Scaling up investigation and treatment of household contacts of tuberculosis patients in Brazil: a cost-effectiveness and budget impact analysis

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Summary

Background In Brazil, investigation and treatment of tuberculosis infection (TBI) in households contacts (HHC) of TB patients is not a priority. We estimated the cost-effectiveness and budget-impact of scaling-up an enhanced HHC management in Brazil.

Methods We conceptualized a cascade-of-care that captures how HHC of tuberculosis patients are investigated in Brazil *(status quo)* and two enhanced strategies for management of HHC focusing on: (1) only tuberculosis disease (TBD) detection and, (2) TBD and TBI detection and treatment. Effectiveness was the number of HHC diagnosed with TBD and completing TBI treatment. Proportions in the cascades-of-care were derived from a meta-analysis. Health-system costs (2019 US$) were based on literature and official data from Brazil. The impact of enhanced strategies was extrapolated using reported data from 2019.

Findings With the *status quo*, 0 (95% uncertainty interval: 0-1) HHC are diagnosed with TBD and 2 (0-16) complete TBI treatment. With strategy(1), an additional 15 (3-45) HHC would be diagnosed with TBD at a cost of US$346 each. With strategy(2), 81 (19-226) additional HHC would complete TBI treatment at a cost of US$84 each. A combined strategy, implemented nationally to enhance TBD detection and TBI treatment would result in an additional 9,711 (845-28,693) TBD being detected, and 51,277 (12,028-143,495) more HHC completing TBI treatment each year, utilizing 10.9% and 11.6% of the annual national tuberculosis program budget, respectively.

Interpretation Enhanced detection and treatment of TBD and TBI among HHC in Brazil can be achieved at a national level using current tools at reasonable cost.

Funding None.

Keywords: Brazil; Tuberculosis; Latent tuberculosis; Cascade-of-care; cost-effectiveness; budget impact; tuberculosis preventive therapy

Introduction

Tuberculosis (TB) remains a major public health concern globally with 10 million new cases and 1.4 million deaths yearly.[2] Modelling studies suggest that a key strategy to reduce the global TB burden is improving uptake of tuberculosis infection (TBI) treatment,[28,29] a condition that affects one quarter of the world population.[28,30]

In view of the individual and public health benefits of TBI treatment, the 2018 United Nations High-level Meeting on TB set a target of 30 million individuals to be offered TBI treatment between 2018 and 2022, among them 24 million household contacts (HHC). This ambitious goal requires massive scale up of TBI diagnosis and treatment by National TB Programs (NTP) in low-and middle-income countries (LMIC).

Abbreviations: TBD, tuberculosis disease; TBI, tuberculosis infection; HHC, household contact; TST, tuberculin skin testing; LMIC, low and middle-income countries; CI, confidence interval; UI, uncertainty interval; MoH, Ministry of Health; WHO, World Health Organization; US$, United States Dollar

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Research in context

Evidence before this study

The 2018 United Nations High-level Meeting on tuberculosis (TB) set a target of 30 million individuals to be offered TBI treatment between 2018 and 2022, among them 24 million household contacts (HHC).[1] Very little progress had been made towards this goal by the end of 2019.[2] Previous studies have assessed interventions targeting HHC to increase diagnosis of TB disease (TBD), improve TB infection (TBI) management, or both.[3-6] We did a systematic review and found 2 studies with interventions to enhance TBI infection in Brazil[4,6] and 22 with interventions studies to enhance TBD in low and middle-income countries (LMIC).[3,7-27] In other LMIC, the cost-effectiveness of these interventions has been evaluated,[5] but not in Brazil. We evaluated the cost-effectiveness of scaling up TBD or TBD plus TBI management among HHC in Brazil, compared to the current status quo.

Added value of this study

We found that per 100 index TB patients, compared to the status quo, an enhanced TBD detection cascade-of-care for HHC investigation would cost US$346 to identify one additional patient with TBD. In an enhanced cascade that would also investigate and treat HHC for TBI using currently available tools for diagnosis and treatment in the country, the cost for each additional HHC completing TBI treatment would be US$84. Expanding nationally, the latter enhanced cascade-of-care would have an added cost of US$4.3 million annually but could avert 3.394 future TB cases through provision of TBI treatment.

Implications of all the available evidence

Enhanced detection and treatment of TBD and TBI among HHC in Brazil can be achieved at a national level at reasonable costs.

In Brazil, TB guidelines recommend the investigation and treatment of TBI in HHC of all ages of new pulmonary TB patients.[31] However, TBI treatment of HHC is not an operational indicator of the NTP, but rather the number of HHC examined for TB disease (TBD).[31,32] As a consequence, in a study of 684 HHC examined for TBD, only 8 (1.2%) initiated TBI treatment.[33]

Previous studies have assessed interventions targeting HHC to increase diagnosis of TBD, improve TBI management, or both.[3-6] Such studies, including two in Brazil,[4,6] have shown substantial improvement after the implementation of targeted interventions, but their cost-effectiveness has not been evaluated. We aimed to evaluate the cost-effectiveness and budget impact of strengthening HHC investigation for TBD only or strengthening HHC investigation for TBD plus management of TBI compared to the current approach in Brazil.

