Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study

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Summary

Background Confirmation of a diagnosis of tuberculosis in children (aged <15 years) is challenging; under-reporting can result even when children do present to health services. Direct incidence estimates are unavailable, and WHO estimates build on paediatric notifications, with adjustment for incomplete surveillance by the same factor as adult notifications. We aimed to estimate the incidence of infection and disease in children, the prevalence of infection, and household exposure in the 22 countries with a high burden of the disease.

Methods Within a mechanistic mathematical model, we combined estimates of adult tuberculosis prevalence in 2010, with aspects of the natural history of paediatric tuberculosis. In a household model, we estimated household exposure and infection. We accounted for the effects of age, BCG vaccination, and HIV infection. Additionally, we tested sensitivity to key structural assumptions by repeating all analyses without variation in BCG efficacy by latitude.

Findings The median number of children estimated to be sharing a household with an individual with infectious tuberculosis in 2010 was 15 319 701 (IQR 13 766 297–17 061 821). In 2010, the median number of *Mycobacterium tuberculosis* infections in children was 7 591 759 (5 800 053–9 969 780), and 650 977 children (424 871–983 118) developed disease. Cumulative exposure meant that the median number of children with latent infection in 2010 was 53 234 854 (41 111 669–68 959 804). The model suggests that 35% (23–54) of paediatric cases of tuberculosis in the 15 countries reporting notifications by age in 2010 were detected. India is predicted to account for 27% (22–33) of the total burden of paediatric tuberculosis in the 22 countries. The predicted proportion of tuberculosis burden in children for each country correlated with incidence, varying between 4% and 21%.

Interpretation Our model has shown that the incidence of paediatric tuberculosis is higher than the number of notifications, particularly in young children. Estimates of current household exposure and cumulative infection suggest an enormous opportunity for preventive treatment.

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Introduction

Tuberculosis is largely a disease of poverty, and therefore children with the disease frequently live in poor communities with few health services.[1] Social, logistic, and financial issues can mean that children are not brought for assessment after the development of symptoms, and even if they are assessed, a confirmed diagnosis can be challenging because of a low bacillary load and difficulties of specimen collection.[2] Therefore, a diagnosis is often made presumptively on the basis of a combination of clinical symptoms, signs, and radiological findings. However, in regions where other diseases with overlapping features (eg, HIV, systemic viral or bacterial infections, parasitic infections, and bacterial, viral, or atypical pneumonia) are also endemic, the sensitivity and specificity of these diagnostic approaches are imperfect.[3]

Even children who are diagnosed and treated are often not recorded in registers or reported to national tuberculosis programmes,[4] meaning that the number of cases is difficult to establish directly. Childhood tuberculosis has been neglected by health programmers and academics, because children frequently have pauci-bacillary disease and are not thought to be infectious; from a public health perspective, they are deemed not to constitute a high risk of disease propagation within a community.[5] Additionally, the global community has not set paediatric-specific targets for reduction of the disease burden. Because of the absence of clear paediatric targets, perceptions of low public health importance, and challenges in presentation, diagnosis, treatment, and reporting, estimates of disease burden have not been prioritised.

Nevertheless, interest in paediatric tuberculosis is increasing, and in 2012, WHO presented estimates of the global burden in children for the first time.[6] WHO started with the number of childhood tuberculosis cases reported to the organisation (for countries in which data are disaggregated into paediatric and adult cases) and then combined this number with an estimate of paediatric notifications for countries in which data are not disaggregated (calculated with the ratio between child and adult cases from the countries in which data are disaggregated). Because of the scarcity of evidence about how the gap between notifications and underlying

disease incidence varies by age, this estimate of notified cases in children was then inflated to account for incomplete case detection with the global, all-ages case detection proportion of 66%, generating an estimate for the underlying tuberculosis incidence. This procedure yielded a global estimate of 490 000 tuberculosis cases per year (uncertainty interval 470 000–510 000) in children younger than 15 years, corresponding to 6% of the 8·7 million estimated incident cases in 2011.[6] Although WHO's approach was straightforward and transparent, difficulties have been acknowledged with each step—ie, notifications for children, extrapolations for non-reporting countries, and especially the inflation to account for undetected cases.

