Author's response to reviews

Title: The effectiveness of providing counselling and financial support to patients receiving treatment for multi-drug resistant TB: mixed method cohort and qualitative studies

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Author's response to reviews: see over
We would like to thank the reviewers for their very useful comments. Below, we respond to each point in turn.

**NB to reflect the changed emphasis of the paper we have changed the title to**

The importance of providing counselling and financial support to patients receiving treatment for multi-drug resistant TB: mixed method qualitative and pilot intervention studies.

**Reviewer:** Petros Isaakidis

**Reviewer’s report:**
I have read this study with great interest: the authors address an extremely important and relevant topic, especially in LIC & MIC. MDR-TB patients go through unacceptable challenges both due to the disease and the current treatment regimens and any effort to alleviate their suffering and to control the epidemic should be encouraged and supported. The authors report on an interesting programme and they looked at different support interventions and their potential associations with treatment outcomes. Interestingly they have used mixed methods which make the study more interesting and "rich". However the quantitative part has some major weaknesses that the authors do not address in their report neither do they discuss the limitations of their study.

Even though the mixed methods design seems promising, I tend to propose to the authors to downsize the quantitative part and focus on the qualitative findings.

**Our response:** We agree that there are limitations in the quantitative part. In our revised document we have downsized the quantitative part (e.g. by describing it as a pilot intervention study) and addressed its weaknesses, and focused more on the qualitative part.

We should also point out that limits on the word count made it difficult for us to incorporate all the points we wanted to make in the original version. This is a common problem in qualitative research; and it is compounded when reporting mixed methods research.

**Major Compulsory Revisions**

The authors should explain how the randomization of DOTS centers was done and whether the cluster randomization was accounted for the sample size calculations and the analyses. Design effect and intra-cluster coefficient (ICC) may be discussed.
Our response: we have now described how randomisation was done, and clarified that no adjustment was made for cluster randomisation (and added a comment in the limitations section of the Discussion to this effect).

The use of Mantel-Haenszel method seems an appropriate choice. However it is better used to calculate risk ratios rather than ORs in RCTs and cohort studies. Logistic regression is better reserved for case-control studies. The fact that the differences with ORs in this particular study are small doesn't change the fact that the authors may seek statistical advise (cluster data) and chose one measure of association rather than several. Then the chosen analysis method should be presented first in the Methods. For example, the M-H method is now only mentioned first time in the Table.

Our response: we have removed the logistic regression (which was left in by mistake), and have now presented the chosen analysis method in the Methods. We have chosen to estimate risk ratios, both unadjusted and adjusted using Mantel-Haenszel, using the epi.2b2 function of the R “epiR” package.

The authors haven't collected additional data from patients not receiving support and they justify it "to avoid dilution effects". Please elaborate.

Our response: we agree this was less than clear, and have now clarified as follows: we have deleted the sentence

We did not collect additional data from patients not receiving support to avoid dilution effects.

and replaced it by

Patients not receiving support were not asked for additional data, as to do so might have started to approximate or resemble counselling, and thus reduced our ability to observe additional effects of counselling.

How the readers will assess whether the 3 arms are comparable?

Our response: we have added the following text to the results:

Distributions of sex and age were similar across all three groups (Table 1); and in addition distributions of marital status, occupation, origin and residence (for migrants only) were similar across the two intervention groups (Table 2).

In the Discussion, we have now clarified that this is a pilot study, and that although the 3 arms are comparable in terms of age and sex distribution, they may or may not be comparable in terms of other factors.

Similarly Table 2 is "crying" for the inclusion of the control group

Our response: as we have explained above in our response to the question about 'dilution', we expressly did not want to obtain information from the control group, so we do not have the data to include the control group in Table 2.

The authors should explain how the increased numbers on the control (no-support) arm partially compensates for not reaching the desired sample size in the intervention arms.
Our response: we have now clarified that increasing numbers in the control group should reduce the expected width of confidence intervals of comparisons.

Again it is not clear how cluster randomization was accounted for

Our response: we have now clarified in the Methods that cluster randomisation was not accounted for in sample size calculations or analysis, and made a comment to this effect in the limitations section of the Discussion.

The Discussion does not discuss at all the existing evidence or the lack of it. This is major issue; references are all used in the introduction, they are mostly from Nepal and authored by the study authors. No single citation was included in the discussion section.

