The potential impact of household contact management on childhood tuberculosis: a mathematical modelling study

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## Abstract

### Background

Tuberculosis is now recognized as a major cause of morbidity and mortality in children, with a majority of cases in children going undiagnosed and suffering poor outcomes. Household contact management, aiming to identify children with active tuberculosis and use preventive therapy for children with HIV or under five, has long been recommended but has very low coverage globally. New guidelines include widespread provision of preventive therapy to tuberculin skin-test positive children over five.

### Methods

We provide the first global and national estimates of the impact of moving from zero to full coverage of household contact management (with and without preventive therapy for tuberculin skin-test positive children over five). We used a mathematical model to estimate households visited, children screened and treatment courses given for active and latent tuberculosis. We calculate the tuberculosis cases, deaths, and life-years lost due to tuberculosis for each intervention scenario and country.

### Findings

Full implementation of household contact management would prevent 159,500 (75% Uncertainty Interval [UI] 147,000 – 170,900) cases and 108,400 (75% UI 98,800 – 116,700) deaths in children (representing the loss of 7 million life-years). On average, preventing one child death from tuberculosis would require visiting 48 households, screening 77 children, 48 extra preventive therapy courses, and around 2 more tuberculosis treatments compared to no household contact management.

### Interpretation

Household contact management could substantially reduce childhood disease and death caused by tuberculosis globally. Funding and research to optimize its implementation should be prioritized.

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# Introduction

Tuberculosis is the leading infectious cause of mortality globally, affecting an estimated 1 million children in 2016, of whom an estimated 253,000 died.[1](https://paperpile.com/c/tfYy63/cJjx) Tuberculosis is a top ten cause of global under-five mortality,[2](https://paperpile.com/c/tfYy63/VZPi) with the vast majority of deaths each year occurring among the roughly half a million children who are never diagnosed or treated.[2,3](https://paperpile.com/c/tfYy63/VZPi+Egvz) Young children are more likely to develop severe forms of tuberculosis, such as tuberculous meningitis, that are often fatal or have long-term sequelae (eg. neurological deficits).[4](https://paperpile.com/c/tfYy63/ubgn) This has a substantial impact on families and society; due to their age, children would otherwise have many decades of productive life ahead of them. To reduce the burden of childhood tuberculosis disease and death, it will be necessary to find and treat more children with tuberculosis as well as prevent children from becoming sick with tuberculosis in the first place. Preventing cases of tuberculosis is especially important in resource-limited settings, where the diagnosis of children with tuberculosis can be particularly challenging.

One of the most effective ways of identifying children with both tuberculosis infection and disease is through household contact investigations, as children living in the homes of adults with tuberculosis are at high risk of both these clinical states.[5](https://paperpile.com/c/tfYy63/C420) Systematically evaluating child household contacts can ensure that children with tuberculosis disease are diagnosed and treated early, and that children with tuberculosis infection or exposure are given preventive therapy (PT) to prevent them from becoming sick in the future. Longstanding World Health Organization (WHO) guidance recommended household contact investigations for infectious tuberculosis patients and PT for those under five years and people living with HIV,[6](https://paperpile.com/c/tfYy63/JHQH) and has recently been updated and extended to include the option of PT for older tuberculin skin test (TST)-positive contacts in high tuberculosis burden settings.[7](https://paperpile.com/c/tfYy63/IFNK) Despite the fact that many national policies incorporate these recommendations,[8,9](https://paperpile.com/c/tfYy63/OWys+2BGH) major gaps exist in the implementation of household contact management (HHCM).[10,11](https://paperpile.com/c/tfYy63/85N0+43db) Globally only 13% of eligible children under five years are estimated to receive PT.[1](https://paperpile.com/c/tfYy63/cJjx) Competing priorities, lack of awareness, infrastructural challenges, stigma and inadequate access to care are all barriers.[10](https://paperpile.com/c/tfYy63/85N0) Until recently, HHCM activities were not included in monitoring and reporting systems; coverage of PT to under 5 household contacts of bacteriologically confirmed pulmonary tuberculosis is now data requested and reported by WHO.1

Given the extremely limited implementation of household contact investigations and PT despite universal acknowledgement of their importance, we sought to quantify the potential impact that full use of these interventions could have. This would permit an evaluation of impact of HHCM as compared to other childhood TB activities or other activities to reduce child mortality. We therefore brought together available data within a mathematical modelling framework to estimate the potential global reduction in childhood tuberculosis disease and death that child-targeted household contact interventions could achieve if taken to scale.

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# Methods

For the global population of children under 15 years cohabiting with notified tuberculosis patients, we assessed the impact of full compared to zero HHCM coverage, estimating outcomes for health system effort and child morbidity and mortality. This was a two-stage process, developing regression-based estimates of numbers of child household contacts, and then combining these with a decision tree model to estimate their outcomes. An overview of the modelling logic is shown in Figure 1.

