Research Paper

Cost-effectiveness of scaling up short course preventive therapy for tuberculosis among children across 12 countries

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ABSTRACT

Background: While household contact investigation is widely recommended as a means to reduce the burden of tuberculosis (TB) among children, only 27% of eligible pediatric household contacts globally received preventive treatment in 2018. We assessed the cost-effectiveness of household contact investigation for TB treatment and short-course preventive therapy provision for children under 15 years old across 12 high TB burden countries.

Methods: We used decision analysis to compare the costs and estimated effectiveness of three intervention scenarios: (a) status quo (existing levels of coverage with isoniazid preventive therapy), (b) contact investigation with treatment of active TB but no additional preventive therapy, and (c) contact investigation with TB treatment and provision of short-course preventive therapy. Using country-specific demographic, epidemiological and cost data from the literature, we estimated annual costs (in 2018 USD) and the number of TB cases and deaths averted across 12 countries. Incremental cost effectiveness ratios were assessed as cost per death and per disability-adjusted life year [DALY] averted.

Findings: Our model estimates that contact investigation with treatment of active TB and provision of preventive therapy could be highly cost-effective compared to the status quo (ranging from $100 per DALY averted in Malawi to $1,600 in Brazil; weighted average $383 per DALY averted [uncertainty range: $248 – $1,130]) and preferred to contact investigation without preventive therapy (weighted average $751 per DALY averted [uncertainty range: $250 – $1,306]). Key drivers of cost-effectiveness were TB prevalence, sensitivity of TB diagnosis, case fatality for untreated TB, and cost of household screening.

Interpretation: Based on this modeling analysis of available published data, household contact investigation with provision of short-course preventive therapy for TB has a value-for-money profile that compares favorably with other interventions.

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1. Introduction

Every year, nearly one million children worldwide develop active tuberculosis (TB), of whom an estimated 239,000 die; 80% of these deaths occur in children under 5 years old [1]. The burden of pediatric TB is highest in low- and middle-income countries, where children represent over a fifth of all cases. Even so, health systems often neglect children when implementing TB control efforts because children are viewed as less infectious and more difficult to diagnose [2]. Partially as a result of this neglect, TB remains a leading infectious cause of global childhood morbidity and mortality [3], and the vast majority of TB deaths in children (96%) occur among those who are never formally diagnosed with TB [4].

Household contact investigation of individuals diagnosed with active TB can ensure that pediatric household contacts receive prompt treatment (if diagnosed with active TB) or preventive therapy, which can reduce their subsequent risk of morbidity and mortality [1, 5, 6]. The World Health Organization (WHO) recommends contact investigation and symptom-based screening for identifying active TB, plus provision of a short-course regimen for preventive therapy for children in high burden settings [2]. Unfortunately, implementation of TB contact investigation has been hindered by various logistical and structural barriers.
barriers include fear of creating drug resistance, poor implementation of guidelines, poor adherence to prolonged isoniazid preventive therapy (IPT), diagnostic difficulties and poor laboratory infrastructure, non-availability of high quality chest radiographs, and non-availability of quality-assured child-friendly formulations [7]. Consequently, only 27% of pediatric household contacts of people diagnosed with active TB received preventive treatment in 2018 [8].

In 2017, Unitaid launched a seven-year initiative, IMPAACT4TB (Increasing Market and Public health outcomes through scaling up Affordable Access models of short Course preventive therapy for TB, 14TB), to promote the scale-up of short-course TB preventive therapy (weekly rifampentine plus isoniazid for 3 months, 3HP). In doing so, the program aims to reduce TB incidence among pediatric household contacts in 12 high-burden countries (Brazil, Cambodia, Ethiopia, Ghana, India, Indonesia, Kenya, Malawi, Mozambique, South Africa, Tanzania, Zimbabwe), representing 50 percent of the global TB burden. As part of this initiative, we sought to estimate costs and cost-effectiveness of household contact investigation for children under 15 years old, compared to the status quo, in these countries.
The estimated cost of a one-time outpatient visit[23]. The per-person average unit costs per diagnostic test (Xpert or chest X-ray)[22] and cation of ef each achieved through TB preventive therapy delivery is equal to multiplication, we assume that the proportional reduction in TB reactivation risk occur in households with adult TB cases[19]. For simplicity of analysis, we assume that the proportional reduction in TB reactivation risk achieved through TB preventive therapy delivery is equal to multiplication of efficacy and completion.

