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The epidemiological impact, costs, and cost-effectiveness of implementing household contact investigation with tuberculosis preventive treatment in Nepal: a model-based analysis

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Abstract

Background The burden of tuberculosis (TB) remains extremely high globally. It is increasingly recognized that contact investigation and preventive treatment are essential components of effective action to reduce TB. High-quality, local evidence of feasibility and impact is urgently needed to catalyse scale-up of preventive treatment in high-burden, resource-constrained settings.

Methods We collected data on the costs and yields of contact investigation and implementation of three months of isoniazid and rifapentine (3HP) to treat latent TB infection (LTBI), among adult household members of people diagnosed with TB, from a pilot conducted in two districts of Nepal (Chitwan and Pyuthan) from August 2022 to March 2023. We developed and calibrated mathematical models representing each district and estimated the number of TB episodes and deaths averted by the intervention during 2023–2042. By combining net discounted costs and discounted impact, we estimated the incremental cost-effectiveness of the intervention (compared to no intervention) from a health system perspective as costs (United States Dollars (USD) in 2022) per disability-adjusted life-year (DALY) averted.

Results The intervention screened 1,711 adult household contact persons for TB and LTBI, and treated 500 individuals for LTBI, achieving 98% 3HP acceptance and 95% completion at 150 USD per contact person treated (including drug and test procurement and implementation costs). Including the impact of treating TB disease, the intervention was projected to avert 141 (95% Uncertainty Interval (UI): 86–224) disease episodes and 24 (95% UI: 13–39) deaths during 2023–2042, or 8.2 episodes and 1.4 deaths averted per 100 contact persons screened. The incremental cost-

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effectiveness of the intervention was 119 USD (95% UI: 51–255) and 163 USD (95% UI: 76–328) per DALY averted in Chitwan and Pyuthan, respectively.

Conclusions Screening and treating household members of people with TB for both TB and LTBI can be successfully implemented in both rural and urban settings, is highly cost-effective and should be prioritized to reduce the TB burden in Nepal and similar high-burden countries.

Keywords Tuberculosis preventive therapy, Cost-effectiveness analysis, Epidemiological model

Background

The World Health Organization (WHO) reported that tuberculosis (TB) caused an estimated 1.25 million deaths worldwide in 2023 and, post-COVID, is once again the leading infectious killer globally [1]. Reducing the incidence of TB has been a major challenge in high-burden settings, despite advances in TB diagnosis and treatment coupled with more intensive active case-finding efforts [1]. It is evident that the current approach to fighting the TB pandemic is inadequate to achieve substantial progress.

One of the most effective strategies for case detection in high-burden settings is contact investigation among household members of people with TB [2]. However, contact tracing in high-burden, low-resource settings is usually targeted to identify active TB cases and does not typically include testing for latent TB infection (LTBI). TB preventive treatment (TPT) has been incorporated into some more recent household contact investigation programmes but the long duration of TPT treatment regimens and risks of adverse effects have limited the feasibility and acceptability. High rates of loss to follow up before treatment completion using the older 6–9 months treatment regimens have also fueled negative perceptions of TB preventive therapy programmes. Therefore, TPT has not historically been considered a priority in high-transmission settings [3]. However, new short TPT regimens with reduced pill counts and lower toxicity have changed the paradigm, increasing patient acceptability and reducing the complexity and resources required for implementation. Multiple studies have shown that we can achieve high acceptance and completion rates with short-course regimens such as 3 months of isoniazid and rifapentine (3HP), with equivalent efficacy and lower risk of adverse effects compared to the older 6–9 months isoniazid-based regimens [4, 5]. However, evidence demonstrating the impact on the epidemic and cost-effectiveness of contact investigation and TPT implementation is limited. The majority of such studies have focused on evaluating the impact of TPT for people living with HIV/AIDS (PLWHA) and household contacts younger than 5 years [6–8]. However, all household contacts of people with TB, including adults, are at a substantially higher risk of being infected with *Mycobacterium tuberculosis* and developing TB disease [9]. These risks are greatly exacerbated for households experiencing extreme poverty, with co-prevalent risk factors such as malnutrition [10]. Although the new shorter regimens are available, the scale-up and integration of preventive treatment with contact investigation among household contacts of people diagnosed with TB has been woefully low, achieving only 21% TPT coverage compared to the new global targets of 90% for 2027, set at the 2023 UN high-level meeting [1].

This challenge is exemplified in Nepal, a high TB-burden country, with an estimated prevalence of 416 per 100,000, in the national prevalence survey of 2019 [11]. This estimate was 1.6 times higher than the previous WHO estimate. The Ministry of Health has since made significant political commitments towards ending TB for the country, with a bold vision to achieve "TB Free Nepal" by 2050 [12]. Scaling up contact investigation including TPT is a major component of this vision. However, in the current practice, only PLWHA and children under five years are eligible for the treatment under the national TB programme [13]. Delays in translating policy to practice in high TB burden settings are, in part, a consequence of the lack of high-quality evidence on the feasibility, cost-effectiveness, and epidemiological impact of integrating TPT with contact investigation in high-risk populations [14, 15], such as household contacts of individuals diagnosed with TB.

This study, therefore, aimed to estimate the long-term epidemiological impact, costs, and cost-effectiveness of implementing contact investigation incorporating LTBI diagnosis and treatment among adult household contacts of individuals diagnosed with TB in Nepal. The study used real-world data collected from a pilot implementation of 3HP, following WHO guidelines [16], in two districts of Nepal, Pyuthan and Chitwan.

Methods

Overview

Our study aimed to estimate the epidemiological impact, costs, and cost-effectiveness of pilot implementation of household contact investigation for TB, including 3HP therapy for 500 household contacts with LTBI, in two districts of Nepal, Pyuthan and Chitwan, between August 2022 to March 2023. We estimated the epidemiological impact of the intervention in terms of TB cases and

deaths averted over 20 years (2023–2042) after completion of the intervention, using transmission models developed and calibrated to represent the two districts. The costs of the intervention were calculated using a health systems perspective based on the data collected during the pilot 3HP implementation in each district. Finally, to evaluate the cost-effectiveness of the intervention, we estimated the incremental cost-effectiveness ratios in each district, comparing the discounted costs of the intervention to the estimated disability-adjusted life years (DALYs) averted by the intervention. Our approach conforms to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 for economic evaluation studies [17] (Supplementary material 1: CHEERS Checklist). Statistical analyses were performed using R, version 4.5.2 (R Foundation for Statistical Computing, Vienna, Austria). Model code is available at https://doi.org/10.5281/zenodo.21790325 [18].