With a more complete understanding of the burden of tuberculosis in children, the children who are developing the disease could be identified, which would allow programmes to target interventions where they are needed most and help with the rational planning of service and resource allocation. Identification of discrepancies between the number of expected cases and the number of treated cases would allow targeting of health systems that are not finding, diagnosing, treating, or reporting appropriate numbers of child cases. From a public health perspective, children with tuberculosis represent recent transmission and can be judged as sentinel markers of disease transmission in the community and therefore as indicators of tuberculosis control.[7] Finally, an understanding of the likely burden of disease is key for advocacy and market assessments, and would be essential for motivation of the research and development of new diagnostics, vaccines, and drugs adapted for the needs of children as well as adults.

In light of the difficulties with diagnosis and notification of childhood tuberculosis, we aimed to develop a mechanistic mathematical model to estimate the number of cases indirectly in the 22 countries with a high burden of tuberculosis. These countries are reported to harbour 80% of the global burden.[6] We estimated the incidence of infection and disease in children, the prevalence of infection, and household exposure. Because predictions are not based on childhood notifications, this method is independent of existing approaches, and can be compared with reporting.

Methods

Study design

We used the same workflow for each of the 22 countries included (figure 1). The age-stratified population determined the total number of children at risk in each country (the denominator). Because most demographic data were available for 2010, we used epidemiological data from this year as well. We calculated exposure and infection with two techniques: one was based on a community model and the other on a detailed model of household exposure.

Community model

We combined WHO estimates of tuberculosis prevalence[6] with notification data for 2010, stratified by disease type (smear positive, smear negative, or extrapulmonary), to estimate the force of *Mycobacterium tuberculosis* infection in the 22 high-burden countries (HBCs). We modelled uncertainty in prevalence estimates with gamma distributions matched to the 95% ranges quoted for each country. We assumed a linear association between force of infection and tuberculosis prevalence, modelling the gradient by a Weibull distribution fitted to pooled data from two reviews[8,9] in which the ratio between annual risk of infection and prevalence of smear-positive tuberculosis
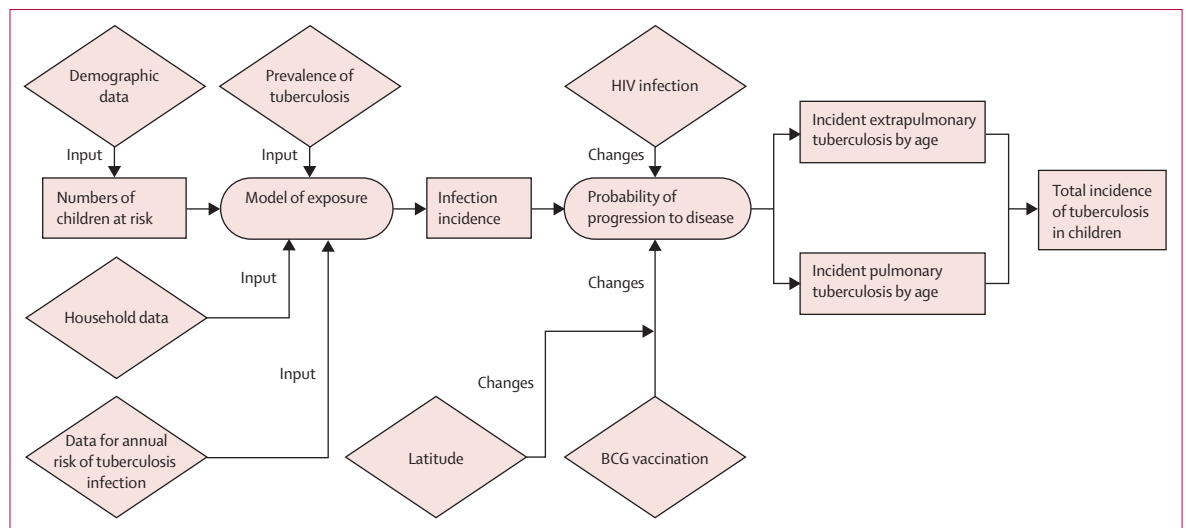

