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*Manuscript

The global burden of drug-resistant tuberculosis in children: a mathematical model

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Abstract

Background: Following infection with *M. tuberculosis*, children are at 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, and suggest there is much more isoniazid-resistant and multidrug-resistant (MDR) disease than is identified. No work has yet quantified the burden of drug-resistant infection, considered other types of drug-resistance, or accounted for 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 estimated the proportions of tuberculosis cases at a country-level with: isoniazid-monoresistance (HMR), rifampicin mono-resistance, MDR, fluoroquinolone-resistant MDR, second-line injectable resistant MDR, and MDR with resistance to both a fluoroquinolone and a second-line injectable (XDR).

Findings: We estimate 850,000 children developed tuberculosis in 2014; 58,000 with HMR-tuberculosis, 25,000 with MDR-tuberculosis, and 1,200 with XDR-tuberculosis. We estimate 67 million children are infected with *M. tuberculosis*; 5 million with HMR, 2 million with MDR, and 100,000 with XDR. Africa and South-East Asia have the highest numbers of tuberculosis in children, but WHO EMR, EUR and WPR regions also contribute substantially to the burden of drug-resistant tuberculosis due to 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 has implications for approaches to empiric treatment and preventive therapy in some regions.

Funding: UNITAID

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 the World Health Organization (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 evaluate programmes and for advocacy.

Following infection with *Mycobacterium tuberculosis* (*M. 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 (IPT) in children under five years who have been exposed to tuberculosis.[7] IPT 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 comparable 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.[10]

Anti-tuberculosis drug resistance is frequently divided into drug-susceptible (DS)-tuberculosis and multidrug-resistant (MDR)-tuberculosis. DS-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* resistant to both of these drugs. This division has programmatic motivations, as patients with strains that are resistant to only isoniazid can largely be treated successfully with standard first-line therapy, whereas those with MDR-tuberculosis cannot. However, the importance of isoniazid-mono-resistant (HMR)-tuberculosis is increasingly recognised. First, MDR strains have normally acquired resistance to isoniazid first and then resistance to rifampicin, in effect making HMR-tuberculosis the usual gateway to MDR disease. Second, those with asymptomatic HMR-tuberculosis infection are unlikely to respond to IPT. In addition to the emerging recognition of the importance of HMR-tuberculosis, a more comprehensive approach to second-line drug (SLD) 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 (DR)-tuberculosis either when DR-tuberculosis is confirmed in an isolate from the child or when a child develops clinical disease in conjunction with exposure to a source case that has DR-tuberculosis.[11] In addition, there is increasing recognition that to reduce the burden of tuberculosis it is necessary to identify and treat infected contacts before they become unwell.[12] Children with DR-tuberculosis infection are a reservoir from which future cases will develop and children exposed to DR-tuberculosis are at times treated with non-standardised preventive therapy.[13] The treatment of DR-tuberculosis infection is usually directed against the drug susceptibility test (DST) pattern of the identified source case as child contacts demonstrate high concordance with the source case, if they do progress to disease.[14,15]

We previously estimated the burden of childhood tuberculosis in the 22 high tuberculosis burden countries but did not estimate a global burden or evaluate drug resistance. Other estimates of paediatric tuberculosis incidence exist, based on upwardly adjusting paediatric notification rates.[3] 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,[3,16] no investigators have quantified the burden of DR-tuberculosis infection in children. In addition, there have been no comprehensive attempts to quantify the different types of DR-tuberculosis disease in children. Moreover, approaches to date have not accounted for sample uncertainty associated with numbers of cases with drug-susceptibility testing.

Methods

We extended a previously published model of tuberculosis burden estimation in children to 180 countries for which the necessary input data were available, accounting for over 99% of the world population (see Appendix pages 3-5).[2] Briefly, this model uses the WHO estimates of adult tuberculosis prevalence and a revised Styblo rule to estimate the annual risk of infection for children. Data on underlying demography, BCG coverage, HIV prevalence, and the natural history of disease in children is then used to estimate incidence of disease at a country-level. Uncertainty in all data is included and propagated through to results.

We used the following classification and notation for drug-resistance types: DS - susceptible to isoniazid and rifampicin; HMR - isoniazid mono-resistant; RMR - rifampicin mono-resistant; MDR - multidrug-resistant (resistant to *at least* isoniazid and rifampicin); MDR# - only resistant to isoniazid and rifampicin; FQR – MDR# with additional resistance to ≥1 fluoroquinolone but not any second line injectables; SLR – MDR# with additional resistance to ≥1 second line injectable but not any fluoroquinolone; XDR – MDR# with additional resistance to ≥1 fluoroquinolone *and* to ≥1 second line injectable. We did not consider resistance to other anti-tuberculosis drugs, such as ethambutol, pyrazinamide, streptomycin, nor any second-line drugs other than the fluoroquinolones and second-line injectable medications. This classification of resistance can thus be summarised as follows:
all TB = DS + HMR + RMR + MDR; and **MDR = MDR# + FQR + SLR + XDR** (see Figure 1).

Given the difficulties of bacteriological confirmation of tuberculosis in children, direct data on drug resistance types are rare. Systematic reviews suggest that the proportion of isoniazid resistance and MDR in treatment-naïve adults is a reasonable proxy for the proportion of the corresponding resistance in children[3,16]. Analysis of surveillance data failed to find a difference between proportions of first-line drug resistance in children and adults regardless of treatment status.[17] For first-line resistance, we therefore based the proportions of children resistant to each compound on data in treatment-naïve adults. For second-line resistance, data were not available stratified by treatment history; we therefore directly applied the proportions of drug resistance in these data.

Drug resistance was determined using data from the Global Project on Anti-tuberculosis Drug Resistance Surveillance at WHO. Data comprised counts of resistance by type from routine surveillance, and proportions (with confidence intervals) for each resistance type from surveys reported to WHO between 1988 and 2014,[4,17] following guidelines for drug resistance surveillance.[18] In most countries these data relate to patients with pulmonary tuberculosis, nearly all of whom are adults. Because of the potential for bias, data were not used from surveillance systems where less than 60% of treatment-naïve patients had a rifampicin-resistance result.[18] For surveys, 82 countries contributed 166 country-years with complete data on HMR, RMR and MDR. For surveillance data, 87 countries contributed 627 country-years with complete data on HMR, RMR and MDR, and there were a further 288 country-years with data on only MDR resistance. 90 countries reported data on second-line resistance among MDR-tuberclosis 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 on XDR and FQR resistance, 43 country-years with only data on XDR resistance. We converted proportions from survey data into counts by multiplying by the survey sample size. Exploratory data analysis suggested no clear trends so we aggregated data over the years 2005-2014.

To sample the uncertain proportions for each DR 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 Appendix page 9); 2) if a country had no data but 2 or more of its 5 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 2 of its 5 nearest neighbours did, 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, we randomly chose a country with data globally and sampled its proportions as in 1). The nine epidemiological regions used for analysis were the those defined in the WHO report methodological appendix[19] for MDR analyses but the results are presented and discussed for the standard six WHO regions (see Appendix pages 8-9).[4]

We combined 1,000 sampled proportions for each country using this algorithm with 10,000 sampled country estimates of tuberculosis disease incidence and *M. tuberculosis* infection prevalence from our model (resampling the proportions to generate 10,000 stratified incidences). Country estimates of tuberculosis disease incidence and *M. tuberculosis* infection prevalence by drug-resistance type were then aggregated by WHO region and globally. Reported aggregate proportions of drug-resistance type are among total tuberculosis incidence in children. Standard world maps and a Gastner-Newman cartogram[20] (which represents data by scaling areas) were used to visualize the geographic variation in median quantities.

Role of the funding source

The sponsor 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

Proportions of DR-tuberculosis

Overall we find that 6.9% (Inter-quartile range [IQR]: 6.6% – 7.1%) of tuberculosis in children is HMR and 2.9% (IQR: 2.7% – 3.1%) MDR (see Figure 2A and Appendix page 11). Of MDR-tuberculosis in children, we find that 4.7% (IQR: 4.3% – 5.1%) is XDR (see Figure 2B and Appendix page 11). These patterns of drug resistance vary strongly both by region (see Figure 2 and Appendix page 11) and within region (see Appendix page 13-14). In the EUR region, in contrast to all the other regions, the proportion of cases that are MDR is now higher than HMR. While uncertain, the proportion of children with MDR who have second-line drug resistance seems lowest in the AFR and WPR regions. Global resampling was not reached for first- or second-line resistance estimates (see Appendix page 10).

Incident DR-tuberculosis disease

We estimate a total global paediatric incidence in 2014 of 847,000 (IQR: 558,000 – 1,280,000) of which 58,300 (IQR: 38,300 – 87,000) were HMR-tuberculosis, 24,800 (IQR: 16,100 – 37,400) MDR-tuberculosis and 1,160 (IQR: 757 – 1,770) XDR-tuberculosis. There is substantial variation regionally (see Table 1 for all drug resistance categories and also incidence in children under 5).

The proportion of incident tuberculosis in children in 2014 with MDR-tuberculosis varies from very low percentages in the Americas and Western Europe (light red in

Figure 3), through to over 30% in some of the former Soviet states in the WHO European (EUR) region (dark red,

Figure 3). However, countries with low or moderate proportions of resistance in the SEA, AFR and WPR regions contribute to the majority of the incident MDR-tuberculosis in children, due to their high incidences and large child populations.

Prevalent DR-tuberculosis infection

We estimate that in 2014 the global paediatric burden of tuberculosis infection was 67.0 million (IQR: 52.3 million – 85.7 million). Of these infections, 4.8 million (IQR: 3.8 million – 6.2 million) were HMR, 2.0 million (IQR: 1.6 million – 2.6 million) were MDR and 101,000 (IQR: 78,100 - 131,000) were XDR. There is substantial regional variation (see Table 2 for all drug resistance categories and Appendix pages 17-18).

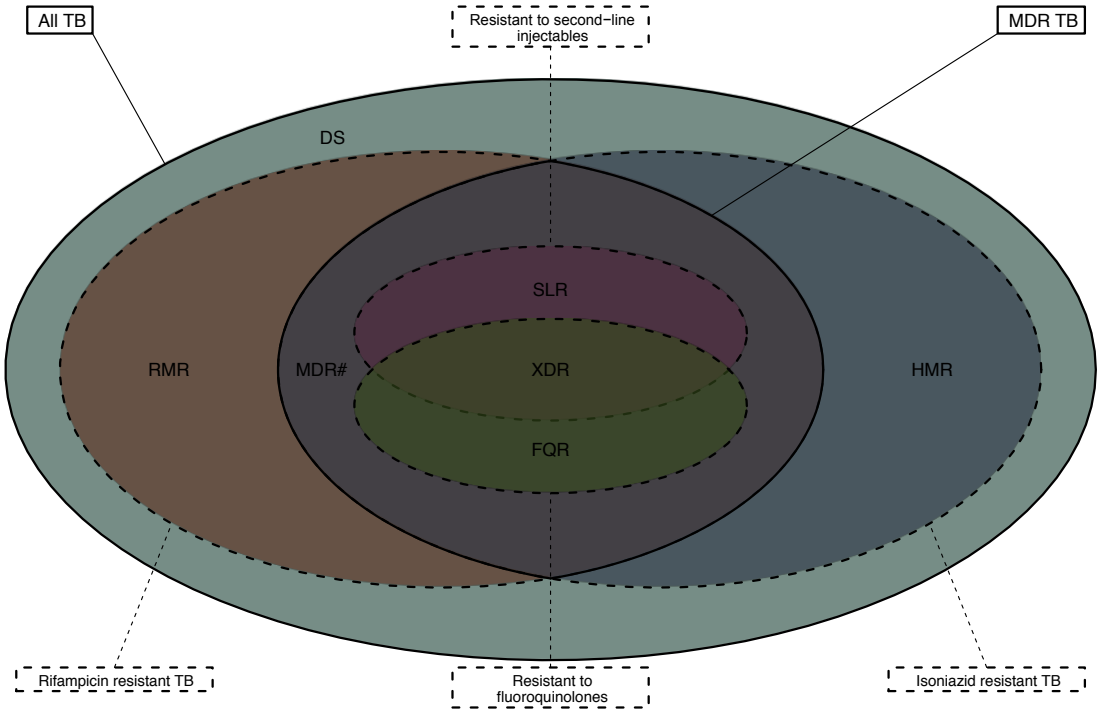

Figure 1: Definitions of drug-resistance types used. DS - susceptible to isoniazid and rifampicin; HMR - isoniazid mono-resistant; RMR - rifampicin mono-resistant; MDR - multidrug-resistant (resistant to *at least* isoniazid and rifampicin); MDR# - only resistant to isoniazid and rifampicin; FQR – MDR# with additional resistance to ≥1 fluoroquinolone but not any second line injectables; SLR – MDR# with additional resistance to ≥1 second line injectable but not any fluoroquinolone; XDR – MDR# with additional resistance to ≥1 fluoroquinolone *and* to ≥1 second line injectable. We did not consider resistance to other anti-tuberculosis drugs.

