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Abstract

Objectives

Despite WHO guidelines recommending household contact investigation, and studies showing the impact of active screening, most TB programs in resource-limited settings only carry out passive contact investigation. The cost of such strategies are often cited as barriers to their implementation. However, little data is available for the additional costs required to implement this strategy. We aimed to estimate the cost and cost-effectiveness of active contact investigation as compared to passive contact investigation in urban Pakistan

Design, participants and intervention:

We estimated the cost-effectiveness of 'enhanced' and 'active' contact investigations compared to 'passive' contact investigation from providers and the program's perspective using a simple decision tree.

Setting and primary and secondary outcome measures:

Costs were collected in Pakistan from a TB clinic performing passive contact investigation and from studies of active contact tracing interventions conducted. The effectiveness was based on the number of TB patients identified among household contacts screened.

Results

The addition of enhanced contact investigation to the existing passive mode detected 3.7 times more cases of TB per index patient compared to passive contact investigation alone. The incremental cost was USD 30 per index patient, which yielded an incremental cost of USD 120 per incremental patient identified with TB. The active contact investigation was 1.5 times more effective than enhanced contact investigation with an incremental cost of USD 238 per incremental TB patient identified.

Conclusion

Our results show that enhanced and active approaches to contact investigation effectively identify additional patients with TB amongst household contacts at a relatively modest cost. These strategies can be added to the passive contact investigation in a high burden setting to find the people with TB who are missed and meet the End TB strategy goals.

Strengths and limitations of this study:

- The study was performed alongside implementation in district tuberculosis clinics in a high-prevalence setting.
- It is one of the first ones to compare the cost effectiveness of multiple active contact investigation approaches.
- The latest WHO guidelines identifies the comparisons of different types of contact investigation as a current knowledge gap and our findings aid this void.
- The study did not consider out-of-pocket expenditures for patients which leads to underestimation of the overall costs for contact investigation.

Background

Tuberculosis (TB) remains a leading cause of morbidity and mortality, especially in low- and middle-income countries. According to the latest estimates, 10 million people fell ill with TB in 2019, though only 7.1 million were reported to national programmes. Eight countries account for two-thirds of the reported TB burden in the world: India (26%), Indonesia (8.5%), China (8.4%), the Philippines (6%), Pakistan (5.7%), Nigeria (4.4%), Bangladesh (3.6%) and South Africa (3.6%).[1,2,3] Reasons for the gap between estimated and notified individuals with TB include limited access to health care, poor diagnosis capacity for people who do access care, as well as underreporting of people diagnosed.[4,5,6]

Undiagnosed people with TB continue to transmit TB to others. The risk of transmission is particularly high amongst members of households living with people with undiagnosed pulmonary TB. Studies have documented an infection rate of 30-50% amongst household contacts of infectious adults, with the infection rate in children under 5 being as high as 72%.[7,8] Of those infected with TB, 10-20% develop the disease over their lifetimes, and this number is even higher for people who are immunocompromised, for example when they are co-infected with HIV.[9,10,11,12]

Household contact investigation is recommended as a means to address these challenges.[13,14] In the light of the high infection rates, household contact investigation is a critical activity for TB programs for two reasons. First, it allows early identification of additional household members who are also sick with TB and require immediate treatment, stopping transmission. Second, it allows programs to identify people who can benefit from the treatment of TB infection (TBI) to prevent disease progression, importantly children and people living with HIV. A meta-analysis of contact investigation showed that 3.1% of contacts in low-resource settings and 1.4% of contacts in high-resource settings have TB disease, making this a potential high yield strategy to find people with TB.[15,16] A large proportion of childhood TB can be identified through contact investigation, which is of particular value since global rates of detection among children are much lower than for adults.[1]

Household contact investigation can be carried out in many different ways along a continuum of passive or active approaches.[17] In passive contact tracing, the index patient is asked to bring in their family members for screening to the facility, while in active contact tracing, health care workers visit the index patient's home. An 'enhanced' form of contact tracing between the active and passive modes, in which health workers make reminder phone calls and follow up with the family and encourages them to come to the facility for screening can also be delivered.

Despite WHO guidelines recommending household contact investigation[18,19] and studies documenting the outcomes of active approaches the most TB programs in resource-limited settings only carry out passive contact investigation and even then, implementation is limited.[20,21] A cluster-randomized controlled trial demonstrated that contact investigation plus passive case finding (PCF) was beneficial compared to passive case finding alone.[22] The cost of active contact investigation, including additional efforts required by already stretched health care providers, has often been cited as a barrier to its implementation.[23] However, little data is available for the additional cost of implementing active contact investigation, and especially so when implemented under routine program conditions. A study from Malaysia reported the cost of active contact investigation to be USD 6.60 per a single contact tracing visit with a yield of 0.5%.[24] In Peru, adding active contact tracing to PCF incurred an incremental cost of USD 48.8 to evaluate household contacts of an index TB patient, with an incremental cost-effectiveness ratio (ICER) of USD 1811 per DALY averted.[25] We were not able to identify studies reporting costs or cost-effectiveness for the enhanced mode of contact tracing.

The objective of this study was to estimate the cost and cost-effectiveness of the enhanced and active contact tracing interventions in a high-burden programmatic setting, compared to the existing passive approach.

Methods

SETTING

The costing study was a subset of a larger study where an active case finding intervention was implemented for children with TB. The study was conducted at four TB treatment and reporting centres in Kotri, a rural town in Sindh, Pakistan. All children presenting to these facilities were verbally screened for symptoms of TB and those considered to be at high risk of having TB were further investigated. Children diagnosed with TB were started on treatment, and we conducted contact investigation for their household contacts.[26] The household contact investigation for adults and children identified with TB reported here was carried out at one of the four centers (Institute of Chest Disease Hospital) from April 2015 to March 2016.

INTERVENTIONS

For the study, the index patient was the first person identified with TB in the family, while household contacts were defined as people living in the same household as the index patient. In passive contact investigation, index patients were counselled to bring their household contacts for evaluation. Contacts who responded were evaluated for TB symptoms and risk factors. A limitation of this approach in regular practice, people screened were recorded only as a TB contact and not linked directly to the index TB patient in a specific household. There was no routine follow-up to see if the specific contacts attended the facility for screening or not.

Enhanced contact investigation added a step to the passive approach. Adults and guardians of children under 15 years of age newly diagnosed with TB were asked about the presence of TB symptoms or household members on TB treatment in their families. They were counselled to bring their enumerated household contacts for evaluation, as in the passive approach. If the enumerated household contacts did not come to the facility for assessment after one week, a reminder phone call was made, followed by second phone call after another week. If the family still had not come two weeks after the second phone reminder, active contact investigation was implemented. Active contact investigation included health workers conducting a household visit to verbally screen the family at home and to counsel the family to go to the clinic for further evaluation (Figure 1).

At the clinic, enumerated household contacts were screened by existing TB doctors in the passive system or by trained health workers for enhanced and active contact investigation. All contacts were verbally screened for symptoms of TB such as cough of more than two weeks, contact with someone other than the index patient who had TB, glandular swelling, fever lasting more than two weeks, night sweats and inappropriate weight loss. Individuals with suggestive symptoms or additional exposure were referred to the project's medical officer for further evaluation. They then received a chest x-ray and were asked to provide a sputum sample for smear microscopy. A complete blood count (CBC) and erythrocyte sedimentation rate (ESR) was done for child contacts to aid in diagnosis as indicated. Contacts diagnosed with TB were started on TB treatment in line with the National TB Program (NTP) guidelines. Children under five years of age in whom TB disease was ruled out were offered isoniazid preventive therapy (IPT) as per NTP guidelines.[26] All clinical evaluations and investigations were provided without any charge to the contacts.

DATA COLLECTION

For the passive approach, health facility staff recorded data using a paper-based system which were then abstracted for the study. For enhanced and active contact interventions project based trained community health workers and doctors administered questions to assess TB symptoms/risks and documented results of clinical evaluation and diagnostic tests using a custom-built smart-phone based data collection application with built-in decision support developed for the project.[26]26

COST PARAMETERS

Costs for this systematic contact tracing activities were collected from the perspective of the operational program and the health facility and included recurrent and capital cost items. As capital costs for the building were not available, we approximated rent and utilities of running a similar structure, and we used these in place of the capital costs.

We identified cost items and quantified resource use for all activities related to contact investigation. They included personnel, diagnostic test, supervision and monitoring by facility or project staff and communications. For the passive system, cost information was obtained from the health facility accounting system. We identified one physician and one health worker who were involved in the existing passive system at the TB clinic. We estimated their time spent on evaluation of household contacts through expert opinion and allocated salaries proportionate to this time as compared to other activities. Unit costs for TB diagnostic tests, chest x-rays, and smear microscopy were as billed to the project by the health facility. Costs for diagnostic tests were estimated by multiplying their unit costs with the number of people tested. As communications, supervision and training costs for the existing passive program were not available through the facility records, we assumed the same costs as incurred by the enhanced contact investigation intervention. At the TB clinic, data was collected on paper-based systems and the costs for registers and forms are reported with stationary.

