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INCIDENCE OF MULTIDRUG-RESISTANT TUBERCULOSIS DISEASE IN CHILDREN: SYSTEMATIC REVIEW AND GLOBAL ESTIMATES

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Abstract

Background—Multidrug-resistant tuberculosis (MDR-TB) threatens to reverse recent reductions in global tuberculosis (TB) incidence. Although children under 15 years of age constitute >25% of the worldwide population, the global incidence of MDR-TB disease in children has never been quantified.

Methods—Our approach for estimating regional and global annual incidence of MDR-TB in children required development of two models: one to estimate the setting-specific risk of MDR-TB among child TB cases, and a second to estimate the setting-specific incidence of TB disease in children. The model for MDR-TB risk among children with TB required a systematic literature review. We multiplied the setting-specific estimates of MDR-TB risk and TB incidence to estimate regional and global incidence of MDR-TB disease in children in 2010.

Findings—We identified 3,403 papers, of which 97 studies met inclusion criteria for the systematic review of MDR-TB risk. Thirty-one studies reported the risk of MDR-TB among both children and treatment-naïve adults with TB and were used for evaluating the linear association

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AUTHOR CONTRIBUTIONS

MCB, TC, and HEJ designed the study. MCB, AWT, and CMY designed the literature search. AWT led and supervised the implementation of the literature search, including collection and cataloguing of reports, as well as contacting authors for additional data. AWT, CMY, JBP, SK, and MCB reviewed reports and extracted data. HEJ, AWT, CMY, and MP performed analyses. HEJ, AWT, CMY, JBP, SK, CMPV, MCB, and TC contributed substantially to interpretation of results. HEJ, AWT, and CMY prepared figures and tables. HEJ and MCB wrote the first draft of the paper. All authors revised it critically for important intellectual content, and HEJ, TC, and MCB prepared the final version of the paper. All authors have approved this version for publication.

between MDR-TB risk in these two patient groups. We found that the setting-specific risk of MDR-TB was nearly identical in children and treatment-naïve adults with TB, consistent with the assertion that MDR-TB in both groups reflects the local risk of transmitted MDR-TB. Applying these calculated risks, we estimated that around 1,000,000 (95% Confidence Interval: 938,000 – 1,055,000) children developed TB disease in 2010, among whom 32,000 (95% Confidence Interval: 26,000 – 39,000) had MDR-TB.

Interpretation—Our estimates highlight a massive detection gap for children with TB and MDR-TB disease. Future estimates can be refined as more and better TB data and new diagnostic tools become available.

Keywords

children; pediatric; drug resistance; epidemiology

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) refers to tuberculosis (TB) disease caused by strains of *Mycobacterium tuberculosis* resistant to isoniazid and rifampicin, the backbone of the current first-line treatment regimen.¹ The emergence of *M. tuberculosis* strains resistant to first- and second-line drugs,^{2–5} and the limited access to second-line drugs for appropriate treatment, have driven calls for urgent action.^{6, 7, 8, 9}

Reliable estimates of the incidence of MDR-TB are essential to quantify existing gaps in diagnosis and treatment and to garner the resources necessary to prevent morbidity and mortality from the disease. Although estimating the incidence of drug-resistant TB is challenging due to limited access to drug-susceptibility testing (DST),¹⁰ data emerging from recent drug-resistance surveys and surveillance have suggested the global MDR-TB incidence exceeds half a million new cases occurring every year.¹ Although children under 15 years old constitute more than a quarter of the global population and 40% of the population of low-income countries,¹¹ the incidence of MDR-TB among children has never been estimated.

The bacteriological confirmation of drug-resistant TB disease is more difficult to attain in children than in adults. Young children are more likely to have paucibacillary and extrapulmonary disease, and cannot expectorate sputum.^{12, 13} Consequently, a high proportion of child TB cases are diagnosed based on clinical criteria without microbiological confirmation. This limits both the ability to directly measure the incidence of TB in children¹² and to routinely assess the risk of MDR-TB amongst these cases.¹⁴ This challenge notwithstanding, estimates of the incidence of MDR-TB disease in children are needed to understand the scale of this problem and to ensure that treatment is available, including child-friendly formulations of essential TB medications. We aim to estimate the regional and global incidence of MDR-TB disease in children.

METHODS

We estimated MDR-TB incidence in children using a three-step approach. First, we conducted a systematic literature review to estimate MDR-TB risk among child TB cases, which we define as the probability of MDR-TB conditional on having TB disease. We estimated this risk by identifying the setting-specific relationship between the MDR-TB risk amongst child TB cases and amongst treatment-naïve adult TB cases. Resistance in these two groups is expected to reflect primary transmission of resistant strains, rather than resistance acquired during prior treatment. We included only treatment-naïve adult cases because resistance in previously treated adults represents a mix of acquired and transmitted resistance. We used these reports to quantify the relationship between the MDR-TB risk among treatment-naïve adults and children. Second, we estimated the child TB incidence for each country, adjusting age-specific notification data by the age-specific risk of smear-positive disease and relating the estimated proportion of TB cases occurring among children to the national TB incidence per 100,000 population. Finally, we multiplied our estimates of (a) MDR-TB risk amongst child TB cases and (b) child TB incidence to produce (c) regional estimates of child MDR-TB incidence.

