Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates

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See Comment page 1530

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Summary

Background Multidrug-resistant tuberculosis threatens to reverse recent reductions in global tuberculosis incidence. Although children younger than 15 years constitute more than 25% of the worldwide population, the global incidence of multidrug-resistant tuberculosis disease in children has never been quantified. We aimed to estimate the regional and global annual incidence of multidrug-resistant tuberculosis in children.

Methods We developed two models: one to estimate the setting-specific risk of multidrug-resistant tuberculosis among child cases of tuberculosis, and a second to estimate the setting-specific incidence of tuberculosis disease in children. The model for risk of multidrug-resistant tuberculosis among children with tuberculosis needed a systematic literature review. We multiplied the setting-specific estimates of multidrug-resistant tuberculosis risk and tuberculosis incidence to estimate regional and global incidence of multidrug-resistant tuberculosis disease in children in 2010.

Findings We identified 3403 papers, of which 97 studies met inclusion criteria for the systematic review of risk of multidrug-resistant tuberculosis. 31 studies reported the risk of multidrug-resistant tuberculosis in both children and treatment-naive adults with tuberculosis and were used for evaluation of the linear association between multidrug-resistant disease risk in these two patient groups. We identified that the setting-specific risk of multidrug-resistant tuberculosis was nearly identical in children and treatment-naive adults with tuberculosis, consistent with the assertion that multidrug-resistant disease in both groups reflects the local risk of transmitted multidrug-resistant tuberculosis. After application of these calculated risks, we estimated that around 999 792 (95% CI 937 877–1 055 414) children developed tuberculosis disease in 2010, of whom 31 948 (25 594–38 663) had multidrug-resistant disease.

Interpretation Our estimates underscore that many cases of tuberculosis and multidrug-resistant tuberculosis disease are not being detected in children. Future estimates can be refined as more and better tuberculosis data and new diagnostic instruments become available.

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Introduction

Multidrug-resistant tuberculosis is tuberculosis disease caused by strains of *Mycobacterium tuberculosis* that are resistant to isoniazid and rifampicin, the backbone of the present first-line treatment regimen.[1] The emergence of *M tuberculosis* strains resistant to first-line and second-line drugs,[2–5] and the restricted access to second-line drugs for appropriate treatment, have driven calls for urgent action.[6–9]

Reliable estimates of the incidence of multidrug-resistant tuberculosis 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 it is challenging to estimate the incidence of drug-resistant tuberculosis because of restricted access to drug-susceptibility testing,[10] data emerging from recent drug-resistance surveys and surveillance have suggested that the global incidence of multidrug-resistant tuberculosis exceeds half a million new cases every year.[1] Despite children younger than 15 years constituting more than a quarter of the global population and 40% of the population of low-income countries,[11] the incidence of multidrug-resistant tuberculosis in children has never been estimated.

Bacteriological confirmation of drug-resistant tuberculosis 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] As a result, a high proportion of child tuberculosis cases are diagnosed on the basis of clinical criteria without microbiological confirmation. This absence of microbiological confirmation restricts both the ability to directly measure the incidence of tuberculosis in children[12] and to routinely assess the risk of multidrug-resistant tuberculosis among these cases.[14] This challenge notwithstanding, estimates of the incidence of multidrug-resistant tuberculosis 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 tuberculosis drugs. We aim to estimate the regional and global incidence of multidrug-resistant tuberculosis disease in children.

Methods

Study design

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

Search strategy and selection criteria

We systematically searched PubMed, Embase, and LILACS electronic databases for primary articles and reviews published up to Jan 12, 2012. The search terms used controlled vocabulary and free text, and included combinations intended to capture reports of drug-resistant tuberculosis (eg, "resist*" and "tuberculosis", "drug-resistant tuberculosis") in children (eg, "infan*", "adolescen*", and "child*"). We contacted authors for additional information if the report met all of the following criteria: the drug-susceptibility testing results were not disaggregated by age group (0–14 and ≥15 years), published since 2000, and published in English or Spanish. We also reviewed the reference lists of primary articles and reviews for additional references and searched the regional WHO databases for the Western Pacific, African, South-East Asia, and Eastern Mediterranean regions. 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 tuberculosis disease who had isolates tested for susceptibility to both isoniazid and rifampicin.