For the additional costs of performing enhanced and active contact investigations, data were extracted from the project accounting system. One full-time health worker was recruited for enhanced intervention while the active contact investigation required three additional health workers. A fixed amount of travel costs for home visits was built into the salary for health workers. For all other personnel such as physician, field supervisor and program coordinators, time spent on the contact investigation intervention was estimated using an activity-based costing (ABC) methodology, and costs were allocated according to the proportion of time spent on the intervention relative to other activities.[27,28] Cost of diagnostic investigations per person screened (chest x-ray, smear microscopy and complete blood), communications (data and phone), training and stationery were as incurred. The cost for the development of electronic data capture was allocated based on the number of patients screened in each intervention, while the cost of phones and laptops used to capture data were allocated as per the personnel time that used them. We annuitized these capital costs over a period of three years using a 3% discount rate.[29,30] Costs were collected in Pakistan Rupees and converted to US dollars using the average exchange rate for the years 2015 and 2016 (1 USD =103.1 PKR).

EFFECTIVENESS OF CONTACT INVESTIGATION

The effectiveness of the contact investigation procedure was evaluated based on the number of people with TB identified per household screened after verbal screening and diagnostic tests. Our study was divided into baseline and intervention periods. Passive contact investigation was performed in the baseline period and used as the comparator. In the year preceding the intervention, the passive approach screened 762 contacts from a total of 231 index patient households to identify 21 people with TB during this baseline period (Figure 1). During the intervention period, enhanced and active contact investigation were implemented, and contacts from 300 households were evaluated. Of these, 1130 people from 144 families came to the health facility after phone reminders (enhanced) and 102 were diagnosed with TB. When home visits were conducted for 156 households that failed to respond to the enhanced strategy (active), we evaluated 1224 people and identified 53 additional people with TB disease (Figure 1).

DECISION MODEL AND ANALYSIS

A simple decision tree was created in TreeAge Pro 2020 (TreeAge Pro Inc., Williamston, MA) to estimate the cost-effectiveness of enhanced and active contact investigation compared to passive contact investigation. The decision tree includes the three alternatives for contact investigation; (i) Passive, (ii) Passive + Enhanced and (iii) Passive + Enhanced +Active (Figure 2). The three intervention alternatives represent different levels of intensity of contact investigation and are considered to be mutually exclusive. The more intense alternatives are more expensive than the less intensive ones, but also represent new possibilities for identifying contacts with TB (Table 1). The results are presented as absolute and incremental costs and TB patients identified, and incremental cost-effectiveness ratios (ICERs) between the alternatives.

We conducted probabilistic sensitivity analyses (PSA) using Monte Carlo simulations with 10,000 iterations to explore the effects of combined uncertainties in key parameters. Gamma distributions were used for cost parameters, and beta distributions for the probability of TB patients per family screened.[31] For sensitivity analyses, upper and lower values were defined for each parameter as mean values ±20%.

Ethical approval was obtained from the Institutional Review Board (IRB) of Interactive Research and Development (IRD), OHRP Registration No. 00005148.

Table 1: Modeling inputs, assumptions and ranges for passive, enhanced and active contact investigation (CI).

Interventions	**Total cost (USD)**	**Index patient with TB**	**Total contacts diagnosed with TB** (Lower and Upper limit)	**Cost per index TB patient family screened (USD)**	**Probability of finding a TB patient per household screened** (Lower and Upper limit)
Passive CI	10,659	231	21 (17– 25)	46 (37-55)	0.09 (0.07 – 0.10)
Passive + Enhanced CI	19,597	300	102 (82 – 122)	76 (61 – 91)	0.34 (0.27 – 0.40)
Passive + Enhanced + Active CI	32,282	300	155 (124 – 186)	118 (94 – 142)	0.52 (0.41 – 0.62)

Results

In the enhanced and active contact tracing, 2,354 household contacts from 300 index patients were screened, of whom 49% were children less than 15 years of age, and 45% were female. The mean age for child contacts was 6.4 years (SD 3.7, IQR: 3-9), and 54% were males and the mean age for adult contacts was 33 years (SD 13.4, IQR: 21-41) and 53% were males. The enhanced contact investigation intervention was able to find 2.45 times (95% CI: 1.52 – 4.14) more people with TB than the passive program when it was implemented. While the active intervention implemented three weeks following the index patient counselling identified 2.11 times (95% CI: 1.33 – 3.52) more people with TB compared to passive contact investigation.

Overall, the passive program incurred USD 10,659 over one year and it cost USD 46 per household screened with TB. The enhanced contact investigation incurred an additional USD 30 to screen a household with an overall addition of USD 8,938 to the yearly program cost. Of the additional costs, human resources (42%) and electronic data collection (24%) were the most significant cost drivers. Active contact investigation incurred an additional USD 42 per household screened for TB above the enhanced model, and the program cost a further USD 12,685 to the enhanced contact investigation of which human resources (57%) and electronic data capture (18%) were the largest components. (Table 2)

Table 2: Cost (USD) of household contact screening for passive, enhanced and active contact investigation activities (upper panel), and cumulative costs per intervention arm (lower panel).

INTERVENTION ACTIVITIES **Cost categories**	**Passive contact investigation N=231 (%)**	**Enhanced contact investigation N=300 (%)**	**Active contact investigation N=300 (%)**
Recurrent costs:			
Clinic rental and maintenance	3,492 (33)	-	-
Personnel	5,354 (50)	3,835 (42)	7,348 (57)
Diagnostic tests	1,478 (14)	2,192 (24)	2,374 (18)
Supervision and monitoring	116 (1)	195 (2)	39 (0)
Communication	58 (1)	204 (2)	204 (2)
Training	72 (1)	72 (1)	70 (1)
Stationary	88 (1)	22 (0)	24 (0)
Subtotal recurrent costs	**10,659**	**6,520**	**10,096**
Capital costs:			
Equipment	-	407 (4)	407 (3)
Data collection system and maintenance	-	2,236 (24)	2,422 (19)
Subtotal capital costs		2,463	2,829
Annuitized capital costs (3% discount rate)		**2,419**	**2,589**
Total costs per activity	**10,659**	**8,938**	**12,685**
Total costs per activity per index patient	**46**	**30**	**42**
INTERVENTON ARM	**Passive**	**Passive + Enhanced**	**Passive + Enhanced + Active**
Total cumulated costs per index patient per arm for household contacts evaluated for TB	**46**	**76**	**118**
Number of contacts diagnosed with TB	**21**	**123**	**176**

The passive + enhanced contact investigation of one index patient was 3.8 times more effective than passive contact investigation alone, increasing absolute case detection rate from 0.09 to 0.34. The incremental cost was USD 30 per index patient, which yielded an incremental cost of USD 120 per incremental patient identified with TB. While the passive + enhanced + active contact investigation of one index patient was 1.5 times more effective than enhanced contact investigation with an incremental cost of USD 238 per incremental TB patient identified as compared to the baseline passive approach (Table 3).

Table 3: Incremental cost-effectiveness of household contact screening for passive, enhanced and active contact investigation interventions from the TB program perspective.

Strategy	Cost per strategy (C)	Incremental Cost (IC)	Effect (E)	Incremental Effect (IE)	ICER
Passive contact investigation	46		0.09		
Passive + Enhanced contact investigation	76	30	0.34	0.25	120
Passive + Enhanced + Active contact investigation	118	42	0.52	0.18	238

The cost-effectiveness acceptability curves (CEACs) illustrate the probabilities that each intervention is cost-effective for a range of willingness to pay for health when taking the combined parameter uncertainty into account. The enhanced strategy becomes optimal if the willingness to pay exceeds USD 120 per additional patient with TB that is identified. If willingness to pay exceeds about 238 USD per TB case identified,[32] the active contact investigation has the highest probability of being cost-effective of the three alternatives (Figure 3).

One-way sensitivity analyses were conducted to explore the impact of uncertainties in single model parameters. These are represented in a tornado diagram in the decreasing order of the parameters' potential influence on the ICER (Figure 4). As the passive contact investigation is standard we plotted the tornado diagram for enhanced vs active contact investigation strategies. Cost and effect parameters were varied over a predetermined range (Table 1). The ICER was most sensitive to the probability of identifying a patient through active case finding, and ranged between some 150 and 600 USD per case detected when probabilities were varied between 0.62 and 0.41, respectively.

Discussion

The enhanced contact investigation strategy, in combination with the passive system, was 3.8 times more likely to identify patients with TB amongst household contacts than the passive contact investigation alone. The addition of household visits further improved case detection and may be necessary if we are to achieve the End TB strategy goals.[33] Unsurprisingly, both the enhanced and active strategies require more resources than the existing passive scheme, and the additional benefits must therefore be weighed against their additional costs, but increased performance and output requires more funding for impactful interventions.[34]

Studies and systematic reviews have documented that enhanced or active household contact investigation has been able to find more people with TB compared to passive case finding.[24,25,35,]22 These studies further conclude that improved case detection is cost-effective compared to the passive approach. Contact investigation can be conducted in a myriad of ways and using different algorithms and approaches.[17] Many programs opt for a more passive approach due to the ease of implementation and lower costs. However, there have been no studies we could identify that have compared different modalities of contact investigation to each other. The current WHO guidelines identify that comparisons of different types of contact investigation is a current knowledge gap and our findings aid this void and should be followed by additional studies with costing analyses.

