PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk Factors of Multi-Drug Resistance Tuberculosis among Tuberculosis Patients at Selected Multi-Drug Resistance Treatment Initiative Centers in Southern Ethiopia: A Case- Control Study
AUTHORS	Admassu, Fantahun; Abera, Ermias; Gizachew, Addisalem; Sedoro, Tagesse; Gari, Taye

VERSION 1 – REVIEW

REVIEWER	Verdecchia, Maria Medecins Sans Frontieres Luxembourg
REVIEW RETURNED	26-Apr-2022

GENERAL COMMENTS	Thank you for letting me review this paper. I have few comments that I think you need to address to make it publishable: 1. It needs an editor review as the English is not readable in some places and inaccurate in others. 2. The conclusion in the abstract repeats the results and it is not necessary. Please draw more robust conclusions 3. Review the literature. For example: a. There are more papers than you refer to that address risk factors for MSDR-TB. b. Page 2 line 50, the study cited is a study in Burundi and not a systematic review that addresses a global Public health problem? You are discussing a global problem. c. Subsequently you report reported cases up to 2019, why not 2020 and 2021? d. Page 3 line 2 you mention RR-TB without mentioning it before. You need to explain what it is. e. Page 3 paragraph starting with line 27 you mention prevalences without specifying the years (when) f. Last paragraph in page 3 you say that the findings of your study can contribute to the planning and policy improvement globally. Why globally? How can this study be generalizable globally? 4. Sample size and sampling procedure: you clearly explain what factors your sample size calculation is based on but you don't say how you decided these factors. For example, why an adjusted OR of 2.1? Is it from previous studies? And what technique did you use to perform systematic random sampling? 5. Patients and public health involvement in page 6: that is a real shame that there was none.

	6. Results a. Please keep digital figures consistent. Sometimes there are none and sometimes 2. 1 would be enough b. The tables are not properly labelled. You should write under the Cases/Controls what the numbers in the table means. In this case it is N (%). All the tables need to be better labelled. c. Clinical characteristics of study participants paragraph page 7. This paragraph needs to be re-written. Why is “cases” and “controls” inside the parenthesis? The sentence should make sense even if not reading the parenthesis. Also patients normally don’t have the habit of treatment interruption, it is history of treatment interruption. d. Page 8 First paragraph. Please also here revise the wording as not clear. e. Define alcohol drinking history. What does it mean? How was it measured? Was it over drinking? Did you use a standardised tool to assess this? You need to specify this. 7. Ethical approval page 12: You did not mention risks for the patients in participating in the study. Even if you think there are no risks you should say why.

REVIEWER	Bessa, Theolis Fundacao Oswaldo Cruz, Instituto Goncalo Moniz
REVIEW RETURNED	19-May-2022

GENERAL COMMENTS	This is a case-control hospital-based study that evaluated risk factors associated with the development of MDR-TB in Ethiopia. Major comments In the Introduction section, page 3, lines 20-25, the authors listed variables that they hypothesized to be risk factors for MDR-TB in the study region, such as diabetes mellitus and malnutrition, that were not addressed in this study. Were these variables assessed? The Materials and Methods section “Data collection procedures and quality assurance” lists variables that were not reported in the Results section (occupation, adverse effects of TB medication, knowledge of TB). It is not clear if those variables were used or discarded in the analyses. Discussion section, page 10, lines 12-13: please identify which factors were measured and found not to be associated with MDR-TB in this study. A very similar study, cited in this work (ref 11), was conducted previously in Ethiopia to clarify risk factors associated with MDR-TB disease. Please discuss how the present study adds to this previous report. In the Introduction section, page 3, lines 49-52, the authors justify the work considering the importance of assessing the risk factors for MDR-TB development to address current gaps in service coverage, as well as monitor the progress of TB detection and treatment. Please discuss how the results presented may be useful to achieve the aforementioned goals, and which gaps persist that should be investigated in further studies. Patient consent, page 13, line 13: Please state that written consent was obtained from all participants. Minor comments Abstract, page 2, line 16 – The variable analyzed was direct contact with a TB or an MDR-TB patient? Abstract, page 2, lines 18-19 – The variable “place of residence” refers to residence in urban vs non-urban settings. Please indicate it

