Author’s response to reviews

Title: Operationalization of bi-directional screening for tuberculosis and diabetes in private sector healthcare clinics in Karachi, Pakistan

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Author’s response to reviews:

I have attached a response letter as supplementary material, which is color-coded and therefore easier to view. I have pasted the contents of the response letter below:

Dear Dr. Anete Trajman,

Thank you for your email enclosing the reviewer’s feedback. We appreciate the concerns raised, and have carefully reviewed the comments and addressed all of them in a revised version of the manuscript. Our responses are enlisted in a point-by-point manner. Changes within the manuscript are delineated in red, underlined text (through the Track Changes option).

I have included two additional tables (Table 1 & 2) and an amendment to the figure (Figure 1) in order to address some of the over-arching concerns raised by Reviewer 2. The tables had been removed previously on account of shortening the manuscript but have been re-introduced to better explain and clarify some of the results of the study. The primary focus of the paper is on
the uptake of testing within a bi-directional screening program for TB and diabetes, and the results section has been re-oriented to reflect this.

We hope the revised version is now suitable for publication and look forward to hearing from you.

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Editor comments

Technical Comments:

1. Figure Legends - Please provide Figure legends after the reference list.

Author response: Figure legends have been included after the reference list.

Editor Comments:

Please, when revising your tables, also make sure you re-check all numbers and eventual typos. Finally, please only conclude what your data have shown. Any speculation should appear as so in the discussion, as pointed out by reviewer 2.

Author response: All numbers have been verified and eventual typos have been corrected. Data that was not directly supported by the results has been moved from the conclusion to the discussion section, specifically in regards to the speculation about user fees as a barrier to uptake.

Reviewer 1 comments

Abstract:

L.72: presumptive TB patients are written twice. Please, correct.
Author response: This has been corrected as shown on Line 72.

Background:

L.87 - typo: poses.

Author response: Has been corrected on Line 87.

Results:

L.188: Table 1's title appears twice, here and on L.190. Better keep the title that appears on L.190.

Author response: The title directly below the table has been retained while the title above the table has been removed. Due to the addition of two tables containing socio-demographic data, this table has now been renamed Table 3, as reflected on Line 252-254.

Table 1: The percentages need revision. On the row for "Underwent Xpert MTB/RIF", what is the percent expressed as 94.1? If it is 48 out of 726, the result would be 6.6%, and if 48 out of 62, 77.4%. I suggest the second, in order to keep up with the other values, obtained from the row immediately above.

Author response: You are absolutely right - there was a typo with this percentage. This has been changed to 77.4% and all other percentages have been re-checked to ensure consistency across values in Table 3.

L.194: I would have this paragraph before the one that starts on L.178, as it has the totals that appear on Table 1. I had to search for those numbers while reading the table.
The study provides a comprehensive approach of a public health problem dealing with private services in a low-middle income country, quite different from countries with huge public sector in access for all context. The challenges and strategies presented here are helpful for those facing the same scenario. I agree that the most important result is the uptake of tests by presumed patients, and in order to increase the uptake, a lot of "by-in" of providers, specifically physicians, will be needed, besides efforts to reduce costs for the patients and to increase their awareness of TB and DM interaction.

Reviewer 2 comments

The authors conducted a study to investigate the feasibility of a bidirectional TB-diabetes screening program in the private health sector in Pakistan. The authors found very low uptake of TB and diabetes screening in private clinics. This manuscript aims to addresses important operational gaps in the implementation of the TB-diabetes bi-directional screening strategy recently endorsed by the WHO, particularly in the private health care sector which is often understudied and may account for a considerable burden of missing cases in high burden countries.

1. Line 125-128. The authors mention screening activities being undertaken at 80 health clinics. Can the authors provide more information on the type of clinics i.e. respiratory clinics vs diabetes clinics vs general primary care clinics to better understand the level of implementation of screening activities? Also, was screening based on a convenience consecutive sample or a more systematic / random sampling approach?

Author response:

• The type of clinics that conducted screening has been provided in the Methods section, Line 125-126, page 6: “Community health workers (CHW) screened patients attending 80 general primary care, health provider clinics for TB and DM”.
• Information on the type of sampling has been provided in the Methods section, line 126-127, page 6: “The screening was based on a convenience consecutive sample”.

2. Line 145-149. Can the authors clarify how previously diagnosed or known TB or diabetes cases were handled in the study and analysis?

Author response:
• Details on how previous cases of TB or DM were handled are described in detail in the Methods section, line 149-156, page 8 (given in purple text quote below).
• We included a Table 1 which identifies socio-demographic characteristics associated with newly diagnosed and previously diagnosed cases of DM.

“Individuals who came to the Centers with a previous diagnosis of TB or DM were re-tested using Sehatmand Zindagi Centers’ Chest X-ray, Xpert MTB/RIF and glucometer-based random blood sugar tests to ensure reliable baseline measures for diagnosis rather than depending on external reports. Known diabetes cases underwent glucometer based random blood sugar testing and then were channeled into the presumptive DM-TB arm (Figure 1). Baseline data for previously diagnosed and newly diagnosed diabetes cases is indicated in Table 1. Previously diagnosed cases of diabetes were further classified as having controlled or uncontrolled diabetes” (Methods, lines 149-156, page 8).

3. Line 149-151. Can the authors specify the cutoff used to diagnose pre-diabetes and diabetes and the type of test used to measure RBS?