In low-burden countries, contact investigation is a requirement for a TB program to be effective.[36] According to the US Centers for Disease Control and Prevention, it played an essential role in decreasing TB incidence by 44% in the USA.[37] A meta-analysis suggests that TB contact investigation should be considered to improve early TB case detection and decrease transmission in high-incidence areas as well.[13] However, in low- and middle-income countries, contact investigation has been viewed as expensive and, therefore, a low-priority. Programs do not undertake TB contact investigation as they have limited human resources. This project added health workers to support phone calls, counselling, and home visits, which led to an increase in costs. However, these are necessary costs if we are to reach all people with TB. With contact investigation, people with TB are diagnosed early and initiated on treatment, which benefits the broader community by reducing continuing transmission.[38] These benefits of future TB cases prevented over time are not captured by the current analytical model, and in this regard our results can be considered to be conservative. If contact investigation interventions result in earlier detection of household contacts with active TB, this program would reduce the spread of TB in the community even more effectively and be even more cost-effectively.

Our study is subject to limitations. We initiated the enhanced intervention if the family did not come to the clinic for evaluation within one week of a TB patient diagnosed and initiated on treatment. The passive system, if given more time than one week may potentially have had a larger yield. However, the historical data shows that the number of people identified by the passive system during the implementation phase was similar to what we estimated in the baseline survey. Secondly, we only consider people with TB detected and did not consider outcomes of subsequent treatment in this analytical model. But in the larger project, in which this study was embedded, 98% of children diagnosed with TB were started on treatment and had over 94% treatment success rate.[26, 39] Thirdly, out-of-pocket expenditures for patients was not considered. Costs such as transportation to the health facilities for evaluation, cost of diagnostic tests and loss of work time may be potential barriers for the majority of the TB affected families coming to the health facilities for evaluation. Arrangements for transportation of contacts to health facilities for diagnostic tests and transportation of sputum specimens for examination should be included in the national policy to increase the detection of TB patients. Future research may consider to conduct similar costing studies in the urban areas as the cost may be different than the rural setting in which our study was based and to integrate data on the overall economic burden to households that can be averted with an active TB contact investigation program. Lastly, the study was conducted at only one center, and other health facilities with different levels of pre-existing capacity and infrastructure may yield different cost-estimates.

An important strength of the study is that it was performed alongside implementation in district tuberculosis clinics in a high-prevalence setting. Data were therefore collected prospectively in a programmatic setting. A robust monitoring and evaluation system was put in place, and the

District TB Control officers verified all notifications as would have been done in routine scale up.

Conclusion

Our results show that active approaches to contact investigation identify more people with TB amongst household contacts at a relatively modest cost addressing an identified global knowledge gap. These strategies can be added to passive contact investigation approaches in a high burden setting to find the missing TB patients and meet the End TB strategy goals.

Figure 1: Household contacts evaluated and diagnosed for TB by passive, enhanced and active contact investigation interventions.

Figure 2: Decision tree for household contacts evaluated for TB by passive, enhanced and active contact investigation interventions.

Figure 3: Cost-effectiveness acceptability curves for passive, enhanced and active contact investigation interventions for a range of willingness to pay per household screened.

Figure 4: One-way sensitivity analyses for the ICERs of enhanced contact investigation compared to active contact investigation.

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Figure 1: Household contacts evaluated and diagnosed for TB by passive, enhanced and active contact investigation interventions.

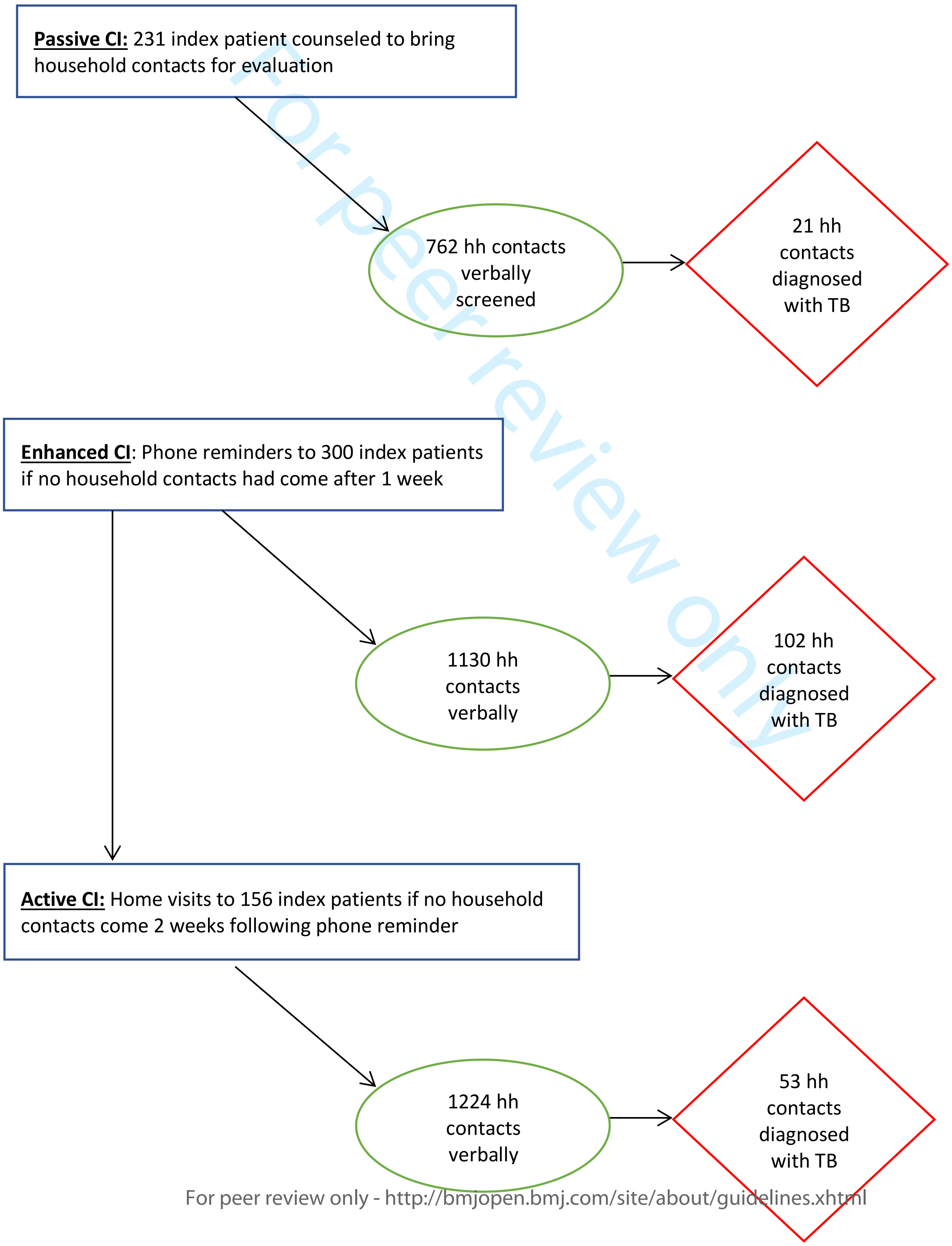


Figure 2: Decision tree for household contacts evaluated for TB by passive, enhanced and active contact investigation interventions.

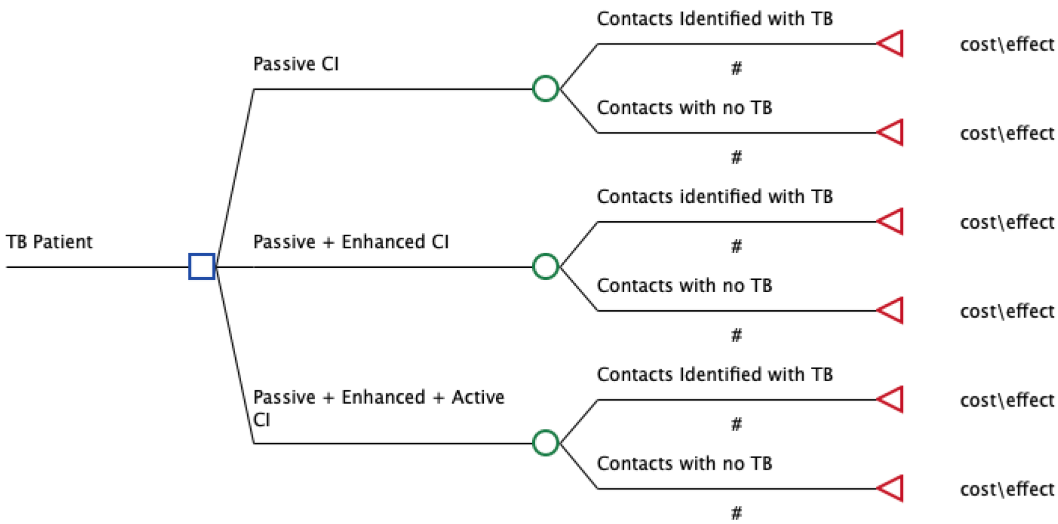


Figure 3: Cost-effectiveness acceptability curves for passive, enhanced and active contact investigation interventions for a range of willingness to pay per household screened.