The appendix shows the complete search strategy, including detailed inclusion and exclusion criteria. We aimed to identify studies reporting the number of children with an isolate showing resistance to both isoniazid and rifampicin (multidrug-resistant tuberculosis) on drug-susceptibility testing as a proportion

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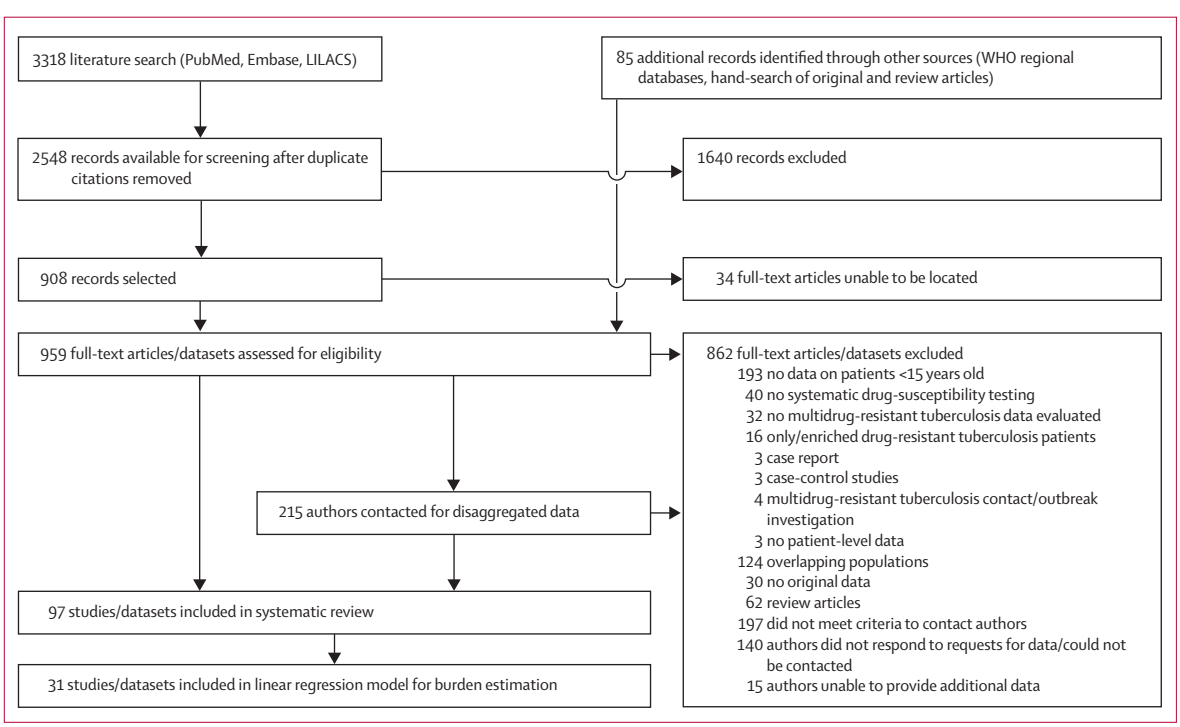

Figure 1: **Search strategy**

of all culture-confirmed cases of child tuberculosis that received sufficient drug-susceptibility testing to diagnose multidrug-resistant tuberculosis. This measure provides an estimate of risk of multidrug-resistant tuberculosis among child tuberculosis cases. We reviewed all published studies that reported this measure in a patient population that we expected would be representative of risk of multidrug-resistant tuberculosis among cases of child tuberculosis in the study base. Accordingly, we excluded reports in which the inclusion of patients could have been related to drug resistance (eg, clinical trials, case-control studies, targeted testing). We also specifically excluded reports from outbreak or contact investigations, in which risk of resistant disease is expected to be highly correlated and less likely to represent risk in the study base of all children with tuberculosis disease. We did not restrict the language of the publications reviewed.

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 2010.

For each study, we extracted data about the number of children with tuberculosis disease who received drug-susceptibility testing for isoniazid and rifampicin, and the proportion of those with isolates resistant to both isoniazid and rifampicin (multidrug-resistant tuberculosis). Where possible, we also extracted the same information for adults. Additional data extracted included location and enrolment years of each study.