Search strategy— Identifying the relationship between risk of MDR-TB among child and treatment-naïve adult TB cases

The complete search strategy is detailed in Appendices 1 and 2, including detailed inclusion and exclusion criteria. We aimed to identify studies reporting the number of children with an isolate demonstrating resistance to both isoniazid and rifampicin (MDR-TB) on DST (Figure 1) as a proportion of all culture-confirmed child TB cases that received sufficient DST to diagnose MDR-TB. This measure provides an estimate of MDR-TB risk among child TB cases. We reviewed all published studies that reported this measure among a patient population that we expected would be representative of MDR-TB risk among child TB cases in the study base. Accordingly, we excluded reports where the inclusion of subjects may have been related to drug resistance (e.g., clinical trials, case-control studies, targeted testing). We also specifically excluded reports from outbreak or contact investigations, where risk of resistant disease is expected to be highly correlated and less likely to represent risk in the study base of all children with TB disease. We did not restrict the language of the publications reviewed.

We systematically searched the PubMed, Embase and LILACS electronic databases for primary studies and review articles published through January 12, 2012. We contacted authors for additional information if the report met all of the following criteria: (a) the DST results were not disaggregated by age group (0–14 and 15 years), (b) published since 2000, and (c) published in English or Spanish. We also reviewed the reference lists of primary studies and reviews for additional references and searched the Western Pacific, Africa, South-East Asia, and Eastern Mediterranean regional World Health Organization (WHO) databases.

Initial review of studies—We compiled an initial database from the electronic searches and removed duplicate citations. Two reviewers (AWT and MCB or CMY) screened these

citations by reviewing the title and abstract. Studies were eligible for inclusion if they reported the proportion of children with culture-confirmed TB disease who had isolates tested for susceptibility to both isoniazid and rifampicin.

Data extraction—Two reviewers (CMY, AWT) extracted all study data. A third reviewer (JBP) arbitrated any discrepancies between the first two reviewers. All final data were double-entered into a relational database designed in Microsoft Access.

For each study, we extracted data about the number of children with TB disease who received DST for isoniazid and rifampicin, and the proportion of those with isolates resistant to both isoniazid and rifampicin (MDR-TB). Where possible, we also extracted the same information for adults. Additional data extracted included location and enrollment year(s) of each study.

For each study that met inclusion criteria, we report the number of children with TB disease who had isolates tested for MDR-TB, and the proportion of those positive for MDR-TB.

Analysis and estimation

Estimation of the proportion of child TB cases that had MDR-TB—Using included studies for which we were able to extract the proportion of MDR-TB cases for both children and treatment-naïve adults, we estimated the relationship between the MDR-TB risk among these two groups. We constructed a linear regression model using the proportion of child TB cases with MDR-TB as the dependent variable and the proportion of treatment-naïve adult TB cases with MDR-TB as the explanatory variable. We weighted the regression by the number of child cases in each study that were tested for MDR-TB. Since there were multiple studies based in some countries, we included a random effect for country to ensure the variance around the parameter estimate was not inappropriately small due to lack of independence among studies. This parameter estimate thus quantified the relationship between the proportion of treatment-naïve adult incident TB cases with MDR-TB and the proportion of incident child TB cases with MDR-TB.

We applied this relationship to the 2008 countrywide estimates of the proportion of treatment-naïve adult incident TB cases with MDR-TB from the WHO¹⁵ to obtain country-level estimates of the proportion of incident child TB cases with MDR-TB.

Estimation of the number of child TB cases—Notification data under-report the incidence of TB disease in children.¹² To correct for this under-reporting, we adjusted smear-positive notifications by a factor reflecting the expected proportion of cases that are smear-positive to estimate the total number of TB cases. We assumed that the proportion of incident new TB cases that are smear-positive varied by age (consistent with data and the approach of Murray et al. See Appendix 2 for further details).¹⁶ For each age group and for all countries reporting at least one child TB case, we used the mean of two previously reported proportions of age-specific risk of smear-positivity^{16,17, 18} to estimate the age- and country-specific total number of new TB cases. Since data on previously treated cases are not reported to the WHO by age group, we assumed that all previously treated are >15 years old and adjusted the notification data by the mean of the proportions of smear-positivity risk

for all age groups >15 years from the aforementioned studies.^{16,17,18} We divided the estimated number of new child TB cases by the total estimated number of TB cases (new and previously treated) to estimate the country-specific proportion of TB cases occurring among children. We used data from the 151 countries/territories that provided smear-positive notification data (age-disaggregated for new cases) and reported at least one child smear-positive TB case.

Because some countries did not report age-disaggregated case notifications to the WHO, we fitted a logistic regression with the estimated proportion of TB cases occurring among children (estimated as described above) as the dependent variable and the log (base 10) of the estimated TB incidence per 100,000 population as the explanatory variable. This relationship between expected proportion of all TB cases that occur in children and overall TB incidence was first described by Peter Donald in 2002.¹⁹ The estimated regression coefficients permitted us to estimate the proportion of TB cases occurring among children for all countries. We then multiplied these proportions by the total estimated TB incidence per 100,000 in each country in 2010¹ and by the population in each country²⁰ to obtain the country-specific estimated number of child TB cases.

Estimation of the number of child MDR-TB cases—Finally, to estimate the incidence of child MDR-TB, we multiplied our estimates of (a) the country-specific risk of MDR-TB among child TB cases by (b) the country-specific number of child TB cases. We summed these country-specific MDR-TB incidences to provide a total estimate of child MDR-TB incidence by WHO regional groupings and worldwide in 2010. We used simulation methods to generate 95% confidence intervals around both the child TB and MDR-TB incidence estimates (see Appendix 2). We carried out sensitivity analyses to assess if our estimation method itself was likely to introduce bias (see Appendix 2).

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Decision to submit manuscript

The lead author and senior authors had access to all the data and were responsible for the decision to submit the manuscript for peer review.

RESULTS

Systematic review

Of the 3,403 abstracts, we identified 97 studies that were eligible for inclusion in the systematic review (Figure 1). Data extraction for 35 of these 97 studies relied on additional information provided by authors.