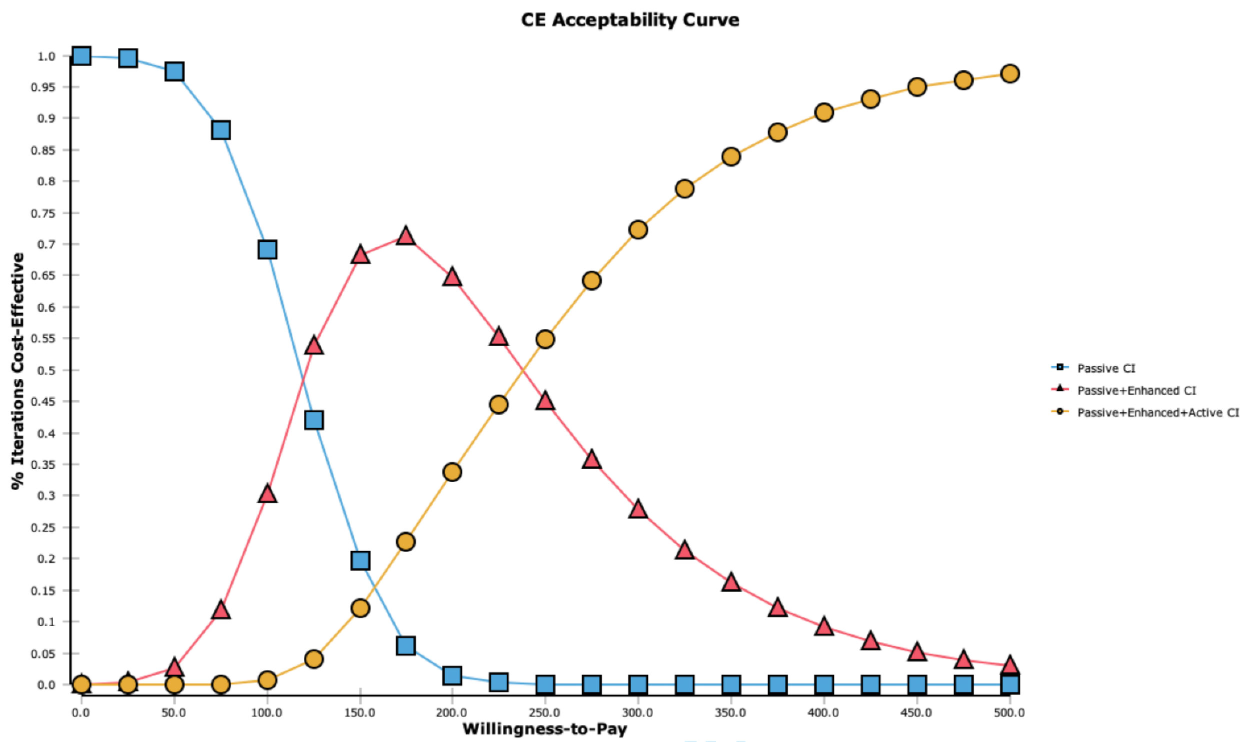
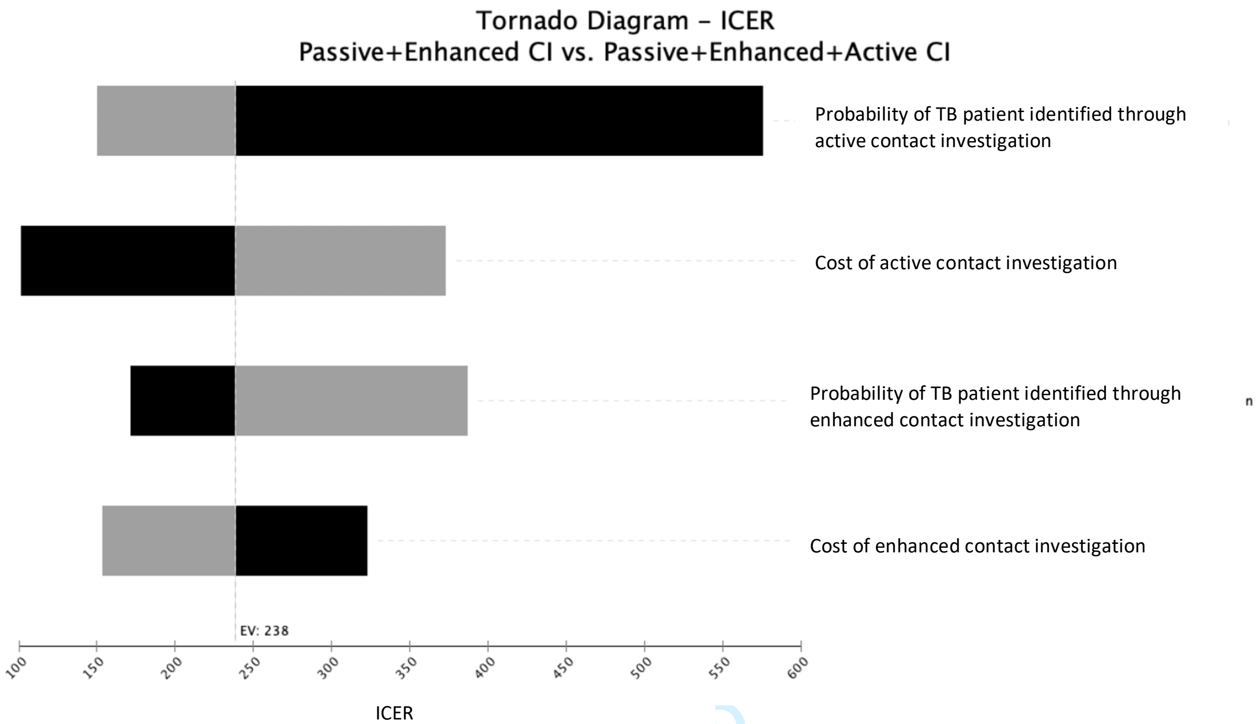


Figure 4: One-way sensitivity analyses for the ICERs of enhanced contact investigation compared to active contact investigation.*



*The black bar denoted the lower part of the parameter range and the red bar shows the higher part of the parameter range. If red bar is on the grey of the expected value (EV) it means that the ICER will increase when the parameter value increase. When the red bar is on the left then the ICER will decrease with the increase in parameter value.

Reporting checklist for economic evaluation of health interventions.

Based on the CHEERS guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title			
	#1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1
Abstract			
	#2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions	Page 2 and 3
Introduction			
Background and objectives	#3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions	Pages 5-7
Methods			

Target population and subgroups	#4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 7
Setting and location	#5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 7
Study perspective	#6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 9
Comparators	#7	Describe the interventions or strategies being compared and state why they were chosen.	Page 8 and 9
Time horizon	#8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 8 and 9
Discount rate	#9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate	Page 11
Choice of health outcomes	#10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed	Page 11 and 12
Meaurement of effectiveness	#11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data	Page 11
Measurement of effectiveness	#11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data	
Measurement and valuation of preference based outcomes	#12	If applicable, describe the population and methods used to elicit preferences for outcomes.	
**Estimating resources and costs **			
	#13a	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	

Methods

Estimating resources and costs	#13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Pages 9, 10 and 11
Currency, price date, and conversion	#14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 11
Choice of model	#15	Describe and give reasons for the specific type of decision analytical model used. Providing a figure to show model structure is strongly recommended.	Page 12
Assumptions	#16	Describe all structural or other assumptions underpinning the decision-analytical model.	Page 11
Analytical methods	#17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Page 12
Results			
Study parameters	#18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Page 13
Incremental costs and outcomes	#19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Page 15, 16
Characterising uncertainty	#20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	Page 16, 17

		of methodological assumptions (such as discount rate, study perspective).	
Characterising uncertainty	#20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Page 17
Characterising heterogeneity	#21	If applicable, report differences in costs, outcomes, or cost effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	
Discussion			
Study findings, limitations, generalisability, and current knowledge	#22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Page 17, 18, 19
Other			
Source of funding	#23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support	Page 22
Conflict of interest	#24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations	Page 22

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Cost-effectiveness of household contact investigation for detection of tuberculosis in Pakistan

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Cost-effectiveness of household contact investigation for detection of tuberculosis in Pakistan

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Abstract

Objectives

Despite WHO guidelines recommending household contact investigation, and studies showing the impact of active screening, most TB programs in resource-limited settings only carry out passive contact investigation. The cost of such strategies are often cited as barriers to their implementation. However, little data is available for the additional costs required to implement this strategy. We aimed to estimate the cost and cost-effectiveness of active contact investigation as compared to passive contact investigation in urban Pakistan

Methods:

We estimated the cost-effectiveness of 'enhanced' (passive with follow-up) and 'active' (household visit) contact investigations compared to standard 'passive' contact investigation from providers and the program's perspective using a simple decision tree. Costs were collected in Pakistan from a TB clinic performing passive contact investigation and from studies of active contact tracing interventions conducted. The effectiveness was based on the number of TB patients identified among household contacts screened.