## Interventions and outcomes

We considered three scenarios: Scenario A approximates the status quo in which HHCM is not routinely done in high-burden settings.[10,11](https://paperpile.com/c/tfYy63/43db+85N0) In this scenario, we assumed that coprevalent and incident tuberculosis in children would be detected and treated with the country-specific case detection rate (CDR) for children cohabiting with notified tuberculosis cases (see below). Scenario B reflects the long-standing WHO recommendations for the management of tuberculosis households in high-burden settings prior to 2018.[6](https://paperpile.com/c/tfYy63/JHQH) In this scenario, we assumed tuberculosis screening for all household contacts under 15 years and PT for all children under 5 years and all HIV-positive children under 15 years. Scenario C extends Scenario B to reflect updated recommendations[7](https://paperpile.com/c/tfYy63/IFNK) by expanding the use of PT to TST-positive children between 5 and <15 years. In both Scenarios B and C, we do not account for screening or PT for cohabiting adults, and assume that the CDR for incident childhood tuberculosis disease was unaffected by screening activities. To assess maximal impact, we assumed complete intervention coverage, recognising that this is an idealized scenario. We based the yield of coprevalent tuberculosis in child household contacts on empiric data derived from household contact studies.5 In each of these studies, the diagnosis of childhood TB was made using the diagnostic tools that were available in their setting, with associated imperfect sensitivity and specificity.

As measures of health system effort, we computed the number of households, the number of cohabiting children who would be screened, the number who would be given anti-tuberculosis treatment (ATT) for active disease (including those found through passive case detection), and the number who would receive PT.

As measures of morbidity and mortality, we computed the numbers of children who have prevalent disease at the time of the index patient’s diagnosis (coprevalent), who develop incident tuberculosis disease within 1 year (incident), and who die from tuberculosis within 1 year. Our estimates of risk of coprevalent TB disease and also mortality if treated or untreated were derived from empiric data, reflecting the realities of diagnosing TB disease in children with imperfect sensitivity and specificity. We also estimated the total years of expected life in cohabiting children to be able to determine years of expected life gained via intervention.

To describe the impact of each intervention scenario, we computed differences in outcomes of interest between Scenarios A and B and Scenarios A and C. In addition, we computed the number of household visits, screened children, PT and ATT courses per tuberculosis death averted and per case averted. We calculated each outcome for each country under each scenario. Uncertainty was modelled in all input parameters and summaries from 1,000 sampled parameter sets reported stratified by age and region as well as globally.

## Model for contact numbers

To predict the number of children age <5 and 5 to <15 years cohabiting with notified pulmonary tuberculosis cases of given age and sex, we developed a Bayesian multivariate regression model. The response data were (simultaneously) the mean number of children in each of the two age groups living with males and females in age groups 15 to <25, 25 to <35, 35 to <45, 45 to <55, 55 to <65 and 65+ for each of 69 countries with comparable Demographic and Health Survey data. A sensitivity analysis for India based on a Demographic and Health Survey that included a question on self-reported tuberculosis explored the potential for households of notified tuberculosis to systematically differ controlling for index case age and sex. Survey design was accounted for in computing confidence intervals for contact numbers, and a measurement model included this sample uncertainty in the regression analysis. World Bank data on per capita gross domestic product, life-expectancy at birth, infant mortality, population fraction under 15 years, population fraction living in urban areas, population density, and total fertility were used as country-level predictors. We used this model on the most recent World Bank data to predict the number of child household contacts in each country and age group for each of 180 countries, and combined this with WHO age- and sex-stratified tuberculosis notification data for 217 countries and territories. Missing data were assigned WHO regional averages. Household tuberculosis status was not a major additional influence on numbers of cohabiting children (Appendix).

## Decision tree model for child contacts

A decision tree model was developed based on published models of tuberculosis incidence[12,13](https://paperpile.com/c/tfYy63/z6Jd+UFeg) and mortality[2](https://paperpile.com/c/tfYy63/VZPi) in children, depending on age, HIV/antiretroviral therapy (ART) status, BCG vaccination status, and whether ATT was received (Figure 2). This was extended using systematic review data on tuberculosis disease and latent tuberculosis infection coprevalence in household tuberculosis contacts by age group and country income;[5](https://paperpile.com/c/tfYy63/C420) the efficacy of PT in preventing tuberculosis disease in children;[14,15](https://paperpile.com/c/tfYy63/kFZF+OQP8) and life-expectancy by age and country (see Appendix Table 4 for parameter description). We assumed no further transmission occurred after HHCM.

