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Cost effectiveness analysis of expanding tuberculosis preventive therapy to household contacts aged 5–14 years in the Philippines

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ABSTRACT

Background: Children aged 5–14 years who are household contacts (HHCs) of index people with active TB disease (PWTB) have limited coverage for TB preventive therapy (TPT) due to variable uptake of the national guideline recommendations in the Philippines. We conducted a cost-effectiveness analysis evaluating the expansion of TB infection (TBI) testing and treatment among pediatric (5–14 years) HHCs of index PWTB in the Philippines to assist the National TB program in choosing the most cost-effective testing and treatment strategy for TBI among HHCs of index PWTB.

Methods: Using a Markov state transition model, eligible HHCs age 5–14 years are screened for TBI with either the tuberculin skin test (TST) or interferon gamma release assay (IGRA). Those who test positive are then simulated to receive one of the following TPT strategies: 6 months of daily isoniazid (6H), 3 months of weekly isoniazid and rifapentine (3HP), 3 months of daily isoniazid plus rifampicin (3HR) and the current practice of no testing or treatment for TBI (NTT). The analysis assesses the projected cost and quality-adjusted life years (QALY) gained for every strategy from the perspective of the Philippines public healthcare system over a time horizon of 20 years. The total cost and gain in QALYs are presented as an incremental cost-effectiveness ratio (ICER) comparing cost per QALY gained for each strategy over NTT.

Results: Our model estimates that expanding TPT coverage to HHCs aged 5–14 years would be cost-effective with incremental cost-effectiveness ratios (ICERs) ranging from 1,024 $/QALY gained when using TST and 6H (Uncertainty range: 497—–2,334) to 2,293 $/QALY gained when IGRA and 3HR are used (Uncertainty range: 1,140 – 5,203). These findings were robust to sensitivity analyses over a wide range of parameter values.

Conclusion: Expanding TPT coverage to HHCs aged 5–14 years is cost-effective when using TST and 6H closely followed by a strategy combining TST and 3HP.

1. Introduction

Tuberculosis (TB) remains one of the infectious diseases with the heaviest burdens worldwide infecting one fourth of the world's population and causing 1.3 million deaths in 2022 including 214,000 children under the age of 15 years [1]. The United Nations included TB elimination as one of its sustainable development goals and the World Health Organization (WHO) has emphasized TB prevention for

Abbreviations: 3HP, 3 months of weekly isoniazid plus rifapentine; 3HR, 3 months of daily isoniazid and rifampicin; 6H, 6 months of daily isoniazid; CEA, Cost-effectiveness analysis; DOTS, directly-observed-therapy short-course; GDP, Gross domestic product; HHC, household contact; ICER, incremental cost-effectiveness ratio; IGRA, interferon gamma release assay; IRB, Institutional review board; TBI, TB infection; NTP, National TB Program; NTT, scenario of no screening or treatment for TBI; PEER-USAID, Partnerships for Enhanced Engagement in Research-United States Agency for International Development; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; TB, Tuberculosis; TPT, TB preventive therapy; TST, tuberculin skin test; USD, US Dollars; WHO, World Health Organization.

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individuals at high risk including household contacts (HHCs) of index people with active TB disease (PWTB) [2,3]. In 2020, an estimated 591,000 people in the Philippines fell ill with TB disease; 73,000 of them were children which further highlights the need to prioritize TB prevention [4]. Additionally, 39.8 million people are estimated to have TBI in the Philippines where overall TB preventive treatment (TPT) coverage remains below 25 % [1,5].Subsequently in their 2020 guidelines, the Philippines National TB Program (NTP) adopted guidance from the WHO to expand TPT to all HHC, rather than just those < 5 years of age, but these guidelines have had variable uptake since their publication highlighting the persistent gap in TPT coverage, especially for pediatric HHCs [6,7]. The Philippines NTP plans to roll out the expansion of TPT coverage to HHCs in an incremental fashion starting with HHCs aged 5–14 years, who are the target of this analysis. Many studies have shown that shorter regimens for TPT are cost-effective compared to the standard isoniazid-only regimens, but these analyses targeted either different age groups or different strategies to the planned expansion of TPT in the Philippines [8,9]. Consequently, this cost-effectiveness analysis was conducted in partnership with the Philippines NTP and PEER-USAID (Partnerships for Enhanced Engagement in Research-United States Agency for International Development) to assess the cost-effectiveness of three recommended regimens: 6 months of daily isoniazid (6H), 3 months of weekly isoniazid plus rifapentine (3HP) and 3 months of daily isoniazid and rifampicin (3HR). All three regimens were selected for evaluation by the Philippines NTP and have been included in the WHO and national TB guidelines for TPT. This analysis did not include the regimen of one month of daily rifapentine and isoniazid since the evidence supporting its use for TPT comes primary from a cohort of people living with HIV who are 13 years and older which does not fit with the target cohort for TPT expansion (all HHCs aged 5–14) [10].