Results

The addition of enhanced contact investigation to the existing passive mode detected 3.7 times more cases of TB per index patient compared to passive contact investigation alone. The

incremental cost was USD 30 per index patient, which yielded an incremental cost of USD 120 per incremental patient identified with TB. The active contact investigation was 1.5 times more effective than enhanced contact investigation with an incremental cost of USD 238 per incremental TB patient identified.

Conclusion

Our results show that enhanced and active approaches to contact investigation effectively identify additional patients with TB amongst household contacts at a relatively modest cost. These strategies can be added to the passive contact investigation in a high burden setting to find the people with TB who are missed and meet the End TB strategy goals.

Strengths and limitations of this study:

- The study was conducted in programmatic conditions in a high-prevalence setting.
- The study compares cost effectiveness of three contact investigation approaches from health system perspective in a sequential approach.
- The data for the passive approach comes from previous years and we were unable to account for any time trend.
- The study did not consider out-of-pocket expenditures for patients which underestimates the overall costs.

Background

Tuberculosis (TB) remains a leading cause of morbidity and mortality, especially in low- and middle-income countries. According to the latest estimates, 10 million people fell ill with TB in 2019, though only 7.1 million were reported to national programmes. Eight countries account for two-thirds of the reported TB burden in the world: India (26%), Indonesia (8.5%), China (8.4%), the Philippines (6%), Pakistan (5.7%), Nigeria (4.4%), Bangladesh (3.6%) and South Africa (3.6%).[1,2,3] Reasons for the gap between estimated and notified individuals with TB include limited access to health care, poor diagnosis capacity for people who do access care, as well as underreporting of people diagnosed.[4,5,6]

Undiagnosed people with TB continue to transmit TB to others. The risk of transmission is particularly high amongst members of households living with people with undiagnosed pulmonary TB. Studies have documented an infection rate of 30-50% amongst household contacts of infectious adults, with the infection rate in children under 5 being as high as 72%.[7,8] Of those infected with TB, 10-20% develop the disease over their lifetimes, and this number is even higher for people who are immunocompromised, for example when they are co-infected with HIV.[9,10,11,12]

Household contact investigation is recommended as a means to address these challenges.[13,14] In the light of the high infection rates, household contact investigation is a critical activity for TB programs for two reasons. First, it allows early identification of additional household members who have TB disease and require immediate treatment, stopping transmission. Second, it allows programs to identify people who can benefit from the treatment of TB infection (TBI) to prevent disease progression, importantly children and people living with HIV. A meta-analysis of contact investigation showed that 3.1% of contacts in low-resource settings and 1.4% of contacts in high-resource settings have TB disease, making this a potential high yield strategy to find people with TB.[15,16] A large proportion of childhood TB can be identified through contact investigation, which is of particular value since global rates of detection among children are much lower than for adults.[1]

Household contact investigation can be carried out in many different ways along a continuum of passive and active approaches.[17] In passive contact tracing, the index patient is asked to bring in their family members for screening to the facility, while in active contact tracing, health care workers visit the index patient's home. Between the active and passive modes, lies the "enhanced" form of contact tracing, in which health workers make reminder phone calls and follow up with the family and encourages them to come to the facility for screening can also be delivered.

Despite WHO guidelines recommending household contact investigation[18,19] and studies documenting the outcomes of active approaches the most TB programs in resource-limited settings only carry out passive contact investigation and even then, implementation is limited.[20,21] A cluster-randomized controlled trial demonstrated that contact investigation plus passive case finding (PCF) was beneficial compared to passive case finding alone.[22] The cost of active contact investigation, including additional efforts required by already stretched health care providers, has often been cited as a barrier to its implementation.[23] However, little data is available for the additional cost of implementing active contact investigation, and especially so when implemented under routine program conditions. A study from Malaysia reported the cost of active contact investigation to be USD 6.60 per a single contact tracing visit with a yield of 0.5%.[24] In Peru, adding active contact tracing to PCF incurred an incremental cost of USD 48.8 to evaluate household contacts of an index TB patient, with an incremental cost-effectiveness ratio (ICER) of USD 1811 per DALY averted.[25] We were not able to identify studies reporting costs or cost-effectiveness for the enhanced mode of contact tracing.

The objective of this study was to estimate the cost and cost-effectiveness of the enhanced and active contact tracing interventions in a high-burden programmatic setting, compared to the existing passive approach.

Methods

SETTING

The costing study was a subset of a larger study where an active case finding intervention was implemented for children with TB. The study was conducted at four TB treatment and reporting centres in Kotri, a rural town in Sindh, Pakistan. All children presenting to these facilities were verbally screened for symptoms of TB and those considered to be at high risk of having TB were further investigated. Children diagnosed with TB were started on treatment, and we conducted contact investigation for their household contacts.[26] The household contact investigation reported here was carried out at one of the four centers (Institute of Chest Disease Hospital) from April 2015 to March 2016.

INTERVENTIONS

For the study, the index patient was the first person identified with TB in the family, while household contacts were defined as people living in the same household as the index patient. As part of the routine program passive contact investigation is conducted where, index patients are counselled to bring their household contacts for evaluation. Contacts who respond are evaluated for TB symptoms and risk factors. A limitation of this approach is that household contacts screened were recorded only as a TB contact and not linked directly to the index TB patient in a specific household. There is no routine follow-up to see if the specific contacts attended the facility for screening or not.

As part of the intervention we instituted enhanced contact investigation as an additional step which included follow-up with the families for contact investigation. Adults and guardians of children under 15 years of age newly diagnosed with TB were asked about the presence of TB symptoms or household members on TB treatment in their families. They were counselled to bring their enumerated household contacts for evaluation, as in the passive approach. If the enumerated household contacts did not come to the facility for assessment after one week, a reminder phone call was made, followed by second phone call after another week. If the family still had not come two weeks after the second phone reminder, active contact investigation was implemented. Active contact investigation included health workers conducting a household visit to verbally screen the family at home and to counsel the family to go to the clinic for further evaluation (Figure 1).

At the clinic, enumerated household contacts were screened by existing TB doctors in the passive system or by trained health workers for enhanced and active contact investigation. All contacts were verbally screened for symptoms of TB such as cough of more than two weeks, contact with someone other than the index patient who had TB, glandular swelling, fever lasting more than two weeks, night sweats and inappropriate weight loss. Individuals with suggestive symptoms or additional exposure were referred to the project's medical officer for further evaluation. They then received a chest x-ray and were asked to provide a sputum sample for smear microscopy. A complete blood count (CBC) and erythrocyte sedimentation rate (ESR) was done for child contacts to aid in diagnosis as indicated. Contacts diagnosed with TB were started on TB treatment in line with the National TB Program (NTP) guidelines. Children under five years of age in whom TB disease was ruled out were offered isoniazid preventive therapy (IPT) as per NTP guidelines.[26] All clinical evaluations and investigations were provided without any charge to the contacts.

DATA COLLECTION

For the passive approach, health facility staff recorded data using a paper-based system which were then abstracted for the study. For enhanced and active contact interventions project based trained community health workers and doctors administered questions to assess TB symptoms/risks and documented results of clinical evaluation and diagnostic tests using a custom-built smart-phone based data collection application with built-in decision support developed for the project.[26]26

COST PARAMETERS

Costs for this systematic contact tracing activities were collected from the perspective of the operational program and the health facility and included recurrent and capital cost items. As capital costs for the building were not available, we approximated rent and utilities of running a similar structure, and we used these in place of the capital costs.

We identified cost items and quantified resource use for all activities related to contact investigation. They included personnel, diagnostic test, supervision and monitoring by facility or project staff and communications. For the passive system, cost information was obtained from the health facility accounting system. We identified one physician and one health worker who were involved in the existing passive system at the TB clinic. We estimated their time spent on evaluation of household contacts through expert opinion and allocated salaries proportionate to this time as compared to other activities. Unit costs for TB diagnostic tests, chest x-rays, and smear microscopy were as billed to the project by the health facility. Costs for diagnostic tests were estimated by multiplying their unit costs with the number of people tested. As communications, supervision and training costs for the existing passive program were not available through the facility records, we assumed the same costs as incurred by the enhanced contact investigation intervention. At the TB clinic, data was collected on paper-based systems and the costs for registers and forms are reported with stationary.

