (0%, 0.0–25.9)	0 (0%, 0.0–25.9)	0 (0%, 0.0–25.9)	1 (10%, 0.3–44.5)	0 (0%, 0.0–25.9)
Poland	668	111 (16.6%, 13.7–20.0)	96 (14.4%, 11.6–17.5)	60 (9.0%, 6.9–11.6)	22 (3.3%, 2.1–5.0)	67 (10%, 7.8–12.7)	57 (8.5%, 6.5–11.1)
Russia							
Orel Oblast	210	154 (73.3%, 66.8–79.2)	149 (71.0%, 64.3–77.0)	89 (42.4%, 35.6–49.4)	92 (43.8%, 37.0–50.8)	139 (66.2%, 59.4–72.6)	89 (42.4%, 35.6–49.4)
Tomsk Oblast	117	71 (60.7%, 51.2–69.6)	60 (51.3%, 41.9–60.6)	56 (47.9%, 38.5–57.3)	16 (13.7%, 8.0–21.3)	67 (57.3%, 47.8–66.4)	51 (43.6%, 34.4–53.1)

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Belgrade, Serbia and Montenegro	30	5 (16.7%, 5-6-34.7)	3 (10%, 2.1-26.5)	0 (0%, 0-0-9.5)	2 (6.7%, 0.8-22.1)	1 (3.3%, 0.1-17.2)	0 (0%, 0-0-9.5)
Slovakia	110	15 (13.6%, 7.8-21.5)	12 (10.9%, 5.8-18.3)	2 (1.8%, 0.2-6.4)	1 (0.9%, 0.0-5.0)	6 (5.5%, 2.0-11.5)	2 (1.8%, 0.2-6.4)
Slovenia	38	4 (10.5%, 2.9-24.8)	3 (7.9%, 1.7-21.4)	0 (0%, 0.0-7.6)	1 (2.6%, 0.1-13.8)	2 (5.3%, 0.6-17.7)	0 (0%, 0.0-7.6)
Spain							
Barcelona	32	10 (31.3%, 16.1-50.0)	9 (28.1%, 13.7-46.7)	4 (12.5%, 3.5-29.0)	3 (9.4%, 2.0-25.0)	6 (18.8%, 7.2-36.4)	4 (12.5%, 3.5-29.0)
Galicia	40	9 (22.5%, 10.8-38.5)	7 (17.5%, 7.3-32.8)	3 (7.5%, 1.6-20.4)	3 (7.5%, 1.6-20.4)	7 (17.5%, 7.3-32.8)	3 (7.5%, 1.6-20.4)
Sweden	22	3 (13.6%, 2.9-34.9)	2 (9.1%, 1.1-29.2)	1 (4.5%, 0.1-22.8)	0 (0%, 0.0-12.7)	1 (4.5%, 0.1-22.8)	1 (4.5%, 0.1-22.8)
Switzerland	57	3 (5.3%, 1.1-14.6)	2 (3.5%, 0.4-12.1)	2 (3.5%, 0.4-12.1)	0 (0%, 0.0-5.1)	0 (0%, 0.0-5.1)	1 (1.8%, 0.0-9.4)
Turkmenistan	98	61 (62.2%, 51.9-71.8)	47 (48.0%, 37.8-58.3)	19 (19.4%, 12.1-28.6)	15 (15.3%, 8.8-24.0)	50 (51.0%, 40.7-61.3)	18 (18.4%, 11.3-27.5)
UK (excluding Scotland)	237	36 (15.2%, 10.9-20.4)	25 (10.5%, 6.9-15.2)	13 (5.5%, 3.0-9.2)	5 (2.1%, 0.7-4.9)	19 (8.0%, 4.9-12.2)	10 (4.2%, 2.0-7.6)