2. Methods

2.1. Model structure

Fig. 1 shows the model structure and transition states. We used a decision tree followed by a Markov state transition model [11–13] to estimate the incremental cost-effectiveness of each scenario of expanded TPT compared to the current practice (e.g. pre-2020 guidelines), which does not include HHCs aged 5–14 years in TPT care. HHCs aged 5–14 years of index PWTB, only enter the model after they complete the recommended contact screening procedures and screen negative for active TB disease, following the prevalent practice in the Philippines [14,15]. The expanded TPT scenarios include testing for TBI by either tuberculin skin test (TST) or interferon gamma release assay (IGRA) followed by treatment with 6H, 3HP or 3HR for those who test positive. TST and IGRA has an estimated sensitivity of 71 % and 79 % and specificity of 89 % and 99 % in the base case scenario, respectively [16]. Individuals who test positive for TBI (whether truly or falsely) are then modelled to undergo TBI treatment with either 6H, 3HP or 3HR. After undergoing TBI testing and treatment (if eligible), individual scenario trajectories were simulated using a Markov model with four transition states: (Eligible for screening for) TBI, active TB, cure (of active TB) and death (related to TB or not related to TB).

2.2. Model parameters and target population

Table 1 shows all model parameters. Based on Data on TB and TBI burden from the Philippines, we estimated that starting with 595,000 index PWTB results in 797,360 HHCs aged 5–14 years (please refer to the Supplementary Appendix for details on the calculated number of HHC aged 5–14 years per index case). Among these pediatric HHCs, 11,163 (1.40 %) will be diagnosed with TB disease and 786,197 (98.60 %) will be eligible for TBI evaluation [17–19]. Of those eligible for evaluation, 417,471 (53.1 %) will have TBI [20].

Annual transition probabilities from TBI to active TB without TBI treatment was assumed to decline steadily between years 2 and 5 and assumed to be constant after year 5 based on published literature [20,21]. Annual transition probabilities from TBI to active TB disease in the setting of TBI treatment were based on data from a *meta*-analysis reflecting real world practice of TPT and incorporating TPT completion rates, thus treatment completion rates were not explicitly modelled [22]. Annual transition probabilities from active TB to cure and death

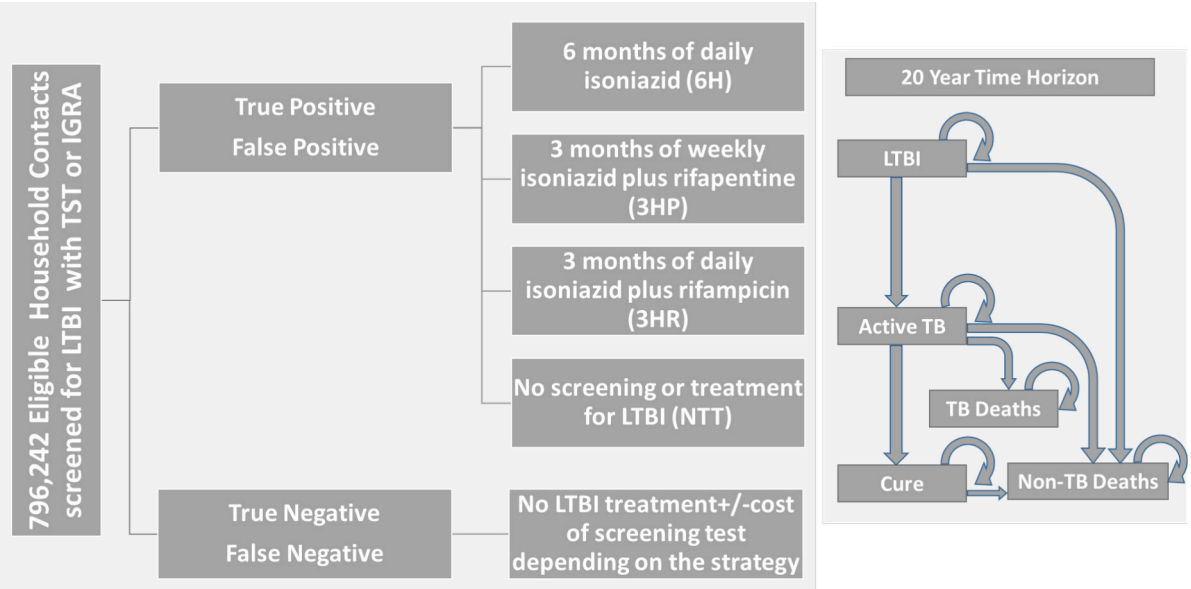

Fig. 1. Model Structure: The model first implements a decision tree among a hypothetical group representing the newly eligible household contacts for TBI screening with either tuberculin skin test (TST) or interferon gamma release assay (IGRA). Those who screen positive are treated with 6 months of daily isoniazid (6H), 3 months of weekly isoniazid and rifapentine (3HP) or 3 months of daily isoniazid plus rifampicin (3HR) and every strategy is then compared to a scenario of no screening or treatment for TBI (NTT). Each subgroup is determined by the outcome of screening then enters a Markov state transition model with four possible states: tuberculosis infection (TBI), active tuberculosis (TB), cured from active TB (Cure) and death (TB and non-TB). This Markov process is simulated over a time horizon of 20 years.

Table 1
Model Parameters.

