

# $\rightarrow @$ $\land \blacksquare$ Universal access to care for multidrug-resistant tuberculosis: an analysis of surveillance data

Dennis Falzon, Ernesto Jaramillo, Fraser Wares, Matteo Zignol, Katherine Floyd, Mario C Raviglione

#### Summary

Lancet Infect Dis 2013; 13: 690-97

Published Online June 4, 2013 http://dx.doi.org/10.1016/ \$1473-3099(13)70130-0 See Comment 644

Stop TB Department, World Health Organization, Geneva, Switzerland (D Falzon MD E Jaramillo MD, F Wares MPH, M Zignol MD, K Floyd PhD, M C Raviglione FRCP)

Correspondence to: Dr Dennis Falzon, Stop TB Department, World Health Organization, 20 avenue Appia, CH-1211 Geneva 27, Switzerland falzond@who.int

Background The prospects for global tuberculosis control in the near future will be determined by the effectiveness of the response of countries to their burden of multidrug-resistant (MDR; resistance to, at least, isoniazid and rifampicin) tuberculosis. During the 2009 World Health Assembly, countries committed to achieve universal access to MDR-tuberculosis care by 2015. We assessed the progress towards the 2015 targets achieved by countries accounting for 90% of the estimated MDR-tuberculosis cases in the world in 2011.

Methods We analysed data reported to WHO by 30 countries expected to have more than 1000 MDR-tuberculosis cases among notified patients with pulmonary tuberculosis in 2011.

Findings In the 30 countries, 18% of the estimated MDR-tuberculosis cases were enrolled on treatment in 2011. Belarus, Brazil, Kazakhstan, Peru, South Africa, and Ukraine each detected and enrolled on treatment more than 50% of their estimated cases of MDR-tuberculosis. In Ethiopia, India, Indonesia, the Philippines, and Russia, enrolments increased steadily between 2009 and 2011 with a mean yearly change greater than 50%: however, in these countries enrolment in 2011 was low, ranging from 4% to 43% of the estimated cases. In the remaining countries (Afghanistan, Angola, Azerbaijan, Bangladesh, China, Democratic Republic of the Congo, Kenya, Kyrgyzstan, Moldova, Mozambique, Burma, Nepal, Nigeria, North Korea, Pakistan, South Korea, Thailand, Uzbekistan, and Vietnam) progress in detection and enrolment was slower. In 23 countries, a median of 53% (IQR 41-71) patients with MDR-tuberculosis successfully completed their treatment after starting it in 2008–09.

Interpretation Six countries (Belarus, Brazil, Kazakhstan, Peru, South Africa, and Ukraine) can achieve universal access to MDR-tuberculosis care by 2015 should they sustain their current pace of progress. In other countries a radical scale-up will be needed for them to have an effect on their MDR-tuberculosis burden. Unless barriers to diagnosis and successful treatment are urgently overcome, and new technologies in diagnostics and treatment effectively implemented, the global targets for 2015 are unlikely be achieved.

#### Funding WHO.

#### Introduction

For a disease that is largely curable with drugs, which have been available for several decades, inequalities in access to health care still exist globally-8.7 million people developed tuberculosis and 1.4 million died as a result in 2011.1 Substantial progress in prevention and treatment of tuberculosis has nonetheless been achieved in recent years through effective public health action driven by political commitment and the required mobilisation of resources. Between 1995 and 2011, 51 million patients with tuberculosis were cured, saving an estimated 20 million lives.1 These gains are now threatened by the emergence and dissemination of multidrug-resistant (MDR) strains of Mycobacterium tuberculosis, which have lost susceptibility to the two most effective antituberculosis drugs, isoniazid and rifampicin. Whereas most patients with tuberculosis can still be cured with a low-cost. 6 month course of antibiotics, those with MDRtuberculosis require a much longer and complicated treatment to ensure cure.2 Globally, about 5% of patients with tuberculosis have the MDR form, but in countries including Belarus, parts of Russia, and Uzbekistan the proportion is up to 32% in previously untreated cases and

at least two times higher in previously treated individuals.<sup>3,4</sup> Some of these cases of MDR-tuberculosis have strains resistant to other antituberculosis drugs in addition to isoniazid and rifampicin,5 and, since 2007, cases of tuberculosis with strains resistant to most or all of the antituberculosis drugs tested have been reported from different countries.6-9 Clinicians and public health authorities alike are now troubled by the prospect that tuberculosis is sliding inexorably back to the preantibiotic era, when it was not amenable to drug treatment.<sup>10</sup>

In 2009, the World Health Assembly agreed on a multipronged approach to rein in drug-resistant tuberculosis worldwide.11 In its resolution, the World Health Assembly urged countries to ensure that by 2015 all patients with tuberculosis receive the appropriate care to prevent, diagnose, and treat MDR-tuberculosis. In 2010, WHO and its partners elaborated the Global Plan to Stop TB and a set of indicators to measure progress from 2011 to 2015.12 In this Article, we look at the progress achieved by the end of 2011-the first year of the Global Plan to Stop TB-and draw attention to the key decisions that countries and donors have to make to achieve the 2015 targets.