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

	Reports	Children
Total child patients with drug-susceptibility testing results for at least isoniazid and rifampicin	97	8382
New	..	2451 (29%)
Previously treated	..	247 (3%)
Unknown/unspecified treatment history	..	5684 (68%)
Total child patients with drug-susceptibility testing-confirmed multidrug-resistant tuberculosis	..	348 (4%)
Number of child patients with drug-susceptibility testing results per report		
0–10	31 (32%)	139 (2%)
11–50	37 (38%)	717 (9%)
51–100	14 (14%)	1025 (12%)
101–500	11 (11%)	2372 (28%)
>500 (maximum 2456)	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 drug-susceptibility testing		
National or supranational reference laboratory	42 (43%)	3777 (45%)
Other laboratory	33 (34%)	1207 (14%)
Not specified	22 (23%)	3398 (41%)
Reports with restricted study populations*	31 (32%)	514 (6%)

Data are n (%). Studies included 60 countries and territories, with data collected between 1969 and 2010. *Includes study populations restricted to patients with pulmonary tuberculosis, smear-positive tuberculosis, extrapulmonary tuberculosis, tuberculosis meningitis, HIV co-infection, no previous treatment, or failed treatment.

Table 1: **Characteristics of 97 studies**

Statistical analysis

Using included studies for which we were able to extract the proportion of multidrug-resistant tuberculosis cases for both children and treatment-naive adults, we estimated the relation between the risk of multidrug-resistant tuberculosis in these two groups. We constructed a linear regression model with the proportion of child tuberculosis cases with multidrug-resistant tuberculosis as the dependent variable and the proportion of treatment-naive adult tuberculosis cases with multidrug-resistant tuberculosis as the explanatory variable. We weighted the regression by the number of child cases in each study that were tested for multidrug-resistant tuberculosis. Because there were several studies based in some countries, we included a random effect for country to ensure the variance around the parameter estimate was not inappropriately small because of absence of independence between studies. This parameter estimate thus quantified the relation between the proportion of treatment-naive adult incident tuberculosis cases with multidrug-resistant disease and the proportion of incident child tuberculosis cases with multidrug-resistant disease.

We applied this relation to the 2008 countrywide estimates of the proportion of treatment-naive adult incident tuberculosis cases with multidrug-resistant disease from WHO[15] to obtain country-level estimates of the proportion of incident child tuberculosis cases with multidrug-resistant disease.

Notification data under-report the incidence of tuberculosis 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 tuberculosis cases. We assumed that the proportion of incident new tuberculosis cases that are smear-positive varied by age (consistent with data and the approach of Murray and colleagues;[16] appendix). For each age group and for all countries reporting at least one child tuberculosis case, we used the mean of two previously reported proportions of age-specific risk of smear-positivity[16,17] to estimate the age-specific and country-specific total number of new tuberculosis cases. Because data for previously treated cases are not reported to WHO by age group, we assumed that all previously treated cases were in patients older than 15 years and adjusted

the notification data by the mean of the proportions of smear-positivity risk for all age groups older than 15 years from the aforementioned studies.[16,17] We divided the estimated number of new child tuberculosis cases by the total estimated number of tuberculosis cases (new and previously treated) to estimate the country-specific proportion of cases occurring in children. We used data from the 151 countries or territories that provided smear-positive notification data (age-disaggregated for new cases) and reported at least one child case of smear-positive tuberculosis.

Because some countries did not report age-disaggregated case notifications to WHO, we fitted a logistic regression with the estimated proportion of tuberculosis cases occurring in children (estimated as described above) as the dependent variable and the log (base 10) of the estimated tuberculosis incidence per 100 000 population as the explanatory variable. This relation between expected proportion of all tuberculosis cases that occur in children and overall tuberculosis incidence was first described by Peter Donald[18] in 2002. Estimation of regression coefficients allowed us to estimate the proportion of tuberculosis cases occurring in children for all countries. We then multiplied these proportions by the total estimated tuberculosis incidence per 100 000 in each country in 2010[1] and by the population in each country[19] to obtain the country-specific estimated number of child tuberculosis cases.