	clearly. Introduction, page 2, lines 46-47 – MDR-TB was defined twice in this paragraph. Introduction, page 2, lines 5-53 – The number of MDR-TB cases in 2018 stated in this sentence is higher than the number of MDR-TB cases in 2019. Please review the epidemiological data provided. Introduction, page 3, lines 40-52 – This paragraph is very confusing. What is “MDR-TB privation and control”? Materials and Methods, page 4, lines 28-29: Please specify clearly which criteria were used for patient inclusion and which criteria were used for patient exclusion from the study. Sputum culture was not performed to complement TB diagnosis for non-MDR-TB patients? Results, Table 3 – The variable “history of migration” refers to migration from non-urban to urban areas? Results, Table 4 – Please define the acronyms COR and AOR. The variable “Direct contact with TB patients” refers to MDR-TB patients? The variable “TB treatment outcome” refers to previous TB treatment?

REVIEWER	Hossain, Shahed icddr,b, Centre for Equity and Health Systems
REVIEW RETURNED	31-May-2022

GENERAL COMMENTS	Title: Risk Factors of Multi-Drug Resistance Tuberculosis among Tuberculosis Patients at Selected Multi-Drug Resistance Treatment Initiative Centers in Southern Ethiopia: A Case-Control Study (bmjopen-2022-061836) General Comment: Methodologically good study. Specific Comments: 1. Sample size- why use 1:4 Case: Control ratio? Any justification? 2. Setting-Two big specialized hospitals. Despite that why more samples are from rural areas? A little description of the setting could be useful 3. Did the authors collect any information on the professions of the respondents? 4. Did the authors collect any information on other reported risk factors for MDR-TB, like Diabetes Mellitus, Drug abuse, alcoholism, malnutrition, and or any other co-morbidities? 5. All the risk factors mentioned are also well studied and known risk factors for drug-sensitive TB. The authors may need to clarify what additional risk, these factors pose for MDR-TB? For example, close contact with a TB patient poses a risk factor for a non-TB person to develop either drug-sensitive TB or MDR-TB? How do differentiate the risk? 6. Clarifications: a. Table 2: History of contact with TB Patient? (Any TB patient or MDR-TB patient?) b. Table 2: History of Previous TB treatment? (Any TB or MDR-TB?) c. Table 2: TB Treatment Outcomes (Failure or default?)? Failure of treatment and default are two different outcomes. While failure indicates earlier resistance during the treatment phase, default could be from totally different causes including behavioral or social causes. Please rethink, before lumping them together. 7. Minors: a. Page 4, Line 2; MDR/RR (please provide full abbreviation for the first-time use. b. Page 7, Line 15; “More than” what? Overall, this is an important study and methodologically sound. The authors may have line space to provide more clarifications or

	describe the possible risks putting in the context and discuss more from other researches.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

1. It needs an editor review as the English is not readable in some places and inaccurate in others

Answer 1: We really appreciate you. We gave full version of manuscript for English language experts to make revisions and they made language revisions and highlighted in yellow color.

2. The conclusion in the abstract repeats the results and it is not necessary. Please draw more robust conclusions

Answer 2: Thank you very much for your genuine comments. We made modifications according to your comments.

3. Review the literature. For example:

   a. There are more papers than you refer to that address risk factors for MSDR-TB.

Answer 3: Yes, several papers that address risk factors of MDR-TB were published at a different parts of Ethiopia like Addis Ababa, Oromia Region, Amhara Region, and Tigray Region; but as far as our knowledge there is no citable infomation in our study area (Southern Region of Ethiopia).

   b. Page 2 line 50, the study cited is a study in Burundi and not a systematic review that addresses a global Public health problem? You are discussing a global problem.