Figure 1: **Overview of the modelling logic**
Numbers at risk are fed through models of exposure and infection, and risks of progression to disease (modified by BCG vaccination and HIV) to arrive at estimates of tuberculosis incidence in children. Diamonds represent data sources, squares represent numbers estimated at each stage, and stadiums represent modelling stages.

was analysed. We obtained the number of children infected every year with *M tuberculosis* in each country by multiplying the predicted force of infection by estimated numbers of children in different age groups (0–1, 1–2, 2–5, 5–10, and 10–15 years) according to UN population estimates.[1] We computed infection prevalence with the survival function for escaping infection, assessed at the midpoints of the age groups.

Household model

As an alternative to modelling the risk of *M tuberculosis* infection, we estimated household exposure to infectious cases of tuberculosis for different age groups, ignoring exposure outside the household. We obtained Demographic and Health Survey data describing the composition of households by age and sex for 16 of the 22 HBCs. We developed an in-silico representation of each population, and, for a specific prevalence, we used the relevant country's age and sex distribution of smear-positive notifications to distribute tuberculosis cases between individuals. We then computed the number of children in each age group in the same household as an individual of any age with tuberculosis, and repeated the process 10 000 times to obtain an estimate of the probability of household exposure. When household data for a country were not available, we imputed the association between tuberculosis prevalence and household exposure risk. We used the number of children cohabiting with an individual with tuberculosis to estimate the incidence of infection (via the household), modelling infection rates (based on contact studies[10–12]) with a log normal distribution and assuming smear-negative tuberculosis to be on average 23% as infectious as smear-positive diseases.[13,14]

Progression to disease

Probabilities of progression from infection to disease in each age group were modelled with beta distributions on the basis of Marais and colleagues' report,[15] as were the probabilities of the ensuing disease being pulmonary or extra-pulmonary. We modelled BCG vaccination efficacy in prevention of extra-pulmonary disease and the fraction of this protection effective against pulmonary tuberculosis as beta distributions, on the basis of systematic reviews.[8,16–18] As suggested by Palmer and colleagues,[19] we allowed a proportion of the efficacy of BCG vaccination to vary with latitude (measured at the countries' capital cities), with efficacy at the equator 59% of that at the poles. We used WHO estimates of BCG coverage for each country. We accounted for the effect of HIV infection on incidence by an incidence rate ratio, modelled as a log normal distribution, on the basis of a study of the effect of HIV infection on risk of tuberculosis in children.[20] HIV prevalence in those younger than 15 years was taken from data from the Joint United Nations Programme on HIV/AIDS, and again we modelled uncertainty with gamma distributions and assumed prevalence to be zero where data were not available. We multiplied the estimates of the

number of children with *M tuberculosis* infection in each age group by probabilities of progression, and then modified values by the effects of BCG vaccination and HIV infection to arrive at estimates of incidence of paediatric tuberculosis by country, age group, and disease type.

Numerical methods

We constructed probability distributions representing uncertainty in estimated quantities with a Latin hypercube sample of size 50 000 from across all the distributions representing uncertainty in model parameters and input data. To assess the sensitivity to key structural assumptions, we repeated all analyses without variation in BCG efficacy by latitude, and repeated the household analysis assuming a uniform distribution of tuberculosis cases by age and sex across adults. We did all computations in the R environment for statistical computing. Further details about the methods, including all parameter values, are in the appendix.