Finally, to estimate the incidence of child multidrug-resistant tuberculosis, we multiplied our estimates of the country-specific risk of multidrug-resistant tuberculosis among child tuberculosis cases by the country-specific number of child tuberculosis cases. We summed these country-specific multidrug-resistant tuberculosis incidences to provide a total estimate of child multidrug-resistant tuberculosis incidence by WHO regional groupings and worldwide in 2010. We used simulation methods to generate 95% CIs around both the child tuberculosis and multidrug-resistant tuberculosis incidence estimates (appendix). We did sensitivity analyses to assess whether our estimation method was likely to introduce bias (appendix).

Role of the funding source

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the 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

Of 3403 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 8382 children with tuberculosis who had drug-susceptibility testing, of whom 348 (4%) had multidrug-resistant tuberculosis. Studies were classified according to their setting, data source, restrictions on study population, and type of laboratory where drug-susceptibility testing was done (table 1). Appendix shows the detailed study characteristics and results, with full references. The appendix also shows the timeline, catchment areas, and data quality of included studies.

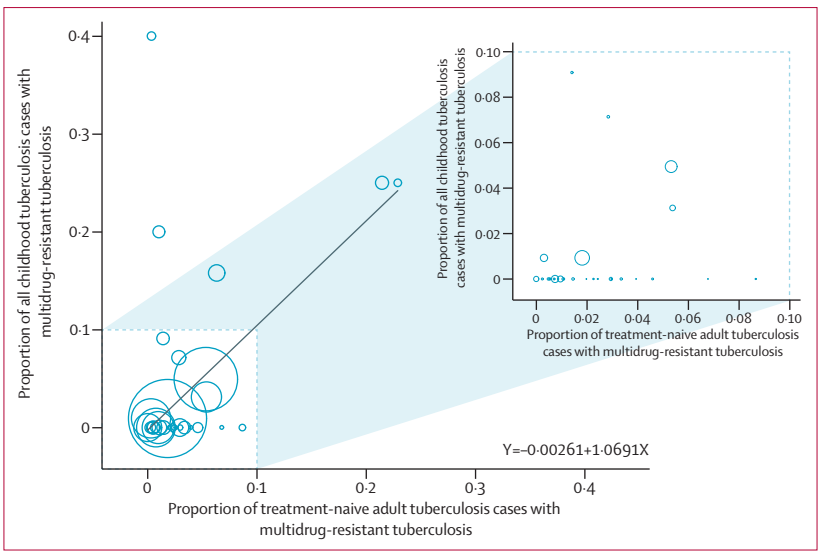

Figure 2: **Linear relation between the proportion of incident treatment-naive adult tuberculosis cases with multidrug-resistant tuberculosis and the proportion of incident child tuberculosis cases with multidrug-resistant tuberculosis from extracted studies**

Each circle represents a study that provided data for the proportion in both adults and children. The size of the circle is proportional to the number of children in the study who had drug-susceptibility testing sufficient to diagnose multidrug-resistant tuberculosis. The solid line shows the fitted linear relation as predicted by our linear regression (which was weighted by the number of children in each study who had drug-susceptibility testing sufficient to diagnose multidrug-resistant tuberculosis). The equation shown represents the fitted linear regression with y equal to the proportion of child tuberculosis cases with multidrug-resistant tuberculosis and x equal to the proportion of adult tuberculosis cases with multidrug-resistant tuberculosis. Note that one study is excluded from the graph for visualisation purposes (this study included only one child with drug-susceptibility testing and that child had multidrug-resistant tuberculosis resulting in a proportion of 1—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 datapoints more clearly. Note that, although the sizes of the datapoints in the inset are proportional to the number of children that received drug-susceptibility testing in those studies, they are proportional relative to the other datapoints in the inset only and are not on the same scale as those in the main plot.

Results of drug-susceptibility testing for both treatment-naive adults and children were 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. In 38 (39%) reports, drug-susceptibility testing data for children only could be extracted.

