Global burden of drug-resistant tuberculosis in children: a mathematical modelling study

Peter J Dodd, Charalambos Sismanidis, James A Seddon

Summary

Background After infection with *Mycobacterium tuberculosis*, children are at an increased risk of progression to tuberculosis disease; a condition that can be challenging to diagnose. New estimation approaches for children have highlighted the gap between incidence and notifications of *M tuberculosis*, and suggest there are more cases of isoniazid-resistant and multidrug-resistant (MDR) disease than are identified. No work has yet quantified the burden of drug-resistant infection, or accounted for other types of drug resistance or sampling uncertainty.

Methods We combined a mathematical model of tuberculosis in children with an analysis of drug-resistance patterns to produce country-level, regional, and global estimates of drug-resistant infection and disease. We determined drug resistance using data from the Global Project on Antituberculosis Drug Resistance Surveillance at WHO, from surveys and surveillance reported between 1988 and 2014. We combined 1000 sampled proportions for each country from a Bayesian approach with 10 000 sampled country estimates of tuberculosis disease incidence and *M tuberculosis* infection prevalence. We estimated the proportions of tuberculosis cases at a country level with isoniazid monoresistance, rifampicin monoresistance, multidrug resistance (MDR), fluoroquinolone-resistant multidrug resistance, second-line injectable-resistant multidrug resistance, and extensive multidrug resistance with resistance to both a fluoroquinolone and a second-line injectable (XDR).

Findings We estimated that 850 000 children developed tuberculosis in 2014; 58 000 with isoniazid-monoresistant tuberculosis, 25 000 with MDR tuberculosis, and 1200 with XDR tuberculosis. We estimate 67 million children are infected with *M tuberculosis*; 5 million with isoniazid monoresistance, 2 million with MDR, and 100 000 with XDR. Africa and southeast Asia have the highest numbers of children with tuberculosis, but the WHO Eastern Mediterranean region, European region, and Western Pacific region also contribute substantially to the burden of drug-resistant tuberculosis because of their much higher proportions of resistance.

Interpretation Far more drug-resistant tuberculosis occurs in children than is diagnosed, and there is a large pool of drug-resistant infection. This finding has implications for approaches to empirical treatment and preventive therapy in some regions of the world.

Funding UNITAID.

Lancet Infect Dis 2016

Published Online
June 21, 2016
http://dx.doi.org/10.1016/S1473-3099(16)30132-3

See Online/Comment
http://dx.doi.org/10.1016/S1473-3099(16)30164-5

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Introduction

Tuberculosis in children is increasingly being recognised as a significant public health problem, and an important component of the total global burden of tuberculosis.[1] New methodological developments for estimating the burden of tuberculosis in children have been adopted in the estimation process used by the Global Tuberculosis Programme (GTB) at WHO.[2,3] The GTB estimated that in 2014, 1 million children developed tuberculosis disease.[4] Understanding the burden is central to resource allocation, estimation of market size for potential drug, diagnostic, or vaccine development, a tool to enable assessment of control programmes, and for advocacy.

After infection with *Mycobacterium tuberculosis*, young children are at particularly high risk of progressing to tuberculosis disease. They are also more likely to develop severe forms of disease such as tuberculous meningitis and disseminated tuberculosis.[5,6] WHO guidance suggests use of isoniazid preventive therapy in children younger than 5 years who have been exposed to tuberculosis.[7] Isoniazid preventive therapy has been shown to reduce the risk of progression from tuberculosis infection to tuberculosis disease by around 60% in HIV-uninfected people (including children),[8] and similar reductions have been seen in children with HIV infection.[9] Without treatment, tuberculosis disease carries a substantial risk of death in children, but if diagnosed and treated, outcomes are excellent (unpublished data).

Antituberculosis drug resistance is frequently divided into drug-susceptible tuberculosis and multidrug-resistant (MDR) tuberculosis. A definition of drug-susceptible tuberculosis suggests that the organism is susceptible to the two most effective first-line medications (isoniazid and rifampicin), whereas MDR tuberculosis is defined as disease caused by *M tuberculosis* that is resistant to both isoniazid and rifampicin. This division has programmatic motivations,

Research in context

Evidence before this study

We searched PubMed on April 3, 2016, for articles providing any estimate for the global burden of drug-resistant tuberculosis in children, looking for the following search terms in the title or abstract with no date or language restrictions: "(TB OR tuberc*) AND (child*OR p*ediatr*) AND incidence AND resistan*". We identified 454 articles, two of which presented global estimates of drug-resistant tuberculosis disease incidence in children; both published in 2010. Additionally, we identified other articles that provided estimates for all tuberculosis in children, and separately examined a systematic review and meta-analysis that had sought to find treatment outcomes in children with multidrug-resistant tuberculosis (this analysis identified only 315 cases, of which 82% were treated successfully). No studies had attempted to quantify the global burden of drug-resistant tuberculosis infection in children.

