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On the spread and control of MDR-TB epidemics: an examination of trends in anti-tuberculosis drug resistance surveillance data

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SUMMARY

Background—Multidrug resistant tuberculosis (MDR-TB) poses serious challenges for tuberculosis control in many settings, but trends of MDR-TB have been difficult to measure.

Methods—We analyzed surveillance and population-representative survey data collected worldwide by the World Health Organization between 1993 and 2012. We examined setting-specific patterns associated with linear trends in the estimated per capita rate of MDR-TB among new notified TB cases to generate hypotheses about factors associated with trends in the transmission of highly drug resistant tuberculosis.

Results—59 countries and 39 sub-national settings had at least three years of data, but less than 10% of the population in the WHO-designated 27-high MDR-TB burden settings were in areas with sufficient data to track trends. Among settings in which the majority of MDR-TB was autochthonous, we found 10 settings with statistically significant linear trends in per capita rates of MDR-TB among new notified TB cases. Five of these settings had declining trends (Estonia, Latvia, Macao, Hong Kong, and Portugal) ranging from decreases of 3-14% annually, while five

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Author contributions

TC and MZ conceived of the study aims. TC, HEJ, and CL designed the analysis plan and HEJ and TC executed the analysis. MM led data collection and reference reviews. TC wrote the first draft of the manuscript, and MZ, KF, and HEJ provided substantial revisions to the initial version of the manuscript. All authors read, edited, and agreed with the decision to submit the final version of the paper. KF and MZ are staff members of the World Health Organization. The Authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of the World Health Organization.

conflicts of interest:

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had increasing trends (four individual oblasts of the Russian Federation and Botswana) ranging from 14-20% annually. In unadjusted analysis, better surveillance indicators and higher GDP per capita were associated with declining MDR-TB, while a higher existing absolute burden of MDR-TB was associated with an increasing trend.

Conclusions—Only a small fraction of countries in which the burden of MDR-TB is concentrated currently have sufficient surveillance data to estimate trends in drug-resistant TB. Where trend analysis was possible, smaller absolute burdens of MDR-TB and more robust surveillance systems were associated with declining per capita rates of MDR-TB among new notified cases.

INTRODUCTION

Individuals infected with *Mycobacterium tuberculosis* resistant to two important first-line drugs, isoniazid and rifampin (designated multidrug-resistant tuberculosis, or MDR-TB), have greatly diminished probability of successful treatment outcomes with standard recommended regimens [1]. The acquisition and subsequent transmission of drug-resistant TB is increasingly recognized as a threat to tuberculosis control [2] and MDR-TB is considered among the major emerging threats [3].

Two decades ago, the World Health Organization (WHO) initiated the Global Project on Anti-tuberculosis Drug Resistance. Through the collection of existing surveillance data, coordination and support of implementing population-representative drug resistance surveys, and development of a global reference network of supranational laboratories providing quality control and quality assurance for in-country drug-susceptibility testing facilities, this Project aimed to document the burden and to assess trends in drugresistant tuberculosis over time [4]. To date, country-specific, regionally-, and globally-aggregated estimates of the burden of drug-resistant tuberculosis have been produced; these were most recently updated in 2012 [5] and are now included in yearly Global Tuberculosis Control Reports [6]. These reports have permitted us to estimate burden and to document our collective failure to thus far scale up the availability of treatment for MDR-TB to meet the magnitude of the need in countries most affected [7].

One shortcoming of anti-tuberculosis drug resistance surveillance remains the difficulty in discerning the trends in the burden of MDR-TB. The absence of clear evidence of whether the MDR-TB problem is getting worse or better over time stems from two problems: the dearth of repeat surveys or routine surveillance in most high-burden areas [5] and the imprecision of surveys which limit the ability to detect small changes that might be observed over several years [8].

The last critical analysis of global MDR-TB trend data worldwide, conducted on data collected through 2007 documented the diversity of trends that have been recorded. The author concluded that, given adequate scale up of public health responses, MDR-TB epidemics can be controlled with currently available diagnostic tools and treatment options [9]. Here we use updated data, collated by the WHO through 2012, to revisit what can be learned from existing sources about trends in MDR-TB. We ask several questions of practical importance: In which country or sub-national settings can we confidently conclude

that the incidence of MDR-TB is increasing or decreasing? Can we identify factors associated with trends of transmitted MDR-TB? What can the experiences in these settings teach us about the potential controllability of MDR-TB in other settings?

METHODS

In the following analyses, we focus on trends of estimated per capita rates of MDR-TB among *new* notified TB cases. Individuals are classified as new TB cases if they have been exposed to less than one month of anti-TB therapy in the past, thus drug resistance among these cases reflects transmitted resistant *M. tuberculosis* [10]. Accordingly, our analysis of trends of MDR among new TB cases aims to provide insight into whether the spread of MDR-TB is increasing or decreasing over time in a given country or setting.

Data sources

Our analyses are based on national and sub-national surveillance data submitted to the World Health Organization (WHO) between 1993 and 2012. Data are generated from special surveys of a representative sample of patients with pulmonary TB or continuous surveillance based on routine diagnostic drug susceptibility testing (DST) of all bacteriologically-confirmed TB patients. A global network of 32 Supranational TB Reference Laboratories controls the quality of DST results in surveys [11]. The number of new notified TB cases is reported by year to the WHO for each country or sub-national area. We calculated TB notification rates per 100,000 by dividing these notification numbers by population estimates obtained from UN sources [12].

We present results from all settings that reported estimates of MDR risk or direct measures of MDR amongst newly notified TB cases in at least two different years. Information on drug resistance among notified cases are derived from two types of sources. In some countries, all newly notified cases receive DST and drug resistance among these cases is reported. In the remaining countries, estimates of the risk of drug-resistance among new cases are obtained through population-representative surveys. For these settings, we estimate the number of MDR-TB cases among new notified TB cases by multiplying the risk of MDR among new TB cases from the population-representative survey by the notification numbers for new notified TB cases reported in each year that a survey was done.

Over the time period covered by this review, recommended DST approaches included several based on solid culture (i.e. proportion method, resistance ratio method, absolute concentration method), liquid culture (i.e. BACTEC, MGIT), and, in more recent years, molecular tests such as line probe assays [10]. Newer molecular tests such as GeneXpert MTB/RIF have recently been approved, but no survey or surveillance results based on this test were included in this time period. While each survey or surveillance data point was based on DST using one of these recommended approaches, the DST method was not uniformly provided to the WHO.

Trend estimation

We estimated the average annual percentage changes in the estimated per-capita rates of MDR-TB among new notified TB cases and per-capita rates of new notified TB cases in

each country/sub-national setting. While we report annual percentage change in any country with at least two surveys or two years of surveillance, we limited our formal analysis of statistically significant trend to countries with at least three data points. For settings with data from at least three years, we identified countries and sub-national settings with statistically significant trends by testing the null hypothesis of no linear trend (see Appendix for details).

When testing for trends in estimated per capita rate of MDR-TB among new notified TB cases, we weighted the regression by the number of TB cases that were tested for MDR-TB in the relevant population-representative survey, since larger surveys have greater precision. When testing for trends in the rate of new TB notifications, we weighted the regression by the population size in the country/sub-national area in each year. For countries reporting no MDR-TB cases in a given year, we made a small adjustment to allow us to test for linear trend on the log scale (see Appendix for details).

Identifying setting-specific factors associated with trends in the incidence of new MDR-TB notification

For countries and sub-national settings where we rejected the null hypothesis of no statistically significant linear trend over time in the estimated per capita rate of MDR-TB among new notified TB cases, we explored the association of these trends with selected demographic, epidemiological, health system and economic factors that we *a priori* considered to be potentially linked to changes in this rate. These factors included variables related to TB programs and surveillance capacity (the number of years of survey/surveillance data, the average TB case detection rate, the percent of new TB cases receiving drug susceptibility testing), epidemiological variables (percent of new TB cases that are MDR, percent of retreatment TB cases that are MDR, average number of estimated MDR-TB cases among notified TB cases, estimated fraction of MDR-TB cases not treated, average HIV prevalence), and economic variables (average GDP per capita and average total health expenditures). We used descriptive analyses and linear regression to identify factors that were associated with statistically significant changes in the estimated per capita rate of MDR-TB among new notified TB cases. We present unadjusted results due to the small number of countries available for inclusion in final trend analyses.

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RESULTS

Our analysis included a total of 129 settings reporting at least two surveys or surveillance covering at least two years to the WHO between 1993 and 2012; this included 89 countries and 40 sub-national and special administrative settings. The sub-national settings included 34 oblasts of the Russian Federation; Barcelona, Spain; Bangui and Bimbo, Central African

Republic; Mpumalanga Province, South Africa; Henan Province, China and two additional special administrative regions within China (Macao and Hong Kong).

Data availability

Figure 1 shows the distribution of numbers of surveys (or years of surveillance) for each of the settings as well as the geographic distribution of information included in this analysis. We note that many additional settings had submitted data for only one year and these are not represented in the figure. In total there were 39 settings (24 country and 15 sub-national) with only two years of surveillance data and 6 countries with zero notified MDR-TB cases in each reporting year (these were excluded from the analysis since these data provide no information about trends) leaving 59 countries and 35 sub-national settings available for the trend analysis. Appendix Table 1 shows the number of notified new cases tested for drug susceptibility and the number found to be MDR for each setting and year of surveillance or survey.

Thirteen of the 27 WHO-designated “high MDR burden” countries [6] had at least two surveys or years of surveillance data, though several of those with the largest burden only had repeat surveys at a sub-national level (e.g. China and the Russian Federation). Of the persons living in these countries, only an estimated 8.3% lived within areas that have been covered by at least two surveys or two years of surveillance data.

In unadjusted analyses, we found a statistically significant positive association between the number of years for which a country provided data and the GDP per capita; each additional year of data was associated with a US$2,281 higher GDP per capita (95% CI: US$1,440 $3,123, $p<0.001$). We also found a statistically significant negative association between the number of years for which a country provided data and the estimated TB incidence per 100,000 population; each additional year of data was associated with 12.2 fewer incident TB cases per 100,000 (95% CI: 19.0-5.3, $p<0.001$).

Trend Analysis

Following Dye [9], we plotted the relationship between the estimated trend in the annual percent change in the per capita rate of new notified TB rate and annual percent change in the estimated per capita rate of MDR-TB among these new TB cases for each setting (Figure 2). The relationship between the trend in TB and that in MDR-TB is useful because it helps to clarify where the rate of MDR-TB was increasing or decreasing concurrently with TB (upper right and lower left quadrants) and where the trends in MDR-TB and TB appeared to be diverging (upper left and lower right quadrants). Furthermore, as suggested by Dye [13], quantifying the relative trend in MDR-TB versus TB-overall may provide insight into the relative reproductive number of MDR-TB versus drug-susceptible TB, a key measure that is influential in projections of the long-term trajectory of MDR-TB. The reproductive number is defined as the expected number of secondary cases of disease attributable to a single infectious case. Consistent with Dye’s earlier analysis, we found that every possible combination of TB and MDR-TB trend has been observed.