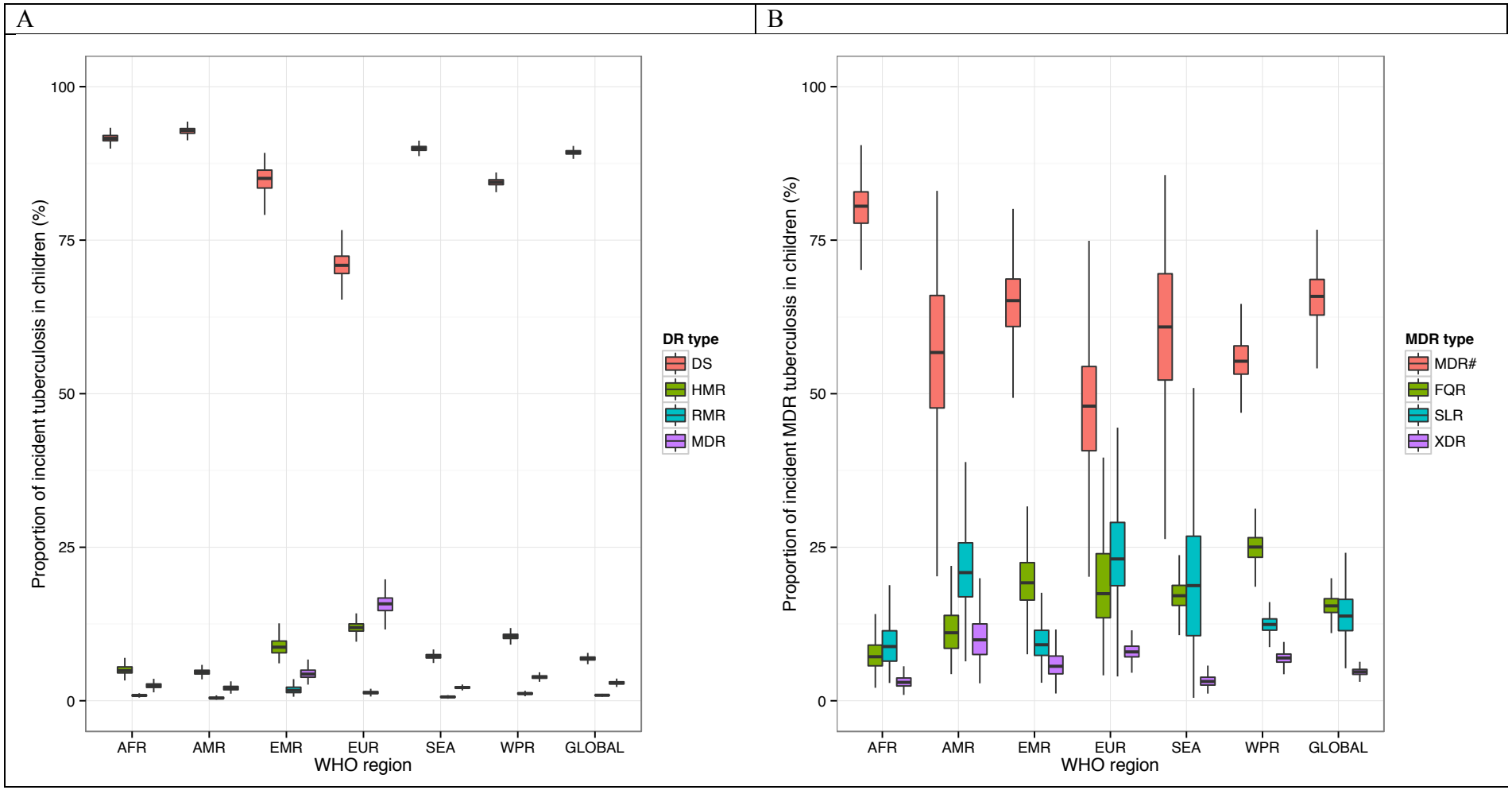

Figure 2: Proportion of incident tuberculosis in children by drug-resistance status, 2014. DS=drug-susceptible, HMR=isoniazid mono-resistant, RMR=rifampicin mono-resistant, MDR=multidrug-resistant; MDR#=MDR only, FQR=MDR# + resistant to a fluoroquinolone, SLR=MDR# + resistant to a second-line injectable, XDR=extensively drug-resistant. WHO regions: AFR=African, AMR=Americas, EMR=Eastern Mediterranean, EUR=European, SEA=South-East Asia, WPR=Western Box-and-whiskers depict mean, inter-quartile range, and 95th percentiles.

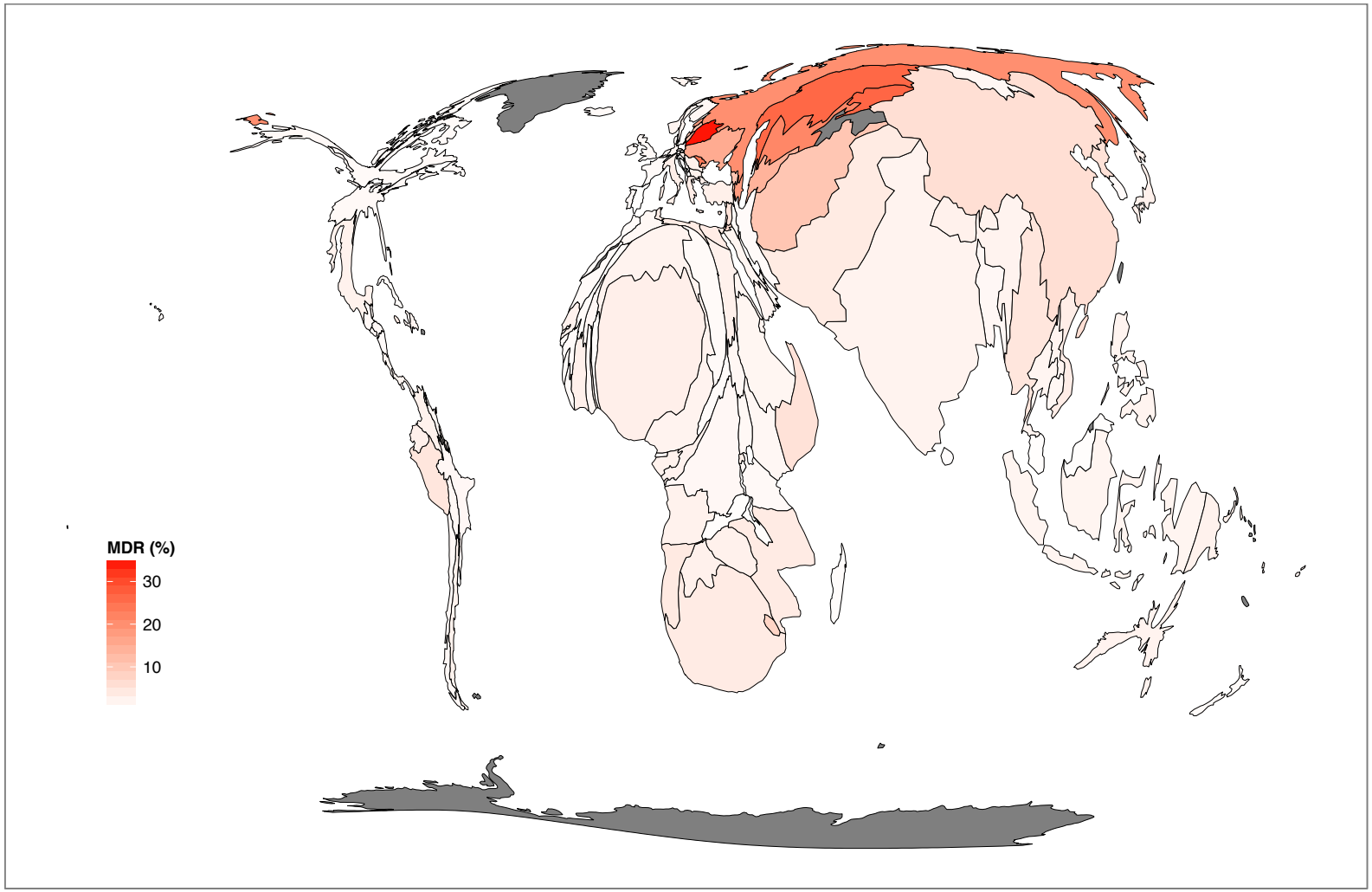

Figure 3: Cartogram showing total incidence of MDR tuberculosis in children in 2014 by area (using the Gastner-Newman method[20]) and the proportion of incident in children with MDR tuberculosis by colour (grey shading indicates no estimate)

Table 1: Estimates of incident tuberculosis in children by drug resistance type and WHO region, 2014. DS=drug-susceptible, HMR=isoniazid mono-resistant, RMR=rifampicin mono-resistant, MDR=multidrug-resistant; MDR#=MDR only, FQR=MDR# + resistant to a fluoroquinolone, SLR=MDR# + resistant to a second-line injectable, XDR=extensively drug-resistant. WHO regions: AFR=African, AMR=Americas, EMR=Eastern Mediterranean, EUR=European, SEA=South-East Asia, WPR=Western Pacific. Brackets denote interquartile range. Numbers to three significant figures.

	Total	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
AFR	338,000 [218,000 - 509,000]	309,000 [200,000 - 466,000]	16,800 [10,800 - 25,700]	2,890 [1,860 - 4,460]	8,230 [5,190 - 12,800]	6,560 [4,120 - 10,200]	577 [346 - 966]	713 [436 - 1,150]	245 [151 - 396]
AMR	25,000 [16,100 - 38,500]	23,100 [14,900 - 35,700]	1,170 [743 - 1,810]	113 [69 - 191]	525 [330 - 816]	287 [177 - 452]	57 [35 - 95]	109 [66 - 179]	51 [31 - 86]
EMR	75,700 [49,700 - 114,000]	64,100 [42,200 - 96,700]	6,640 [4,280 - 10,100]	1,290 [811 - 2,040]	3,340 [2,120 - 5,160]	2,140 [1,360 - 3,320]	635 [397 - 1,000]	303 [179 - 510]	185 [110 - 311]
EUR	13,500 [8,690 - 21,000]	9,590 [6,180 - 14,900]	1,610 [1,030 - 2,510]	179 [113 - 280]	2,120 [1,320 - 3,310]	981 [603 - 1,540]	374 [215 - 654]	480 [286 - 813]	168 [105 - 265]
SEA	294,000 [190,000 - 455,000]	264,000 [171,000 - 410,000]	21,200 [13,700 - 33,000]	1,820 [1,180 - 2,840]	6,370 [4,100 - 9,910]	3,780 [2,400 - 5,870]	1,080 [678 - 1,730]	1,070 [520 - 2,020]	199 [124 - 322]
WPR	91,800 [60,400 - 139,000]	77,600 [51,000 - 118,000]	9,670 [6,320 - 14,700]	1,080 [705 - 1,690]	3,540 [2,320 - 5,400]	1,960 [1,280 - 3,020]	877 [573 - 1,350]	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]	7,630 [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]	1,160 [757 - 1,770]

Table 2: Estimates of the numbers of children infected with *Mycobacterium tuberculosis* by drug resistance type and WHO region, 2014. DS=drug-susceptible, HMR=isoniazid mono-resistant, RMR=rifampicin mono-resistant, MDR=multidrug-resistant; MDR#=MDR only, FQR=MDR# + resistant to a fluoroquinolone, SLR=MDR# + resistant to a second-line injectable, XDR=extensively drug-resistant. WHO regions: AFR=African, AMR=Americas, EMR=Eastern Mediterranean, EUR=European, SEA=South-East Asia, WPR=Western Pacific. Brackets denote interquartile range. Numbers to three significant figures.

	Total	**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
AFR	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]
AMR	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 [6,760 - 14,200]	44,500 [33,000 - 60,900]	24,300 [17,400 - 34,500]	4,920 [3,360 - 7,180]	9,340 [6,300 - 13,800]	4,480 [3,030 - 6,720]
EMR	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]
EUR	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]
SEA	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]
WPR	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]

Discussion

Our modelling analysis suggests large numbers of children develop tuberculosis disease each year with a global incidence estimate of nearly 847,000. We also estimate a large burden of children with DR-tuberculosis each year: in the region of 58,000 with HMR-tuberculosis, 25,000 with MDR-tuberculosis, and 1,200 with XDR-tuberculosis. A much larger number of children will be infected with *M. tuberculosis*; our estimate is that there are currently nearly 67 million children globally infected. Of these there are a significant number with drug-resistant infections: approaching 5 million with HMR, 2 million with MDR, and 100,000 with XDR. While the WHO Africa and South-East Asia regions dominate the overall contribution to tuberculosis in children, EMR, EUR and WPR are substantial contributors to the burden of DR disease due to their much higher proportions of drug resistance.

