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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See Online for an audio interview with James Seddon

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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 paucibacillary 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

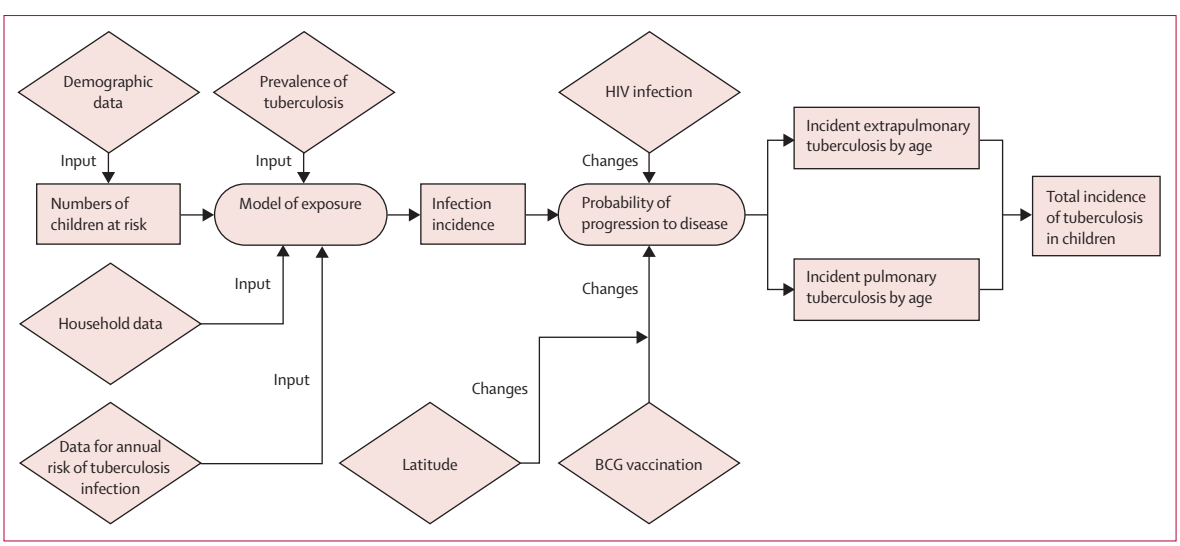

Figure 1: **Overview of the modelling logic**
Numbers at risk are fed through models of exposure and infection, and risks of progression to disease (modified by BCG vaccination and HIV) to arrive at estimates of tuberculosis incidence in children. Diamonds represent data sources, squares represent numbers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