Data on progression risks were mainly from children judged to have latent tuberculosis infection by TST;[16](https://paperpile.com/c/tfYy63/sK7h) the predicted number of latently infected (coprevalent active tuberculosis excluded) was therefore combined with progression rates to determine incidence. Consistent with this, PT was assumed effective only in TST-positive children, with an efficacy based on the variance-weighted average of PT studies in only TST-positive children identified by systematic review,[14](https://paperpile.com/c/tfYy63/kFZF) and a separate efficacy for children living with HIV.[15](https://paperpile.com/c/tfYy63/OQP8)

The probability of children being diagnosed with tuberculosis disease and receiving ATT in the absence of HHCM was based on the CDR for each age-group and country from WHO estimates and notification data. Since children with tuberculosis cohabiting with notified tuberculosis cases are probably more likely to receive ATT than average population-matched children with tuberculosis, we used a distribution that interpolated between the population-average and an upper bound CDR by an uncertain amount (Appendix). We modelled the higher HIV-prevalence in children living with HIV-positive tuberculosis cases using data on HIV prevalence by age in child household contacts of HIV-positive tuberculosis cases from Uganda,[17](https://paperpile.com/c/tfYy63/ZsEU) and the WHO data on the prevalence of HIV and ART amongst notified tuberculosis cases. We assumed the same ART coverage in child household contacts as in HIV-positive notified tuberculosis cases.

A table of all parameter inputs is available in the Appendix.

## Data sharing

Scripts for data handling are available in a GitHub repository, which also includes input data, model analyses, test output graphs, and country-level estimates. All analyses were conducted using the R environment for statistical computing.

## 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.

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# Results

## Health system effort

If HHCM was performed on all notified pulmonary cases in 2016, the number of households visited would have been 5,100,000. This would have reached an estimated 8,258,000 (75% Uncertainty Interval [UI] 8,154,000 – 8,349,000) children <15 years for screening; 2,789,000 (75%UI 2,744,000 – 2,834,000) children <5 years and 5,469,000 (75%UI 5,371,000 – 5,555,000) children 5 to <15 years (Table 1). Without HHCM (Scenario A), we estimated these children age <15 years receive 594,200 (75%UI 530,000 – 649,000) ATT courses, which would increase in Scenario B to 862,500 (75%UI 797,600 – 917,900), or to 797,200 (75%UI 734,500 – 851,100) in Scenario C since some cases would be averted by expanded PT use. Both ATT courses resulting from passive detection of incident and coprevalent cases and ATT courses resulting from HHCM identifying and treating coprevalent child cases are included. We estimated 2,543,000 (75%UI 2,497,000 – 2,588,000) PT courses would be needed for Scenario B and 5,174,000 (75%UI 5,076,000 – 5,261,000) for Scenario C.

## Morbidity and mortality

In Scenario A, we estimated 996,500 (75%UI 930,300 – 1,049,000) coprevalent and incident tuberculosis cases in children <15 living with notified tuberculosis cases, resulting in 133,500 (75%UI 123,400 – 142,400) deaths (Table 2). We estimated 382,800 (75%UI 358,100 – 404,300) of these tuberculosis cases were in children 5 to <15 years. A substantial majority of the deaths –101,000 (75%UI 92,500 – 108,200) – were in children <5 years. We found Scenario B averted 66,700 (75%UI 59,790 – 72,370) cases of tuberculosis disease, and Scenario C averted 159,500 (75%UI 147,000 – 170,900) cases. Scenario B averted 103,600 (75%UI 94,480 – 111,900) deaths, and Scenario C averted 108,400 (75%UI 98,800– 116,700) deaths; in both Scenarios B and C, most deaths were averted in children <5 years. Scenario B gained 7,006,000 (75%UI 6,373,000 – 7,567,000) life-years, and Scenario C, 7,305,000 (75%UI 6,663,000 – 7,874,000) life-years, in both scenarios mainly among children <5 years.

The WHO South-East Asia region had the largest share of preventable deaths, followed by the African region, the Western Pacific region, the Eastern Mediterranean region, and the Region of the Americas and European region (see Appendix supplementary figure).

Only 3% of tuberculosis deaths in children cohabiting with notified tuberculosis cases under no HHCM were estimated to be HIV-positive globally, although this rose to 7% in the WHO African region. In Scenario A, over 70% of tuberculosis cases in children were coprevalent upon index case notification, rather than incident during the subsequent year, with a similar split in ATT courses given to coprevalent vs. incident child tuberculosis cases (Appendix). The increases in ATT courses for coprevalent cases found by HHCM (Scenarios B and C) were partially offset by ATT courses averted through PT-mediated reductions in incidence. More detailed regional and outcome breakdowns are available in the Appendix.

## Impact of interventions

Moving from Scenario A to Scenario B (Figure 3), meant that, globally, for every child tuberculosis case averted: 78 (75%UI 70 – 85) households were visited; 126 (75%UI 113 – 138) children were screened; 42 (75%UI 35 – 39) PT courses were given; and an additional 4 (75%UI 3 – 5) ATT courses were given (Figure 3). Moving from Scenario A to Scenario C, for every child tuberculosis case averted: 32 (75%UI 30 – 35) households were visited; 52 (75%UI 48 – 56) children were screened; 33 (75%UI 30 – 35) PT courses were given; and 1 (75%UI 1 – 2) additional ATT course was given.