The estimated burden of DR-tuberculosis disease cases highlights a vast gap between incidence and treatment. Currently few children globally are treated for DR-tuberculosis. A recent individual patient systematic review and meta-analysis of children treated at any time in the past for MDR-tuberculosis was only able to identify 1,000 children.[21] As we estimate 25,000 children develop MDR-tuberculosis each year, clearly many children not being diagnosed and started on treatment, especially considering that rifampicin mono-resistance 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.

With the roll out of Xpert MTB/RIF, the significant risk of HMR in some regions may be overlooked and result in suboptimal treatment. If only Xpert MTB/RIF is used, HMR source cases may be diagnosed but considered susceptible to both rifampicin and isoniazid, and child contacts (who are likely infected with a HMR strain) given IPT. Although IPT will be effective for RMR-tuberculosis, it is unlikely that this will 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. The child is unlikely to be given isoniazid, although this would be effective. In areas with high rates of HMR, where Xpert MTB/RIF is used alone, consideration could be given to using three months of both isoniazid and rifampicin as preventive therapy, so that if the source case has undiagnosed HMR-tuberculosis, the child will still benefit from rifampicin. It is also vital that Xpert MTB/RIF testing is followed up with testing for isoniazid susceptibility. If a child is exposed to an MDR-tuberculosis case, it is unlikely that either rifampicin or isoniazid would be effective as preventive therapy. An evolving body of evidence suggests fluoroquinolone-based regimens may be effective and three clinical trials are underway to investigate alternative treatments.[22] The high rates of drug resistance in some regions will also have implications for the choice of drugs in the treatment of children with confirmed disease prior to the full DST becoming available (or where a full DST is unavailable) and also for children with clinically-diagnosed disease without a full DST profile from the source case.

We can compare our estimates of paediatric MDR-tuberculosis and isoniazid-resistant tuberculosis with those of Jenkins *et al*.[3] and Yuen *et al*.,[16] respectively. Our estimates of the incidence of MDR-tuberculosis are somewhat lower than the 32,000 estimate of Jenkins *et al*.[3] for 2013. Our global paediatric tuberculosis incidence estimate is approximately 20% smaller than that of Jenkins *et al*.[3], but differences are heterogeneous by location: the

difference in MDR-tuberculosis incidence estimates 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. These countries account for a difference of over 7,000 paediatric MDR cases assuming the same proportion of MDR resistance (data not shown). To compare with the existing estimate of isoniazid resistance of 120,000 in Yuen *et al*.[16] (which uses the underlying burden estimates from Jenkins *et al*.[3]), we need to aggregate our HMR 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 of Yuen *et al*.[16] and as with MDR, the difference is largest in the WHO EUR, SEA and WPR regions and almost entirely accounted for by differences in underlying burden (data not shown), notably in China, India and Russia. It is a limitation of our approach that we have aggregated over subnational data in India and Russia; nationally-representative surveys of drug-resistance in India and China are on-going.

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 naïve 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 produces estimates that are comparable with an independent approach based on notification data,[3] and has strengths in generating estimates of latent infection and age-disaggregated incidence.

Our main focus was on TB disease in the year 2014, but in the absence of clear trends, we used aggregated drug-resistance data over a decade to inform proportions with each type. This may 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 during years 1999 – 2014. The global tuberculosis prevalence per capita (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 today's burden of latent *M. tuberculosis* infection is up to 30% larger than an estimate based on current infection risks.

Some of the limitations may apply particularly to the inclusion of drug resistance: we have assumed that drug-resistance type is not correlated with exposure, infectiousness or likelihood of progression. We have assumed that the proportion of first-line drug resistance types in treatment-naïve patients reflects that in children and have not included any uncertainty in this relation. However, this assumption is supported for isoniazid resistance and MDR by systematic review.[3,16] For second-line drug resistance, we have assumed that the proportions of different drug resistance in all patients reflects that in children, which may over-estimate 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) may be epidemiologically and socially different to other groups with drug-resistant tuberculosis. They may be more likely to have been hospitalised or imprisoned and clustering may mean that the probability of a child being

exposed to a case is less than for other forms of disease. Although, they are more likely to have been retreated, it is reassuring that analysis of surveillance data has failed to find a difference between first-line resistance proportions in children and adults of any treatment status.[17] Finally, we have only evaluated the drug resistance categories determined by the drugs defining MDR- and XDR-tuberculosis. Resistance to other drugs has not been estimated due to shortage of data, partly resulting from technical difficulties in DST (e.g. cycloserine and clofazimine) and partly due to lack of good quality diagnostics in much of the world (e.g. pyrazinamide). As a result we expect that global needs in terms of effective regimens will be higher than that implied by the burden estimates that we report.

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. While a geographically-structured hierarchical model may 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, it may be possible validate the model and also use it to make predictions into the future. Quantifying 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 DR-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.

Conclusion

Far more DR-tuberculosis occurs in children than is diagnosed, and there is a large pool of DR-tuberculosis infection. This could have implications for approaches to empiric treatment and preventive therapy in some regions.

Acknowledgements

We would like to 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.

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Contributions

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

Conflicts of interest

We declare that we have no conflicts of interest.

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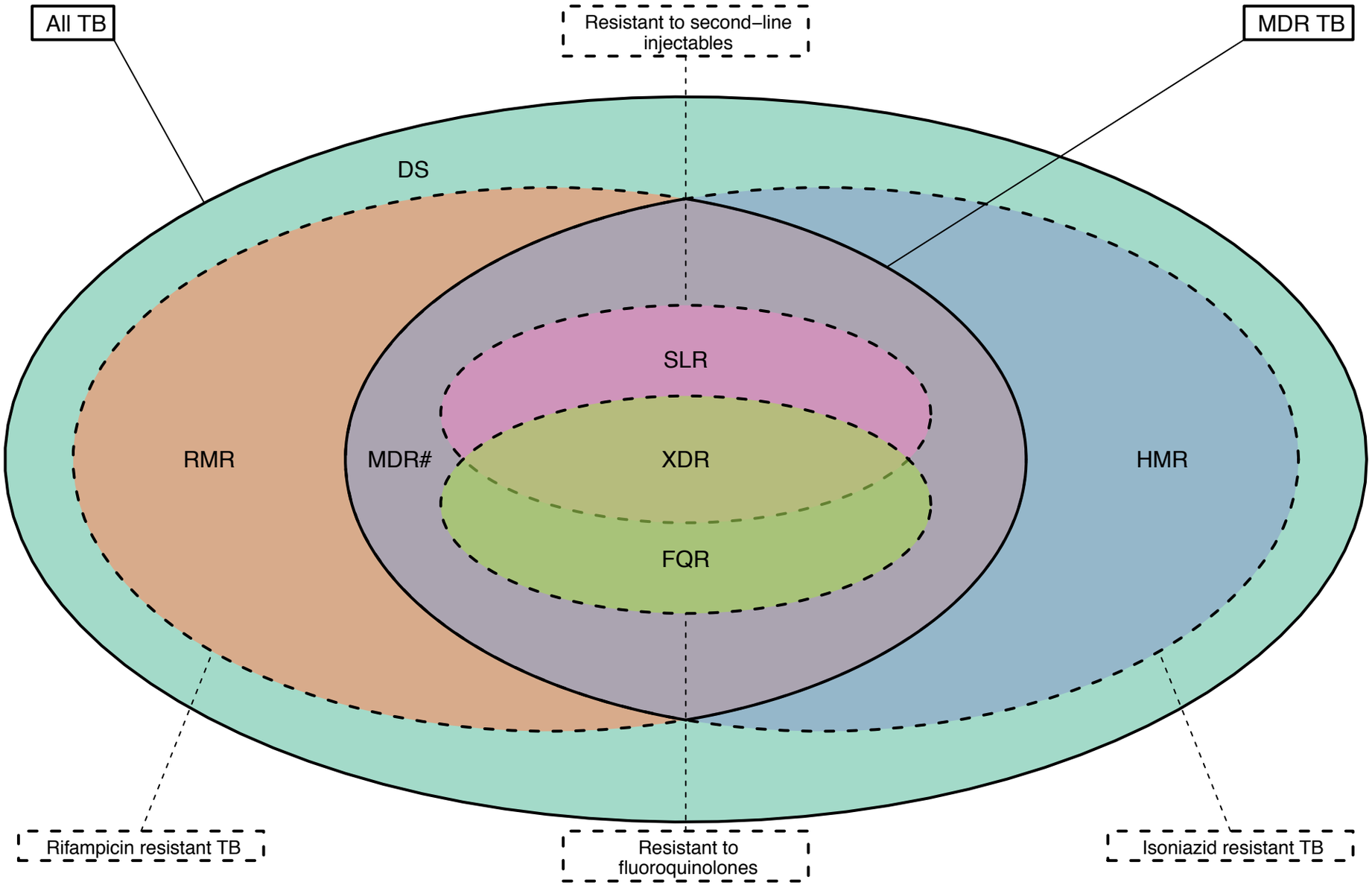
Figure 1


All TB
Resistant to second−line injectables
MDR TB
DS
SLR
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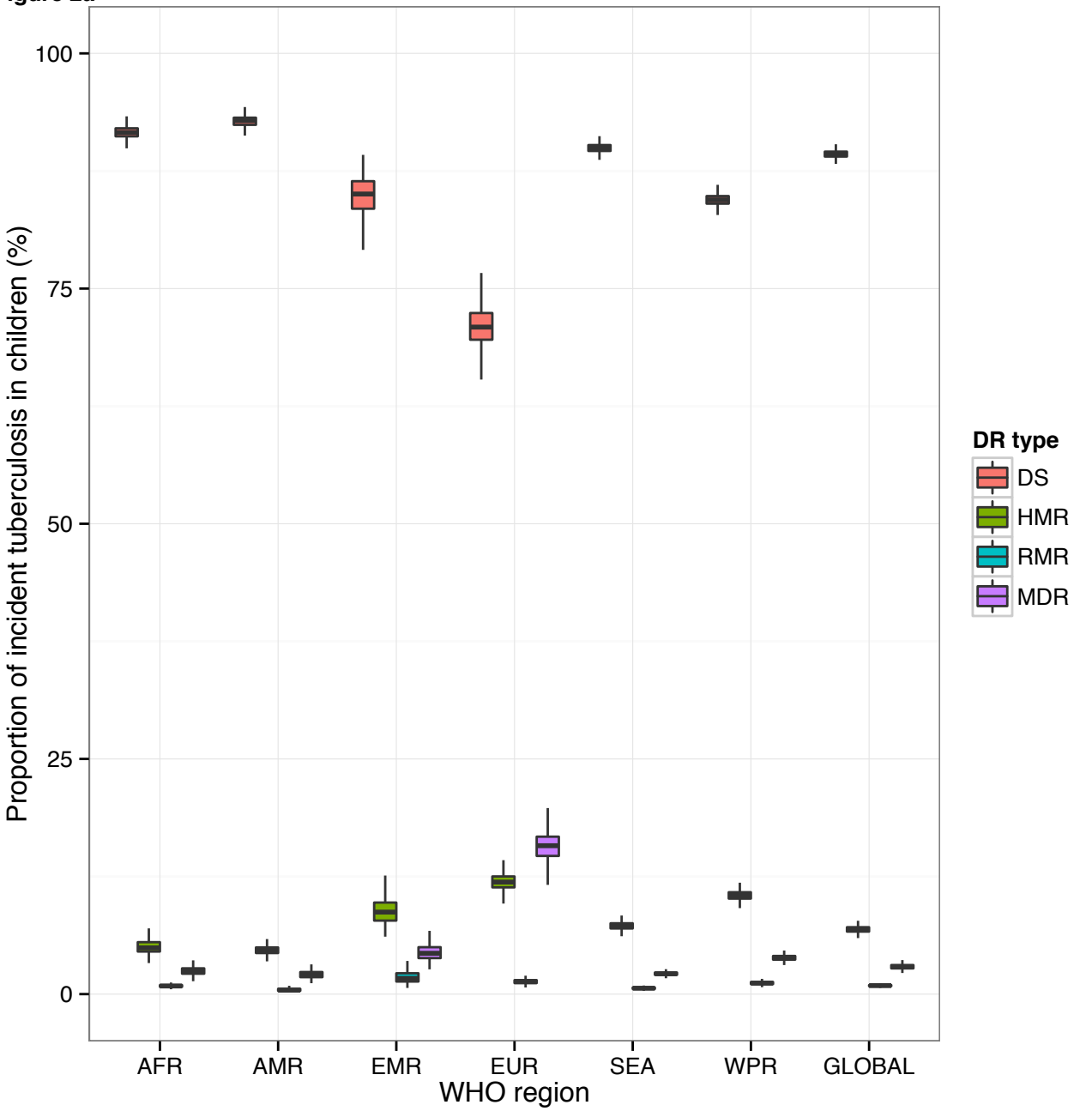
MDR#
XDR
HMR
FQR
Rifampicin resistant TB
Resistant to fluoroquinolones
Isoniazid resistant TB

