Author’s response to reviews

Title: Disparities in access to diagnosis and care in Blantyre, Malawi identified through enhanced tuberculosis surveillance and spatial analysis

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Author’s response to reviews:

Tuesday, 30th October 2018

Dear Dustin Graham,

Re: BMED-D-18-01128. Disparities in access to diagnosis and care in Blantyre, Malawi identified through enhanced citywide tuberculosis surveillance and spatial analysis

I write on behalf of my co-authors to thank the reviewers for their careful re-review, and appreciate the opportunity to respond with a revised submission.

Please see point-by-point responses below.

Yours Sincerely,
Responses to Reviewer 2’s comments

1. I thank the authors for revising the paper. I have had the opportunity to read the revised paper (which I believe is now clearer) than the earlier version. I feel the authors have fairly addressed the issues raised in my previous review. However, there are three more points that deserve further clarification.

We thank the Reviewer for these comments, and their careful re-review of our manuscript.

2. The authors make the case for an "enhanced surveillance of TB" using high-quality spatially-resolved surveillance data...to identify the most important and modifiable barriers to TB diagnosis and treatment. The "enhanced surveillance of TB" constituted three components:

a) enhanced surveillance form that recorded registration centre, age, sex, any sputum smear results taken as part of routine care (positive, negative, or not done), TB treatment category (using standard Ministry of Health/WHO categories), TB classification (pulmonary or extrapulmonary TB) and HIV status (positive, negative or unknown).

b) Geolocation the physical location of each TB case's dwelling using satellite maps

c) Microbiological surveillance using a single sputum sample for smear and culture collected from registered TB patients

Comment: The information collected using the enhanced surveillance form are routine information collected from all TB patients and recorded in the TB registers. Thus, what constituted the enhanced surveillance mainly are geolocation of cases and additional microbiological screening. Please, did the authors attempt to differentiate between the smear/culture status (registered for each patient) through the NTP processes and the smear/culture status obtained using the additional microbiological screening. Which of these was the numerator in the smear positive:negative ratio and other analysis performed?

Thanks for these comments. We are grateful that the Reviewer recognises the substantial efforts the study team and Blantyre TB Officers undertook in implementing enhanced TB surveillance...
activities for registering TB cases in this resource-limited African setting. To the best of our knowledge, no study has attempted to integrate demographic, clinical, microbiological and geospatial TB surveillance at this scale previously in a high TB burden setting. We believe the study provides important epidemiological insights into barriers to TB diagnosis and treatment.

With regards to differentiating smear/culture status on registering TB patients:

a) Please note that (as described on Page 7, Lines 27-31), TB culture was not performed by the National Tuberculosis Programme as part of routine clinic activities. This is standard in many African settings, where TB culture is prohibitively expensive, requires sophisticated specimen transport and laboratory infrastructure, and is slow. We cannot therefore compare enhanced surveillance TB culture specimen results with routine care.

b) We have however reported differences between routine clinic and enhanced surveillance sputum smear results. In Table 1, and in Page 11, Paragraph 2 we report the fraction of routine clinic and enhanced surveillance sputum samples that were smear positive. Overall, 62% of routine clinic specimens and 45% of enhanced surveillance specimens were smear positive respectively. The difference can be explained by the fact that a substantially greater number of patients did not have a sputum sample taken by routine clinic programme. This is to be expected, and reflects the difficulty in completing TB investigations in resource-limited settings. In contrast, we obtained substantially greater additionality by routine collection of a single spot sputum sample at the point of registration through study enhanced surveillance activities.

c) In the analysis, the sputum smear positivity ratio obtained through routine clinic samples was used. We specified this in the Methods, when we stated:

“[...] as a marker of late presentation for diagnosis – of the ratio of sputum smear-positive to smear-negative notified cases (on smears done by the routine health system; [...]”

3. I understand the authors planned to identify the most important and modifiable barriers to TB diagnosis and treatment. However, from the study results, I struggle to understand or identify these "modifiable barriers to TB diagnosis and treatment". Also, it appears that a priori the potential modifiable barriers were not considered in the design of the study.

