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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Dodd PJ, Yuen CM, Sismanidis C, Seddon JA, Jenkins HE. The global burden of tuberculosis mortality in children: a mathematical modelling study. *Lancet Glob Health* 2017; **5:** e898–906.

The global burden of tuberculosis mortality in children: a mathematical modelling study (supplementary information)

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Supplementary methods

Data preparation

HIV/ART data

Data were downloaded from http://aidsinfo.unaids.org (accessed 2/12/2016).

There were some countries without paediatric HIV estimates for 2015 that had estimates for 2014 in the previous year's dataset (ISO3 codes: COG, ETH, GNB, KGZ, KHM, LA, NGA). For these countries, we assumed that their paediatric HIV prevalence as a proportion of the global paediatric HIV prevalence remained unchanged from 2014 to 2015, assigning their paediatric HIV prevalence (and uncertainty bounds) by applying the relevant country proportion to the revised global paediatric HIV estimate.

Similarly, for paediatric ART coverage, there were some countries with missing data in the 2016 estimates (ISO3 codes: COL, COG, ETH, GNB, KGZ, KHM, LAO, NGA); for these countries we used the ART coverage for 2014 in the previous year's estimates.

For one large, high TB burden country (India), data were not available in either year's HIV dataset. However, http://aidsinfo.unaids.org reported both the number of children on ART, and the coverage; we used this data to compute the paediatric HIV prevalence for India in 2015.

Other data preparation and analysis

Scripts for the above data cleaning, as well as all subsequent merging and data handling are available on github here. This repository also includes all input data, model analysis scripts, and a set of test output graphs around representation of input parameter uncertainty etc. It also contains additional output data, including country level estimates.

Odds ratios for death on TB treatment given HIV/ART status

We use US data on deaths in children on TB treatment from Shah et al., as presented in Jenkins et al. Table 3. These data are counts of number of children treated, and the number that died, stratified by HIV-status and by early or late time periods (meaning 1993-1996 or 1997-2011, reflecting the introduction of ART as standard of care). These data are interpreted as HIV-positive children in the early period not being on ART, but HIV-positive children in the late period being on ART. However, the case-fatality in HIV-negative children in the early period is higher than in the late period. We therefore used his data to generate odds ratios (ORs) for the effects of HIV-infection and ART on mortality while on TB treatment, adjusting for the time period.

Specifically, we took

$$logit(p_{ijk}) = mu + HIV \times i + ART \times j + late \times k$$

Where p_{ijk} is the probability of death for a child whose HIV status is *i* (0 negative, 1 positive), whose ART status is *j* (0 negative, 1 positive), and whose period is *k* (0 early, 1 late).

Because the estimates for the log-ORs *HIV* and *ART* were negatively correlated (see Figure 1), we represented these variables in the probabilistic sensitivity analysis using a multivariate normal distribution, with empirically-estimated mean and variance:

$$\mu = (2.64, -0.57), \Sigma = [0.23, -0.23; -0.23, 0.64]$$

The Cholesky decomposition of Σ was used to sample correlated pairs of ORs for HIV/ART mortality on treatment within the overall Latin hypercube design.

