

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Cost-effectiveness of household contact investigation for detection of tuberculosis in Pakistan
AUTHORS	Hussain, Hamidah; Malik, Aryn; Ahmed, Junaid; Siddiqui, Sara; Amanullah, Farhana; Creswell, Jacob; Tylleskär, Thorkild; Robberstad, Bjarne

VERSION 1 – REVIEW

REVIEWER	Shrestha, Sourya JHU
REVIEW RETURNED	18-Jun-2021

GENERAL COMMENTS	<p>bmjopen-2021-049658</p> <p>Overall, a really important and generally well described study. Implementing contact investigation in high-burden low-resource settings are arguably the most critical and urgent interventions that we need to prioritize to combat TB. Finding and demonstrating impactful and cost-effective ways to improve TB case-finding, as this study does, goes a long way towards this. I have a few suggestions below for authors' consideration.</p> <p>Major comments</p> <p>1. I think the authors should make it clear upfront that this study was based on HH-contacts of child TB. Interventions based on contacts of child TB may not be generalizable to all HH contact investigation. On the one hand, HH with child TB are more likely to have transmission in the household, hence CI are more likely to find TB cases (and be more effective and cost-effective). On the other hand, pediatric TB is harder to diagnose, and generally constitute a smaller burden of overall TB. It may harder to scale up or have as large an impact. I think authors should discuss this specific medium of HH CI: both that HH CI based on child TB may be highly efficient (which is really great to have demonstrated), and that including followup to enhance the CI or including house visits maybe highly cost-effectiveness in these contacts, but may not be generalizable for all HH CI (which could be an important limitation).</p> <p>2. I think there is some confusion as to how passive and enhanced and active CIs are defined from a study design standpoint. In</p>
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particular, I was confused whether passive CI and the others were done in the same year (hence, enhance would only follow if passive resulted in no response), or in separate years. Making this clearer and consistent throughout the paper would add to the readability of the paper. Additionally, I am also curious about the HHs that could be captured via passive versus those that required enhance or active CI. If there are socio-demographic data describing these HHs, it would add a lot to understanding the need of improving CI. The fact that this study was conducted in a high-burden, low resource setting, where these types of interventions are most needed, makes this study really important, and data from actual implementation in this setting are incredibly valuable!

3. The authors have made cases detected their primary outcome, which is perfectly understandable. However, the goals of CI are not just finding cases, but preventing transmission and future cases. In this regard, I would like the authors to perhaps discuss the potential impact of enhanced and active CI in the context of preventing transmission -- in fact one could argue that there could be even larger impact if, for example preventive therapy was included, or if benefits of downstream transmission were included.

Minor comments/edits

Abstract:

1. Define "active", "enhanced", and "passive" contact investigation.

Introduction:

2. pg 6, line 54: suggest "..who have TB disease and require immediate treatment, thereby stopping further transmission"

3. pg 7, line 22: suggest ".. along a continuum of passive and active "

4. pg 7, line 27: Using the term "enhanced" to describe a moderate form of contact tracing is a bit confusing. Perhaps passive + followup?

5. pg 7, line 27: suggest "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."

Methods:

6. Setting: From the description here, it appears as if only contacts of children diagnosed with TB are included in this study. Make this clearer.

7. Interventions: Make clear when (under what condition) enhanced CI were initiated.

It is unclear whether Passive CI was conducted in a separate year to capture the baseline (which is what it seems like from the description in the subsection Effectiveness of Contact

Investigation), or whether it was conducted in the same year as the other interventions (from the Discussion, page 20, lines 3-7).

Discussion:

8. page 18, line 55: citation 22 is not superscripted/

9. page 19, lines 8-12: Very important point made here!

10. page 20, line 10-14: If citable, please provide the reference to the historical data.

11. Figure 1: Include an arrow from Passive CI to Enhanced CI to make it clear that Enhanced CI was initiated only when passive CI resulted in no response (if this the case).

12. Figure 3: Include units, US\$.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Sourya Shrestha, JHU

Response:

Thank you for your kind words and careful review of this manuscript and suggestions to improve our work

Major comments

1. I think the authors should make it clear upfront that this study was based on HH-contacts of child TB. Interventions based on contacts of child TB may not be generalizable to all HH contact investigation. On the one hand, HH with child TB are more likely to have transmission in the household, hence CI are more likely to find TB cases (and be more effective and cost-effective). On the other hand, pediatric TB is harder to diagnose, and generally constitute a smaller burden of overall TB. It may harder to scale up or have as large an impact. I think authors should discuss this specific medium of HH CI: both that HH CI based on child TB may be highly efficient (which is really great to have demonstrated), and that including followup to enhance the CI or including house visits maybe highly cost-effectiveness in these contacts, but may not be generalizable for all HH CI (which could be an important limitation).