Added value of this study

We have presented a new approach to determining the proportions of tuberculosis drug resistance in each country of the world, incorporating sampling uncertainty. We report the first global mechanistic model of tuberculosis disease in children, estimating around 850 000 incident cases for 2014 (uncertainty overlapping with a previous estimate). By combining these results with our analysis of drug-resistance patterns, we obtained the first incidence estimates of paediatric rifampicin monoresistant tuberculosis, multidrug-resistant tuberculosis with additional resistance to the fluoroquinolones or second-line injectable medications, and extensively drug-resistant tuberculosis. By comparing our results against previous country-level estimates, we were able to identify priority countries for attention by refining paediatric tuberculosis estimates. We have also presented the first estimates of the prevalence of tuberculosis infection by resistance type in children.

Implications of all the available evidence

Vastly more drug-resistant tuberculosis disease exists in children than is currently diagnosed, with the number of reported cases of multidrug-resistant tuberculosis in the scientific literature dwarfed by our estimate of 25 000 global cases annually. The pool of latent tuberculosis infections with drug-resistant strains is much larger than the number of incident cases of disease, with around 5 million children infected with isoniazid-monoresistant organisms and 2 million infected with multidrug-resistant organisms. This finding has substantial implications for the design of empirical regimens for disease treatment and for preventive therapy, especially in the era of the GeneXpert diagnostic test roll-out. A better understanding of the burden of tuberculosis in children is especially needed in China, India, and Russia to improve estimates of global burden.

because patients with strains that are resistant to only isoniazid can be treated largely successfully with standard first-line therapy, whereas those with MDR tuberculosis cannot. However, the importance of isoniazid-monoresistant tuberculosis is increasingly recognised. First, MDR strains have normally acquired resistance to isoniazid first and then resistance to rifampicin, in effect making isoniazid-monoresistant tuberculosis the usual gateway to MDR disease. Second, individuals with asymptomatic isoniazid-monoresistant tuberculosis infection are unlikely to respond to isoniazid preventive therapy. In addition to the emerging recognition of the importance of isoniazid-monoresistant tuberculosis, a more comprehensive approach to second-line drug resistance is required. The most important drug classes for treating MDR tuberculosis are the fluoroquinolones and the second-line injectable medications; resistance to these drugs can influence MDR tuberculosis treatment outcomes.

Children are increasingly being identified, diagnosed, and started on treatment for drug-resistant-tuberculosis either when drug-resistant-tuberculosis is confirmed in an isolate from the child or when a child develops clinical disease in conjunction with exposure to an individual who has drug-resistant-tuberculosis.[10] Additionally, to reduce the burden of tuberculosis it is necessary to identify and treat infected patients before they become unwell.[11] Children with drug-resistant tuberculosis infection are a reservoir from whom future cases will develop, and children exposed to drug-resistant tuberculosis are at times treated with non-standardised preventive therapy.[12] The treatment of drug-resistant tuberculosis infection is usually directed against the drug susceptibility test pattern of the identified source case because child contacts show high concordance with the source case if they do progress to disease.[13,14]

We previously estimated[2] the burden of childhood tuberculosis in the 22 countries with a high tuberculosis burden, but did not estimate a global burden or assess drug resistance. Other estimates of paediatric tuberculosis incidence exist,[3] based on upwardly adjusting paediatric notification rates. These approaches do not, however, permit quantification of the burden of infection. Although previous estimates of isoniazid-resistant disease and MDR disease in children have been made,[3,15] no investigators have quantified the burden of drug-resistant tuberculosis infection in children. Additionally, no comprehensive attempts have been made to quantify the different types of drug-resistant-tuberculosis disease in children. Moreover, approaches up to now have not accounted for sample uncertainty associated with numbers of cases with drug-susceptibility testing. We aimed to investigate these outcomes with a mathematical modelling study.

Methods

Model of tuberculosis burden estimation

We extended a previously published model[2] of tuberculosis burden estimation in children to 180 countries for which the necessary input data were available, accounting for more than 99% of the world population (appendix).[2] Briefly, this model uses WHO estimates of adult tuberculosis prevalence and a revised Styblo rule to estimate the annual risk of infection for children. We then used data for underlying demographic characteristics, BCG coverage, HIV prevalence, and the natural history of disease in children to estimate incidence of disease at a country level. We included uncertainty for all data in calculations and propagated it through to results.

To estimate the proportions of cases of tuberculosis at a country level, we used the following classifications and notation for drug-resistance types: drug susceptible (susceptible to isoniazid and rifampicin), isoniazid mono-resistant, rifampicin monoresistant, multidrug resistant (MDR; resistant to at least isoniazid and rifampicin), only resistant to isoniazid and rifampicin (MDR#), MDR# with additional resistance to at least one fluoroquinolone but not any second-line injectable medication (FQR), MDR# with additional resistance to at least one second-line injectable but not any fluoroquinolone (SLR), and extensive multidrug resistance (XDR; MDR# with additional resistance to both at least one fluoroquinolone and at least one second-line injectable medication). We did not consider resistance to other antituberculosis drugs, such as ethambutol, pyrazinamide, or streptomycin, or to any second-line drugs other than the fluoroquinolones and second-line injectable medications. Our classification of resistance can thus be summarised as follows: all cases of tuberculosis=drug-susceptible plus isoniazid mono-resistant plus rifampicin monoresistant plus MDR; and all MDR cases of tuberculosis=MDR# plus FQR plus SLR plus XDR (figure 1).