From studies for which sufficient data were available, we estimated that the relation between the proportion of incident child tuberculosis cases with multidrug-resistant disease (Y) and the proportion of incident treatment-naive adult tuberculosis cases with multidrug-resistant disease (X) was Y=–0·00261+1·0691X (95% CI for the X coefficient 0·53–1·61). Figure 2 shows the relation between the proportion of incident treatment-naive adult tuberculosis cases with multidrug-resistant

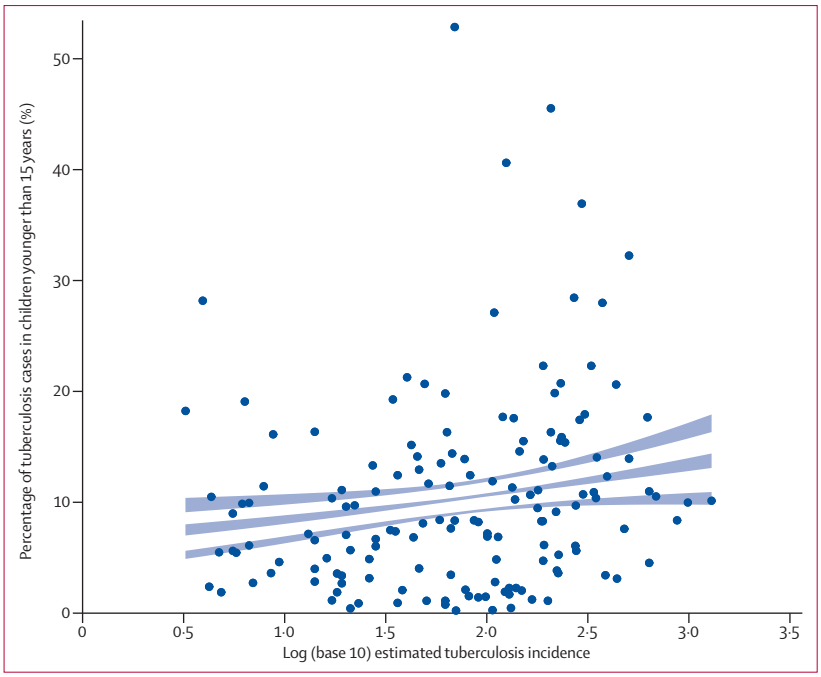

Figure 3: **Relation between the estimated percentage of tuberculosis cases in children (aged 0–14 years) and the log (base 10) estimated tuberculosis incidence per 100 000 by country or territory**

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

	Estimated number of child tuberculosis cases (95% CI)	Estimated number of child multidrug-resistant tuberculosis cases (95% CI)
African region	279 825 (250 187–308 717)	4736 (2829–6848)
Eastern Mediterranean region	71 162 (60 320–83 193)	2417 (339–5087)
European region	43 224 (39 572–47 242)	5645 (4206–7463)
Region of the Americas	27 199 (24 935–29 635)	606 (374–854)
South-East Asia region	397 040 (350 615–447 474)	10 000 (4993–15 568)
Western Pacific region	179 515 (159 246–202 626)	8349 (5639–11 610)
Total	999 792 (937 877–1 055 414)	31 948 (25 594–38 663)

These regions correspond to those defined by WHO.

Table 2: **Estimated number of incident cases of tuberculosis disease and multidrug-resistant tuberculosis disease in children by WHO region, 2010**

disease and the proportion of incident child tuberculosis cases with multidrug-resistant disease in the 31 studies that reported both proportions. In a sensitivity analysis that excluded the two outlying points with proportion of treatment-naive adult cases of multidrug-resistant tuberculosis of roughly 0·2 (figure 2), we found similar results (estimated regression line 0·000093+0·9514X).

Figure 3 shows the relation between the proportion of tuberculosis cases in children (0–14 years) and the log (base 10) of the estimated tuberculosis incidence per 100 000 by country or territory. Table 2 summarises the regional and worldwide estimates of the incidence of child tuberculosis and multidrug-resistant tuberculosis in 2010. We estimated that there were 999 792 (95% CI 937 877–1 055 414) incident child tuberculosis cases in 2010. Globally, we estimated that 31 948 (95% CI 25 594–38 663) children developed multidrug-resistant tuberculosis disease in 2010.