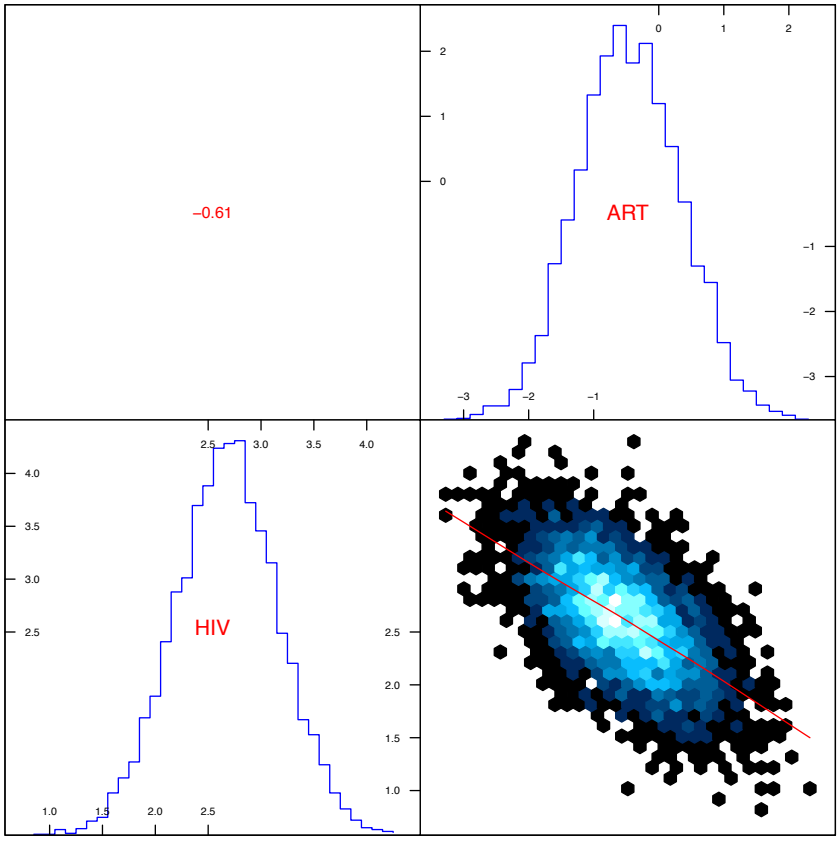

Figure 1 :Pairs plot of posterior densities for parameters in model for odds ratios of mortality on TB treatment given HIV/ART status. Red numbers are correlations and red lines are LOESS smoothers.

Elicitation details

For ethical reasons, data on HIV infected children with TB (necessarily in the chemotherapy era) who have not been treated for TB do not exist. We therefore elicited CFRs from six clinical experts for HIV-infected children not treated for TB by age and ART-status.

Participating in our elicitation exercise were the following paediatric physicians with direct experience of treating children with TB in high HIV-burden settings: Chishala Chabala, Steve Graham, Veronica Mulenga, Helena Rabie, James Seddon, Elisabetta Walters.

The participants were sent an email with the instructions contained in **Figure 2**, went to the MATCH website (see reference in article, link in **Figure 2**) and used the 'roulette' method to specify their beliefs.

For many aspects of the model we can use published data to inform risk but it is not possible to do this for children with HIV who have untreated TB as obviously studies of this have not been done for ethical reasons.

For this bit of the model we are trying to see what a selection of specialists might expect. We are going to ask a number of people (5-10) for their thoughts and will use pooled beliefs to inform the model. We would also plan to include anonymised individual opinions in the supplementary information. If you are happy to be acknowledged, we would be keen to mention you at the end of the article, in the acknowledgements section. We expect it will take around 5 minutes to do this exercise.

We are seeking to quantify your beliefs about the Case Fatality Rate (proportion of cases that die) for TB cases not treated for TB, among children in the following categories:

1. Children aged <5 with HIV, not receiving ART
2. Children aged <5 with HIV, receiving ART
3. Children aged 5-15 with HIV, not receiving ART
4. Children aged 5-15 with HIV, receiving ART

We are using a website to try to help people convert their opinions (and the uncertainty around those opinions) into something that we can use mathematically. This website has been used in a number of other pieces of research. To quantify your beliefs, please go to this website: http://optics.eee.nottingham.ac.uk/match/uncertainty.php

Please follow these steps for each category:

1. In the 'Elicitation options' box (top right), set the lower limit to 0 (CFR=0%) and the upper limit to 1 (CFR=100%), click 'update limits' and then check the 'Roulette' box under 'Input Mode'. A grid should appear to represent a histogram on, with an x-axis going from 0 to 1.
2. By clicking on the grid, please arrange 20 'chips' that form a histogram, which best represents your beliefs about the fraction of children in the relevant category that die if not treated for TB. (Note: chips can be unplaced by clicking again)
3. Click 'Fitting & feedback' at the top of the page
4. Check the box 'Scaled Beta' under 'Distribution' on the right of the new graph.
5. A smooth distribution representing your beliefs will appear below your histogram. Please adjust the histogram if necessary, so that the smooth curve is a reasonable representation of your beliefs.
6. Please take a screenshot of the result you are happy with and copy it into a word document and write in text above or below clearly describing which category this corresponds to.
7. Without needing to go back, you can now click on the top graph re-allocate your 20 chips. Please follow steps 5 and 6 until you have generated graphs for each of the four categories requested.
8. Please email the completed word document

Figure 2: Text used in elicitation instructions

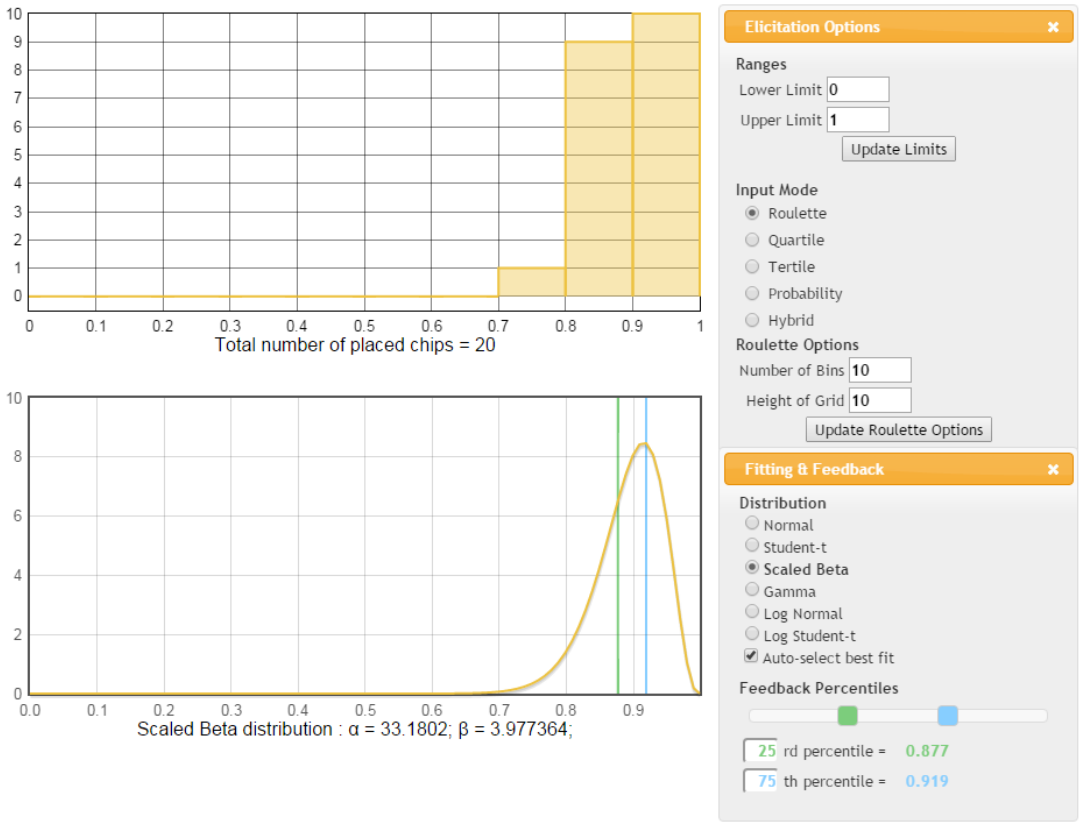

Figure 3: Example elicitation screen shot (HIV+ ART- <5 years)

The roulette method involves placing 20 chips on a grid to sketch out a probability distribution, which is then fitted to a beta distribution (see screenshot in **Figure 3**). The beta distribution shape parameters were recorded (see **Table 1**) and the distributions geometrically pooled (i.e. an arithmetic mean of the beta exponent/shape parameters taken). A plot of the four pooled distributions (2 age categories x 2 ART categories) for CFRs in HIV-infected children without TB treatment is shown in **Figure 4**.

