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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. These

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Research in Context

Evidence before this study

While several studies have shown that pediatric tuberculosis (TB) mortality could be reduced substantially if diagnosis and treatment of pediatric TB could be improved, evidence to inform the cost and cost-effectiveness of household contact investigation with treatment and preventive therapy for children and adolescents remains limited. We searched PubMed for economic evaluation studies of household contact investigation up to May 30, 2020 with the search terms ("economic evaluation" OR "cost-effectiveness") AND ("TB" OR "tuberculosis") AND ("contact investigation" OR "contact screening"). This search yielded 35 articles, of which two reported specific operational costs of household contact investigation in low- or middle-income countries (namely, Uganda and Myanmar).

Added value of this study

We performed a multi-country cost-effectiveness analysis of household contact investigation, including TB treatment and 3HP provision to children and adolescents. We considered comprehensive health systems cost of contact investigation, including household screening visits, TB testing, and TB/3HP treatment and assessed the incremental cost effectiveness using country- and age-specific epidemiological and cost data. We estimated that the country specific cost-effectiveness of contact investigation would fall between $100 and $1390 per disability-adjusted life year (DALY) averted, with higher cost-effectiveness ratios in wealthier countries.

Implications of all the available evidence

Household contact investigation for tuberculosis, with the provision of preventive therapy to children and adolescents, is likely to be cost-effective in regions with high TB prevalence, low TB case notification levels and low existing coverage of preventive therapy. Future evaluations of implementation, including the collection of setting-specific data, will further inform decision-making.

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, I4TB), to promote the scale-up of short-course TB preventive therapy (weekly rifapentine 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.

2. Methods

2.1. Study design

We used decision analysis to estimate the incremental cost-effectiveness of contact investigation with treatment of active TB and provision of 3HP for latent TB infection (LTBI) among household contacts under five and 15 years of age. We compared this scenario to the status quo (i.e., existing country- and age-specific TB case notification and provision of six months of isoniazid for preventive therapy, IPT) and to contact investigation with diagnosis and treatment for active TB but no provision of preventive therapy. For each of our 12 countries, we estimated the total number of TB cases and premature deaths due to TB in each treatment scenario (Appendix Fig. S1).

2.2. Interventions

We modeled household contact investigation as including TB testing for child contacts with symptoms, TB treatment for children with presumed TB disease, and 3HP treatment for all child contacts without clear evidence of TB disease (i.e., without requiring a test for LTBI). For simplicity of analysis, we did not consider other forms of close contact or outbreak investigation among children and adolescents. For each country's status quo, we used existing country- and age-specific TB case notification rates and preventive therapy coverage (Table 1 and Appendix Table S1) [10]. These estimates, coupled with data from the scientific literature [9], enabled us to project the number of future TB cases and deaths due to reactivation of TB infection that would be experienced by child contacts with LTBI at the time of potential household contact investigation. Based on published cohort studies [10–13], we assumed that 37% of pediatric contacts would have symptoms (such as poor appetite, chronic cough, weight loss, fever, night sweats) at the time of potential household contact investigation, and would all be evaluated for active TB with sputum Xpert testing. We assumed that diagnostic testing plus clinician decision-making would have 65% sensitivity and 90% specificity for the diagnosis of active TB among pediatric household contacts [14], using wide ranges for sensitivity analysis. For the status quo, we considered probabilities of TB treatment based on existing estimates of the age-specific TB notification rate and presumed specificity to be 95% [9].

2.3. Target population

We estimated the size of the eligible number of pediatric household contacts based on published estimates (Table 2 and Appendix Table S2) [15]. We estimated this number as the average number of children under 15 years old per household in each country based on the most recent Demographic and Health Survey [16], multiplied by the number of adult pulmonary TB cases notified by each country to the World Health Organization in 2018 [11]. We assumed that 9% (uncertainty range [UR]: 3·5%–24%) of all pediatric household contacts under fifteen years old would have prevalent TB disease, and an additional 48% (UR: 39%–59%) would have prevalent LTBI, based on pooled estimates in low and middle income countries [4]. For children with prevalent TB infection, we assumed that 5% would progress to active TB within one year, and that an additional 10% would progress to active TB at an average time of 10 years [17]. We assumed that TB treatment would have 90% efficacy in treating TB disease and that 3HP would have 90% efficacy in preventing reactivation of prevalent LTBI [12]. We also assumed that 90% of children prescribed 3HP would complete treatment, versus 80% of children prescribed IPT [12]. We estimated the case fatality of TB based on published estimates of age-specific case fatality among children treated for TB (2% for children age 0–5 and 0·8% for children age 5–14) and without treatment (43·6% for children age 0–4 and 14·9% for children age 5–14) [18]. We assumed that 70% of all child TB cases in children

Table 1
Epidemic and cost input parameters.