Role of the funding source

The funders 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

Table 1 shows the model estimates for children aged 0–1, 1–2, 2–5, 5–10, and 10–15 years. Tuberculosis exposure, infection, and disease was lower in under-5s than children aged 5–15 years. The most likely model prediction (the mode) is that about 500 000 cases of tuberculosis occurred in children younger than 15 years in the 22 HBCs in 2010 (figure 2). The median number of cases predicted was 650 977 (IQR 424 871–983 118). The median number of children younger than 15 years estimated to be sharing a household with an individual with infectious tuberculosis in the 22 HBCs was 15 319 701 (13 766 297–17 061 821), and the median number of *M tuberculosis* infections occurring in children younger than 15 years in 2010 was 7 591 759 (5 800 053–9 969 780). The cumulative incidence of infection yielded a median estimated number of children younger than 15 years with latent tuberculosis infection at the end of 2010 of 53 234 854 (41 111 669–68 959 804). The mode value for incidence of infection in the household was about 300 000 (figure 2). The median number of household infections was 396 078 (IQR 271 905–565 304).

A uniform distribution of ages in the household model of exposure led to disease estimates that were 11% higher than the distribution based on adult age and sex notifications (appendix). An assumption that the efficacy of BCG vaccination did not wane towards the equator resulted in disease estimates that were 27% lower for all methods of estimating infection (appendix).

The proportion of the total incidence of paediatric tuberculosis in the 22 HBCs occurring in children with

	Children younger than 5 years	Children aged 5–15 years
Number of children sharing household with an individual with tuberculosis*	5 354 128 (4 814 454–5 953 851)	9 969 007 (8 951 616–11 099 616)
Number of children infected with *Mycobacterium tuberculosis* in 2010†	2 645 968 (2 020 926–3 474 245)	4 946 152 (3 780 256–6 498 346)
Number of children infected with *M tuberculosis* at the end of 2010†	6 530 442 (4 993 555–8 518 986)	46 864 335 (36 110 021–60 525 588)
Number of children developing tuberculosis in 2010†	327 237 (205 206–494 575)	281 431 (134 237–526 014)

Data are median (IQR). *From household model. †From community model.

Table 1: Estimates of tuberculosis exposure, latent infection, and disease in children in 22 high-burden countries in 2010
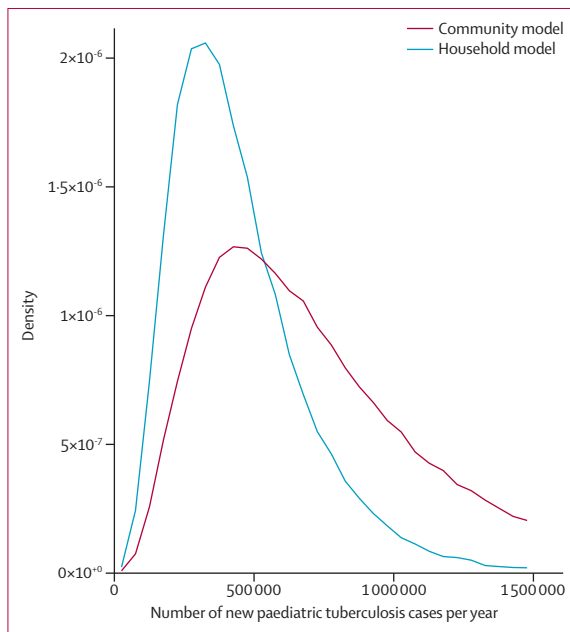

Figure 2: Density estimates of the probability distribution of total incidence of paediatric tuberculosis for the 22 high-burden countries in 2010
The household model estimates infection through household exposure, and so only includes incidence of disease from this route of infection. The community model relates infection to overall tuberculosis prevalence in adults, and aggregates all routes of infection (household and community). The density estimates are based on binning the outputs of model runs to form a histogram that represents how likely different model estimates are in view of the uncertainty in the inputs.

HIV infection was estimated at 5·0% (IQR 2·4–10·1). However, in both South Africa and Zimbabwe, this proportion was predicted to be more than 25% (appendix). Tuberculosis incidence at younger ages (<5 years) was predicted to make up 58% (IQR 40–77) of the total, and 23% (13–36) of the disease in this age group was predicted to be extrapulmonary (appendix). In all children younger than 15 years, 14% (8–22%) of disease was estimated to be extrapulmonary.