Eighteen settings (12 countries, Hong Kong, Macao, and four oblasts of the Russian Federation) had statistically significant linear trends in per capita rate of MDR-TB among

newly notified cases over time. Nine of these settings had significant decreases in MDR-TB over time (Figure 2, red markers); these decreases ranged from -3.3% per annum in Estonia to -14.8% per annum in Macao. Nine had significant increases in MDR-TB over time (Figure 2, green markers); these increases ranged from 3.6% per annum in the United Kingdom to 20.7% per annum in Botswana. Thirteen of these seventeen settings also had statistically significant trends in new TB notification (Figure 3, open markers); the trend in notified TB was in the same direction as the trend in the estimated MDR-TB notification rate in all but three of these countries (Finland and Austria where MDR-TB was increasing while TB was decreasing, and Australia where MDR-TB was decreasing while TB was increasing).

Immigration patterns and MDR-TB trends—In eight of the 18 settings with statistically significant MDR-TB trends, the majority of TB cases occurred among the foreign born. Four of these settings experienced decreasing trends of MDR-TB (United States of America, Israel, Germany, and Australia), while four experienced increasing trends (United Kingdom, Sweden, Finland, and Austria).

In settings in which the foreign born dominate TB epidemiology, trends in MDR-TB may reflect changes in immigration patterns (e.g. the numbers and origins of the foreign-born), changes in the type or effectiveness of screening practices (e.g. pre-arrival screening practices), and/or changes in the epidemiology of TB in the immigrants countries of origin. Accordingly, since these trends reflect several factors that may be extrinsic to the situation within the country of destination, ascribing trends in MDR-TB to local program performance or to differences in the reproductive number of MDR-TB may be misleading.

Trends in countries where MDR-TB trends may reflect local dynamics—The remainder of our analysis is restricted to the 10 settings where the burden of MDR-TB is not concentrated amongst the foreign-born. In these settings, changes in MDR-TB over time likely reflect changes in the intrinsic dynamics of drug-resistant TB and thus may be useful in identifying local factors associated with these trends. These included five settings with declining MDR-TB incidence (Latvia, Estonia, Portugal, and the two special administrative regions of China) and five settings with rising MDR-TB incidence (Botswana and four oblasts in the Russian Federation).

Declining trends of MDR-TB: The clearest success stories of control of the spread of MDR-TB were found in the Baltic states of Latvia (between 1996-2012) and Estonia (1998-2012). Consistent with earlier analyses [9, 14], we found that Estonia and Latvia reduced the incidence of notified cases of transmitted MDR TB by approximately 3-4% per annum (alongside slightly faster rates of reduction in non-MDR-TB) (Figure 3).

The speed of decline in MDR-TB incidence in Hong Kong (1996-2012), Macao (2005-2012) and Portugal (2000-2011) exceeded the rates at which non-MDR-TB declined, suggesting that the effective reproductive number of MDR-TB in these settings may have been lower than that of non-MDR-TB in these settings [13].

Rising trends of MDR-TB: The estimated per capita rate MDR-TB among new notified cases appeared to be rising over time in the epidemiologically and geographically disparate settings of Africa (Botswana) and several oblasts of the Russian Federation. In the Russian Federation, an area of substantial global interest because of the historically high prevalence of MDR-TB among both new and previously treated cases, we found evidence of rising rates of MDR-TB among new notified cases over the study period in four of the 22 oblasts with at least three data points. The remaining 18 oblasts had no significant linear trends (possibly due to lack of statistical power or the presence of more complicated non-linear trends (Appendix Figure 1)) and twelve additional oblasts had only two data points to consider. In the four oblasts with increasing per capita rates of MDR-TB, data were available in Mary-El between 2006-2011, in Karelia between 2009-2011, in Ivanovo between 1998 and 2011, and in Tomsk between 1999-2011. It is notable that the four oblasts had similar rates of increase (ranging from 14.0-19.2% per annum). It is important to note that in Tomsk, where we found a statistically significant increasing linear trend between 1999 and 2011, visual inspection of the data series suggests that this estimated rate of MDR-TB may actually have begun to decline beginning around 2005. We reflect on potential drivers of this pattern further in the Discussion.

In Botswana, the sole African setting in our analysis with three or more data points, the estimated per capita rate of MDR-TB among new notified cases was rising more than 20% per annum between 1996 and 2008, while new TB notification rates overall appeared to be relatively stable.

In each of these settings, the rate at which the MDR-TB was increasing exceeded the rate at which TB overall was increasing, consistent with a higher relative effective reproductive number of MDR-TB.

Other countries of note without statistically significant trends: While we restricted our formal analysis to countries with statistically significant linear trends, we elected to also highlight trends in Peru and the Republic of Korea, two countries that had increasing MDR-TB trends in previous analyses [5, 9]. Based on updated data, including new 2012 surveillance data from Peru and revised TB notification data from the Republic of Korea, we found that these countries no longer had statistically significant increasing linear trends our estimate of MDR-TB (Appendix Figure 2). We offer additional thoughts about the situation in these countries in the Discussion.

Factors associated with trends—We list several demographic, epidemiological, health systems, and economic variables that we *a priori* considered might be associated with trends in the incidence of transmitted MDR-TB (Table 1). Given the limited number of countries in which significant linear trends reflected dynamics intrinsic to that country, we present unadjusted linear regression as a means to generate hypotheses about which factors were potentially related to effective control of transmitted MDR-TB (Table 2).

We found that the following factors had statistically significant associations with trends in the estimated per capita rate of notified new MDR-TB: the number of years for which a country had survey or surveillance data, the estimated fraction of active TB cases that were

detected, the estimated burden of new MDR-TB cases (i.e. the estimated number of MDR-TB cases among notified TB cases), and the per capita GDP. Better surveillance (more years with survey data and higher case detection rates) and higher GDP per capita were associated with improving MDR-TB trends among new cases while a higher existing absolute burden of MDR-TB was associated with a worsening trend.

DISCUSSION

This analysis provides an update of country and sub-national trends of estimated per capita rates of MDR-TB among new notified TB cases and offers an assessment of what may be learned from settings that have been able to reverse rising rates of MDR-TB.

In contrast to earlier approaches for documenting and understanding trends in MDR-TB [9], we separated out countries in which the majority of TB (and MDR-TB) occurs among immigrants, since these trends may be related to factors other than local transmission of MDR-TB. The separate consideration of these countries is not intended to diminish the importance of international migration to MDR-TB trends. Indeed, previous analyses have demonstrated the importance of migration in the dissemination of MDR-TB [15, 16]. It is possible that transnational dissemination of MDR-TB may be important in other settings as well, for example, by migrant workers in sub-Saharan Africa [17].

We found that stronger surveillance systems were associated with a downward trend in MDR-TB (Table 2). Both the capacity to do routine surveillance (i.e. testing all new TB cases for drug susceptibility) and, in the absence of surveillance, the ability to do multiple surveys, was associated with declining MDR-TB among new TB cases. In Latvia and Estonia, two clear examples of countries that have reversed rising epidemics of MDR-TB, the ability to offer DST routinely to all new cases, is a key element of MDR-TB control [14, 18, 19]. These Baltic countries also share an aggressive approach to MDR-TB care, with individualized regimens based on DST results and high and increasing rates of MDR-TB treatment success over time. We note that these countries never had very large absolute burdens of MDR-TB, a factor that we found associated with potential controllability of MDR-TB. These countries have relatively low HIV co-infection rates (though this has been rising in Estonia) which likely contributes to the high MDR-TB treatment success rates and possibly to the ability to reverse the upward trend in the estimated rate of MDR-TB among new notified TB. While Tomsk oblast had a rising linear trend in estimated per capita MDR-TB among new notified TB over the analysis period, this trend may have been reversing in recent years (Figure 3). In Tomsk, as in Estonia and Latvia, all new patients receive DST, thus allowing patients to access MDR-TB treatment before failing a course of first-line treatment. Estonia, Latvia, and Tomsk also share a substantial history of strong political commitment toward addressing the threat of MDR-TB and partnership between national TB programs and established links with the Green Light Committee (GLC), which facilitated access to quality assured second-line drugs at reduced prices. Of note, in none of these settings is access to TB care and treatment for MDR-TB widely available through private sector providers [20].

The situations in Estonia, Latvia (and even Tomsk) provide important reassurance even in places where the prevalence of MDR-TB among new cases is very high, MDR-TB epidemics may be reversible within the context of highly organized programs that 1) aggressively identify MDR-TB cases through routine testing of all TB suspects, even those that have never previously been treated for TB and 2) deliver individualized quality-assured MDR-TB treatment consistent with DOTS-plus guidelines. Based on the experiences of these settings, which are more fully described in other publications [21], we would anticipate that if Tomsk can maintain its current efforts, and if the other Russian oblasts can implement similar systems of surveillance and treatment, that the incidence of new MDR-TB in these settings could begin to decline. Additionally, as stronger economic conditions were associated with decreasing trends in MDR-TB (as measured by per capita GDP) in settings included in our analysis, it is possible that more favorable economic conditions will be associated with better control of MDR-TB in other settings.

Is there anything to be learned from the experience in Peru? As with Estonia, Latvia, and Tomsk, Peru is a setting in which MDR-TB was aggressively addressed by partnerships between the national TB program, a well-established nongovernmental organization with strong capacity to treat MDR-TB, and the GLC. Despite a DOTS program that had been driving down the incidence of TB, the per capita rate of MDR-TB among new notified TB cases continued to rise over time with a statistically significant upward trend of approximately 4% per annum prior to the addition of 2012 data. What might explain the difference in outcomes between Peru and these other countries? While we cannot draw definitive conclusions, we note that in Peru, because of limited laboratory capacity, DST was reserved for individuals returning for retreatment and individuals otherwise considered at high risk of MDR-TB or death (e.g. household contacts of MDR cases and HIV co-infected cases). Accordingly, individuals with MDR-TB may have cycled through several courses of treatment (during which they may have amplified their resistance [22]), prior to receiving an MDR-TB diagnosis and being placed on appropriate therapy. These delays in diagnosis of MDR-TB may contribute to prolonged infectiousness and thus a relatively high effective reproductive number of MDR-TB in this setting [23]. We note expanded efforts to provide early access to DST, originally included within the Peruvian technical guidelines in 2006 [24] and most recently codified as policy for universal access to rapid pre-treatment tests for resistance for all TB patients in 2013 [25], was associated in time with declining per capita rate of MDR-TB among new TB cases.