Answer 4: Sorry we made mistake. We corrected during period of investigation and replaced by current global facts of MDR/RR-TB. ---- “Globally in 2020, 71% (2.1/3.0 million) of people diagnosed with bacteriologically confirmed pulmonary TB were tested for rifampicin resistance, up from 61% (2.2/3.6 million) in 2019 and 50% (1.7/3.4 million) in 2018”.

   c. Subsequently, you report reported cases up to 2019, why not 2020 and 2021?

Answer 5: We made the revisions of the introduction section and we wrote updated information.

   d. Page 3 line 2 you mention RR-TB without mentioning it before. You need to explain what it is.

Answer 6: We made the correction accordingly. “Among these, 132222 cases of multidrug and rifampicin resistance (MDR/RR-TB) (MDR/RR-TB)”

e. Page 3 paragraph starting with line 27 you mention prevalences without specifying the years (when).

Answer 7: Thank you. We modified whole paragraph by replacing new sentences that address the objective of the study.

f. Last paragraph in page 3 you say that the findings of your study can contribute to the planning and policy improvement globally. Why globally? How can this study be generalizable globally?

Answer 8: Sorry it was mistaken during manuscript preparation. We made revisions according to comments. “Understanding the risk factors that contribute to MDR-TB is important to design effective prevention and control strategies against its transmission”

The findings of this study is limited the generalizability globally because of data was collected from hospitalized patients.

4. Sample size and sampling procedure: you clearly explain what factors your sample size calculation is based on but you don’t say how you decided these factors. For example, why an adjusted OR of 2.1? Is it from previous studies? And what technique did you use to perform systematic random sampling?

   Answer 9: Thank you. We corrected sample size determination and where the exposure variable and adjusted OR was taken. Yes, both exposure variable and adjusted OR was taken from previous studies. We used systematic random sampling techniques to select study participants from both hospitals. “39.7% proportions of direct contact to known TB patients among controls as exposure variable and odds ratio of 2.1 from study conducted in Amhara Region Ethiopia, 95% confidence level, 80% power of the study, 1:4 cases and controls ratio. Accordingly, a total of 392 study participants were included (49 cases and 199 controls from NEMMCSH and 30 cases and 114 controls from Butajira General Hospital)”.

5. Patients and public health involvement in page 6: that is a real shame that there was none.

Answer 10: We made mistake during preparing manuscript and sorry for that.

6. Results

   a. Please keep digital figures consistent. Sometimes there are none and sometimes 2. 1 would be enough

      Answer 11: We selected non digital figures because the BMJ manuscript submission guideline not support digital figures (example 2.1, 2.2---etc).

b. The tables are not properly labelled. You should write under the Cases/Controls what the numbers in the table means. In this case it is N (%). All the tables need to be better labelled.

Answer 12: We made modification during period of investigations.

c. Clinical characteristics of study participants paragraph page 7. This paragraph needs to be re-written. Why is "cases" and "controls" inside the parenthesis? The sentence should make sense even if not reading the parenthesis. Also patients normally don't have the habit of treatment interruption, it is history of treatment interruption.

Answer 13: We made revision.

d. Page 8 First paragraph. Please also here revise the wording as not clear.

Answer 14: We made revision

e. Define alcohol drinking history. What does it mean? How was it measured? Was it over drinking? Did you use a standardized tool to assess this? You need to specify this.

Answer 15: Definition of alcohol consumption is alcoholic beverages that are typically somebody consumed may include beer, wine, or locally made (arake), and beverages that contain combinations of these or other additives.

Simply we asked the study respondent, "Did you consume or use alcohol?" (1. Yes 2. No). Lastly, we categorized their response as yes and no. We assumed if study respondents had answered yes, they were categorized as had a history of alcohol drinking.

7. Ethical approval page 12: You did not mention risks for the patients in participating in the study. Even if you think there are no risks you should say why.

Answer 16: We modified it. "The study was conducted in accordance with the guidelines of the Declaration of Helsinki".