Parameter	Base Value	Distribution*	Low	High	Reference
TBI prevalence	53.1 %	Beta	47.79 %	58.41 %	[20]
Total number of HHCs to be screened	786,197	Random	707,578	864,817	[17,18,20]
Annual transition probability from TBI to active TB without TPT	0.0205	Beta	0.0185	0.0226	[3]
Proportion Progressing to Active TB with 6H compared to NTT	0.40	Beta	0.36	0.44	[22]
Proportion Progressing to Active TB with 3HP compared to NTT	0.36	Beta	0.32	0.40	[22]
Proportion Progressing to Active TB with 3HR compared to NTT	0.33	Beta	0.30	0.36	[22]
Annual transition probability from active TB to death	0.02	Beta	0.018	0.028	[17]
Annual transition probability from active TB to cure	0.84	Beta	0.76	0.92	[17]
6H Drug Cost (180 tablets of 300 mg) in USD	3.18	Gamma	2.86	3.49	[24]
3HP Drug Cost (36 tabs of 300–300) in USD	15.00	Gamma	13.50	16.50	[24]
3HR Drug Cost (6x84 doses of RH 75–50 mg) in USD	23.70	Gamma	21.33	26.07	[24]
Cost per TBI outpatient visit in USD	2.55	Gamma	2.31	2.81	[27]
Total cost for one case of active TB in USD	113.82	Gamma	102.44	125.21	[17,25,27]
Utility-TBI	1.00	–	1.00	1.00	[33]
Utility-Active TB	0.67	Beta	0.60	0.73	[33]
Utility-Cure	0.95	Beta	0.85	1.00	[35]
TST cost in USD	3.39	Gamma	3.05	3.73	[27]
TST sensitivity	0.71	Beta	0.64	0.78	[16]
TST specificity	0.89	Beta	0.80	0.98	[16]
IGRA cost in USD	18.45	Gamma	16.61	20.30	[26]
IGRA sensitivity	0.79	Beta	0.71	0.87	[16]
IGRA specificity	0.99	Beta	0.89	0.99	[16]
Discount rate (for cost and effect)	3 %				[36,37]

* Refers to the statistical distribution used to vary the model value between the low and high values.
Based on estimated annual TB cases in the Philippines and the prevalence of active TB among HHCs of.

were based on WHO data, including pediatric-specific data when available, on reported TB outcomes averaged from 2019 and 2020 (Pediatric case fatality for TB does not explicitly mention whether patients received TB disease treatment before death) [17]. Annual probability of death in the absence of active TB was based on published lifetables for the Philippines [23].

The cost of TBI treatment regimens was based on procurement estimates provided by the Stop TB Partnership and corroborated through the Philippines NTP [24]. To estimate the cost of active TB, we used the reimbursement rate for community-based directly-observed-therapy short-course (DOTS) package in the Philippines of $111.03 and added a cost of hospitalization assuming a 5-day length of stay on average and 3 % chance of hospitalization based on WHO reporting on drug sensitive TB for all ages in the Philippines [17,25]. The cost of IGRA was based on the reported cost of QuantiFERON-TB Gold Plus as reported by the Stop TB Partnership [26]. The cost of outpatient visits, TSTs, and hospitalizations were based on the average values at the community health unit for outpatient care and primary hospital level for inpatient care as reported by the Value TB study [27]. All costs were measured in 2021 US Dollars after adjusting for inflation in the following ways: Philippines specific inflation calculator was used when cost was estimated from local sources; consumer price index was used for inflation adjustment when cost was derived from international supplier; official exchange rates from the Philippines central bank were used when cost estimates were provided in Philippine Pesos [28–30].

Effectiveness was estimated as the number of quality adjusted life years (QALYs) gained as they are more intuitive, but due to the lack of Philippines-specific utility estimates we relied on published disability weights and converted them to utilities (1-disability weight) based on published methodology [31,32]. We assumed that utility for the TBI state was similar to that of the underlying general population estimated to be 1.0, whereas the utility for active TB was assumed to be 0.67 based on published literature [33,34]. Based on literature regarding post-TB sequelae, we also assumed a decrement in health utility of 0.053 following successful treatment of active TB [34,35]. Utilities were applied on an annual basis. The total costs and total effects were used to generate an incremental cost-effectiveness ratio (ICER) by dividing the incremental cost for every strategy compared to the current pre-2020 guideline strategy of no testing or treatment for TBI (NTT) by the incremental QALY gain for every strategy compared to NTT. We also provide a second set of ICERs comparing each strategy to the next most cost-effective strategy. Both costs and effectiveness were discounted by 3 % per year based on the recommendations of the U.S. Second Panel on Cost-Effectiveness in Health and Medicine and WHO Guide to Cost-effectiveness Analysis, we also explored the effects of 0 % and 5 % discount rates on the results [36,37]. The model used a time horizon of 20 years in consultation with the Philippines NTP to account for the long-term benefit of TPT expansion and was performed from the perspective of the Philippines public healthcare system which covers TB care [25]. Willingness to pay threshold explored in this analysis relied upon the Philippines GDP per capita as estimated by the World Bank and based on the recommendations of the WHO Guide to Cost-Effectiveness Analysis [36–38]. For additional details on model parameters, please refer to the Supplementary Appendix.

2.3. Model assumptions

We assumed that, in the absence of progression or reactivation to active TB, individuals with TBI have no risk of TB-related death. We assumed the cost of TBI treatment to include an initial outpatient visit for consultation followed by a monthly outpatient visit for follow-up and

refill over the duration of treatment per the Philippines TB guidelines [7]. We assumed that TBI treatment would be delivered per the same guidelines by self-administered therapy and thus excluded costs of directly observed therapy.