Pilot implementation of 3HP

In Nepal, Birat Nepal Medical Trust (BNMT) conducted a pilot implementation of 3HP therapy for adult (above 18 years) household contacts of people with TB in two districts, Pyuthan and Chitwan, from August 2022 to March 2023. Pyuthan district lies in the mid-hills region of Nepal and is predominantly rural, with a human development index of 0.281, a total population of 232,019, and a tuberculosis case notification rate of 173 per 100,000 (all forms) in 2021 [19, 20]. Chitwan district, comprising both urban plains and rural hills, is more economically developed with a human development index of 0.474, with a total population of 719,859 and a reported case notification rate of 166 per 100,000 (all forms) in 2021 [19, 20]. These contrasting settings provided an opportunity to evaluate the potential impact of the intervention implemented in two different contexts, representing different demographic regions of Nepal. The WHO algorithm [16] was applied for contact investigation, to identify household contacts requiring referral for active TB testing, and individuals with LTBI. BNMT employed community health workers (CHWs) in each district who liaised with government health facilities to identify people diagnosed with TB within the last 12 months in the district for contact tracing. Consenting household members were first screened for TB symptoms verbally using a standardised questionnaire [21]. Symptomatic individuals were referred for GeneXpert testing (Cepheid, United States of America) and supported by CHWs to complete the diagnostic pathway. Household members with no TB symptoms were tested for LTBI using a mantoux tuberculin skin test (TST) using a purified protein derivative (PPD) reagent. Individuals who were TST positive then underwent a chest X-ray to rule out active TB disease. Those with an abnormal chest X-ray suggestive of TB were referred for GeneXpert testing and further clinical evaluation. Eligible individuals diagnosed with LTBI were provided with counseling by clinical staff using a customized, culturally relevant flipchart and enrolled into preventive treatment. Contacts with history of liver disease, HIV infection, high alcohol consumption, and those pregnant or planning to become pregnant were excluded from 3HP preventive treatment and received counselling on TB symptoms, CHW contact details for follow up and local diagnostic services. The pilot implementation activities were managed by dedicated BNMT District Program Coordinators (DPCs) in each district. The screening algorithm that was used is shown in Supplementary Material 1: Figure S1.

Epidemiological Model

We developed district-level deterministic compartmental models representing the districts of Chitwan and Pyuthan. The models incorporated the natural history and local epidemiology of TB to assess the long-term epidemiological impacts of the modeled intervention in each district. Adapting prior models of TB [22], we captured the natural history of TB by modeling the transition of individuals between six states: uninfected; two stages of LTBI, early LTBI and late LTBI; two states of active TB disease, asymptomatic and symptomatic; and a recovered state (Fig. 1A). In this model, uninfected individuals develop early LTBI upon acquiring TB infection, which can either stabilize to become late LTBI or progress early to active TB disease. Individuals with late LTBI can also develop active TB through late progression. Individuals with LTBI can also self-clear the infection and progress to a recovered state. Active TB was assumed to start in an asymptomatic form, which can either progress to a symptomatic form or resolve spontaneously to the recovered state without treatment. Symptomatic TB can either be diagnosed and treated (and transition to the recovered state) or regress to the asymptomatic form. Individuals with late LTBI or who have recovered from previous TB disease can be reinfected (i.e., return to the early LTBI state) but are assumed to have partial immunity. Births and both TB-related and TB-unrelated deaths were included in the model, but emigration and immigration to and from districts were not. The set of ordinary differential equations that describe the model is included in Supplementary Material 1: Model Equations.

Data and model calibration

To ensure that the models reflected the local demography and TB epidemiology, we calibrated the models to key epidemiological features of TB in Chitwan and Pyuthan separately. Calibration targets for each district included estimated 2022 population sizes, birth rates, TB prevalence, annual incidence rates, annual mortality rates, and