# Methods

# Definitions

MDR-tuberculosis is in-vitro resistance to, at least, rifampicin and isoniazid. Extensively drug resistant (XDR) tuberculosis is MDR-tuberculosis with additional resistance to any fluoroquinolone and to at least one of three injectable second-line antituberculosis drugs used in the treatment (capreomycin, kanamycin, and amikacin).<sup>13</sup> A new case is a patient with tuberculosis who has no history of tuberculosis treatment or who received antituberculosis drugs for less than 1 month.14 A previously treated case is a patient with tuberculosis who has completed at least 1 month of antituberculosis treatment for active disease. First-line tuberculosis treatment refers to the 6-8 month basic regimens used in the treatment of drug-susceptible tuberculosis; generally, these regimens include combinations of rifampicin, isoniazid, ethambutol, pyrazinamide, and streptomycin.<sup>14</sup> Second-line tuberculosis treatment refers to the regimens used in the treatment of drug-resistant tuberculosis that includes drugs from the second-line group and usually lasts 20 months or more.<sup>2</sup>

Countries assign treatment outcomes to patients with MDR-tuberculosis using definitions that were standardised in 2005.<sup>15</sup> For the purposes of this Article, treatment success refers to the total number of patients who were cured or who completed their treatment according to the programme protocol but who had insufficient bacteriological results to define cure. Loss to follow-up represents all patients assessed for outcomes who were classified as defaulted or transferred out.

#### Indicators

In this Article, the estimate of the burden of MDRtuberculosis used to benchmark a country's progress towards universal access represents the number of cases of MDR-tuberculosis that would be expected to be detected if drug-susceptibility testing for isoniazid and rifampicin was to be done routinely on all new and previously treated cases of pulmonary tuberculosis notified in a country (about 4.6 million cases of pulmonary tuberculosis in total were notified by the 30 countries included in this Article in 2011). It thus does not include cases of MDR-tuberculosis among people who developed tuberculosis but who were not diagnosed or who were diagnosed but not captured by the surveillance systems of the countries. The MDRtuberculosis estimate is derived by use of the latest available value for the proportion of cases of tuberculosis with MDR-tuberculosis and multiplication of this proportion by the number of cases of pulmonary tuberculosis notified by the respective country in 2011. The proportion of cases of MDR-tuberculosis among tuberculosis cases is measured separately for new and previously treated cases of tuberculosis with drugresistance surveys done on a nationally representative

sample of patients with tuberculosis presenting for care.<sup>16</sup> Some countries use routine surveillance systems based on diagnostic drug-susceptibility testing to measure these proportions. In countries without a measured value, an estimate based on actual data from countries thought to have a similar epidemiological profile of tuberculosis is used. The point (best) value of the MDR-tuberculosis estimate was used to select the 30 countries that were expected to have more than 1000 cases of MDR-tuberculosis in 2011 (table). These countries accounted for 90% of the 310 000 cases of MDR-tuberculosis (range 220 000–400 000) estimated to arise among notified cases of pulmonary tuberculosis globally in 2011.

	MDR-tuberculosis estimate, 2011	Detected			Enrolled		
		2009	2010	2011	2009	2010	2011
India	66 000 (58 000-73 000)	1660	2967	4237	1136	2967	3384
China	61000 (54000-68000)	474	2792	1601	458	1222	1155
Russia	44000 (40000-48000)	14686	13692	13785	8143	13692	18902
Philippines	11000 (8000–13000)	1073	522	1148	501	548	2397
Pakistan*	10 000 (0-26 000)	49	444	344	368	424	344
Ukraine	9500 (8700-10000)	3482	5336	4305	3186	3870	4957
Kazakhstan	8200 (8000-8400)	3644	7387	7408	3209	5705	5261
South Africa	8100 (6900-9400)	9070	7386	10085	4143	5402	5643
Indonesia	6600 (5000-8200)		182	383	20	142	260
Burma	5500 (4200–6800)	815	192	690	64	192	163
Bangladesh	3800 (2900–4800)		339	509	352	339	390
Vietnam	3700 (2900-4400)	217	101	601	307	101	578
North Korea*	3500 (3000-4100)			37			25
Azerbaijan	3400 (3200–3700)		552	811		286	592
Democratic Republic of Congo*	3400 (44–6800)	91	87	121	176	191	128
Kenya*	3400 (280–6500)	150	112	166	140	118	156
Nigeria*	3400 (150-6600)	28	21	95		23	38
Uzbekistan	3000 (2700–3400)	654	1023	1385	464	628	855
Ethiopia	2200 (1300–3200)	233	140	212	88	120	199
Thailand	2200 (1700–2700)			510	296	9	123
Peru	2100 (1800–2400)	1578	1048	1663	1856	1702	1374
Belarus	2000 (1900–2100)	1342	1576	1594		200	1446
Mozambique	1800 (1200–2500)	140	165	283	103	87	146
South Korea	1800 (1500–2200)		450	516			307
Angola*	1600 (800-2400)		3	40		3	5
Moldova	1600 (1500–1700)	1069	1082	1001	334	791	765
Kyrgyzstan	1500 (1400–1700)	785	566	806	545	566	492
Afghanistan*	1100 (0–2600)		19	19			21
Brazil	1100 (810–1400)	449	573	566	398	573	630
Nepal	1100 (740–1400)	69	229	213	156	229	213
Total	280 000 (190 000-330 000)	41758	48986	55134	26443	40130	50949