Methods

Setting and current TBI management program

In Brazil, nearly 74,000 new TB patients are reported each year, i.e., an incidence rate of 36.2 per 100,000 persons.[32] Currently, the Brazilian NTP recommends that all HHC should be investigated for TBD and TBI. TBI treatment should be started if TBI is confirmed and TBD is excluded by symptom screen, and chest x-ray, plus microbiological tests when indicated.

TBI treatment surveillance was initiated in 2018. This system includes information on indication for TBI treatment (e.g., immunosuppression or HHC) and TBI treatment, but does not include information on the cascade-of-care before TBI treatment initiation, such as the number of HHC who were identified or tested.

Strategies for investigation of HHC of TB patients (Figure 1)

We considered the current algorithm for HHC investigation in Brazil as the *status quo*[3] and considered two *enhanced HHC management strategies*: 1) enhanced TBD: investigations ONLY to detect prevalent active TBD among HHC's; and 2) enhanced TBD and TBI: detection of prevalent TBD PLUS investigation and treatment of TBI.

For each of the three strategies, we conceptualized a cascade-of-care. For the *status quo*, we conceptualized the cascade according to current recommendations of the Brazilian NTP. For enhanced strategies (Figure 1), we conceptualized one cascade that considered detection of TBD (steps 1, 2, 3, and 4, and outcome 1; black arrows in Figure 1A), and another that included detection of TBD plus investigation and treatment of TBI (steps 1, 2, 3a, 3b, 4, and 5, and outcomes 1 and 2; grey arrows in Figure 1B). Steps 1, 2 and 4, and outcome 1 are the same in the two enhanced cascades. Steps 3a, 3b, 5 and outcome 2 are exclusive of the enhanced TBD and TBI cascades-of-care.

Effectiveness measures and data sources

The two outcomes of interest were the number of HHC diagnosed with TBD and the number of HHC that completed TBI treatment. Both outcomes were expressed per 100 index pulmonary TB patients.

Because the national TBI treatment surveillance system does not report all the steps of the cascade-of-care, nor the number of new TB patients diagnosed among HHC, we conducted a systematic search in Medline (Table S1-A) for published studies conducted in Brazil that provided data on completion of key steps involved in HHC management under routine practice.

We included studies of data collected under routine practice (i.e., no intervention to enhance HHC management), that reported at least two consecutive steps of the HHC cascade-of-care and the number of index pulmonary TB patients (either microbiologically confirmed or