40% (397 040) of estimated child tuberculosis cases were in the WHO South-East Asia region, 28% (279 825) in the WHO African region, and 18% (179 515) in the WHO Western Pacific region. The largest regional incidence of multidrug-resistant tuberculosis in children was in the WHO South-East Asia region, where around 10 000 children (a third of global estimated cases) were estimated to have developed multidrug-resistant tuberculosis disease in 2010. In the same year, the WHO Western Pacific region is estimated to have had more than 8000 child cases of multidrug-resistant tuberculosis (more than a quarter of global estimated cases), the WHO European region more than 5000 cases, and the WHO African region more than 4000 cases.

Sensitivity analyses showed that our estimation method did not introduce substantial bias (appendix).

Discussion

Our estimate of multidrug-resistant tuberculosis incidence in children provides an initial assessment of the vast unmet need for diagnosis and treatment annually (panel). Notably, our estimate of total incident child cases of all forms of tuberculosis is twice that estimated by WHO for 2011 and three times the number of child tuberculosis cases notified globally every year.[20] However, no other estimates of multidrug-resistant tuberculosis incidence exist specifically for children. A recent systematic review of treatment outcomes in paediatric multidrug-resistant tuberculosis identified reports spanning the past decade with only 315 children treated for multidrug-resistant tuberculosis,[14] whereas the systematic review of 40 years of literature that we report here only identified another 348 children with confirmed multidrug-resistant tuberculosis. Thus, the total cases of child multidrug-resistant tuberculosis that have ever been reported in the literature is only 2% of those that we estimate occurred globally in 2010.

Several factors might explain the sizeable underestimate of the incidence of tuberculosis disease in children. A key factor is that incidence estimates often have as their starting point the number of child tuberculosis cases reported to a government tuberculosis agency. Yet in most countries, these reported cases represent only the tip of the iceberg of child tuberculosis cases; children are

more likely than adults to have paucibacillary disease and young children (<5 years old) cannot expectorate sputum, preventing microbiological diagnosis. Young children have the highest risks of severe disease and death once infected, but are the least likely to be confirmed bacteriologically as tuberculosis cases. Furthermore, all available microbiological tests have very low sensitivity for child tuberculosis disease: under programme conditions, the sensitivity of sputum smear microscopy and of sputum cultures is less than 5% and 15%, respectively. In most of the world, however, tuberculosis diagnosis relies heavily on smear microscopy, and most or all reported child tuberculosis cases are smear-positive, underlining the vast gap between true incidence and reported cases.

The potential reporting gap of child tuberculosis cases is further emphasised by post-mortem examinations and by the yield of intensified case-detection initiatives in private clinics.[21,22] Irrespective 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 tuberculosis drugs.[23] Even novel diagnostic tests about which much enthusiasm abounds are unlikely to improve child case detection owing to their very low sensitivity (<15% of those diagnosed by clinical case definitions).[24] All these factors together suggest an enormous need to improve the detection of child tuberculosis cases; increased access to care, heightened clinical suspicion of tuberculosis, and more sensitive diagnostic instruments are likely to be needed to address this gap.

Our approach has limitations. First, our quantification of the relation between the multidrug-resistant tuberculosis risk among children with tuberculosis with that of treatment-naive adults with tuberculosis assumes that the relation is generalisable to settings not represented in the systematic review. Despite potential issues with generalisability, it is reassuring that the relation we estimated is consistent with that recently reported by Zignol and colleagues[25] based on surveillance data reported directly to WHO. We also note that 14 (45%) of 31 studies we analysed excluded children with extrapulmonary disease, who constitute a large proportion of the youngest children with tuberculosis disease. However, Zignol and colleagues'[25] analysis found that the risk of multidrug-resistant tuberculosis is similar between children younger than 5 years and aged 5–14 years old, suggesting that this limitation might not undermine our estimates.

Second, our approach for estimating tuberculosis incidence in children used age-specific, smear-positive tuberculosis notification data reported to the WHO[1] and adjusted these notification data using expected age-specific proportions of tuberculosis cases that are smear-positive, from previous studies.[16,17] The implicit assumption that the results from the previous studies are generalisable to other settings is supported by results from more recent studies from around the world.[26–30] 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 tuberculosis cases that occur among children will remain unbiased. We also assume that all children with tuberculosis have never previously been treated for tuberculosis, an assumption that should be robust in most settings. Additionally, we assume that an insignificant fraction of tuberculosis cases in children are currently prevented by the treatment of latent infection, because the use of preventive therapy in children has only been used widely in high-resource, low-incidence settings.[31]