Because of the difficulties of bacteriological confirmation of tuberculosis in children, direct data for drug-resistance types are rare. Findings from some systematic reviews suggest that the proportion of isoniazid resistance and MDR in treatment-naive adults is a reasonable proxy for the proportion of the corresponding resistance in children,[3,15] and analyses of surveillance data have not shown a difference between proportions of first-line drug resistance in children and adults irrespective of treatment status.[16] Therefore, to obtain data for first-line resistance in children, we based the proportions of children resistant to each compound on data obtained in treatment-naive adults. For second-line resistance, data were not available stratified by treatment history, and therefore we directly applied the proportions of drug resistance in these data.

Determination of drug resistance and uncertainty

We determined drug resistance using data from the Global Project on Anti-tuberculosis Drug Resistance Surveillance at WHO. The data comprised counts of resistance by type from routine surveillance, and proportions (with 95% CIs) for each resistance type from surveys reported to WHO between 1988 and 2014,[4,16] following guidelines for drug-resistance surveillance.[17] In most countries, these data relate to patients with pulmonary tuberculosis, nearly all of whom are adults. Because of the potential for bias, data from surveillance systems where less than 60% of treatment-naive patients had a rifampicin-resistance result were excluded.[17] For surveys, 82 countries contributed 166 country-years with complete data for isoniazid-monoresistant tuberculosis, rifampicin-monoresistant tuberculosis, and MDR tuberculosis. For surveillance data, 87 countries contributed 627 country-years with complete data on isoniazid-monoresistant disease, rifampicin-mono-resistant disease, and MDR disease, and there were a further 288 country-years with data for only MDR resistance (ie, missing data for isoniazid and rifampicin monoresistance). 90 countries reported data for second-line resistance among MDR tuberculosis individuals (MDR#, FQR, SLR, and XDR): 33 country-years from surveys and 273 country-years from surveillance; 227 country-years with complete data, 40 country-years with only data for XDR and FQR, and 43 country-years with only data for XDR. We converted proportions from survey data into counts by multiplying them by the survey sample size. Exploratory data analyses suggested no clear trends so we aggregated data over the years 2005–14.

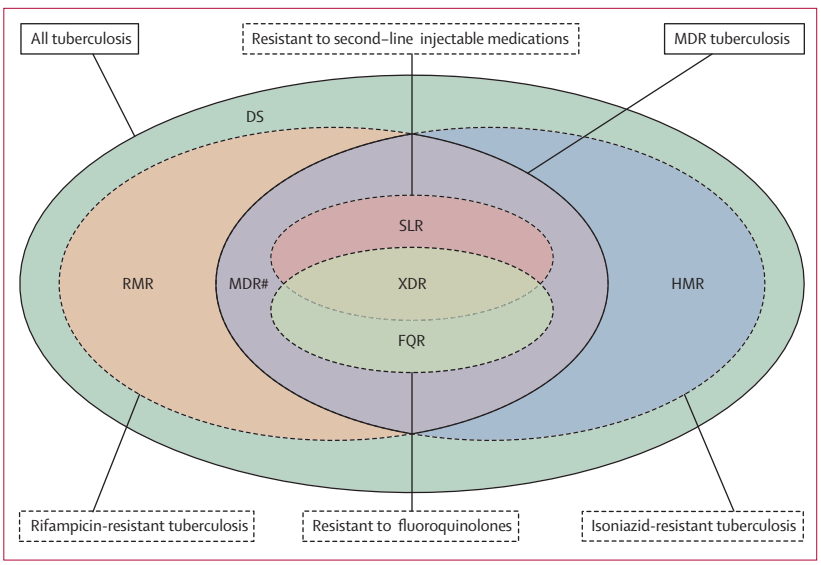

Figure 1: **Definitions of drug-resistance types used in our analysis**
DS=drug-susceptible (susceptible to isoniazid and rifampicin). HMR=isoniazid monoresistant. RMR=rifampicin monoresistant. MDR=multidrug resistant. MDR#=multidrug resistant only to isoniazid and rifampicin. FQR=multidrug resistant to isoniazid and rifampicin plus resistant to a fluoroquinolone but not any second-line injectable. SLR=multidrug resistant to isoniazid and rifampicin, plus resistant to a second-line injectable but not to any fluoroquinolone. XDR=extensively drug resistant (multidrug resistant to isoniazid and rifampicin plus resistant to at least one fluoroquinolone and at least one second-line injectable). We did not consider resistance to other antituberculosis drugs.