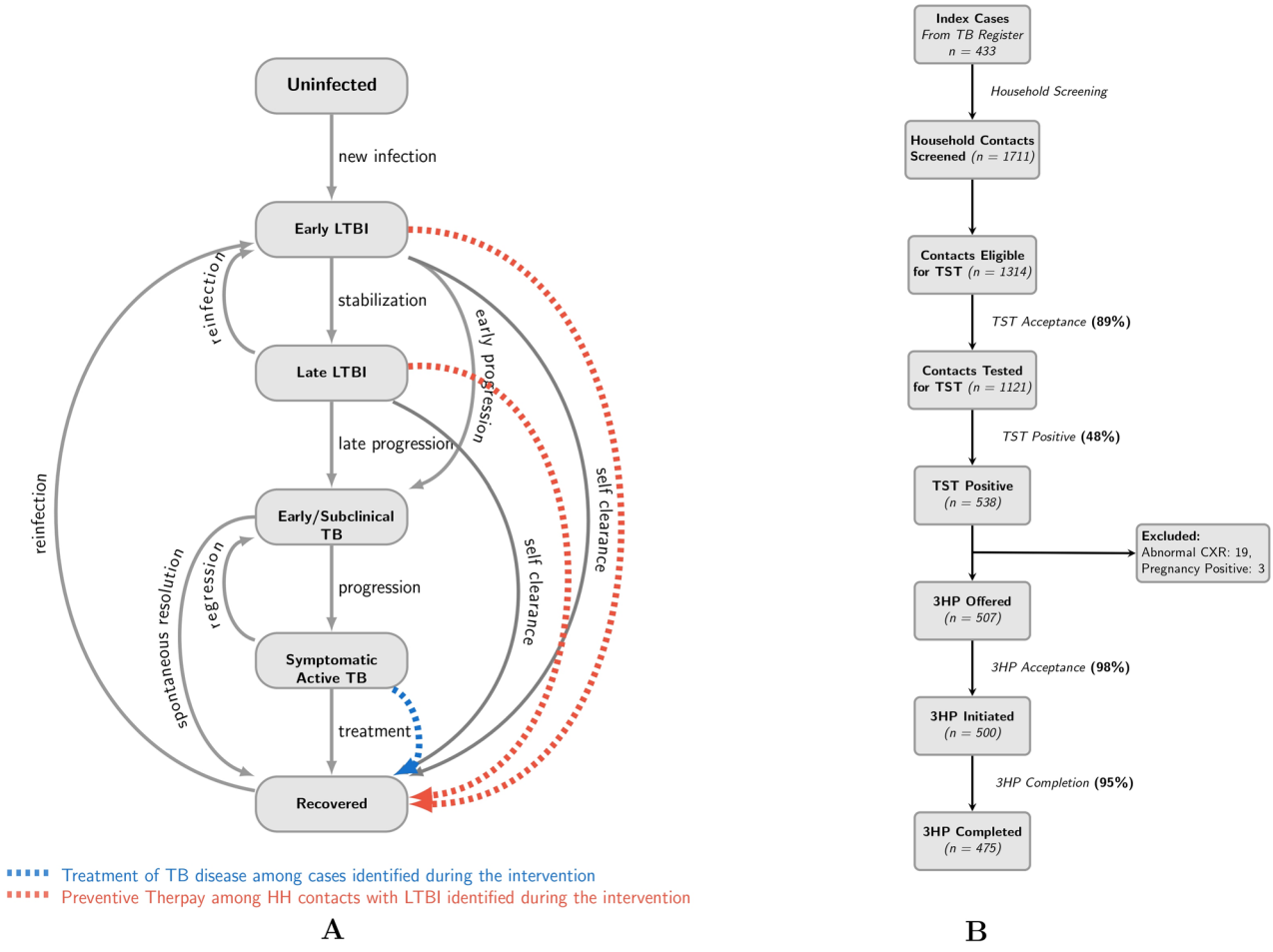

Fig. 1 Transmission Model including the intervention pathways and testing algorithm, including the number of individuals from pilot intervention. **A** shows the compartmental modeling framework used to model the natural history of tuberculosis. The compartmental models included six stages – uninfected, early latent infection, late latent infection, early/subclinical TB, symptomatic TB, and recovered. Individuals enter into the model through birth and exit due to death due to TB or death due to other causes. When uninfected individuals get infected, they develop an early latent infection, which may either stabilize into a late latent state or progress rapidly to active TB (subclinical). Those moving to a late latent state can also progress to active TB but at a slower rate and can also move to an early latent state after reinfection. Individuals in both of these latent states can self-clear without developing active TB. We modeled active TB to be asymptomatic but progress to a symptomatic state or resolve on its own, not requiring any treatment. Symptomatic individuals are treated but can regress to an asymptomatic state. Recovered individuals either stay in that state or get reinfected. Red arrows show the movement of individuals from early and late latent to recovery after the preventive treatment (intervention). The blue arrow shows the recovery of symptomatic individuals following active case finding and treatment. **B** shows the cascade, including the number of household contacts of index persons, individuals eligible, tested, positive, offered, initiated, and completed 3HP using WHO's algorithm

annual rates of decline in TB incidence. The complete list of model parameters is available in Supplementary Material 1: Table S1 and the details of the calibration approach employed and the distribution of parameter values consistent with the calibration data are available in Supplementary Material 1: Figure S2 and S3. District-specific calibration target ranges and their sources and derivations are shown in Supplementary Material 1: Table S2. Key outputs of the calibrated models, which comprise simulations of data-consistent model parameters, are shown in Fig. 2.

Description of intervention

We conceptualized the intervention to reflect the actual implementation of a single round of contact investigation and integrated TPT during the pilot study as a time limited intervention screening adult household contacts of TB cases and offering 3HP to eligible adults diagnosed with LTBI. Individuals completing 3HP who were expected to resolve LTBI successfully were modeled to transition from the LTBI states to the recovered state, and the number of such individuals was estimated based on the yield of the study (see Fig. 1B) accounting for the rates of documented loss at each stage of the cascade of care for LTBI diagnosis and treatment. Furthermore, since this study implemented the WHO algorithm to identify active

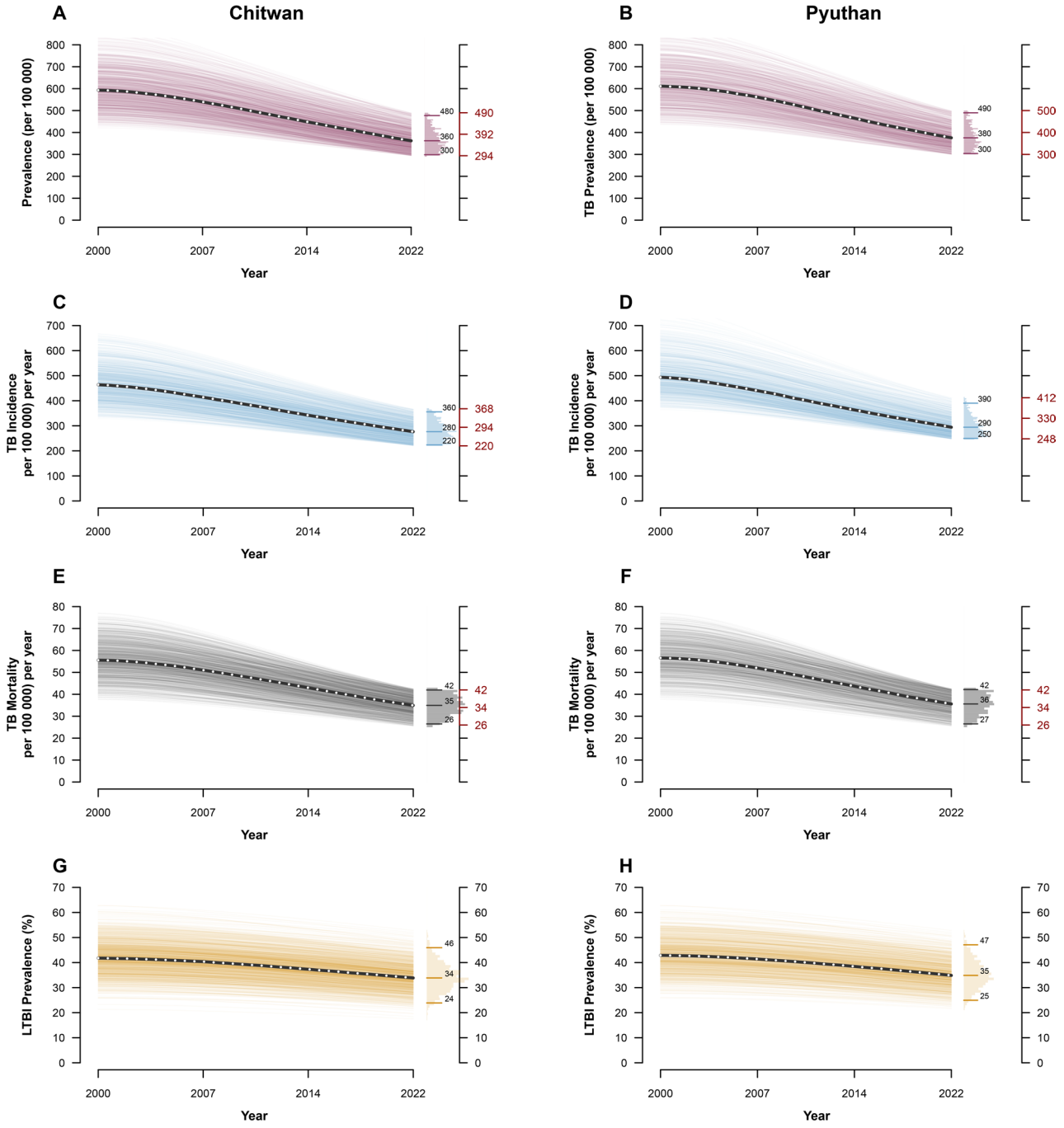

Fig. 2 Calibration results for Chitwan and Pyuthan, including calibration ranges. Panels **A**, **C**, **E** and **G** show TB prevalence, TB incidence, TB mortality and LTBI prevalence respectively, for Chitwan district. Panels **B**, **D**, **F** and **H** show TB prevalence, TB incidence, TB mortality and LTBI prevalence respectively, for Pyuthan district. The models were calibrated separately to capture the prevalence, incidence, mortality, and annual tuberculosis incidence decline in each district. The ranges for calibration are shown in red on the right y-axis for each indicator. Each line in the model represents a simulation, dotted lines represent the median values, and the horizontal histograms represent the overall distribution of the indicators in 2022. The calibration targets and demographic assumptions are tabulated in Supplementary Material 1: Table S2; TB: Tuberculosis; LTBI: Latent Tuberculosis Infection