The relation we estimate between tuberculosis incidence and the fraction of all cases that occur in children was based on that described by Peter Donald[18] using a different set of studies. Our decision to incorporate this relation was based on our understanding of the epidemiology of infectious disease: first, 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 second, 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. Characterisation of the relation between tuberculosis incidence and the fraction of all cases that

Panel: Research in context

Systematic review

We systematically searched PubMed, Embase, LILACS and WHO regional electronic databases for primary studies and review articles published up to Jan 12, 2012. The search terms used controlled vocabulary and free text and included combinations intended to capture reports of drug-resistant tuberculosis (eg, "resist*" and "tuberculosis", "drug-resistant tuberculosis") in children (eg, "infan*", "adolescen*", and "child*"). To identify relevant articles not identified 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 tuberculosis 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 did not find any studies that attempted to synthesise publications reporting the proportion of children with tuberculosis disease who had multidrug-resistant tuberculosis nor to estimate the global incidence of multidrug-resistant tuberculosis in children. We did not restrict the language of the publications reviewed.

Interpretation

Our study is the first to estimate the global and regional incidences of multidrug-resistant tuberculosis in children. We also produced new estimates of tuberculosis incidence in children that acknowledge the lower smear-positivity rates in children than in adults. These incidence estimates are essential to improve understanding of the gap between the number of children that are identified and treated for tuberculosis and multidrug-resistant tuberculosis and the number that need treatment. Only with such understanding can sufficient resources be allocated to diagnose and treat all children with tuberculosis and avert preventable disability and deaths.

occur in children is dependent on data from a small number of studies. Improved estimates of the incidence of childhood tuberculosis will be possible as more countries report age-disaggregated data and use diagnostic tests that are more sensitive for the detection of tuberculosis disease in 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 WHO[15]—for example, for tuberculosis incidence per 100 000 and for proportions of tuberculosis cases that have multidrug-resistant tuberculosis for which drug resistance surveys had not been done. If these modelled estimates are systematically biased, these errors will be propagated in our estimates of both tuberculosis and multidrug-resistant tuberculosis incidence. Therefore, although 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, the true numbers of child cases could well fall outside our reported confidence limits.

We propose that our estimate provides an important starting place for documenting the incidence of multidrug-resistant tuberculosis in children and that our method should motivate further discussions on statistical and mathematical techniques that might improve the precision of these estimates. More direct approaches for measurement of multidrug-resistant tuberculosis risk in children and tuberculosis incidence in children will help to reduce uncertainty about multidrug-resistant tuberculosis incidence in children, and, more importantly, will allow the delivery of appropriate treatment. New methods for diagnosing tuberculosis disease and determining drug resistance are becoming available[32] and, if their use can be scaled up to improve routine diagnosis of tuberculosis in children, future estimates of multidrug-resistant tuberculosis in children can be based on more robust evidence.

Our estimate of tuberculosis incidence in children is substantially higher than 2011 WHO estimates.[20] We used a different approach from that used by WHO: we explicitly acknowledged that case detection in children is lower than that in adults because of difficulty in attaining microbiological confirmation, and on this basis estimated the proportions of all tuberculosis cases that occurred in children. We note that our estimates of child tuberculosis incidence are similar to previously published estimates of roughly 1·3 million cases in 1989[33] and nearly 900 000 cases in 2000.[34]

We estimate that each year there is a vast unmet need for treatment of both tuberculosis and multidrug-resistant tuberculosis 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 tuberculosis and multidrug-resistant tuberculosis in children, including systematic work to gather more and better empirical data that can be used to estimate disease incidence. Treatment for children with multidrug-resistant tuberculosis 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 tuberculosis and multidrug-resistant tuberculosis will result in the unnecessary deaths of large numbers of children. Improved estimates of the incidence of tuberculosis and multidrug-resistant tuberculosis disease in children—especially in high-incidence countries—will enable improved predictions of the resources that will be needed to find and treat children with tuberculosis and multidrug-resistant tuberculosis successfully.

Contributors

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 did analyses. HEJ, AWT, CMY, JBP, SK, CMP-V, 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.

Declaration of interests

We declare that we have no competing interests.

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