Data are number or best estimate (95% CI). MDR=multidrug resistant. \*Estimates and 95% CIs are based on a modelled value derived from countries in the same region

Table: MDR-tuberculosis cases estimated in 2011 and detected and enrolled on second-line treatment in 2009, 2010, and 2011

We used three sets of indicators to assess the progress of the respective national programmes in scaling up their efforts to address the MDR-tuberculosis burden in the country—namely, detection, enrolment, and treatment outcomes. Detection referred to the number of cases of MDR-tuberculosis diagnosed and notified

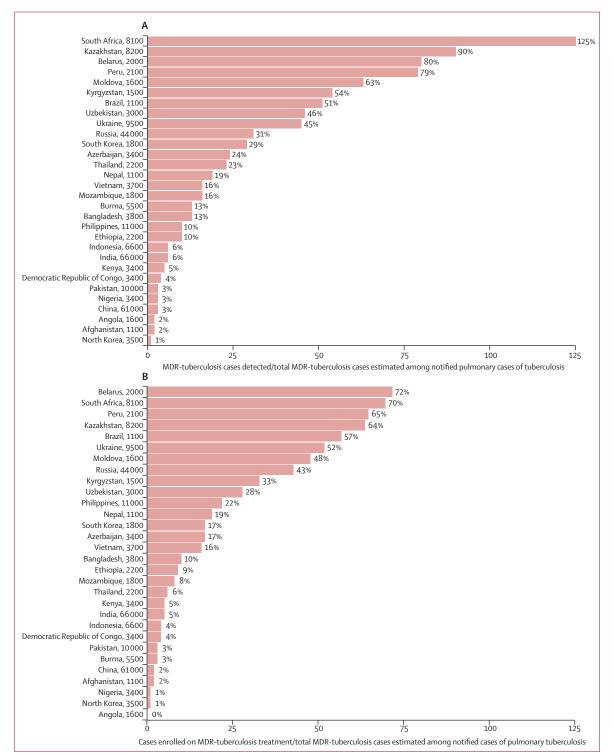


Figure 1: Ratios of detection of cases of MDR-tuberculosis (A) and enrolment on second-line treatment (B) in 30 countries in 2011 The estimated number of cases of MDR-tuberculosis among cases of notified pulmonary tuberculosis in 2011 is shown beside the country names. MDR=multidrug resistant.

by a country in 2011, expressed as an absolute number to compare burden and trends with time and as a percentage of the point value of the estimate of MDR-tuberculosis in the same year (detection ratio). Enrolment referred to the number of tuberculosis cases with laboratory confirmed or presumptive MDR-tuberculosis reported by a country to have been placed on second-line tuberculosis treatment in 2011, expressed as an absolute number to compare programme performance and trends with time and as a percentage of the point value of the MDR-tuberculosis estimate in the same year (enrolment ratio).

Fluctuations in the numbers of cases enrolled between 2009 and 2011 are expressed as the yearly change in percentage; the mean change for the two intervals (2009–10 and 2010–11) was used when data were reported for all 3 years (appendix p 1).

Treatment outcomes were reported as the percentages of patients with confirmed MDR-tuberculosis on treatment with an outcome assigned as success, death, treatment failure, or loss to follow-up. The denominator used in the calculation is all the cases of MDR-tuberculosis started and followed up on treatment in the course of 1 calendar year (cohort) and includes cases that were not assessed because of no information about the final outcome. Because of the long duration of treatment for MDR-tuberculosis, outcomes were monitored 36 months after the start of the year of enrolment. Thus, in this Article, we present the outcomes for patients who started treatment in 2009. We used the same methods for the subanalysis of patients with XDR-tuberculosis.

#### Statistical analysis

The data in this Article were as reported to WHO by countries until Dec 20, 2012, using an internet-based system in operation since 2009.<sup>17</sup> These data were submitted in aggregated format by the national authorities who were responsible for tuberculosis control. The methods used to gather the data at national level varied from case-based electronic databases with nationwide span to solely paper-based reporting. During and after submission, the data were checked and validated, and at the end they were consolidated with legacy data in a single electronic register hosted by the Stop TB Department, WHO, Geneva, Switzerland. Selected data and updated WHO estimates are available from WHO.