Figure 2a


100
75
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Proportion of incident tuberculosis in children (%)
AFR
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WPR
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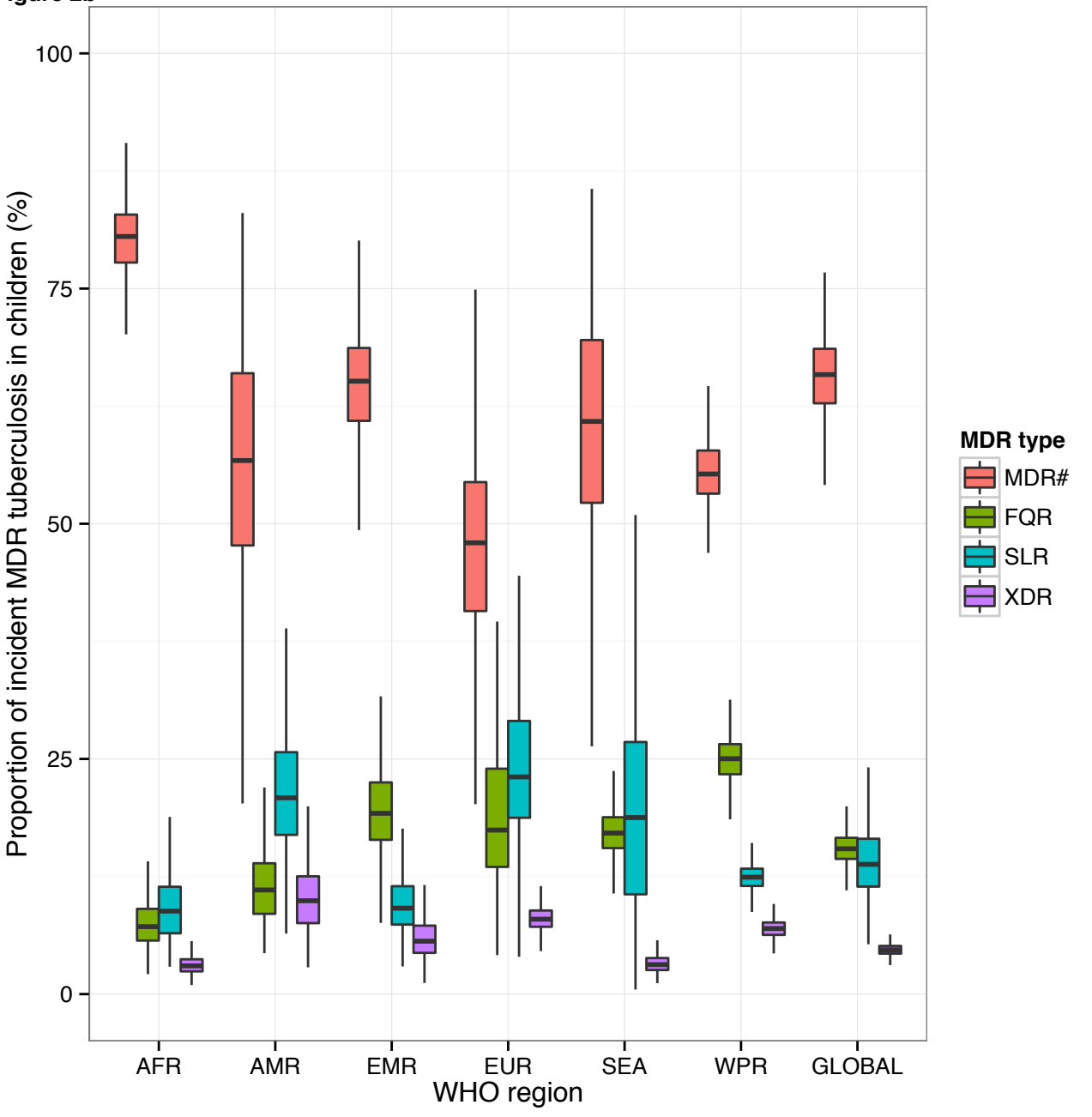
WHO region
DR type
DS
HMR
RMR
MDR

Figure 2b


100
75
50
25
0
Proportion of incident MDR tuberculosis in children (%)
AFR
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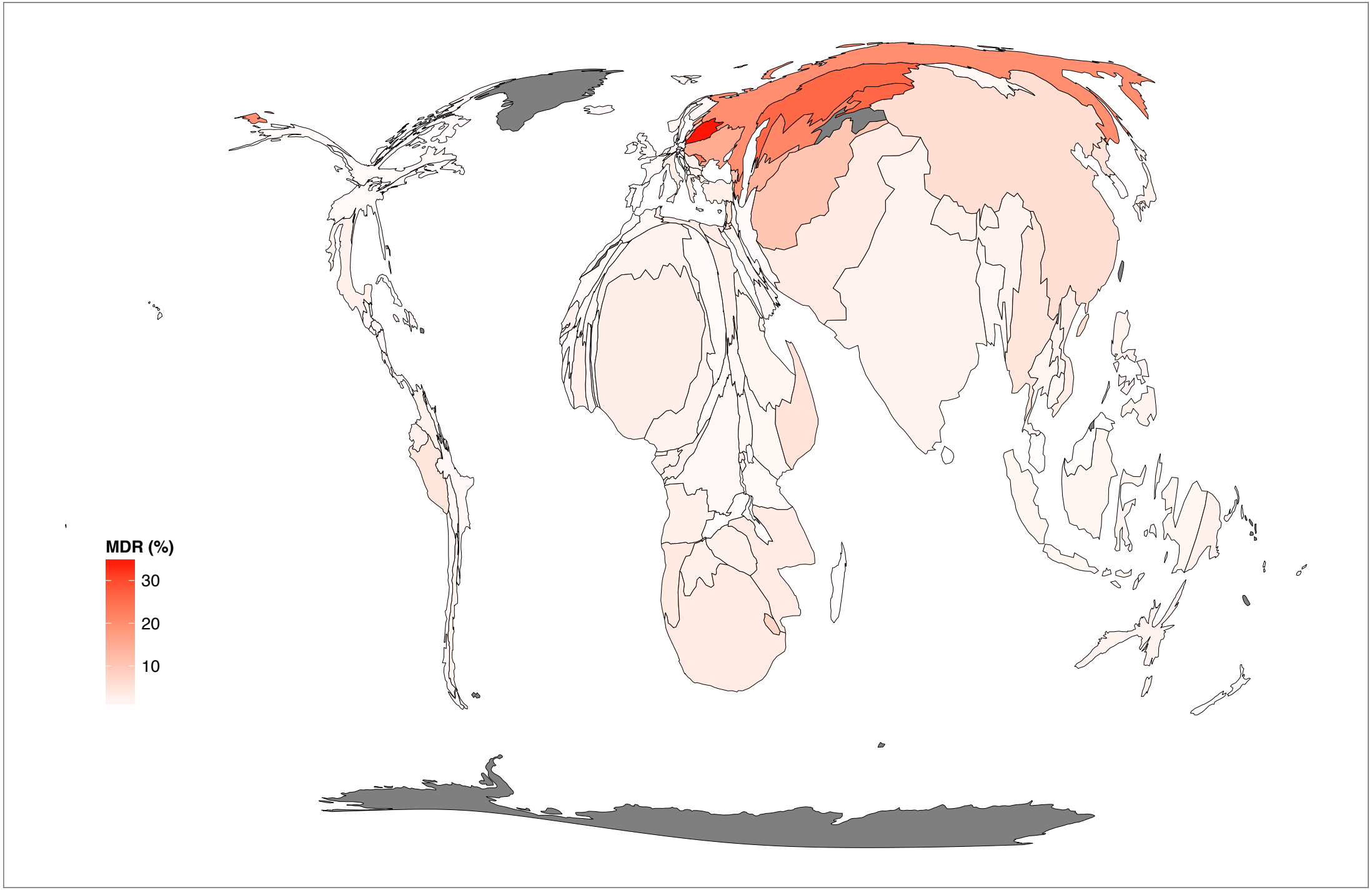
EMR
EUR
SEA
WPR
GLOBAL
WHO region
MDR type
MDR#
FQR
SLR
XDR

Figure 3



Appendix
Click here to download Necessary additional data: DR_burden_appendixR1.pdf

The global burden of drug-resistant tuberculosis in children: a mathematical model (Supplementary Information)

P.J. Dodd[1], C. Sismanidis[2], and J.A. Seddon[3]

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Underlying mathematical model of tuberculosis burden in children

A mechanistic mathematical model that uses estimates of adult tuberculosis prevalence to model the process of infection and progression to disease in different age-groups was used to generate estimates of latent infection and tuberculosis incidence in 180 countries in 2013. The model has been previously published and subsequently extended from the 22 high tuberculosis burden countries to a global model covering 180 countries.

The model has a number of uncertain data and natural history inputs, and the uncertainty inherent in these quantities is represented by generating a sample of 10,000 outputs running the model across a Latin hypercube sample from the distributions characterizing these input values. A summary is provided below.

Summary of methods

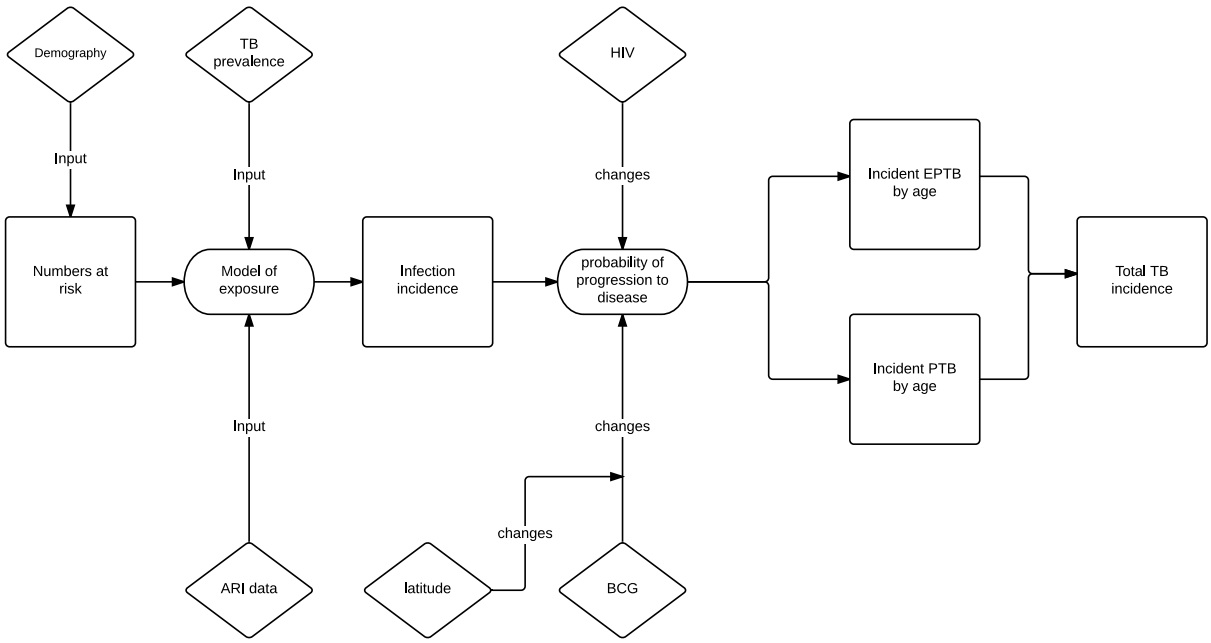


Figure 1: Overview of modelling logic. Diamonds represent data sources, squares represent numbers estimated at each stage, and stadiums represent modelling stages.

Description of data used

We obtained data on country demography for 2013 from UN ESA, Population Division. Where necessary, 5-year age categories were disaggregated under the assumption of uniformly distributed ages. These data were used to generate the number of children at risk in each country by age.