In previous analyses, the Republic of Korea has had a statistically significant rising trend in MDR-TB [5, 9]. Here, based on recent modifications to TB case notifications dating back to 1999 [26], we no longer find a statistically significant increasing trend, though the best fit line remains consistent with an annual increase of >4% per annum (Appendix Figure 2). While we have not included this country in our group with increasing MDR-TB, we believe that the situation in the Republic of Korea warrants additional discussion. As described by Seung et al., in the Republic of Korea, the National Tuberculosis Program's role is largely restricted to the treatment of new TB cases, while a large private sector is responsible for patients returning for retreatment [27]. Over the past few years, the relative importance of the private sector appears to be growing, with recent estimates that 70% of treatment offered in the private sector [28]. This is concerning given the historically high rates of poor

treatment outcome and default associated with care delivered by private sector providers [29]. As was previously the case in Peru, new cases of TB diagnosed in the public sector do not receive DST in the Republic of Korea. Accordingly, individuals with transmitted MDR-TB may need to cycle through failed treatment before receiving proper diagnosis and care, resulting in higher morbidity and mortality and increased opportunity for onward transmission of MDR-TB. Future studies that measure the prevalence of drug resistance among TB cases treated in the private sector would provide valuable information in settings where large fractions of patients seek care outside of the national tuberculosis program [30].

Another potentially important difference between Peru and the Republic of Korea compared to Estonia, Latvia, and Tomsk is the burden and risk of MDR that these countries/settings must be equipped to address. While the average risk of MDR among new TB patients is relatively low in Peru and the Republic of Korea, the average estimated annual number of new MDR-TB cases is far higher in these countries than it is in Latvia, Estonia or Tomsk (Table 2). This means that Peru and the Republic of Korea must maintain systems for adequately diagnosing and treating MDR among a far larger cohort of patients which could prove a more difficult task than dealing with a smaller and more highly prevalent condition in parts of the former Soviet Union. The low pre-test probability of MDR-TB among new cases complicates the diagnosis of drug resistance (as the positive predictive value of even sensitive and specific tests for resistance may be compromised) and these tests will need to be delivered to very large numbers of new cases with important implications for the affordability of such approaches.

Botswana is the sole country in Africa with sufficient data to estimate an MDR-TB trend. It is worrisome that in this setting of high HIV prevalence, we observed increasing rates of MDR-TB over time while the incidence of TB overall appeared stable. While the information is too limited to attribute these trends to specific causes or to understand how HIV may or may not impact the controllability of MDR-TB epidemics, this pattern suggests that in this setting MDR-TB had a higher relative reproductive number than TB. The lack of sufficient data from other African settings is particularly vexing given the recent documentation of outbreaks of XDR-TB in South Africa [31] and the very high prevalence of MDR-TB found in most recently in Swaziland [32](see point 104 on Figure 2). A planned national drug resistance survey in South Africa will provide much needed information to better understand the threat of the spread of MDR-TB in areas where HIV is highly prevalent.

The majority of countries and settings included in this analysis did not have statistically significant linear changes in the estimated per capita rates of MDR-TB among new notified TB cases over time. This was due to stability of the estimated per capita rate of MDR-TB, a lack of sufficient number of repeat samples or large enough studies to detect trends that might have been present, or the presence of more complicated time trends in disease burden. In Appendix Figure 1 we present the time trends in estimated per capita incidence of MDR-TB among new notified TB cases for all countries and settings included in our analyses.

Our analysis of trends in the incidence of new notified MDR-TB highlights several issues related to assessing trends in MDR-TB. First, as clearly shown in Figure 1, the data

available are from a subset of countries and these data cannot be readily used to estimate global trends. In general, countries with more resources relative to TB burden are more likely to be included in the analysis. In many settings, we currently lack sufficiently robust capacity for either the systematic testing of resistance among all new TB cases or the capacity to do intermittent population-representative surveys of drug resistance among new cases. This is particularly evident in Africa and much of Asia, including India, which is not yet represented in this dataset for lack of sufficient numbers of repeat drug resistance surveys at either national or sub-national levels. While several settings in China have repeat surveys or surveillance data, and decreasing MDR-TB trends were detected in Macao and Hong Kong, recent national survey data suggest a serious problem with MDR-TB in the country with 5.7% of new TB cases infected with MDR-TB [33]. At this time, less than 10% of the populations within the 27 designated high-MDR-TB burden countries are reflected in this analysis. Of China, India, and Russia, only China is currently performing nationwide repeat survey of drug resistance. Given the strong association between strong surveillance systems and declining MDR-TB trends among countries with adequate data for trend analysis, the inability to assess the burden of drug resistance over time bodes poorly for countries with weak surveillance systems.

Second, the data upon which our analyses are based are imperfect. We have analyzed trends in estimated per capita rate of new notified MDR-TB cases. If surveillance systems have changed over time, trends in notifications may reflect these administrative changes rather than true epidemiological shifts. The variable timing between *M. tuberculosis* transmission events and progression to clinical disease also makes it more difficult to clearly link factors with trends, but the relatively high risk of progression soon after infection allays some of this concern [34]. Furthermore, we have performed aggregated analyses at the level of country or sub-national region, but there is substantial local heterogeneity in the burden of TB [35] and MDR-TB [36-39]. Surveys in such countries may either underestimate or overestimate resistance, depending on which study sites contribute to the study [40] and assessing these aggregated trends may smooth over important local differences in disease trajectory. Additionally, we have used a simple approach for detecting linear trends in the percentage change in estimated new MDR-TB among notified TB cases. The selection of this approach was motivated by the limited data available for detecting more complex trends, but this approach can fail to detect important changes in disease burden over time. This is best illustrated by the analysis in Tomsk, which led us to include it as a location with increasing MDR-TB, when visual analysis suggests that after a period of early worsening of the epidemic, the situation appears to be improving. Given what has been documented about the interventions that have been deployed in this oblast [21], the timing of this reversal is quite credible. Non-linear patterns in MDR-TB trends may be present in other settings as well (Appendix Figure 1), though the limited sample sizes and wide confidence intervals are obstacles for the rigorous detection of these patterns. Fourth, the drugs to which resistance were tested and reported was limited; in particular, we have no reliable measures of trends in XDR-TB over time since testing for resistance to fluoroquinolone and injectable antibiotics is currently more challenging and less reproducible than for isoniazid and rifampicin. Fifth, given the limited number of settings in which we detected trends, our analysis of factors that are associated with these trends was limited. We used publically available data to test for

unadjusted associations with trend. Accordingly, we have characterized these associations as hypothesis generating and anticipate that this analysis can be improved as more data become available in the future.

These limitations notwithstanding, our analyses provide both guarded optimism and reason to be concerned about our ability to mitigate the spread of MDR-TB. The good news first: the spread of MDR-TB appears controllable in countries that have made substantial investments in surveillance and response. In particular, based on the findings in Estonia and Latvia, it appears that universal DST for all TB patients and individualized second-line treatment regimens for MDR-TB cases may be needed to control the transmission of MDR-TB in areas where the risk of transmitted resistance is already very high. The limited data do not yet clarify whether these measures are sufficient, but we believe they are likely to be a necessary condition to curb the growth of MDR-TB in other settings. Higher GDP was also associated with declining MDR in the settings included in our analysis. We caution that our analysis should not be used to assign causality to factors we found to be associated with controllability of transmitted MDR-TB, but do suggest that increasing investment in surveillance systems (including laboratory infrastructure to conduct DST) and improving treatment capacity for MDR-TB [7] may be necessary to successfully mitigate the spread of MDR-TB. The introduction of rapid, more easily scalable technologies for rapid DST, such as GeneXpert MTB/RIF [41], may facilitate such responses. The more concerning news: at present, we do not have evidence of successful control of the spread of MDR-TB in areas of high HIV co-infection (e.g. Botswana), areas where drug susceptibility testing is reserved for those failing one (or multiple courses) of standardized treatment, or in areas where the private sector plays an important role in TB treatment. These findings should provide strong support for efforts to improve the strength of surveillance systems and the vigor of the response to MDR-TB, especially in countries with the highest absolute burden of disease including China, India and Russia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

APPENDIX

Since incidence rates changing at a constant percentage every year change linearly on a log scale, we modeled the natural logarithm of the TB and MDR-TB incidence rates as the dependent variable with year as the explanatory variable:

$$ln\,(\mathrm{R_y}) = \mathrm{b_0} + \mathrm{b_1 y} \quad (1)$$

where ln is the natural logarithm and R_y is the TB (or MDR-TB) incidence per 100,000 in year y

The annual percentage change in TB (or MDR-TB) incidence from year y to year y+1 = $[(R_{y+1} - R_y) / R_y] \times 100$

Substituting in (1), the annual percentage change in TB or (MDR-TB) incidence =

$$[[\exp(b_0+b_1(y+1))-exp(b_0+b_1y)]/exp(b_0+b_1y)]\times 100=(exp(b_1)-1)\times 100 \quad (2)$$

We fitted the regression line (1) to estimate b_1 for TB and MDR-TB incidence among newly notified cases in each country and sub-national area separately.

When modeling TB incidence, we weighted the regression by the population size in the country/sub-national area in each year. When modeling MDR-TB incidence, we weighted the regression by the number of TB cases that were tested for MDR-TB in the population-representative survey that was used, since larger surveys will have higher precision.

To identify countries or sub-national areas with statistically significant increasing or decreasing trends in TB or MDR-TB incidence, we assessed the statistical significance of b_1 at $p<0.05$. We note that in some low very low TB burden countries, the estimated number of MDR-TB cases in some years was zero. Since the logarithm of zero does not exist, in these cases we added 0.5 to the number of individuals tested positive for MDR-TB for all datapoints in that country's survey or surveillance data (0.5 was chosen to avoid bias as per: Cox D. Some statistical methods connected with series events. Journal of the Royal Statistical Society Series B - Methodological 1955:129-64).

