Author’s response to reviews

Title: Spatial Analysis of HIV-TB Co-clustering in Uganda

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Author’s response to reviews:

Answers to the reviewers’ comments

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Editor’s Comments

Comment 1

The consensus is that your manuscript is interesting and has some merit. However, the reviewers have raised some important issues, with which I agree, and I have thus decided that major revision is in order before we can reconsider it for publication. Please be aware that additional review does not guarantee acceptance.

Response

We are happy that you found our research interesting. We are also thankful for the insightful comments that we believe have improved the paper substantially.

Summary of what we have changed

- The manuscript was updated based on the comments.
- Some parts of the “methodology” and “results” sections have been shortened based on the comments of the second reviewer.
Some texts were added especially in the “data subsection” and “discussion section” based on the comments of both reviews.

Comment 1

Please, proof your manuscript for mistakes. The phrase “Error! Reference source not found” is found multiple times in your manuscript.

Response

We have fixed this error. It was generated whenever a (Figure) caption was moved or deleted.

Comment 2

Your statement on line 111: “The recorded TB and HIV were all diagnosed cases and not necessarily newly diagnosed” - does this statement mean that your data could be redundant, that is, patients were returning from previous years and recorded at each visit? Would it be possible to include newly diagnosed patients only? Please clarify.

Response

Thank you for this observation. The related sentences have been edited to read, “The recorded TB and HIV were all diagnosed cases ....” (line 111-112). Uganda does not have a centralized health registry system; patient historical records are therefore hard to follow precisely, especially when one changes a hospital or point of care. These admissions are thus recorded as new cases.

Comment 3

Line 335: “We thus think that the TB/HIV hotspot around Lake Victoria is driven by the high HIV prevalence rates among the fishing communities”. You may consider discussing the results of a recent report that high HIV prevalence may be due to infections from the general population into the fishing community (Bosna et al. Phylogeography of HIV-1 suggests that Ugandan fishing communities are a sink for, not a source of, virus from general populations. Sci Reports Sci Rep. 2019 Jan 31;9(1):1051. doi: 10.1038/s41598-018-37458-x, pmid: 30705307).

Response

We have read the mentioned study and used the observations by Bbosa et al., (2019) in our discussion (line 293-300).
Reviewer 1 (Dr. Zahid Butt)

Comment 1

This is an interesting study on HIV-TB clustering in Uganda. The authors have used various spatial methods to highlight HIV-TB coinfection clusters across Uganda which may be used for targeted interventions.

Response

Thank you for your positive review of our manuscript. Thank you for the comments also; undoubtedly, the manuscript has improved thence.

Comment 2 (major)

For spatial scan statistics, was an analysis done on HIV-TB coinfection? This would show clusters that have HIV-TB co-infection, which could then be compared with HIV-TB hotspots obtained through co-clustering analysis (Figure 5).

Response

Since we did not have reliable HIV-TB coinfection data, we were not able to run a clustering analysis on HIV-TB coinfection. In the paper, we added the reason why the data was not reliable (line 115-117). Instead, in order to study the co-occurrence behavior of TB/HIV, we used Bivariate Local Moran’s I as described in section 2.3.3 and the results are provided in section 3.3.

Comment 3 (major)

The Poisson cluster analysis in SatScan has the ability to adjust for various factors. Did the authors have information on factors related to HIV and TB in the DHIS2 system? If so, could they have been used to do a more robust analysis in SaTScan? Could the authors comment on this?

Response

Unfortunately, we did not have additional information about risk factors. The DHIS2 system is an aggregate system mainly concerned with recording diagnosed cases only. Indeed, if we had this information, we would have run a (spatial) regression analysis. We have added an explanation in this regard to the last paragraph of the discussion section (line 340-345).
Comment 4 (major)

In the discussion section, the authors have highlighted most of the findings from a HIV standpoint. However, what are the factors that are driving the TB epidemic especially from the perspective of co-clustering of HIV-TB co-infection? Is it population dynamics (overcrowding, high population density) or sociodemographic characteristics (poverty, health care access issues)? This has public health implications especially since the study recommends targeted interventions. Could the authors elaborate on this?

Response

Yes, population-level factors like malnutrition, smoking, diabetes, alcohol abuse, poverty, contact with persons with active TB, overcrowding, indoor air pollution, etc. are partly responsible. A text-portion discussing the additional TB risk factors was added to the text (line 293-300).

Comment 5 (major)

The authors have reported a TB/HIV hotspot cluster around Lake Victoria. High HIV prevalence has been documented before but what could be the factors responsible for the TB component of the HIV/TB co-infection in this particular population.