2.4. Costs

We estimated all costs from a health systems perspective. Intervention costs included the cost of household visits for screening, TB testing, treatment of TB disease, and provision of TB preventive therapy (including management of toxicity)[20]. To estimate the costs of household screening visits, we used data from Uganda ($16 in 2013), inflated these to 2018 USD using GDP deflator[21], and multiplied these costs by the relative GDP per capita in order to extrapolate to other countries. The cost of TB testing was based on country-specific average unit costs per diagnostic test (Xpert or chest X-ray)[22] and the estimated cost of a one-time outpatient visit[23]. The per-person cost of TB disease treatment was estimated based on per-capita GDP according to a formula [Cost of TB treatment = e^{-2.2 + 1.1*ln(GDP per capita)}] published by the World Health Organization[24]. We estimated the per-patient drug cost of 3HP as $15[25] and IPT as $2.20[26], to which we added country-specific outpatient visit costs[20]. We also considered the cost of managing toxicity – both milder (requiring laboratory investigation only) and more severe (with attendant hospitalization costs)[20, 27, 28] – for both 3HP and IPT. We inflated all costs to 2018 USD using country-specific GDP deflators and discounted future costs and effectiveness by 3% annually, with sensitivity analysis for a range from 0% to 7%.

2.5. Incremental cost-effectiveness

We estimated the annual number of cases and deaths averted by the intervention as described above. We calculated the incremental cost per incremental DALY averted based on the number of cases and

| Table 1 | Epidemic and cost input parameters. |
|---|---|---|---|---|
| **Efficacy and completion** | **Base case** | **Range** | **References** |
| Rifapentine plus isoniazid for 3 months (3HP) efficacy and completion | 81% | 67–97% | 12 |
| Isoniazid preventive therapy (IPT) efficacy and completion | 72% | 58–86% | 13 |
| Tuberculosis (TB) treatment efficacy and completion | 90% | 80–95% | Target |
| Latent tuberculosis infection reactivation rate | Early reactivation rate (within 1 year) | 5% | 2–7% | 17 |
| Late reactivation rate (average year of late reactivation: 10 years) | 10% | 8–12% | 18 |
| Un-treated/treated TB case fatality rate (children younger than 5 and 15 years old) | Country specific | Country specific | 8 |
| Prevalence and coverage | % of child contacts receiving IPT in status quo | Country specific | Country specific | 9 |
| % of child contacts receiving IPT in status quo | Country specific | Country specific | 9 |
| % of child contacts without TB who are inappropriately treated in status quo | 19.4% | 15–23% | 14 and Expert opinion |
| % of children with symptoms | 37% | 20–60% | 10, 11, 12, 13 |
| Sensitivity of TB diagnosis by contact investigation | 65% | 30–80% | 14 and Expert opinion |
| % of child contacts without TB who are inappropriately treated by contact investigation | 10% | 5–40% | 20, 27 |
| % of child contacts receiving 3HP by contact investigation | 90% | 80–95% | Target |
| % of child contact experiencing TPT(3HP/IPT) induced hepatotoxicity | 0.83% | 0.63–1% | 20, 27 |
| % of child contact experiencing hospitalization due to toxicity | 0.015% | 0.012–0.018% | 20, 27 |
| **Cost parameters** | **3HP drug regimen (3 months)** | $15 | $10–$19 | 22 |
| **IPT drug regimen (6 months)** | $2.20 | $1.0–$6.08 | 26 |
| **Cost per household contact investigation screening** | Country specific | Country specific | 32 |
| **Cost per testing one child for TB** | Country specific | Country specific | 19 |
| **Cost per TB treatment** | Country specific | Country specific | 21 |
| **Cost per outpatient visit** | Country specific | Country specific | 20 |
| **Cost per TPT (3HP/IPT) induced hepatotoxicity treatment** | Country specific | Country specific | 25 |