WHO estimates of adult tuberculosis prevalence were obtained from for 2014, together with 95% uncertainty bounds. Uncertainty in per-capita prevalence was represented by gamma distributions, parameterised by taking the quoted ranges defined by the upper and lower bounds as 1.96 x the standard deviation, and the quoted point estimate as the mean. WHO notification data from 2010 were used to estimate the proportion of incident tuberculosis that is smear positive for the community ARI estimate. The same estimate was used for all countries to avoid bias resulting from different case detection infrastructures etc.

BCG vaccination coverage estimates were obtained for 2014 from WHO. The BCG vaccination coverages were used to determine the fraction of children whose risks of progression from infection to disease were moderated by BCG.

HIV prevalence estimates in those aged under 15 were available for 82 countries from UNAIDS, together with 95% uncertainty bounds. Countries for which there were not estimates reported from this source were assumed to have negligible HIV prevalence in those under 15 years of age. Uncertainty in the prevalences was represented by gamma distributions, parameterised by taking the quoted ranges defined by the upper and lower bounds were taken as 1.96 x the standard deviation, and the quoted point estimate as the mean. This HIV prevalence was assumed to be uniform by age in those under 15. Degree of immunosuppression or ART was not considered.

Country linking and exclusions

The WHO tuberculosis estimate and notification data were linked with the demographic, HIV, and BCG sets by 3 letter ISO code where possible, and by hand otherwise. Various countries were excluded where it was not possible to link them across the data. The WHO version of country names was used.

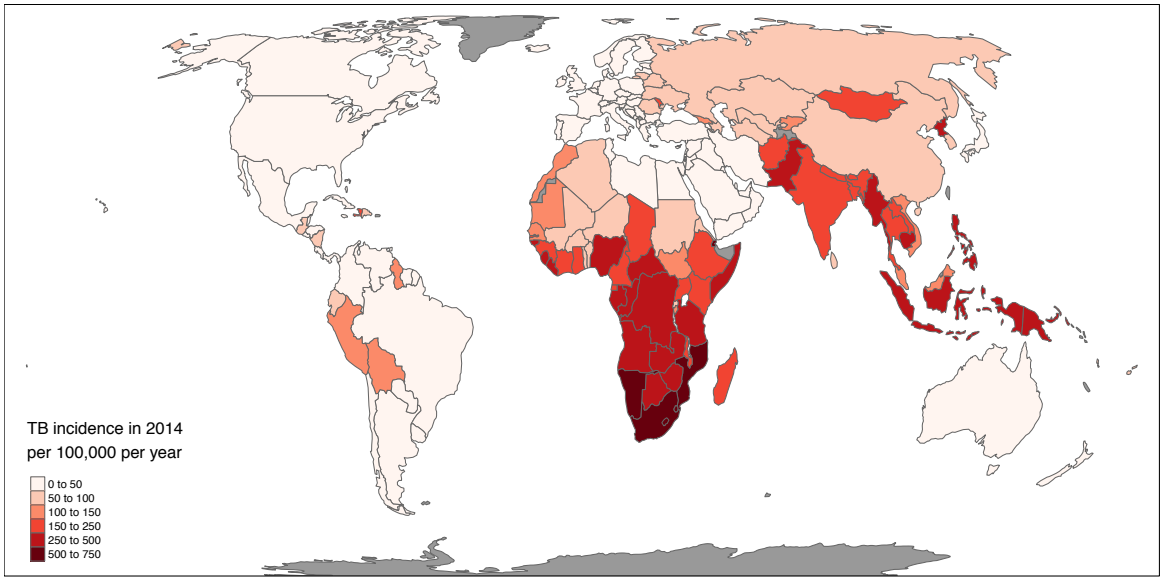


Figure 2: The 180 countries included in our analysis (color by estimated per-capita tuberculosis incidence)

Summary of differences from previous work

The largest difference is the set of countries to which the method is applied. Here, we apply the model to a set of 180 countries and use tuberculosis data from 2014; whereas in our previously published report (see reference in main article), we considered only the 22 highest burden tuberculosis countries (HBCs), using data largely from 2010.

We only consider the 'community' model of infection in this work, as data to inform the household method were not available for a large enough number of countries. We also shifted from using the latitude of a country's capital to the latitude of a country's centroid in the model variant with latitude variation in BCG efficacy.

Analysis of drug-resistance patterns

Data availability by region

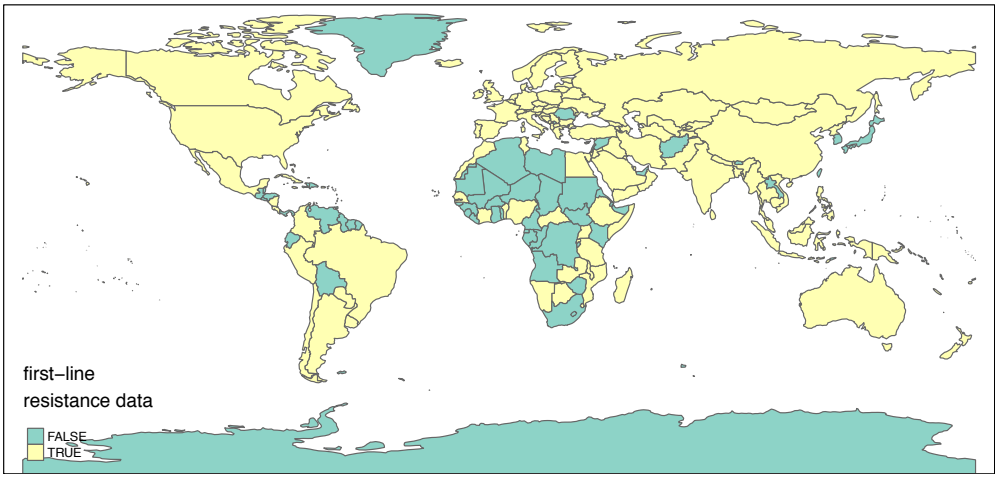


Figure 3: Countries with data on resistance to first-line anti-tuberculosis drugs in new cases

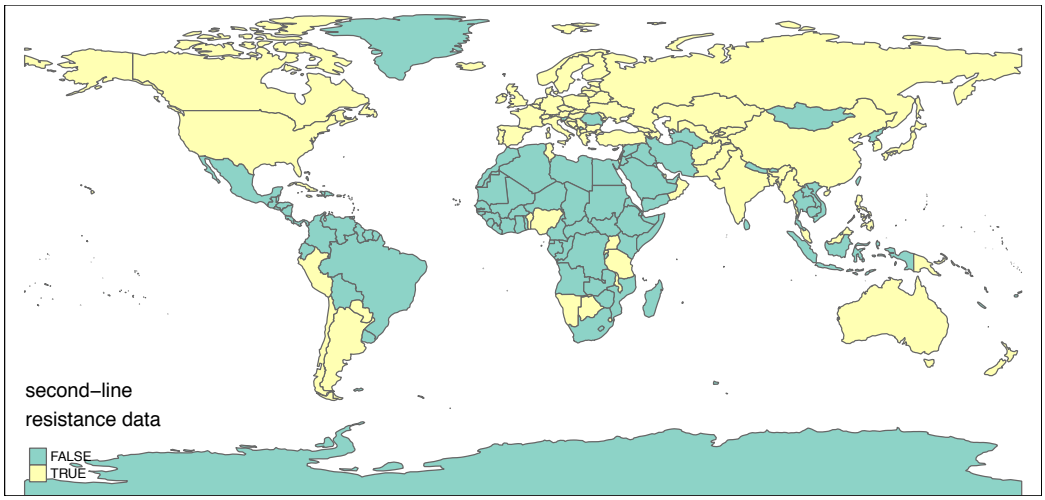


Figure 4: Countries with data resistance to second-line anti-tuberculosis drugs.

Nearest neighbor construction & interpretation of survey data

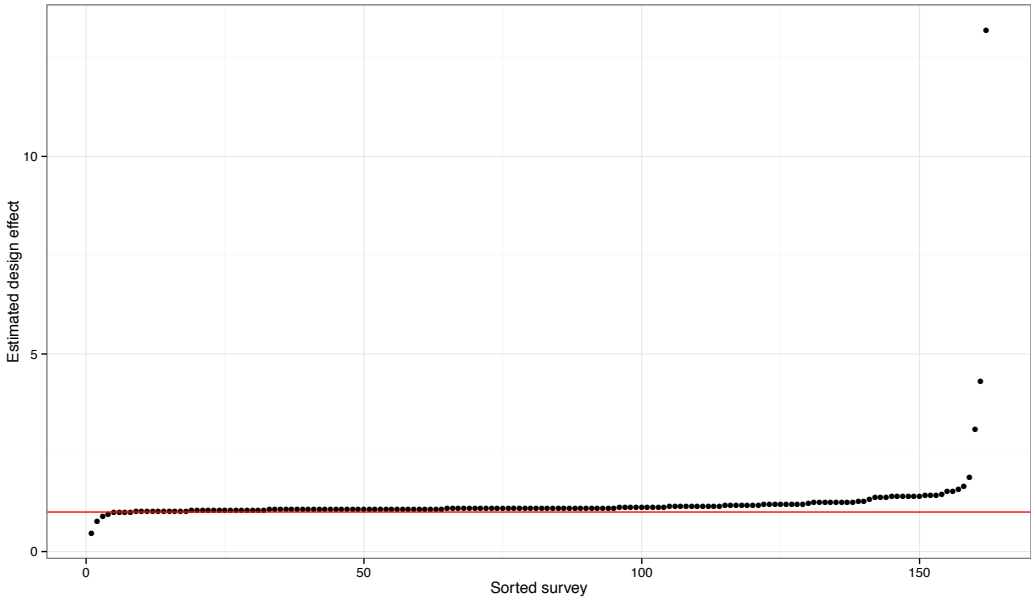


Figure 5: Ranked implied design effects in survey data on MDR in new cases based on reported confidence intervals and sample size. Red line at 1.

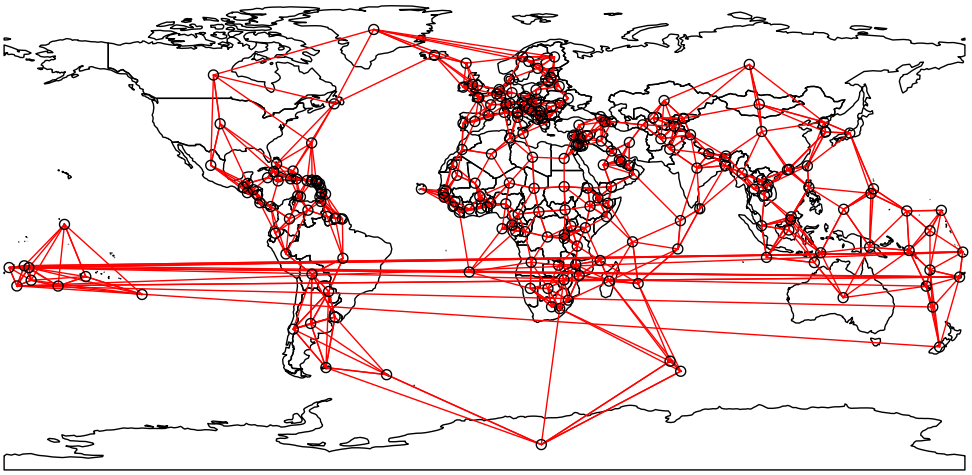


Figure 6: The network of 5 nearest-neighbors used for imputing drug resistance patterns for countries without data.

WHO regions used

The three key differences between the two sets of regions are (i) the split between Central and Eastern Europe based on well-studied and known differences in MDR-TB epidemiology, (ii) the separate region of high-income countries across the world who are expected to have stronger health systems that are closer to universal health coverage (considered proxy for lower levels of acquired drug resistance), and (iii) the split of the African region into high and low HIV prevalence (HIV being a key determinant of TB burden). The nine epidemiological regions are African countries with high HIV prevalence, African countries with low HIV prevalence, Central Europe, Eastern Europe, high-income countries, Latin America, the Eastern Mediterranean Region (excluding high-income countries), the South-East Asia Region (excluding high-income countries) and the Western Pacific Region (excluding high-income countries).