Moving from Scenario A to Scenario B (Figure 3), for every child tuberculosis death averted: 49 (75%UI 46 – 54) households were visited; 81 (75%UI 74 – 87) children were screened; 25 (75%UI 23 – 27) PT courses were given; and an additional 3 (75%UI 2 – 3) ATT courses were given (Figure 3). Moving from Scenario A to Scenario C meant that, globally, for every child tuberculosis death averted: 48 (75%UI 44 – 52) households were visited; 77 (75%UI 71 – 83) children were screened; 48 (75%UI 44 – 52) PT courses were given; and an additional 2 (75%UI 2 – 2) ATT courses were given.

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# Discussion

In this mathematical modelling study, we found that HHCM implemented at full scale may prevent around 110,000 deaths in children every year and around 160,000 cases of tuberculosis disease in children every year. The deaths averted would amount to over seven million expected life-years saved. Children under five years old would derive the greatest benefit, comprising two in five of averted cases and three in four of the averted deaths. Extending use of PT to TST-positive children over 5 years old, consistent with 2018 updated WHO guidelines,[7](https://paperpile.com/c/tfYy63/IFNK) would more than double the number of paediatric cases averted.

We have considered the scenario where long-time recommended interventions are implemented for children exposed at home to tuberculosis, with perfect coverage of both screening and treatments. We have not considered the best approaches for achieving these ends, and it is likely that varying approaches would be needed in different contexts. We have also not taken into account the true costs of these activities, nor considered the quality-of-life gains from reductions in tuberculosis disease and its sequelae. Our aim here is to project the expected benefits – in terms of the reduction of tuberculosis disease and death in children – that could be achieved through child-specific household management interventions. Certainly, the numbers screened and given PT are large, and the numbers of children screened and treated are far larger than most tuberculosis programmes are currently reaching, but there are examples of successful implementations in resource limited settings.[18](https://paperpile.com/c/tfYy63/dVl6) Quantifying this additional workload is a first step for global planning: projecting what the effort required i.e., the numbers of household visits, children screened and PT courses needed. The numbers required *to avert one tuberculosis death* compare favourably with estimates of numbers needed to screen *to find one case* for other tuberculosis screening activities.[19](https://paperpile.com/c/tfYy63/BcF0)

These results can be used to help identify the envelope within which alternative service provisions may be deemed cost-effective in different countries. Recent evidence shows that interventions generating health gain at less than US$200 per disability-adjusted life-year (DALY)-averted would be deemed cost-effective in many countries,[20](https://paperpile.com/c/tfYy63/xeew) even those classified as amongst the poorest in the world. Assuming that each death avoided generates 30 DALYs-averted per child saved after discounting, a country programme able to pay $200 per DALY-averted should be willing to spend up to $6000 ($200 times 30) to save one child’s life. The question is whether the costs required to do this (here estimated for Scenario B as 50 household visits, screening 80 children for active tuberculosis, administering 25 PT courses, 3 courses of anti-tuberculosis treatment), plus any net downstream costs of treatments, can be delivered within this envelope. Analyses of the health system costs of contact screening and diagnosing and treating tuberculosis infection from Uganda, Malaysia, and Vietnam suggest that this is a highly feasible target.[21–23](https://paperpile.com/c/tfYy63/t7wI+wfWc+haO7) If in a particular setting the costs of intervention exceed this amount, then a priority task becomes how to deliver the necessary interventions more efficiently.

To reliably determine the cost-effectiveness of scaling-up household contact management across different countries would require full costing of those interventions, as well as measures of morbidity and mortality such as DALYs. One would need to consider the feasibility of delivery given constraints within health care systems and uptake by different population groups. All of these factors are context-specific and could depend importantly upon the scale of delivery (e.g. average costs may fall initially as intervention programmes are scaled up, but rise as they are taken into hard-to-reach areas). This should be the focus for further research, in which epidemiologic and health economic modellers work hand-in-hand with implementation scientists. Novel models of service provision may have advantages, such as the use of community health workers or integrating with maternal and child health programmes; these will need to be evaluated using implementation research. It is also acknowledged that mandatory monitoring and reporting are often necessary to drive implementations of this kind. The health technology landscape is also changing rapidly. Shorter, more patient-acceptable and more implementable treatments for tuberculosis infection would help to increase uptake of PT and promote adherence to treatment completion.[24](https://paperpile.com/c/tfYy63/Rgnq) In addition, the development of tests that could better identify those at increased risk of progressing to tuberculosis disease would mean that fewer contacts would require PT.[25](https://paperpile.com/c/tfYy63/sltu)

We have considered full coverage of the intervention scenarios, but we used yield data from household screening activities that employed imperfectly sensitive and specific approaches to diagnosing tuberculosis disease in child household contacts, after realistic delays in reaching households (during which tuberculosis could have developed or, potentially, deaths occurred). These imperfect approaches are also the basis of entry to the studies on which we base our estimates of risk of death with treated and untreated TB disease. We have modelled TST-positivity rather than true latent tuberculosis infection as this is what most of the data on household infection rates and progression rates are based on. We may therefore have been conservative in our assessment of PT impact, in assuming no benefit to TST-negative children.