Note: Please refer to Table S1 in the Appendix for upper and lower bounds used for each of these values in sensitivity and uncertainty analyses.

| Table 2 | Description of the population of children younger than fifteen years eligible for household TB contact investigation in 12 countries. |
|---|---|---|---|---|---|---|---|---|---|
| **Number of child contacts younger than 15 years** | **Number of child contacts with TB symptom (and TB testing)** | **Number of child contacts with TB** | **Number of child contacts with LTBI** | **Outcomes of contact investigation: Children younger than 15 years** |
| **Country** | **Children** | **TB treatment for children with TB disease** | **TB treatment for children without TB disease** | **3HP therapy for children with LTBI** | **3HP therapy for children without LTBI** |
| Brazil | 81,000 | 30,000 | 7000 | 39,000 | 6000 | 2000 | 34,000 | 34,000 |
| Cambodia | 28,000 | 10,000 | 3,000 | 13,000 | 10,000 | 4000 | 79,000 | 47,000 |
| Ethiopia | 151,000 | 56,000 | 13,000 | 54,000 | 3000 | 500 | 8000 | 8000 |
| Ghana | 19,000 | 7000 | 2000 | 9000 | 124,000 | 59,000 | 864,000 | 857,000 |
| India | 2,079,000 | 769,000 | 184,000 | 989,000 | 23,000 | 9000 | 138,000 | 136,000 |
| Indonesia | 332,000 | 123,000 | 29,000 | 157,000 | 8000 | 3000 | 52,000 | 50,000 |
| Kenya | 124,000 | 46,000 | 11,000 | 38,000 | 1000 | 700 | 10,000 | 10,000 |
| Malawi | 23,000 | 9000 | 2000 | 11,000 | 6000 | 3000 | 46,000 | 44,000 |
| Mozambique | 108,000 | 40,000 | 10,000 | 50,000 | 26,000 | 11,000 | 162,000 | 164,000 |
| South Africa | 393,000 | 146,000 | 35,000 | 189,000 | 6000 | 3000 | 42,000 | 40,000 |
| Tanzania | 99,000 | 37,000 | 9000 | 46,000 | 3000 | 1000 | 18,000 | 17,000 |
| Zimbabwe | 42,000 | 16,000 | 4000 | 20,000 | 215,000 | 98,000 | 1,464,000 | 1,418,000 |
| **Total** | 3,481,000 | 1,288,000 | 308,000 | 1,636,000 | 218,000 | 98,000 | 1,464,000 | 1,418,000 |

Note: Please refer to Tables S2 and S3 in the Appendix for upper and lower bounds used for each of these values in sensitivity and uncertainty analyses.
Table 3

| Country      | TB treatment and 3HP provision vs. Status quo | Child contacts younger than 5 years | Child contacts younger than 15 years |
|--------------|---------------------------------------------|-----------------------------------|------------------------------------|
|              |                                              | Incremental cost (in thousand)    | Incremental DALY averted (in thousand) |
| Brazil       | $7,006 ($5,362-$10,728)                     | $29 ($22-$66)                    | $913 ($721-$2,210)                |
| Ethiopia     | $2,312 ($1,437-$2,475)                     | $121 ($75-$204)                  | $6,667 ($4,139-$7,225)            |
| Ghana        | $724 ($513-$948)                           | $5 ($2-$6)                       | $14 ($2-$9)                       |
| India        | $62,142 ($42,630-$80,070)                  | $12,100 ($7,900-$22,300)         | $186,627 ($128,202-$260,062)      |
| Indonesia    | $16,253 ($13,424-$23,235)                  | $121 ($75-$204)                  | $469 ($311-$984)                  |
| Malawi       | $257 ($242-$287)                           | $102 ($51-$184)                  | $722 ($511-$1,918)                |
| Mozambique   | $1,286 ($1,184-$1,491)                     | $46 ($22-$91)                    | $299 ($121-$423)                  |
| South Africa | $24,969 ($20,672-$38,895)                  | $1,300 ($600-$2,900)             | $84,097 ($68,374-$143,488)        |
| Tanzania     | $2,008 ($1,312-$2,269)                     | $190 ($93-$306)                  | $5,404 ($3,446-$6,417)            |
| Total        | $122,519 ($90,447-$163,823)                | $10,000 ($7,200-$14,000)         | $373,626 ($293,344-$565,526)      |