The 97 included studies evaluated 8,382 children with TB disease who had DST, of whom 348 (4.2%) had MDR-TB. Studies were classified according to their setting, data source, restriction(s) on study population, and type of laboratory where DST was performed (Table 1). Detailed study characteristics and results are reported in Table 2.^{21–117} The timeline, catchment areas, and data quality of included studies are illustrated in Appendices 3 and 4.

Estimation

DST results for both treatment-naïve adults and children could be extracted from 31 (32%) of the 97 included reports. Studies that included adults but did not provide a breakdown by treatment history accounted for a further 28 (29%) reports. There were 38 (39%) reports from which DST data for only children could be extracted.

From studies where sufficient data were available, we estimated that the relationship between the proportion of incident child TB cases with MDR-TB (Y) and the proportion of incident treatment-naïve adult TB cases with MDR-TB (X) was $Y = -0.00261 + 1.0691X$ (95% Confidence Interval (CI) for the X coefficient: 0.53, 1.61). Figure 2 shows the relationship between the proportion of incident treatment-naïve adult TB cases with MDR-TB and the proportion of incident child TB cases with MDR-TB in the 31 studies that reported both proportions. In a sensitivity analysis that excluded the two outlying points with log TB incidence of approximately 0.2 (Figure 2), we found similar results (estimated regression line: $0.000093 + 0.9514X$).

Figure 3 shows the relationship between the proportion of TB cases that are amongst children (0–14 years) and the log (base 10) of the estimated TB incidence per 100,000 by country/territory. Table 3 summarizes the regional and worldwide estimates of the incidence of child TB and MDR-TB in 2010. We estimated that there were 999,792 (95% CI: 937,877 – 1,055,414) incident child TB cases in 2010.

Globally, we estimated that 31,948 (95% CI: 25,594 – 38,663) children developed MDR-TB disease in 2010.

Sensitivity analyses showed that our estimation method did not introduce substantial bias (see Appendix 2).

Regional estimates

Approximately 40% (397,040) of estimated child TB cases were in the WHO South-East Asia region, nearly 30% (279,825) in the WHO African region, and nearly 20% (179,515) in the WHO Western Pacific region. The largest regional child MDR-TB incidence was in the WHO South-East Asia region where around 10,000 children (one third of global estimated

cases) were estimated to have developed MDR-TB disease in 2010. In the same year, the WHO Western Pacific region is estimated to have had more than 8,000 child MDR-TB cases (over one quarter of global estimated cases), the WHO European region over 5,000 cases, and the African region over 4,000 cases.

DISCUSSION

Our estimate of MDR-TB incidence in children provides an initial assessment of the vast unmet need for diagnosis and treatment annually. Notably, our estimate of total incident child cases of all forms of TB is twice that estimated by the WHO for 2011 and three times the number of child TB cases notified globally every year.¹¹⁸ However, no other estimates of MDR-TB incidence exist specifically for children. A recent systematic review of pediatric MDR-TB treatment outcomes found reports spanning the previous decade of only 315 children treated for MDR-TB,¹⁴ while the systematic review of 40 years of literature that we report here only found another 348 children with confirmed MDR-TB. Thus the sum total of MDR-TB child cases that have ever been reported in the literature is just 2% of those that we estimate occurred globally in the year 2010 alone.

There are multiple factors that would explain the present sizeable underestimate of the incidence of TB disease in children. A key factor is that incidence estimates often have as their starting point the number of child TB cases reported to a government TB agency. Yet in most countries these reported cases represent only the tip of the iceberg of child TB cases. This reflects the fact that children are more likely than adults to have paucibacillary disease and that young children (< 5 years old) cannot expectorate sputum, preventing microbiological diagnosis. Young children experience the highest risks of severe disease and death once infected, but are the least likely to be confirmed bacteriologically as TB cases. Furthermore, all currently available microbiological tests have very low sensitivity for child TB disease: under program conditions, the sensitivity of sputum smear microscopy and of sputum cultures is less than 5% and 15%, respectively. In most of the world, however, TB diagnosis relies heavily on smear microscopy, and most or all reported child TB cases are smear-positive, underlining the vast gap between true incidence and reported cases.

The potential reporting gap of child TB cases is further highlighted by post-mortem examinations and by the yield of intensified case-detection initiatives in private clinics.^{119, 120} Regardless of whether a sick child presents to the private or public sector, clinicians are frequently hamstrung by the dearth of child-friendly formulations of many TB drugs.¹²¹ Even novel diagnostic tests about which much enthusiasm abounds are unlikely to improve child case detection given their very low sensitivity (<15% of those diagnosed by clinical case definitions).¹²² All these factors together suggest an enormous need for improving the detection of child TB cases; it is likely that increased access to care, heightened clinical suspicion of tuberculosis, and more sensitive diagnostic tools will be needed to address this gap.

There are limitations in our approach. Firstly, our quantification of the relationship between the MDR-TB risk among children with TB with that of treatment-naïve adults with TB assumes that the relationship is generalizable to settings not represented in the systematic

review. Despite potential issues with generalizability, it is reassuring that the relationship we estimated is consistent with that recently reported by Zignol et al.¹²³ based on surveillance data reported directly to WHO. We also note that 45% (14/31) of the studies we analyzed excluded children with extrapulmonary disease, who constitute a large proportion of the youngest children with TB disease. However, Zignol et al.'s analysis found that the MDR-TB risk is similar between children <5 and 5–14 years old,¹²³ suggesting that this limitation may not undermine our estimates.