The analysis of data and generation of graphics were done with the packages ggplot2 and rmeta (meta.MH function) running in the R environment (version 2.15.1; appendix pp 1-2).<sup>18</sup> A p value of less than 0.05 was judged to be significant when comparing the odds ratio of success in MDR-tuberculosis versus XDR-tuberculosis (appendix p 2).

#### Role of the funding source

There was no external funding source for this study.

#### Results

The table shows the numbers of cases of MDR-tuberculosis detected and cases of tuberculosis enrolled on second-line treatment regimens between 2009 and 2011 in the 30 countries with the highest expected number of cases of See Online for appendix

<2000 MDR-tuberculosis cases 57% Brazil, 1100 48% Moldova, 1600 Kyrgyzstan, 1500 33% 19% Nepal, 1100 South Korea, 1800 17% 8% Mozambique, 1800 Afghanistan, 1100 2% Angola, 1600 0% 20 40 60 2000-<9000 MDR-tuberculosis cases 72% Belarus, 2000 South Africa, 8100 70% 65% Peru, 2100 64% Kazakhstan, 8200 28% Uzbekistan, 3000 17% Azerbaijan, 3400 Vietnam, 3700 16% Bangladesh, 3800 10% 9% Ethiopia, 2200 6% Thailand, 2200 Kenya, 3400 5% Indonesia, 6600 4% Democratic Republic 4% of Congo, 3400 3% Burma, 5500 Nigeria, 3400 1% North Korea, 3500 1% 20 40 60 80 ≥9000 MDR-tuberculosis cases 52% Ukraine, 9500 43% Russia, 44000 22% Philippines, 11000 India, 66000 3% Pakistan, 10000 China, 61000 10 20 30 40 50 60 Cases enrolled on MDR-tuberculosis treatment/total MDR-tuberculosis cases estimated among notified cases of pulmonary tuberculosis

**Figure 2: Enrolment ratios by countries according to estimated MDR-tuberculosis caseload, 2011** The estimated numbers of cases of MDR-tuberculosis among notified patients with pulmonary tuberculosis in 2011 are shown next to the country names. MDR=multidrug resistant. MDR-tuberculosis in 2011. Four large Asian countries (China, India, Pakistan, and the Philippines) and Russia and Ukraine had more than 9000 estimated MDRtuberculosis cases in 2011.

Figure 1 shows countries ranked according to their detection ratios in 2011. Seven countries (Belarus, Brazil, Kazakhstan, Kyrgyzstan, Peru, Moldova, and South Africa) detected more than 50% of their estimated cases of MDR-tuberculosis (figure 1). Detection ratios were lower in the five countries with the highest estimated burdens: China (3%), India (6%), Pakistan (3%), the Philippines (10%), and Russia (31%; figure 1).

Overall, about 18% of the estimated cases of MDRtuberculosis were enrolled on second-line treatment in 2011 in the 30 countries (table). Six countries (Belarus, Brazil, Kazakhstan, Peru, South Africa, and Ukraine) enrolled more than 50% of their estimated cases of MDR-tuberculosis on second-line treatment (figure 1). Enrolment ratios were low in four of the countries with the highest global burden of MDR-tuberculosis-China (2%), India (5%), Pakistan (3%), and the Philippines (22%)—but higher in Russia (43%; figure 2). Enrolment ratios were higher than detection ratios in 2011 in Brazil, the Philippines, Russia, and Ukraine, were equivalent in seven other countries (Afghanistan, Democratic Republic of Congo, Kenya, Nepal, North Korea, Pakistan, and Vietnam), and lagged behind detection in the remaining countries (appendix p 1). Enrolment might surpass detection when treatment is started on the presumption of MDR-tuberculosis but without a laboratory confirmation, or else because of the enrolment on treatment of cases detected before 2011.

Overall, cases of MDR-tuberculosis detected in the 30 countries increased by 32% from 41758 in 2009 to 55134 in 2011, and enrolments on treatment for MDR-tuberculosis increased by 93% from 26443 to 50949 during the same period (table). These increments are a result of increases in most of the countries, including China and India, with the largest burdens, even if the enrolment ratio reached only 2% and 5%, respectively, in 2011. In five countries (Ethiopia, India, Indonesia, the Philippines, and Russia), enrolments have increased steadily during 2009–11 with a mean yearly change greater than 50%, but in all of these countries the enrolment ratio in 2011 was less than 50% (range 4–43).