By the change in life expectancy, assuming a discount rate of 3% per year and a TB disability weight of 0.24 [29], which we applied for an average of 6 months for children who developed future TB. We considered a range of cost effectiveness thresholds between $5000 and $20,000 per death averted (approximately $167-$667 per DALY averted), based on previously used cost-effectiveness thresholds for home-based/preventive interventions in low- and middle-income countries [5, 30].

2.6. Sensitivity analysis

We performed one-way sensitivity analyses on all model parameters to describe the associations between each input variable in our model and the primary outcome (i.e., cost per death averted). We also performed a three-way sensitivity analysis that simultaneously varied the three most influential parameters while holding all others fixed.

2.7. Statistical analysis

To further explore the simultaneous effect of uncertainty ranges across our model parameters, we conducted a probabilistic sensitivity analysis (PSA) in which all model parameter values were randomly sampled over uniform distributions. This process was repeated 1000 times to generate uncertainty estimates around the primary ICER estimate, with 95% uncertainty ranges reported as the 2.5th and 97.5th percentiles of the corresponding distributions.

2.8. Ethics statement

Neither ethical approval nor informed consent was required for this analysis which did not involve human subjects’ research.

2.9. Role of the funding

The funder 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. The findings and conclusions in this report are those of the authors and do not represent the official position of Unitaid.

3. Results

Of an estimated 3.5 million children under 15 years old (1.1 million children under 5 years old) eligible for household contact investigation across 12 high-burden countries, we estimated that 308,000 (UR: 122,000 – 824,000) would have prevalent TB disease and 1.6 million (UR: 1.3 million – 2.1 million) would have prevalent LTBI. We estimated that 1.3 million (37%) of these children would have TB symptoms at the time of household screening, of whom an estimated 264,000 (180,000 with TB and 84,000 without TB) would be treated for TB disease following household contact investigation. We also assumed that comprehensive household contact investigation would result in 3 million children receiving TB preventive therapy (1.6 million with LTBI and 2.4 million without LTBI; Table 2). Similar data for children under five are presented Table S3 in the Appendix. Under the status quo, we estimated that 274,000 children would be treated for active TB (84,000 with TB and 190,000 without TB), and that 899,000 children would receive IPT following household contact investigation. India accounted for 60% of all eligible pediatric household contacts (2 million) across the 12 countries studied. Relative to the status quo, we estimated that household contact investigation could avert 94,7300 (UR: 9,810v – 43,1500) future TB cases (60,710 in India) and 32,560 TB deaths (UR: 10,000 - 72,00000) (22,930 in India) at an incremental cost of $374 million (UR: 293 million - 566 million) in India and 32,560 TB deaths (UR: 10,000 - 72,00000) (22,930 in India).
million) ($187 million in India). (Table 3) The cost of household contact investigation per child ranged from $48 in Malawi to $544 in Brazil. Of this cost, 47% represented costs of household visits for screening, 30% costs of TB treatment and 15% costs of preventive therapy.