Secondly, our approach for estimating TB incidence in children uses age-specific, smear-positive TB notification data reported to the WHO¹ and adjusts these notification data using expected age-specific proportions of TB cases that are smear-positive, from previous studies.^{17, 18} The implicit assumption that the results from the previous studies are generalizable to other settings is supported by results from more recent studies from around the globe.^{124–128} Our method also assumes that after this adjustment, there are no further age-specific differences in case detection within one setting. In other words, we expect that even if there is under-reporting, provided it is consistent across age groups, our estimated proportions of TB cases that occur among children will remain unbiased. We also assume that all child TB cases have never previously been treated for TB, an assumption that should be robust in the majority of settings. In addition, we assume that an insignificant fraction of TB cases among children are currently prevented by the treatment of latent infection, as the use of preventive therapy among children has only been used widely in high-resource, low-incidence settings.¹²⁹

The relationship that we estimated between TB incidence and the fraction of all cases that occur in children was based on that described by Peter Donald using a different set of studies.¹⁹ Our decision to incorporate this relationship was based on our understanding of the epidemiology of infectious disease: (a) in higher incidence countries, children tend to comprise a larger fraction of the population (in other words, the population pyramids are more triangular in high incidence countries); and (b) the fraction of all cases that are child cases is likely to be highest in high incidence settings because the higher force of infection leads to a reduction in the average age of infection. Characterizing the relationship between TB incidence and the fraction of all cases that occur among children is dependent on data from a limited number of studies. Improved estimates of the incidence of childhood TB will be possible as more countries report age-disaggregated data and use diagnostic tests that are more sensitive for the detection of TB disease among children. Further refinements to incidence estimates will be possible as more and larger studies including children are undertaken.

Our approach also relies on estimates obtained from models developed by the WHO,¹⁵ for example, for TB incidence per 100,000 and for proportions of TB cases that are MDR-TB where drug resistance surveys had not been carried out. If these modeled estimates are systematically biased, these errors will be propagated in our estimates of both TB and MDR-TB incidence. Therefore, while our confidence limits capture the precision of our estimates, if there is any systematic bias present due to these estimated inputs or potentially unmet assumptions discussed above, the true numbers of child cases may well fall outside our reported confidence limits.

We propose that our estimate provides an important starting place for documenting the incidence of MDR-TB disease in children and that our method should motivate further discussions on statistical and mathematical techniques that may improve the precision of these estimates. More direct approaches for measuring MDR-TB risk in children and TB incidence in children will help to reduce uncertainty about MDR-TB incidence in children, and, more importantly, will facilitate the delivery of appropriate treatment. New tools for diagnosing TB disease and determining drug resistance are becoming available,¹³⁰ and, if their use can be scaled up to improve routine diagnosis of TB among children, future estimates of MDR-TB in children can be based on more robust evidence.

Our estimate of TB incidence in children is substantially higher than current (2011) WHO estimates.¹¹⁸ We used a different approach from that used by WHO: we explicitly acknowledged that case detection amongst children is lower than amongst adults due to difficulty in attaining microbiological confirmation, and on this basis estimated the proportions of all TB cases that occurred in children. We note that our estimates of child TB incidence are similar to previously published estimates of approximately 1.3 million cases in 1989¹³¹ and nearly 900,000 cases in 2000.¹³²

We estimate that every year there is a vast unmet need for treatment of both TB and MDR-TB disease in children, the former previously underestimated and the latter heretofore unknown. Our results point to an urgent need for expanded investment to respond globally to TB and MDR-TB in children, including systematic work to gather more and better empirical data that can be used for estimating disease incidence. Treatment for children with MDR-TB is highly effective if they can be diagnosed promptly and placed on appropriate drug regimens.¹⁴ Continued failure to detect and treat child cases of TB and MDR-TB will result in the unnecessary deaths of large numbers of children. Improved estimates of the incidence of TB and MDR-TB disease in children—especially in high-incidence countries—will enable improved predictions of the resources that will be required to find and treat children with TB and MDR-TB successfully.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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PANEL: RESEARCH IN CONTEXT**Systematic review**

We systematically searched the PubMed, Embase and World Health Organization regional electronic databases for primary studies and review articles published through January 12, 2012. The search terms used controlled vocabulary and free text and included combinations intended to capture reports of drug-resistant tuberculosis in children. To identify relevant articles not found in these primary electronic databases, we also reviewed the reference lists of primary studies and reviews for additional references. Studies were eligible for inclusion if they reported the proportion of children with culture-confirmed TB disease who had isolates tested for susceptibility to both isoniazid and rifampicin. We extracted characteristics of included studies which we consider informative about these studies' representativeness of children in the study base. We found no studies that attempted to synthesize publications reporting the proportion of children with TB disease who had MDR-TB nor to estimate the global incidence of MDR-TB in children.

Interpretation

Our study is the first to estimate the global and regional incidences of MDR-TB in children. We also produced new estimates of TB incidence in children that acknowledge the lower smear-positivity rates in children as compared with adults. These incidence estimates are essential to advance a better understanding of the gap between the number of children that are currently identified and treated for TB and MDR-TB and the number that require treatment. Only with such understanding can sufficient resources be allocated to diagnose and treat all children with TB and avert preventable disability and deaths.

Figure 1.
Search strategy

Figure 2. The linear relationship between the proportion of incident treatment-naïve adult TB cases with MDR-TB and the proportion of incident child TB cases with MDR-TB from extracted studies

LEGEND. Each black circle represents a study which provided data on the proportions among both adults and children. The size of the circle is proportional to the number of children in the study who had DST sufficient to diagnose MDR-TB. The red line shows the fitted linear relationship as predicted by our linear regression (which was weighted by the number of children in each study who had DST sufficient to diagnose MDR-TB). The equation shown represents the fitted linear regression with y equal to the proportion of child TB cases with MDR-TB and x equal to the proportion of adult TB cases with MDR-TB. Note that one study is excluded from the graph for visualization purposes (this study included only one child with DST and that child had MDR-TB resulting in a proportion of 1, currently off the scale of our graph). The inset shows the portion of the main plot that lies nearest to the X-Y intercept to show those data points more clearly. Note that, while they sizes of the data points in the inset remain proportional to the number of children that received DST in those studies, they are proportional relative to the other data points in the inset only and are not on the same scale as those in the main plot.