The modifiable barriers to TB diagnosis and treatment identified were: increasing proportion of the neighbourhood living poverty; neighbourhood distance to the nearest TB registration clinic; and higher adult male-to-female ratio. These are all modifiable determinants of access to TB diagnosis and care that could be addressed by public health programmes. For example, we
provided some suggestions for neighbourhood interventions that could reduce these disparities, and improve access to TB diagnosis and care in Page 19, Paragraph 1, where we stated:

“[…] policy-makers should strongly consider prioritising the implementation of pro-poor interventions to improve access to TB services in these underserved neighbourhoods. This could include expanding or relocating primary health care centres with comprehensive TB and HIV services,[19] periodic mobile TB screening camps,[20] or targeted community-wide active case-finding interventions.[21, 22] There may also be a potential impact from wider development interventions, not specific to TB.”

Potential barriers identified for inclusion in our analysis were informed a priori (i.e. prior to analysis) by our knowledge of important epidemiological drivers of TB burden and access to care, by our previous qualitative and quantitative studies the study neighbourhoods, and by the data that was possible to collect through the enhanced surveillance activities.

4. Also, the authors stated that "Where notified TB cases were resident within a study-mapped CWH catchment area, we classified them as CHW-catchment area residents; where TB cases were resident in an area of the city not mapped by study activities, or in another part of the country, we classified them as non-CHW catchment area resident."

I find the fact that the authors assumed that: "TB cases that are resident in an area of the city not mapped by study activities, or in another part of the country" to have the same characteristics and therefore grouped together concerning. I feel it will be good to consider these (TB cases resident in an area of the city not mapped by study activities, and those in another part of the country) as two independent population in their analysis.

Thanks for this comment. Please see Table 1 (and the accompanying paragraphs), where we compared the demographic clinical and microbiological characteristics of TB cases resident – and not resident – in Community Health Worker areas mapped by study activities. We did find differences in demographic characteristics between these groups, and described these in Pages 11 and 12, where we stated:

“Characteristics of CHW-resident and non-resident TB cases were broadly similar, but with some important differences (Table 1). Overall, 61% (3727/6077) of TB cases were male, 60% (3629/6076) had pulmonary TB, and 60% (1536/4089) were recorded as being sputum smear positive in the clinic TB register. Ascertainment of HIV status by TB Officers was very high, with HIV-status recorded in >99% of cases. Overall, 67% (3964/5915) of TB cases were HIV-positive. However, compared to non-CHW area resident cases, CWH area resident cases were more likely to be male (64% vs. 58%), have pulmonary TB (62% vs. 55%), be sputum smear-positive on routine clinic sample (62% vs. 56%), and on study laboratory sample (45% vs. 39%), and be culture positive on study laboratory sample (59% vs. 49%).”
Because we did not have geospatial data on TB cases not resident in mapped Community Health Worker areas, they cannot contribute to any geospatial analysis of TB cases. We have therefore, within the constraints of the data available, already analysed these groups as separate populations.

5. Also, I also find that the authors excluded TB patients from business and industrial areas and the most affluent areas of Blantyre concerning. Considering that almost 39% of the patients in this study were from non-CHW catchment area resident, I feel there is a need to further clarify the two groups (TB cases were resident in an area of the city not mapped by study activities, and those in another part of the country).

Thanks for these helpful comments. It is important to note that TB cases classified as Non-Community Health Worker residents may have in fact been resident either within an area of Blantyre District that had not been mapped by study activities, or alternatively another district somewhere else in Malawi. We have provided data to show the breakdown of cases by geographical area in Page 11:

“Overall, 6077 (78%) registering TB cases were captured by the ePAL geolocation system. Of these, 3723 cases were resident within a CHW catchment area, and 2354 were not: 1722 residing in a District outside Blantyre city, and 632 resided inside Blantyre city but outside of a study CHW catchment area or in an area of the city that had not been mapped by study activities and where enhanced surveillance GPS coordinates could not be obtained.”

To provide additional clarity, we have added a sentence to the Discussion:

“Additionally, because we could only collect geospatial data from TB cases who were resident within neighbourhoods mapped by our study activities, we are unable to include TB cases resident outwith mapped areas in our regression analysis.”