According to the Philippines TB guidelines, chest x-rays are used for all HHCs over the age of 5 as part of active TB disease evaluation and thus we assumed their cost to be equal in all strategies. Individuals with false-positive test results were assumed to have no risk of progression to active TB. Reinfection with TB after the testing and treatment period was assumed to occur equally in all groups and was thus not explicitly modeled. We also assumed all cases of active TB to be drug sensitive as are the vast majority of TB cases in the Philippines, and occurring in individuals without HIV co-infection given the prior inclusion of people living with HIV in TPT recommendations [7,17]. Based on published literature, the probability of severe adverse events that would require medical attention in the context of TBI treatment in this age group is exceedingly rare and thus we did not explicitly include incremental adverse events in the model [22,39,40]. Finally, we assumed that the ratio between reported and estimated TB cases to be constant across age groups and that TB outcomes remain constant during the time horizon of the analysis.

2.4. Base case and sensitivity analyses

Our base case starts with a population of 786,197 HHCs age 5–14, which is the estimated number of individuals eligible for the intervention in the Philippines. To determine the parameters that had the most effect on model outputs, we performed a one-way deterministic sensitivity analysis by varying each parameter by +/-10 % of the base value without violating logical boundaries (e.g. 0–1 for probabilities). We also performed multivariate probabilistic sensitivity analysis (PSA) based on 1000 trials. In each trial, parameters were sampled following a uniform statistical distribution to account for parameter uncertainty. The PSA was used to generate a cost-effectiveness plane comparing different TPT strategies to NTT. In addition, we used the PSA to quantify the probability of cost-effectiveness for each regimen based on either testing strategy by employing a net monetary benefit approach [11,12]. We used our PSA to calculate uncertainty ranges at the 2.5th and 97.5th percentile for each reported value; we provided these ranges within parentheses when presenting results. We also explored price points under which IGRA would achieve similar results to TST (Supplementary Appendix, figure S1). All analyses were performed using Microsoft Excel 2016 (Microsoft; Redmond, Washington, USA).

Institutional review board (IRB) approval was not required according to guidelines from the University of Virginia IRB office, as this

Table 2
Base case results using TST (top half) and IGRA (bottom half) as the screening test.

	People Treated (Thousands)	Active TB	TB-Related Deaths	Cost (3 % discounted, thousands USD)	QALY (3 % discounted, thousands)	ICER (Strategy-next best strategy) (3 % discounted, USD/QALY))
NTT	0	15,671 (12518, 19221)	393 (294, 511)	2,055 (1533, 2680)	12,089 (10935, 13254)	
6H	337 (263, 412)	9,078 (7053, 11476)	226 (165, 302)	10,935 (8908, 13026)	12,097 (10944, 13264)	1,024 (497, 2334)
3HP	337 (263, 412)	8,590 (6345, 10471)	215 (157, 287)	12,282 (9979, 14656)	12,098 (10944, 13264)	146 (−28868, 28635)
3HR	337 (263, 412)	8,254 (6638, 10863)	207 (150, 277)	15,170 (12211, 18224)	12,098 (10944, 13264)	6,603 (−82470, 84700)
Incremental (Strategy-NTT)	**People Treated (Thousands)**	**Active TB**	**TB-Related Deaths**	**Cost (3 % discounted, thousands)**	**QALY (3 % discounted, thousands)**	**ICER (Discounted) USD/QALY)**
6H-NTT	337 (263, 412)	−6,593 (−8,467, −5,024)	−166 (−226, −119)	8,880 (7111, 10743)	8.67 (3.71, 17.85)	1,024 (497, 2334)
3HP-NTT	337 (263, 412)	−7,081 (−9,454, −5,682)	−177 (−240, −128)	10,227 (8177, 12340)	9.26 (3.96, 18.90)	1,105 (537, 2503)
3HR-NTT	337 (263, 412)	−7,417 (−9,063, −5,404)	−186 (−251, −134)	13,115 (10369, 15980)	9.69 (4.18, 19.73)	1,353 (661, 3046)
NTT	0	15,671 (12522, 19140)	393 (295, 511)	2,055 (1531, 2680)	12,089 (10935, 13255)	–
6H	333 (271, 412)	8,335 (6367, 10574)	208 (150, 277)	22,604 (19357, 26177)	12,098 (10942, 13265)	2,046 (−26776, 26776)
3HP	333 (271, 412)	7,792 (5563, 9492)	195 (140, 262)	23,930 (20487, 27679)	12,099 (10943, 13266)	2,124 (1050, 4839)
3HR	333 (271, 412)	7,419 (5868, 9950)	186 (133, 250)	26,783 (22894, 31197)	12,099 (10943, 13267)	3,683 (1086, 35162)
Incremental (Strategy-NTT)	**People Treated (Thousands)**	**Active TB**	**TB-Related Deaths**	**Cost (3 % discounted, thousands)**	**QALY (3 % discounted, thousands)**	**ICER (Discounted) USD/QALY)**
6H-NTT	333 (271, 412)	−7,336 (−9495, −5538)	−185 (−250, −133)	20,549 (17529, 23886)	9.65 (4.13, 19.96)	2,129 (1052, 4900)
3HP-NTT	333 (271, 412)	−7,879 (−10545, −6307)	−197 (−266, −143)	21,875 (18659, 25394)	10.30 (4.41, 21.16)	2,124 (1050, 4839)
3HR-NTT	333 (271, 412)	−8,252 (−10087, −6034)	−207 (−278, −150)	24,728 (21079, 28873)	10.79 (4.63, 22.18)	2,293 (1140, 5203)

research did not involve human subjects.