Discrepancies between the number of reported cases and estimated incidence were heterogeneous between countries but under-reporting was more pronounced in the younger age group (figure 3). India is predicted to account for 27% (22–33) of the total burden of paediatric tuberculosis in the 22 HBCs (figure 4). The model suggests that 35% (IQR 23–54) of paediatric cases of tuberculosis in the 15 HBCs reporting notifications by age in 2010 were detected, compared with 74% of all cases of tuberculosis in these countries (on the basis of WHO estimates). The predicted proportion of total tuberculosis burden occurring in children for each country ranged from 4% to 21% (figure 5).

Discussion

Overall, although the uncertainty ranges were large, our model predicted that about 7·6 million children younger than 15 years in the 22 HBCs became infected with *M tuberculosis* in 2010, and roughly 650 000 developed tuberculosis (panel). We have estimated that about 15 million children younger than 15 years in these countries were living in the same household as an adult with tuberculosis, and roughly 53 million children were estimated to be infected with *M tuberculosis* in 2010. These figures are medians for the corresponding probability distributions. We chose medians as a Bayes estimator with a linear penalty in the error, and to allow natural reporting of uncertainty ranges.

As far as we are aware, we are the first to attempt to estimate the burden of childhood tuberculosis with a mechanistic model, using prevalence of tuberculosis in adults to estimate rates of infection and disease in children. We used an updated version of Styblo's rule[8,9] to relate tuberculosis prevalence to the incidence of infection, and used a model of household exposure and infection. We then incorporated evidence about age-related progression risks, BCG vaccination efficacy, and the effect of HIV. This strategy is complementary to other approaches in which paediatric notification data are used more directly, and synthesises a more complete picture of the epidemiology by modelling intermediate steps to disease. Because we modelled paediatric incidence starting from estimates of adult prevalence, predicted incidence in children can be compared with paediatric notifications to identify potential shortfalls in reporting. Many aspects of the natural history of paediatric tuberculosis, and the data used as inputs for the model, have large uncertainties. These uncertainties are fairly reflected in the model outputs, and quantification of their relative contributions helps to identify areas in which precise understanding would most improve the accuracy of our approach. The approach lends itself to automation, which means that estimates can be updated on the basis of new data.

The 22 HBCs we assessed are estimated to have 80% of the global tuberculosis burden.[6] Although the varying

association between tuberculosis burden in adults and children by setting means these countries are likely to have a higher proportion of global paediatric tuberculosis, extrapolation of our approach would suggest a global burden that is up to 25% higher than our prediction for the 22 HBCs.

Our model has identified large populations that could benefit from preventive treatment, although not all children would be eligible. In view of the efficacy of isoniazid preventive therapy,[21,22] children who progress to disease after household exposure should be thought to have developed preventable tuberculosis; screening of individuals sharing a household with an adult who has been diagnosed with tuberculosis and treatment of child contacts would probably substantially reduce the numbers of children who develop the disease. The large numbers predicted by our model also represent the present and accumulated result of a failure to identify and treat adults with tuberculosis effectively.

These estimates of child tuberculosis burden are somewhat higher than those in the 2012 WHO report,[6] similar to the notification-based estimates of Nelson and colleagues (although these estimates are from more than 10 years ago),[23] and lower than the value of 1 million cases suggested by some commentators[24,25] and the estimates of Jenkins and colleagues.[26] The comparison of notifications and model estimates suggests under-reporting, most notably in children younger than 5 years. However, some countries do have notification rates similar to estimated incidence. Further investigation is necessary to improve understanding of the reasons for the difference between the number of estimated and notified cases in every country. In our model, India had by far the highest burden of paediatric tuberculosis, which is probably a result of its large size, demographic composition, and moderate tuberculosis prevalence.