For the additional costs of performing enhanced and active contact investigations, data were extracted from the project accounting system. One full-time health worker was recruited for enhanced intervention while the active contact investigation required three additional health workers. A fixed amount of travel costs for home visits was built into the salary for health workers. For all other personnel such as physician, field supervisor and program coordinators, time spent on the contact investigation intervention was estimated using an activity-based costing (ABC) methodology, and costs were allocated according to the proportion of time spent on the intervention relative to other activities.[27,28] Cost of diagnostic investigations per person screened (chest x-ray, smear microscopy and complete blood), communications (data and phone), training and stationery were as incurred. The cost for the development of electronic data capture was allocated based on the number of patients screened in each intervention, while the cost of phones and laptops used to capture data were allocated as per the personnel time that used them. We annuitized these capital costs over a period of three years using a 3% discount rate.[29,30] Costs were collected in Pakistan Rupees and converted to US dollars using the average exchange rate for the years 2015 and 2016 (1 USD =103.1 PKR).

EFFECTIVENESS OF CONTACT INVESTIGATION

The effectiveness of the contact investigation procedure was evaluated based on the number of people with TB identified per household screened after verbal screening and diagnostic tests. Our study was divided into baseline and intervention periods. Historical data for passive contact investigation was used as the comparator. In the year preceding the intervention, the passive approach screened 762 contacts from a total of 231 index patient households to identify 21 people with TB during this baseline period (Figure 1). During the intervention period, enhanced and active contact investigation were implemented, and contacts from 300 households were evaluated. Of these, 1130 people from 144 families came to the health facility after phone reminders (enhanced) and 102 were diagnosed with TB. When home visits were conducted for 156 households that failed to respond to the enhanced strategy (active), we evaluated 1224 people and identified 53 additional people with TB disease (Figure 1).

DECISION MODEL AND ANALYSIS

A simple decision tree was created in TreeAge Pro 2020 (TreeAge Pro Inc., Williamston, MA) to estimate the cost-effectiveness of enhanced and active contact investigation compared to passive contact investigation. The decision tree includes the three alternatives for contact investigation; (i) Passive, (ii) Passive + Enhanced and (iii) Passive + Enhanced +Active (Figure 2). The three intervention alternatives represent different levels of intensity of contact investigation and are considered to be mutually exclusive. The more intense alternatives are more expensive than the less intensive ones, but also represent new possibilities for identifying contacts with TB (Table 1). The results are presented as absolute and incremental costs and TB patients identified, and incremental cost-effectiveness ratios (ICERs) between the alternatives.

We conducted probabilistic sensitivity analyses (PSA) using Monte Carlo simulations with 10,000 iterations to explore the effects of combined uncertainties in key parameters. Gamma distributions were used for cost parameters, and beta distributions for the probability of TB patients per family screened.[31] For sensitivity analyses, upper and lower values were defined for each parameter as mean values ±20%.

Ethical approval was obtained from the Institutional Review Board (IRB) of Interactive Research and Development (IRD), OHRP Registration No. 00005148.

Table 1: Modeling inputs, assumptions and ranges for passive, enhanced and active contact investigation (CI).

Interventions	Total cost (USD)	Index patient with TB	Total contacts diagnosed with TB (Lower and Upper limit)	Cost per index TB patient family screened (USD)	Probability of finding a TB patient per household screened (Lower and Upper limit)
Passive CI	10,659	231	21 (17– 25)	46 (37-55)	0.09 (0.07 – 0.10)
Passive + Enhanced CI	19,597	300	102 (82 – 122)	76 (61 – 91)	0.34 (0.27 – 0.40)
Passive + Enhanced + Active CI	32,282	300	155 (124 – 186)	118 (94 – 142)	0.52 (0.41 – 0.62)

Results

In the enhanced and active contact tracing, 2,354 household contacts from 300 index patients were screened, of whom 49% were children less than 15 years of age, and 45% were female. The mean age for child contacts was 6.4 years (SD 3.7, IQR: 3-9), and 54% were males and the mean age for adult contacts was 33 years (SD 13.4, IQR: 21-41) and 53% were males. The enhanced contact investigation intervention was able to find 2.45 times (95% CI: 1.52 – 4.14) more people with TB than the passive program when it was implemented. While the active intervention implemented three weeks following the index patient counselling identified 2.11 times (95% CI: 1.33 – 3.52) more people with TB compared to passive contact investigation.

Overall, the passive program incurred USD 10,659 over one year and it cost USD 46 per household screened with TB. The enhanced contact investigation incurred an additional USD 30 to screen a household with an overall addition of USD 8,938 to the yearly program cost. Of the additional costs, human resources (42%) and electronic data collection (24%) were the most significant cost drivers. Active contact investigation incurred an additional USD 42 per household screened for TB above the enhanced model, and the program cost a further USD 12,685 to the enhanced contact investigation of which human resources (57%) and electronic data capture (18%) were the largest components. (Table 2)

Table 2: Cost (USD) of household contact screening for passive, enhanced and active contact investigation activities (upper panel), and cumulative costs per intervention arm (lower panel).

INTERVENTION ACTIVITIES **Cost categories**	**Passive contact investigation N=231 (%)**	**Enhanced contact investigation N=300 (%)**	**Active contact investigation N=300 (%)**
Recurrent costs:			
Clinic rental and maintenance	3,492 (33)	-	-
Personnel	5,354 (50)	3,835 (42)	7,348 (57)
Diagnostic tests	1,478 (14)	2,192 (24)	2,374 (18)
Supervision and monitoring	116 (1)	195 (2)	39 (0)
Communication	58 (1)	204 (2)	204 (2)
Training	72 (1)	72 (1)	70 (1)
Stationary	88 (1)	22 (0)	24 (0)
Subtotal recurrent costs	**10,659**	**6,520**	**10,096**
Capital costs:			
Equipment	-	407 (4)	407 (3)
Data collection system and maintenance	-	2,236 (24)	2,422 (19)
Subtotal capital costs		2,463	2,829
Annuitized capital costs (3% discount rate)		**2,419**	**2,589**
Total costs per activity	**10,659**	**8,938**	**12,685**
Total costs per activity per index patient	**46**	**30**	**42**
INTERVENTON ARM	**Passive**	**Passive + Enhanced**	**Passive + Enhanced + Active**
Total cumulated costs per index patient per arm for household contacts evaluated for TB	**46**	**76**	**118**
Number of contacts diagnosed with TB	**21**	**123**	**176**

The passive + enhanced contact investigation of one index patient was 3.8 times more effective than passive contact investigation alone, increasing absolute case detection rate from 0.09 to 0.34. The incremental cost was USD 30 per index patient, which yielded an incremental cost of USD 120 per incremental patient identified with TB. While the passive + enhanced + active contact investigation of one index patient was 1.5 times more effective than enhanced contact investigation with an incremental cost of USD 238 per incremental TB patient identified as compared to the baseline passive approach (Table 3).

Table 3: Incremental cost-effectiveness of household contact screening for passive, enhanced and active contact investigation interventions from the TB program perspective.

Strategy	Cost per strategy (C)	Incremental Cost (IC)	Effect (E)	Incremental Effect (IE)	ICER
Passive contact investigation	46		0.09		
Passive + Enhanced contact investigation	76	30	0.34	0.25	120
Passive + Enhanced + Active contact investigation	118	42	0.52	0.18	238

The cost-effectiveness acceptability curves (CEACs) illustrate the probabilities that each intervention is cost-effective for a range of willingness to pay for health when taking the combined parameter uncertainty into account. The enhanced strategy becomes optimal if the willingness to pay exceeds USD 120 per additional patient with TB that is identified. If willingness to pay exceeds about 238 USD per TB case identified,[32] the active contact investigation has the highest probability of being cost-effective of the three alternatives (Figure 3).

One-way sensitivity analyses were conducted to explore the impact of uncertainties in single model parameters. These are represented in a tornado diagram in the decreasing order of the parameters' potential influence on the ICER (Figure 4). As the passive contact investigation is standard we plotted the tornado diagram for enhanced vs active contact investigation strategies. Cost and effect parameters were varied over a predetermined range (Table 1). The ICER was most sensitive to the probability of identifying a patient through active case finding, and ranged between some 150 and 600 USD per case detected when probabilities were varied between 0.62 and 0.41, respectively.

Discussion

The enhanced contact investigation strategy, in combination with the passive system, was 3.8 times more likely to identify patients with TB amongst household contacts than the passive contact investigation alone. The addition of household visits further improved case detection and may be necessary if we are to achieve the End TB strategy goals.[33] Unsurprisingly, both the enhanced and active strategies require more resources than the existing passive scheme, and the additional benefits must therefore be weighed against their additional costs, but increased performance and output requires more funding for impactful interventions.[34]

Studies and systematic reviews have documented that enhanced or active household contact investigation has been able to find more people with TB compared to passive case finding.[24,25,35,]22 These studies further conclude that improved case detection is cost-effective compared to the passive approach. Contact investigation can be conducted in a myriad of ways and using different algorithms and approaches.[17] Many programs opt for a more passive approach due to the ease of implementation and lower costs. However, there have been no studies we could identify that have compared different modalities of contact investigation to each other. The WHO guidelines identify that comparisons of different types of contact investigation is a current knowledge gap and our findings aid this void and should be followed by additional studies with costing analyses.