23 countries provided outcome data for a total of 16612 patients with confirmed MDR-tuberculosis enrolled in 2009 (figure 3). A median of 53% (IQR 41–71) of people had treatment success, 11% (8–17) died, 8% (2–11) had treatment failure, 13% (8–18) were lost to follow-up, and 4% (1–14) were not assessed. Distinct differences were noted in treatment outcomes between countries. Success was higher than 70% in six countries (Azerbaijan, Burma, Ethiopia, Indonesia, Nepal, and Vietnam), all situated in the lower half of the series in order of cohort size. Deaths occurred in more than 20% of the cohorts in Ukraine (31%), Pakistan (22%), and Kenya (21%), and treatment failure occurred in more than 10% in China (25%), Brazil (16%), and in five eastern European countries—Azerbaijan, Belarus,

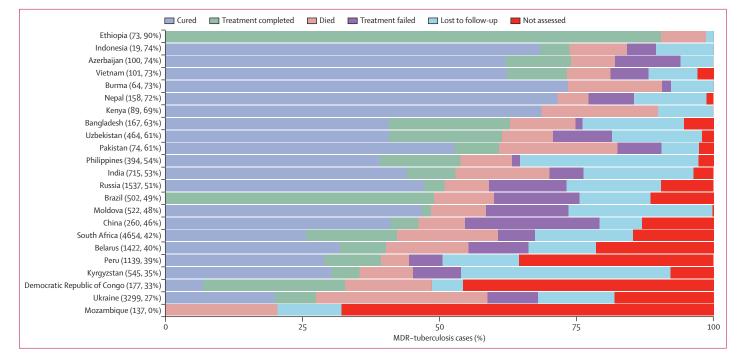


Figure 3: Treatment outcomes in patients with MDR-tuberculosis starting treatment in 2009

Data for Moldova and Russia are for enrolments in 2008. Cohort sizes and percentages for treatment success are shown next to country names. MDR=multidrug resistant.

Moldova, Russia, and Uzbekistan (11–15%; figure 3). Loss to follow-up was 20% or more in India, Kyrgyzstan, Moldova, and the Philippines (figure 3). In the Democratic Republic of Congo, Mozambique, and Peru, more than a third of the patients who started treatment were not assessed (figure 3). No significant correlation was noted between outcome (success or death) and changes in enrolment or detection over time (data not shown). In five countries, treatment outcomes for five or more cases of XDR-tuberculosis were reported separately from cases of MDR-tuberculosis and in all of them success was significantly higher in the patients with non-XDR, MDR-tuberculosis than in those with XDR-tuberculosis (appendix p 2).

### Discussion

The latest data reported to WHO allowed us to classify the 30 countries with more than 1000 estimated cases of MDR-tuberculosis according to the progress that they had achieved in diagnosis and treatment. Three broad patterns can be discerned. In 2011, in six countries-Belarus, Brazil, Kazakhstan, Peru, South Africa, and Ukraineboth detection and enrolment on treatment exceeded 50% of the estimated cases of MDR-tuberculosis in each country (figure 1). In three of these countries (Brazil, South Africa, and Ukraine), the number of patients placed on second-line treatment increased steadily since 2009 (table). These six countries can achieve universal access to MDR-tuberculosis care by 2015 if they continue expanding at a similar pace the services that they have put in place in recent years. In another group of five countries (Ethiopia, India, Indonesia, the Philippines, and Russia), the enrolment ratio varied from 4% to 43% in 2011 (figure 1), but enrolments increased steadily during 2009-11 with a mean yearly change greater than 50%. If these countries are to achieve universal access by 2015, they would need to expand their achievements to their entire populations. In the remaining 19 countries, including top-end MDR-tuberculosis burden countries such as China and Pakistan, substantial improvements will be needed to reach the expected coverage of access by 2015.

Worldwide, the under detection of cases of MDR-tuberculosis is largely caused by a combination of lack of awareness by carers about the need to test for drug resistance, low capacity to do drug-susceptibility testing in countries with poor access to adequate laboratory services, and deficiencies in the management of data for laboratory results.<sup>19,20</sup> Global coverage with drug-susceptibility testing for rifampicin and isoniazid only reached 4% of new cases in 2011 (Global Plan to Stop TB target for 2015, 20%), whereas for previously treated cases it was 6% (target 100%).1 In some higher burden countries known to perform drug-susceptibility testing on a large number of patients with tuberculosis, results reported were incomplete (eg, Russia and Ukraine), thus precluding a proper assessment of the coverage of drug-susceptibility testing.