Figure 3. The relationship between the estimated percentage of TB cases that are amongst children (aged 0–14 years) and the log (base 10) estimated TB incidence per 100,000 by country/territory

Each point represents country/territory-specific data. The log (base 10) estimated TB incidence per 100,000 was as reported to the WHO for 2010. The percentage of TB cases that are amongst children was estimated as described in the methods using smear-positive reported incidence by age reported to the WHO for 2010. These were scaled up using data from previous studies to estimate the total TB incidence (smear-positive and negative) in each age group and thus the percentage of cases that were amongst children. When fitting a regression line to these data, we used simulation methods that incorporated the errors in the estimated percentage of TB cases amongst children and the TB incidence. Therefore, we generated 1000 regression lines to capture the errors in these input data (see methods for further details). The middle grey shaded area shows the region covered by the median values of the predictions from the 1000 fitted regression lines of the relationship between the percentage of TB cases that were amongst children and the log (base 10) estimated TB incidence per 100,000. The upper and lower grey shaded areas show the equivalent areas covered by the upper and lower 95% confidence limits (respectively) for the predicted values of the percentage of TB cases that were amongst children.

Table 1

Characteristics of 97 studies

Reports included	97	
Countries and territories included	60	
Year range during which data were collected	1969–2010	
Total pediatric patients with drug-susceptibility testing (DST) results for at least isoniazid and rifampicin	8382	
New (%)	2451 (29)	
Previously treated (%)	247 (3)	
Unknown/unspecified treatment history (%)	5684 (68)	
Total pediatric patients with DST-confirmed MDR-TB (%)	348 (4)	
	Number of reports (%)	Number of pediatric patients (%)
Number of pediatric patients with DST results per report		
0–10	31 (32)	139 (2)
11–50	37 (39)	717 (9)
51–100	14 (14)	1025 (12)
101–500	11 (11)	2372 (28)
>500 (max. 2,456)	4 (4)	4129 (49)
Source of data used in report		
Reported surveillance data	24 (25)	4266 (51)
Hospital records	46 (48)	2268 (27)
Laboratory records	11 (11)	1154 (14)
Representative population sample	10 (10)	144 (2)
Other	6 (6)	550 (7)
Type of laboratory used for DST		
National or supra-national reference laboratory	42 (44)	3777 (45)
Other laboratory	33 (34)	1207 (14)
Not specified	22 (23)	3398 (41)
Reports with restricted study populations *	31 (32)	514 (6)

* Includes study populations restricted to patients with pulmonary TB, smear positive TB, extrapulmonary TB, TB meningitis, HIV coinfection, no previous treatment, or failed treatment.

Table 2

Percentage of MDR-TB in children and adults in each of 97 studies

Location	Reference	Years of enrollment or surveillance	Data source	Restrictions on study population	Specimen type(s)	Children with active TB	Children with DST (% MDR)			Adults with active TB	Adults with DST (% MDR)		
							No previous treatment	Previously treated	All		No previous treatment	Previously treated	All
Argentina, Buenos Aires province	21	2002–2007	Regional surveillance	none	not specified	4276	256 (5)	27 (4)	283 (5)	26508	1616 (5)	426 (14)	2042 (7)
Australia, Queensland state	22	1990–2007	Regional surveillance	none	not specified	85	—	—	16 (6)	—	—	—	—
Austria, Vienna, Northern Austria and Norburgentl and provinces	23	1992–1993	National surveillance	none	not specified	—	—	—	14 (0)	—	—	—	Not extractable
Austria [†]	24	1995–1998	National surveillance	none	not specified	225	94 (1)	3 (0)	108 (1)	5832	2653 (0.3)	366 (2)	3451 (0.5)
Bangladesh, Greater Mymensingh District	25	1994	Representative population sample	Pulmonary smear positive	sputum	—	8 (0)	Not extractable	8 (0)*	—	421 (0.2)	Not extractable	421 (0.2)*
Bangladesh, Greater Mymensingh District [†]	26	2001	Hospital-based, comprehensive	Pulmonary smear positive	sputum	14	11 (0)	0	11 (0)	—	933 (0.5)	99 (3)	1032 (1)
Bosnia and Herzegovina [†]	27	1996–2007	Survey of pediatricians	none	sputum	714	324 (0.3)	120 (5)	444 (2)	—	—	—	—
Brazil, Rio de Janeiro	28	2004–2006	Hospital-based, comprehensive	none	not specified	—	1 (0)	0	1 (0)	—	432 (4)	156 (18)	588 (7)
Brazil, Sao Paolo [†]	29	1995–1997	Hospital-based, comprehensive	none	not specified	—	3 (0)	1 (0)	4 (0)	—	222 (2)	40 (18)	302 (6)
Brazil, Sao Paolo [†]	30	2000–2002	Hospital-based, comprehensive	Pulmonary	sputum	—	5 (40)	0	5 (40)	—	293 (0.3)	114 (17)	415 (5)
Burundi, Bujumbura [†]	31	2002–2003	Hospital-based, comprehensive	Pulmonary smear positive	sputum	17	13 (0)	0	13 (0)	—	483 (1)	69 (12)	552 (3)
Canada	32	1993–1994	Representative population sample	none	not specified	—	—	—	14 (0)	—	—	—	444 (1)
Central African Republic, Bangui	33	1998–2000	Hospital-based, comprehensive	No previous treatment	sputum, gastric aspirate	407	164 (0.6)	Excluded from study	164 (0.6)	—	—	—	—
China, Beijing	34	1996–2009	Hospital-based, comprehensive	none	not specified	—	—	—	18 (33)	—	—	—	3252 (18)
China, Shanghai	35	2000–2006	Lab-based, comprehensive	Pulmonary	sputum	—	—	—	23 (9)	—	—	—	8395 (4)
China, Hong Kong SAR [†]	36	1986–1999	Lab-based, comprehensive	none	not specified	—	428 (0.7)	1 (100)	429 (1)	—	48496 (2)	3856 (12)	52352 (3)
Colombia	37	2001–2009	National surveillance	none	sputum, gastric aspirate, BAL, CSF, lymph node, tissue, other	—	123 (7)	5 (20)	128 (7)	—	—	—	—
Cote d'Ivoire, Abidjan	38	2000–2003	Hospital-based, comprehensive	HIV co-infected	sputum, gastric aspirate, CSF, lymph node, blood, other	11	—	—	5 (40)	—	—	—	—
Denmark	39	1991–1998	National surveillance	none	not specified	—	18 (0)	Not extractable	18 (0)*	—	—	—	Not extractable