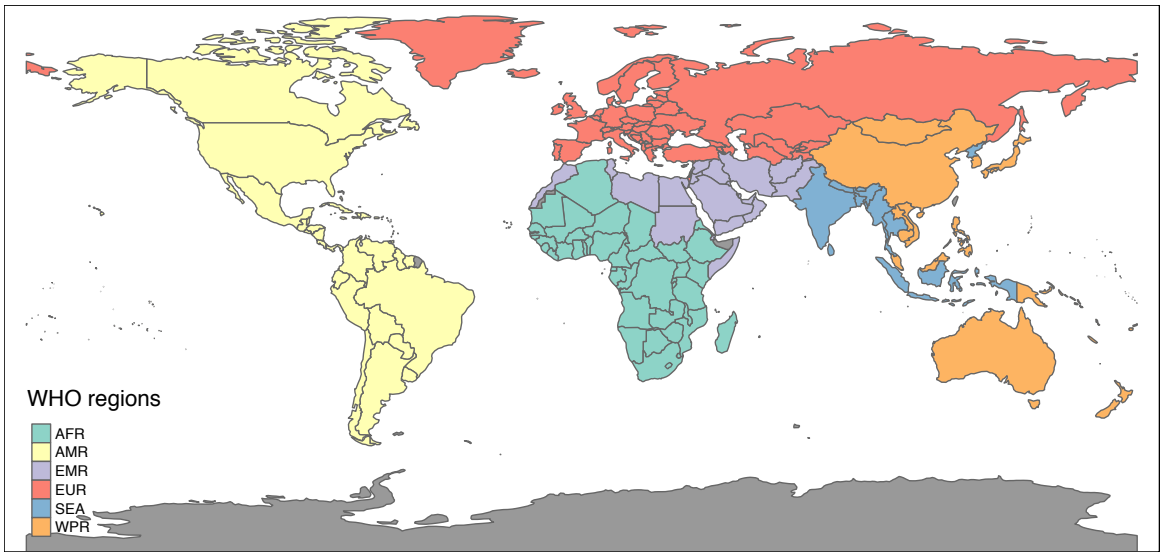


Figure 7: Map of standard WHO regions

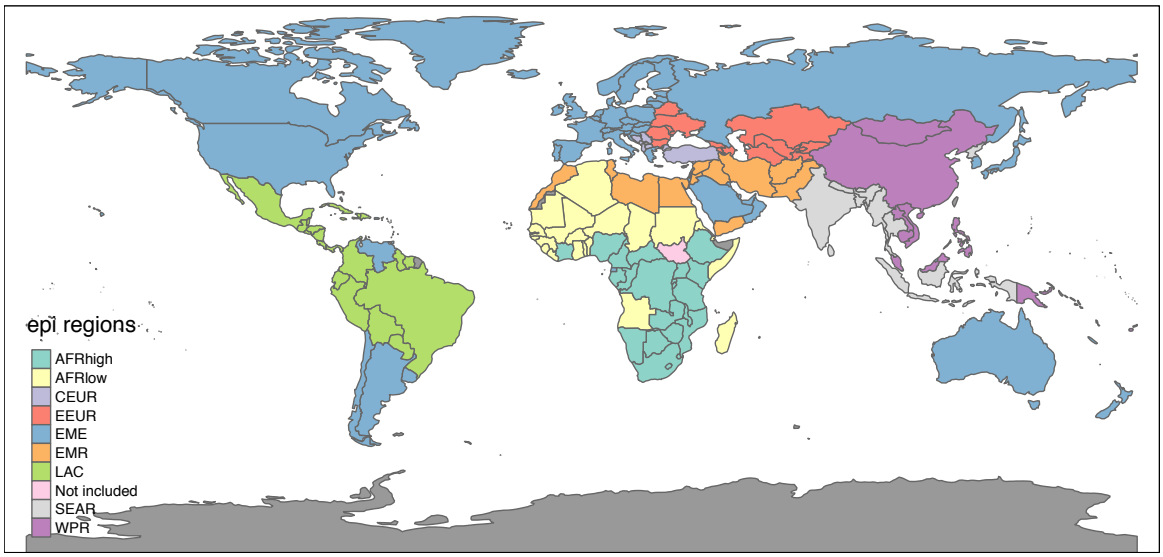


Figure 8: Map of WHO epidemiological regions used for resampling scheme.

Missing data

With complete data on the counts (n_S, n_H, n_R, n_M) of susceptible, HMR, RMR, and MDR tuberculosis we assumed a $Dir(1,1,1,1)$ (i.e. flat) prior on the proportions. Since this is conjugate to the multinomial distribution, the posterior was therefore $Dir(1 + n_S, 1 + n_H, 1 + n_R, 1 + n_M)$.

When, additionally (and e.g.) data was available on the total count $N' = n_S' + n_H' + n_R' + n_M'$, and the number MDR ($n_S', n_H', n_R'$ all missing due to incomplete DST), we sampled from the posterior summing over all possible unobserved missing counts compatible with the total. In effect, this amounts to a draw from a mixture of Dirichlet distributions. In combination

$$\propto \sum \binom{N'}{n_S' n_H' n_R' n_M'} \times Dir(1 + n_S + n_S', 1 + n_H + n_H', 1 + n_R + n_R', 1 + n_M + n_M')$$

Gibbs sampling was used to sample from these distributions using every 30th draw in a chain of 30,000 iterations (after a burn-in of 1,000 iterations).

Other combinations of missing drug resistance counts described in the article were handled analogously.

Source of data for country estimates

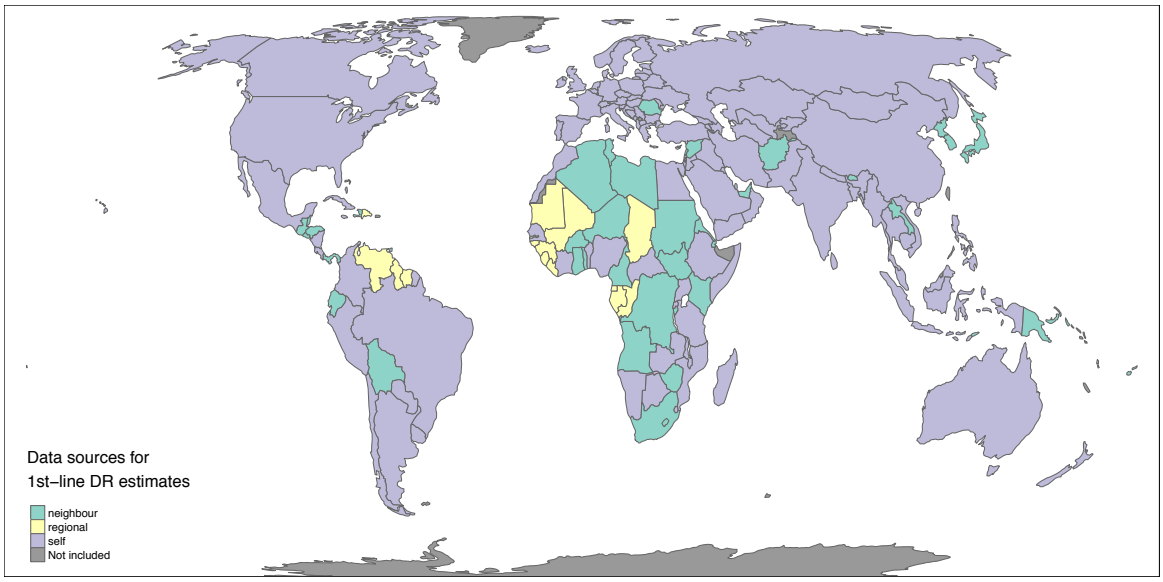


Figure 9: Source of data for each country used in first-line drug-resistance estimates

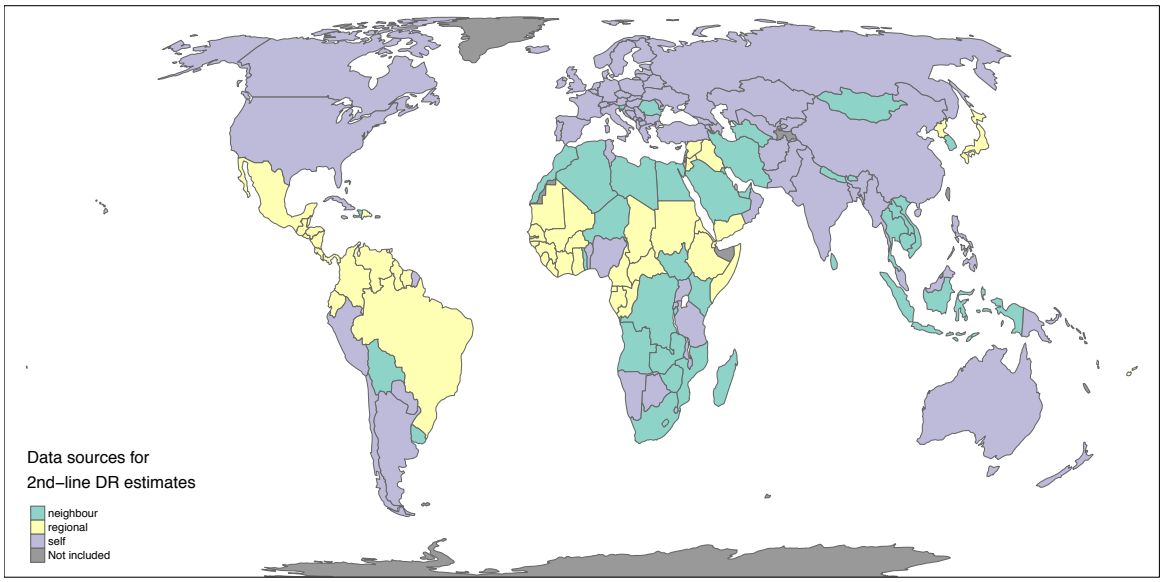


Figure 10: Source of data for each country used in second-line drug-resistance estimates

Supplementary results

Tables

Table 1: Percentage of incident tuberculosis in children by resistance type in 2014. IQR in brackets.

	% of incident children by resistance type				% of incident MDR children by resistance type			
	S	INH	RIF	MDR	MDR#	FQR	SLR	XDR
AFR	91.6 [91.2 - 92.0]	4.9 [4.5 - 5.5]	0.9 [0.8 - 1.0]	2.5 [2.2 - 2.7]	80.5 [77.8 - 82.9]	7.2 [5.7 - 9.1]	8.8 [6.5 - 11.4]	3.0 [2.4 - 3.7]
AMR	92.9 [92.4 - 93.2]	4.7 [4.4 - 5.0]	0.4 [0.3 - 0.6]	2.0 [1.8 - 2.3]	56.7 [47.7 - 66.0]	11.1 [8.5 - 13.9]	20.9 [16.9 - 25.7]	9.9 [7.5 - 12.5]
EMR	85.1 [83.5 - 86.4]	8.7 [7.8 - 9.7]	1.7 [1.3 - 2.2]	4.3 [3.8 - 5.0]	65.2 [60.9 - 68.7]	19.2 [16.4 - 22.5]	9.1 [7.4 - 11.5]	5.6 [4.4 - 7.3]
EUR	70.9 [69.6 - 72.4]	11.9 [11.3 - 12.5]	1.3 [1.2 - 1.5]	15.8 [14.7 - 16.7]	48.0 [40.7 - 54.4]	17.4 [13.5 - 24.0]	23.1 [18.7 - 29.0]	8.0 [7.2 - 8.9]
SEA	89.9 [89.6 - 90.3]	7.3 [7.0 - 7.5]	0.6 [0.6 - 0.7]	2.2 [2.0 - 2.3]	60.9 [52.2 - 69.5]	17.1 [15.5 - 18.8]	18.8 [10.6 - 26.8]	3.1 [2.6 - 3.8]
WPR	84.4 [84.0 - 84.8]	10.5 [10.2 - 10.8]	1.2 [1.1 - 1.3]	3.9 [3.7 - 4.1]	55.3 [53.2 - 57.8]	25.0 [23.4 - 26.6]	12.4 [11.5 - 13.3]	7.0 [6.3 - 7.6]
GLOBAL	89.3 [89.0 - 89.6]	6.9 [6.6 - 7.1]	0.9 [0.8 - 1.0]	2.9 [2.7 - 3.1]	65.9 [62.8 - 68.6]	15.4 [14.4 - 16.6]	13.8 [11.4 - 16.5]	4.7 [4.3 - 5.1]

Table 2: Estimates of incident tuberculosis in children under 5 by drug resistance type and WHO region, 2014.