Response:

Thank you for raising this important point.

We had mentioned that the household contact investigation was conducted for children diagnosed with TB in the Methods under “Setting” (sentence highlighted). We have deleted the words highlighted in red to avoid confusion.

*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.** 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. (line 146-153)*

We have added the following sentence as limitation in the discussion section

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. (line 393-396)

2. I think there is some confusion as to how passive and enhanced and active CIs are defined from a study design standpoint. In particular, I was confused whether passive CI and the others were done in the same year (hence, enhance would only follow if passive resulted in no response), or in separate years. Making this clearer and consistent throughout the paper would add to the readability of the paper. Additionally, I am also curious about the HHs that could be captured via passive versus those that required enhance or active CI. If there are socio-demographic data describing these HHs, it would add a lot to understanding the need of improving CI. The fact that this study was conducted in a high-burden, low resource setting, where these types of interventions are most needed, makes this study really important, and data from actual implementation in this setting are incredibly valuable!

Response:

The data for passive contact investigation is from the previous year prior to the implementation of the study. We have amended the **Intervention** and **Effectiveness of contact investigation** sections to clarify the language.

Unfortunately, we do not have either the socio-economic data or the out of pocket expenditure from these households as it was beyond the scope of the project at that time. We have also mentioned this as a limitation in the discussion section.

3. The authors have made cases detected their primary outcome, which is perfectly understandable. However, the goals of CI are not just finding cases, but preventing transmission and future cases. In this regard, I would like the authors to perhaps discuss the potential impact of enhanced and active CI in the context of preventing transmission -- in fact one could argue that there could be even larger impact if, for example preventive therapy was included, or if benefits of downstream transmission were included.

Response:

We agree that the reviewer's comment. The project did not have time to document prevention of future TB cases. Therefore, we included the following sentences (paragraph 3) in the discussion

With contact investigation, people with TB are diagnosed early and initiated on treatment, which benefits the broader community by reducing continuing transmission. 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. (line 373-378)

Minor comments/edits

Abstract:

1. Define "active", "enhanced", and "passive" contact investigation.

Response:

Amended – the sentence now read

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. (line 56-58)

Introduction:

2. pg 6, line 54: suggest "..who have TB disease and require immediate treatment, thereby stopping further transmission"

Response:

Amended as suggested.

3. pg 7, line 22: suggest ".. along a continuum of passive and active "

Response:

Amended as suggested.

4. pg 7, line 27: Using the term "enhanced" to describe a moderate form of contact tracing is a bit confusing. Perhaps passive + followup?

Response:

Thank you for this suggestion. WHO uses the term "enhance" to describe small additional efforts added to routine program. This is therefore, an accepted term within the TB circles and might be best to keep as such.

5. pg 7, line 27: suggest "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."

Response:

Amended as suggested

Methods:

6. Setting: From the description here, it appears as if only contacts of children diagnosed with TB are included in this study. Make this clearer.

Response:

We have amended the paragraph under Setting as per the response to comment 1. It now reads:
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. 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. (line 146-153)

7. Interventions: Make clear when (under what condition) enhanced CI were initiated.

It is unclear whether Passive CI was conducted in a separate year to capture the baseline (which is what it seems like from the description in the subsection Effectiveness of Contact Investigation), or whether it was conducted in the same year as the other interventions (from the Discussion, page 20, lines 3-7).

Response:

The data for passive contact investigation is from the previous year prior to the implementation of the study. We have amended the **Intervention** and **Effectiveness of contact investigation** sections to clarify the language.

Discussion:

8. page 18, line 55: citation 22 is not superscripted

We have not been able to identify citation 22 in the discussion.

9. page 19, lines 8-12: Very important point made here!

Response:

Thank you, we appreciate your kind words.

10. page 20, line 10-14: If citable, please provide the reference to the historical data.

Response:

The historical data is from NTP quarterly notification reports which are not available for citation. Though we have provided the numbers we refer to in the **Effectiveness of contact investigation** section. It reads as follows:

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). (line 239-249)

11. Figure 1: Include an arrow from Passive CI to Enhanced CI to make it clear that Enhanced CI was initiated only when passive CI resulted in no response (if this the case).

Response:

As mentioned before, we used historical data for the passive system and therefore, did not indicate an arrow from passive to enhanced as it was not a continuous cohort.

12. Figure 3: Include units, US\$.

Response:

US \$ added as suggested.

VERSION 2 – REVIEW

REVIEWER	Shrestha, Sourya JHU
REVIEW RETURNED	08-Sep-2021
GENERAL COMMENTS	The authors have adequately addressed the concerns I raised.