Our response: we have searched the literature and can find no existing evidence, or any reference to lack of evidence. We have added a comment to this effect in the Discussion.

The authors do not discuss the study limitations nor the strengths.

Our response: we have now added a limitations and strengths section in the Discussion.

The suggestions to the NTP to incorporate support interventions therefore are therefore not supported neither by the study-produced evidence, nor any existing evidence. The only argument being "it will take time to run RCTs".

Our response: although we agree that there is no quantitative evidence for the provision of support, we disagree that there is no evidence at all: the qualitative findings clearly indicate that some kind of support is required, at least in this setting, and we believe other NTPs should consider what kind of support is possible while they wait for hard evidence. In the light of the reviewer's comment, we have modified our suggestion to:

... NTPs should consider how they can support this disadvantaged and vulnerable group of people.

Minor Essential Revisions

The qualitative methodology (formative and explanatory part) should be elaborated more. The authors should describe the theory their approach was based on, the details of data collection, whether saturation was reached or not, how emerging themes were iterated.

Our response: we have added further text to the Methods section giving more detail on the qualitative methodology, as follows:

Areas explored included: socio-demographic characteristics; employment history; sources of income; living costs; reason(s) for relocation (non-local residents only) and relocation costs; knowledge of MDR-TB including communicability and curability; knowledge and experience of drug side effects and how they were addressed; care-seeking practices during diagnosis and treatment stages; distance to MDR TB centre; travel costs; interactions with family, friends and others; and implications of daily visits to
the DOTS+ centre. Interviews were recorded and notes taken. Interviews lasted between 45 and 60 minutes.

and

The data were coded by SCB and YA, and analysed thematically using a framework approach, combining a-priori and emergent themes. At the start of the coding process, SCB and YA read the initial transcripts and generated preliminary codes. Repeated discussion, reasoning and reflection during the coding process led to a well-defined set of codes. The two researchers then coded the remaining transcripts. When necessary, new codes were discussed and agreed upon and the code set was updated accordingly.

We do not wish to claim that saturation was reached. In very straightforward studies, with highly homogenised respondents, sometimes a point is reached at which no further themes emerge. However, with most studies, including this one, the diversity of respondents (in terms of age, ethnicity, socioeconomic status, gender) and questions mean that it is difficult to claim saturation has been reached.

Reviewer: Christine Heidebrecht

This is important and timely study. As rates of MDR-TB continue to rise, it is critical that interventions to improve treatment outcomes (such as those described in this paper) are explored alongside efforts to reduce transmission and combat further development of resistant bacterial strains. While the authors acknowledge that larger RCTs are required to verify their findings, this mixed-method study is a valuable initial investigation.

Major Compulsory Revisions:

1. Consider using “intervention study” rather than “cohort study”

Our response: thanks for this useful suggestion. In the light of this and the other reviewer's comments, we have decided to refer to it as a 'pilot intervention study'. Because the study did not take clustering into account (see responses below), we regard it as a pilot, and have clarified this in the title and throughout the paper.

2. The paper does not mention the impact that individual DOTS+ treatment centres may have had on treatment outcomes. It would be helpful for the authors to address this in the discussion section, and to include some characteristics of the centres in the results section.

Our response: we agree that it would have been good to have been able to adjust for the effects of the different Treatment Centres on treatment outcomes, but this was not possible due to the small number of centres involved. We have added some details of characteristics of the centres in the results section, and a comment in the limitations section of the Discussion.

3. The intervention component incorporates a cluster randomized design; did the sample size calculation account for this (i.e. account for the fact that within-cluster variation is going to differ from between-cluster variation)? If not, this should be identified as a limitation.
Our response: we were not able to account for clustering in the sample size calculation. We have added comments to this effect in the Methods and limitations section of the Discussion.

4. I’m unclear about the order in which recruitment of interview respondents and randomization of intervention sites occurred, given that all interview respondents were from the five centres that were allocated to the intervention arms. Please clarify this.

Our response: we randomised DOTS+ centres and then recruited interview respondents. We have now clarified this at the start of the Methods.

5. The authors state that age was the only variable that had a significant effect when the model was fitted; it would be helpful for the paper to include the other variables that were considered for inclusion in the model.

Our response: we have now included the other variables that were considered for inclusion in the model.