In low-burden countries, contact investigation is a requirement for a TB program to be effective.[36] According to the US Centers for Disease Control and Prevention, it played an essential role in decreasing TB incidence by 44% in the USA.[37] A meta-analysis suggests that TB contact investigation should be considered to improve early TB case detection and decrease transmission in high-incidence areas as well.[13] However, in low- and middle-income countries, contact investigation has been viewed as expensive and, therefore, a low-priority. Programs do not undertake TB contact investigation as they have limited human resources. This project added health workers to support phone calls, counselling, and home visits, which led to an increase in costs. However, these are necessary costs if we are to reach all people with TB. With contact investigation, people with TB are diagnosed early and initiated on treatment, which benefits the broader community by reducing continuing transmission.[38] These benefits of future TB cases prevented over time are not captured by the current analytical model, and in this regard our results can be considered to be conservative. If contact investigation interventions result in earlier detection of household contacts with active TB, this program would reduce the spread of TB in the community even more effectively and be even more cost-effectively.

Our study is subject to limitations. We initiated the enhanced intervention if the family did not come to the clinic for evaluation within one week of a TB patient diagnosed and initiated on treatment. The passive system, if given more time than one week may potentially have had a larger yield. However, the historical data shows that the number of people identified by the passive system during the implementation phase was similar to what we estimated in the baseline survey. Secondly, we only consider people with TB detected and did not consider outcomes of subsequent treatment in this analytical model. But in the larger project, in which this study was embedded, 98% of children diagnosed with TB were started on treatment and had over 94% treatment success rate.[26, 39] Thirdly, out-of-pocket expenditures for patients was not considered. Costs such as transportation to the health facilities for evaluation, cost of diagnostic tests and loss of work time may be potential barriers for the majority of the TB affected families coming to the health facilities for evaluation. Arrangements for transportation of contacts to health facilities for diagnostic tests and transportation of sputum specimens for examination should be included in the national policy to increase the detection of TB patients. Lastly, the household with child TB is likely to have transmission with in the household making contact investigation efficient and cost-effective in these contacts, but it may not be generalizable in household with an adult TB patients. Future research may consider to conduct similar costing studies in the urban areas as the cost may be different than the rural setting in which our study was based and to integrate data on the overall economic burden to households that can be averted with an active TB contact investigation program. In addition, the study was conducted at only one center, and other health facilities with different levels of pre-existing capacity and infrastructure may yield different cost-estimates.

An important strength of the study is that it was performed alongside implementation in district tuberculosis clinics in a high-prevalence setting. Data were therefore collected prospectively in a programmatic setting. A robust monitoring and evaluation system was put in place, and the District TB Control officers verified all notifications as would have been done in routine scale up.

Conclusion

Our results show that active approaches to contact investigation identify more people with TB amongst household contacts at a relatively modest cost addressing an identified global knowledge gap. These strategies can be added to passive contact investigation approaches in a high burden setting to find the missing TB patients and meet the End TB strategy goals.

Figure 1: Household contacts evaluated and diagnosed for TB by passive, enhanced and active contact investigation interventions.

Figure 2: Decision tree for household contacts evaluated for TB by passive, enhanced and active contact investigation interventions.

Figure 3: Cost-effectiveness acceptability curves for passive, enhanced and active contact investigation interventions for a range of willingness to pay per household screened.

Figure 4: One-way sensitivity analyses for the ICERs of enhanced contact investigation compared to active contact investigation.

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Patient consent for publication: Not required.

Ethics approval: This study was approved by the Institutional Review Board (IRB) of Interactive Research and Development (IRD), OHRP Registration No. 00005148.

Data sharing statement: No data are available. Costing data were collected by the research team which are confidential**.**

Patient and public involvement statement: No patient involved

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Figure 1: **Household contacts evaluated and diagnosed for TB by passive, enhanced and active contact investigation interventions.**

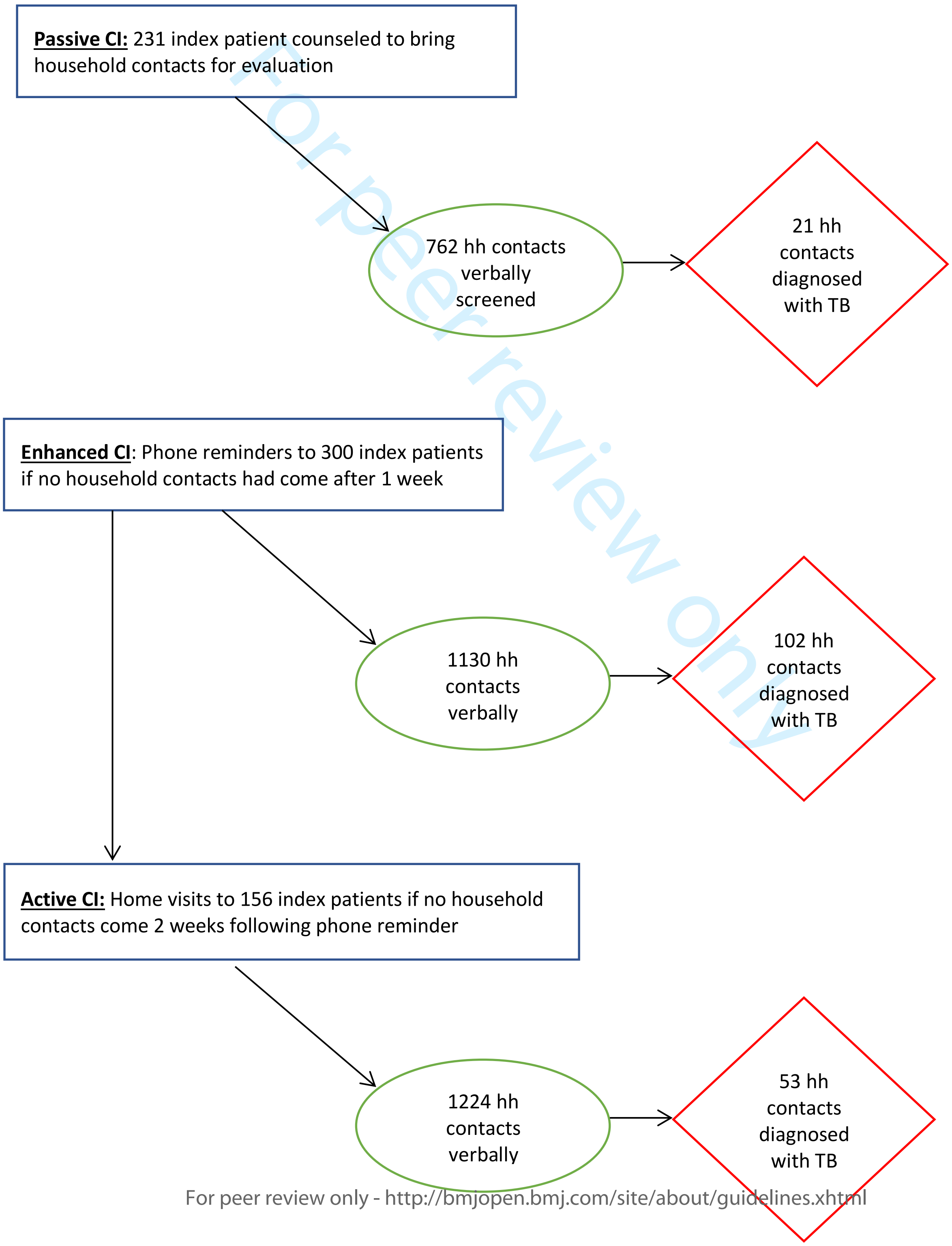


Figure 2: Decision tree for household contacts evaluated for TB by passive, enhanced and active contact investigation interventions.

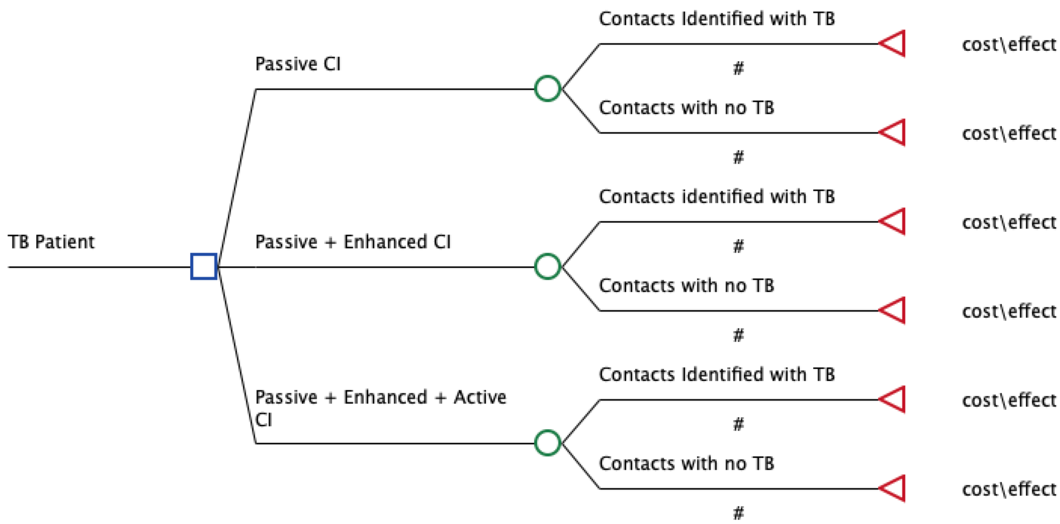


Figure 3: Cost-effectiveness acceptability curves for passive, enhanced and active contact investigation interventions for a range of willingness to pay per household screened.