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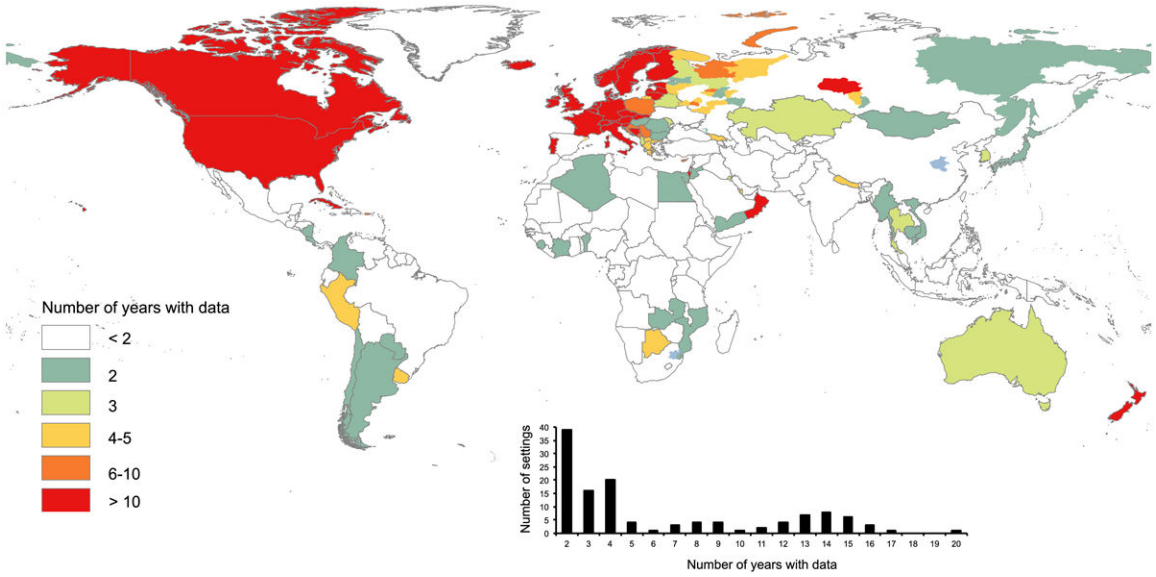
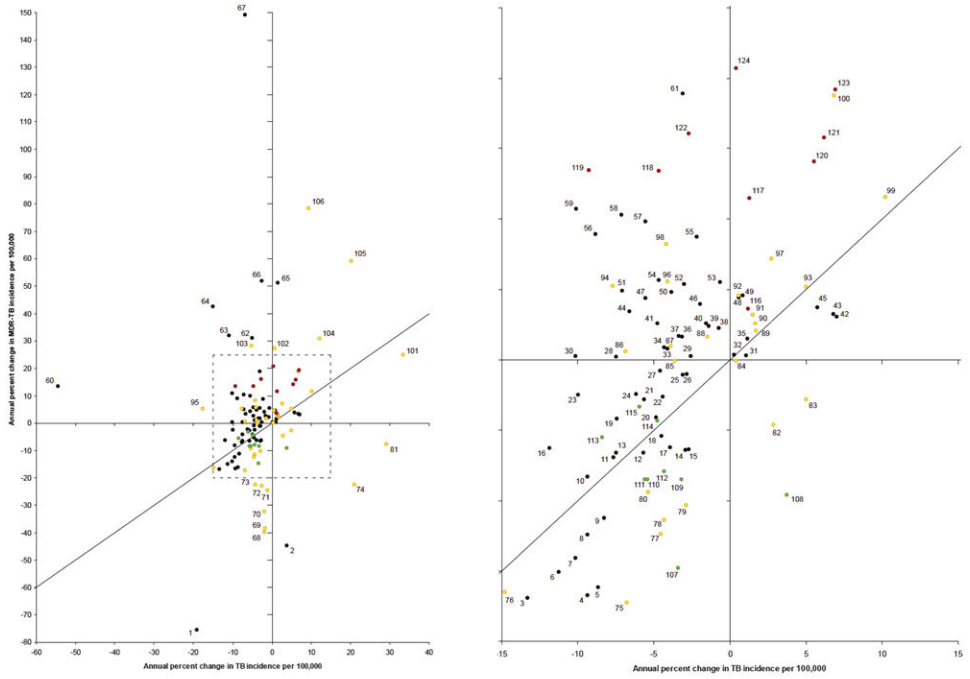


Figure 1. Global map of drug resistance surveillance data available for trend analysis

Countries and sub-regional settings reporting at least two years of representative data on the prevalence of drug-resistance among new notified TB cases. Among countries reporting at least two years of data, there is an inverse relationship between estimate TB incidence and numbers of years of reported data.



Non-significant trends
1 Kuwait
2 Mauritius
3 Russian Federation - Belgorod Oblast
4 Russian Federation - Tula Oblast
5 Russian Federation - Pskov Oblast
6 Greece
7 Puerto Rico
8 The Former Yugoslav Republic of Macedonia
9 Russian Federation - Komi Republic
10 Slovakia
11 Slovenia
12 Belgium
13 Russian Federation - Bryansk Oblast
14 New Zealand
15 Northern Mariana Islands
16 Russian Federation - Kaliningrad Oblast
17 Poland
18 Ireland
19 Croatia
20 Russian Federation - Murmansk Oblast
21 Kazakhstan
22 Bosnia and Herzegovina
23 Luxembourg
24 France
25 Peru
26 Canada
27 Cuba
28 Czech Republic
29 Lithuania
30 Russian Federation - Vladimir Oblast
31 Norway
32 Iceland
33 Switzerland
34 Russian Federation - Kemerovo Oblast
35 Uruguay
36 Albania
37 Russian Federation - Arkhangelsk Oblast
38 Oman
39 Georgia
40 Republic of Moldova
41 Russian Federation - Novgorod Oblast
42 Republic of Korea
43 Guam
44 Malta
45 Italy
46 Thailand
47 Singapore
48 Russian Federation - Chuvasia Republic
49 Nepal
50 Netherlands
51 Montenegro
52 Qatar
53 Cyprus
54 Denmark
55 Russian Federation - Orel Oblast
56 Spain - Barcelona
57 Belarus
58 Serbia
59 Russian Federation - Voronezh Oblast
60 Palau
61 Russian Federation - Tambov Oblast
62 Russian Federation - Kostroma Oblast
63 Russian Federation - Penza Oblast
64 Marshall Islands
65 Bahamas
66 Russian Federation - Vologda Oblast
67 Bahrain

Two datapoints
68 Russian Federation - Sakhalin Oblast
69 Russian Federation - Adygea Republic
70 Costa Rica
71 Paraguay
72 Sierra Leone
73 Zambia
74 Hungary
75 Russian Federation - Ulyanovsk Oblast
76 Russian Federation - Primorsky Krai
77 Nicaragua
78 Yemen
79 Central African Republic - Bangui and Bimbo
80 Japan
81 Russian Federation - Chukotka Autonomous Okrug
82 Cote d'Ivoire
83 Russian Federation - Sakha (Yakutia) Republic
84 Russian Federation - Khakassia Republic
85 Argentina
86 Bulgaria
87 Egypt
88 Jordan
89 Romania
90 Algeria
91 Viet Nam
92 Benin
93 Mozambique
94 Chile
95 Russian Federation - Nizhni Novgorod Oblast
96 Colombia
97 Mongolia
98 Russian Federation - Khabarovsk Krai
99 Myanmar
100 South Africa - Mpumalanga Province
101 China - Henan Province
102 Russian Federation - Samara Oblast
103 Russian Federation - Leningrad Oblast
104 Swaziland
105 Russian Federation - Kamchatka Krai Oblast
106 Cambodia

Decreasing trends
107 Macao
108 Australia
109 Hongkong
110 United States of America
111 Portugal
112 Israel
113 Germany
114 Latvia
115 Estonia

Increasing trends
116 United Kingdom
117 Sweden
118 Finland
119 Austria
120 Russian Federation - Tomsk Oblast
121 Russian Federation - Ivanovo Oblast
122 Russian Federation - Karelia Republic
123 Russian Federation - Mary El Republic
124 Botswana

Figure 2. Associations between changes in per capita new TB notification rate and estimated per capita MDR-TB rate among new cases for countries with at least two years of data

The graphs show the estimated annual percent change in the per capita rate of new notified TB (x-axis) against the annual percent change in the estimated per capita rate of MDR-TB among notified new TB cases (y-axis). The graph on the right is provided to allow for better visualization of the points closest to the origin. The green markers depict settings with statistically significant decreasing trend of MDR-TB, the red markers depict settings with statistically significant increasing trend of MDR-TB, and the yellow markers depict settings with no statistically significant trend of MDR-TB. The black markers depict settings with only two data points for which no formal trend analysis was conducted.