Our analysis is also subject to several simplifications. Our scope explicitly excluded benefits and treatments in cohabiting adults, who would normally be screened for tuberculosis disease. It is anticipated that the treatment of these adults would increase impact with limited increase in effort. We also limited HHCM to pulmonary tuberculosis cases; HHCM for other forms of tuberculosis may provide benefits by identifying children at risk from a common exposure. We assumed that the number of cohabiting children depended on adult age and sex but was not different for households of notified tuberculosis cases. An analysis for India (Appendix) suggested this assumption to be reasonable. We also made the simplifying assumptions that all notified adult tuberculosis cases lived in households and that none shared a household, which could potentially have overestimated the number of children living in households affected by tuberculosis. However, the proportion of notified adult cases sharing a house is limited,[5](https://paperpile.com/c/tfYy63/C420) and by only considering children cohabiting with tuberculosis cases, we conservatively underestimate the reach of contact management, which should include non-cohabiting young children who spent significant time in the household. This might include contact with caregivers, such as grandparents, who do not live with the child. We were similarly conservative in assuming that household management would not improve household awareness of tuberculosis and therefore improve case detection in subsequent incident disease in children. We also did not make allowance for any reductions in life-expectancy in children currently living with HIV (although children with HIV only comprised a small fraction of deaths). Finally, we did not consider multidrug-resistant tuberculosis, expected to affect around 3% of these children;[26](https://paperpile.com/c/tfYy63/M4ZH) this is a group with different case detection rates, and treatment and PT outcomes. Given how few drug-resistant paediatric cases are currently diagnosed and treated, the impact of appropriate household management may be even more pronounced than for drug-susceptible tuberculosis. A recent study estimated that with universal HHCM following the diagnosis of an adult with multidrug-resistant tuberculosis, twelve times as many children would be treated for multidrug-resistant tuberculosis than are currently.[26](https://paperpile.com/c/tfYy63/M4ZH)

Our analysis is the first to project the total global health impact that could be achieved by child-targeted household management. It includes an emphasis on uncertainty propagation, and a detailed model of tuberculosis natural history in children. Our study brings together estimates of household structure and a model of intervention effect and outcomes focussed on children, and it uses recent evidence from systematic review.[3,5,14,15](https://paperpile.com/c/tfYy63/kFZF+OQP8+C420+Egvz) Yuen et al[27](https://paperpile.com/c/tfYy63/UVFy) estimated numbers of children with coprevalent disease in household contacts, obtaining comparable results. A cost-effectiveness modelling study[28](https://paperpile.com/c/tfYy63/cpOl) considered tuberculosis infection testing and PT to reduce tuberculosis incidence in cohorts of child household contacts under five years for a particular setting, concluding that all strategies were cost-effective. We included both these elements – the substantial benefits from household management to coprevalent paediatric cases and the reductions in incidence from PT – and extended our analysis to 217 countries and territories. The balance between cases averted through PT and deaths averted depends strongly on the coprevalence levels from a systematic review;[5](https://paperpile.com/c/tfYy63/C420) lower coprevalence in some settings would shift the benefits of HHCM towards those derived from case-prevention rather than case-finding. However, our lower projected effort per death averted than per case averted indicates HHCM achieves substantial benefit through its case-finding component and cannot simply be considered as a mode of delivering PT. Benchmarking our estimates of cases averted against global incidence estimates of around 1 million tuberculosis cases in children per year suggests 16% of incidence could be avoided by full HHCM implementation. While a direct comparison is not appropriate between global mortality estimates of 250,000 child tuberculosis deaths per year and our estimate of 110,000 deaths averted by one year of full HHCM (since the case-finding intervention component includes prevalent cases incident in previous years), this does indicate the potential for a large impact on mortality.

## Conclusion

HHCM for tuberculosis has the potential to prevent substantial morbidity and mortality in children, with impact-for-effort that compares favourably with other interventions. The low global coverage of this proven intervention needs to increase; funding and implementation research to enable this should be prioritized.

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Contributors

PJD & JAS led the conceptual modelling, with all authors critiquing the approach and results. PJD coded and ran the model and also performed analyses of inputs and outputs. All authors contributed to writing the article.

Declaration of interests

All authors declare that they have no conflicting interests.

# References

1 [World Health Organisation. Global tuberculosis report 2017. 2017.](http://paperpile.com/b/tfYy63/cJjx)

2 [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.](http://paperpile.com/b/tfYy63/VZPi)

3 [Jenkins HE, Yuen CM, Rodriguez CA, *et al.* Mortality in children diagnosed with tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis* 2017; **17**: 285–95.](http://paperpile.com/b/tfYy63/Egvz)

4 [Chiang SS, Khan FA, Milstein MB, *et al.* Treatment outcomes of childhood tuberculous meningitis: a systematic review and meta-analysis. *Lancet Infect Dis* 2014; **14**: 947–57.](http://paperpile.com/b/tfYy63/ubgn)

5 [Fox GJ, Barry SE, Britton WJ, Marks GB. Contact investigation for tuberculosis: a systematic review and meta-analysis. *Eur Respir J* 2013; **41**: 140–56.](http://paperpile.com/b/tfYy63/C420)