3. Results

3.1. Base case scenario

Table 2 shows the base case scenario results when using TST to test for TBI. Among the 786,197 HHCs screened for TB using TST, 336,964 (42.86 %) would be eligible for TBI treatment; of those 296,404 (87.96 %) are truly positive for TBI. In this scenario, using 6H achieved the lowest ICER estimated to be 1,024 USD/QALY gained (Uncertainty range: 497 – 2,334) closely followed by 3HP with an estimated ICER of 1,105 USD/QALY gained (Uncertainty range: 537 – 2,503). In addition, using TST and treating those who test positive with 6H compared to NTT results in 6,593 (Uncertainty range: 5,024– 8,467) fewer active TB cases and 166 (Uncertainty range: 119 – 226) fewer TB-related deaths. This strategy yields an estimated gain in QALYs of 8,674 (Uncertainty range: 3,705 – 17,845) at an estimated additional cost of 8.88 million USD (Uncertainty range: 7.11 million – 10.74 million). Table 2 also shows results for 3HP and 3HR. Table 2 also shows the base-case results when IGRA is used as the screening test for TBI. Given the higher proportion of pediatric HHCs who are truly positive for TBI when using IGRA (329,802 compared to 296,404 when using TST), 3HP achieved the lowest ICER. However, ICERs for all three strategies were almost twice as high compared to strategies using TST but still below the Philippines GDP per capita.

3.2. One-way and probabilistic sensitivity analyses

Fig. 2 shows the results of one-way sensitivity analysis where utility of cure and annual transition probability from TBI to active TB without TPT were the parameters that produced the most variability in ICERs. For example, as seen in Fig. 3A, a 10 % decrease in the total cost of IGRA led to a 7 % improvement in ICER in the IGRA + 6H strategy.

In a probabilistic sensitivity analysis shown in Fig. 3, all simulations projected a gain in QALYs for all regimens using either TST or IGRA. When using TST (panel A) almost all simulations resulted in an ICER lower than the Philippines' GDP per capita and the remaining simulations resulted in ICER between 1–3 times GDP per capita for the Philippines. The analysis also showed significant overlap between the three regimens for gain in QALYs but 3HR had the highest cost in most simulations. When using IGRA (Panel B) many simulations resulted in an ICER below the Philippines' GDP per capita, with the remainder of simulations producing an ICER between 1–3 GDP per capita. The analysis showed significant overlap among regimens for both incremental cost and effect, as the cost of IGRA was the main driver of overall cost in this scenario.

3.3. Probability of Cost-Effectiveness

Fig. 3 also shows the probability of cost-effectiveness (based on achieving the highest net monetary benefit) for every strategy when using TST (panel C) compared to IGRA (panel D) over a range of willingness to pay thresholds. As the willingness to pay increased with both testing strategies, the probability of NTT being cost-effective fell. When using TST and a willingness to pay threshold of the Philippines GDP per capita, the NTT has a projected probability of cost-effectiveness of 15 % compared to 42 % for 6H and 46 % for 3HP.

3.4. Impact of discount rate and cost of IGRA

Variation in discount rate had limited effect on the results of our analysis as shown in Tables S1-S4 in Supplementary Appendix. A lower discount rate of 0 % resulted in a slight improvement in cost-effectiveness for all strategies while increasing discount rate to 5 % resulted in slight worsening of cost-effectiveness across all strategies. However, the effect was small in either direction. We also found that significant reduction in the cost of IGRA, down to approximately $5.5 from $18.45 in the base case scenario, is required to achieve similar cost-effectiveness to that achieved with TST. Fig. S1 in the Supplementary Appendix shows the impact of IGRA cost on ICERs for all three IGRA strategies.

4. Discussion

Our analysis found the expansion of TPT to HHCs aged 5–14 years to be cost-effective when using both TST and IGRA with strategies using TST achieving ICERs in the low 1,000′s USD/QALY gained. The most cost-effective strategy combines TST testing for TBI with treatment with 6H for those who test positive, closely followed by the strategy combining TST with 3HP, which has significant importance for implementation in this high burden country.

Our findings are in line with published literature on pediatric TPT when studied in various settings. For example, Mandalakas et al evaluated isoniazid preventive therapy for pediatric HHCs in South Africa and found it to be cost-effective without a screening test when compared to various testing modalities [41]. However, their analysis which was conducted in 2013 focused on those under the age of 5 years. In a more similar example to our analysis, Jo et al found household contact screening, with treating TB cases as well as providing preventive treatment to those who do not have active TB, to be cost-effective. Jo et al reported cost per disability-adjusted life years (DALY) averted ranging from 102 USD/DALY-averted in Malawi to 1,600 $/DALY-averted in Brazil for pediatric HHCs. Their analysis evaluated the cost-effectiveness of a more comprehensive strategy that included screening and treatment all forms of TB among pediatric HHCs aged 0–15 years, along with a home-based care program, but the analysis did not include the Philippines [42].