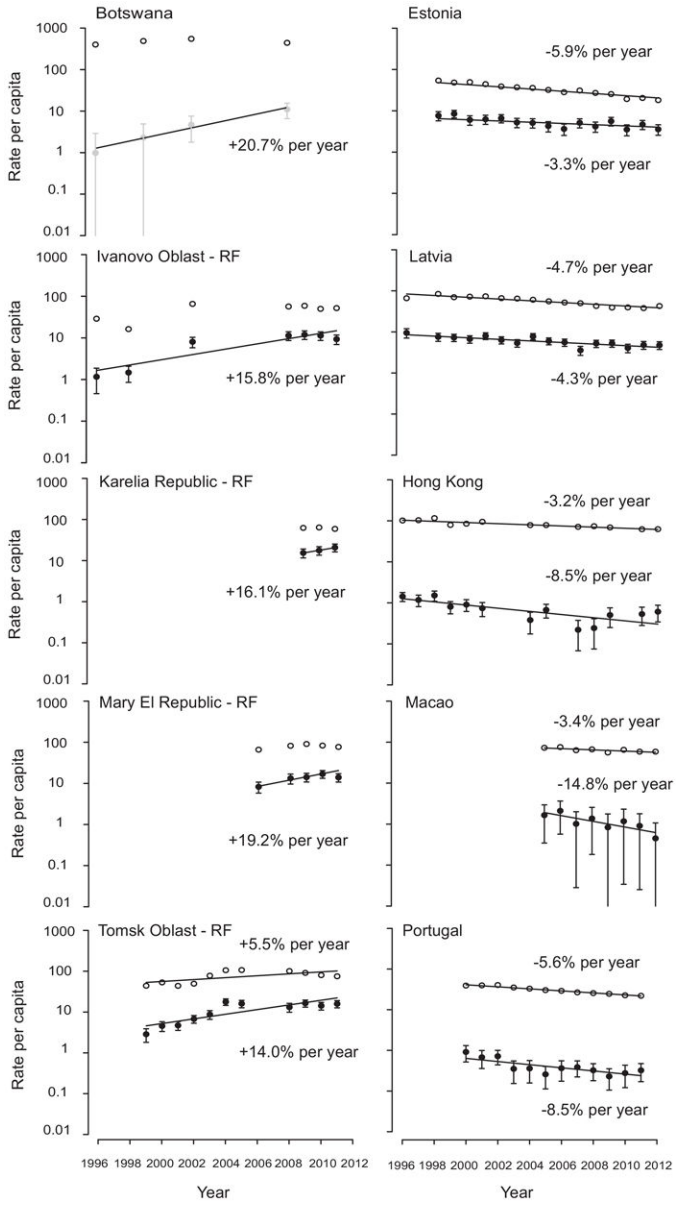
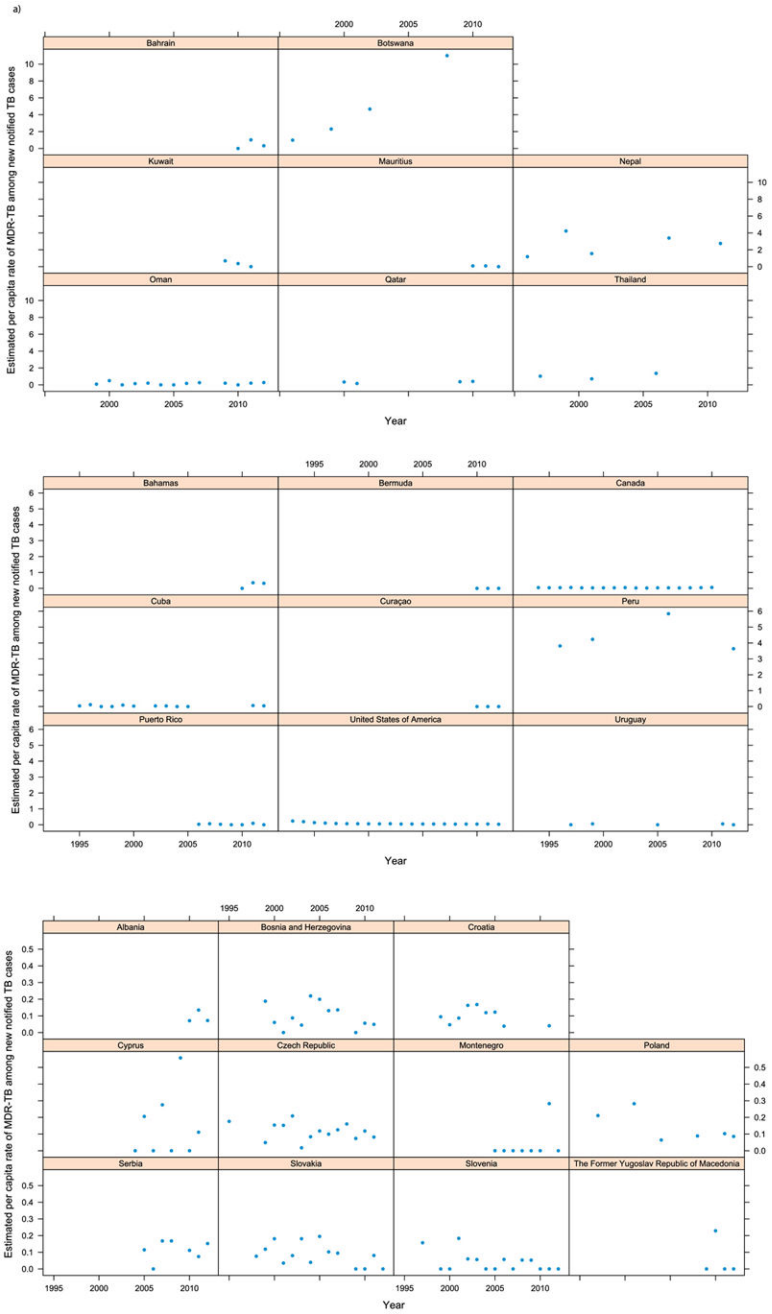
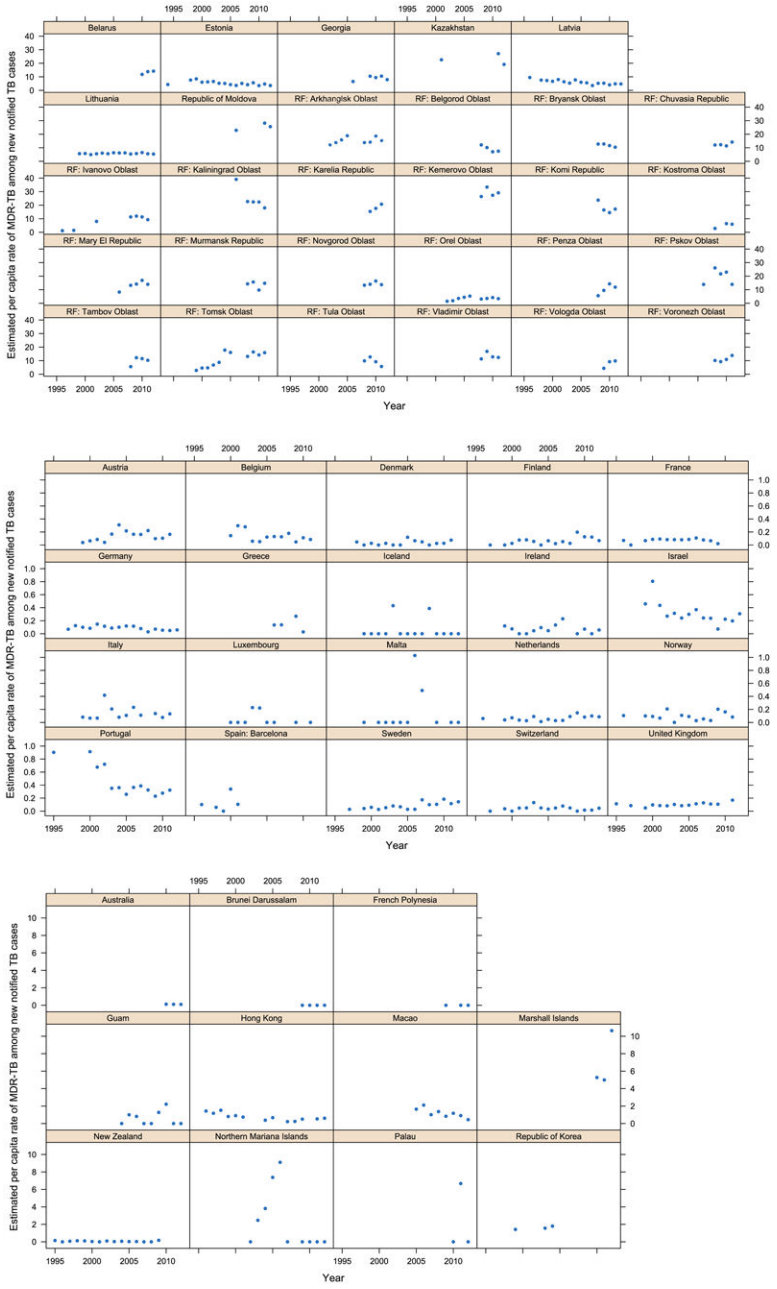


Figure 3. Settings with statistically significant linear trends in estimated per capita rates of MDR-TB among notified new TB cases

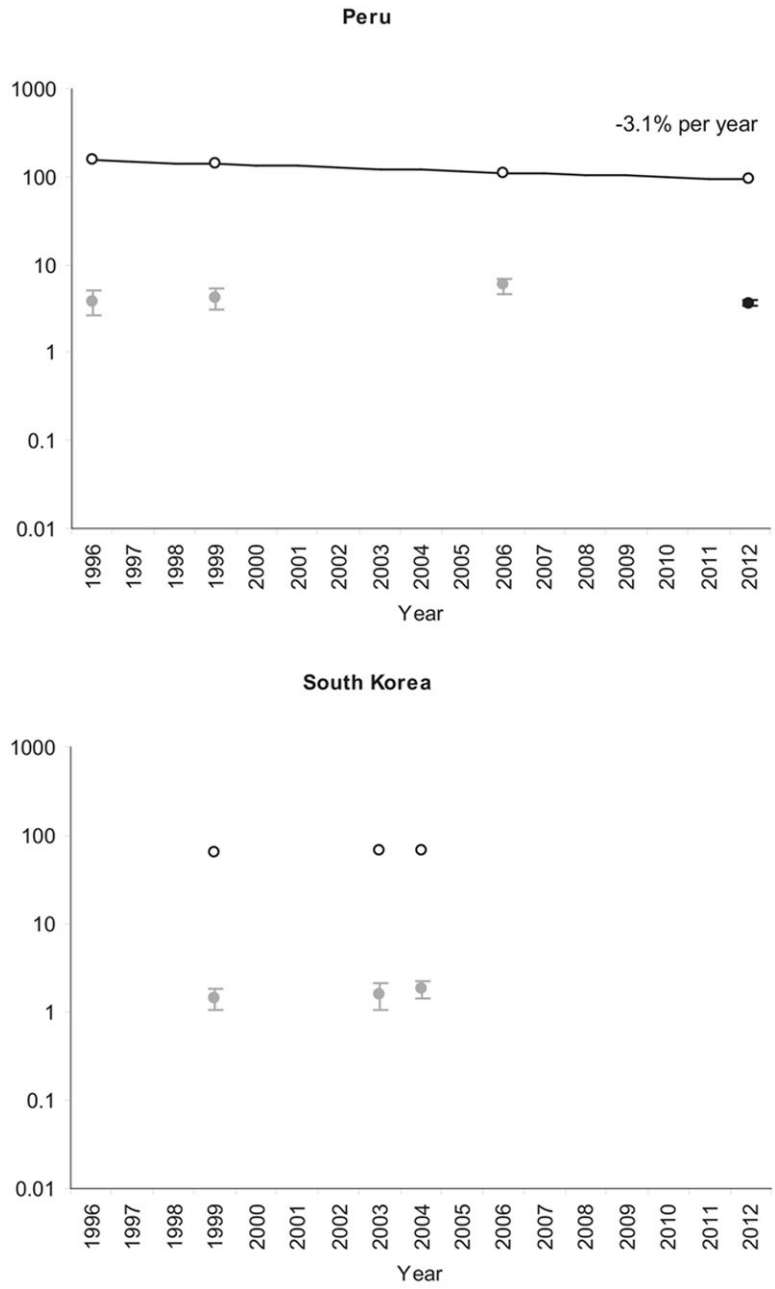
Each panel displays the time trend for settings with a statistically significant linear trend in estimated incidence of MDR-TB among newly notified TB cases. The black solid markers and associated confidence intervals show MDR-TB data from surveillance while the gray solid markers and associated confidence intervals show MDR-TB data from surveys. The open circles show new TB notification data. Points are only connected where statistically significant linear trends were detected.





Appendix Figure 1. Time series of estimated per capita rates of MDR-TB among notified new TB cases for each country with at least 3 data points

Sequential panels depict the rates by WHO region (or sub-region): a) Africa, Eastern Mediterranean, and South East Asia; b) Americas; c) Europe, Central; d) Europe, Eastern; e) Europe, Western; f) Western Pacific.



Appendix Figure 2. Patterns of notified TB and estimated MDR-TB among notified cases in Peru and South Korea

The black solid markers and associated confidence intervals show MDR-TB data from surveillance while the gray solid markers and associated confidence intervals show MDR-TB data from surveys. The open circles show new TB notification data.

Table 1

ta from settings with statistically significant linear trends in estimated per capita rates of MDR-TB among new notified TB cases

	MDR-TB trend (annual % change)*	Number of years of data**	Type of data	Average*** TB case detection rate (%) [26]	Percent of new TB cases receiving DST (%)[42]	Percent of new TB cases that are MDR (%) [42]	Percent of retreatment TB cases that are MDR (%) [42]	Average*** number of estimated MDR-TB among notified TB cases[42]	Estimated gap in MDR-TB treatment (% of estimated cases not treated) [38, 42]	Average*** annual estimated TB incidence (per 100,000) [26]	Average*** HIV prevalence (%)[43]	Average*** population size[12]	Average*** GDP per capita (US $)[44]	Average*** total health expenditure per capita (US$)[45]
	20.71	4	Survey	60	9	9.6	25.1	823	61	820	24.8	1778702	3869	188
sian	19.18	5	Surveillance	70	42	16.6	40.6	n/a	59	123	0.6	702283	5412	309
ian Fed)	16.05	3	Surveillance		57							685388		
sian Fed)	15.79	7	Surveillance		58							1144743		
an Fed)	14.05	11	Surveillance		72							1002691		
	-3.34	16	Surveillance	87	70	16.0	45.7	72	23	45	0.9	1354230	10021	567
	-4.32	16	Surveillance	79	72	10.5	31.9	134	11	84	0.5	2320459	7613	1710
	-8.50	13	Surveillance	87	38	1.4	6.6	45	51	102	0.7	10541469	18150	1835
	-8.52	13	Surveillance	87	53	0.9	6.6	6	54	76	n/a	6756500	27799	n/a
	-14.81	8	Surveillance	89	74	1.9	5.2	46	0	37	n/a	518487	42039	n/a

current analysis

x Table for data from all settings

re calculated over years for which MDR trend data were available for each setting

Table 2

Variables associated with trend in estimated per capita MDR-TB rates among new notified TB cases. All variables in Table 1 were tested, only those with statistically significant univariable associations are reported here.