Reviewer 2:

1. In the Introduction section, page 3, lines 20-25, the authors listed variables that they hypothesized to be risk factors for MDR-TB in the study region, such as diabetes mellitus and malnutrition that were not addressed in this study. Were these variables assessed?

Answer 1: Thank you. We made some mistakes. We made details revisions in the introduction section and we almost replaced current information in introduction section. We didn't assess the variables like diabetes mellitus and malnutrition." Mycobacterium tuberculosis infection is associated with factors such as smoking, occupation, alcoholism, TB-HIV co-infection. Previous TB treatment and history of contact with known TB patient and interruption of treatment is the strongest risk factor to the development of drug resistant".

2. The Materials and Methods section “Data collection procedures and quality assurance” lists variables that were not reported in the Results section (occupation, adverse effects of TB medication, knowledge of TB). It is not clear if those variables were used or discarded in the analyses.

Answer 2: Thank you for reminding missed variables. We incorporated the variables mentioned by reviewer. We deleted some variables that you mentioned above were due to sake of minimizing page numbers of manuscript. We understood that is not good for readers.

3. Discussion section, page 10, lines 12-13: please identify which factors were measured and found not to be associated with MDR-TB in this study.
A very similar study, cited in this work (ref 11), was conducted previously in Ethiopia to clarify risk factors associated with MDR-TB disease. Please discuss how the present study adds to this previous report.

   Answer 3: We revised the discussion section. “However, variables like age, sex, educational status, adverse effect, knowledge of TB symptoms, history of prison and TB treatment outcome were not statistically associated with MDR-TB in this study”.

   Yes, a similar study was conducted previously in Ethiopia. There are different reasons:

   - Study setting difference, a previous study was conducted in the Oromia region of Ethiopia (Adama and Bishotu Hospitals), and our study was conducted in Southern Region Ethiopia (NEMMCS and Butajira Hospitals). The quality of care and infrastructures might not be similar at hospitals.
   - The smoking cigarette was not identified as a risk factor in the previous study, but in our case smoking cigarette was one potential risk factor for the occurrence of MDR-TB.
   - Sample size and listed variables were somewhat different.

4. In the Introduction section, page 3, lines 49-52, the authors justify the work considering the importance of assessing the risk factors for MDR-TB development to address current gaps in service coverage, as well as monitor the progress of TB detection and treatment. Please discuss how the results presented may be useful to achieve the aforementioned goals, and which gaps persist that should be investigated in further studies.

   Answer 4: We revised this paragraph.

5. Patient consent, page 13, line 13: Please state that written consent was obtained from all participants.

   Answer 5: Thank you. We obtained informed consent other than written consent. Because in our cases most of the study respondents were not read and write. So, our study reports also indicated this issue.

6. Abstract, page 2, line 16 – The variable analyzed was direct contact with a TB or an MDR-TB patient?

Answer 6: Individuals had a history of direct contact with either TB patients or MDR-TB patients before developing TB.

7. Abstract, page 2, lines 18-19 – The variable “place of residence” refers to residence in urban vs non-urban settings. Please indicate it clearly.

   Answer 7: Thank you. We modified as rural residence. “rural residence (AOR=4.71; 95%CI=3.13-9.58)”

8. Introduction, page 2, lines 46-47 – MDR-TB was defined twice in this paragraph.

   Answer 8: We made revision during the period of investigations.

9. Introduction, page 2, lines 5-53 – The number of MDR-TB cases in 2018 stated in this sentence is higher than the number of MDR-TB cases in 2019.

   Answer 9: We modified the introduction section by incorporating current information of MDR-TB.

10. Introduction, page 3, lines 40-52 – This paragraph is very confusing. What is “MDR-TB privation and control”?

    Answer 10: We made modifications by replacing other sentences.

11. Materials and Methods, page 4, lines 28-29: Please specify clearly which criteria were used for patient inclusion and which criteria were used for patient exclusion from the study. Sputum culture was not performed to complement TB diagnosis for non-MDR-TB patients?

Answer 11: Thank you.