TB and LTBI among adult household contacts, we modeled the intervention to include the impact of diagnosing active TB cases, assuming that individuals diagnosed with active TB during LTBI screening would initiate and complete TB treatment. Individuals diagnosed with active TB were modeled to transition from the active TB state to the recovered state (accounting for national treatment success rates), and the expected number of individuals with active TB per household contact was estimated

based on yields from previous BNMT household contact case finding interventions [23].

Cost and cost-effectiveness analysis

To estimate the cost of implementing the 3HP intervention in Pyuthan and Chitwan, we used the ingredient-based costing approach using BNMT financial records. We identified and valued the resources required for the intervention and organized these into categories, excluding costs not directly relevant to 3HP project implementation. The costs were categorized as drug procurement, field implementation, human resources, and equipment costs. During implementation, monetary incentives were provided to treatment centers or healthcare workers for enrolling index persons diagnosed with TB, providing counseling for TST, and communicating X-ray test results. Travel reimbursements were also provided to the participants undergoing TST and chest X-ray investigations and those enrolled to 3HP treatment. We enumerated the unit costs for each component of the intervention and the total costs, by multiplying the unit costs by the appropriate multipliers (Table 1). In order to include the cost of TB diagnosis within the intervention cost, we estimated the unit cost based on a review of financial expenditure records from a previous BNMT community based active case finding project implemented in similar settings [24]. The cost of treating people diagnosed with TB was included using the unit cost of treatment reported in the literature and the estimated number of people testing positive (see Supplementary Material 1: Table S3). All costs are expressed in USD, using the Nepalese Rupees to USD conversion rates in 2022 and inflated using the World Bank consumer price index inflation rates [25].

We conducted a cost-effectiveness analysis of the 3HP intervention in Chitwan and Pyuthan districts from a health system perspective, comparing the 3HP intervention to no intervention for the time horizon of 20 years using a 3% discount rate. Benefits were measured as DALYs averted, based on the TB cases and deaths averted estimated using the epidemiological model, and disability weights using Global Burden of Diseases (GBD) assumptions (see Supplementary Material 1: Table S3). We subtracted estimated future cost savings (of treating potential TB cases) from the total cost of implementing the intervention to calculate the net cost of the intervention. We did not consider the benefits or potential benefits of averting post-TB-sequelae. The estimates are calculated and reported separately for the two districts, to account for the different programmatic results and costs. Our primary outcome was the incremental cost-effectiveness ratio (ICER), defined as the mean incremental discounted costs (in 2022 USD) of the 3HP implementation program, divided by the estimated mean incremental discounted DALYs averted between 2023 and 2042.

Sensitivity and Scenario Analyses

We conducted a multivariate sensitivity analysis to explore the sensitivity of the primary outcome to uncertainty in parameter values in each district. We compared the difference in projected incremental cost-effectiveness between the calibrated simulations in which the value of the parameter of interest was in the top decile vs. the bottom decile. To evaluate the epidemiological impact of a potential scale-up of the intervention, we modeled a hypothetical scenario where the intervention was scaled-up to screen all household contacts for five years. Finally, we performed a probabilistic sensitivity analysis and generated cost-effectiveness acceptability curves across various willingness-to-pay (WTP) thresholds for both Chitwan and Pyuthan.

Results

Estimated costs of household contact 3HP intervention

As shown in Fig. 1B, a total of 1,711 household contacts were screened by the pilot intervention for active TB and LTBI. 538 individuals tested positive for LTBI after ruling out individuals with active TB, of which 500 initiated treatment and 475 completed the treatment. The total test and drug procurement costs, which included the price of drug components of 3HP (Rifapentine and Isoniazid, procured via the Global Drug Facility (operated by the Stop TB Partnership, facilitates global access to quality-assured, affordable TB medicines, diagnostics, and medical devices [26]), and Pyridoxine procured locally), costs for acquiring approval, customs, and logistics, cost of TST (Mantoux test) and pregnancy tests, were respectively $7,522 and $4,116 in Chitwan and Pyuthan (Table 1).

The total implementation costs, which included costs associated with field implementation of household contact screening, TB diagnostic testing, TST testing, enrollment into 3HP, estimated healthcare worker salaries, and patient reimbursement costs, were $52,897 in Chitwan and $42,942 in Pyuthan (Table 1). The aggregated total costs of the intervention were $60,419 and $47,058 in Chitwan and Pyuthan, respectively (Table 2).

Epidemiological impact of the intervention

The calibrated models matched the target data characterizing TB epidemiology in both districts. In the calibrated model representing Chitwan, the median prevalence of TB per 100,000 population in 2022 was 360 (95% uncertainty interval across model simulations: 300–480), compared to a data estimate of 392; the median annual incidence (per 100,000) in 2022 was 280 (95% UI: 220–360) compared to 294; and the median annual mortality

Table 1 Costs of implementing 3 months of weekly rifapentine and isoniazid to adult household contacts of people with tuberculosis