6 [World Health Organization. Recommendations for Investigating Contacts of Persons with Infectious Tuberculosis in Low- and Middle-Income Countries. World Health Organization, 2012.](http://paperpile.com/b/tfYy63/JHQH)

7 [World Health Organisation. Latent TB Infection : Updated and consolidated guidelines for programmatic management. 2018.](http://paperpile.com/b/tfYy63/IFNK)

8 [Jagger A, Reiter-karam S, Hamada Y, Getahun H. National policies on the management of latent tuberculosis infection: review of 98 countries. *Bull World Health Organ* 2018; **96**: 173–84F.](http://paperpile.com/b/tfYy63/OWys)

9 [Rodriguez CA, Sasse S, Yuengling KA, Azzawi S, Becerra MC, Yuen CM. A systematic review of national policies for the management of persons exposed to tuberculosis. *Int J Tuberc Lung Dis* 2017; **21**: 935–40.](http://paperpile.com/b/tfYy63/2BGH)

10 [Szkwarko D, Hirsch-Moverman Y, Du Plessis L, Du Preez K, Carr C, Mandalakas AM. Child contact management in high tuberculosis burden countries: A mixed-methods systematic review. *PLoS One* 2017; **12**: e0182185.](http://paperpile.com/b/tfYy63/85N0)

11 [Hill PC, Rutherford ME, Audas R, van Crevel R, Graham SM. Closing the policy-practice gap in the management of child contacts of tuberculosis cases in developing countries. *PLoS Med* 2011; **8**: e1001105.](http://paperpile.com/b/tfYy63/43db)

12 [Dodd PJ, Gardiner E, Coghlan R, Seddon JA. Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study. *Lancet Glob Health* 2014; **2**: e453–9.](http://paperpile.com/b/tfYy63/z6Jd)

13 [Dodd PJ, Sismanidis C, Seddon JA. Global burden of drug-resistant tuberculosis in children: a mathematical modelling study. *Lancet Infect Dis* 2016; **16**: 1193–201.](http://paperpile.com/b/tfYy63/UFeg)

14 [Ayieko J, Abuogi L, Simchowitz B, Bukusi EA, Smith AH, Reingold A. Efficacy of isoniazid prophylactic therapy in prevention of tuberculosis in children: a meta-analysis. *BMC Infect Dis* 2014; **14**: 91.](http://paperpile.com/b/tfYy63/kFZF)

15 [Zunza M, Gray DM, Young T, Cotton M, Zar HJ. Isoniazid for preventing tuberculosis in HIV-infected children. *Cochrane Database Syst Rev* 2017; **8**: CD006418.](http://paperpile.com/b/tfYy63/OQP8)

16 [Marais BJ, Gie RP, Schaaf HS, *et al.* The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era [State of the Art]. *Int J Tuberc Lung Dis* 2004; **8**: 392–402.](http://paperpile.com/b/tfYy63/sK7h)

17 [Martinez L, Shen Y, Handel A, *et al.* Effectiveness of WHO’s pragmatic screening algorithm for child contacts of tuberculosis cases in resource-constrained settings: a prospective cohort study in Uganda. *Lancet Respir Med* 2017; published online Dec 19. DOI:](http://paperpile.com/b/tfYy63/ZsEU)[10.1016/S2213-2600(17)30497-6](http://dx.doi.org/10.1016/S2213-2600(17)30497-6)[.](http://paperpile.com/b/tfYy63/ZsEU)

18 [Fox GJ, Nhung NV, Sy DN, *et al.* Household-Contact Investigation for Detection of Tuberculosis in Vietnam. *N Engl J Med* 2018; **378**: 221–9.](http://paperpile.com/b/tfYy63/dVl6)

19 [Shapiro AE, Chakravorty R, Akande T, Lonnroth K, Golub JE. A systematic review of the number needed to screen to detect a case of active tuberculosis in different risk groups. *World Health Organization Google Scholar* 2013.](http://paperpile.com/b/tfYy63/BcF0) <http://www.who.int/entity/tb/Review3NNS_case_active_TB_riskgroups.pdf?ua=1&ua=1>[.](http://paperpile.com/b/tfYy63/BcF0)

20 [Woods B, Revill P, Sculpher M, Claxton K. Country-Level Cost-Effectiveness Thresholds: Initial Estimates and the Need for Further Research. *Value Health* 2016; **19**: 929–35.](http://paperpile.com/b/tfYy63/xeew)

21 [Minh HV, Mai VQ, Nhung NV, *et al.* Costs of providing tuberculosis diagnosis and treatment services in Viet Nam. *Int J Tuberc Lung Dis* 2017; **21**: 1035–40.](http://paperpile.com/b/tfYy63/t7wI)

22 [Atif M, Sulaiman SAS, Shafie AA, Ali I, Asif M. Tracing contacts of TB patients in Malaysia: costs and practicality. *Springerplus* 2012; **1**: 40.](http://paperpile.com/b/tfYy63/wfWc)