Among the cohorts of patients with MDR-tuberculosis followed up for outcome, only Ethiopia (73 patients; figure 3) exceeded the 75% minimum threshold for treatment success conventionally targeted by the Global Plan to Stop TB for 2015.12 This analysis also showed that in patients with XDR-tuberculosis the likelihood of an unfavourable outcome often surpasses that of a successful one, a finding that concurs with results from other recent reviews.<sup>21,22</sup> This is indicative of the very limited treatment options for this subset of patients with MDR-tuberculosis in many parts of the world. The poor results in patients with MDR-tuberculosis in most countries, high mortality in different geographical settings, and the small number of patients being reported with MDR-tuberculosis attest to the challenges faced by programmes to mount an effective intervention. Additional factors are the insufficient experience of health-care workers in many programmes to administer a complex treatment regimen, broad resistance patterns of many patients, unstable market for second-line drugs that results in frequent delays and stockouts in supplies, and the difficulties encountered by patients to adhere to treatment regimens that very often last 20 months or more, which are less well tolerated, and less curative than are first-line regimens.<sup>20,23</sup> Difficulties in the procurement of costly second-line antituberculosis drugs and their delivery to patients sometimes also reflect inefficiencies in pharmaceutical management within the health services. As a result of such difficulties, a gap is starting to develop between the cases detected and those enrolled on treatment in some countries (appendix p 1).

Investments to address the global burden of MDR-tuberculosis pale when compared with the response to the pandemic of HIV/AIDS in the past three decades.24 In 2015, an estimated US\$2 billion will be required for the diagnosis and treatment of MDR-tuberculosis worldwide.1 Four (Brazil, Kazakhstan, Peru, and Ukraine) of the six countries judged to be on track for MDR-tuberculosis scale-up reported tuberculosis finance data to WHO (data not shown). These data show that by 2013 all of these countries might have 85-100% of their funding for MDR-tuberculosis services derived from domestic sources. Of the countries that have registered less progress, Russia is also funding nearly all of the MDR-tuberculosis programme internally. However, in China, India, and Indonesia, the substantial increase in funding for MDR-tuberculosis since 2009 has been largely accomplished as a result of non-domestic funding. Future progress could thus be at stake if external funding for these national programmes diminishes. Most of the countries where the MDR-tuberculosis burden is high are characterised by low health-care coverage in general. It is unrealistic to expect that the high-cost interventions associated with MDR-tuberculosis care be borne by the patients themselves without them and their families incurring catastrophic expenditures.25

This analysis has some limitations. In most cases, we had no means to verify independently the data reported

by countries beyond the validation routinely done for internal consistency. The aggregated format of the data precluded certain adjustments to render head-to-head comparisons more meaningful, including compensation for age, and incomplete data and variations in the degree of drug-resistance patterns beyond MDR-tuberculosis when outcomes from different countries were contrasted. The accuracy of the MDR-tuberculosis estimates vary between countries, some are based on drug-resistance surveys done several years ago and which might therefore be outdated (which might explain, for instance, the >100% detection ratio for South Africa: figure 1); in others a modelled value has been used because no direct measurements had been undertaken. The estimates of MDR-tuberculosis burden depend on the notifications and are therefore underestimated where tuberculosis case detection is low. Cases treated in the private sector might not have been reported to the national surveillance programmes, and the numbers might be substantial in Asian countries where the non-public sector is huge and tuberculosis case detection by the national programmes is low. When interpreting detection and enrolment ratios, the reader should also refer to the confidence limits for the estimates (table). Incomplete data for a single year can lead to swings in the estimates of mean percentage change for enrolment.

#### Panel: Research in context

#### Systematic review

The information analysed in this Article was reported to WHO by national authorities responsible for tuberculosis programmes during the latest round of yearly data gathering for the worldwide monitoring of tuberculosis control. These surveillance data have been gathered since 1997 and thus place WHO in a unique position to assess changes in the global epidemiology of tuberculosis and efforts to control it using a single dataset obtained with well established, standardised methods. Validation checks on the data are done routinely for internal consistency and when discrepancies are detected programmes have the opportunity to correct them. Specific analyses have been restricted to countries in which an acceptable level of completeness and validity of data coherence were achieved.

## Interpretation

Three main indicators—for detection, enrolment on multidrug-resistant (MDR)-tuberculosis regimens, and treatment outcome—showed clear differences between the 30 countries that have 90% of the global burden of MDR-tuberculosis in the effectiveness of their response to this disease in recent years. Access to care has been benchmarked against the expected number of cases of MDR-tuberculosis among known cases of pulmonary tuberculosis in each country, based on the best available information. The analyses are largely data driven and indicate the most likely constraints in further progress. In some instances (eg, outcomes of extensively drug-resistant tuberculosis) results obtained under programmatic conditions could be contrasted with those in published series. The work has also drawn attention to the limitations of using specific information and led to recommendations about improvements that could be made, such as the need to update the prevalence estimates of MDR-tuberculosis in specific settings and to survey country-specific bottlenecks hampering the earlier diagnosis of more cases and their initiation on effective treatment.

The quality of laboratory practices used to diagnose MDR-tuberculosis and to assign outcomes defined by bacteriological endpoints (cure and failure) is known to vary between countries and is not always supervised by the supranational laboratory network. The quality of drugs used and the composition and the duration of treatment regimens also differ between countries. The assignment of treatment success based on completion of treatment without sufficient bacteriological evidence to discern failure might explain the favourable results reported by countries like Ethiopia (figure 3). Outcome data from two countries (Angola and Kazakhstan) required further validation at the time of analysis and were therefore excluded. Cases without data for outcome were retained in the denominator and might therefore affect the percentage outcomes (eg, success ratios might be conservative if patients who feel well do not return for an assessment at the end of their treatment).