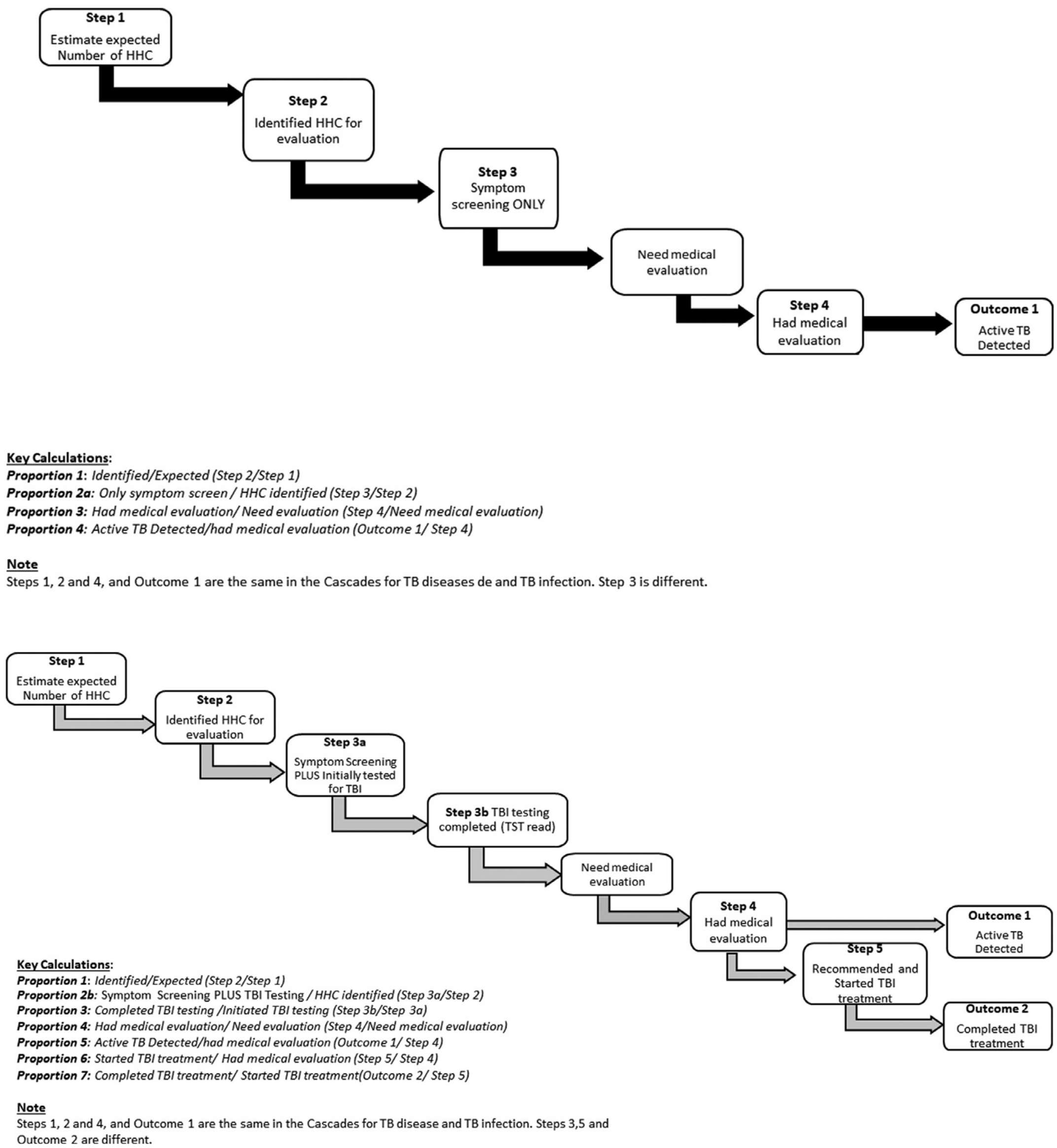

Figure 1. Schematic design of the enhanced cascade-of-care.

clinically diagnosed), and at least one of the two outcomes of interest (i.e., HHC diagnosed with TBD and the number of HHC that completed TBI treatment). We collected data on the number of HHC retained in different steps of the HHC management cascade-of-care who: 1) were identified, 2) underwent symptom screen 3) had a tuberculin skin test and symptom screen, 4) had the tuberculin skin test read, 5) needed medical evaluation (positive tuberculin skin test or symptoms of TBD), 6) underwent medical evaluation and 7) started TBI treatment.

We also collected information on study design, setting (urban vs rural), city, year of the study, and level of health care (primary, secondary, or tertiary).

We excluded modelling studies, letters, case reports and studies that reported only prevalence of TBI among HHC.

For the enhanced HHC management strategies, we performed the same search strategy. However, for the strategy of enhanced TBD detection only, we also included studies conducted in LMIC in case there were not enough studies conducted in Brazil (Table S1-B). We included studies that reported using interventions to increase TBI investigation and treatment, and/or TBD detection. Inclusion and exclusion criteria were the same as above; as well, we collected the same information from each study plus the country and intervention descriptions.

Estimation of cascade-of-care parameters

All the proportions of individuals completing the steps of the cascade-of-care were estimated by a meta-analysis. In each study, the proportions were calculated dividing the number of people completing each step by the number of people completing the previous step (refer to Figures 1A and 1B for key calculations). The proportions estimated at each step in individual studies were log transformed and meta-analysed (pooled) using generalised linear mixed models with random effects.[34] Pooled estimates and their 95% CI were back transformed into proportions. The package meta (version 4.18-0) in R was used.[35]

Costing

The costs associated with each step of the HHC cascade-of-care were estimated from the health system perspective, using a micro-costing approach, as described elsewhere.[5] For each cascade step, specific cost components included: 1) personnel costs associated with the activities, 2) materials/supplies associated with testing and treatment and 3) outpatient medical visits.

For personnel costs associated with activities for each step, the number of minutes required by healthcare workers to conduct different clinical activities was taken from a published study conducted in LMIC.[36] We multiplied the estimated time by the annual salary of each worker to arrive at a personnel cost.[37]

For supplies, tests, and medication required in different steps of the cascade, we consulted the publicly available Brazilian National Reimbursement Table.[38] For activities during TBI treatment (including visits and medication), we assumed nine months of daily isoniazid as the treatment used as this is the standard regimen for most HHC in Brazil. To estimate the cost of tuberculin skin testing and TBI treatment, we obtained information from two studies conducted in Brazil.[39,40] Finally, we estimated outpatient visit cost (costs of routine personnel and overhead) using data from WHO-CHOICE.[41]

Costing data was first inflated using local inflation indices to 2019 and then converted to United States dollars (US$) using either direct exchange rates (for tradable items) or purchasing power parity exchange (for salary and non-tradable items).

To calculate the total health system costs associated with the *status quo* and both enhanced HHC management strategies, the number of HHC retained at each step of the cascade was multiplied by the cost per contact at each cascade step. The total cost per step was summed to give the total health system cost associated with the care in *status quo* or enhanced cascades.

Cost-effectiveness

Using data from the meta-analyses, we estimated the number of HHC completing each step for a hypothetical cohort of all HHC expected with 100 index pulmonary TB patients, together with associated costs. The number of HHC expected per index TB patient was derived from a systematic review estimating 3.8 (95% CI 2.3 to 5.0) HHC per index TB patient in LMICs.[42]

To capture uncertainty, we fit costs and the number of HHC per index TB patient to gamma distributions and the proportion of persons completing each step of the cascades to beta distributions. Table S2 presents the parameters used in the probabilistic analyses. We performed 1,000 simulations, resampling from probabilistic distributions each time, to estimate costs and the number of HHC detected with TBD and HHC completing TBI treatment. We used the 50th percentile across the simulations for the point estimate, while the 2.5th percentile and 97.5th percentile as the lower and upper bounds of the 95% uncertainty interval (95% UI), respectively.