See **Online** for appendix

To sample the uncertain proportions for each drug-resistance category in each country, we used the following algorithm: (1) if a country had data, we used a Bayesian approach assuming multinomial counts with a flat Dirichlet prior on proportions, allowing sampling from the closed-form posterior for proportions (approach to missing category counts described in the appendix); (2) if a country had no data but two or more of its five nearest neighbours did, for each sample we randomly chose a neighbouring country and sampled its proportions as in (1); (3) if a country had no data and fewer than two of its five nearest neighbours did, for each sample we randomly chose a country from the same epidemiological region and sampled its proportions as in (1); (4) if a country had no data, and no countries in the same epidemiological region had data, for each sample we randomly chose a country with data globally and sampled its proportions as in (1). The nine epidemiological regions used for analysis were those defined in the WHO report methodological appendix[18] for MDR analyses, but the results are presented and discussed for the standard six WHO regions: the African region, region of the Americas, the Southeast Asia region, the European region, the Eastern Mediterranean region, and the Western Pacific region (appendix).[4]

We combined 1000 sampled proportions for each country using this algorithm with 10 000 sampled country estimates of tuberculosis disease incidence in 2014 and *M tuberculosis* infection prevalence from our model (resampling the proportions to generate 10 000 stratified incidences). We then stratified country estimates of disease incidence and infection prevalence by drug-resistance type and aggregated them by WHO region and globally. Reported aggregate proportions of drug-resistance type are among the total tuberculosis incidences in children. We used standard world maps and a Gastner-Newman cartogram[19] (which represents data by scaling areas) to visualise the geographic variation in median quantities.

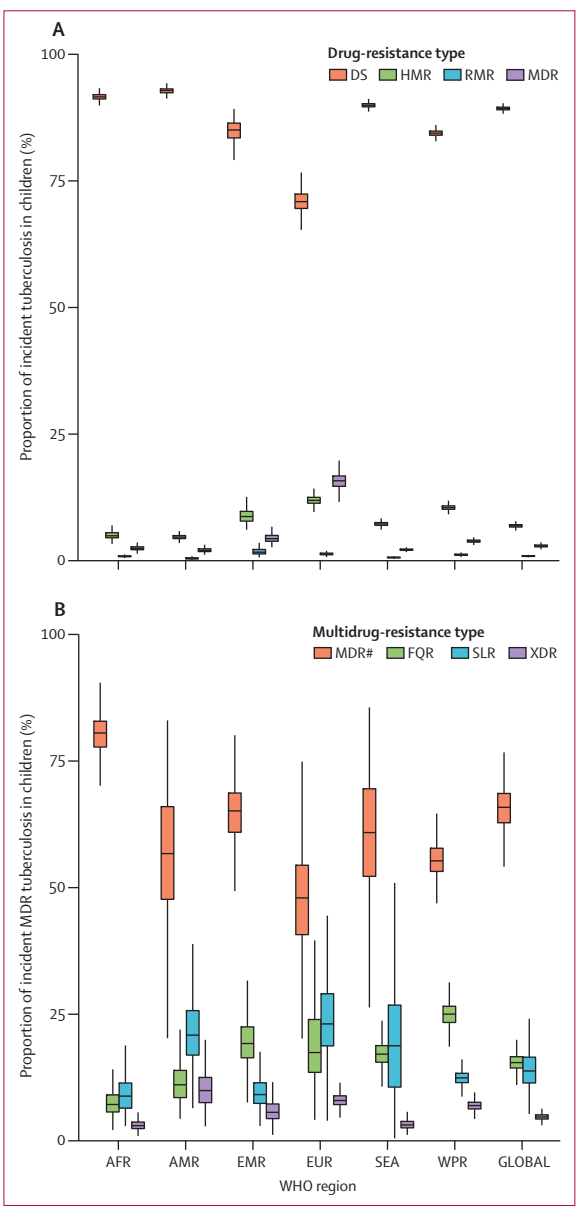

Figure 2: **Proportion of incident tuberculosis in children by drug-resistance status, 2014**
Tukey box plots, with boxes depicting median and IQR. DS=drug-susceptible (susceptible to isoniazid and rifampicin). HMR=isoniazid monoresistant. RMR=rifampicin monoresistant. MDR=multidrug resistant. MDR#=multidrug resistant only to isoniazid and rifampicin. FQR=multidrug resistant to isoniazid and rifampicin plus resistant to a fluoroquinolone but not any second-line injectable. SLR=multidrug resistant to isoniazid and rifampicin plus resistant to a second-line injectable but not to any fluoroquinolone. XDR=extensively drug resistant (multidrug resistant to isoniazid and rifampicin plus resistant to at least one fluoroquinolone and at least one second-line injectable). AFR=African region. AMR=Americas region. EMR=Eastern Mediterranean region. EUR=European region. SEA=Southeast Asia region. WPR=Western Pacific region.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
We showed that overall in 2014, a median 6·9% (IQR 6·6–7·1) of incident tuberculosis disease in children was isoniazid monoresistant and 2·9% (2·7–3·1) was MDR (figure 2, appendix). Of MDR tuberculosis in children, we showed that a median 4·7% (IQR 4·3–5·1) was XDR (figure 2, appendix). These patterns of drug resistance varied strongly both between WHO regions (figure 2, appendix) and within the regions (appendix). In the European region, by contrast with all other regions, the proportion of cases that was MDR was higher than the proportion that was isoniazid mono-resistant. Although uncertain, the proportion of children with MDR tuberculosis who had second-line drug resistance seemed lowest in the African and Western