		% annual change in estimated new notified MDR-TB cases (95% CI)
Surveillance variables		
	Number of years of data (per year additional data)	**-1.95 (-3.60, -0.30)**
	Average TB case detection rate (per 1% increase)	**-1.20 (-1.70, -0.71)**
Epidemiological variables		
	Estimated number of MDR-TB cases among notified TB cases (per 100 additional cases)	**3.83 (2.56, 5.10)**
Economic variables		
	GDP per capita (per $1000 increase)	**-0.76 (-1.51, -0.01)**

Appendix Table

Sizes of surveys and number of isolates that were found to be MDR for all settings included in this analysis.

Country/setting	Year	Number of new cases tested	Number of MDR cases identified
Albania	2010	186	1
Albania	2011	194	2
Albania	2012	172	1
Andorra	1999	6	0
Andorra	2000	4	0
Andorra	2003	2	0
Andorra	2004	5	0
Andorra	2005	9	0
Andorra	2006	8	0
Andorra	2007	3	0
Andorra	2008	3	0
Andorra	2009	2	0
Andorra	2010	4	0
Andorra	2011	1	0
Argentina	1999	679	12
Argentina	2005	683	15
Australia	1995	705	5
Australia	2010	868	21
Australia	2011	652	14
Australia	2012	861	16
Austria	1999	703	2
Austria	2000	694	3
Austria	2001	589	4
Austria	2002	633	2
Austria	2003	554	8
Austria	2004	600	17
Austria	2005	570	11
Austria	2006	500	8
Austria	2007	481	8
Austria	2008	439	11
Austria	2009	265	5
Austria	2010	203	5
Austria	2011	257	9
Bahamas	2010	21	0
Bahamas	2011	31	1
Bahamas	2012	27	1
Bahrain	2010	162	0
Bahrain	2011	154	9
Bahrain	2012	160	3

Country/setting	Year	Number of new cases tested	Number of MDR cases identified
Belarus	2010	1972	507
Belarus	2011	934	302
Belarus	2012	2164	753
Belgium	2000	562	7
Belgium	2001	562	13
Belgium	2002	629	15
Belgium	2003	510	3
Belgium	2004	622	3
Belgium	2005	588	7
Belgium	2006	606	8
Belgium	2007	707	10
Belgium	2008	630	15
Belgium	2009	621	4
Belgium	2010	466	7
Belgium	2011	524	7
Benin	1997	333	1
Benin	2010	403	2
Bermuda	2010	1	0
Bermuda	2011	1	0
Bermuda	2012	2	0
Bosnia and Herzegovina	1999	1154	3
Bosnia and Herzegovina	2000	993	1
Bosnia and Herzegovina	2001	1132	0
Bosnia and Herzegovina	2002	933	2
Bosnia and Herzegovina	2003	951	1
Bosnia and Herzegovina	2004	1048	4
Bosnia and Herzegovina	2005	1035	4
Bosnia and Herzegovina	2006	993	3
Bosnia and Herzegovina	2007	1267	3
Bosnia and Herzegovina	2009	854	0
Bosnia and Herzegovina	2010	600	1
Bosnia and Herzegovina	2011	704	1
Botswana	1996	407	1
Botswana	1999	638	3
Botswana	2002	1182	10
Botswana	2008	924	23
Brunei Darussalam	2009	164	0
Brunei Darussalam	2010	181	0
Brunei Darussalam	2011	205	0
Brunei Darussalam	2012	166	0
Bulgaria	2010	801	16
Bulgaria	2012	687	16

Country/setting	Year	Number of new cases tested	Number of MDR cases identified
Cambodia	2001	638	0
Cambodia	2007	781	11
Canada	1994	1325	10
Canada	1995	1242	8
Canada	1996	1203	9
Canada	1997	1366	12
Canada	1998	1206	7
Canada	1999	1268	7
Canada	2000	1162	7
Canada	2001	1262	9
Canada	2002	1172	12
Canada	2003	1153	6
Canada	2004	1154	5
Canada	2005	1130	8
Canada	2006	1058	8
Canada	2007	1113	7
Canada	2008	1098	9
Canada	2009	1321	13
Canada	2010	987	15
Cayman Islands	2011	1	0
Cayman Islands	2012	5	0
Central African Republic, Bangui and Bimbo	1998	464	5
Central African Republic, Bangui and Bimbo	2009	225	1
Chile	1997	732	3
Chile	2001	867	6
China, Henan Province	1996	646	70
China, Henan Province	2001	1222	95
China, Hong Kong SAR	1996	4424	62
China, Hong Kong SAR	1997	3432	39
China, Hong Kong SAR	1998	3753	49
China, Hong Kong SAR	1999	3460	35
China, Hong Kong SAR	2000	3479	37
China, Hong Kong SAR	2001	3470	27
China, Hong Kong SAR	2004	2682	13
China, Hong Kong SAR	2005	3271	28
China, Hong Kong SAR	2007	2593	8
China, Hong Kong SAR	2008	2443	8
China, Hong Kong SAR	2009	2056	15
China, Hong Kong SAR	2011	1992	17
China, Hong Kong SAR	2012	2061	20

Country/setting	Year	Number of new cases tested	Number of MDR cases identified
China, Macao SAR	2005	265	6
China, Macao SAR	2006	251	7
China, Macao SAR	2007	251	4
China, Macao SAR	2008	243	5
China, Macao SAR	2009	201	3
China, Macao SAR	2010	221	4
China, Macao SAR	2011	258	4
China, Macao SAR	2012	261	2
Colombia	2000	1087	16
Colombia	2005	925	22
Costa Rica	2006	263	4
Costa Rica	2012	273	0
Côte d'Ivoire	1996	320	17
Côte d'Ivoire	2006	320	8
Croatia	1999	761	2
Croatia	2000	780	1
Croatia	2001	713	2
Croatia	2002	747	4
Croatia	2003	732	4
Croatia	2004	669	3
Croatia	2005	586	3
Croatia	2006	614	1
Croatia	2011	353	1
Cuba	1995	337	1
Cuba	1996	426	4
Cuba	1997	241	0
Cuba	1998	284	0
Cuba	1999	321	3
Cuba	2000	377	1
Cuba	2002	195	1
Cuba	2003	193	1
Cuba	2004	177	0
Cuba	2005	169	0
Cuba	2011	313	3
Cuba	2012	269	2
Curaçao	2010	5	0
Curaçao	2011	1	0
Curaçao	2012	1	0
Cyprus	2004	15	0
Cyprus	2005	16	1
Cyprus	2006	22	0
Cyprus	2007	28	2

Country/setting	Year	Number of new cases tested	Number of MDR cases identified
Cyprus	2008	29	0
Cyprus	2009	27	4
Cyprus	2010	14	0
Cyprus	2011	25	1
Czech Republic	1995	199	2
Czech Republic	1999	628	2
Czech Republic	2000	616	7
Czech Republic	2001	663	8
Czech Republic	2002	488	9
Czech Republic	2003	610	1
Czech Republic	2004	480	4
Czech Republic	2005	562	7
Czech Republic	2006	552	6
Czech Republic	2007	487	8
Czech Republic	2008	483	10
Czech Republic	2009	413	5
Czech Republic	2010	352	7
Czech Republic	2011	392	6
Denmark	1998	412	2
Denmark	1999	392	0
Denmark	2000	392	1
Denmark	2001	356	0
Denmark	2002	273	1
Denmark	2003	283	0
Denmark	2004	267	0
Denmark	2005	307	5
Denmark	2006	286	3
Denmark	2007	269	2
Denmark	2008	253	0
Denmark	2009	209	1
Denmark	2010	209	1
Denmark	2011	257	3
Egypt	2002	632	14
Egypt	2011	1047	36
Estonia	1994	266	27
Estonia	1998	377	53
Estonia	1999	428	75
Estonia	2000	410	50
Estonia	2001	375	53
Estonia	2002	373	63
Estonia	2003	361	51
Estonia	2004	358	51

Country/setting	Year	Number of new cases tested	Number of MDR cases identified
Estonia	2005	316	42
Estonia	2006	279	36
Estonia	2007	316	52
Estonia	2008	272	42
Estonia	2009	245	54
Estonia	2010	197	36
Estonia	2011	210	48
Estonia	2012	193	38
Finland	1997	410	0
Finland	1999	371	0
Finland	2000	374	1
Finland	2001	348	3
Finland	2002	325	3
Finland	2003	271	2
Finland	2004	200	0
Finland	2005	198	2
Finland	2006	250	1
Finland	2007	216	2
Finland	2008	238	1
Finland	2009	295	6
Finland	2010	184	4
Finland	2011	237	5
Finland	2012	206	3
France	1996	1491	8
France	1997	787	0
France	1999	910	6
France	2000	947	8
France	2001	1056	10
France	2002	1255	11
France	2003	1485	13
France	2004	1431	14
France	2005	1291	14
France	2006	1368	19
France	2007	1255	12
France	2008	1313	16
France	2009	2890	13
French Polynesia	2009	42	0
French Polynesia	2011	47	0
French Polynesia	2012	30	0
Georgia	2006	799	54
Georgia	2009	1777	183
Georgia	2010	1987	188

Country/setting	Year	Number of new cases tested	Number of MDR cases identified
Georgia	2011	2197	239
Georgia	2012	1931	177
Germany	1997	1556	8
Germany	1998	1515	15
Germany	1999	1930	16
Germany	2000	1561	12
Germany	2001	2354	43
Germany	2002	3013	43
Germany	2003	3041	35
Germany	2004	3194	46
Germany	2005	3094	57
Germany	2006	3258	65
Germany	2007	2998	44
Germany	2008	2360	16
Germany	2009	2343	39
Germany	2010	2215	29
Germany	2011	2382	28
Germany	2012	2198	32
Greece	2006	507	13
Greece	2007	488	13
Greece	2009	140	9
Greece	2010	115	1
Guam	2004	29	0
Guam	2005	39	1
Guam	2006	34	1
Guam	2007	38	0
Guam	2008	37	0
Guam	2009	50	1
Guam	2010	56	2
Guam	2011	43	0
Guam	2012	31	0
Hungary	2009	486	16
Hungary	2010	474	10
Iceland	1999	7	0
Iceland	2000	8	0
Iceland	2001	11	0
Iceland	2002	6	0
Iceland	2003	4	1
Iceland	2004	7	0
Iceland	2005	7	0
Iceland	2006	12	0
Iceland	2007	10	0