23 [Sekandi JN, Dobbin K, Oloya J, Okwera A, Whalen CC, Corso PS. Cost-effectiveness analysis of community active case finding and household contact investigation for tuberculosis case detection in urban Africa. *PLoS One* 2015; **10**: e0117009.](http://paperpile.com/b/tfYy63/haO7)

24 [Villarino ME, Scott NA, Weis SE, *et al.* Treatment for preventing tuberculosis in children and adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of a combination of rifapentine and isoniazid. *JAMA Pediatr* 2015; **169**: 247–55.](http://paperpile.com/b/tfYy63/Rgnq)

25 [Zak DE, Penn-Nicholson A, Scriba TJ, *et al.* A blood RNA signature for tuberculosis disease risk: a prospective cohort study. *Lancet* 2016; **387**: 2312–22.](http://paperpile.com/b/tfYy63/sltu)

26 [Jenkins HE, Yuen CM. The burden of multidrug-resistant tuberculosis in children (In Press). *Int J Tuberc Lung Dis* 2018. DOI:](http://paperpile.com/b/tfYy63/M4ZH)[10.5588/ijtld.17.0357](http://dx.doi.org/10.5588/ijtld.17.0357)[.](http://paperpile.com/b/tfYy63/M4ZH)

27 [Yuen CM, Jenkins HE, Chang R, Mpunga J, Becerra MC. Two methods for setting child-focused tuberculosis care targets. *Public Health Action* 2016; **6**: 83–96.](http://paperpile.com/b/tfYy63/UVFy)

28 [Mandalakas AM, Hesseling AC, Gie RP, Schaaf HS, Marais BJ, Sinanovic E. Modelling the cost-effectiveness of strategies to prevent tuberculosis in child contacts in a high-burden setting. *Thorax* 2013; **68**: 247–55.](http://paperpile.com/b/tfYy63/cpOl)

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# Figure captions

Figure 1: Overview of modelling logic. The dotted box represents elements of the overall model that are evaluated using the decision tree model shown in Figure 2 (TB=tuberculosis; WHO=World Health Organization; BCG=Bacillus Calmette-Guérin vaccination; UNICEF=United Nations Children’s Fund)

Figure 2: Decision tree for tuberculosis household contacts. (HH=household; LTBI=latent tuberculosis infection; TST=tuberculin skin test; IGRA=interferon gamma release assay; TB=tuberculosis; PT=preventive therapy; HIV=human immunodeficiency virus; ART=antiretroviral therapy.)

Figure 3: Impact of fully implemented household contact management in children under 15 years as incremental health system effort required to avert one tuberculosis case or death (Scenarios B and C variants described in text). (Error bars denote the range between 25th and 75th percentiles.)

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# Tables

Table 1: Health system effort for tuberculosis household contact management interventions in children under 15 years old (brackets denote the range between 25th and 75th percentiles of uncertainty). Anti-tuberculosis (anti-TB) treatments include those as a result of routine services. (TB=tuberculosis; HHCM=household contact management; PT=preventive therapy; TST=tuberculin skin test; HIV=human immunodeficiency virus.) NB the difference between Scenarios B and C is in the eligibility of some older children for PT: this means some values are the same between columns (shown as merged cells).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Indicator** | **Age group (years)** | **A: No HHCM** | **B: PT to under 5 & HIV+ve** | **C: PT to under 5 & HIV+ve & TST+** | **Change going from:** | |
| **A to B** | **A to C** |
| Children screened | <5 | 0 (0 – 0) | 2,789,000 (2,744,000 – 2,834,000) | | 2,789,000 (2,744,000 – 2,834,000) | |
| Anti-TB treatments | 163,200 (151,200 – 175,300) | 163,200 (151,200 – 175,300) | | 132,200 (115,000 – 147,800) | |
| PT courses | 0 (0 – 0) | 2,511,000 (2,465,000 – 2,556,000) | | 2,511,000 (2,465,000 – 2,556,000) | |
| Children screened | 5 to <15 | 0 (0 – 0) | 5,469,000 (5,371,000 – 5,555,000) | | 5,469,000 (5,371,000 – 5,555,000) | |
| Anti-TB treatments | 431,100 (367,900 – 480,300) | 567,100 (506,400 – 616,900) | 501,800 (442,500 – 552,200) | 136,000 (107,700 – 158,700) | 70,690 (38,620 – 95,280) |
| PT courses | 0 (0 – 0) | 31,900 (31,100 – 32,690) | 2,663,000 (2,585,000 – 2,745,000) | 31,900 (31,100 – 32,690) | 2,663,000 (2,585,000 – 2,745,000) |
| Children screened | <15 | 0 (0 – 0) | 8,258,000 (8,154,000 – 8,349,000) | | 8,258,000 (8,154,000 – 8,349,000) | |
| Anti-TB treatments | 594,200 (530,000 – 649,000) | 862,500 (797,600 – 917,900) | 797,200 (734,500 – 851,100) | 268,300 (235,100 – 297,300) | 202,900 (166,000 – 236,400) |
| PT courses | 0 (0 – 0) | 2,543,000 (2,497,000 – 2,588,000) | 5,174,000 (5,076,000 – 5,261,000) | 2,543,000 (2,497,000 – 2,588,000) | 5,174,000 (5,076,000 – 5,261,000) |