Uzbekistan	107	85 (79.4%, 70.5-86.6)	74 (69.2%, 59.5-77.7)	43 (40.2%, 30.8-50.1)	37 (34.6%, 25.6-44.4)	76 (71.0%, 61.5-79.4)	43 (40.2%, 30.8-50.1)
Nepal	171	70 (40.9%, 33.5-48.7)	57 (33.3%, 26.3-40.9)	35 (20.5%, 14.7-27.3)	17 (9.9%, 5.9-15.4)	53 (31.0%, 24.2-38.5)	35 (20.5%, 14.7-27.3)
Thailand	172	67 (39.0%, 31.6-46.7)	53 (30.8%, 24.0-38.3)	39 (22.7%, 16.6-29.7)	26 (15.1%, 10.1-21.4)	42 (24.4%, 18.2-31.5)	35 (20.3%, 14.6-27.1)
Cambodia	96	17 (17.7%, 10.7-26.8)	16 (16.7%, 9.8-25.6)	3 (3.1%, 0.6-8.9)	0 (0%, 0.0-3.1)	7 (7.3%, 3.0-14.4)	3 (3.1%, 0.6-8.9)
China							
Henan	265	161 (60.8%, 54.6-66.7)	125 (47.2%, 41.0-53.4)	113 (42.6%, 36.6-48.8)	48 (18.1%, 13.7-23.3)	114 (43.0%, 37.0-49.2)	97 (36.6%, 30.8-42.7)
Hong Kong	169	39 (23.1%, 17.0-30.2)	32 (18.9%, 13.3-25.7)	19 (11.2%, 6.9-17.0)	10 (5.9%, 2.9-10.6)	30 (17.8%, 12.3-24.4)	19 (11.2%, 6.9-17.0)
Hubei	238	106 (44.5%, 38.1-51.1)	79 (33.2%, 27.2-39.6)	64 (26.9%, 21.4-33.0)	21 (8.8%, 5.5-13.2)	61 (25.6%, 20.2-31.7)	52 (21.8%, 16.8-27.6)
Liaoning	86	48 (55.8%, 44.7-66.5)	36 (41.9%, 31.3-53.0)	25 (29.1%, 19.8-39.9)	12 (14.0%, 7.4-23.1)	36 (41.9%, 31.3-53.0)	21 (24.4%, 15.8-34.9)
Japan	264	112 (42.4%, 36.4-48.6)	87 (33.0%, 27.3-39.0)	57 (21.6%, 16.8-27.0)	40 (15.2%, 11.1-20.1)	64 (24.2%, 19.2-29.9)	52 (19.7%, 15.1-25.0)
New Zealand	22	2 (9.1%, 1.1-29.2)	1 (4.5%, 0.1-22.8)	0 (0%, 0.0-12.7)	0 (0%, 0.0-12.7)	2 (9.1%, 1.1-29.2)	0 (0%, 0.0-12.7)
Singapore	126	15 (11.9%, 6.8-18.9)	8 (6.3%, 2.8-12.1)	3 (2.4%, 0.5-6.8)	1 (0.8%, 0.0-4.3)	7 (5.6%, 2.3-11.1)	1 (0.8%, 0.0-4.3)

*Resistance to at least isoniazid and rifampicin. Data are number of positive isolates (%; 95% CI).

Table 4: Prevalence of drug resistance in previously treated cases in 66 countries or settings, 1999-2002