The proportion of tuberculosis burden occurring in children has frequently been used to estimate probable paediatric burden where direct measurements do not exist.[6] Local estimates for the proportion of tuberculosis burden in children vary widely, with some investigators reporting up to 39% of the burden in children.[27] Donald[28] pointed out that increased proportions would be expected in countries where overall burden is highest, because of the correlation with younger-skewed demographics. He also noted that a high force of infection leads to a younger average age at infection, when risks of progression are highest.[28] Our model reproduces this expected trend, with proportions predicted in a similar range to estimates by Nelson and colleagues.[23] However, the countries with the largest contribution from HIV to tuberculosis incidence (South Africa and Zimbabwe) do not follow this pattern, reflecting the lower HIV prevalence in children than adults.

As with any model, our approach involved assumptions and has limitations. The limiting assumptions were
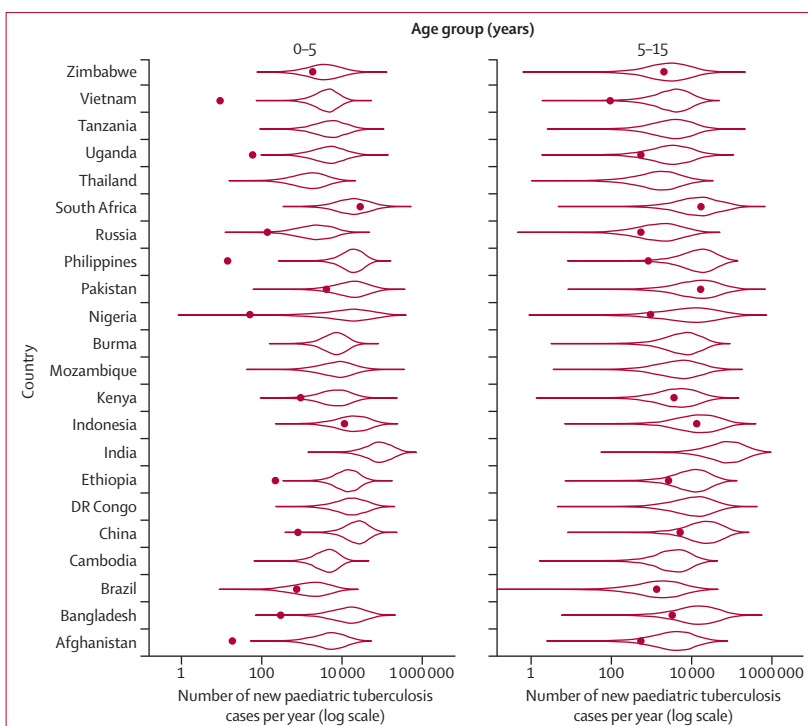

Figure 3: Violin plot comparing model estimates of paediatric tuberculosis incidence in 2010, with numbers of cases in each age group reported to WHO by each country

Dots show the numbers of cases reported to WHO. The absence of a dot means paediatric notifications were not reported by that country in 2010. The violins give a visual representation of the range and distribution of model estimates for each country on the basis of the community model. DR=Democratic Republic.
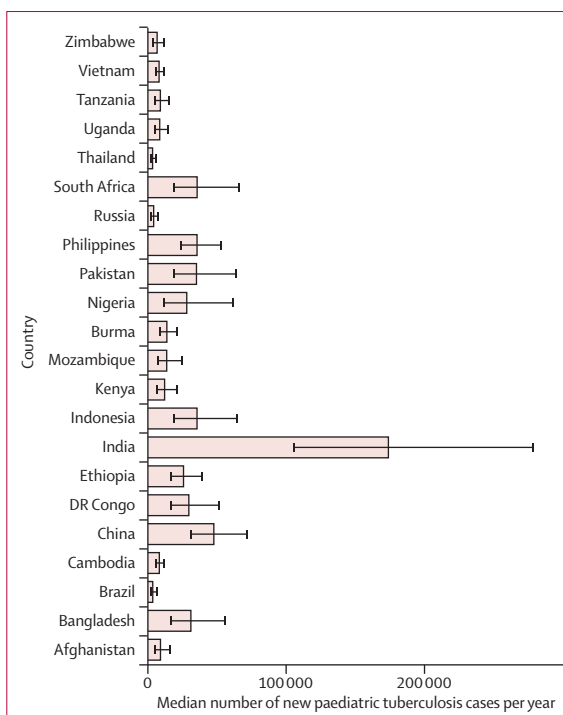