Country/setting	Year	Number of new cases tested	Number of MDR cases identified
Iceland	2008	5	1
Iceland	2009	6	0
Iceland	2010	19	0
Iceland	2011	4	0
Iceland	2012	4	0
Ireland	1999	101	1
Ireland	2000	136	1
Ireland	2001	67	0
Ireland	2002	186	0
Ireland	2003	191	1
Ireland	2004	197	2
Ireland	2005	200	1
Ireland	2006	145	2
Ireland	2007	127	3
Ireland	2009	162	0
Ireland	2010	200	2
Ireland	2011	176	0
Ireland	2012	190	2
Israel	1999	346	18
Israel	2000	404	37
Israel	2001	360	19
Israel	2002	348	13
Israel	2003	344	15
Israel	2004	312	11
Israel	2005	259	14
Israel	2006	241	18
Israel	2007	278	12
Israel	2008	226	12
Israel	2009	258	4
Israel	2010	245	12
Israel	2011	275	10
Israel	2012	318	15
Italy	1999	683	8
Italy	2000	688	8
Italy	2001	746	7
Italy	2002	196	12
Italy	2003	390	11
Italy	2004	510	6
Italy	2005	485	8
Italy	2006	847	28
Italy	2007	653	16
Italy	2009	1051	34

Country/setting	Year	Number of new cases tested	Number of MDR cases identified
Italy	2010	836	23
Italy	2011	760	30
Japan	1997	1374	12
Japan	2002	2705	19
Jordan	2004	111	6
Jordan	2009	95	6
Kazakhstan	2001	359	51
Kazakhstan	2011	5293	1604
Kazakhstan	2012	8154	1864
Kuwait	2009	427	9
Kuwait	2010	437	5
Kuwait	2011	282	0
Latvia	1996	347	50
Latvia	1998	789	71
Latvia	1999	825	86
Latvia	2000	897	83
Latvia	2001	911	99
Latvia	2002	953	91
Latvia	2003	965	80
Latvia	2004	895	114
Latvia	2005	873	94
Latvia	2006	796	85
Latvia	2007	810	58
Latvia	2008	684	83
Latvia	2009	618	83
Latvia	2010	613	63
Latvia	2011	562	71
Latvia	2012	666	74
Lithuania	1999	819	64
Lithuania	2000	701	61
Lithuania	2001	972	75
Lithuania	2002	925	84
Lithuania	2003	955	86
Lithuania	2004	1128	104
Lithuania	2005	1293	127
Lithuania	2006	1346	128
Lithuania	2007	1257	126
Lithuania	2008	1259	113
Lithuania	2009	1074	114
Lithuania	2010	959	121
Lithuania	2011	1031	114
Lithuania	2012	1017	116

Country/setting	Year	Number of new cases tested	Number of MDR cases identified
Luxembourg	2000	39	0
Luxembourg	2001	28	0
Luxembourg	2002	31	0
Luxembourg	2003	53	1
Luxembourg	2004	31	1
Luxembourg	2005	36	0
Luxembourg	2006	33	0
Luxembourg	2011	7	0
Malta	1999	13	0
Malta	2001	9	0
Malta	2002	13	0
Malta	2003	9	0
Malta	2004	7	0
Malta	2005	11	0
Malta	2006	14	2
Malta	2007	18	1
Malta	2009	17	0
Malta	2011	17	0
Malta	2012	13	0
Marshall Islands	2010	68	1
Marshall Islands	2011	50	1
Marshall Islands	2012	73	3
Mauritius	2010	105	1
Mauritius	2011	100	1
Mauritius	2012	121	0
Mongolia	1999	405	4
Mongolia	2007	650	9
Montenegro	2005	82	0
Montenegro	2006	90	0
Montenegro	2007	76	0
Montenegro	2008	75	0
Montenegro	2009	80	0
Montenegro	2010	61	0
Montenegro	2011	57	1
Montenegro	2012	58	0
Mozambique	1999	1028	36
Mozambique	2007	1102	39
Myanmar	2003	733	29
Myanmar	2008	1071	45
Nepal	1996	787	9
Nepal	1999	668	25
Nepal	2001	755	10

Country/setting	Year	Number of new cases tested	Number of MDR cases identified
Nepal	2007	766	22
Nepal	2011	664	15
Netherlands	1996	1042	6
Netherlands	1999	899	4
Netherlands	2000	768	7
Netherlands	2001	484	2
Netherlands	2002	636	2
Netherlands	2003	518	6
Netherlands	2004	636	1
Netherlands	2005	709	5
Netherlands	2006	645	3
Netherlands	2007	553	3
Netherlands	2008	696	11
Netherlands	2009	720	16
Netherlands	2010	741	10
Netherlands	2011	695	12
Netherlands	2012	628	10
New Caledonia	1996	93	0
New Caledonia	2011	24	0
New Caledonia	2012	28	0
New Zealand	1995	144	2
New Zealand	1996	136	0
New Zealand	1997	123	1
New Zealand	1998	155	2
New Zealand	1999	228	2
New Zealand	2000	231	1
New Zealand	2001	272	0
New Zealand	2002	263	3
New Zealand	2003	304	1
New Zealand	2004	278	2
New Zealand	2005	247	1
New Zealand	2006	250	1
New Zealand	2007	214	0
New Zealand	2008	231	0
New Zealand	2009	236	6
Nicaragua	1998	564	7
Nicaragua	2006	320	2
Northern Mariana Islands	2002	29	0
Northern Mariana Islands	2003	27	1
Northern Mariana Islands	2004	21	1
Northern Mariana Islands	2005	24	2
Northern Mariana Islands	2006	18	2

Country/setting	Year	Number of new cases tested	Number of MDR cases identified
Northern Mariana Islands	2007	14	0
Northern Mariana Islands	2009	21	0
Northern Mariana Islands	2010	17	0
Northern Mariana Islands	2011	19	0
Northern Mariana Islands	2012	15	0
Norway	1996	138	3
Norway	1999	144	3
Norway	2000	160	3
Norway	2001	182	2
Norway	2002	181	7
Norway	2003	219	0
Norway	2004	223	4
Norway	2005	193	3
Norway	2006	216	1
Norway	2007	225	2
Norway	2008	180	1
Norway	2009	210	8
Norway	2010	139	4
Norway	2011	229	3
Oman	1999	133	1
Oman	2000	173	6
Oman	2001	171	0
Oman	2002	169	2
Oman	2003	153	3
Oman	2004	157	0
Oman	2005	125	0
Oman	2006	150	2
Oman	2007	145	3
Oman	2009	248	4
Oman	2010	185	0
Oman	2011	219	4
Oman	2012	248	6
Palau	2010	11	0
Palau	2011	8	1
Palau	2012	3	0
Paraguay	2001	235	5
Paraguay	2008	319	1
Peru	1996	1500	37
Peru	1999	1879	57
Peru	2006	1809	95
Peru	2012	14484	564
Poland	1997	2976	18

Country/setting	Year	Number of new cases tested	Number of MDR cases identified
Poland	2001	3037	35
Poland	2004	2716	8
Poland	2008	3758	18
Poland	2011	4416	23
Poland	2012	4073	20
Portugal	1995	815	14
Portugal	2000	860	20
Portugal	2001	999	17
Portugal	2002	1404	25
Portugal	2003	1203	12
Portugal	2004	1099	12
Portugal	2005	1407	12
Portugal	2006	1120	14
Portugal	2007	1446	21
Portugal	2008	1496	19
Portugal	2009	1391	13
Portugal	2010	982	12
Portugal	2011	1155	17
Puerto Rico	2006	97	1
Puerto Rico	2007	85	2
Puerto Rico	2008	89	1
Puerto Rico	2009	54	0
Puerto Rico	2010	69	0
Puerto Rico	2011	44	3
Puerto Rico	2012	52	0
Qatar	2000	279	2
Qatar	2001	284	1
Qatar	2009	322	3
Qatar	2010	324	4
Republic of Korea	1994	2486	39
Republic of Korea	1999	2370	52
Republic of Korea	2003	1348	32
Republic of Korea	2004	2636	71
Republic of Moldova	2006	825	160
Republic of Moldova	2011	1379	359
Republic of Moldova	2012	1264	299
Romania	1995	1636	45
Romania	2004	849	24
Russian Federation, Adygea Republic	2010	154	6
Russian Federation, Adygea Republic	2011	123	3

Country/setting	Year	Number of new cases tested	Number of MDR cases identified
Russian Federation, Arkhangelsk Oblast	2002	301	56
Russian Federation, Arkhangelsk Oblast	2003	299	59
Russian Federation, Arkhangelsk Oblast	2004	316	69
Russian Federation, Arkhangelsk Oblast	2005	297	85
Russian Federation, Arkhangelsk Oblast	2008	290	69
Russian Federation, Arkhangelsk Oblast	2009	292	75
Russian Federation, Arkhangelsk Oblast	2010	316	111
Russian Federation, Arkhangelsk Oblast	2011	321	94
Russian Federation, Belgorod Oblast	2008	442	85
Russian Federation, Belgorod Oblast	2009	359	71
Russian Federation, Belgorod Oblast	2010	342	52
Russian Federation, Belgorod Oblast	2011	308	57
Russian Federation, Belgorod Oblast	2008	549	71
Russian Federation, Belgorod Oblast	2009	562	73
Russian Federation, Belgorod Oblast	2010	447	59
Russian Federation, Belgorod Oblast	2011	409	54
Russian Federation, Chukotka Autonomous Okrug	2010	35	3
Russian Federation, Chukotka Autonomous Okrug	2011	49	3
Russian Federation, Chuvasia Republic	2008	613	87
Russian Federation, Chuvasia Republic	2009	579	88
Russian Federation, Chuvasia Republic	2010	503	78
Russian Federation, Chuvasia Republic	2011	550	108
Russian Federation, Ivanovo Oblast	1996	248	10
Russian Federation, Ivanovo Oblast	1998	222	20
Russian Federation, Ivanovo Oblast	2002	350	43
Russian Federation, Ivanovo Oblast	2008	275	55

Country/setting	Year	Number of new cases tested	Number of MDR cases identified
Russian Federation, Ivanovo Oblast	2009	276	56
Russian Federation, Ivanovo Oblast	2010	238	54
Russian Federation, Ivanovo Oblast	2011	268	48
Russian Federation, Kaliningrad oblast	2006	521	151
Russian Federation, Kaliningrad oblast	2008	436	84
Russian Federation, Kaliningrad oblast	2009	354	79
Russian Federation, Kaliningrad oblast	2010	326	78
Russian Federation, Kaliningrad oblast	2011	295	67
Russian Federation, Kamchatka Krai Oblast	2010	57	11
Russian Federation, Kamchatka Krai Oblast	2011	90	23
Russian Federation, Karelia Republic	2009	195	48
Russian Federation, Karelia Republic	2010	185	51
Russian Federation, Karelia Republic	2011	151	53
Russian Federation, Kemerovo Oblast	2008	1565	280
Russian Federation, Kemerovo Oblast	2009	1661	377
Russian Federation, Kemerovo Oblast	2010	1614	339
Russian Federation, Kemerovo Oblast	2011	1491	327
Russian Federation, Khabarovsk Krai	2010	684	160
Russian Federation, Khabarovsk Krai	2011	636	168
Russian Federation, Khakassia Republic	2010	233	63
Russian Federation, Khakassia Republic	2011	249	67
Russian Federation, Komi Republic	2008	305	79
Russian Federation, Komi Republic	2009	318	61
Russian Federation, Komi Republic	2010	277	54
Russian Federation, Komi Republic	2011	236	56
Russian Federation, Kostroma Oblast	2008	119	8
Russian Federation, Kostroma Oblast	2010	112	17