To assess the cost-effectiveness of the enhanced TBD strategy versus *status quo*, we estimated the incremental cost associated with the necessary activities per additional HHC detected to have TBD. We then estimated incremental costs for steps only related to enhanced TBI detection and treatment per additional HHC completing TBI treatment. From the 1000 simulations, we used the 50th percentile estimate for the difference in cost and divided it by the 50th percentile estimate for the difference in number of persons diagnosed with TBD or number of persons completing TBI treatment to calculate the incremental cost-effectiveness ratio for each outcome.

Epidemiological and budget impact

Using the actual number of new pulmonary TB patients diagnosed in Brazil in 2019,[32] we estimated the number of HHC that would complete each step of the cascade, either in the *status quo* or the two enhanced strategies, using data obtained from our systematic review and meta-analysis. We then estimated how many prevalent TB patients would be detected among the HHC, and how many new TB cases could be averted by completing TBI treatment. For the latter, we stratified the number of HHC completing TBI treatment into three age groups (<5 years, 5-14 years, >14 years) and used five-year cumulative TB incidence rates: 27.8% among the HHC <5 years old, 13.4% among the HHC 5-14 years old and 4.8% among HHC >14 years old.[43] We assumed that the proportions of HHC in each age group would be similar to the overall population reported in the Brazilian 2010 census, i.e. 6.8%, 13.9% and 79.3%; respectively.[44]

Using the same probabilistic approach described for the cost-effectiveness analyses above, we fit parameters to beta distributions for proportions in the cascade-of-care, cumulative TB incidence, and effectiveness of TBI treatment with 9 months of isoniazid, the standard of care in Brazil.[31] For costs and expected number of

HHC, we applied gamma distribution (Table S2). We used the 50th percentile across the simulations for the point estimate, while the 2.5th percentile and 97.5th percentile as the lower and upper bound of the 95% UI, respectively. For each simulation, we expressed the total cost of the three strategies as a proportion of the annual NTP budget.[2]

Role of the funding source

Funders had no role in study design, data collection, analysis, interpretation, or manuscript preparation. All authors had full access to all study data and the corresponding author had the final responsibility for the decision to submit for publication.

Results

Characteristics of studies used to estimate effectiveness

We included 7 studies from Brazil,[4,6,33,45-48] of which five reported only the *status quo* in Brazil[45-49] (Figure S1). One reported the *status quo* and enhanced TBD and TBI detection and treatment[6] and one reported enhanced TBD and TBI detection and treatment.[50] We did not find studies that only described an enhanced TBD detection and treatment strategy that had been conducted in Brazil (without also describing enhanced TBI detection and treatment). From our search of other LMIC, we identified 1,688 titles, of which we included 22,[3,7-27] all of which described an enhanced TBD strategy. The characteristics of the included studies are summarized in Table S3. Strategies to enhance TBD and TBI detection and treatment included home visits (N=1) and healthcare worker or patient education (N=2). Among 22 studies reporting only enhanced TBD detection, home visits (N=13), healthcare worker or patient education (N=4), transport costs reimbursement (N=5), phone calls as reminders for visits (N=4), free-of-charge chest x-ray (N=2), and nutritional incentives (N=1) were used (Table S4).

Effectiveness measures: N of TBD detected, N of HHC completing TBI treatment

The pooled proportion of HHC completing each step of the *status quo* and enhanced strategies cascades are displayed in Table 1. In *status-quo*, most losses were earlier in the cascade with 67.3% of HHC being identified and 6.6% of HHC having a tuberculin skin test; among the HHC examined, 4.3% were found to have TBD. With enhanced TBD detection, 10.1% of HHC examined were found to have TBD. With enhanced TBD and TBI detection and treatment, primary losses were with tuberculin skin testing and TBI completion (65.8% and 69.0% of HHC, respectively). Additional information of each step of the *status-quo* and the enhanced HHC cascade-of-care are described in Tables S5-S9.

Cost-effectiveness and budget impact

Table 2 describes each activity—the unit cost and time associated with it—performed in each step of the HHC cascade-of-care. Total costs of each step are shown in Table S10. The costliest steps were medical evaluation (US$15, 95% UI 11 to 21) and follow-up required during TBI treatment (US$36, 95% UI 24 to 50). HHC identification (US$4.0, 95% UI US$3.3 to US$5.0) was the most inexpensive step.

Cost-effectiveness analyses are shown in Table 3. In the *status quo* situation, 0 patients (95%UI: 0 to 1) with prevalent TBD are detected, and 2 HHC (95%UI: 0 to 16) complete TBI treatment. In the enhanced TBD cascade-of-care, 15 patients (95%UI: 3 to 45) with TBD would be detected, at a cost of US$346 per additional TBD patient detected. In the enhanced TBD and TBI detection and treatment cascade-of-care, 81 HHC (95%UI: 19 to 226) would complete TBI treatment, at a cost of US$84 per added HHC completing TBI. As seen in Figure 2, in all 1,000 simulations, enhanced strategies were more costly, but more effective than the *status quo*.