When implemented in all 12 countries, our model estimated the incremental cost-effectiveness of contact investigation with TB treatment and 3HP provision, relative to the status quo, as $11,474 per death averted ($2900 in Malawi to $50,000 in Brazil) for children younger than 15 years old and $383 per DALY averted ($100 in Malawi to $1600 in Brazil). (Fig. 1) Corresponding estimates for contact investigation with treatment of active TB only were $22,185 per death averted ($3000 in Malawi to $292,000 in Brazil) or $751 per DALY averted ($110 in Malawi to $9500 in Brazil). (Appendix Table S4) When TB treatment and preventive therapy were limited to children younger than five years old, cost-effectiveness improved, with a mean estimate of $5143 per death averted, and $173 per DALY averted relative to the status quo (Fig. 1), but overall impact on TB incidence and mortality was reduced (Appendix Table S4). If reactivation rates were considered to be age-specific (20% two-year cumulative incidence for children 0–4 years and 10% for children 5–14 years) [6], corresponding ICERs were $154 per DALY averted among children 0–4 years old and $412 per DALY averted among children 5–14 years old.

In our one-way sensitivity analysis, the major drivers of cost-effectiveness in most countries were TB prevalence, sensitivity of TB diagnosis, untreated case fatality, and the cost of household screening (Fig. 2 and Appendix Fig. S2). In some countries, including Brazil and Indonesia, the TB case notification rate was highly influential, reflecting these countries’ higher existing TB notification rates among children (48%) compared to those of other countries. In our probabilistic sensitivity analysis, 30% of simulations fell below our a priori stringent cost-effectiveness threshold of $10,000 per death averted (approximately $334 per DALY averted) for children under 15 years old, whereas 80% of simulations fell below a more lenient cost-effectiveness threshold of $20,000 per death averted (Fig. 3). If limited to children under five years old, 98% of simulations fell within the $10,000 per death averted threshold. These estimates varied by country, with lower-income countries generally having lower absolute estimates of incremental cost-effectiveness. For example, considering interventions limited to children under 5 years old, 100% of simulations in Malawi fell below a threshold of $5000 per death averted, versus 70% in India, 20% in South Africa and 0% in Brazil (Appendix Fig. S3).

4. Discussion

In this multi-country economic evaluation of household contact investigation for TB with treatment and short-course preventive therapy for children, we estimated that expanded contact investigation across 12 countries could avert over 95,000 future cases of TB and over 33,000 future TB deaths among household contacts under the age of 15. The incremental cost of this intervention was estimated at $374 million compared to the status quo, resulting in an estimated...
The cost-effectiveness of household child contact investigation was projected to be more cost effective in settings (e.g., Ghana, Malawi, Mozambique) where TB prevalence among child contacts is high, sensitivity of TB diagnosis is high, untreated case fatality rate is high (i.e., existing TB notification is low), and the cost of household screening is low. This analysis supports existing guidelines recommending household contact investigation with provision of short-course preventive therapy to children (without testing for LTBI) in high burden settings. To date, relatively few studies have evaluated the cost-effectiveness of household contact investigation as a means to reduce the burden of pediatric TB. One study in Vietnam estimated that household contact investigation is highly cost effective ($563 per DALY averted) and estimated a mean cost of $188 (in 2018 USD) per contact evaluated [31]. Another study in Uganda suggested that passive case finding and household contact investigation was cost-effective, at an estimated cost of $548 (in 2018 USD) per additional TB case detected compared to passive case finding alone [32]. A third model-based study assessed the cost-effectiveness of contact investigation in

Fig. 2. One-way sensitivity analysis: cost-effectiveness of household contact investigation with TB treatment and provision of preventive therapy versus status quo

The parameters shown had the greatest absolute influence (among parameters evaluated in the model) on the incremental cost-effectiveness ratio (ICER) of household contact investigation with TB treatment and provision of short course TB preventive therapy (weekly rifapentine plus isoniazid for 3 months, 3HP) in one-way sensitivity analyses. Bars show the ICER (incremental dollars per death averted in 2018 US dollars) of household contact investigation under variation of each parameter over the range specified, with the dark blue bar representing the high parameter value and light blue bar representing the low parameter value, holding the values of all other parameters as constant. For example, we varied the prevalence of active TB among child contacts younger than 5 years old from 0.05 to 0.20 versus the baseline (0.10), which caused the ICER to vary from its baseline value of $5143/death averted to $6686/death averted (assuming a lower prevalence) and $4037/death averted (assuming a higher prevalence). Please refer to Fig. S2 in the Appendix for the country (Brazil, India, Malawi, South Africa) specific one way sensitivity analyses. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 3. Cost effectiveness plane and cost effectiveness acceptability curves describing TB contact investigation followed by treatment and/or preventive therapy