Although the data used in this Article were gathered in preparation of WHO's Global Tuberculosis Report 2012,1 the latter dealt largely with the situation at global and regional levels. In this Article, by contrast, the focus is on the enrolment ratios, the relation between detection and enrolment, changes in detection and enrolment over time, and the outcomes in patients with MDR-tuberculosis and XDR-tuberculosis in individual countries (panel). The countries included in the report are not identical to those on WHO's list of 27 countries with high burden of MDR-tuberculosis: they have a broader geographical spread. This analysis has allowed the useful stratification of countries by their progress towards expanding provision of care for patients with MDR-tuberculosis care. In 2009, the World Health Assembly urged countries to strive towards the prevention and control of drugresistant tuberculosis.11 The report is particularly timely at this juncture because 2011 is the first year of the global plan developed by the Stop TB Partnership and WHO to guide progress towards tuberculosis control by 2015.12

In conclusion, significant progress at the global level can only be expected when countries take the necessary actions to broaden access to care for all their populations. Treatment of patients with MDR-tuberculosis still results in very unsatisfactory outcomes across the different geographical settings, including countries on track to achieve universal access to MDR-tuberculosis care, with the attendant risk that they will forfeit the benefit gained through their efforts to find and place their patients with MDR-tuberculosis on treatment. The manner by which countries worldwide were able to mount an effective response in the decade after the declaration of tuberculosis as a global health emergency in the early 1990s should be held up as an example of how different barriers can be overcome on the way to effective action.<sup>24</sup> Recent innovations in the diagnostic techniques for tuberculosis are contributing to the rapid identification of patients in need of treatment with second-line drugs.<sup>26,27</sup> More effective tuberculosis drugs,

which are affordable and can improve the likelihood of cure and reduce the duration of treatment and adverse reactions, are urgently needed. The prospect of the release of new drugs for MDR-tuberculosis on the market over the coming months and years is thus a welcome development.<sup>28,29</sup> Improved access to general health care and social protection for all patients with tuberculosis would help some countries accelerate the progress that they are making and break the deadlock holding them back from expanding good-quality services adequately. Models of care based primarily on ambulatory care are preferred over those relying principally on hospital admission.<sup>30</sup> Surveillance should be stepped up in most countries to ensure that the progress of scale-up is monitored with the best possible information.

#### Contributors

EJ and DF were responsible for the ideation of the analysis and the writing of the Article. DF had full access to the data, analysed the data, developed the first draft of the Article, organised the references and had final responsibility for the decision to submit for publication. The other authors provided substantive contributions to the Article and all authors agree with the inferences and conclusions drawn.

#### **Conflicts of interest**

We declare that we have no conflicts of interest.

#### Acknowledgments

We thank Hazim Timimi who manages the surveillance data for WHO's Stop TB Department used in this Article for his support. We are all staff members of WHO. USAID was a principal salary supporter of WHO staff involved in this Article. We alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of WHO. The designations used and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area, or of its authorities, nor concerning the delimitation of its frontiers or boundaries. The country names in this Article are in accordance with *The Lancet Infectious Diseases* style and do not always follow WHO's naming convention.

#### References

- WHO. Global tuberculosis report 2012 (WHO/HTM/TB/2012.6). Geneva: World Health Organization, 2012.
- 2 Falzon D, Jaramillo E, Schünemann HJ, et al. WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. *Eur Respir J* 2011; 38: 516–28.
- 3 Zignol M, van Gemert W, Falzon D, et al. Surveillance of anti-tuberculosis drug resistance in the world: an updated analysis, 2007–2010. *Bull World Health Organ* 2012; **90**: 111–119D.
- 4 Skrahina A, Hurevich H, Zalutskaya A, et al. Multidrug-resistant tuberculosis in Belarus: the size of the problem and associated risk factors. *Bull World Health Organ* 2013; **91**: 36–45.
- 5 Dalton T, Cegielski P, Akksilp S, et al. Prevalence of and risk factors for resistance to second-line drugs in people with multidrug-resistant tuberculosis in eight countries: a prospective cohort study. *Lancet* 2012; 380: 1406–17.
- 6 Migliori GB, De Iaco G, Besozzi G, Centis R, Cirillo DM. First tuberculosis cases in Italy resistant to all tested drugs. *Euro Surveill* 2007; 12: E070517.1.
- 7 Velayati AA, Masjedi MR, Farnia P, et al. Emergence of new forms of totally drug-resistant tuberculosis bacilli: super extensively drug-resistant tuberculosis or totally drug-resistant strains in Iran. *Chest* 2009; **136**: 420–25.
- 8 Udwadia ZF, Amale RA, Ajbani KK, Rodrigues C. Totally drug-resistant tuberculosis in India. *Clin Infect Dis* 2012; 54: 579–81.
- 9 Murase Y, Maeda S, Yamada H, et al. Clonal expansion of multidrug-resistant and extensively drug-resistant tuberculosis, Japan. Emerg Infect Dis 2010; 16: 948–54.