Epidemic parameters	Base case	Range	References
Efficacy and completion			
Rifapentine plus isoniazid for 3 months (3HP) efficacy and completion	81%	67–97%	12
Isoniazid preventive therapy (IPT) efficacy and completion	72%	58–86%	
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%	
Untreated/treated TB case fatality rate (children younger than 5 and 15 years old)	Country specific	Country specific	18
Prevalence and coverage			
TB notification rate for children younger than 5 and 15 years old in status quo	Country specific	Country specific	8
% of child contacts receiving IPT in status quo	Country specific	Country specific	
% of child contacts without TB who are inappropriately treated in status quo	19·4%	15–23%	9
% 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%	
% of child contacts receiving 3HP by contact investigation	90%	80–95%	Target
% of child contact experiencing TPT(3HP/IPT) induced hepatoxicity	0·83%	0·63–1%	20,27
% of child contact experiencing hospitalization due to toxicity	0·015%	0·012–0·018%	
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 hepatoxicity 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.

	Target population: Children younger than 15 years				Outcomes of contact investigation: Children younger than 15 years			
	Number of child contacts younger than 15 years [a]	Child contacts with any TB symptom (and TB testing)	Number of child contacts with TB [b]	Number of child contacts with LTBI [c]	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	3,0000	13,000	2000	800	12,000	12,000
Ethiopia	151,000	56,000	13,000	54,000	10,000	4000	79,000	47,000
Ghana	19,000	7000	2000	9000	1000	500	8000	8000
India	2,079,000	769,000	184,000	989,000	124,000	59,000	864,000	857,000
Indonesia	332,000	123,000	29,000	157,000	23,000	9000	138,000	136,000
Kenya	124,000	46,000	11,000	58,000	8000	3000	52,000	50,000
Malawi	23,000	9000	2000	11,000	1000	700	10,000	10,000
Mozambique	108,000	40,000	10,000	50,000	6000	3000	46,000	44,000
South Africa	393,000	146,000	35,000	189,000	26,000	11,000	162,000	164,000
Tanzania	99,000	37,000	9000	46,000	6000	3000	42,000	40,000
Zimbabwe	42,000	16,000	4000	20,000	3000	1000	18,000	17,000
Total	3,481,000	1,288,000	308,000	1,636,000	215,000	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.

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 = $e^{-2.2 + 1.1*\ln(\text{GDP per capita})}$] 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 3
Incremental costs, deaths averted and cost effectiveness of household contact investigation for pediatric tuberculosis in 12 countries.