Inclusion Criteria: The inclusion criteria were MDR-TB and non-MDRTB patients who were under treatment follow up during the study period. Patients were confirmed by culture and sensitivity testing considered as MDR-TB and patients were either newly or previously treated TB patients who had smear microscopy that was positive for acid-fast bacilli (AFB) or had clinical and/or radiological evidence of disease were included considered as TB.

Exclusion Criteria: Patients with extra pulmonary tuberculosis or extensively drug-resistant tuberculosis (XDR-TB) were excluded from the study.

12. Results, Table 3 – The variable “history of migration” refers to migration from non-urban to urban areas?

    Answer 12: No, if patients had a history coming from outside of the country. We included this variable because there are a large number of migrations in our setting.

13. Results, Table 4 – Please define the acronyms COR and AOR. The variable “Direct contact with TB patients” refers to MDR-TB patients? The variable “TB treatment outcome” refers to previous TB treatment?

    Answer 13: Thank you for your genuine comments. We revised as per your comments.

Reviewer: 3

1. Sample size- why use 1:4 Case: Control ratio? Any justification?

Answer 1: Thank you. We selected 1:4 case to control ratio because in our situation cases were rarely found. In such situation most of epidemiologists recommend to take case to controls ratio1:4 during sample size determination that will increase power to detect statistically significant differences between cases and controls.

2. Setting-Two big specialized hospitals. Despite that why more samples are from rural areas? A little description of the setting could be useful.

   Answer 2: We didn't classify study population as urban and rural before data collection. Simple we asked them where you are live, then we categorized as urban and rural during data analysis. In such way the sample size might not be increased for some specified group of population.

3. Did the authors collect any information on the professions of the respondents?

   Answer 3: No, we didn't collect information for respondents' professions.

4. Did the authors collect any information on other reported risk factors for MDR-TB, like Diabetes Mellitus, Drug abuse, alcoholism, malnutrition, and or any other co-morbidities?

   Answer 4: We made some modification about variables information. And, we didn't collect data about diabetes mellitus, drug abuse, alcoholism and malnutrition, but we collect data about cigarette smoking, alcohol consumption, history of migration, etc.

5. All the risk factors mentioned are also well studied and known risk factors for drug-sensitive TB. The authors may need to clarify what additional risk, these factors pose for MDR-TB? For example, close contact with a TB patient poses a risk factor for a non-TB person to develop either drug-sensitive TB or MDR-TB? How do differentiate the risk?

   Answer 6: Thank you for your constructive comments and suggestions. Such kind of study was not conducted in our setting and the gaps about occurrence of MDR-TB were not study very well. We didn't really know what factors are potentials risk factors for occurrence of MDR-TB in our setting. So, such conditions were motivated us to conducted research in this topic.

6. Clarifications:

   a. Table 2: History of contact with TB Patient? (Any TB patient or MDR-TB patient?)

   Answer 7: Either TB patients or MDR-TB patients before developing TB.

   b. Table 2: History of Previous TB treatment? (Any TB or MDR-TB?)

   Answer 8: Patients that have received 1month or more of anti-TB drugs (of any TB) in the past may have positive or negative bacteriology result.

   c. Table 2: TB Treatment Outcomes (Failure or default?)? Failure of treatment and default are two different outcomes. While failure indicates earlier resistance during

the treatment phase, default could be from totally different causes including behavioral or social causes. Please rethink, before lumping them together.

Answer 9: Sorry we made mistake during categorization of variable value. We revised based on your comments.

7. Minors:

   a. Page 4, Line 2; MDR/RR (please provide full abbreviation for the first-time use.

Answer 10: We revised during period of revision of comments.

   b. Page 7, Line 15; “More than” what?