Figure 4: Numbers of new paediatric tuberculosis cases in 2010, by country

Estimates were calculated with the community model. Error bars show IQRs. DR=Democratic Republic.
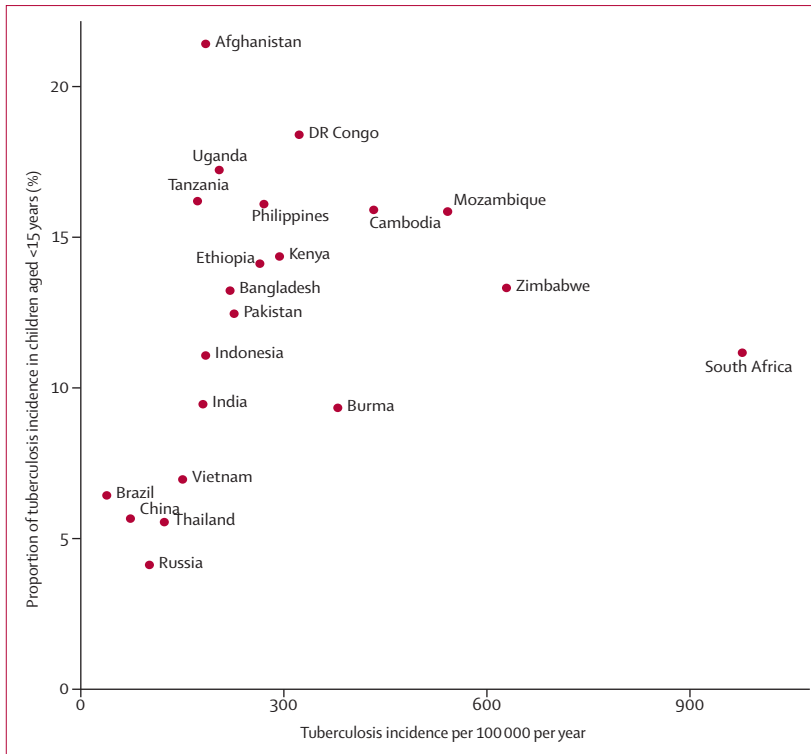
Figure 5: **Proportion of total tuberculosis burden that occurs in children and tuberculosis incidence in 2010 for 22 high-burden countries**
Proportions are based on mean model estimates from the community method. Incidences are based on WHO point estimates. DR=Democratic Republic.

***Panel:* Research in context**

Systematic review

We did a literature review of English language publications in PubMed, employing no date restrictions. Search terms included combinations of "mycobac*", "tuberc*", "tb", "child*", "ped*", "paed*", "burden", "epidemiology", "global", "model". We identified no previous studies which had used a mechanistic model to estimate the burden of tuberculosis in children. In our model, we used official estimates from WHO, the UN, DHS data and UNAIDS, and combined them with several systematic reviews to inform transitions. The reviews by Bourdin Trunz and colleagues[8] and Van Leth and colleagues[9] informed the association between tuberculosis prevalence and force of infection. The review by Fox and colleagues[12] informed risk of infection after household exposure, and the review by Marais and colleagues[15] informed the risk of progression to disease after infection. The effect of BCG vaccination was informed by several reviews and the effect of HIV was informed by the study from Hesseling and colleagues.[20]

Interpretation

Our model predicts that about 650 000 children developed tuberculosis in 2010 in the 22 countries with a high burden of the disorder. Because our estimates do not use paediatric notifications as a starting point, the estimates can be compared with reported cases in each country to identify shortfalls. Our model also identifies vast numbers of children predicted to be exposed to tuberculosis every year and the even greater number of children who harbour latent tuberculosis infection.

approximations in representation of HIV infection in children and uncertainties surrounding the nature, size, and variation of protection conferred by BCG vaccination.