Location	Reference	Years of enrollment or surveillance	Data source	Restrictions on study population	Specimen type(s)	Children with active TB	Children with DST (% MDR)			Adults with active TB	Adults with DST (% MDR)		
							No previous treatment	Previously treated	All		No previous treatment	Previously treated	All
Denmark [†]	40	2000–2008	National surveillance	Meningitis	CSF	11	6 (0)	1 (0)	7 (0)	39	—	—	34 (3)
Dominican Republic	41	1994–1995	Representative population sample	none	sputum	—	—	—	2 (0)	—	—	—	415 (10)
Egypt, Cairo	42		Enrolled trial of diagnostic method	none	sputum, gastric aspirate, lymph node	150	—	—	72 (3)	—	—	—	—
Equatorial Guinea, five districts [†]	43	1999–2001	all TB patients in districts where testing was possible	none	sputum, gastric aspirate	24	5 (0)	0	5 (0)	509	—	—	228 (4)
Ethiopia, Addis Abbaba [†]	44	2005	Convenience sample	Pulmonary smear positive	sputum	11	9 (0)	2 (0)	11 (0)	220	179 (3)	28 (54)	207 (10)
French Guiana, Guadeloupe and Martinique [†]	45	1994–2003	Lab-based, comprehensive	none	not specified	—	—	—	16 (0)	—	—	—	558 (2)
Georgia	46	2005–2006	National surveillance	Pulmonary smear positive	sputum	—	1 (0)	0	1 (0)	—	798 (7)	515 (27)	1313 (15)
Germany	47	2003	National surveillance	none	not specified	285	—	—	97 (2)	—	—	—	—
Germany	48	2004	National surveillance	none	not specified	269	—	—	90 (2)	—	—	—	—
Greece, Heraklion [†]	49	2000–2009	Hospital-based, comprehensive	none	not specified	—	—	—	12 (0)	—	—	—	209 (0.5)
Haiti, Central department	50	1988	Hospital-based, comprehensive	none	sputum, gastric aspirate, other(s) not specified	—	7 (0)	0	12 (0)	—	210 (0.5)	39 (0)	256 (0.4)
India, Mumbai [†]	51	2007–2008	Convenience sample	Extrapulmonary	tissue, other	25	6 (0)	8 (88)	14 (50)	—	—	—	Not extractable
India, Delhi [†]	52	2003	Hospital-based, comprehensive	Extrapulmonary	tissue	15	12 (25)	0	12 (25)	20	14 (21)	0	14 (21)
India, Andhra Pradesh state [†]	53	2004–2005	Hospital-based, comprehensive	none	sputum	40	18 (0)	4 (0)	22 (0)	1275	476 (3)	103 (21)	579 (6)
India, Delhi	54	2004–2005	Hospital-based, comprehensive	Meningitis	CSF	100	—	—	22 (18)	—	—	—	—
India, Ernakulam District	55	2004	Representative population sample	No previous treatment	sputum	—	1 (0)	Excluded from study	1 (0)	—	304 (2)	Excluded from study	304 (2)
India, New Delhi	56	2000–2005	Hospital-based, comprehensive	HIV co-infected and failed treatment	gastric aspirate, CSF, lymph node	76	—	—	6 (33)	—	—	—	—
India, Chennai	57	1995–1997	Hospital-based, comprehensive	none	sputum, gastric aspirate, lymph node	201	—	—	175 (4)	—	—	—	—
India, Mumbai [†]	58	2010	Hospital-based, comprehensive	Extrapulmonary	CSF, lymph node, tissue, other	23	12 (42)	0	12 (42)	260	—	—	138 (33)
Iran, Tehran	59	2000–2003	Hospital-based, comprehensive	none	sputum, other(s) not specified	—	—	—	7 (14)	—	—	—	541 (19)
Ireland and the United Kingdom	60	2003–2005	National surveillance	none	sputum, gastric aspirate, BAL, CSF, lymph node, tissue	385	—	—	102 (2)	—	—	—	—
Italy, Palermo	61	1994–2002	Hospital-based, comprehensive	Pulmonary	sputum, gastric aspirate	62	13 (0)	0	13 (10)	—	—	—	—