Table 1: Elicited parameters of beta distributions for CFRs of untreated children with HIV. (Last row in bold shows pooled parameters)

u5 no ART a	u5 no ART b	u5 on ART a	u5 on ART b	5-14 no ART a	5-14 no ART b	5-14 on ART a	5-14 on ART b
33.180	3.977	5.078	2.982	16.181	2.640	4.354	5.828
13.832	3.568	17.379	13.900	19.202	6.914	12.836	15.163
13.123	12.197	3.501	30.015	3.794	10.052	2.287	13.303
13.900	3.123	20.857	19.789	17.278	8.891	10.204	18.697
194.374	21.892	16.565	6.715	23.448	8.140	15.621	11.114
194.374	21.892	27.741	3.849	37.642	4.745	17.301	2.400
77.131	**11.108**	**15.187**	**12.875**	**19.591**	**6.897**	**10.434**	**11.084**

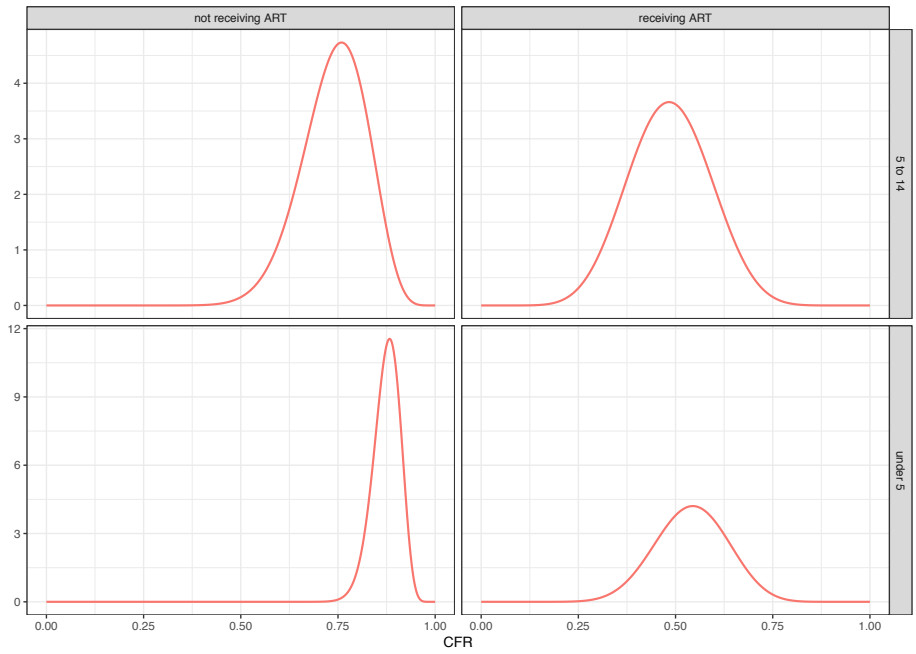

Figure 4: Pooled distributions corresponding to the elicited CFRs in children with HIV not treated for TB