- 10 Raviglione MC, Smith IM. XDR tuberculosis—implications for global public health. N Engl J Med 2007; 356: 656–59.
- Resolution WHA62.15. Prevention and control of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis. Sixty-second World Health Assembly, Geneva, Switzerland; May 18–22, 2009. Resolutions and decisions; annexes. Geneva: World Health Organization, 2009. (WHA62/2009/REC/1). apps.who.int/gb/ebwha/pdf\_files/WHA62-REC1/WHA62\_REC1en.pdf (accessed April 11, 2012).
- 12 WHO. The Global Plan to Stop TB 2011–15: transforming the fight towards elimination of tuberculosis (WHO/HTM/STB/2010.2). Geneva: World Health Organization, 2010.
- 13 WHO. WHO Global Task Force outlines measures to combat XDR-TB worldwide. 2006. http://www.who.int/mediacentre/news/notes/2006/ np29/en/ (May 22, 2013).
- 14 WHO. Guidelines for treatment of tuberculosis. 4th edn. (WHO/ HTM/TB/2009.420). Geneva: World Health Organization, 2009.
- 15 Laserson KF, Thorpe LE, Leimane V, et al. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2005; **9**: 640–45.
- 16 Guidelines for surveillance of drug resistance in tuberculosis. 4th edn. (WHO/TB/2009.422). Geneva: World Health Organization, 2009.
- 17 Global tuberculosis control: WHO report 2010 (WHO/HTM/ TB/2010.7). Geneva: World Health Organization, 2010.
- 18 R Project. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing, 2012.
- Shin SS, Yagui M, Ascencios L, et al. Scale-up of multidrug-resistant tuberculosis laboratory services, Peru. *Emerg Infect Dis* 2008; 14: 701–08.
- 20 WHO. Towards universal access to diagnosis and treatment of multidrug-resistant and extensively drug-resistant tuberculosis by 2015. WHO progress report 2011. (WHO/HTM/TB/2011.3). Geneva: World Health Organization, 2011.
- 21 Jacobson KR, Tierney DB, Jeon CY, Mitnick CD, Murray MB. Treatment outcomes among patients with extensively drug-resistant tuberculosis: systematic review and meta-analysis. *Clin Infect Dis* 2010; **51**: 6–14.
- 22 Falzon D, Gandhi N, Migliori GB, et al. Resistance to fluoroquinolones and second-line injectable drugs: impact on MDR-TB outcomes. *Eur Respir J* 2012; published online Oct 25, 2012. DOI:10.1183/09031936.00134712.
- 23 Nathanson E, Nunn P, Uplekar M, et al. MDR Tuberculosis— Critical steps for prevention and control. N Engl J Med 2010; 363: 1050–58.
- 24 Keshavjee S, Farmer PE. Tuberculosis, drug resistance, and the history of modern medicine. N Engl J Med 2012; 367: 931–36.
- 25 Rouzier VA, Oxlade O, Verduga R, Gresely L, Menzies D. Patient and family costs associated with tuberculosis, including multidrug-resistant tuberculosis, in Ecuador. Int J Tuberc Lung Dis 2010; 14: 1316–22.
- 26 Chang K, Lu W, Wang J, et al. Rapid and effective diagnosis of tuberculosis and rifampicin resistance with Xpert MTB/RIF assay: a meta-analysis. J Infect 2012; 64: 580–88.
- 27 WHO. WHO policy statement. Molecular line probe assays for rapid screening of patients at risk of multidrug resistant tuberculosis (MDR-TB). Geneva: World Health Organization, 2008. http://www.who.int/entity/tb/laboratory/line\_probe\_assays/ (May 22, 2013).
- 28 Diacon AH, Donald PR, Pym A, et al. Randomized pilot trial of eight weeks of bedaquiline (TMC207) treatment for multidrug-resistant tuberculosis: long-term outcome, tolerability, and effect on emergence of drug resistance. *Antimicrob Agents Chemother* 2012; 56: 3271–76.
- 29 Gler MT, Skripconoka V, Sanchez-Garavito E, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. N Engl J Med 2012; 366: 2151–60.
- 30 Fitzpatrick C, Floyd K. A systematic review of the cost and cost effectiveness of treatment for multidrug-resistant tuberculosis. *Pharmacoeconomics* 2012; 30: 63–80.

O 2013. World Health Organization. Published by Elsevier Ltd/Inc/BV. All rights reserved.