Table 2: Morbidity and mortality outcomes for tuberculosis household contact management interventions in children under 15 years old (brackets denote the range between 25th and 75th percentiles of uncertainty). Tuberculosis (TB) cases, deaths and life-expectancy all include both contributions from both incident and coprevalent cases of TB. TB=tuberculosis; HHCT=household contact tracing; PT=preventive therapy; TST=tuberculin skin test; HIV=human immunodeficiency virus. NB the difference between Scenarios B and C is in the eligibility of some older children for PT: this means some values are the same between columns (shown as merged cells).

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|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Outcome** | **Age group (years)** | **A: No HHCM** | **B: PT to under 5 & HIV+ve** | **C: PT to under 5 & HIV+ve & TST+** | **Change moving from:** | |
| **A to B** | **A to C** |
| TB cases | <5 | 382,800 (358,100 – 404,300) | 318,000 (294,500 – 338,800) | | -64,800 (-70,490 – -57,820) | |
| TB deaths | 101,000 (92,500 – 108,200) | 17,550 (15,520 – 19,000) | | -83,460 (-90,150 – -75,800) | |
| Total life expectancy (years) | 182,900,000 (179,800,000 – 185,900,000) | 188,600,000 (185,400,000 – 191,700,000) | | 5,724,000 (5,181,000 – 6,188,000) | |
| TB cases | 5 to <15 | 613,700 (553,000 – 666,900) | 611,800 (551,100 – 664,900) | 519,000 (459,300 – 569,700) | -1,906 (-2,037 – -1,765) | -94,710 (-103,700 – -84,700) |
| TB deaths | 32,480 (27,460 – 36,430) | 12,290 (10,810 – 13,440) | 7,584 (6,611 – 8,334) | -20,180 (-23,180 – -16,090) | -24,900 (-28,450 – -20,320) |
| Total life expectancy (years) | 343,400,000 (337,000,000 – 348,800,000) | 344,700,000 (338,300,000 – 350,300,000) | 344,900,000 (338,600,000 – 350,600,000) | 1,282,000 (1,016,000 – 1,479,000) | 1,581,000 (1,281,000 – 1,816,000) |
| TB cases | <15 | 996,500 (930,300 – 1,049,000) | 929,800 (863,900 – 983,300) | 837,000 (771,700 – 892,400) | -66,700 (-72,370 – -59,790) | -159,500 (-170,900 – -147,000) |
| TB deaths | 133,500 (123,400 – 142,400) | 29,840 (27,300 – 31,750) | 25,130 (22,850 – 26,880) | -103,600 (-111,900 – -94,480) | -108,400 (-116,700 – -98,800) |
| Total life expectancy (years) | 526,200,000 (519,400,000 – 532,200,000) | 533,200,000 (526,400,000 – 539,300,000) | 533,500,000 (526,700,000 – 539,600,000) | 7,006,000 (6,373,000 – 7,567,000) | 7,305,000 (6,663,000 – 7,874,000) |

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# Research in context

## Evidence before this study

Morrison et al and Fox et al each conducted a systematic review and meta-analysis on the coprevalence of tuberculosis disease and infection in household contacts, with comparable findings that we used in our analysis. There have been systematic reviews and meta-analyses on the efficacy of isoniazid preventive therapy in preventing tuberculosis in children who are HIV-negative (Ayieko et al) and HIV-positive (Zunza et al), which we used in our analysis.

A PubMed search (3/18) using Tuberculosis AND Household AND Contact AND Child\* AND Model\* yielded 65 articles, which were sifted to identify studies modelling the impact of household contact management of children. Mandalakas et al undertook a cost-effectiveness analysis of household contact activities focussed on children under five years old using South African cost data and found it to be a cost-effective intervention, but did not consider coprevalent cases. This analysis focussed on hypothetical cohorts of household contacts and did not assess the numbers of household contacts. Yuen et al did estimate the number of child contacts expected from household contact activities, but not the impact of such activities on tuberculosis disease and death in the children.

## Added value of this study

Our study is the first to project the impact on childhood disease and death of tuberculosis household contact management among children, by bringing together models of contact numbers and of cohort outcomes for 217 countries and territories. We incorporate recent systematic review evidence on yields of household contact investigations in children, child-specific efficacy of preventive therapy and tuberculosis outcomes, and data around HIV and ART. We also include the benefits of both identifying coprevalent tuberculosis disease in children and preventing incident disease.

## Implications of all the available evidence

Household contact activities for tuberculosis could potentially prevent the loss of around 110,000 lives with 7 million years of life expectancy in children under 15 years old, with measures of effort that suggest excellent value. The global use of household contact management should increase above its current low level. Operational research and local cost-effectiveness analysis to inform implementation should be priorities.

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