Supplementary Results

Untreated HIV-positive mortality sensitivity analysis

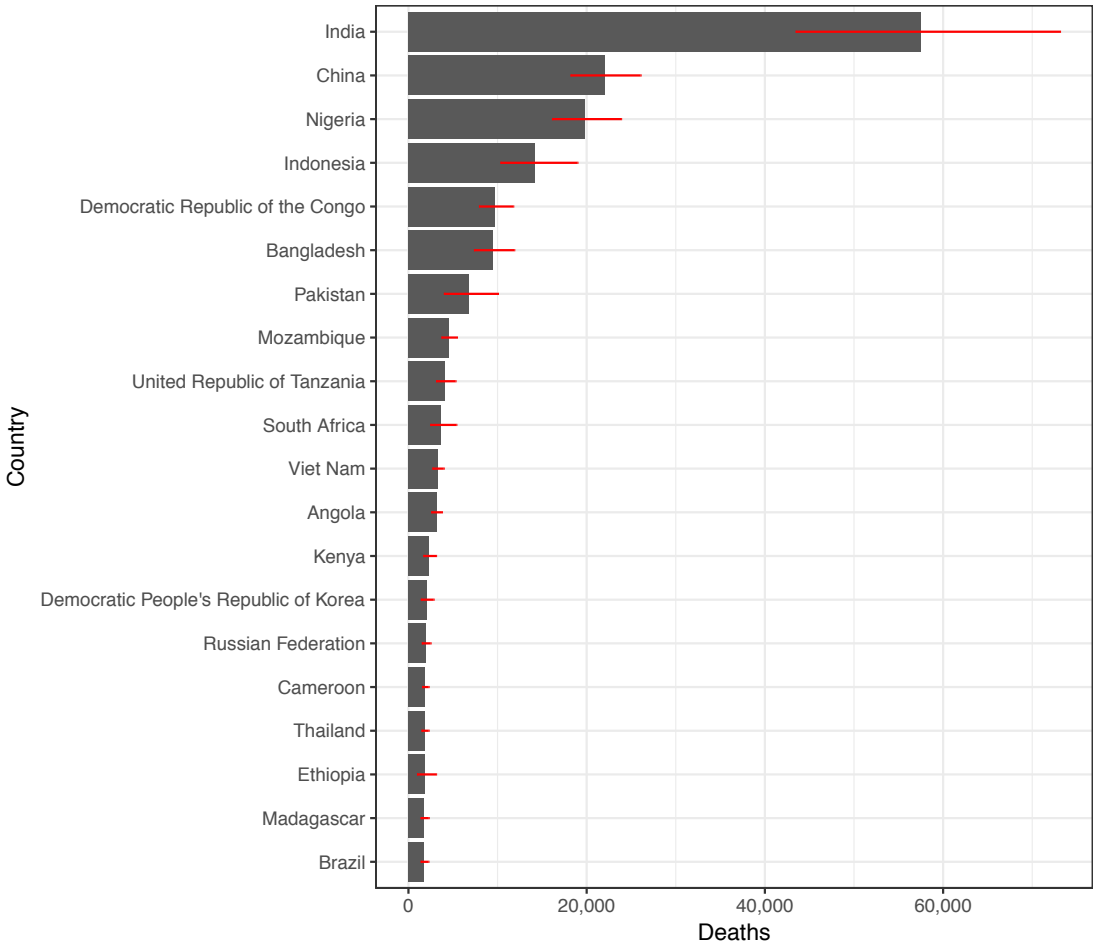

Figure 5: Top 20 countries by median estimated TB mortality in children <15 (error bars are IQR), HIV sensitivity analysis