Answer 11: Thank you. We made correction. “More than half of the respondents were male (55.12% of cases and 55.27% of controls) and More than half of respondents had no formal education (58.23% of cases and 51.11% of controls)”

VERSION 2 – REVIEW

REVIEWER	Verdecchia, Maria Medecins Sans Frontieres Luxembourg
REVIEW RETURNED	02-Sep-2022

GENERAL COMMENTS	Thank you for the opportunity to review this paper. In general, I think that it has greatly improved since last revision but I think that the conclusion is very weak as it states the findings of the results session without elaborating on them. Also, the author talks about adherence but the study doesn’t really determine if patients were adherent to the previous treatment. It is true that the "failure" outcome from previous TB could be a proxy for poor adherence but this is not elaborated. It also states the need for further studies but, again, it does not elaborate the reasons for this. Additionally, limitations of the study are not very well described. Therefore, I suggest that the conclusion and discussion paragraphs are revised and elaborated further. I also suggest and editorial review as the English is still not really appropriate for publication. Other observations: Line 24. “The study” or “the analysis” is missing. Line 26: what is the minimum age of the participants? It is not clear and if there are minors an explanation of how consent was sought should be given. Line 39-40: reference (8). It is missing a verb.

REVIEWER	Hossain, Shahed icddr,b, Centre for Equity and Health Systems
REVIEW RETURNED	07-Sep-2022

GENERAL COMMENTS	Risk Factors of Multi-Drug Resistance Tuberculosis among Tuberculosis Patients at Selected Multi-Drug Resistance Treatment Initiative Centers in Southern Ethiopia: A Case-Control Study (Ref: bmjopen-2022-061836.R1) General Comments: 1. Thanks for the revision of this important study manuscript 2. The manuscript needs further English editing and proofing 3. Result section: i. Please conduct an initial comparison of the socio-economic characteristics (Table 1) between the cases and control. They seem to be highly dissimilar at the baseline and therefore may bias the findings. ii. Please provide and upload (if necessary, in the accompanying document section) the bivariate results of all the variables with the exact p values and their confidence intervals. iii. If possible, please check interaction results in MLR of some suspicious variables (HIV infection, Knowledge of TB symptoms, etc.) with all 4 significant variables' outcomes. 4. Discussion: The discussion is not well articulated and needs further development. Thanks.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1:

1. In general, I think that it has greatly improved since last revision but I think that the conclusion is very weak as it states the findings of the results session without elaborating on them. **Answer 1:** We want to thank you for constructive comments and suggestions. English language experts made intensive revisions on English language and highlighted in yellow color.
2. Additionally, limitations of the study are not very well described. Therefore, I suggest that the conclusion and discussion paragraphs are revised and elaborated further.

   Answer 2: Thank you. We made major corrections in the discussion, conclusion section and limitations of the study.
3. Line 26: what is the minimum age of the participants? It is not clear and if there are minors an explanation of how consent was sought should be given.

Answer 3: Thank you for your comments. The minimum age of the study participants were 19 years

4. Line 39-40: reference (8).It is missing a verb.

   Answer 4: We made correction during period of investigation.

Reviewer 2:

1. The manuscript needs further English editing and proofing

   Answer 1: Thank you. English language experts made intensive revisions on English language and highlighted in yellow color.

2. Please conduct an initial comparison of the socio-economic characteristics (Table 1) between the cases and control. They seem to be highly dissimilar at the baseline and therefore may bias the findings.

   Answer 2: Thank you very much. We constructed table 1 for descriptive statistics only. It describe frequency and percentage of cases and controls.

3. Please provide and upload (if necessary, in the accompanying document section) the bivariate results of all the variables with the exact p values and their confidence intervals.

   Answer 3: We attached bivariate analysis output as supplementary materials.

4. If possible, please check interaction results in MLR of some suspicious variables (HIV infection, Knowledge of TB symptoms, etc.) with all 4 significant variables' outcomes.

   Answer 4: We really appreciate for comments and suggestions. We tried to check variables interaction some variables (HIV infections, knowledge of TB symptoms, direct contact to TB patients, and previous history of TB treatment), but none of them made interaction effects. The interaction results were statistically insignificant.

5. Discussion: The discussion is not well articulated and needs further development.

   Answer 5: Thank you. We tried to articulate discussion very well and we made some additional points in discussion section.

