PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Optimizing diagnosis and treatment of tuberculosis infection in community and primary care settings in two urban provinces of Viet Nam: a cohort study
AUTHORS	Vo, Luan; Nguyen, Viet Nhung; Nguyen, Nga Thi Thuy; Dong, Thuy Thi Thu; Codlin, Andrew; Forse, Rachel; Truong, Huyen Thanh; Nguyen, Hoa Binh; Dang, Ha Thi Minh; Truong, Vinh Van; Nguyen, Lan Huu; Mac, Tuan Huy; Le, Phong Thanh; Tran, Khoa Tu; Ndunda, Nduku; Caws, Maxine; Creswell, Jacob

VERSION 1 – REVIEW

REVIEWER	Kawatsu, Lisa Japan Anti-Tuberculosis Association Research Institute of Tuberculosis
REVIEW RETURNED	10-Jan-2023

GENERAL COMMENTS	Thank you for the opportunity to review this paper. It is well-written, and adds new knowledge and data to a very important topic. There are some minor comments/clarifications - 1. Study population - please give a brief description of "elderly" "urban poor" "economic migrant" and "children" (whose participation was consented by their parents). 2. Please include a brief description of the current program/practice regarding CI, IGRA/TST and LTBI treatment in Vietnam. At the moment it is not clear exactly what component(s) are newly being introduced. For example, Line 158-159 "Community TB officers conducted phone or in-person follow-up in regular intervals or as needed." ← is this currently not done in the routine NTP? 3.Please briefly describe how active TB is ruled out among those with positive results for IGRA. 4. In the methods, there is a mention of "urban poor" and "economic migrants" but I do not see them in the results section- or are they grouped as "vulnerable community members" (i.e. Table 3) 5.Discussion - could you elaborate a little more on the possible reasons for pre-treatment LTFU. For example, "lack of understanding of the implications of TBI" and "benefits of TPT" are related to patients or healthcare workers or both? And what is meant by "de-prioritization of TPT by healthcare providers"?

REVIEWER	Erawati , Meira Universitas Diponegoro
REVIEW RETURNED	10-Jan-2023

GENERAL COMMENTS	One of the factors that contribute to the feasibility of a program is the availability of funds. The IGRA examination requires high costs. In my humble opinion, this research should also discuss the availability of funds if the program is to be implemented later.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 comments

- Please give a brief description of "elderly" urban poor" "economic migrant" and "children".
    - *Thank you for this suggestion to clarify the definitions of these target populations. We have made relevant additions to the manuscript to meet this request.*
    - *In lines 128-130, we have added "Briefly, elderly persons were ≥55 years, urban poor were based on national poverty definitions and economic migrants were categorized based on residency registration in rural provinces outside of the intervention districts."*
    - *In line 130 we have also include two additional sources that provide further details on these definitions.*[1,2]
    - *In line 138 we have added the phrase "under 18 years" to clarify the definition.*
- Please include a brief description of the current program/practice regarding CI, IGRA/TST and LTBI treatment in Vietnam.
    - *While summarizing national TBI guidelines in detail would exceed the scope of the manuscript, we understand your request for further programmatic baseline information. Thus, we have made minor edits to the manuscript, and have furnished more information below.*
    - *In line 92-95, we added a sentence to encapsulate TPT under the newly introduced national guidelines as follows: "These guidelines expanded TPT eligibility to all adults with TBI confirmed by recommended diagnostic tools and excluding active TB, permitted the use of various shortened regimen, and described contact investigation and follow-up requirements."*
    - *In line 163, we have added the phrase "as recommended in national guidelines" to highlight that follow-up is a core part of standard practice.*
    - *However, it needs to be stated that the implementation of many of the recommended practices within national guidelines, such as follow-up with persons receiving TPT, varies greatly with the availability of human resources across the country.*
- Please briefly describe how active TB is ruled out among those with positive results for IGRA.
    - *In line 158, we have added the following phrase to clarify: "by CXR and symptomatic presentation."*
- In the methods, there is a mention of "urban poor" and "economic migrants" but I do not see them in the results section- or are they grouped as "vulnerable community members" (i.e Table 3)
    - *You are absolutely correct in that these target populations were grouped as "vulnerable community members."*
    - *There are two reasons for this practice. First, our key point of interest was to distinguish participants between persons with documented exposure (i.e., contacts of a person with active TB) and vulnerable persons without exposure, wherein the root cause of their vulnerability was not of interest in this study. However, we will keep in mind the suggestion of dichotomizing these risk groups further in future study design.*
    - *The second reason is that data collection of urban poor and economic migrant statuses would be declarative and thus likely highly biased without an additional verification step. While this step could have been conducted through verification of government poverty*

registers and household registration cards, these steps were deemed unnecessary in light of the objectives of this particular study.