	Year									p value*
	1994	1995	1996	1997	1998	1999	2000	2001	2002	
Resistance to any drug										
Barcelona, Spain	13/44 (29.5%)	..	16/69 (23.2%)	15/44 (34.1%)	6/27 (22.2%)	10/32 (31.3%)	..	NS
Botswana	17/114 (14.9%)	33/145 (22.8%)	23/106 (21.7%)	NS
Canada	25/156 (16.0%)	15/135 (11.1%)	17/124 (13.7%)	20/119 (16.8%)	NS
Cuba	21/23 (91.3%)	..	14/43 (32.6%)	..	6/38 (15.8%)	<0.0001
Czech Republic	..	2/16 (12.5%)	6/70 (8.6%)	3/22 (13.6%)	NS
Denmark	4/32 (12.5%)	4/24 (16.7%)	9/33 (27.3%)	NS
Estonia	12/26 (46.2%)	49/82 (59.8%)	49/89 (55.1%)	68/117 (58.1%)	NS
Finland	0/2 (0%)	..	1/27 (3.7%)	4/29 (13.8%)
France	..	42/195 (21.5%)	..	13/65 (20.0%)	..	17/106 (16.0%)	23/82 (28.0%)	NS
Germany	59/281 (21.0%)	52/263 (19.8%)	49/248 (19.8%)	43/236 (18.2%)	NS
Hong Kong	211/783 (26.9%)	85/314 (27.1%)	68/266 (25.6%)	58/220 (26.4%)	49/207 (23.7%)	39/169 (23.1%)	..	NS
Latvia	168/228 (73.7%)	..	69/224 (30.8%)	64/190 (33.7%)	94/247 (38.1%)	<0.0001
Lithuania	103/167 (61.7%)	136/220 (61.8%)	..	218/321 (67.9%)	NS
Netherlands	27/172 (15.7%)	4/42 (9.5%)	8/95 (8.4%)	NS
New Zealand	..	0/6 (0%)	1/15 (6.7%)	3/14 (21.4%)	3/11 (27.3%)	4/23 (17.4%)	5/17 (29.4%)	2/22 (9.1%)
Norway	1/6 (16.7%)	1/40 (2.5%)	1/10 (10.0%)	NS
Puerto Rico	6/22 (27.3%)	7/12 (58.3%)	1/14 (7.1%)	1/7 (14.3%)	1/4 (25.0%)	NS

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Slovakia	25/157 (15.9%)	8/122 (6.6%)	15/110 (13.6%)	NS
Slovenia	3/36 (8.3%)	..	2/35 (5.7%)	4/38 (10.5%)	NS
Sweden	4/24 (16.7%)	..	8/31 (25.8%)	3/22 (7.1%)	NS
Switzerland	11/40 (27.5%)	..	12/57 (21.1%)	3/57 (5.3%)	0.006
Tomsk Oblast, Russia	134/232 (57.8%)	..	75/121 (62.0%)	94/139 (67.6%)	71/117 (60.7%)	NS
UK (England and Wales only)†	..	48/148 (32.4%)	..	42/189 (22.2%)	..	13/220 (5.9%)	36/237 (15.2%)	NS
USA	..	197/833 (23.6%)	..	128/612 (20.9%)	114/672 (17.0%)	106/599 (17.7%)	98/539 (18.2%)	101/537 (18.8%)	..	<0.0001
Multidrug resistance										
Barcelona, Spain	9/44 (20.5%)	..	8/69 (11.6%)	9/44 (20.5%)	3/27 (11.1%)	4/32 (12.5%)	..	NS
Botswana	7/114 (6.1%)	13/145 (9.0%)	11/106 (10.4%)	NS
Canada	5/156 (3.2%)	5/135 (3.7%)	4/124 (3.2%)	4/119 (3.4%)	NS
Cuba	3/23 (13.0%)	..	3/43 (7.0%)	..	1/38 (2.6%)	NS
Czech Republic	..	1/16 (6.3%)	2/70 (2.9%)	2/22 (9.1%)	NS
Denmark	1/32 (3.1%)	0/24 (0%)	1/33 (3.0%)
Estonia	5/26 (19.2%)	31/83 (37.8%)	43/89 (48.3%)	43/89 (45.3%)	<0.0001
Finland	0/2 (0%)	..	0/27 (0%)	1/29 (3.4%)
France	..	8/195 (4.1%)	..	2/65 (3.1%)	..	9/106 (8.5%)	7/82 (8.5%)	NS
Germany	27/281 (9.6%)	19/263 (7.2%)	17/248 (6.9%)	14/236 (5.9%)	NS
Hong Kong	75/783 (9.6%)	24/314 (7.6%)	30/266 (11.3%)	17/220 (7.7%)	19/207 (9.2%)	19/169 (11.2%)	..	NS
Latvia	124/228 (54.4%)	..	53/224 (23.7%)	51/190 (26.8%)	67/247 (27.1%)	<0.0001
Lithuania	71/167 (42.5%)	95/220 (43.2%)	..	171/321 (53.3%)	0.007
Netherlands	1/172 (0.6%)	0/42 (0%)	1/95 (1.1%)
New Zealand	..	0/6 (0%)	0/15 (0%)	0/14 (0%)	1/11 (9.1%)	0/23 (0%)	0/17 (0%)	0/22 (0%)
Norway	1/6 (16.7%)	0/40 (0%)	0/19 (0%)	NS
Puerto Rico	3/22 (13.6%)	2/12 (16.7%)	0/14 (0%)	1/7 (14.3%)	1/4 (25.0%)
Slovakia	13/157 (8.3%)	3/122 (2.5%)	2/110 (1.8%)	0.009
Slovenia	1/36 (2.8%)	..	2/35 (5.7%)	0/38 (0%)	NS
Sweden	2/24 (8.3%)	..	4/31 (12.9%)	1/22 (2.4%)	NS
Switzerland	5/40 (12.5%)	..	6/57 (10.5%)	1/57 (1.8%)	NS
Tomsk Oblast, Russia	62/234 (26.7%)	..	39/121 (32.2%)	59/139 (42.4%)	51/117 (43.6%)	0.0002
UK (England and Wales only)†	..	25/148 (16.9%)	..	25/189 (13.2%)	..	6/220 (2.7%)	10/237 (4.2%)	NS
USA	..	59/833 (7.1%)	..	34/612 (5.6%)	23/672 (3.4%)	24/599 (4.0%)	21/539 (3.9%)	28/537 (5.2%)	..	0.01