Country	Child contacts younger than 5 years				Child contacts younger than 15 years			
	TB treatment and 3HP provision vs. Status quo				TB treatment and 3HP provision vs. Status quo			
	Incremental cost (in thousand)	Incremental deaths averted	Cost per death averted (in thousand)	Cost per DALY averted	Incremental cost (in thousand)	Incremental deaths averted	Cost per death averted (in thousand)	Cost per DALY averted
Brazil	$7,006 ($6,342-$11,425)	250 (115–468)	$29 ($22-$66)	$913 ($721-$2,210)	$22,162 ($20,356-$39,828)	440 (190–1,025)	$50 ($36-$122)	$1,600 ($1,200-$4,100)
Cambodia	$736 ($468-$837)	190 (89–346)	$4 ($2-$6)	$128 ($71-$206)	$2,090 ($1,315-$2,493)	230 (104–521)	$9 ($5-$14)	$293 ($151-$479)
Ethiopia	$2,312 ($1,437-$2,475)	1,000 (468–1,904)	$2 ($1-$4)	$78 ($38-$119)	$6,667 ($4,139-$7,225)	1,050 (514–2,732)	$6 ($2-$9)	$217 ($83-$296)
Ghana	$724 ($513-$948)	210 (96–383)	$4 ($2-$6)	$121 ($75-$204)	$2,126 ($1,484-$3,049)	310 (141–727)	$7 ($4-$12)	$234 ($133-$394)
India	$62,142 ($42,630-$80,070)	17,100 (7,900–32,300)	$4 ($2-$6)	$121 ($74-$211)	$186,627 ($128,202-$260,062)	22,930 (10,170–55,644)	$8 ($4-$14)	$268 ($149-$464)
Indonesia	$16,253 ($13,424-$23,235)	1,140 (540–2,244)	$14 ($9-$30)	$469 ($311-$984)	$46,855 ($38,881-$71,731)	1,730 (768–4,119)	$27 ($17-$58)	$878 ($552-$1,918)
Kenya	$3,356 ($1,978-$3,536)	720 (329–1,420)	$5 ($2-$7)	$161 ($73-$233)	$9,355 ($5,325-$10,352)	1,070 (469–2,690)	$9 ($4-$13)	$299 ($121-$423)
Malawi	$257 ($242-$287)	200 (114–375)	$1 ($1-$2)	$45 ($27-$76)	$722 ($679-$837)	250 (130–581)	$3 ($1-$5)	$102 ($51-$184)
Mozambique	$1,286 ($1,184-$1,491)	800 (396–1,601)	$2 ($1-$3)	$60 ($34-$111)	$3,422 ($3,148-$4,170)	860 (350–2,250)	$4 ($2-$9)	$147 ($69-$333)
South Africa	$24,969 ($20,672-$38,895)	1,300 (600–2,900)	$19 ($12-$41)	$666 ($398-$1,364)	$84,097 ($68,374-$143,488)	2,410 (1,035–6,943)	$35 ($20-$76)	$1,231 ($653-$2,517)
Tanzania	$2,008 ($1,312-$2,269)	680 (318–1,300)	$3 ($2-$5)	$102 ($52-$160)	$5,404 ($3,446-$6,417)	970 (418–2,220)	$6 ($3-$9)	$190 ($93-$306)
Zimbabwe	$1,470 ($1,021-$1,781)	220 (100–420)	$7 ($4-$12)	$237 ($126-$396)	$4,100 ($2,800-$5,278)	310 (136–748)	$13 ($7-$23)	$468 ($222-$773)
Total	$122,519 ($90,447-$163,823)	23,824 (8,000–44,000)	$5 ($3-$13)	$173 ($114-$421)	373,626 ($293,344-$565,526)	32,560 (10,000–72,000)	$11 ($7-$34)	$383 ($248-$1,130)

deaths for each scenario and country-specific 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