	Unit cost (2022 USD)*	Multiplier (n)	Total cost (2022 USD)*
Drug and Test procurement[d]costs -Chitwan			
Rifapentine (150mg)	20.48[a]	307 (participant)	6,286.8
Isoniazid (300mg)	0.67[b]	307 (participant)	193.0
Pyridoxine (40mg)	0.50[c]	307 (participant)	144.6
Drugs procurement cost			847.5
Cost of purchase of Mantoux and Pregnancy test			49.7
Total (Chitwan)			**7,521.7**
Drug and Test procurement[d]costs–Pyuthan			
Rifapentine (150mg)	20.48[a]	168 (participant)	3,440.4
Isoniazid (300mg)	0.67[b]	168 (participant)	105.6
Pyridoxine (40mg)	0.50[c]	168 (participant)	79.2
Drugs procurement cost			463.8
Cost of purchase of Mantoux and Pregnancy test			27.2
Total (Pyuthan)			**4,116.1**
Total (both districts)			**11,637.9**
Implementation costs			
Field implementation of HH contact screening and testing – Chitwan district			
Incentive to treatment center for obtaining contact list of index cases	0.79	261(index case)	205.0
Incentive to healthcare workers for successfully counseling contacts to agree for the Mantoux test	1.57	722 (TST done)	1,134.0
Cost of Mantoux test	0.55	722 (TST done)	396.9
Cost of X-ray test	3.34	350 (X-ray done)	1,168.1
Communication cost for X-ray test result	0.39	350 (X-ray done)	137.4
Cost of 3HP medication counseling to providers	1.57	323 (participant)	507.3
Participant reimbursement costs			
Travel cost for Mantoux test	4.71	722 (TST done)	3,401.9
Travel cost for X-ray test	4.71	350 (X-ray done)	1,649.1
Travel cost for taking 3HP medication	4.32	323 (participant × 12 times)	16,740.7
Healthcare worker salaries			
CHW	101.5[e]	40 (4 CHW × 10 months)	4,063.0
DPC	292.0[f]	10 (1 DPC × 10 months)	2,920.5
Cost of TB diagnosis and treatment (estimated)			
Cost of TB diagnosis	14.07	650[g] (TB screened)	9,143.1
Cost of TB treatment	300.24	38.07[h] (active TB treated)	11,430.14
Total Implementation Costs (Chitwan)			**52,897.0**
Field implementation of HH contact screening and testing – Pyuthan district			
Incentive to treatment center for obtaining contact list of index cases	0.79	172 (index case)	135.0
Incentive to healthcare workers for successfully counseling contacts to agree for the Mantoux test	1.57	399 (TST done)	626.7
Cost of Mantoux test	0.55	399 (TST done)	219.3
Cost of X-ray test	3.34	182 (X-ray done)	607.4
Communication cost for X-ray test result	0.39	182 (X-ray done)	71.5
Cost of 3HP medication counseling to providers	1.57	177 (participant)	278.0
Participant reimbursement costs			
Travel cost for Mantoux test	4.71	399 (TST done)	1,880.0
Travel cost for X-ray test	4.71	182 (X-ray done)	857.5
Travel cost for taking 3HP medication	8.64	177 (participant × 12 times)	18,347.4
Healthcare worker salaries			
CHW	92.0[e]	40 (4 CHW × 10 months)	3,679.8
DPC	237.2[f]	10 (1 DPC × 10 months)	2,372.9

Table 1 (continued)

	Unit cost (2022 USD)*	Multiplier (n)	Total cost (2022 USD)*
Cost of TB diagnosis and treatment (estimated)			
Cost of TB diagnosis	14.07	370[g] (TB screened)	5,204.5
Cost of TB treatment	300.24	28.85[h] (active TB treated)	8,661.83
Total Implementation Costs (Pyuthan)			**42,941.9**
Total Cost for Chitwan			**60,418.7**
Total Cost for Pyuthan			**47,058.1**
Total Cost for both districts			**107,476.8**

*1 USD Nepali Rupees 127.34 (Sept 1 2022); [a]1 participant = 72 tablets; [b]1 participant = 36 tablets; [c]1 participant = 12 tablets; [d] Includes approval cost, bank commission, custom clearance and courier charges; Community health worker (CHW); District Program Coordinator (DPC); [e] Weighted average monthly salary based on the time spent on field implementation activities; [f] Weighted average monthly salary based on the number of projects managed by DPCs in each district; [g] The number of adult household contacts who had their sputum tested during the pilot implementation in each district; [h] estimated from the model with the assumption of proportion of household contact with active TB to be in the range of 0.02–0.06 (also see Supplementary Material 1: Table S7)

Table 2 Cost-effectiveness of implementing 3 months of weekly rifapentine and isoniazid to adult household contacts of people with tuberculosis

	Costs in 2022 figures (95% UI)			Impact (95% UI)			Cost-effectiveness (95% UI)
	Total cost of intervention	Estimated future cost savings (associated with TB treatment)	Net cost	TB cases prevented	TB deaths averted	Discounted estimated DALYs averted	Cost per DALYs averted
Chitwan	$60,419 (51,500– 104,096)	$19,633 (11,888–31,828)	$40,786 (27,224–80,471)	85 (51–140)	14 (8–25)	371 (216–616)	$119 (51–255)
Pyuthan	$47,058 (40,289–86,900)	$13,050 (7,828–19,778)	$34,008 (25,799–70,434)	56 (33–89)	9 (5–16)	237 (135–383)	$163 (76–328)
Combined	$107,477 (91,790–190,996)	$32,683 (19,716–51,607)	$74,794 (53,024–150,905)	141 (86–224)	24 (13–39)	608 (351–999)	$141 (64–292)

95% UI: Uncertainty Interval, TB: Tuberculosis, DALYs: Disability-adjusted life years

rate per 100,00 was 35 (95% UI: 26–42) compared to 34. Similarly, in Pyuthan, the prevalence was 380 (95% UI: 300–490), incidence was 290 (95% UI: 250–390), and mortality was 36 (95% UI: 27–42) per 100,000 in 2022 as compared to a data estimate of 400, 330 and 34 per 100,000 respectively. TB incidence was declining in both districts at 2.30% (95% UI: 1.75% – 2.89%) per year pre-intervention between 2000 and 2022. The model estimated LTBI prevalence in 2022 was 34% (95% UI: 24%-46%) in Chitwan and 35% (95% UI: 25% – 47%) in Pyuthan. The simulated outcomes from the calibrated model are shown in Fig. 2.

We estimated that the pilot intervention that screened for and treated both TB and LTBI among adult household contacts of TB cases was projected to avert 85 (95% UI: 51–140) cases and 14 (95% UI: 8–25) deaths in Chitwan, and 56 (95% UI: 33–89) cases and 9 (95% UI: 5–16) deaths in Pyuthan, resulting in a total of 141 (95% UI: 86–224) cases and 24 (95% UI: 13–39) deaths averted in the two districts over a 20-year analytic time horizon (Fig. 3 and Supplementary Material 1: Figure S4). Considering the number of household contacts screened and initiated on 3HP, this translates to 8.5 cases and 1.4 deaths per 100 individuals screened in Chitwan and 7.9 cases and 1.3 deaths in Pyuthan. Overall, 76% of the cases averted and 79.9% of prevented deaths were averted within 10 years of the intervention in the two districts, and 45% of the cases and 30% of the deaths prevented were attributable to treatment of LTBI.