Country/setting	Year	Number of new cases tested	Number of MDR cases identified
Russian Federation, Kostroma Oblast	2011	102	17
Russian Federation, Leningrad Oblast	2010	378	101
Russian Federation, Leningrad Oblast	2011	335	121
Russian Federation, Mary El Republic	2006	304	38
Russian Federation, Mary El Republic	2008	267	43
Russian Federation, Mary El Republic	2009	365	57
Russian Federation, Mary El Republic	2010	330	67
Russian Federation, Mary El Republic	2011	330	60
Russian Federation, Murmansk Oblast	2008	173	49
Russian Federation, Murmansk Oblast	2009	190	55
Russian Federation, Murmansk Oblast	2010	173	36
Russian Federation, Murmansk Oblast	2011	164	54
Russian Federation, Nizhni Novgorod Oblast	2010	798	186
Russian Federation, Nizhni Novgorod Oblast	2011	598	178
Russian Federation, Novgorod Oblast	2008	152	30
Russian Federation, Novgorod Oblast	2009	139	29
Russian Federation, Novgorod Oblast	2010	156	42
Russian Federation, Novgorod Oblast	2011	147	34
Russian Federation, Orel Oblast	2002	379	10
Russian Federation, Orel Oblast	2003	330	11
Russian Federation, Orel Oblast	2004	328	19
Russian Federation, Orel Oblast	2005	311	23
Russian Federation, Orel Oblast	2006	317	28
Russian Federation, Orel Oblast	2008	296	16
Russian Federation, Orel Oblast	2009	254	16
Russian Federation, Orel Oblast	2010	241	21

Country/setting	Year	Number of new cases tested	Number of MDR cases identified
Russian Federation, Orel Oblast	2011	196	15
Russian Federation, Penza Oblast	2008	457	33
Russian Federation, Penza Oblast	2009	532	66
Russian Federation, Penza Oblast	2010	425	91
Russian Federation, Penza Oblast	2011	375	81
Russian Federation, Primorsky Krai	2010	1011	210
Russian Federation, Primorsky Krai	2011	825	168
Russian Federation, Pskov oblast	2006	343	55
Russian Federation, Pskov oblast	2008	370	101
Russian Federation, Pskov oblast	2009	302	75
Russian Federation, Pskov oblast	2010	312	87
Russian Federation, Pskov oblast	2011	279	54
Russian Federation, Sakha (Yakutia) Republic	2010	245	83
Russian Federation, Sakha (Yakutia) Republic	2011	303	95
Russian Federation, Sakhalin Oblast	2010	225	53
Russian Federation, Sakhalin Oblast	2011	242	35
Russian Federation, Samara Oblast	2010	939	235
Russian Federation, Samara Oblast	2011	960	304
Russian Federation, Tambov Oblast	2008	307	26
Russian Federation, Tambov Oblast	2009	343	60
Russian Federation, Tambov Oblast	2010	312	53
Russian Federation, Tambov Oblast	2011	309	53
Russian Federation, Tomsk Oblast	1999	417	27
Russian Federation, Tomsk Oblast	2000	561	48
Russian Federation, Tomsk Oblast	2001	532	57
Russian Federation, Tomsk Oblast	2002	533	73

Country/setting	Year	Number of new cases tested	Number of MDR cases identified
Russian Federation, Tomsk Oblast	2003	527	59
Russian Federation, Tomsk Oblast	2004	565	95
Russian Federation, Tomsk Oblast	2005	515	77
Russian Federation, Tomsk Oblast	2008	424	55
Russian Federation, Tomsk Oblast	2009	439	79
Russian Federation, Tomsk Oblast	2010	390	69
Russian Federation, Tomsk Oblast	2011	351	74
Russian Federation, Tula Oblast	2008	489	58
Russian Federation, Tula Oblast	2009	454	64
Russian Federation, Tula Oblast	2010	417	55
Russian Federation, Tula Oblast	2011	377	33
Russian Federation, Ulyanovsk Oblast	2010	265	80
Russian Federation, Ulyanovsk Oblast	2011	280	75
Russian Federation, Vladimir Oblast	2008	422	59
Russian Federation, Vladimir Oblast	2009	421	88
Russian Federation, Vladimir Oblast	2010	400	78
Russian Federation, Vladimir Oblast	2011	377	77
Russian Federation, Vologda Oblast	2009	214	21
Russian Federation, Vologda Oblast	2010	240	49
Russian Federation, Vologda Oblast	2011	176	41
Russian Federation, Voronezh Oblast	2008	597	87
Russian Federation, Voronezh Oblast	2009	534	78
Russian Federation, Voronezh Oblast	2010	461	89
Russian Federation, Voronezh Oblast	2011	394	108
Serbia	2005	1112	4
Serbia	2006	990	0
Serbia	2007	1130	7
Serbia	2008	923	6

Country/setting	Year	Number of new cases tested	Number of MDR cases identified
Serbia	2010	811	4
Serbia	2011	863	3
Serbia	2012	716	6
Sierra Leone	1996	463	5
Sierra Leone	1997	117	1
Singapore	1996	980	3
Singapore	2001	823	4
Singapore	2002	785	2
Singapore	2003	862	1
Singapore	2004	838	2
Singapore	2005	895	2
Singapore	2006	861	3
Singapore	2007	827	3
Singapore	2008	919	1
Singapore	2009	915	3
Singapore	2010	923	2
Singapore	2011	952	6
Singapore	2012	1178	19
Slovakia	1998	589	2
Slovakia	1999	456	3
Slovakia	2000	465	5
Slovakia	2001	464	1
Slovakia	2002	407	2
Slovakia	2003	350	4
Slovakia	2004	292	1
Slovakia	2005	248	4
Slovakia	2006	340	3
Slovakia	2007	343	3
Slovakia	2009	191	0
Slovakia	2010	185	0
Slovakia	2011	147	2
Slovakia	2012	142	0
Slovenia	1997	290	2
Slovenia	1999	304	0
Slovenia	2000	282	0
Slovenia	2001	281	3
Slovenia	2002	262	1
Slovenia	2003	226	1
Slovenia	2004	202	0
Slovenia	2005	217	0
Slovenia	2006	176	1
Slovenia	2007	174	0

Country/setting	Year	Number of new cases tested	Number of MDR cases identified
Slovenia	2008	182	1
Slovenia	2009	167	1
Slovenia	2010	123	0
Slovenia	2011	171	0
Slovenia	2012	114	0
South Africa, Mpumalanga Province	1997	661	10
South Africa, Mpumalanga Province	2002	702	18
Spain, Barcelona	1996	218	1
Spain, Barcelona	1998	315	1
Spain, Barcelona	1999	128	0
Spain, Barcelona	2000	135	3
Spain, Barcelona	2001	133	1
Swaziland	1995	334	3
Swaziland	2009	352	27
Sweden	1997	356	2
Sweden	1999	377	3
Sweden	2000	322	4
Sweden	2001	338	2
Sweden	2002	319	4
Sweden	2003	322	6
Sweden	2004	347	5
Sweden	2005	425	2
Sweden	2006	377	2
Sweden	2007	346	12
Sweden	2008	349	7
Sweden	2009	424	8
Sweden	2010	288	9
Sweden	2011	375	9
Sweden	2012	453	11
Switzerland	1997	322	0
Switzerland	1999	428	3
Switzerland	2000	330	0
Switzerland	2001	342	3
Switzerland	2002	368	3
Switzerland	2003	336	8
Switzerland	2004	340	3
Switzerland	2005	326	2
Switzerland	2006	382	4
Switzerland	2007	264	5
Switzerland	2008	258	3
Switzerland	2009	269	0

Country/setting	Year	Number of new cases tested	Number of MDR cases identified
Switzerland	2010	270	1
Switzerland	2011	304	1
Switzerland	2012	246	3
Thailand	1997	1137	24
Thailand	2001	1505	14
Thailand	2006	1150	19
The Former Yugoslav Republic of Macedonia	2009	191	0
The Former Yugoslav Republic of Macedonia	2010	153	2
The Former Yugoslav Republic of Macedonia	2011	130	0
The Former Yugoslav Republic of Macedonia	2012	155	0
United Kingdom of Great Britain and Northern Ireland	1995	2742	29
United Kingdom of Great Britain and Northern Ireland	1997	3053	24
United Kingdom of Great Britain and Northern Ireland	1999	2138	10
United Kingdom of Great Britain and Northern Ireland	2000	2312	21
United Kingdom of Great Britain and Northern Ireland	2001	2752	23
United Kingdom of Great Britain and Northern Ireland	2002	3110	22
United Kingdom of Great Britain and Northern Ireland	2003	2919	28
United Kingdom of Great Britain and Northern Ireland	2004	3105	22
United Kingdom of Great Britain and Northern Ireland	2005	3428	23
United Kingdom of Great Britain and Northern Ireland	2006	4677	39
United Kingdom of Great Britain and Northern Ireland	2007	3441	34
United Kingdom of Great Britain and Northern Ireland	2008	3749	38
United Kingdom of Great Britain and Northern Ireland	2009	3957	37
United Kingdom of Great Britain and Northern Ireland	2011	4549	61

Country/setting	Year	Number of new cases tested	Number of MDR cases identified
United States of America	1993	16601	407
United States of America	1994	16415	353
United States of America	1995	16022	254
United States of America	1996	15358	207
United States of America	1997	14448	155
United States of America	1998	13420	132
United States of America	1999	12655	127
United States of America	2000	11825	120
United States of America	2001	11510	115
United States of America	2002	10813	132
United States of America	2003	10751	95
United States of America	2004	10481	100
United States of America	2005	10064	98
United States of America	2006	9901	102
United States of America	2007	9642	104
United States of America	2008	9296	86
United States of America	2009	8196	94
United States of America	2010	7593	90
United States of America	2011	6899	94
United States of America	2012	6790	70
Uruguay	1997	484	0
Uruguay	1999	315	1
Uruguay	2005	335	0
Uruguay	2011	422	1
Uruguay	2012	466	0
Viet Nam	1997	640	15
Viet Nam	2006	1619	44
Yemen	2004	510	15
Yemen	2011	1108	19
Zambia	2000	445	8
Zambia	2008	604	2

Data on the Russian Federation are obtained from the annual report: Tuberculosis in the Russian Federation: an analytical review of statistical indicators used in the Russian Federation and in the world (in Russian). Moscow: Ministry of Health of the Russian Federation et al.