The cost effectiveness plane (panel A) depicts the simulated outputs from probabilistic sensitivity analyses for household contact investigation with TB treatment and provision of short course TB preventive therapy (3HP) versus status quo. The horizontal axis denotes the incremental number of deaths averted in each simulation, and the vertical axis indicates the incremental cost of contact investigation compared to the status quo. In the cost effectiveness acceptability curves (panel B), the horizontal axis denotes the willingness to pay (WTP) per death averted (incremental cost-effectiveness ratio, ICER), and the vertical axis indicates the probability of cost-effectiveness based on the proportion of simulations in which the comparison of the contact investigation to the status quo falls below the WTP threshold shown on the x-axis. Costs are expressed in 2018 US dollars. Please refer to Fig. S3 in the Appendix for the country (Brazil, India, Malawi, South Africa) specific cost effectiveness planes and acceptability curves.
South Africa, comparing different screening strategies for provision of preventive therapy to children; this study argued that preventive therapy without testing for TB infection would be a cost-effective strategy for children aged under five, with an estimated cost-effectiveness ratio of $391 per life saved (in 2018 USD, versus $887 per life saved if preventive therapy were only offered to children testing positive for LTBI) [33]. Our results are broadly consistent with these previous studies, illustrating the wide variation in cost-effectiveness across countries but nonetheless supporting contact investigation (especially with provision of short-course preventive therapy to children and adolescents without prior LTBI testing) as a cost-effective strategy. Notably, our estimated cost-effectiveness ratios were generally higher than those of prior studies, reflecting our inclusion of the full spectrum of health system costs, such as the cost of visiting households to perform screening, costs of providing TB treatment to symptomatic children who did not have underlying TB, and provision of more expensive short-course therapy to all children under 15 years old. Despite consideration of the full spectrum of these costs, our point estimates still suggest that contact investigation and provision of preventive therapy without a requirement for LTBI testing is likely to be cost-effective.

Our estimate of cost-effectiveness ($383 per DALY averted summed across 12 countries, with country-specific estimates ranging from $100 to $1600) is similar to estimates from other models of different community/home-based interventions for children in low- and middle-income countries. The cost-effectiveness of scaling up such interventions, however, should also reflect regional and setting-specific conditions, such as HIV/TB co-prevalence, case fatality, and health system capacity. Our sensitivity analyses suggest that TB contact investigation and preventive therapy for children will be most cost-effective in settings with high TB prevalence, low TB case notification at baseline and low existing preventive therapy coverage. Although contact investigation and provision of IPT are likely to be most cost-effective in settings with low TB case notification and existing coverage of preventive therapy, these settings are also those most likely to lack sufficient infrastructure to scale up activities such as TB household contact investigation. In making implementation decisions, it is therefore important to consider not only cost-effectiveness but also feasibility, availability of local resources (i.e., affordability) and quality of services. Future implementation research, including the collection of setting-specific data on costs, implementation, and effectiveness in the real-world context, is also essential to identify mechanisms by which contact investigation and provision of preventive therapy can be effectively performed in such very-resource-constrained settings. For example, countries can improve the cost-effectiveness of household contact investigation through the development of tests and operational protocols that better identify incident TB disease, promote treatment adherence and reduce household screening costs through coordination with other home-based services. Overall, the strength of our model-based cost-effectiveness analysis lies in the comparison of two feasible intervention scenarios (i.e. TB treatment only versus TB treatment and 3HP provision) relative to country-specific status quo and the use of country- and age-specific epidemiological and cost data - including operational costs of household screening visits - with comprehensive uncertainty analyses. Our finding is thus helpful for countries to plan and promote implementation and scaling up of the child household contact screening for TB preventive treatment intervention in resource-limited settings.