	Total estimates of incident tuberculosis in children	Estimates of incident tuberculosis in children by drug-resistance type				Estimates of incident MDR tuberculosis in children by drug-resistance type			
		DS	HMR	RMR	MDR	MDR#	FQR	SLR	XDR
WHO region									
African	338 000 (218 000–509 000)	309 000 (200 000–466 000)	16 800 (10 800–25 700)	2890 (1860–4460)	8230 (5190–12 800)	6560 (4120–10 200)	577 (346–966)	713 (436–1150)	245 (151–396)
Americas	25 000 (16 100–38 500)	23 100 (14 900–35 700)	1170 (743–1810)	113 (69–191)	525 (330–816)	287 (177–452)	57 (35–95)	109 (66–179)	51 (31–86)
Eastern Mediterranean	75 700 (49 700–114 000)	64 100 (42 200–96 700)	6640 (4280–10 100)	1290 (811–2040)	3340 (2120–5160)	2140 (1360–3320)	635 (397–1000)	303 (179–510)	185 (110–311)
European	13 500 (8690–21 000)	9590 (6180–14 900)	1610 (1030–2510)	179 (113–280)	2120 (1320–3 310)	981 (603–1540)	374 (215–654)	480 (286–813)	168 (105–265)
Southeast Asia	294 000 (190 000–455 000)	264 000 (171 000–410 000)	21 200 (13 700–33 000)	1820 (1180–2 840)	6370 (4 100–9 910)	3780 (2400–5870)	1080 (678–1730)	1070 (520–2020)	199 (124–322)
Western Pacific	91 800 (60 400–139 000)	77 600 (51 000–118 000)	9670 (6 320–14 700)	1080 (705–1690)	3540 (2320–5400)	1960 (1280–3020)	877 (573–1350)	437 (284–671)	244 (159–376)
Global	847 000 (558 000–1 280 000)	756 000 (499 000–1 140 000)	58 300 (38 300–87 800)	7630 (5 010–11 500)	24 800 (16 100–37 400)	16 200 (10 500–24 500)	3 810 (2 500–5 840)	3 390 (2 140–5 290)	1160 (757–1770)

Data are median (IQR) to three significant figures. DS=drug-susceptible (susceptible to isoniazid and rifampicin). HMR=isoniazid monoresistant. RMR=rifampicin monoresistant. MDR=multidrug resistant. MDR#=multidrug resistant only to isoniazid and rifampicin. FQR=multidrug resistant to isoniazid and rifampicin plus resistant to a fluoroquinolone but not to a second-line injectable. SLR=multidrug resistant to isoniazid and rifampicin plus resistant to a second-line injectable but not to any fluoroquinolone. XDR=extensively drug resistant (multidrug resistant to isoniazid and rifampicin plus resistant to at least one fluoroquinolone and at least one second-line injectable).

Table 1: **Estimates of incident tuberculosis in children by drug-resistance type and WHO region, pertaining to 2014**

Pacific regions. Global resampling was not reached for first-line or second-line resistance estimates (appendix).

We estimated a total global paediatric median incidence in 2014 of 847 000 (IQR 558 000–1 280 000) of which 58 300 (38 300–87 000) were isoniazid-monoresistant tuberculosis, 24 800 (16 100–37 400) were MDR tuberculosis and 1160 (57–1770) were XDR tuberculosis. Incidences varied substantially between regions (table 1).

The proportion of incident tuberculosis in children in 2014 with MDR tuberculosis varied from very low percentages in the Americas and Western Europe (lighter colours in figure 3), to more than 30% in some of the former Soviet states in the WHO European region (dark red in figure 3). However, countries with low or moderate proportions of resistance in the Southeast Asian, African, and Western Pacific regions contributed to most of the incident MDR tuberculosis cases in children, because of their high incidences and large child populations.

We estimated that in 2014, the global median paediatric burden of tuberculosis infection was 67·0 million (IQR 52·3 million–85·7 million). Of these infections, a median 4·8 million (3·8 million–6·2 million) were isoniazid monoresistant, 2·0 million (1·6 million–2·6 million) were MDR, and 101 000 (78 100–131 000) were XDR. The paediatric burden varied substantially between regions (table 2, appendix).

Discussion

The findings from our modelling analysis suggest that large numbers of children develop tuberculosis disease each year with a global incidence estimate of nearly 850 000. We also estimated that a large burden of children have drug-resistant tuberculosis each year: around 58 000 with isoniazid-monoresistant tuberculosis, 25 000 with MDR tuberculosis, and 1200 with XDR-tuberculosis. A much larger number of children are infected with *M tuberculosis*; our estimate is that nearly 67 million children are globally infected. Of these, a substantial number had drug-resistant infections: approaching 5 million with isoniazid-monoresistant infections, 2 million with MDR infections, and 100 000 with XDR infections. Although the WHO Africa and Southeast Asia regions dominated the overall contribution to tuberculosis in children, the Eastern Mediterranean, European, and Western Pacific regions were substantial contributors to the burden of drug-resistant disease because of their much higher proportions of drug resistance.

The estimated burden of drug-resistant tuberculosis disease cases highlights a vast gap between incidence and treatment. Few children globally are treated for drug-resistant tuberculosis. An individual patient systematic review and meta-analysis[20] of children treated at any time in the past for MDR tuberculosis was only able to identify 1000 such children. Since we estimated that 25 000 children developed MDR tuberculosis each year, clearly many children are not being diagnosed and started on treatment, especially considering that rifampicin monoresistance is clinically managed in the same way as MDR tuberculosis. If more children are to be treated, the implications for diagnostics, funding, training, and an adequate supply of child-friendly drugs are profound.