..=no data. NS=not significant. Data are number of resistant isolates/total number of isolates (%). *p values for χ^2 for trend. †Data from England and Wales reported before 1999 cannot be compared with data reported after 1999 because of changes in surveillance methodologies.

Table 5: Trends in resistance in previously treated cases in 24 countries or settings

With regard to describing a country's burden of MDR tuberculosis, percent prevalence as well as absolute numbers must be considered. For example, a relatively low prevalence of multidrug resistance has been reported in settings with a high tuberculosis burden—eg, South Africa, some provinces in China, and some states in India—however, these still represent a very high absolute number of cases of MDR tuberculosis. On the basis of data reported here, one can estimate that 424 000 cases (95% CI 376 019–620 061) of MDR tuberculosis emerged worldwide in 2004—ie, 4.3% (3.8–6.1) of all new and previously treated tuberculosis cases globally. Three

countries—China, India, and Russia—account for 261 362 cases (180 779–414 749) of MDR tuberculosis, or 62% of the estimated global burden.³⁵ Ultimately, the burden of MDR tuberculosis must be placed in the context of the ability of the country to address the problem.

With regard to trends determined in the third round of the Global Project, the increasing prevalence of MDR tuberculosis and the significant increase in any resistance reported from Botswana is worrisome.³² Given the high prevalence of HIV infection in Botswana, relatively small increases in resistance could have a major effect on efforts to control tuberculosis in the country and serious

implications for HIV treatment and care. The relation between HIV and drug-resistant tuberculosis is not well understood; therefore, current drug resistance surveys in selected locations have incorporated an HIV component to better understand this relation. Significant increasing trends for most resistance patterns, including MDR tuberculosis, were also recorded in Tomsk Oblast in Russia. The ongoing surveillance in this region will be critical in helping to anticipate the direction of the epidemic in the region, especially in settings where high-quality DOTS is implemented and DOTS-Plus programmes exist to manage existing cases of MDR tuberculosis. In the USA, steady decreases in overall tuberculosis notifications as well as the absolute number of drug-resistant cases over the past decade have been recorded. The decrease in any resistance in Cuba and Hong Kong could well be the result of stable and well-performing tuberculosis control programmes, as evidenced by other programmatic indicators, such as high case detection and low proportion of retreatment cases. At present, trend data are limited from most low income and high tuberculosis burden countries, and no trend data are available from African countries, with the exception of Botswana.