- Discussion - could you elaborate a little more on the possible reasons for pre-treatment LTFU. For example, “lack of understanding of the implications of TBI” and “benefits of TPT” are related to patients or healthcare workers or both? And what is meant by “de-prioritization of TPT by healthcare providers”?
    - *Thank you for this suggestion, we have made edits in the manuscript to clarify these points.*
    - *With respect to the lack of understanding, the principle issue is the moral hazard around preventive care as TB infection is asymptomatic and untransmissible, and TPT is considered optional prophylaxis. This is the case among participants and healthcare providers.*
    - *The manuscript has been edited in lines 288-291 to state the following: “Based on informal qualitative feedback from field staff, reasons for the large drop-offs in the cascade included a lack of understanding of the risk of progression from TBI to active TB and the benefits of TPT in the general population, but also among healthcare providers, which leads to the de-prioritization of TPT as optional prophylaxis rather than valuable intervention.”*

Reviewer 2 comments

- One of the factors that contribute to the feasibility of a program is the availability of funds. The IGRA examination requires high costs. In my humble opinion, this research should also discuss the availability of funds if the program is to be implemented later.
    - *We sincerely thank you for your observations and very much concur with your assessment.*
    - *We respectfully refer to lines 103-104, where we have highlighted that “the prohibitively high costs per test have precluded serious consideration for routine TB program activities” and lines 323-324, where we lamented that a “limitation of our study was the lack of a formal assessment of the cost barrier of IGRAs in our low-resource setting” to conclude in lines 328-331 that “given the lack of an accompanying health economic evaluation, future research should conduct impact evaluations and cost-effectiveness analyses of integrated TB and TBI testing and treatment on ACF campaigns and differences in incidence and disability-adjusted life years compared to a control cohort.”*
    - *With that said, we highly appreciate your point and have added to line 324 the phrase “with limited program budgets.”*

Thank you very much once again for your review and assessment of our manuscript and please do not hesitate to contact us, if there are any additional requests.

Sincerely and on behalf of the study team,

Luan Nguyen Quang Vo

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References

1. Mac, T.H.; Phan, T.H.; Nguyen, V. Van; Dong, T.T.T.; Le, H. Van; Nguyen, Q.D.; Nguyen, T.D.; Codlin, A.J.; Mai, T.D.T.; Forse, R.J.; et al. Optimizing Active Tuberculosis Case Finding : Evaluating the Impact of Community Referral for Chest X-ray Screening and Xpert Testing on Case Notifications in Two Cities in Viet Nam. *Trop. Med. Infect. Dis.* **2020**, *221*, 1–15, doi:10.3390/tropicalmed5040181.

2. Vo, L.N.Q.; Codlin, A.J.; Forse, R.J.; Nguyen, H.T.; Vu, T.N.; Van Truong, V.; Do, G.C.; Nguyen, L.H.; Le, G.T.; Caws, M. Tuberculosis among economic migrants: a cross-sectional study of the risk of poor treatment outcomes and impact of a treatment adherence intervention among temporary residents in an urban district in Ho Chi Minh City, Viet Nam. *BMC Infect. Dis.* **2020**, *20*, 134, doi:10.1186/s12879-020-4865-7.

VERSION 2 – REVIEW

REVIEWER	Kawatsu, Lisa Japan Anti-Tuberculosis Association Research Institute of Tuberculosis
REVIEW RETURNED	20-Jan-2023

GENERAL COMMENTS	Thank you for the swift revision and for considering the comments - I believe all the comments have been addressed thoroughly. It was a pleasure reviewing the manuscript and I look forward to the paper being published.