Response

A paragraph addressing the TB component of the TB/HIV infection has been added to the text (line 321-325).

Comment 6 (major)

What are some of the limitations of this study and of the methods used in this study? The district level HIV-TB co-infection clusters identified in this study are at a higher level of geography. With regards to targeted interventions, would a lower (e.g. sub-district level) more granular analysis be more appropriate? Could the authors comment on this?

Response

The primary limitation to the study was higher level of geographical analysis. Finer-level data would inform intervention better. However, data was only available at the district level. A paragraph discussing the limitations has been added to the text (line 340-345).
Minor comments

Please correct "Error! Reference source not found. "This is found in multiple places in the manuscript. * Figure 5: Please indicate what a to i signify in the figure legend.

Changes

The legend for Figure 5 has been fixed. Reference Error has been fixed too.

Reviewer 2 (Dr. Suparna Das)

Comment 1

Thank you for this opportunity. The study is an important piece for Uganda or for any developing country which is suffering from similar health comorbidities. I believe that the paper is an important contribution to the field which struggles to gauge spatial health issues thus inform prevention intervention.

Response

Thank you for your positive review of our manuscript. We believe that your comments have improved the study significantly.

Comment 2

The analysis suffers from tremendous redundancies. The paper should be simplified. The idea is simple - to identify spatial clusters of TB-HIV coinfections for prevention intervention. The outcome is lost in translation, where the zeal of the author(s) was primarily evident in using several methods to say the same thing. While, colored maps and cool graphs grab people's attention, we must be careful of the implications of statistics.

Response

We have eliminated some parts to make the text more concise. Other parts were summarized.

- Section 2.3 and its subsections were summarized and the description of methods modified for more clarification.

- Cluster detection by LISA and its results were removed from the text (section 2.3.3 and section 3.2.2 in the previous version).
Comment 3

Retrospective space time analysis using SaTScan would identify space-time clusters.

Response

Given the fact that we had data for just 3 years, we opted for purely spatial analysis as the temporal dimension was limited. Still, if you think such analysis using the three years data is needed, we would be happy to add that to the next version of the manuscript.

Comment 4

I am guessing the author(s) used discrete Poisson probability model to identify spatial clusters (it is not clearly mentioned in the method section). Then, what is the point of LISA? It does the same thing. Global Moran's I can be used to identify whether the data was spatially autocorrelated or not to justify the spatial cluster analysis and that would be sufficient.

Response

We apologize for not being clear about the Poisson probability. The text was modified to reflect the utilization of Discrete Poisson probability (Line 169, 171).

About LISA and Spatial SatScan, the LISA part has been eliminated and its ‘would be’ results have discussed from the SatScan perspective.

Comment 5

I am not sure if data is available that can be matched - people who have HIV and coinfected with TB. If not I see the reason for bivariate Moran's I. Though it is not the most effective way of identifying spatial clusters.

Response

You are right. We did not have reliable data about HIV-TB coinfection. We outlined the reason why the data was not reliable in the text (Page5; line 115-117). We, thus, used BiLISA to investigate the simultaneous TB/HIV occurrence and hence co-clustering in both TB and HIV. This was clarified by revising the sentences in line 143-145 and line 238-258.

Comment 6

I would rather use a spatial regression, controlling for other explanatory variables too.
Response

We fully agree with your suggestion. Unfortunately, the only data available (collected by DHIS2) was the TB and HIV diagnosis records. Had other explanatory variables been available, spatial regression analysis would have been used.

Comment 7

With multiple methods, the results became confusing.

Response

We agree with your comment. Hence, in order to address the problem, we have reduced the methods by excluding LISA. We have retained results from SatScan and BiLISA. Hopefully, the reduction along with other polishing in the manuscript makes it more concise.

Comment 8

Statistical guidelines across nations are strictly opposing use of p values as measure of statistical significance. I am sure this journal is using the same guidelines, the authors should check them. More over p < 0.05 is used as both significant and not significant in the result section. This error completely changes the results. Attention needs to be paid.

Response

We have made amendments to the text, with regard to the SAMPL guidelines (BMC) and the American Statistical Association statement on P-values (line 198-199 and line 231-237).

Comment 9

The methods used by the author(s) are not new, including the formula in the method section is not required, they can just cite the paper, which they have not. This will help simplify the manuscript as well.

Response

The Global Moran’s I formula has been removed. However, we suggest that the equations about SatScan and BiLISA remain in the text to help the readers. Meanwhile, if the reviewer still think that even with the current shortenings, the equations for SatScan and BiLISA should be removed, then we will do so.