Drug resistance surveillance methods are evolving in light of increasing availability of treatment for MDR tuberculosis, the advent of newer diagnostic technologies, and the recognition of the need to determine trends. Culture and drug susceptibility tests for all cases of tuberculosis are considered the gold standard for diagnosis and surveillance of drug resistance. However, such tests are not feasible in most settings. Where continuous surveillance of all cases of tuberculosis is not possible, WHO recommends periodic surveys of new cases to monitor trends. The revised WHO surveillance guidelines will recommend several methods for better determination of trends in resistance in previously treated cases. Furthermore, the Global Plan to Stop TB 2006–2015 includes the provision of culture and drug susceptibility testing by 2015 to all retreatment cases and risk populations, such as category 1 failures and contacts of patients with MDR tuberculosis.³⁶

Baltic countries have moved from periodic surveys to continuous surveillance of all cases of tuberculosis, or routine diagnostic culture and drug susceptibility testing for all patients with tuberculosis. Most countries of the former Soviet Union will move in this direction since culture coverage is extensive, but to do so laboratory methods and reporting mechanisms must become more reliable. Chile does surveys of new cases every 3 years but culture and drug susceptibility testing are done for every retreatment case. Several countries will probably move towards this model as access to culture increases, and many control programmes have started treating patients with MDR tuberculosis routinely. A number of countries with a high tuberculosis burden, including India and China, are making good progress in the expansion of

baseline coverage for surveys. However, restricted laboratory capacity has been the main obstacle that limits the expansion of baseline survey coverage. Although genotypic methods might have a role in the rapid detection of rifampicin resistance in settings with high prevalence of multidrug resistance, their use on a large scale is currently restricted by the high cost and technical proficiency required for the amplification.

As HIV testing becomes more widespread in many African countries and in areas of the former Soviet Union, it will become increasingly incorporated into antituberculosis drug resistance surveys, and will provide a platform for further investigation of the interaction between HIV and drug-resistant forms of tuberculosis from both a biological and epidemiological perspective. At this time, population level data on antituberculosis drug resistance and HIV are scarce.

Recent documentation of the emergence of strains with extensive drug resistance (XDR tuberculosis)—ie, multi-drug-resistant strains with resistance to at least three of the six main classes of second-line drugs—is extremely worrisome.^{37,38} As a result, standardised drug susceptibility testing for second-line drugs—mainly in cases of MDR tuberculosis—will be required to further establish the magnitude of XDR tuberculosis. All means should be put in place urgently to control these deadly strains.

The achievements of the Global Project on Anti-tuberculosis Drug Resistance Surveillance over the past decade have been remarkable. Since 1994, drug susceptibility testing data have been collected from 109 countries or geographical settings. Prevalence and patterns of drug resistance from areas that represent almost 40% of newly notified sputum-positive cases worldwide have been assessed. Three global reports were published in 1997, 2000, and 2004; 11 rounds of proficiency testing among supranational reference laboratories have been done; and strong relations between such institutes and national tuberculosis reference laboratories have strengthened global laboratory capacity. The findings of the Global Project emphasise the importance of the implementation of sound tuberculosis control activities to prevent further creation of MDR tuberculosis and the necessity of mainstreaming high-quality treatment for MDR tuberculosis as a routine component of tuberculosis control programmes, using financing and monitoring mechanisms such as the Global Fund to fight AIDS, Tuberculosis and Malaria and the Green Light Committee to ensure optimum outcomes.²²

Surveillance is an essential component of monitoring tuberculosis control and should be expanded both to gather baseline data and establish trends. Despite the expansion of coverage of the Global Project since its start in 1994, there remain important gaps in data from many countries with the highest burden of tuberculosis, areas where the HIV epidemic is fuelling the tuberculosis epidemic, and countries where prevalence of drug resistance is expected to be high because of historically

poor tuberculosis control. Yet, one of the main obstacles to expansion of surveillance and development of appropriate treatment programmes is the absence of functioning laboratory networks. Although drug resistance has captivated the attention of the international community for the past decade, the laboratories responsible for diagnosing cases have not improved to meet the challenge. Although laboratory strengthening is beginning to gain higher priority on the tuberculosis agenda, as are many of the areas outlined in the new Stop TB strategy, more is required to improve access to, and optimum use of, existing diagnostics, as well as call for development and implementation of new technologies.