Cost-effectiveness of 3HP intervention

Based on the projected cases and deaths averted over 20 years, we estimated that a total of 608 (95% UI: 351–999) DALYs would be averted, 237 (95% UI: 135–383) of which were averted in Pyuthan and 371 (95% UI: 216–616) in Chitwan (Table 2). The incremental cost-effectiveness of providing 3HP to adult household contacts (compared to the status quo) was $141 (95% UI: 64–292) per DALY averted overall, and $ 119 (95% UI: 51–255) and $163 (95% UI: 76–328) per DALY averted in Chitwan and Pyuthan, respectively (Supplementary Material 1: Figure S5). When comparing it against the country-specific

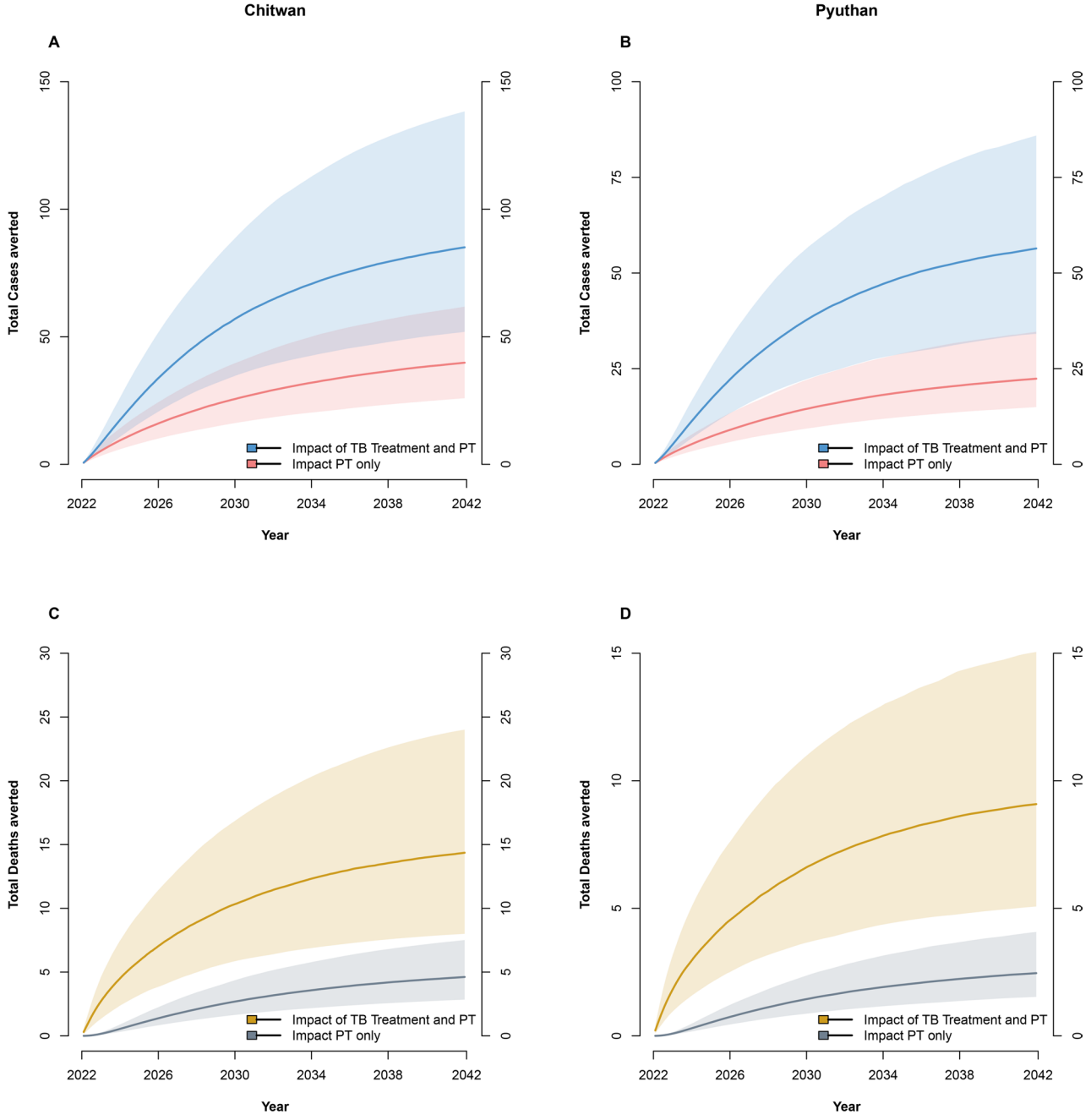

Fig. 3 Cases and deaths averted in Chitwan and Pyuthan over 20 years. Panels **A** and **B** show the total number of cases averted in Chitwan and Pyuthan, respectively, with either preventive treatment only (in red) or with both TB and preventive treatment (in blue). Panels **C** and **D** show the total number of deaths averted for Chitwan and Pyuthan, respectively, with preventive treatment only (in grey) or TB and preventive treatment (in yellow)

cost-effectiveness threshold of $38 - $612 [27] (inflated to USD in 2022), at the incremental cost-effectiveness of $119 and $163, the intervention was cost effective.

Sensitivity Analysis

Multivariate sensitivity analysis showed that the most influential parameters of the cost-effectiveness of the intervention were the proportion of household contacts with active TB and the overall unit cost of the intervention per case. The median cost-effectiveness ratios did not vary by more than 64% across the sensitivity analysis, in which we varied individual model parameters over their calibrated distributions using values at the 10th and 90th percentiles (Fig. 4A). Despite this variation, the results remained well within Nepal's cost effectiveness threshold of $38-$612 per DALY averted across all parameter combinations (Fig. 4A).