As seen in Table 4, in the *status quo* strategy, 95 HHC (95% UI: 4 to 841) are detected with prevalent TBD each year (representing 0.1% of all new pulmonary TB patients notified in Brazil in 2019) and 1,448 HHC (95% UI: 67 to 10,370) would complete TBI treatment each year, thereby avoiding 91 (95% UI: 4 to 698) TB cases (representing 0.1% of new pulmonary TB patients in Brazil in 2019). With the enhanced TBD strategy, 9,711 HHC (95% UI: 2,225 to 28,693) with prevalent TBD would be found (representing 15.3% of new pulmonary TB patients) each year; this would utilize 10.9% of the 2019 NTP budget. In the enhanced TBD and TBI detection and treatment cascade-of-care, 51,277 HHC (95% UI: 12,028 to 143,495) would complete TBI treatment, thereby avoiding 3,394 (95% UI: 690 to 9,889) TB cases (representing 5.3% of all new pulmonary TB patients) and utilizing 11.6% of the NTP budget.

Discussion

We found that, compared to the *status quo*, an enhanced TBD detection for HHC investigation cascade-of-care would cost US$346 to identify one additional patient with TBD. In an enhanced cascade that would also investigate and treat HHC for TBI, the cost for each additional HHC completing TBI treatment would be US$84. Expanding nationally, the TBD/TBI enhanced cascade-of-care would have an added cost of US$4.3 million annually but could avert 3,394 future TB cases through provision of TBI treatment.

Active TBD screening and detection among HHC is a key component for TB prevention and care due to the

Proportions of the cascade-of-care‡	*Status quo** Pooled estimates (95% CI) (N=6 studies)	Enhanced TB Disease Cascade Pooled estimates (95% CI)	Enhanced TB Disease and Infection Cascade Pooled estimates (95% CI)
Proportion 1: HHC identified/ HHC expected	67.3% (95% CI: 49.7% to 81.0%)	99.9% (95% CI: 95.4% to 100%)‡	
Steps (activities) exclusively in the cascade-of-care for enhanced TB disease			
Proportion 2A: Only symptom screen / HHC identified	-	99.2% (95% CI: 94.3% to 99.9%)#	NA
Steps (activities) exclusively in cascade-of-care for enhanced TB disease and infection			
Proportion 2B: Initiated TBI testing (symptom screen also performed at same time)/ HHC identified	6.6% (95% CI: 1.4% to 25.7%)	NA	65.8% (95% CI: 62.8% to 68.8%) ‡
Proportion 3: Completed TBI testing **/** Initiated TBI testing	90.0% (95% CI: 81.7% to 94.7%)	NA	92.2% (95% CI: 89.9% to 94.1%) ‡
Steps reported in both enhanced cascade-of-care			
Proportion 4: Had medical evaluation/ Need medical evaluation¶,	99.7% (95% CI: 79.6% to 100%)	98.9% (95% CI: 92.2% to 99.8%)‡	
Proportion 5: Active TB patients detected/ Had medical evaluation	4.3% (95% CI: 2.3% to 8%)	10.1% (95% CI: 7% to 14.4%)‡	
Steps (activities) exclusively in cascade-of-care for enhanced TB Disease and Infection			
Proportion 6: Started TBI treatment / Had medical evaluation	78.9% (95% CI: 60.8% to 90%)	NA	77% (95% CI: 72.5% to 81%)†
Proportion 7: Completed TBI treatment / Started TBI treatment	77.2% (95% CI: 72.8% to 81.1%)	NA	69% (95% CI: 63.1% to 74.3%)†

***Table 1*: Estimated pooled proportions of HHCs completing each step of the cascade-of-care, with different strategies.**

Abbreviations: CI-confidence interval, HHC- household contacts, NA- Not applicable, TBI- tuberculosis infection, TB -Tuberculosis

Note: need medical evaluation = HHC who were TST positive and/or had symptoms

* Pooled proportions from meta-analysis of results from six studies (Figure S1B) for status quo

‡ Pooled proportions from meta-analysis of results 24 studies (22 that focused on enhanced TB disease detection only and 2 that reviewed TB disease and TB infection - see Methods)

Pooled proportions from meta-analysis of results from 22 studies that focussed on TB disease detection only (see Methods).

† Pooled proportions from meta-analysis of results from two studies that only evaluated an enhanced TBI management that included active TB detection.