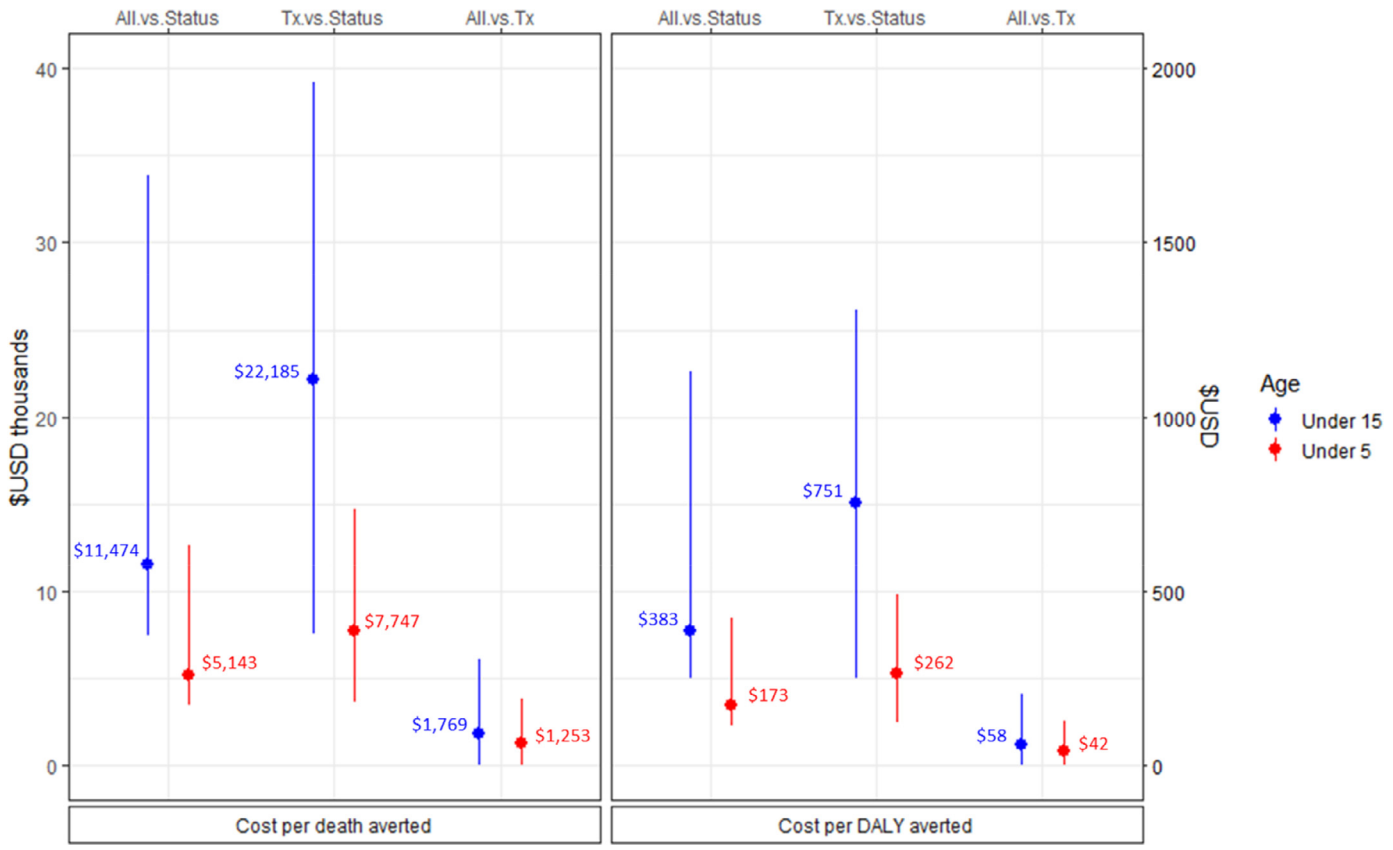


Fig. 1. Incremental cost-effectiveness of household contact investigation for pediatric TB, weighted average across 12 countries

The figure illustrates the mean incremental cost effectiveness ratio (ICER) of household contact investigation, with interventions focused on all children and adolescents under 15 years old (blue) or specifically on children under five years old (red). Three comparisons are depicted: 1) contact investigation with treatment of active TB and short course preventive therapy ("All") versus the status quo (left); 2) contact investigation with treatment of active TB only ("Tx") versus status quo (center); and 3) contact investigation with treatment of active TB and short-course preventive therapy versus treatment of TB only (right). The left set of three panels indicate cost per death averted and right set of three panels indicate cost per DALY averted. All scenarios assume country-specific life expectancy, a 3% annual discount rate, and a TB disability weight of 0.24 over an average of six-month duration of illness for future episodes of active TB. The lines indicate 95% uncertainty ranges reported as the 2.5th and 97.5th percentiles of the corresponding distributions. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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%) [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