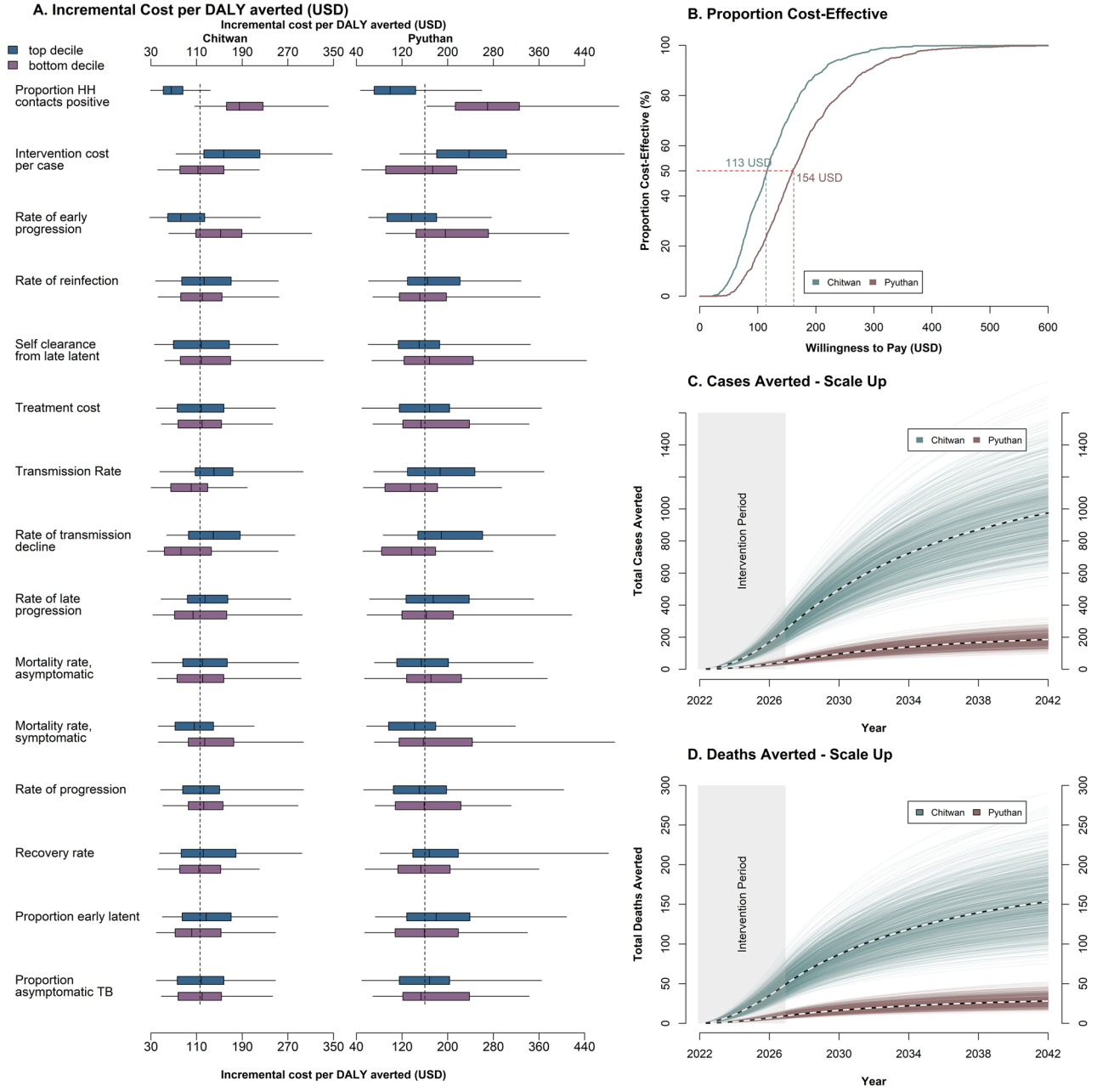

Fig. 4 **A** compares the incremental cost per DALY averted in simulations where the indicated model parameter was in the top decile (shown in blue) vs. the bottom decile (in maroon). The edges of each box denote the quartiles, the middle line in the boxes denote the median, and the edges of the whiskers denote the 2.5th and 97.5th percentiles. The dashed vertical lines show the average incremental cost observed for each district in the simulation for the combination of these parameters. Panel **B** shows the proportion of interventions that would be cost-effective across willingness to pay threshold. The dashed colored lines show the willingness-to-pay at 50% of the interventions to be cost-effective. Panels **C** and **D** show the cases and deaths averted under the hypothetical intervention that would screen all the household contacts of people with TB for 5 years in both districts. The dashed lines in panels **C** and **D** indicate the median values DALY: Disability-adjusted life years

The probabilistic sensitivity analysis showed that 39% of simulations in Chitwan and 17% in Pyuthan were cost-effective at the willingness to pay threshold of $100 per DALY averted, and 90% of the simulations were cost-effective at the threshold of $212 and $289 for Chitwan and Pyuthan respectively (Fig. 4B).

In hypothetical intervention scale-up scenarios, in which we modeled screening and treatment of TB and LTBI among all the household contacts of expected index patients for 5 years, we projected that the intervention would result in 974 (95% UI: 665–1437) cases averted, and 153 (95% UI: 99–233) deaths averted in Chitwan, and 186 (95% UI: 126–269) cases and 28 (95% UI: 18–44)

deaths averted in Pyuthan as shown in Fig. 4C and D. For every 100 household contacts screened for LTBI, this translated to 5.77 (95% UI: 3.95–8.57) cases and 0.91 (95% UI: 0.59–1.38) deaths averted in Chitwan and 5.23 (95% UI: 3.54–7.57) cases and 0.79 (95% UI: 0.51–1.24) deaths averted in Pyuthan. This hypothetical intervention is expected to contribute to an incidence reduction of 5.28% (95% UI: 3.6–7.49) in Chitwan and 2.93% (95% UI: 2.01–4.28) in Pyuthan.

Discussion

In this model-based analysis, we evaluated the epidemiological impact and cost-effectiveness of contact investigation and screening of adult household contacts for TB and LTBI using the WHO-recommended diagnostic algorithm and providing 3HP-based TB preventive treatment in Nepal. Costs were estimated from a health systems perspective using data from a pilot program conducted in Chitwan and Pyuthan districts (August 2022-March 2023). The epidemiological impact was projected using district-level TB transmission models, calibrated to data from the pilot implementation and designed to capture population-level outcomes over a 20-year horizon. The cost-effectiveness ratios—US$119 (95% UI: 51–255) in Chitwan and 163 (95% UI: 76–328) in Pyuthan per DALYs averted averted—are well within the country-specific cost-effectiveness threshold of $38 - $612 [27].

These findings were robust across a wide range of uncertainties in TB natural history, epidemiology, and implementation costs. Even under conservative assumptions, cost-effectiveness remained below US$163 per DALY averted, equivalent to one-ninth of Nepal's per capita gross domestic product (GDP) of $1,386 in the year 2022 [28]. Moreover, the intervention remained cost-effective under more constrained scenarios, such as evaluating the impact over shorter time horizons (e.g., ~ 76% of impact was projected to occur in the first 10 years) or excluding the impact of TB disease treatment (with almost half of the effect attributed solely to LTBI treatment). These results align with—and in some cases exceed—the cost-effectiveness reported in previous studies of short-course TB preventive treatment in other high-burden, low- and middle-income countries [6, 8]. While effective and cost-effective, household contact screening alone is unlikely to shift the broader TB epidemiological trajectory. Even under a scaled-up scenario—screening and treating all eligible household contacts for five years—the maximum projected reduction in TB incidence was only ~ 5%. This is partly due to the limited scope of household-based screening: nearly 54% of incident TB cases in Nepal are not notified, and household transmission accounts for only 10–20% of overall transmission [29, 30]. As such, while prioritizing household contacts represents a key component, case-finding and preventive treatment must be scaled up more broadly if ambitious targets of the END-TB strategy and "TB-Free Nepal" are to be achieved [31]. Additionally, the cases averted per 100 contacts screened declined in the scale-up scenario which likely reflects the gradual decrease in the individuals with LTBI and active TB over the 5-year intervention period as 3% annual decline in TB incidence was assumed.