	Unit cost or Time per HHC	Range		Source*
		Low	High	
Step 1 - HHC expected				
No costs	-	-	-	
Step 2 - HHC identification				
Outpatient visit	US$3.80	US$3.42	US$5.02	(41)
Time for HHC identification (minutes)	7.5	0.5	14.2	(36)
Salary for one nurse to conduct HHC identification	US$0.31	US$0.21	US$0.33	(37)
HIV test for HHC	US$2.63	US$0.67	US$5.78	(2, 38)
Step 3A - TST application & symptom screening at same time				
Outpatient visit	US$3.80	US$3.42	US$5.02	(41)
Time for apply TST & symptom screening (minutes)	4.5	0.0	9.5	(36)
Salary of nurse to apply TST & symptom screening per min	US$0.31	US$0.21	US$0.33	(37)
Costs of TST	US$8.64	US$6.19	US$24.76	(39)
Step 3B -Only symptom screening to detect active TB finding				
Outpatient visit	US$3.80	US$3.42	US$5.02	(41)
Time for symptom screening (minutes)				(36)
Salary of nurse to conduct symptom screening per min	US$0.31	US$0.21	US$0.33	(37)
Step 4- TST reading and referral for medical evaluation				
Outpatient visit	US$3.80	US$3.42	US$5.02	(41)
Time for nurse to read TST and refer for medical evaluation (minutes)	2.9	0.0	5.8	(36)
Salary of nurse to read TST and referral for medical evaluation if needed per min	US$0.31	US$0.21	US$0.33	(37)
Step 5 Had medical evaluation				
Outpatient visit	US$3.80	US$3.42	US$5.02	(41)
Time for physician conduct medical evaluation (minutes)	9.7	5.0	14.4	(36)
Salary for physician to conduct medical evaluation (per min)	US$0.42	US$0.21	US$0.73	(37)
Liver function tests	US$2.60	US$1.99	US$7.97	(38)
Sputum	US$2.30	US$0.53	US$3.78	(38)
Culture	US$5.17	US$3.00	US$11.99	(38)
Chest x-ray	US$2.59	US$2.14	US$8.53	(38)
Step 6 TBI treatment or TB treatment recommended and started				
Outpatient visit	US$3.80	US$3.42	US$5.02	(41)
Time for physician recommend medical evaluation (minutes)	5.5	0.0	11.7	(36)
Salary of physician to recommend TPT or TB treatment	US$0.42	US$0.21	US$0.73	(37)
TBI treatment completion				
Total costs for completion treatment (included visits and drugs)	US$36.0	US$29.2	US$42.8	(40)

***Table 2*: Component costs related to activities performed in each step of the TBI cascade-of-care (US$ 2019).**
Abbreviations: HHC-household contacts, TBI- tuberculosis infection, TB- tuberculosis disease, TBI-tuberculosis infection TST- tuberculin skin test, MoH- Brazilian Ministry of Health, WHO- World Health Organization, US$- United States dollar
* References found in main text.

high prevalence of TBD in this population.[42] An enhanced cascade-of-care that would early detect TB patients among HHC could have important public health implications for Brazil. Early detection of TB patients could result in reduced TB transmission[51] and early diagnosis of disease could help minimize long-term disability related to TB.[52] This strategy would reduce costs from the health system and patients' perspective, since it prevents multiple healthcare visits required before a patient is diagnosed with TBD.

However, enhancing TBD detection among HHC without enhancing TBI investigation and treatment would represent a missed opportunity. HHC are individuals who are at higher risk of developing TBD than the general population. It is estimated that 5% of adults who have TBI will develop TBD in the first two years after being in contact with an index TB patient. The risk is higher among those under 15 years of age.[43] TBI treatment is highly effective and safe,[53] and provides benefits for the patient and for the population since it reduces the number of persons developing TBD, decreasing transmission in the community. A previous economic evaluation estimated that the costs for treating one patient with TB disease in Brazil were US$1,142. If the 3,394 HHC had developed the avoided TBD, the total costs to treat them would be close to the total cost to avoid them - 3.9 and 4.3 million, respectively.[54] However, TB prevention would result in other benefits for

<table>
<tr><th></th><th>Status quo cascade of care (95% UI)</th><th>Enhanced TB Disease Cascade (95% UI)</th><th>Enhanced TB Disease and Infection Cascade (95% UI)</th></tr>
<tr><td>Effectiveness (per 100 new pulmonary TB patients)</td><td></td><td></td><td></td></tr>
<tr><td>N of expected HHC</td><td>334 (81 to 896)</td><td colspan="2">334 (81 to 896)</td></tr>
<tr><td>N of HHC identified</td><td>227 (55 to 598)</td><td colspan="2">334 (81 to 896)</td></tr>
<tr><td>N TB patients detected (prevalent) at time of HHC investigation</td><td>0 (0 to 1)</td><td colspan="2">15 (3 to 45)</td></tr>
<tr><td>N TBI treatment initiated</td><td>3 (0 to 21)</td><td>NA</td><td>117 (27 to 326)</td></tr>
<tr><td>N TBI treatment completed</td><td>2 (0 to 16)</td><td>NA</td><td>81 (19 to 226)</td></tr>
<tr><td>Costs in USD (per 100 new pulmonary TB patients)</td><td></td><td></td><td></td></tr>
<tr><td>Investigation only for detection of HHC with active TB (Steps 1, 2, 3B and 5)</td><td>US$1011 (US$242 to US$2807)</td><td colspan="2">US$6222 (US$1478 to US$16493)</td></tr>
<tr><td>TBI management-related steps only (TST application & reading, LTBI treatment initiation and follow-up - Steps 3A, 4, 6, 7)</td><td>US$248 (US$10 to US$1770)</td><td>NA</td><td>US$6908 (US$1643 to US$19004)</td></tr>
<tr><td>Incremental cost per additional active TB patient detected</td><td>-</td><td colspan="2">US$346</td></tr>
<tr><td>Incremental cost per additional HHC with TBI completing TBI treatment</td><td>-</td><td colspan="2">US$84</td></tr>
</table>

***Table 3:* Outcomes predicted - Effectiveness, costs and cost-effectiveness with three strategies for household contact management.**
Abbreviations: HHC-household contacts, TB-tuberculosis, TBI- tuberculosis infection, N-number, US$- United States dollar, UI- uncertainty interval. NA: Not applicable

these HHC, such as avoidance of TB-related stigma,[55] economic losses,[56,57] possible long-term disability[52] and transmission. Moreover, in the enhanced TBD/TBI HHC management cascade-of-care, most of the costs would be already used for TBD detection, but without the benefit of preventing future TBD. Finally, most of the interventions of interventions found in our review to enhance TBD finding are the same that could be used for TBI investigation and treatment.