We did not have data for the age distribution of HIV infection in children, antiretroviral therapy coverage, or CD4 cell count in infected individuals; we treated HIV infection as one risk factor uniformly spread between children. Exposure to *M tuberculosis* and infection were not affected by HIV in our model, but, in reality, household clustering of HIV means that children with HIV infection could be expected to have more exposure to tuberculosis than do children without HIV infection. Although the crudeness of the approach to HIV means that our conclusions for countries with high HIV prevalences should be treated with caution, the estimate that HIV contributes to 5% of the total incidence means that this issue is likely have little effect on the overall estimate.

The efficacy of BCG vaccination and the causes of recorded variability remain controversial,[18] and could be affected by the variation in vaccine strain used.[29] In addition to incorporation of uncertain distributions that characterise the efficacy of BCG vaccination against pulmonary and extrapulmonary tuberculosis, we considered structural model variants with unvarying BCG efficacy by latitude. This approach might reflect an interpretation that perceived variation of BCG vaccination efficacy is due to masking by heterologous immunity from non-tuberculous mycobacteria. Overall disease estimates were 27% lower under this assumption (infection estimates were unaffected).

Neither our model nor the studies on which estimates of progression were based differentiated between *M tuberculosis* infection and a positive test of *M tuberculosis* sensitisation. Some children are anergic and can progress to tuberculosis without ever showing evidence of sensitisation. Risks of progression were based on reports from the early 20th century in white people and might not fully apply to populations that we assessed, which can differ systematically in factors affecting risks of progression, such as host genetics, dominant *M tuberculosis* strain types, malnutrition, or vitamin D levels. We did not consider possible correlations between risk of exposure and infection, did not take account of any previous infection protecting against reinfection, and assumed that risks of progression were concentrated in the 1–2 years after infection. We did not consider subnational heterogeneity in transmission of tuberculosis, assuming that risks of infection were proportional to prevalence. Although some of this variation will average out for overall estimates, it could be important for specific countries and country-level estimates, which should therefore be viewed with caution.

All model variants started from WHO estimates of adult tuberculosis prevalence, and therefore inherited their limitations. The most recent underlying demographic data were for 2010, and so we used tuberculosis, HIV, and BCG vaccination estimates for that year. We did not consider transmission of *M tuberculosis* from children, differentiate between drug-resistant and drug-susceptible tuberculosis, or include preventive treatment.

Our approach of taking infection via household exposure as a starting point provided an independent route to estimates, but only accounted for infections occurring in the household (probably a worse assumption in older age groups). Therefore, it is reassuring and revealing that estimates from the household model are lower than, but not radically different from, those from the community method, which implicitly includes all contexts of infection. In addition to those of our analysis, the household approach had its own limitations (appendix). We used notification data to inform the age and sex distribution of prevalent tuberculosis in each country. Notification data are subject to biases, even with restriction to smear-positive cases. However, our sensitivity analysis with a model variant assuming an age-independent distribution of tuberculosis cases in adults increased disease estimates by 11%. Detailed comparable household data were not always for 2010 and not available at all for Russia or China, and our imputations in these cases might not have captured effects due to any idiosyncrasies in these countries' household compositions.

In conclusion, the burden of childhood tuberculosis that we have estimated through mathematical modelling represents a substantial fraction of the total global tuberculosis burden. The estimated incidence is higher than that of paediatric notifications, with under-reporting most acute in the youngest ages. Our model also predicts high numbers of children with household exposure to *M tuberculosis* and infection, many of whom will go on to develop disease. Effective household contact tracing and preventive therapy could have a substantial effect on these preventable future cases.

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