6. In addition, given that the study demonstrated "inverse care law" whereby poorer neighbourhoods and those furthest from TB clinics have lower relative CNR, there is a need to truly demonstrate the existence of this law considering that a substantial proportion of patients residing in business and industrial areas were excluded and these areas are likely to attract the poorest (including accommodate them in shanties and informal crowded setting) as they will most likely migrate to these areas for better economic survival coupled with the fact that areas in the more peripheral and semirural areas were sparsely populated. These might confound the relationships between poverty, distance and TB CNRs.
We thank the Reviewer for this comment. Please note that, in discussing our results, we were extremely careful not to use the phrase “demonstrated an inverse care law”. In fact, the first paragraph of our Discussion is carefully worded to state:

“Through enhanced citywide TB surveillance in Blantyre, Malawi, we found evidence supporting the “inverse case law […] If a high burden of undiagnosed TB is confirmed, then, policy-makers should strongly consider prioritising the implementation of pro-poor interventions to improve access to TB services in these underserved neighbourhoods.”

Nevertheless, we agree that these factors may be potentially important confounding factors. In our multivariable models we adjusted for neighbourhood poverty, population density, and adult male-to-female ratios.

7. The authors recommend: "If a high burden of undiagnosed TB is confirmed, then, policy-makers should strongly consider prioritising the implementation of pro-poor interventions to improve access to TB services in these underserved urban neighbourhoods". Unless I am missing something, I thought the challenge of poverty and notifications was for catchment areas in the poorer, and less-densely populated outer suburbs/semi-rural areas. Why are the authors recommending TB services in underserved urban neighbourhoods?

Thank you for this comment. We have reworded this sentence for clarity:

“If a high burden of undiagnosed TB is confirmed, then, policy-makers should strongly consider prioritising the implementation of pro-poor interventions to improve access to TB services in these underserved neighbourhoods”.

Responses to Reviewer 3’s comments

1. The authors have thoroughly addressed all reviewer’s comments and have considerably improved the manuscript by adding additional information to the methods section, revising parts of the result section, and elaborating on the discussion section including the limitations.

We thank the Reviewer for these comments.
2. I am struggling to understand/find the reason why some data were changed, e.g. the total number of TB cases in the first paragraph under "TB case notifications". Thanks for clarifying.

Thank you for this comment. In the previous round of review, Reviewer’s requested clarity around definitions of TB cases’ residency status, which prompted us to undertake an amended analysis of baseline characteristics of study participants. In doing so, we merged datasets containing data on all TB cases registering for treatment during the three-year study period with geospatial datasets. In doing so, there were small changes in the numbers of TB cases included within denominators. To ensure openness, we have made all datasets and analysis for reproduction available. We hope that this addresses the Reviewer’s question.

3. Exclusion of most affluent and industrial catchment areas - could you provide information on how these were identified? Personal opinion? Income data? Thanks.

Community Health Worker areas were identified for inclusion in the mapping activities based on our collective experience of >10 years of undertaking research activities in Blantyre. Additionally, we sought advice from Blantyre District Health Office and from Community Health Workers who had participated in previous cluster-randomised trials and epidemiological studies. Whilst we acknowledge that mapping coverage of the entire city was not complete, we believe that our knowledge of the city of Blantyre allowed prioritisation of the poorest neighbourhoods with the highest TB burden. With additional resources in future studies, we may be able to expand mapping activities to neighbourhoods not currently mapped by study activities. We emphasised these points in the Limitations paragraph when we stated:

“We concentrated mapping activities on the largest, and most deprived neighbourhoods of the city, and excluded business districts and the most affluent neighbourhoods. Thus, we will have systematic under-sampled TB patients from middle-class homes. Reflecting these different underlying populations, non-CHW catchment area resident cases did have different characteristics compared to CHW resident cases. Additionally, because we could only collect geospatial data from TB cases who were resident within neighbourhoods mapped by our study activities, we are unable to estimate what fraction of non-Community Health Worker resident TB cases lived in an unmapped area of Blantyre or alternately in another District of Malawi.”

Responses to Reviewer 5’s comments

1. This is a well analysed and well written manuscript. I recommend authors to publish their Bayesian codes as a supplementary file.

Thank you for these comments and for the careful review.
Our analysis datasets and code have already been published in a GitHub repository, and are additionally made available for download as an R package. Please see Page 24, Lines 26-31 in the submitted manuscript, where we stated:

“The datasets and code supporting the conclusions of this article are available in the GitHub repository (https://github.com/petermacp/BlantyreTBEpi), or installed as an R package by running `devtools::install_github("petermacp/BlantyreTBEpi")`.”