	Total	Estimates of incident tuberculosis in children <5 by drug resistance type				Estimates of incident MDR-tuberculosis in children <5 by drug resistance type			
		DS	HMR	RMR	MDR	MDR#	FQR	SLR	XDR
AFR	181,000 [113,000 - 274,000]	166,000 [104,000 - 251,000]	9,030 [5,600 - 13,900]	1,560 [968 - 2,390]	4,380 [2,720 - 6,790]	3,500 [2,150 - 5,430]	304 [179 - 508]	376 [222 - 620]	130 [78 - 210]
AMR	12,100 [7,750 - 18,600]	11,200 [7,210 - 17,300]	564 [357 - 875]	56 [33 - 92]	253 [156 - 396]	139 [84 - 219]	28 [16 - 46]	53 [31 - 87]	25 [15 - 41]
EMR	38,400 [24,300 - 58,000]	32,700 [20,700 - 49,200]	3,320 [2,110 - 5,110]	666 [399 - 1,070]	1,680 [1,050 - 2,610]	1,080 [671 - 1,660]	322 [199 - 512]	152 [89 - 257]	95 [55 - 159]
EUR	6,770 [4,170 - 10,700]	4,790 [2,970 - 7,510]	815 [499 - 1,300]	92 [56 - 146]	1,070 [652 - 1,730]	496 [301 - 795]	188 [106 - 335]	245 [142 - 420]	86 [52 - 139]
SEA	143,000 [90,100 - 216,000]	128,000 [81,100 - 194,000]	10,300 [6,500 - 15,800]	883 [559 - 1,360]	3,080 [1,940 - 4,710]	1,810 [1,140 - 2,780]	521 [323 - 816]	508 [243 - 958]	96 [58 - 155]
WPR	45,900 [29,300 - 69,400]	38,800 [24,700 - 58,500]	4,840 [3,080 - 7,260]	548 [345 - 843]	1,790 [1,140 - 2,720]	990 [629 - 1,500]	445 [278 - 681]	221 [139 - 338]	124 [77 - 189]
GLOBAL	435,000 [278,000 - 651,000]	389,000 [248,000 - 581,000]	29,500 [18,800 - 44,300]	3,920 [2,510 - 5,960]	12,700 [8,020 - 19,000]	8,330 [5,270 - 12,500]	1,940 [1,210 - 2,910]	1,720 [1,050 - 2,680]	596 [377 - 898]

Maps of incidence and infection burden

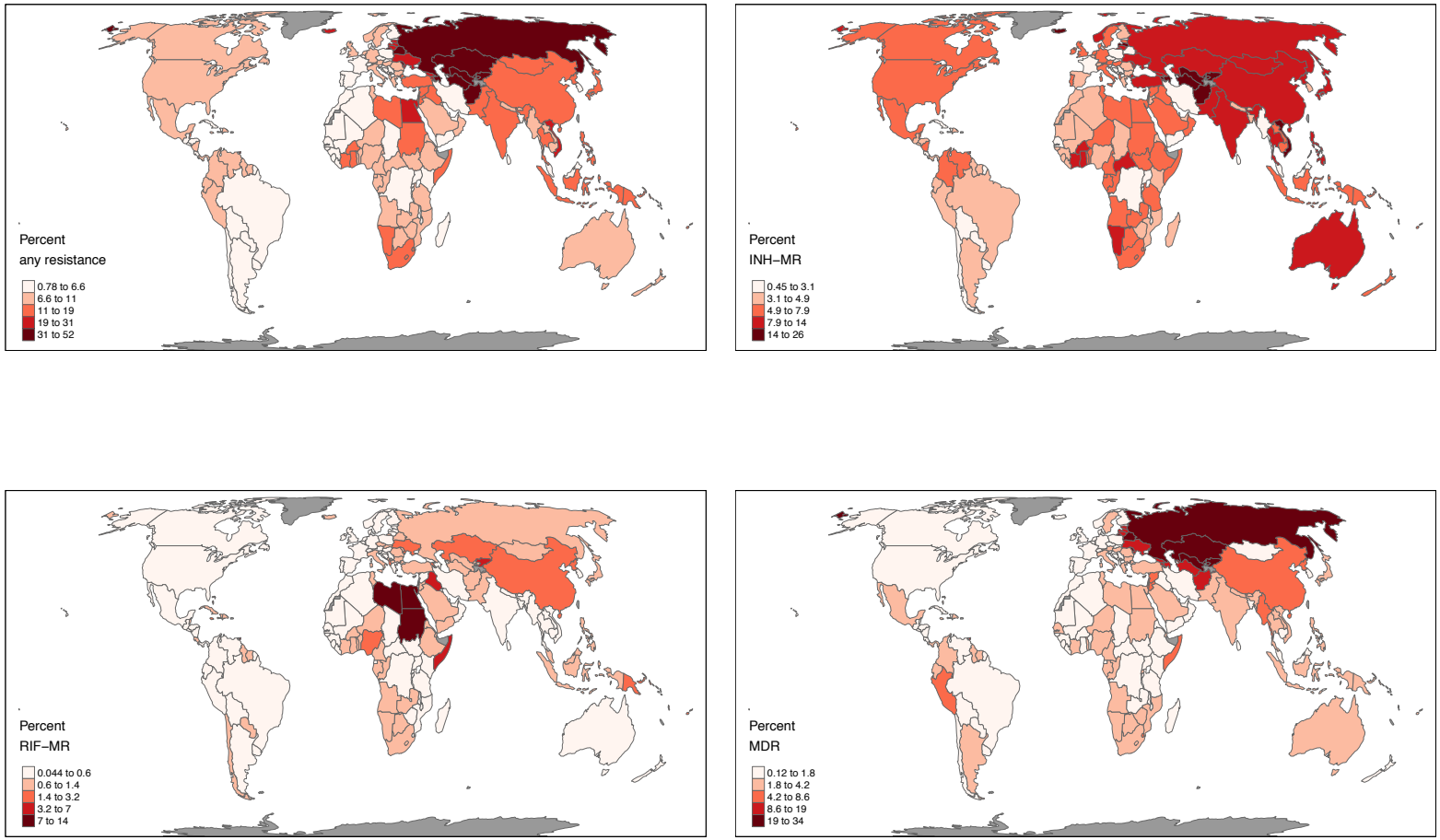


Figure 11: Percentage of tuberculosis disease in children by first-line resistance types, 2014

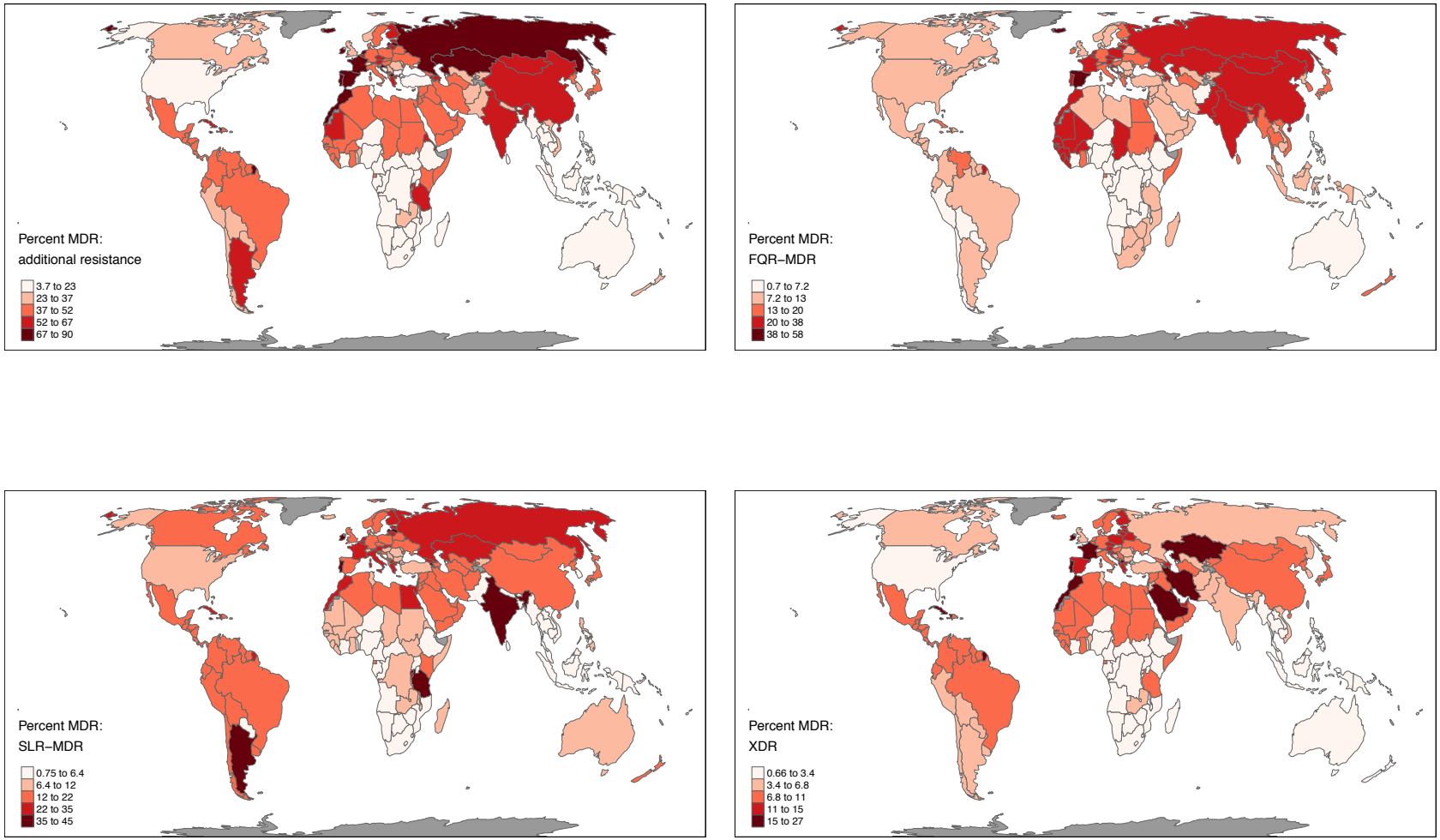


Figure 12: Percentage of MDR tuberculosis disease in children by second-line resistance type, 2014

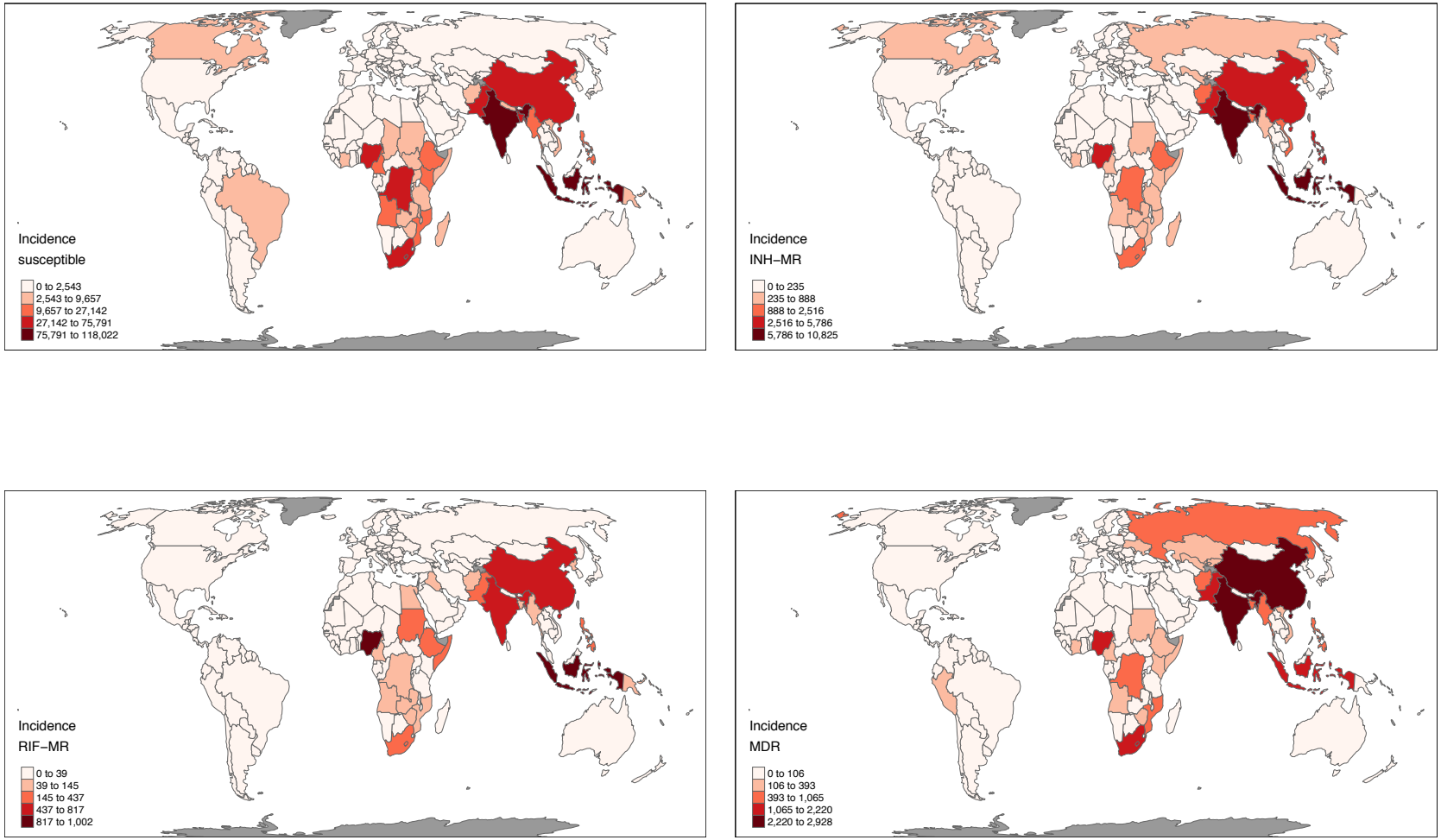


Figure 13: Tuberculosis incidence in children by first-line resistance type, 2014