Our study has several limitations. First, we did not have programmatic data from the Brazilian NTP to estimate different steps of the cascade-of-care for the *status quo*; therefore, we relied on published studies from six cities (four capitals and two medium-size cities), that may not represent the national scenario. Second, most of the studies of the impact of enhanced strategies included in the review were small intervention studies, which could overestimate rates of TPT completion. Scaling up interventions nationally may not achieve the same impact at the same cost. Third, because of the absence of studies evaluating enhanced TBD detection in Brazil, we used estimates from other LMICs, which may not be generalizable. Fourth, we did not estimate costs of interventions to enhance the HHC management cascade-of-care, as well as costs for treating TB patients. We also did not consider the effect of averting TB cases on TB transmission in Brazil, likely underestimating the population level effect of TBI treatment. Additionally, we did not include patients' costs in our analysis. However, the economic burden for patients during TBD is high in Brazil, likely more than the Brazilian minimum wage.[58,59] Finally, we only estimated health system costs and impacts using isoniazid-based regimens, as the studies included in our meta-analysis only used mono-isoniazid regimens, and isoniazid is the first line TPT regimen recommended in Brazilian national guidelines for most risk groups. However, we can expect that national expansion of TPT using the shorter rifamycin-based TPT regimens would be even more cost-effective as the TPT completion rates would be higher, with similar effectiveness, and lower costs, as recently shown for the four-month rifampicin regimen.[40]

Despite these limitations, our study has several strengths. We applied a framework of health system costs which included detailed information of activities performed at each step of the cascade-of-care. We used a comprehensive search strategy with defined inclusion and exclusion criteria, and a meta-analysis to estimate the proportions of patients completing each step of both cascades, instead of choosing unique studies. This should have reduced the risk of bias in selecting parameter estimates, thereby improving the accuracy and generalizability of our results.

In conclusion, implementing interventions to improve tuberculosis disease detection and TBI treatment among HHC in Brazil can support TB elimination efforts to attain the United Nations TBI goals at a reasonable cost.