Location	Reference	Years of enrollment or surveillance	Data source	Restrictions on study population	Specimen type(s)	Children with active TB	Children with DST (% MDR)			Adults with active TB	Adults with DST (% MDR)		
							No previous treatment	Previously treated	All		No previous treatment	Previously treated	All
Japan [†]	62	2002	Hospital-based, comprehensive	none	not specified	—	7 (0)	0	7 (0)	—	2698 (0.7)	417 (10)	3115 (2)
Kenya, 11 districts	63	1984	Regional surveillance	none	sputum	523	55 (0)	Not extractable	55 (0)*	1438	693 (0)	Not extractable	693 (0)*
Kenya, 22 districts	64	1995	Representative population sample	Pulmonary smear positive	sputum	—	—	—	14 (0)	—	—	—	477 (0)
Lebanon, Beirut	65	1996–1998	Hospital-based, comprehensive	none	sputum, gastric aspirate, BAL, CSF, lymph node, other	—	—	—	8 (13)	—	—	—	66 (15)
Madagascar	66	2005–2007	Representative population sample	Pulmonary smear positive	sputum	—	—	—	14 (0)	—	—	—	999 (1)
Madagascar, Antananarivo	67	1997–2000	Lab-based, comprehensive	none	not specified	—	—	—	97 (0)	—	—	—	—
Malawi, Karonga district [†]	68	1986–2010	Regional surveillance	none	sputum	761	63 (0)	6 (0)	69 (0)	—	—	—	Not extractable
Malaysia	69	2008–2009	Lab-based, comprehensive	none	sputum, BAL	—	—	—	1 (0)	—	—	—	48 (8)
Mexico, Monterrey [†]	70		Hospital-based, comprehensive	none	sputum, other(s) not specified	2	0	1 (100)	1 (100)	—	136 (7)	49 (45)	185 (17)
Mexico, Jalisco state [†]	71	1993–1999	Hospital-based, comprehensive	none	not specified	—	2 (50)	2 (0)	4 (25)	—	118 (23)	115 (53)	233 (38)
Mexico, Sinaloa state [†]	72	1997–2004	Lab-based, comprehensive	Pulmonary	sputum	233	7 (0)	0	7 (0)	5820	458 (5)	185 (48)	730 (18)
Mongolia	73	2007	Representative population sample	Pulmonary smear positive	sputum	—	10 (0)	1 (100)	11 (9)	—	640 (1)	199 (27)	839 (8)
Morocco [†]	74		Convenience sample	Pulmonary	sputum	—	—	—	3 (0)	—	—	—	196 (28)
New Zealand [†]	75	2001–2010	National surveillance	none	not specified	298	104 (0)	1 (0)	105 (0)	3108	2433 (0.7)	91 (11)	2524 (1)
Norway, Oslo	76	1998–2009	Hospital-based, comprehensive	none	sputum, gastric aspirate, BAL, CSF, lymph node, tissue, other	24	—	—	19 (0)	—	—	—	—
Pakistan	77	1990–2007	Lab-based, comprehensive	none	not specified	—	—	—	571 (22)	—	—	—	14495 (28)
Peru	78	2005–2006	Representative population sample	none	not specified	—	61 (2)	3 (33)	64 (3)	—	1748 (5)	357 (24)	2105 (8)
Poland	79	1996–1997	National surveillance	none	sputum	—	—	—	24 (0)	—	—	—	3946 (2)
Portugal, Vila Nova De Gaia [†]	80		Hospital-based, comprehensive	none	sputum, gastric aspirate, BAL, CSF, other(s) not specified	21	—	—	17 (0)	—	—	—	—
Qatar	81	1996–1998	National surveillance	none	not specified	—	—	—	3 (0)	—	—	—	403 (1)
Republic of Korea	82	1994	Representative population sample	none	sputum	—	2 (0)	Not extractable	2 (0)*	—	—	—	Not extractable
Republic of Moldova	83	1995–1999	Lab-based, comprehensive	none	not specified	—	—	—	5 (0)	—	—	—	3148 (9)
Saudi Arabia, Riyadh [†]	84	1995–2000	Hospital-based, comprehensive	none	sputum, tissue, other	—	9 (11)	1 (100)	10 (20)	—	297 (1)	11 (36)	308 (2)
Singapore [†]	85	2000–2009	National surveillance	none	not specified	200	32 (0)	1 (0)	33 (0)	18800	—	—	11138 (1)