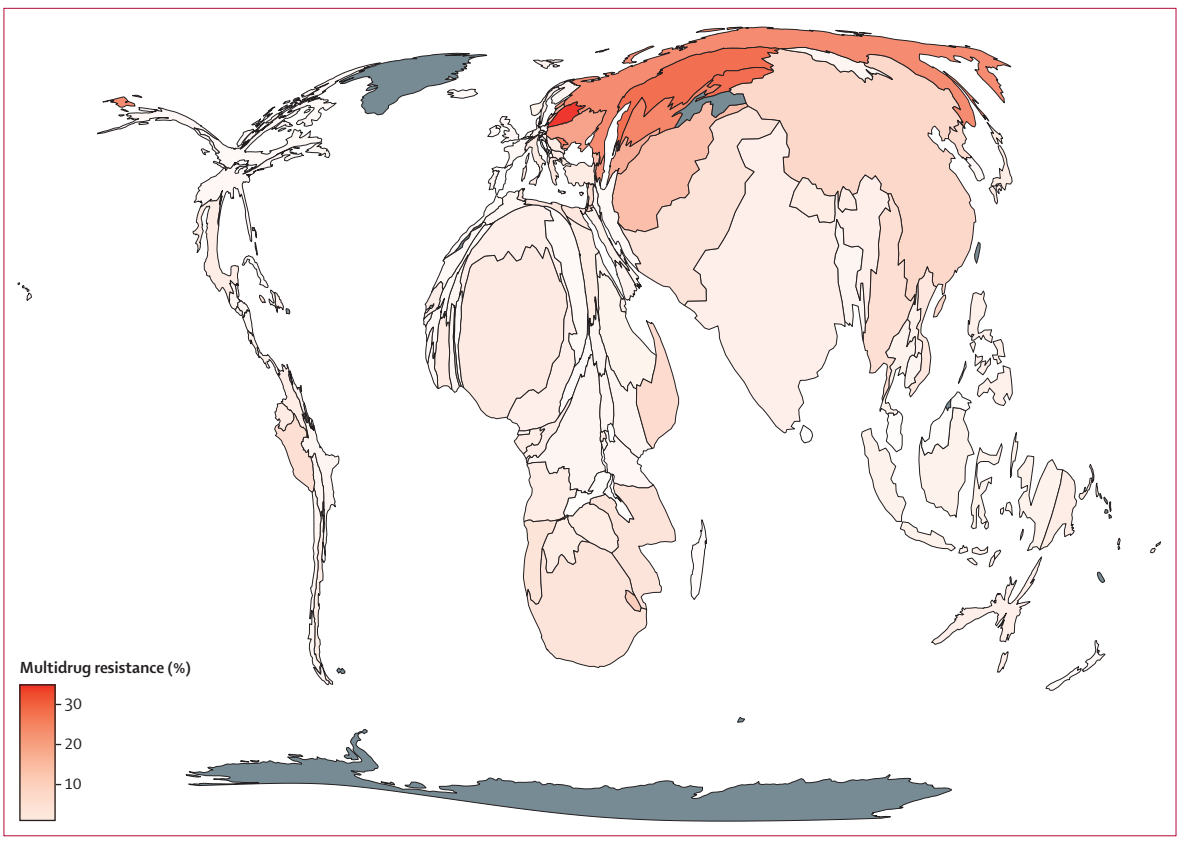

Figure 3: **Cartogram showing total incidence of MDR tuberculosis in children in 2014 by area**
We used the Gastner-Newman method[19] to calculate incidences and depict the proportion of incidences in children with multidrug resistant (MDR) tuberculosis by colour (grey shading indicates no estimate).

With the roll-out of the Xpert MTB/RIF diagnostic test, the substantial risk of isoniazid-monoresistant tuberculosis in some regions might be overlooked and result in suboptimum treatment. If only Xpert MTB/RIF is used, isoniazid-monoresistant source cases might be diagnosed but considered susceptible to both rifampicin and isoniazid, and child contacts (who are likely to be infected with an isoniazid-monoresistant strain) will be given isoniazid preventive therapy. Although this therapy would be effective for rifampicin-monoresistant tuberculosis, this is unlikely to be diagnosed if only Xpert MTB/RIF is used; a positive *rpoB*-gene mutation result usually results in the case being managed as MDR tuberculosis, and the child is unlikely to be given isoniazid. In regions with high occurrences of isoniazid-monoresistant tuberculosis, where Xpert MTB/RIF is used alone, consideration could be given to using 3 months of both isoniazid and rifampicin as preventive therapy, so that if a child has undiagnosed isoniazid-monoresistant tuberculosis, they will still benefit from being given rifampicin. Xpert MTB/RIF testing should also be followed up with testing for isoniazid susceptibility. If a child is exposed to an individual with MDR tuberculosis, neither rifampicin nor isoniazid is likely to be effective as preventive therapy. An evolving body of evidence suggests that fluoroquinolone-based regimens might be effective[21] and three clinical trials (V-QUIN, TB-CHAMP, and PHOENIx) are in development to investigate alternative treatments. The high levels of drug resistance in some regions will also affect the choice of drugs for the treatment of children with confirmed disease before the full range of drug-susceptibility tests becomes available (or where a full range of tests is unavailable), and also for children with clinically diagnosed disease without a full drug-susceptibility test profile from the source case.