Table 2: Regional and global paediatric TB mortality, HIV sensitivity analysis

Age	WHO region	Received TB treatment (HIV-negative)	Did not receive TB treatment (HIV-negative)	Received TB treatment (HIV-positive)	Did not receive TB treatment (HIV-positive)	TOTAL
<5	AFR	654 [369 - 1,350]	44,500 [30,800 - 61,200]	1,900 [753 - 5,610]	9,600 [5,190 - 20,200]	58,100 [41,600 - 76,700]
	AMR	93 [61 - 153]	3,920 [2,160 - 5,960]	27 [6 - 148]	52 [13 - 238]	4,130 [2,340 - 6,180]
	EMR	332 [166 - 831]	10,400 [3,480 - 20,800]	34 [8 - 179]	93 [21 - 402]	10,900 [3,980 - 21,400]
	EUR	72 [47 - 133]	4,450 [2,600 - 6,490]	1 [0 - 7]	12 [3 - 69]	4,550 [2,690 - 6,600]
	SEA	998 [490 - 2,130]	70,700 [24,300 - 127,000]	247 [52 - 1,200]	1,360 [171 - 10,100]	74,600 [26,200 - 131,000]
	WPR	367 [140 - 1,160]	25,300 [10,700 - 41,600]	15 [2 - 106]	124 [30 - 532]	25,900 [11,300 - 42,200]
	TOTAL	2,690 [1,850 - 4,170]	160,000 [108,000 - 220,000]	2,370 [1,090 - 6,080]	12,100 [6,640 - 25,400]	179,000 [124,000 - 240,000]
<15	AFR	981 [640 - 1,700]	54,800 [42,100 - 69,900]	2,890 [1,310 - 7,180]	12,100 [6,940 - 23,500]	71,900 [58,700 - 88,000]
	AMR	147 [110 - 209]	4,900 [3,570 - 6,540]	42 [11 - 203]	71 [25 - 257]	5,190 [3,850 - 6,850]
	EMR	628 [378 - 1,180]	11,500 [5,420 - 21,500]	61 [15 - 287]	113 [34 - 431]	12,400 [6,220 - 22,500]
	EUR	137 [103 - 202]	5,250 [3,890 - 6,950]	3 [0 - 12]	15 [4 - 79]	5,420 [4,050 - 7,120]
	SEA	2,150 [1,350 - 3,590]	83,000 [47,700 - 132,000]	567 [123 - 3,010]	1,690 [304 - 11,200]	88,700 [52,400 - 139,000]
	WPR	613 [340 - 1,410]	31,700 [21,000 - 44,700]	35 [6 - 229]	156 [42 - 599]	32,600 [21,900 - 45,600]
	TOTAL	4,810 [3,710 - 6,560]	193,000 [152,000 - 244,000]	3,920 [1,930 - 8,760]	15,000 [8,830 - 29,200]	218,000 [176,000 - 270,000]

Under-notification sensitivity analysis

Table 3: Assumptions made for under-notification sensitivity analysis. Proportion of tuberculosis patients treated but not notified in the 10 countries with highest estimated child TB mortality (72% of global mortality)

Country (ISO3 code)	Percentage of TB patients treated in non-NTP sector[§]	Source/reference	Percentage of global TB deaths in children
IND	46%	cross-sectional door-to-door interviews, 2011 (1)	26%
CHN	23%	upper bound from analysis of drug sales data, 2010 (2)	11%
NGA	10%	national prevalence survey, 2012 (3)	10%
IDN	56%	national prevalence survey, 2015	6%
COD	0%	assumption	5%
BGD	7%	upper bound from analysis of drug sales data, 2010 (2)	4%
PAK	32%	national inventory study, 2012 (4)	3%
MOZ	0%	assumption	2%
TZA	0%	regulatory study 2009-2011 (5)	2%
VNM	9%	national prevalence survey, 2006-7 (6)	2%

[§] Public and private not reported to the NTP=National Tuberculosis Programme; all numbers are for adults – we assume these proportions apply equally to children.