The optimal threshold for cost-effectiveness in the Philippines is unknown, we chose the Philippines GDP per capita as a reasonable threshold which is considered as highly cost-effective in the WHO guidance on CEAs [36]. Since the original document was published in 2003 many subsequent publications argued that using 3 times a country's GDP as a threshold for cost-effectiveness would make it difficult for decision makers to choose interventions that can be truly implemented in a relevant setting [43]. For example, Woods et al estimated that a middle income country such as El Salvador with a GDP per capita similar to that of the Philippines should have a cost-effectiveness threshold of $422 to $1967 which is 11 %–51 % of its GDP per capita [44]. In another example, Horton et al listed the most cost-effective health-related interventions in childhood most of which had an ICER under 1,000 USD per QALY gained/DALY averted [45]. Another examples provided by Ochalek et al suggests a cost-effectiveness thresholds ranging $765.09-$1,123.73 (adjusted to 2021 US Dollars), based on modeling estimates of the relationship between mortality and variations in healthcare expenditure in the Philippines that takes into account the opportunity cost of adopting new health initiatives [46]. Using Ochalek's conservative estimates, only 2 of the strategies we evaluated would be considered cost-effective: TST to test for TBI followed by treatment with either 6H or 3HP for those who test positive.

The major strengths of our analysis are the data provided directly by the Philippines NTP and the multitude of scenarios it explored. In addition, we used NTT scenario as the comparator for all other strategies as well as comparing every strategy to the next most cost-effective alternative to facilitate decision making by the Philippines NTP [11].

Our analysis does have the following limitations: we chose the maximum possible dose for every regimen for this age group and an upper end estimate for HHCs who would be eligible for screening and treatment to account for the highest possible cost to the Philippines healthcare system. This approach would underestimate the overall cost-effectiveness and increase the implementation cost of TPT expansion respectively. In addition, this analysis used the cost of regimens that are