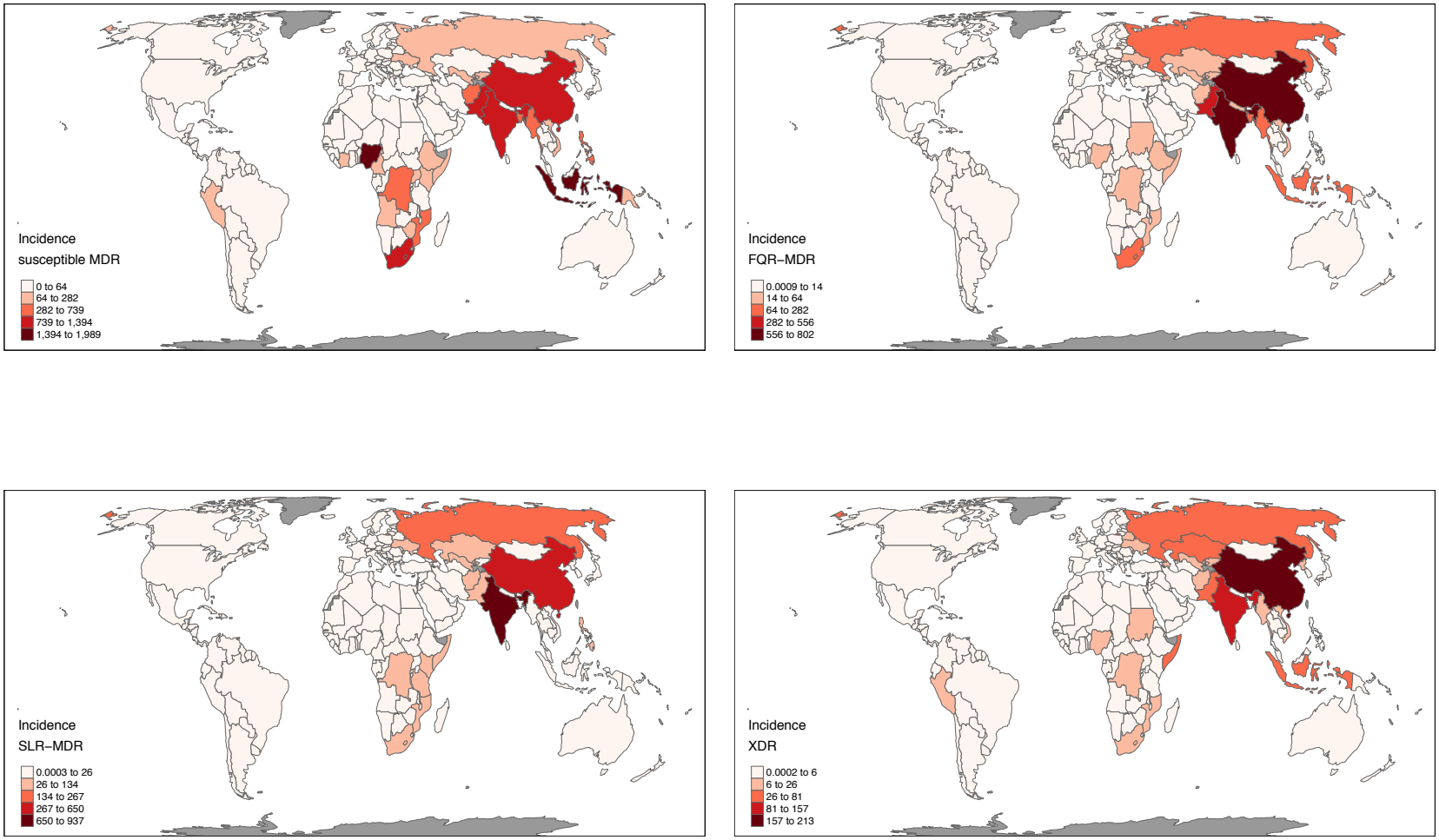


Figure 14: Tuberculosis incidence in children by second-line resistance type, 2014

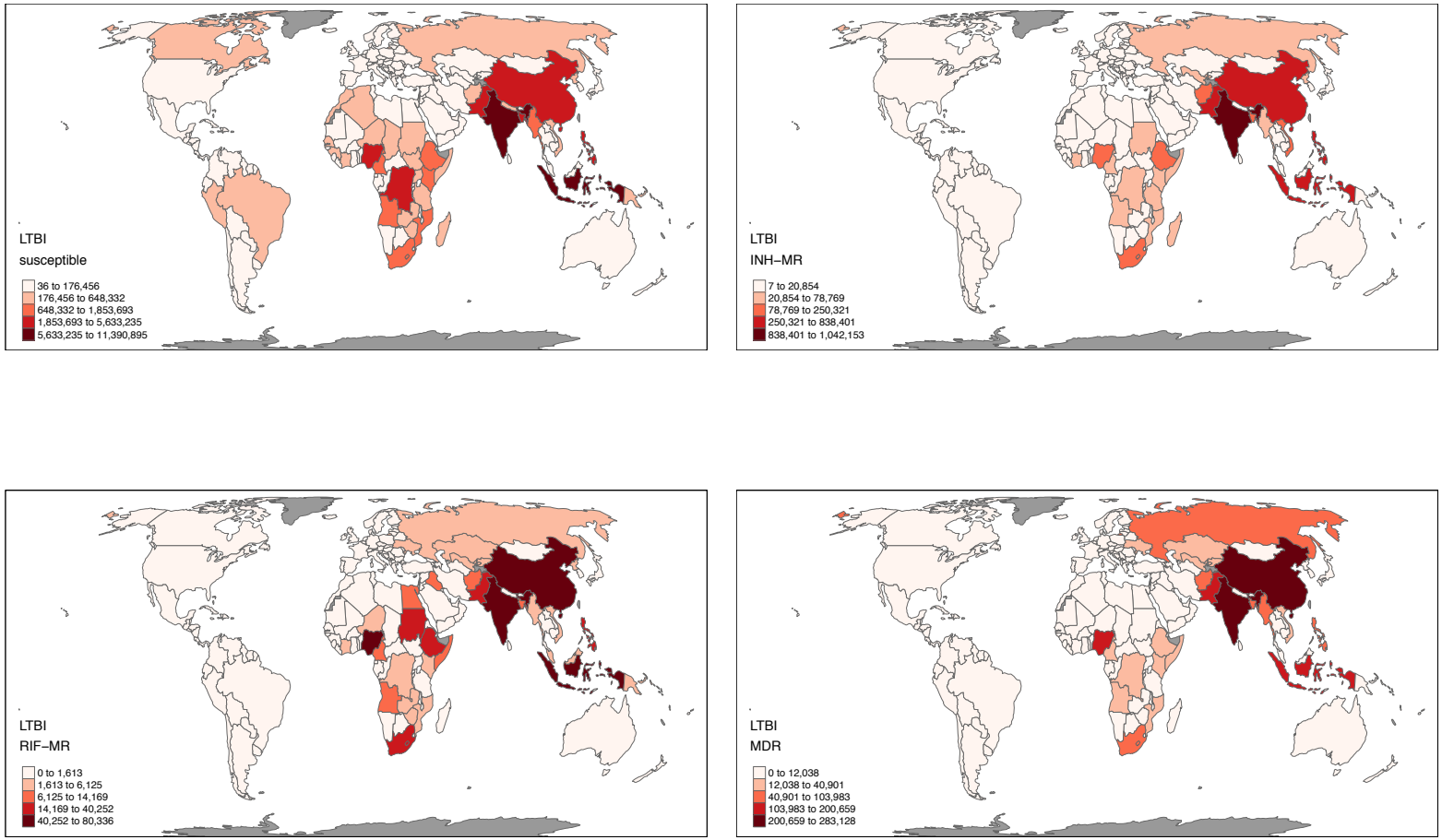
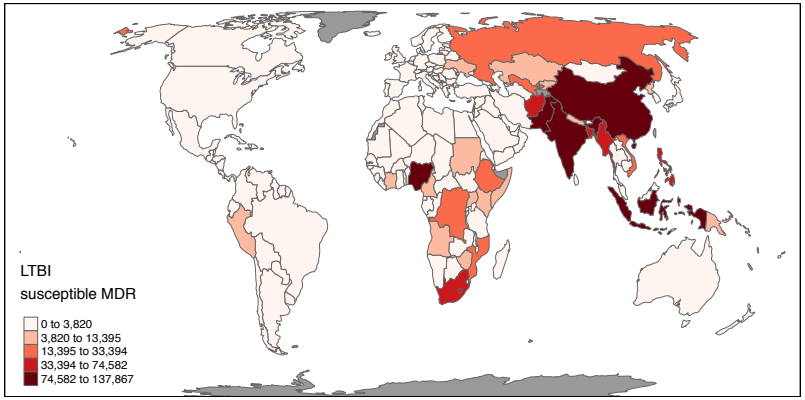
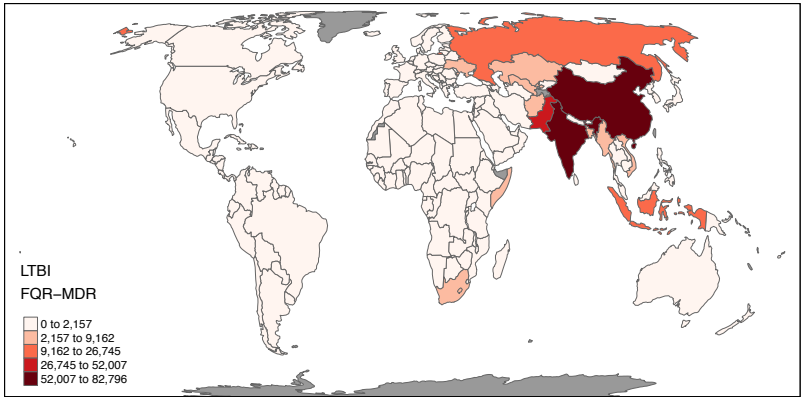
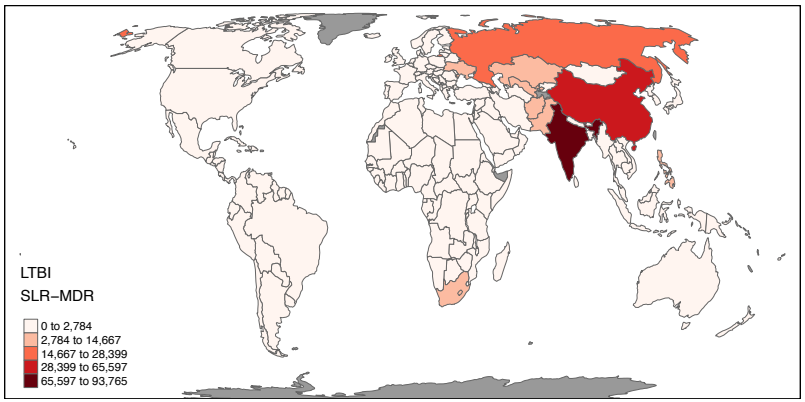


Figure 15: LTBI in children by first-line resistance type, 2014







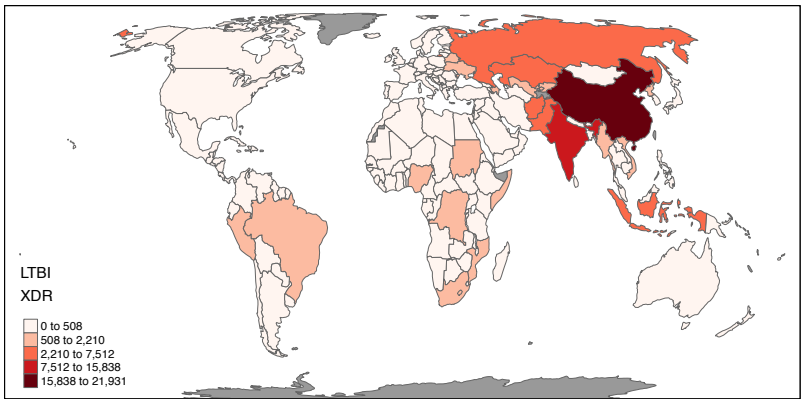


Figure 16: LTBI in children by second-line resistance type, 2014