6. What were the inclusion criteria for interview respondents and participants in the intervention study? Did all individuals approached to participate in the intervention study consent? If not, please describe the number who refused, and address the possibility of selection bias.

Our response: our original text stated that all patients were eligible for inclusion, and all consented, but we accept that this could have been made clearer: we have now done so.

7. The Discussion section should be expanded to include limitations of the study, generalizability of results (this will differ between the qualitative and quantitative components), and the impact of the lower than desired sample size in the intervention arms.

Our response: we have now added a limitations and strengths section in the Discussion. We have included a discussion of generalisability of results and the impact of the small sample size.

8. Please outline the types of questions that were asked in the formative and explanatory studies.

Our response: we have added outlines of the types of question asked in the formative and explanatory studies, as follows.

In the formative study:
- Areas explored included: socio-demographic characteristics; employment history; sources of income; living costs; reason(s) for relocation (non-local residents only) and relocation costs; knowledge of MDR-TB including communicability and curability; knowledge and experience of drug side effects and how they were addressed; care-seeking practices during diagnosis and treatment stages; distance to MDR TB centre; travel costs; interactions with family, friends and others; and implications of daily visits to the DOTS+ centre.
In the explanatory study:
   Areas explored included: experience with family members, relatives, friends, community people, and at the workplace before and after MDR-TB; impact of illness on general living and employment; mechanisms for coping with MDR-TB and other associated illness; experience with the health system especially in routine management of illness; management of drug side effects; support from the health system, service providers, family, relatives, at the workplace and in the community; disclosure of their disease status to others; problems/issues experienced by the respondents and their management; and perceptions of the interventions.

9. Please expand on the interview coding process, including whether coding reliability between researchers was assessed.

Our response: we have added the following text in the Methods section.
   At the start of the coding process, SCB and YA read the initial transcripts and generated preliminary codes. Repeated discussion, reasoning and reflection during the coding process led to a well-defined set of codes. The two researchers then coded the remaining transcripts. When necessary, new codes were discussed and agreed upon and the code set was updated accordingly.

10. Were there seven DOTS+ centres in the Kathmandu Valley at the time of study initiation (i.e. did the study include all DOTS+ centres in the area)? If not, how were the sites chosen?

Our response: yes, there were only 7 DOTS+ centres – we have now clarified this at the start of the Methods.

11. Who conducted the counseling in the two intervention arms – were they members of the research team or centre staff? Please describe the nature of the counseling (including duration). Was the frequency (“every 2-3 weeks”) consistent across sites?

Our response: we have deleted the following text in the Methods section
   Patients receiving counselling were counselled individually and in small groups once every 2-3 weeks.

and replaced it by
   Patients receiving counselling were counselled individually and in a Public Health Nurse who was trained to provide counselling for this research. Counselling was provided every 2-3 weeks across all sites. The counsellor and researchers met regularly to discuss issues raised during counselling.

12. Please expand on “dilution effects” (Methods section). Was there a concern that more time spent with patients in the control arm to collect additional characteristics would start to approximate/resemble counseling?

Our response: we agree this was less than clear, and have now clarified as follows:
   We did not collect additional data from patients not receiving support to avoid dilution effects.

and replaced it by
Patients not receiving support were not asked for additional data, as to do so might have started to approximate or resemble counselling, and thus reduced our ability to observe additional effects of counselling.

13. Table 3 presents adjusted ORs produced by logistic regression and Mantel-Haenszel tests, but the text does not describe why both tests were used. Please address.

Our response: we have removed the logistic regression (which was left in by mistake), and have now presented the chosen analysis method in the Methods.

Minor Essential Revisions:

14. “Extremely drug resistant TB” (first paragraph in Introduction section) should be “extensively drug resistant TB”

Our response: thanks for pointing this out. Now corrected.

15. There is an individual listed under Roles of Authors who is not identified as an author (PM). Please address.

Our response: this line was included in error and has now been removed. Thanks for picking this up.

16. Tables 1 and 2: identify count (or N), and %

Our response: thanks for pointing this out – now addressed.

Discretionary Revisions:

17. Consider modifying the title of the article to reflect the outcome.

Our response: different journals have different conventions on this – we prefer to encourage readers to read the article to be aware of the nuanced findings, rather than judge from the title.

18. Table 3: consider using N instead of “count”

Our response: now addressed.

19. Table 3: consider using sub-headings rather than footnotes.

Our response: now addressed.