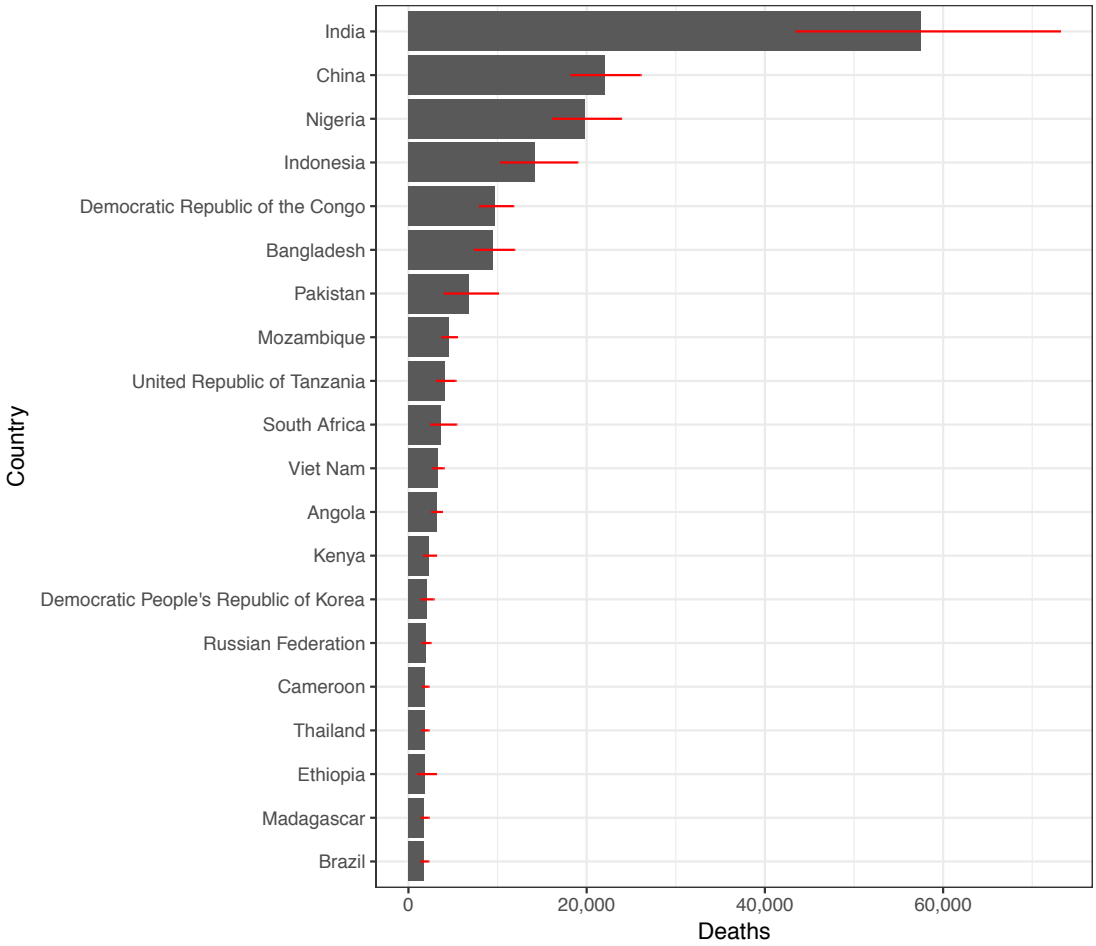

Figure 6: Top 20 countries by median estimated TB mortality in children <15 (error bars are IQR), under-notification sensitivity analysis

Table 4: Regional and global paediatric TB mortality, under-notification sensitivity analysis