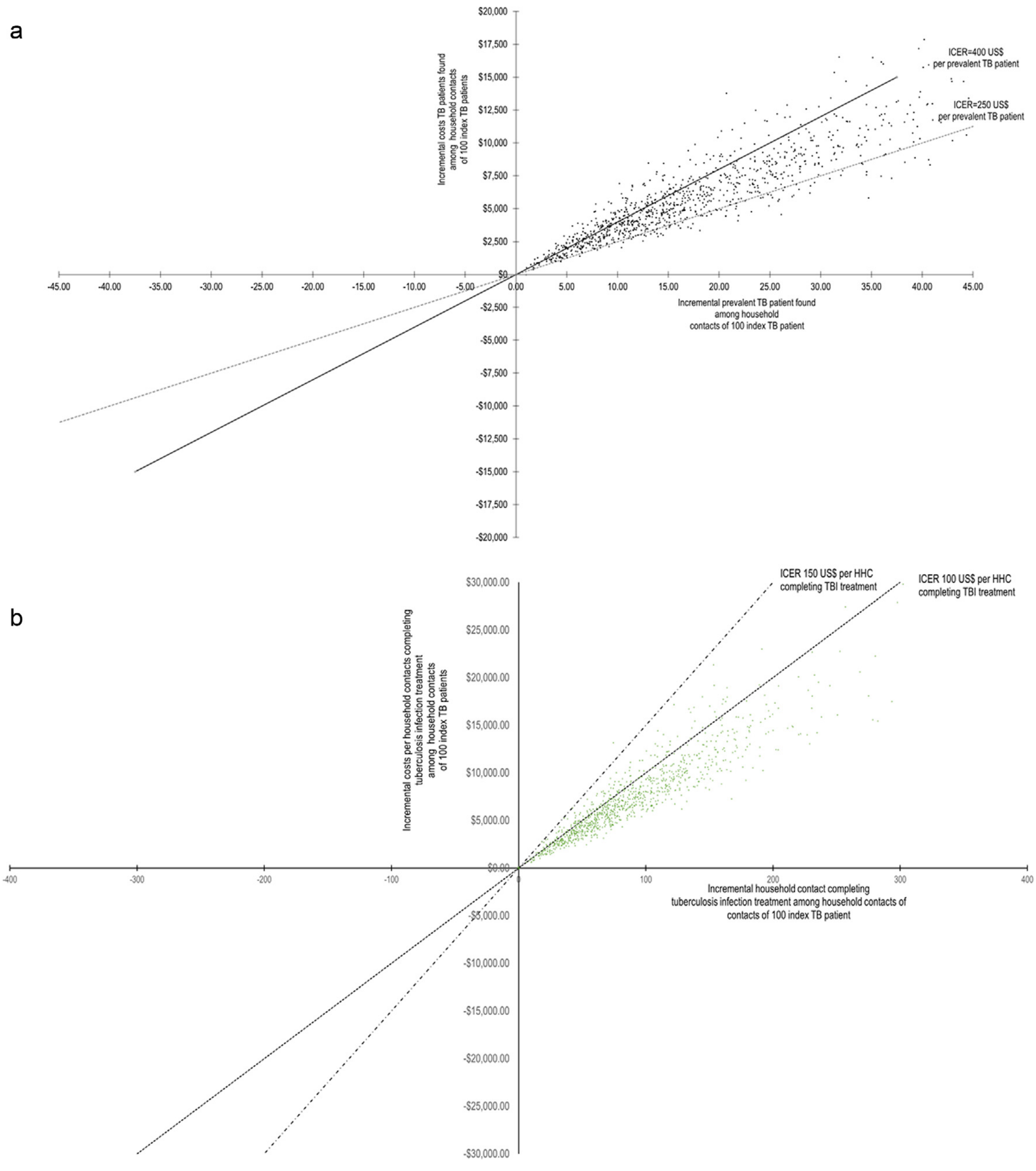

Figure 2. (A) Cost-effectiveness plane, enhanced cascade of care vs. status quo for active TB detection (TB patients detected as part of HHC investigation). (B) Cost-effectiveness plane, enhanced cascade of care vs. status quo for HHC completing TBI treatment.

Estimates	*Status quo cascade of care* (95%UI)	Enhanced TB Disease Cascade *(95%UI)*	Enhanced TB Disease and Infection Cascade (95%*UI*)
Brazilian TB indicators*			
Total new TB patients	73,684		
Total new pulmonary TB patients (microbiologically or clinically confirmed)	63,591		
NTP Budget in 2019#	US$38,000,000		
Costs and Effectiveness related to active TB detection			
N of expected HHC	212,660 (51,671 to 569,957)	212,660 (51,671 to 569,957)	
N of HHC identified	144,175 (34,769 to 380,270)	212,659 (51,671 to 569,957)	
TBD patients detected as part of HHC investigation	95 (4 to 841)	9,711 (2,225 to 28,693)	
% of TB detected in HHC, over the N of total new pulmonary TB patients	0.1% (0.0% to 1.3%)	15.3% (3.5% to 45.1%)	
Total costs	US$746,241 (US$238,869 to US$1,929,616)	US$4,058,807 (US$1,049,119 to US$10,528,846)	
% of NTP budget	2.0% (0.6% to 5.1%)	10.9% (2.8% to 28.4%)	
Costs and Effectiveness related only to TBI management			
N of HHC starting TBI treatment	1,857 (87 to 13657)	-	74,450 (17,216 to 207,247)
N of HHC completing TBI treatment‡	1,448 (67 to 10,370)	-	51,277 (12,028 to 143,495)
HHC < 5 years old	98 (5 to 705)	-	3,487 (818 to 9,758)
HHC 5-14 years old	201 (9 to 1,441)	-	7,128 (1,672 to 19,946)
HHC > 14 years old	1,148 (53 to 8,223)	-	40,663 (9,539 to 113,791)
Expected N TB cases if HHC completing TBI treatment were untreated (total)	102 (5 to 808)	-	3,872 (786 to 11,220)
HHC < 5 years old	24 (1 to 213)	-	922 (124 to 3,431)
HHC 5-14 years old	24 (1 to 232)	-	922 (166 to 3,144)
HHC >14 years old	52 (2 to 435)	-	1,963 (434 to 5,847)
Expected N of averted TB cases among HHC completing LTBI treatment (total)	91 (4 to 698)	-	3,394 (690 to 9,889)
% of averted TB cases over the N of index cases	0.1% (0.0% to 1.1%)	-	5.3% (1.1% to 15.6%)
Total costs	US$157,562 (US$6,652 to US$1,125,604)	-	US$4,393,179 (US$1,044990 to US$12,084,872)
% of NTP budget	0.4% (0.0% to 3.0%)	-	11.6% (2.7% to 31.8%)

***Table 4*: Budget impact of the two enhanced strategies, if they had been applied to the cohort of all new pulmonary tuberculosis cases reported in Brazil, 2019.**

Abbreviations: HHC-household contacts, TBI- tuberculosis infection, N- number, NTP- National Tuberculosis Program, TST- tuberculin skin test, TB-Tuberculosis, US$- United States dollar, UI-uncertainty interval.

* Reference (32).

\# Reference (2).

‡ Assumed that distribution of age among HHC is the same of the general Brazilian population, reference (44).

Contributions

MLB, OO, DM, AT were responsible for the study concept and design. MLB, DM, AT wrote the initial draft. MLB, JRC and DM performed the statistical analysis.

MLB, OO, JRC, EF, DM, AT contributed to data interpretation and to the critical revision of the manuscript for important intellectual content.

Data sharing

All data used in the analysis is available as supplementary material, no additional data available.

Declaration of interests

No conflict of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lana.2021.100166.

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