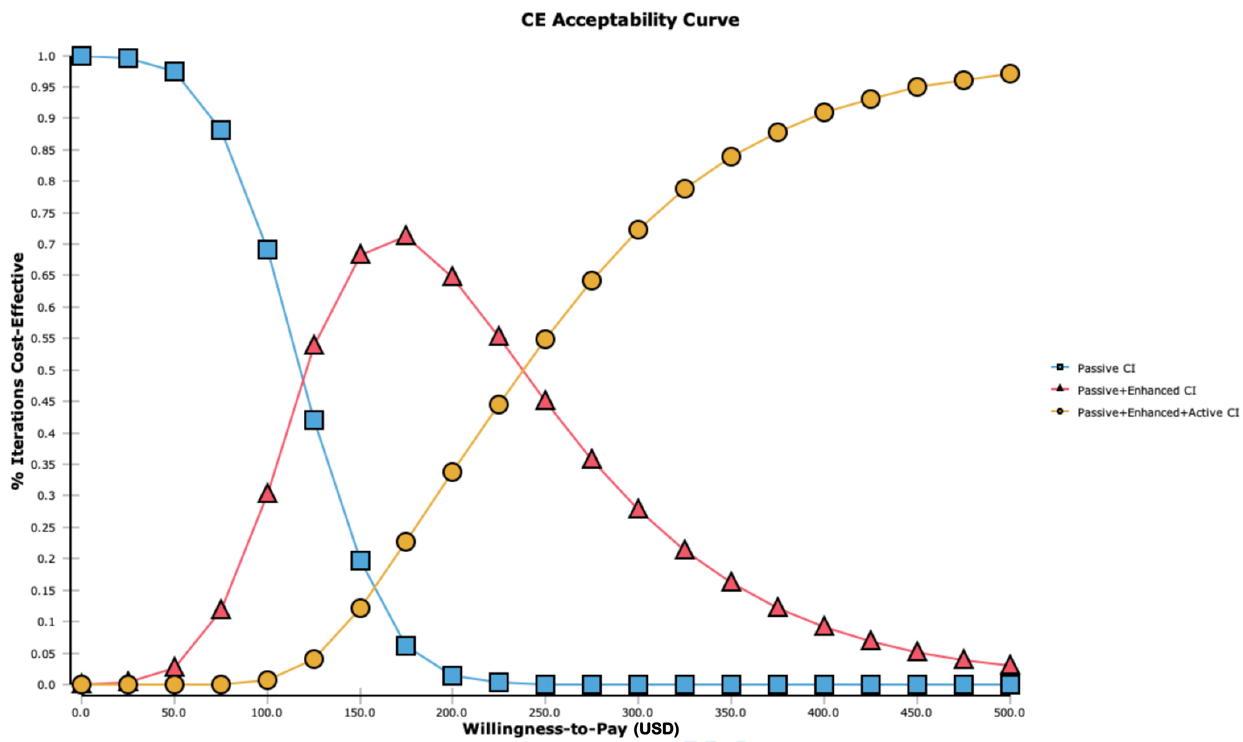
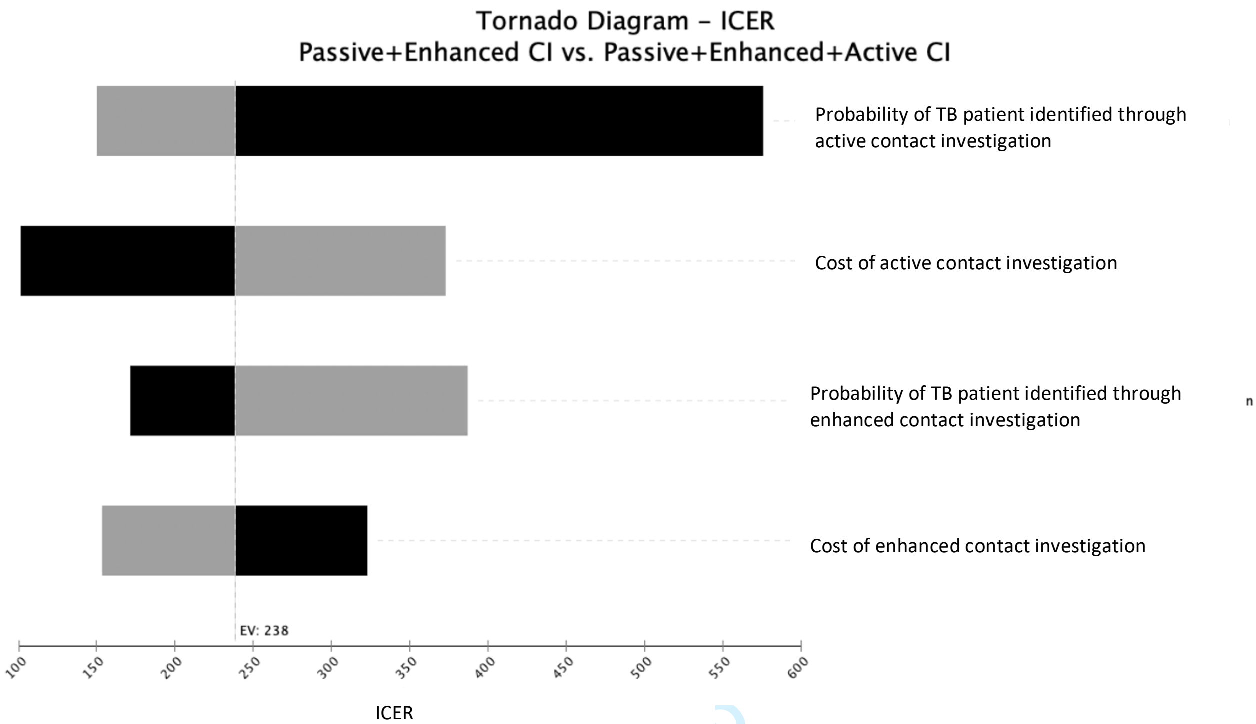


Figure 4: One-way sensitivity analyses for the ICERs of enhanced contact investigation compared to active contact investigation.*



*The black bar denoted the lower part of the parameter range and the red bar shows the higher part of the parameter range. If red bar is on the grey of the expected value (EV) it means that the ICER will increase when the parameter value increase. When the red bar is on the left then the ICER will decrease with the increase in parameter value.

Reporting checklist for economic evaluation of health interventions.

Based on the CHEERS guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title			
	#1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1
Abstract			
	#2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions	Page 2 and 3
Introduction			
Background and objectives	#3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions	Pages 5-7
Methods			

Target population and subgroups	#4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 7
Setting and location	#5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 7
Study perspective	#6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 9
Comparators	#7	Describe the interventions or strategies being compared and state why they were chosen.	Page 8 and 9
Time horizon	#8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 8 and 9
Discount rate	#9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate	Page 11
Choice of health outcomes	#10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed	Page 11 and 12
Meaurement of effectiveness	#11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data	Page 11
Measurement of effectiveness	#11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data	
Measurement and valuation of preference based outcomes	#12	If applicable, describe the population and methods used to elicit preferences for outcomes.	
**Estimating resources and costs **			
	#13a	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	

Methods

Estimating resources and costs	#13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Pages 9, 10 and 11
Currency, price date, and conversion	#14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 11
Choice of model	#15	Describe and give reasons for the specific type of decision analytical model used. Providing a figure to show model structure is strongly recommended.	Page 12
Assumptions	#16	Describe all structural or other assumptions underpinning the decision-analytical model.	Page 11
Analytical methods	#17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Page 12
Results			
Study parameters	#18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Page 13
Incremental costs and outcomes	#19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Page 15, 16
Characterising uncertainty	#20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	Page 16, 17

		of methodological assumptions (such as discount rate, study perspective).	
Characterising uncertainty	#20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Page 17
Characterising heterogeneity	#21	If applicable, report differences in costs, outcomes, or cost effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	
Discussion			
Study findings, limitations, generalisability, and current knowledge	#22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Page 17, 18, 19
Other			
Source of funding	#23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support	Page 22
Conflict of interest	#24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations	Page 22

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