Age	WHO region	Received TB treatment (HIV-negative)	Did not receive TB treatment (HIV-negative)	Received TB treatment (HIV-positive)	Did not receive TB treatment (HIV-positive)	TOTAL
<5	AFR	661 [377 - 1,390]	44,400 [30,700 - 61,600]	1,900 [757 - 5,580]	17,300 [9,290 - 38,000]	66,100 [47,000 - 89,700]
	AMR	93 [62 - 151]	3,910 [2,180 - 5,900]	27 [6 - 154]	84 [20 - 424]	4,170 [2,410 - 6,200]
	EMR	417 [193 - 1,140]	8,400 [3,020 - 18,900]	38 [8 - 200]	170 [37 - 769]	9,150 [3,660 - 19,800]
	EUR	72 [47 - 134]	4,460 [2,590 - 6,480]	1 [0 - 7]	17 [4 - 98]	4,560 [2,680 - 6,580]
	SEA	1,660 [790 - 3,710]	59,500 [14,700 - 116,000]	415 [83 - 2,150]	1,960 [108 - 17,600]	65,500 [17,500 - 125,000]
	WPR	372 [143 - 1,170]	25,200 [10,600 - 41,100]	15 [2 - 107]	221 [53 - 905]	26,000 [11,300 - 41,800]
	TOTAL	3,480 [2,300 - 5,700]	147,000 [95,300 - 209,000]	2,640 [1,210 - 6,610]	21,300 [11,500 - 46,600]	177,000 [120,000 - 244,000]
<15	AFR	989 [649 - 1,740]	54,700 [42,100 - 70,000]	2,920 [1,300 - 7,230]	28,100 [16,300 - 54,600]	88,600 [71,700 - 112,000]
	AMR	147 [111 - 209]	4,890 [3,630 - 6,490]	42 [10 - 210]	166 [57 - 551]	5,300 [3,990 - 6,930]
	EMR	817 [471 - 1,630]	9,250 [4,160 - 19,600]	70 [17 - 339]	250 [75 - 939]	10,500 [5,290 - 21,000]
	EUR	136 [103 - 202]	5,250 [3,860 - 6,940]	3 [0 - 12]	26 [7 - 144]	5,430 [4,030 - 7,130]
	SEA	3,540 [2,150 - 6,230]	64,300 [25,900 - 119,000]	967 [199 - 5,630]	2,480 [383 - 18,800]	73,400 [32,300 - 132,000]
	WPR	630 [348 - 1,430]	31,400 [20,800 - 44,200]	35 [6 - 229]	354 [96 - 1,290]	32,500 [21,900 - 45,400]
	TOTAL	6,460 [4,750 - 9,330]	171,000 [127,000 - 230,000]	4,460 [2,190 - 10,400]	33,000 [19,500 - 63,300]	218,000 [169,000 - 282,000]

HIV prevalence results

Table 5: Paediatric HIV prevalence for countries with HIV prevalence over 0.1% in children

Country ISO3 code	HIV prevalence (%)	HIV in incident TB (%)	HIV in TB deaths (%)
AGO	0.2	11	23.7
BDI	0.2	9.9	21.7
BEN	0.1	4.9	10.9
BFA	0.1	5.1	11.9
BHS	0.1	1.5	10.7
BLZ	0.1	2	3.7
BWA	1.2	24.2	41
CAF	0.5	23.8	44.6
CIV	0.3	16.2	32.8
CMR	0.4	21.1	40.9
COD	0.1	7	16
COG	0.3	18	37.4
DJI	0.2	12.5	26.6
DOM	0.1	2.8	6.8
ERI	0.1	3.1	7.6
ETH	0.1	8.5	28.5
GAB	0.4	15.7	31.2
GHA	0.2	9.8	21.9
GIN	0.1	7.8	17.8
GMB	0.2	10.6	22.8
GNB	0.4	22.2	43.1
GNQ	0.7	34.5	58.7
GUY	0.1	2.7	4.8
HTI	0.3	13.4	35.6
KEN	0.5	13.2	25.6
KHM	0.1	2.6	7.7
LBR	0.2	12.8	27.9
LSO	1.7	43.4	65
MLI	0.1	8.3	18.6
MMR	0.1	1.9	14.8
MOZ	0.9	22.6	38.3
MRT	0.1	5	12.2
MWI	1.1	30.8	51.7
NAM	1.1	22.5	43.3
NER	0.1	3.9	9.8
NGA	0.3	15.3	31.9
PNG	0.1	6.3	14.6
RWA	0.2	6.8	12.9
SEN	0.1	4.4	10.4
SLE	0.2	10.1	22.9
SOM	0.1	4.5	13.4
SSD	0.3	16.8	70
SWZ	2.1	40.3	64.2
TCD	0.3	14.6	31.5
TGO	0.3	13.9	27.9
TZA	0.4	13.9	28.3
UGA	0.5	17.1	33.5
ZAF	1.5	34.5	69.3
ZMB	1.1	32.6	53.1
ZWE	1.2	26.2	42.9

References

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