Over the past 10 years a solid foundation has been laid to measure and treat drug-resistant forms of tuberculosis. Political commitment and improved capacity of laboratory networks are imperative for the control of tuberculosis and the future of surveillance. Although the drug resistance picture for many countries is limited, the future for generating better data on drug resistance looks hopeful.

Contributors

All authors participated in the data analysis and development of the manuscript, and saw and approved the final version.

Conflict of interest statement

We declare that we have no conflict of interest.

The Supranational Laboratory Network

Département de Microbiologie, Unité de Mycobactériologie, Institut de Médecine Tropicale Prince Léopold, Antwerp, Belgium (F Portaels); Laboratoire de la Tuberculose, Institut Pasteur d'Algérie-Alger, Algiers, Algeria (F Boulhalbal); Queensland Mycobacterium Reference Laboratory, Chermerside, Australia (C Gilpin); National Institute of Public Health, Prague, Czech Republic (M Havelkova); Instituto de Salud Pública de Chile, Santiago, Chile (A Luna); Centre national de Référence des Mycobactéries, Institut Pasteur, Paris, France (V Vincent); National Reference Centre for Mycobacteria, Forschungszentrum, Borstel, Germany, (S Rüesch-Gerdes); Kuratorium Tuberkulose in der Welt e.V., Gauting, Germany (K Feldmann); Tuberculosis Research Centre (TRC), Indian Council of Medical Research, Chennai, India (C N Paramasivan); Laboratory of Bacteriology, Istituto Superiore di Sanità, Rome, Italy (G Orefici); Japan Anti-Tuberculosis Association, Tokyo, Japan (S Mitarai); Instituto Nacional de Saúde, Porto Codex, Portugal (M Filomena Rodrigues); Korean Institute of Tuberculosis, Seoul, Republic of Korea (G Bai, S Jae Kim); Unit for Tuberculosis Operational and Policy Research, Medical Research Council, Pretoria, South Africa (K Weyer); Servicio de Microbiología, Hospital Universitari Vall d'Hebron, Autonomous University, Barcelona, Spain (N Martin-Casabona); Swedish Institute for Infectious Disease Control, Solna, Sweden (S Hoffner); National Institute of Public Health and the Environment (RIVM), Bilthoven, Netherlands (D van Soolingen); Health Protection Agency, Mycobacterium Reference Laboratory Unit, King's College Hospital (Dulwich), London, UK (F Drobniewski); Mycobacteriology/Tuberculosis Laboratory, Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA (B Metchock); Department of Public Health, Massachusetts State Laboratory Institute, Boston, MA, USA (A Sloutsky).

Contributing members of the working group

Algeria: Fadila Boulhalbal; Andorra: Margarida Coll Armangué; Argentina: Lucia Barrera, Omar Latini; Australia: Richard Lumb; Austria: John-Paul Klein; Belgium: Maryse Wanlin, An Aerts; Bosnia and Herzegovina: Biljana Stefanovic, Zehra Dizdarevic; Botswana: Lisa J Nelson, Gasekgale Moalosi, Michael Mwasekaga; Cambodia: Ikushi Onozaki, Kousuke Okada; Canada: Melissa Phipers, Edward Ellis; Chile: Andrea Luna Heine, Rosario Lepe; China: Wu Xongrong, Kai Man Kam, Su Ya, Du Changmei, Daniel Chin; Colombia:

Clara Inés León Franco, Martha Inírida Guerrero, Claudia Sierra, Nancy Naranjo, Maria Consuelo Garzón; Croatia: Ira Gjenero Margan; Cuba: Ernesto Montoro, Mária J Llanes, Dihadenys Lemus; Czech Republic: Vlasta Mazánková, Jiri Holub; Democratic Republic of the Congo: Francoise Portaels, Henrietta Wembanyama; Ecuador: Judith Vaca, Dolores Kuffo; Egypt: Essam Elmoghazy; El Salvador: Julio Garay Ramos; Estonia: Vahur Hollo; Finland: Petri Ruutu; France: Bénédicte Decludt, Jerome Robert; Georgia: George Khechinashvili; Germany: Walter Haas, Michael Forßbohm; Honduras: Noemi Paz de Zavala, Hilda Membreno; Iceland: Blöndal Thorsteinn; India: Chinnambedu Paramasivan, Lakhbir Singh Chauhan, Reuben Granich; Ireland: Joan O'Donnell; Israel: Daniel Chemtob, Zohar Mor; Italy: Dina Caraffa de Stefano, G B Migliori; Japan: Chyoji Abe; Kazakhstan: Rimma Agzamova, Galemzhan Borankulovich Rakishev; Latvia: Janis Leimans; Lithuania: Edith Davidaciené, Anaída Sosnovskaja, Puneet Dewan; Luxembourg: Pierrette Huberty-Krau, Nobeit Charlé; Malta: Malcolm P Micallef; Mongolia: Gombagaram Tsogt, Naranbat Nymadawa; Nepal: Dirgh Singh Bam, Christian Gunnenburg; Netherlands: Paul van Gerven, Nico Kalisvaart; New Zealand: Helen Heffernan; Norway: Einar Haldal, Brita Winje Askeland; Oman: Suleiman Al-Busaidy; Poland: Maria Korzeniewska-Kosela; Puerto Rico: Ada Martinez; Qatar: Zubaida Daham F Al-Suwaidi; Russia (Orel): Paul Arguin, Evgenia Nemtsova, Boris Kazzeony, Helen Kiryanova; Russia (Tomsk): Irena Gelmananova, Donna Barry, Mikhail I Perelman, Olga Sirotkina, Vera Pavlova; San Marino: Antonella Sorcinelli; Serbia and Montenegro: Dusan Popovac, Radmila Curcic; Singapore: Cynthia Chee; Slovakia: Eva Rajecova, Ivan Solovic; Slovenia: Jurij Sorli; South Africa: Karin Weyer; Spain (Barcelona): Nuria Martin-Casabona; Spain (Galicia): Elena Cruz Ferro, Emma Fernández Nogueira, María Luisa Pérez del Molino Bernal; Sweden: Victoria Romanus; Switzerland: Peter Helbling, Ekkehardt Altpeter; Thailand: Dhanida Rienthong; The Gambia: Richard Adegbola, Francis Drobniewski; Turkmenistan: Babakuli Jumaev, Ashir Ovezov; UK (excluding Scotland): John Watson, Alistair Story, Delphine Antoine; Scotland: Jim McMenamin, Fiona Johnston; USA: Marisa Moore; Uruguay: Valentín Cuesta, Jorge Rodríguez; Uzbekistan: Helen Cox, Gulnoz Tulkunovna Uzakova, Roy Male; Venezuela: Raimond Armengol, Albina Vasquez; Zambia: Vincent Tihon; WHO Regional Office (The Americas): Rodolfo Rodriguez Cruz, Pilar Ramon-Pardo; WHO Regional Office (Africa): Daniel Kibuga, Eugene Nyarko; WHO Regional Office (Eastern Mediterranean): Akihiro Seit, Samiha Baghdadi; WHO Regional Office (Europe): Richard Zaleskis, Jerod Scholten; WHO Regional Office (South-East Asia): Jai P Narain, Nani Nair; WHO Regional Office (Western Pacific): Dongil Ahn, Marcus Hodge.

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