Our study has important limitations. Country-specific data were scant to inform certain key parameters, including pediatric TB/LTBI prevalence, the natural history of pediatric tuberculosis and reactivation, sensitivity/specificity of pediatric TB diagnoses, the case-fatality ratio of untreated pediatric TB, costs of performing household screening, and case notification among child contacts who subsequently develop TB. As such a limited evidence is both cause and consequence of the challenge of systematic implementation of this practice, we emphasize the need to collect country specific data and include them in assessing cost effectiveness evaluation. Our estimate of this latter quantity (based on the estimated case notification ratio for all children with active TB [14]) may be overestimated for countries with poor existing implementation of household contact investigation implementation. Similarly, we may have overestimated IPT coverage among pediatric household contacts, as the registered numbers of pediatric contacts eligible for TB preventive treatment [13] were much lower than the estimated total numbers of child contacts with TB infection based on TB prevalence and demographic surveillance data [15]. Accordingly, our model-based estimates of cost-effectiveness are likely conservative. Moreover, our general cost estimates for preventative therapy (IPT and 3HP as $2 and $15) may be overestimated, given the lower doses required (about a third of those for adults) for children. However, these estimates might properly reflect total cost of service provision, considering additional operational costs associated with supply chain management of the preventive therapy. Since there is a dearth of data on the costs of household contact investigation from the participant/caregiver perspective, we took a conservative approach of only incorporating costs from the perspective of the health system. We also did not consider the cost of supplies that might be needed to obtain sputum in children (e.g., for gastric and nasopharyngeal aspirates). This could cause our estimates of the cost of household contact investigation to be over- or underestimated, depending on the relative cost of undergoing contact investigation and taking preventive therapy versus the averted cost of future TB disease. Future research should also consider the potential impact of contact investigation (and averted future TB) on catastrophic costs to households, given the importance of avoiding such costs as part of any health intervention. We also limited our analysis to household contact investigation and did not consider outbreak investigations or other forms of close-contact investigation. In our scenario analysis, assuming 3HP completion levels as low as 73% [34], variation in this parameter did not materially affect our findings (e.g., $383 per DALY averted in the reference scenario assuming 81% completion versus $377 assuming 73% completion). This partially reflects the fact that, if 3HP is not taken, the corresponding drug costs are lowered substantially. Finally, we did not consider HIV and antiretroviral therapy status, BCG vaccination status, or multidrug-resistant tuberculosis, which is expected to affect about 3% of children with tuberculosis [18] and we did not account for any reductions in life expectancy among children with co-morbidities [5]. The prevalence of such life-limiting comorbidities, however, is likely insufficient to substantially affect our primary conclusions.

In conclusion, this analysis incorporating data from across 12 countries suggests that contact investigation with treatment of active TB and provision of preventive therapy is likely to be cost-effective compared to contact investigation with TB treatment only (summary estimate: $58 per DALY averted) or the status quo ($383 per DALY averted). Key drivers of cost-effectiveness included TB prevalence, sensitivity of TB diagnosis, untreated case fatality, and the cost of household screening. Household contact investigation for TB has the potential to prevent substantial morbidity and mortality in children; this analysis suggests that this intervention is likely to be cost-effective as well.

Declaration of Interests

Dr. Chaisson reports personal fees from Sanoﬁ, outside the submitted work, and grants from Unitaid. All the other authors declare no conﬂict of interest.

Authors’ contribution

Dr. Jo had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Dowdy, Jo Acquisition, analysis, or interpretation of data: Jo, Flack, Salazar-Austin
Drafting of the manuscript: Jo Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Jo, Flack Obtained funding: Churchyard Study supervision: Dowdy, Churchyard, Chaisson

Data sharing
All data are reported in the manuscript and appendix.

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Supplementary materials
Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2020.100707.

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