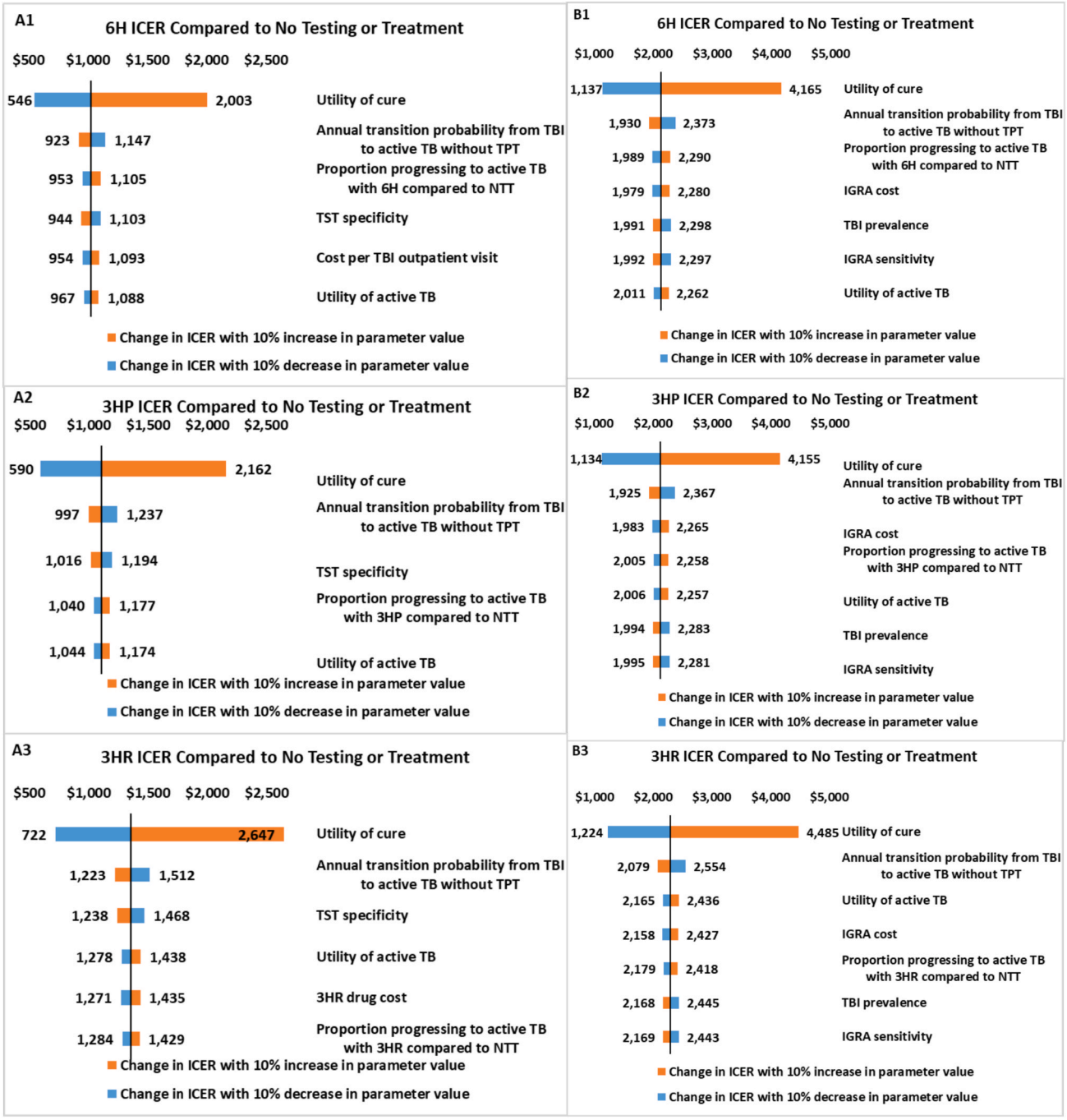

Fig. 2. One-way sensitivity analysis: X-access shows change in incremental cost-effectiveness ratio (ICER) with predefined percentage increase/decrease in parameter value, on the y-axis is the parameter evaluated. Panel A: One-way sensitivity analysis when using TST: Scenarios consider outcomes when eligible household contacts (HHCs) age 5–14 in the Philippines are tested with tuberculin skin testing (TST) and provided treatment for TB infection (TBI) if positive; comparing the use of 6 months of daily isoniazid (6H) in subpanel A1, 3 months of weekly isoniazid and rifapentine (3HP) in subpanel A2 and 3 months of daily isoniazid plus rifampicin (3HR) in subpanel A3. All subpanels show ICERs under high and low values of each model parameter. All regimens are compared to a scenario of no testing or treatment for TBI (NTT). Orange bars represent the outcome when the parameter's value is increased by 10 % while the blue bars represent the outcome when the parameter's value is decreased by 10 %. All model parameters where analyzed, but this figure only includes parameters that produced a significant change in outcome greater than 5 % of the base case scenario (shown as a dark vertical line in each subpanel). **Panel B**: One-way sensitivity analysis when using IGRA: Scenarios consider outcomes when eligible household contacts (HHCs) age 5–14 in the Philippines are tested with Interferon gamma release assay (IGRA) and provided treatment for TB infection (TBI) if positive; comparing the use of 6 months of daily isoniazid (6H) in subpanel B1, 3 months of weekly isoniazid and rifapentine (3HP) in subpanel B2 and 3 months of daily isoniazid plus rifampicin (3HR) in subpanel B3. All subpanels show ICERS under high and low values of each model parameter (varied in deterministic fashion). All regimens are compared to a scenario of no testing or treatment for TBI (NTT). Orange bars represent the outcome when the parameter's value is increased by 10 % while the blue bars represent the outcome when the parameter's value is decreased by 10 %. All model parameters where analyzed, but this figure only includes parameters that produced a change in outcome that is greater than 5 % of the outcome in the base case scenario (shown as a dark vertical line in each subpanel). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