Location	Reference	Years of enrollment or surveillance	Data source	Restrictions on study population	Specimen type(s)	Children with active TB	Children with DST (% MDR)			Adults with active TB	Adults with DST (% MDR)		
							No previous treatment	Previously treated	All		No previous treatment	Previously treated	All
South Africa, Cape Town	86	1992–1997	Hospital-based, comprehensive	HIV co-infected	gastric aspirate, CSF, other	—	—	—	9 (11)	—	—	—	—
South Africa, Cape Town	87	2000–2001	Hospital-based, comprehensive	none	sputum, gastric aspirate, BAL, CSF, lymph node	238	41 (5)	52 (12)	93 (9)	—	—	—	—
South Africa, Cape Town	88	2003–2005	Hospital-based, comprehensive	none	sputum, gastric aspirate, CSF, lymph node	—	—	—	592 (4)	—	—	—	—
South Africa, Cape Town	89	2005–2007	Hospital-based, comprehensive	none	not specified	—	—	—	285 (7)	—	—	—	—
South Africa, Cape Town	90	2006–2008	Hospital-based, comprehensive	Meningitis	gastric aspirate, CSF	98	—	—	27 (7)	—	—	—	—
South Africa, Durban	91	1996–1997	Hospital-based, comprehensive	Neonates	gastric aspirate, CSF, other	—	11 (0)	0	11 (0)	—	—	—	—
South Africa, Johannesburg	92	2008	Hospital-based, comprehensive	none	sputum, gastric aspirate, CSF, blood, tissue, other	1317	—	—	148 (9)	—	—	—	—
Spain, Barcelona	93	1995–1997	Hospital-based, comprehensive	none	not specified	—	68 (0)	4 (0)	72 (0)	—	1467 (1)	210 (10)	1677 (2)
Spain, Barcelona [†]	94	2003–2004	Regional surveillance	none	sputum, other(s) not specified	52	15 (0)	0	15 (0)	840	469 (1)	33 (6)	502 (1)
Spain, Madrid	95	1978–2007	Hospital-based, comprehensive	Pulmonary	gastric aspirate	414	—	—	48 (4)	—	—	—	—
Spain, Castellon province	96	1992–1998	Regional surveillance	none	not specified	—	—	—	17 (0)	—	—	—	515 (1)
Spain, Santiago de Compostela [†]	97	1996–2006	Hospital-based, comprehensive	DOTS patients	not specified	186	2 (0)	0	2 (0)	2279	135 (3)	60 (10)	195 (5)
Sweden, Stockholm [†]	98	2000–2009	Hospital-based, comprehensive	none	not specified	97	39 (10)	1 (0)	40 (0)	—	—	—	—
Taiwan, Taipei	99	1998–2002	Hospital-based, comprehensive	none	sputum, gastric aspirate, BAL, CSF, lymph node, blood, tissue, other	—	—	—	9 (0)	—	—	—	Not extractable
Taiwan, Taoyuan [†]	100	1998–2002	Hospital-based, comprehensive	none	not specified	59	40 (0)	0	40 (0)	—	—	—	—
Taiwan, Changhua [†]	101	2001–2002	Hospital-based, comprehensive	none	not specified	6	2 (0)	0	2 (0)	656	454 (2)	57 (16)	511 (4)
Thailand, 4 provinces	102	2004–2006	Regional surveillance	none	sputum, gastric aspirate	279	—	—	33 (3)	—	—	—	—
Thailand [†]	103	2001–2009	Lab-based, comprehensive	Pulmonary smear positive	sputum	—	—	—	1 (100)	—	—	—	14461 (5)
Thailand, Chiang Rai province [†]	104	1996–1998	Hospital-based, comprehensive	Pulmonary smear positive	sputum	34	17 (18)	2 (0)	19 (16)	1590	1077 (6)	151 (34)	1228 (10)
Turkey, Malatya	105	2000–2007	Hospital-based, comprehensive	none	not specified	—	—	—	51 (0)	—	—	—	288 (6)
Turkey, Ankara	106	1975–1995	Hospital-based, comprehensive	none	sputum, CSF, lymph node, tissue, other	—	60 (0)	Not extractable	60 (0)*	—	—	—	—
Turkey, Ankara [†]	107	1998–2001	Lab-based, comprehensive	none	sputum, gastric aspirate, CSF, tissue, other	—	—	—	1 (0)	—	—	—	469 (2)

Location	Reference	Years of enrollment or surveillance	Data source	Restrictions on study population	Specimen type(s)	Children with active TB	Children with DST (% MDR)			Adults with active TB	Adults with DST (% MDR)		
							No previous treatment	Previously treated	All		No previous treatment	Previously treated	All
Turkmenistan and Uzbekistan, Karakalpakstan and Dashoguz provinces [†]	108	2001–2002	Lab-based, comprehensive	Pulmonary smear positive	sputum	—	3 (0)	0	3 (0)	—	208 (9)	205 (30)	413 (19)
United Kingdom	109	1993–1999	National surveillance	none	sputum, other(s) not specified	—	—	—	510 (1)	—	—	—	23778 (1)
United Kingdom, London	110	2003	Regional surveillance	none	not specified	92	—	—	29 (7)	1840	—	—	1088 (6)
United States of America	111	1991	National surveillance	none	not specified	—	—	—	53 (2)	—	—	—	3154 (3)
United States of America	112	1993–2001	National surveillance	none	sputum, gastric aspirate	11480	—	—	2456 (2)	169587	—	—	125836 (1)
United States of America, Miami	113	1981–1990	Hospital-based, comprehensive	HIV co-infected	gastric aspirate, BAL, CSF, lymph node, blood, other	9	—	—	9 (33)	—	—	—	—
United States of America, New York City	114	1969–1972	Hospital-based, comprehensive	none	not specified	169	79 (0)	0	79 (0)	—	—	—	—
United States of America, New York City	115	1973–1980	Hospital-based, comprehensive	none	gastric aspirate	—	72 (1)	0	72 (1)	—	—	—	—
United States of America, New York City	116	1981–1984	Hospital-based, comprehensive	none	not specified	68	—	—	19 (0)	—	—	—	—
Yemen	117	2004	Representative population sample	Pulmonary smear positive	sputum	—	14 (7)	0	14 (7)	—	493 (3)	0	493 (3)

[†] (indicates unpublished data received from authors.)

Table 3

Estimated numbers of incident cases of TB disease and MDR-TB disease in children by region, 2010.

WHO region *	Estimated number of child TB cases			Estimated number of child MDR-TB cases		
	Estimate	95% Lower Confidence Bound	95% Upper Confidence Bound	Estimate	95% Lower Confidence Bound	95% Upper Confidence Bound
African region	279,825	250,187	308,717	4,736	2,829	6,848
Eastern Mediterranean region	71,162	60,320	83,193	2,417	339	5,087
European region	43,224	39,572	47,242	5,645	4,206	7,463
Region of the Americas	27,199	24,935	29,635	606	374	854
Southeast Asia region	397,040	350,615	447,474	10,000	4,993	15,568
Western Pacific region	179,515	159,246	202,626	8,349	5,639	11,610
Total	999,792	937,877	1,055,414	31,948	25,594	38,663

* These regions are aligned with those as defined by the World Health Organization (WHO)