In this study, implementation costs (excluding drug and test procurement costs; detailed components shown in Table 1) constituted over 90% of the total intervention cost, with patient travel for screening and healthcare worker observed treatment comprising a substantial portion. Notably, per person costs were about 1.5 times higher in Pyuthan—a more remote and mountainous district—than in Chitwan. This highlights the importance of designing locally adapted, cost-efficient delivery strategies, such as decentralizing diagnostic services or optimizing drug distribution to reduce patient burden in settings like Nepal where a substantial portion of the country face geographic barriers to access healthcare. Directly Observed Treatment by healthcare workers was incorporated during the pilot implementation due to lack of experience in Nepal with the 3HP treatment regimen, to allay concerns about unmonitored side effects and to gather robust adverse event data. Studies in other settings have shown 3HP can be safely administered using adherence monitoring technologies, unsupervised self-administration or family-based Directly-observed treatment, short-course (DOTS). Our costing data also suggest such a strategy would further enhance the cost-effectiveness of the intervention and should be evaluated in Nepal. BNMT is now evaluating 3HP treatment with monthly evaluation by a clinician within the CRITIC project [32].

Cost-effectiveness will also be further strengthened by the recently negotiated price reductions in 3HP medication and the availability of fixed dose combination tablets. The price for a single adult treatment course of 3HP with fixed dose combination (FDC) drugs is now 10.96 USD via the Global Drug Facility.

An important strength of this study was that we incorporated detailed, Nepal-specific primary data on implementation and costing, which captured district-level differences in intervention cascade and delivery costs—factors often omitted or generalized in modeling studies. As we show here, implementation costs, which are likely to be key drivers of the overall cost-effectiveness of these interventions, can vary considerably even across settings within a country. Thus, these findings based on primary data provide more reliable evidence for the intervention. Additionally, we developed setting-specific transmission models that integrated local epidemiological data and allowed us to estimate both direct and indirect (transmission-mediated) impacts over time. This modeling

framework also enabled a more systematic sensitivity analysis to quantify parameter-driven uncertainties and identify key drivers of impact.

Our approach also has several limitations. The transmission models make several simplifying assumptions regarding the natural history progression of TB and in characterizing the underlying risks and mixing and mobility patterns. The model does not include age structure and hence does not account for potential age-specific differences in TB and LTBI prevalence, contact patterns (which tend to be higher among young adults), or LTBI progression rates, and the costs of implementation (which could be lower among adults) [33, 34]. However, given that preventive treatment is generally thought to be more cost-effective among children and adolescents under 15 years old, the intervention is likely even more cost-effective when scaled to the entire population [8]. We assumed individuals with asymptomatic and symptomatic active TB are equally infectious because there is no clear evidence whether there are significant differences in their infectiousness. We modeled closed populations representing the two districts but immigration and emigration may dilute the impact of the intervention that can be observed within the districts, unless the intervention is also applied across neighbouring regions, even though the impact of the intervention on risk of TB among emigrants will extend beyond the district boundaries. We assumed that individuals with LTBI reached by the intervention were predominantly recent infections (50–80%), who are more likely to progress to active disease (compared to remote infections). This is consistent with findings from prior studies [9], but underestimating the time elapsed since infection among household contacts can lead to overestimating the impact of the intervention [35]. We projected the future declines in tuberculosis incidence to continue at 3% per year, without intervention, as reported in the Nepal TB Prevalence Survey [11]; however, this estimate is subject to uncertainties, including fluctuations in programme activities and resource allocation (notably the recent substantial reductions in global fund financing), and broader health system shocks such as COVID-19 or major natural disasters.

Our assumptions regarding the yields of the intervention, as well as the costs, were informed by our small pilot study and may not translate during the scale-up of the intervention or generalize to other settings. In particular, 3HP acceptance and treatment completion rates were relatively high in the pilot study, and the incidence of adverse events was rare (and none required hospitalization, possibly due to the relatively stringent exclusion criteria). Studies involving the implementation or evaluation of 3HP and other regimens have reported acceptance and completion rates ranging from 73% to 95% [36–38] and 90% to 97% [37, 38], respectively, and incidence of drug-related adverse events in 7.8% of cases, some requiring hospitalization [39]. Finally, our TB-centric health systems perspective on evaluating the costs and health benefits does not account for improvements in general health (outside of TB-related outcomes), benefits from averting post-TB sequelae [40], and reductions in other societal costs such as loss in productivity and patient costs. A more comprehensive accounting benefits and costs may provide an even stronger rationale for prioritizing 3HP among contacts.

Conclusions

In summary, this analysis shows that a TB intervention that screens and treats household contacts of people with TB for both TB and LTBI is highly cost effective. The intervention can be successfully implemented in both rural and urban settings in Nepal with existing tools and drugs and within the existing healthcare structure, achieving high acceptance and adherence. In a high-burden setting like Nepal, comprehensive household contact tracing, including short course, patient-centered TB preventive treatment for LTBI should be a high priority in order to accelerate progress towards achieving the END TB strategy goals.

Abbreviations

BNMT	Birat Nepal Medical Trust
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CHW	Community Health Workers
DALY	Disability–adjusted life years
DOTS	Directly–observed treatment, short–course
DPC	District Program Coordinator
FDC	Fixed–Dose combination
GBD	Global Burden of Diseases
GDP	Gross domestic product
ICER	Incremental cost effectiveness ratio
LTBI	Latent Tuberculosis Infection
PLWHA	People living with HIV/AIDS
PPD	Purified Protein Derivative
TB	Tuberculosis
TPT	Tuberculosis Preventive Therapy
TST	Tuberculin Skin Test
UI	Uncertainty Interval
USD	United States Dollars
WHO	World Health Organization
WTP	Willingness–to–pay

Supplementary Information

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Supplementary Material 1

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Author contributions

RP and AT contributed equally. Conceptualization: SoS, MC and DD. Study Design, RP, AT, SuS, KD, RD, DD, MC, SoS, Data synthesis: RP, AT, RD and MC, Model development and simulation: RP and AT, Interpretation of results: RP, AT, SuS, DD, MC, SoS, Writing (original draft): RP and AT, Writing (review and editing): All. All authors read and approved the final version of the manuscript.

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Data availability

All data generated or analysed during this study are included in this published article and the supplementary information files. Scripts used for the model development and simulation in this study is available in the following repository: [https://doi.org/10.5281/zenodo.21790325] [18].

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and ethical approval was obtained for this study from Nepal Health Research Council (Protocol registration number: 326/2021). Written informed consent was obtained from all participants included in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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