VERSION 3 – REVIEW

REVIEWER	Verdecchia, Maria Medecins Sans Frontieres Luxembourg
REVIEW RETURNED	14-Nov-2022

GENERAL COMMENTS	This version of the paper his majorly improved. I still think that the limitations of the study are not well described. Not only it should be described what are the limitations but also what has been done to mitigate them. More emphasis should be put on this aspect.

REVIEWER	Hossain, Shahed icddr,b, Centre for Equity and Health Systems
REVIEW RETURNED	15-Nov-2022

GENERAL COMMENTS	Risk Factors of Multi-Drug Resistance Tuberculosis among Tuberculosis Patients at Selected Multi-Drug Resistance Treatment Initiative Centers in Southern Ethiopia: A Case-Control Study (BMJ Open Manuscript # 2022-061836.R2) General Comments: This second revised version is much more improved than the earlier

	versions. However, further revision of the language is required (e.g., Grammar and Tense used etc.) Few specific Comments: 1. Many repetitions all through the body of the text 2. Not consistent in the use of numbers (e.g., number of digits after decimals) 3. In the statistical analysis it is not clear why the authors used two estimates of p values for the significance tests (P≤ 0.25 for bivariate analysis and P≤ 0.05 for multivariate analysis) 4. Results section: Cases seems to be younger (Age between 19-30), more Rural and engaged more in informal occupation (e.g., Farmers). Some of these were identified as risk factor for RR/MDR TB. The authors can discuss further whether these had any bearings in the selection procedures (despite being selected randomly) or the y have any conjugate interaction on the development of RR/MDR TB! Thanks!

VERSION 3 – AUTHOR RESPONSE

Reviewer 1:

1. This version of the paper his majorly improved. I still think that the limitations of the study are not well described. Not only should it be described what are the limitations but also what has been done to mitigate them. More emphasis should be put on this aspect.
Answer 1: We want to thank you for constructive comments and suggestions. We incorporated some limitations and what will been done to mitigate them, but there were some difficult to include all points that address limitation of our study, which was BMJ open manuscript preparation guideline does not allow more than 5 bullets in study strength and limitation sections.

Reviewer 3:

1. This second revised version is much more improved than the earlier versions. However, further revision of the language is required (e.g., Grammar and Tense used etc.)

Answer 1: Thank you. English language experts made intensive revisions on English language and highlighted in yellow color.

2. Many repetitions all through the body of the text.

Answer 2: Yes, We made repetitions due to maintain consistence of idea and study subjects.

3. Not consistent in the use of numbers (e.g., number of digits after decimals)

Answer 3: Thank you for your reminding us how to use digits after decimals. We made correction in main document.

4. In the statistical analysis it is not clear why the authors used two estimates of p values for the significance tests (P≤ 0.25 for bivariate analysis and P≤ 0.05 for multivariate analysis)

Answer 4: Thank you for raising these kind of critical comments and questions. We used P-value ≤ 0.25 for bivariate analysis to select candidate variables to fit multivariable logistic regression analysis. However, parsimonious/condensed model was not recommended that only include the predictors has P-value <0.05 or even stricter criteria, because the potential for residual confounding in such models is substantial and p-value <0.05 for multivariate analysis was used to declare statistical significance.

5. Results section: Cases seems to be younger (Age between19-30), more Rural and engaged more in informal occupation (e.g., Farmers). Some of these were identified as risk factor for RR/MDR TB. The authors can discuss further whether these had any bearings in the selection procedures (despite being selected randomly) or they have any conjugate interaction on the development of RR/MDR TB!

Answer 5: We really appreciated you for comments and suggestions. We computed frequency and percentages of cases and controls separately (we used column value for computing percentage cases and controls variables). Most of cases (56.96%) were presented in age between 30-40 years old and 54.43% were come from rural setting. We tried to check variables interaction in some variables, such as HIV infections, knowledge of TB symptoms, direct contact to TB patients, and previous history of TB treatment),but the interaction results were statistically insignificant.