If we compare our estimates of paediatric MDR tuberculosis and isoniazid-resistant tuberculosis with those of Jenkins and colleagues,[3] and Yuen and colleagues,[15] our estimates of the incidence of MDR tuberculosis were somewhat lower than the 32 000 estimate of Jenkins and colleagues[3] for 2013. Our estimate of global paediatric tuberculosis incidence was also approximately 20% smaller than that noted by Jenkins and colleagues,[3] but the differences were heterogeneous by location: the difference in the estimates of MDR tuberculosis incidence is largely accounted for by our substantially smaller estimates for underlying paediatric tuberculosis incidence in China, India, and Russia, without considering any differences in

drug-resistance proportions. China, India, and Russia account for a difference of more than 7000 paediatric MDR cases of tuberculosis if we assume the same proportions of MDR resistance (data not shown). To compare with the existing estimate of isoniazid resistance of 120 000 noted in the study by Yuen and colleagues[15] (that used the underlying burden estimates from Jenkins and colleagues[3]), we needed to aggregate data from our isoniazid monoresistant and MDR categories (giving a global estimate in the region of 84 000 for all isoniazid resistance). Thus, our estimate for isoniazid resistance is lower than that from Yuen and colleagues[15] and as with MDR, the difference is largest in the WHO European, southeast Asian, and Western Pacific regions and almost entirely accounted for by differences in the underlying burdens (data not shown), notably in China, India, and Russia. One limitation of our approach is that we aggregated over subnational data in India and Russia; nationally representative surveys of drug resistance in India and China are ongoing.

Our global estimate of 2·9% MDR in incident childhood tuberculosis is slightly lower than the WHO global estimate of 3·3% in all treatment-naive cases, largely reflecting lower MDR proportions in regions with higher proportions of tuberculosis incidence among children.

Our analysis has several limitations, associated both with the mathematical model quantifying the burden of infection and disease, and with the analysis of patterns of drug resistance. The burden model inherits any limitations associated with WHO's estimates of tuberculosis prevalence, and has recognised uncertainties in its treatment of HIV as a risk factor for disease progression, BCG vaccination as a source of protection, and ignores potential host or pathogen variation as sources of variation in progression rates.[2] However, our burden model produced estimates that were similar to an independent approach based on notification data,[3] and had strengths in generating estimates of latent infection and age-disaggregated incidence.

Our main focus was on tuberculosis disease in the year 2014, but in the absence of clear trends, we used aggregated drug-resistance data over a decade to inform of proportions with each type. This approach might average over trends that exist in reality but for which these data do not have the power to detect. In estimating the burden of *M tuberculosis* infection, we also assumed that the annual risk of infection has remained constant from 1999 to 2014. The global tuberculosis prevalence per person (country mean weighted by current child population) was nearly 60% higher in 1999 than in 2014: the higher annual risks of infection in the past could imply that the burden of latent *M tuberculosis* infection is up to 30% larger than an estimate based on current infection risks.

Some of the limitations might apply particularly to the inclusion of drug resistance: we assumed that drug-resistance type is not correlated with exposure,

	Total estimates of children infected with *M tuberculosis*	Estimates of children infected with *M tuberculosis* by drug-resistance type				Estimates of children infected with MDR-*M tuberculosis* by drug-resistance type			
		DS	HMR	RMR	MDR	MDR#	FQR	SLR	XDR
WHO region									
African	20 900 000 (16 400 000–27 000 000)	19 200 000 (15 000 000–24 700 000)	1 040 000 (797 000–1 360 000)	180 000 (137 000–233 000)	489 000 (373 000–640 000)	385 000 (291 000–505 000)	35 800 (24 500–52 700)	45 000 (31 600–65 100)	15 800 (11 200–22 100)
Americas	2 110 000 (1 590 000–2 780 000)	1 950 000 (1 470 000–2 580 000)	97 600 (73 300–130 000)	9 560 (6760–14 200)	44 500 (33 000–60 900)	24 300 (17 400–34 500)	4920 (3360–7180)	9340 (6300–13 800)	4480 (3030–6720)
Eastern Mediterranean	6 500 000 (4 960 000–8 350 000)	5 490 000 (4 190 000–7 050 000)	583 000 (437 000–775 000)	106 000 (75 300–152 000)	288 000 (212 000–390 000)	188 000 (137 000–257 000)	52 900 (39 000–71 600)	26 300 (17 800–39 700)	15 400 (10 500–22 800)
European	1 400 000 (1 040 000–1 880 000)	992 000 (746 000–1 330 000)	166 000 (123 000–227 000)	17 800 (13 200–24 200)	219 000 (160 000–304 000)	100 000 (72 100–140 000)	38 300 (25 100–61 300)	50 400 (33 700–76 600)	17 300 (12 500–24 100)
Southeast Asia	27 000 000 (20 500 000–35 300 000)	24 300 000 (18 400 000–31 700 000)	1 950 000 (1 470 000–2 570 000)	162 000 (122 000–215 000)	586 000 (442 000–769 000)	339 000 (251 000–453 000)	102 000 (74 700–140 000)	105 000 (56 300–176 000)	18 300 (12 900–26 100)
Western Pacific	8 600 000 (6 670 000–11 100 000)	7 250 000 (5 630 000–9 370 000)	901 000 (696 000–1 170 000)	103 000 (79 100–135 000)	344 000 (264 000–445 000)	185 000 (142 000–241 000)	89 300 (67 900–116 000)	43 800 (33 500–57 100)	24 700 (18 600–32 300)
Global	67 000 000 (52 300 000–85 700 000)	59 600 000 (46 500 000–76 200 000)	4 810 000 (3 750 000–6 160 000)	594 000 (463 000–763 000)	2 000 000 (1 560 000–2 580 000)	1 250 000 (968 000–1 610 000)	339 000 (262 000–439 000)	301 000 (221 000–412 000)	101 000 (78 100–131 000)