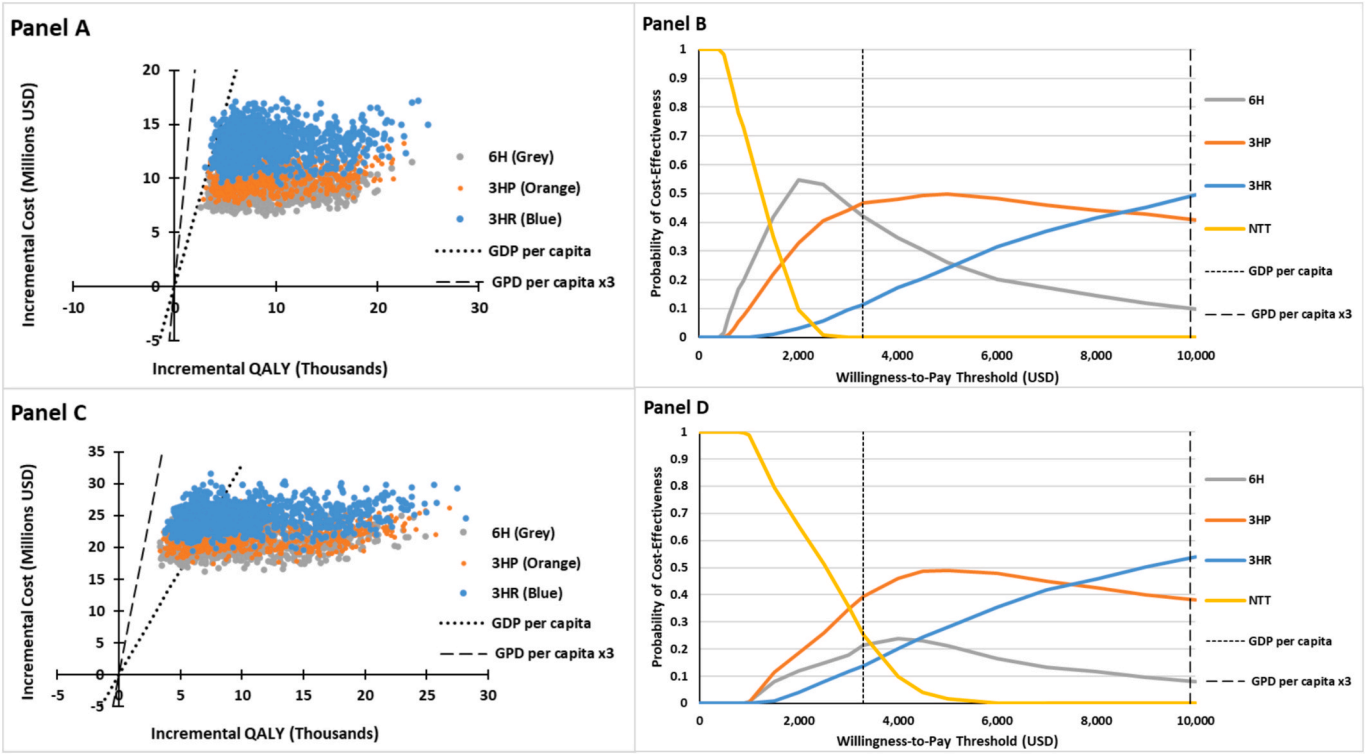

Fig. 3. Multivariate probabilistic sensitivity analysis (Panels A and B) and Probability of cost-effectiveness (Panels C and D). This figure shows 1,000 probabilistic trials evaluating the cost-effectiveness of TB preventive therapy with 6 months of daily isoniazid (6H shown in grey), 3 months of weekly isoniazid and rifapentine (3HP shown in orange) or 3 months of daily isoniazid plus rifampicin (3HR shown in blue) all compared to no testing or treatment for TBI. All eligible household contacts age 5–14 years in the Philippines are tested with tuberculin skin test (TST) in Panel A or interferon gamma release assay (IGRA) in Panel B and provided treatment for TB infection (TBI) if positive. In order to account for uncertainty in parameter value, in each trial all model parameters were chosen in a probabilistic fashion following an appropriate statistical distribution. The x-axis shows incremental gains in thousands quality adjusted life years (QALYs) and the y-axis shows a corresponding incremental cost in millions of 2021 US dollars. Dotted lines represent the Philippines GDP per capita, and the dashed line represent 3 times the GDP per capita of the Philippines highlighting the recommended willingness-to-pay threshold according to WHO guidelines. This figure also shows the probability of cost-effectiveness for every strategy compared to no testing or treatment for TBI (NTT) when using TST (Panel C) and IGRA (Panel D) for screening eligible household contacts age 5–14 years of index people with active TB disease in the Philippines and then treating those who test positive with either 6 months of daily isoniazid (6H shown in grey), 3 months of weekly isoniazid and rifapentine (3HP shown in orange) or 3 months of daily isoniazid plus rifampicin (3HR shown in blue) all compared to NTT. For panels C and D, a net monetary benefit approach is used to factor in the willingness-to-pay threshold per quality adjusted life year (QALY) gained, and then averaged over a thousand probabilistic draws to estimate the probability of being cost-effective for every strategy at each willingness-to-pay threshold. The WHO recommended thresholds for interventions that are cost-effective (less than 3 times the country's GDP per capita) and highly cost-effective (less than the country's GDP per capita) are shown as the dashed and dotted lines respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

available to the Philippines at the NTP's request, this includes a dispersible formulation of 3HR which is likely more desirable when treating young children but also more expensive, but non-dispersible tablet formulations for 6H and 3HP. Other short course options that may be endorsed by the WHO such as 4 months of daily rifampicin (4R) or 1 month of daily isoniazid and rifapentine (1HP), have been left out of this analysis due to the lack of local endorsement within the Philippines national guidelines. Also, this analysis was performed from the perspective of the Philippines public healthcare system and therefore did not incorporate the significant direct and indirect costs incurred by patients and families [47]. We also did not account for secondary transmission which would be significant in a high burden setting and likely to improve the cost-effectiveness of TBI testing and treatment, particularly over a 20 year horizon. The analysis also used a generic range for PSA parameters due to the limited availability of uniform confidence intervals in the published literature; this approach is supported by CEA methodology and allows the analysis to avoid combining confidence intervals derived from non-uniform statistical methods. Finally, the analysis did not account for strategy-specific upfront costs such as personnel training or the differential needs for ongoing case management of pediatric HHCs using a traditional 6-month regimen compared to shorter-course regimens as these costs were beyond the scope of this work.

In conclusion and based on the findings of this analysis, a HHC management strategy that incorporates TST-based screening for TBI followed by 6H treatment for those who test positive is likely to be the most cost-effective strategy, closely followed by a strategy that combines TST testing with 3HP treatment. Significant improvement in the price of IGRA is required to achieve results similar to TST-based strategies.

5. Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Studies on patients or volunteers require ethics committee approval and fully informed written consent which should be documented in the paper.

Authors must obtain written and signed consent to publish the case report from the patient (or, where applicable, the patient's guardian or next of kin) prior to submission. We ask Authors to confirm as part of the submission process that such consent has been obtained, and the

manuscript must include a statement to this effect in a consent section at the end of the manuscript, as follows: "Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request".

Patients have a right to privacy. Patients' and volunteers' names, initials, or hospital numbers should not be used. Images of patients or volunteers should not be used unless the information is essential for scientific purposes and explicit permission has been given as part of the consent. If such consent is made subject to any conditions, the Editor in Chief must be made aware of all such conditions. Even where consent has been given, identifying details should be omitted if they are not essential. If identifying characteristics are altered to protect anonymity, such as in genetic pedigrees, authors should provide assurance that alterations do not distort scientific meaning and editors should so note.

CRediT authorship contribution statement

Ghassan Ilaiwy: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Jessica Keim-Malpass:** Writing – review & editing, Formal analysis, Conceptualization. **Romella Tuppal:** Writing – review & editing, Methodology, Conceptualization. **Alexander F. Ritua:** Writing – review & editing, Methodology, Conceptualization. **Flordeliza R. Bassiag:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Tania A. Thomas:** Writing – review & editing, Funding acquisition, Formal analysis, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jctube.2025.100519.

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