Author response: The IDF cut-offs were used to diagnose pre-diabetes and diabetes in this study. They are as follows: DM (≥200 mg/dL (11.1 mmol/L)), Pre-DM (140-199 mg/dL (7.8-11.0 mmol/L)) or non-diabetes (<140 mg/dL (7.8 mmol/L)). (Methods, Line 159-160, page 8).
4. Line 151-154. The authors mention that those with both presumptive TB and diabetes were referred for either TB or diabetes screening at the discretion of the treating physician. Can the authors comment on what proportion of these individuals with a presumptive diagnosis of both TB and diabetes were referred to TB screening vs diabetes screening? How many were referred for both? Was this referral affected by participant, physician or clinic characteristics or price of test considering associated reimbursement?

Author response:

• Thank you for pointing this out. After re-reading this sentence, the authors realized that this was a bit misleading and does not accurately convey the referral mechanism in place in the primary health provider clinics. According to the protocol, clinicians were meant to refer all patients who were presumptive for DM and TB to undergo both diagnostic tests. This is reflected in the Methods section (lines 160-163, page 8):

> “Individuals with both presumptive TB and DM, were assigned to another diagnostic arm where the private health provider referred patients for both tests: a point of care glucometer test for DM and Chest X-ray and Xpert MTB/RIF testing at the diagnostic centers.”

• Recognizing that the original Figure 1 left out some crucial information about this distinct group (presumptive for DM and TB), based on your recommendation, we amended Figure 1 to include a third arm (the central arm of the figure). As shown in the diagram, 14,550 individuals were presumptive for both DM and TB, all of whom (100% of patients) were referred to both arms. However only a small proportion actually underwent a DM test and TB test. Details on the uptake of testing in each of these arms has been delineated in Figure 1, and described in the Results section (line 196-202, page 9):

> “The overall uptake of DM testing among those identified with presumptive diabetes was 26.1% while the overall uptake of TB testing among those with presumptive TB was 5.9% (Figure 1). Individuals with a presumptive diagnosis of both DM and TB were referred for both a glucometer based random blood sugar test and a Chest X-ray and Xpert MTB/RIF test. Among the group that was presumptive for both DM and TB, the uptake of DM testing was 12.5% and the uptake of TB testing was 24.2% (Figure 1).”
• Additionally, in the original submission, factors that may have affected the referral mechanism are discussed at length in the discussion section (lines 277-288, pg 13-14) with speculation around physician’s prescriptive practices, the price of the diagnostic tests and the distance to the centers.

5. Lines 164-167. Please specify how the primary study outcomes will be calculated, particularly for diabetes screening where the authors have instead provided definitions for diabetes burden.

Author response: This has been corrected to provide a more accurate definition of how the primary study outcomes i.e. uptake of TB testing and uptake of DM testing are calculated. Please refer to the Methods section (lines 181-189, page 9) to see these changes.

6. Line 170 and beyond, Results. This manuscript would benefit from a "Table-1" describing the general socio-demographic and clinical characteristics of the study population. Additionally, identifying participant, physician or clinic characteristics associated with TB and diabetes uptake will be informative, if these data are available.

Author response:
• Table 1 and Table 2 with socio-demographics and clinical characteristics of the study population were included in a previous version of this manuscript but removed based on editor feedback. These tables have now been re-included to address this point. Narrative explaining the results from these two tables has also been inserted into the Results section (lines 204-223, page 10-11).
• Unfortunately, additional information on physician and clinic characteristics are not available and so could not be included in a separate table.

7. Line 175-176. The authors report on the prevalence of prediabetes and diabetes among TB patients in their program. Are these data from another study or were these calculated from the current analysis? If it is the latter, the authors should specify this in the methods. Additionally, as the authors rightly noted, there are considerable limitations to reporting estimates as prevalence in this study and defining estimates as such should be avoided.
Author response:

• The prevalence data are from the same study, and this has been mentioned in the Methods section, line 189-190, page 9. Due to the limitations with reporting these estimates we removed the prevalence data from the conclusion and instead reported it in the Discussion section (lines 260-262, page 13):

“In this study, TB prevalence among diabetics and pre-diabetics was 23.5% while pre-DM/DM prevalence among TB patients was 12.4%” (Figure 1)

8. Line 274-275. The speculation that test costs is a likely barrier to test uptake seems reasonable but is not supported by data presented in this manuscript. It may be better to move this point to the discussion rather than conclusion.

Authors response: This point has been removed from the conclusion, and instead placed in the Discussion section, lines 296-297, page 14.

9. Figure-1. How were participants with both TB and diabetes accounted for in this figure? It seems they were included in both arms thus duplicating results, can the authors please clarify? It may be more informative to create a 3rd arm in this figure specifically for those with both presumptive TB and diabetes as this is clinically and operationally a distinct group.

Author response:

• As stated in response to reviewer 2’s point #4, Figure 1 has been amended to include a third diagnostic arm which accounts for 14,550 individuals who were presumptive for both DM and TB. Furthermore, this diagram also includes colored boxes indicating the primary outcome – uptake of testing. Overall uptake of TB testing among arm 1 and 2, overall uptake of DM testing among arm 2 and 3, uptake of TB testing in arm 2 (presumptive for both DM and TB) and uptake of DM testing in arm 2 (presumptive for both DM and TB) are depicted in the amended Figure 1.