Data are median (IQR) to three significant figures. DS=drug-susceptible (susceptible to isoniazid and rifampicin). HMR=isoniazid monoresistant. RMR=rifampicin monoresistant. MDR=multidrug resistant. MDR#=multidrug resistant only to isoniazid and rifampicin. FQR=multidrug resistant to isoniazid and rifampicin plus resistant to a fluoroquinolone but not to a second-line injectable. SLR=multidrug resistant to isoniazid and rifampicin plus resistant to a second-line injectable but not to any fluoroquinolone. XDR=extensively drug resistant (multidrug resistant to isoniazid and rifampicin plus resistant to at least one fluoroquinolone and at least one second-line injectable).

Table 2: **Estimates of the numbers of children infected with *Mycobacterium tuberculosis* by drug-resistance type and WHO region, pertaining to 2014**

infectiousness, or likelihood of progression. We also assumed that the proportion of first-line drug-resistance types in treatment-naive patients reflects that in children and did not include any uncertainty in this relation. However, this assumption is supported for isoniazid resistance and MDR by systematic review.[3,15] For second-line drug resistance, we assumed that the proportions of different drug resistance in all patients reflects that in children, which might have overestimated levels of second-line drug resistance in children by including data from previously treated patients. Patients with MDR tuberculosis with additional second-line resistance (including XDR tuberculosis) could be epidemiologically and socially different from other groups with drug-resistant tuberculosis. They might be more likely to have been admitted to hospital or imprisoned and clustering might mean that the probability of a child being exposed to such a case is less than that of being exposed to other forms of the disease. Although these patients are more likely to have been previously treated, analysis of surveillance data reassuringly did not find a difference between first-line resistance proportions in children and adults of any treatment status.[16] Finally, we only assessed the drug-resistance categories determined by the drugs defining MDR tuberculosis and XDR tuberculosis. Resistance to other drugs has not been estimated because of a shortage of data, partly resulting from technical difficulties in drug-susceptibility testing (eg, with cycloserine and clofazimine) and partly due to a shortage of good-quality diagnostics in most of the world (eg, pyrazinamide). As a result, we expect that global needs in terms of effective regimens are higher than that implied by the burden estimates that we have reported.

A strength of our work is our treatment of uncertainty. Our analysis of drug-resistance patterns is an improvement over previous work in this respect, since it captures the uncertainty implicit in the numbers of cases determining proportions, and could be applied to determining the burden of drug-resistant tuberculosis in all age groups. Although a geographically structured hierarchical model might have allowed use of country-level variables in imputing missing drug-resistance patterns, our regional resampling approach does capture regional patterns and variance from resampling, and is relatively simple and transparent.

This approach could be built upon to analyse differences between countries and between regions, and to identify drivers of drug resistance patterns. As more data become available, validation of the model might be possible and it could also be used to make predictions about tuberculosis incidence in the future. Quantification of the levels of disease incidence and infection prevalence with particular drug-resistance phenotypes can also feed into market-size calculations for second-line drugs and for new drugs. Finally, this framework would allow investigation of different options for empirical studies and their location to improve the precision of these estimates. Comparison with other burden estimates of drug-resistant tuberculosis, where there is overlap, highlights the importance of better quantifying the underlying burden of childhood tuberculosis in key settings such as China, India, and Russia.

In conclusion, far more drug-resistant tuberculosis occurs in children than is diagnosed, and there is a large pool of drug-resistant tuberculosis infection. This finding could have implications for approaches to empirical treatment regimens and preventive therapy in some regions.

Contributors

PJD and JAS conceived and designed the study, and wrote a first draft of the article. CS advised on interpretation of the data, critiqued the method, and contributed to writing the article. PJD did all data analyses and modelling.

Declaration of interests

We declare no competing interests.

Acknowledgments

We thank Helen Jenkins for sharing country-level burden estimates for comparison, and Anna Dean, Dennis Falzon, Matteo Zignol, and Philippe Glaziou for comments on the manuscript. Charalambos Sismanidis is a staff member of WHO. 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. This work was funded from the STEP-TB grant from UNITAID to TB Alliance.

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