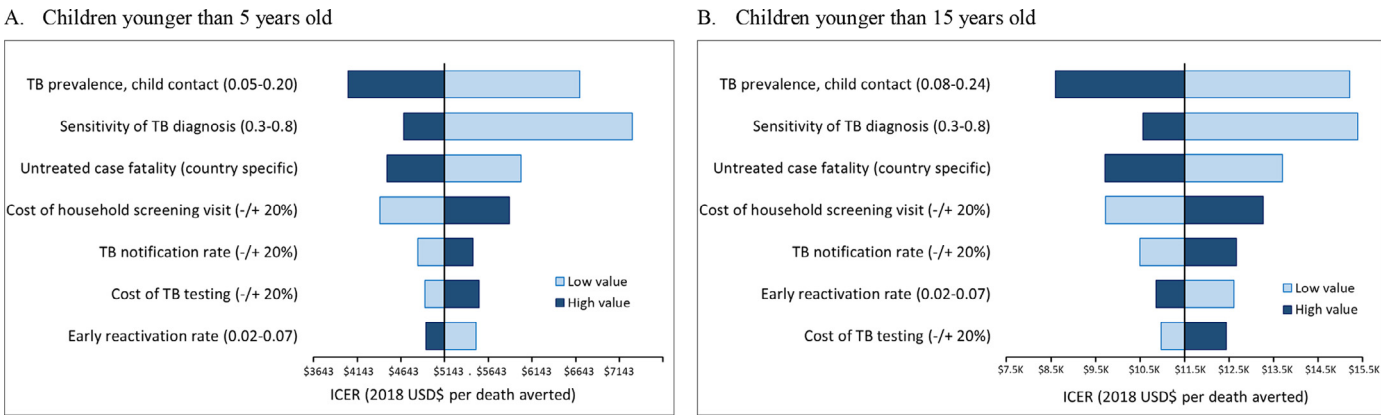


Fig. 2. One-way sensitivity analysis: cost-effectiveness of household contact investigation with TB treatment and provision of preventive therapy versus status quo

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.)

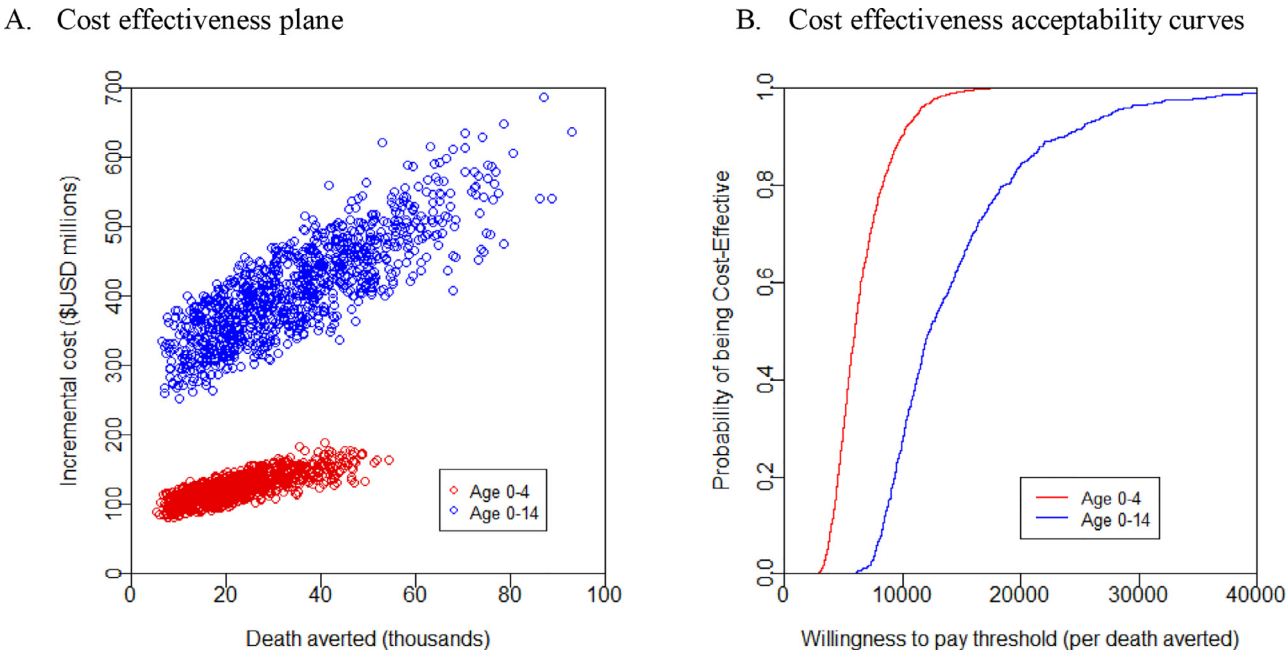


Fig. 3. Cost effectiveness plane and cost effectiveness acceptabilty curves describing TB contact investigation followed by treatment and/or preventive therapy

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.

cost-effectiveness of $383 per DALY averted (between $100 and $1600 per DALY averted across countries). 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

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 age 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 systems 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 3HP 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 needs 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 under-estimated, 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 ($383per 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 theaccuracy 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

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