Author’s response to reviews

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

Authors:

Peter MacPherson (peter.macpherson@lstmed.ac.uk; petermacp@gmail.com)
Mcewen Khundi (mcewenkhundi@gmail.com)
Marriott Nliwasa (mnliwasa@gmail.com)
Augustine Choko (augutc@gmail.com)
Vincent Phiri (vincentkatungaphiri@gmail.com)
Emily Webb (emily.webb@lshtm.ac.uk)
Peter Dodd (p.j.dodd@sheffield.ac.uk)
Ted Cohen (ted.cohen@gmail.com)
Rebecca Harris (Rebecca.Harris@lshtm.ac.uk)
Elizabeth Corbett (lizcorbett04@gmail.com)

Version: 1 Date: 20 Sep 2018

Author’s response to reviews:

Dr Peter MacPherson MBChB PhD
Wellcome Trust Fellow and Senior Lecturer
Liverpool School of Tropical Medicine &
Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Blantyre, Malawi

Honorary Consultant in Communicable Disease Control
Public Health England
Mob: +265997176230
Email: peter.macpherson@lstmed.ac.uk
Thursday, 20th September 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 review, and appreciate the opportunity to respond with a revised submission.

Please see point-by-point responses below.

Yours Sincerely,

Peter MacPherson
(On behalf of the authors)

Responses to Reviewer 1’s comments

1. The enumerated people from the census ranged from 162-13,066 per catchment area. Why is the range so broad, and can the smallest areas be directly compared to the largest areas?

Thank you. As described in the Methods, Blantyre is divided into non-overlapping geographical areas, each served by locally-resident community health workers. During this census, residents of each study community health worker catchment were enumerated. Some areas, particularly those in the centre of the city, which is comprised of informal settlements and slums, were more densely populated than others (See Figure 1). Whereas areas in the more peripheral and semi-rural areas were sparsely populated.

We did not directly compare the smallest areas to the largest areas. Instead the estimated case notification rates are compared, adjusted for population size (as well as for other important variables associated with TB risk).
2. Which are possible strategies to confirm low case detection? Wouldn't one such a strategy have been to include a symptom screen in the census, which would in addition address the "detection gap" as was mentioned a few times in the article?

We thank the Reviewer for raising this issue. The optimal method to confirm low case detection would be to undertake a tuberculosis prevalence survey across all study neighbourhoods. Tuberculosis prevalence surveys require extremely large sample sizes, and are very costly undertakings. We have not yet conducted a TB prevalence survey in Blantyre, but do plan to do so in 2019 as part of a community cluster randomised trial. We emphasised this point in the discussion, when we stated:

“This supports our hypothesis that late and/or underdiagnosis of TB from the poorest, more distant neighbourhoods was explained by poor access to diagnosis rather than by less prevalent disease. However, confirming this would need neighbourhood-level data from TB prevalence surveys (and in particular prevalence-to-notification ratios), ideally combined with local data on other intermediary determinants.”

The reviewer suggests we undertake a systematic survey of catchment area residents for TB symptoms to estimate the prevalence of undiagnosed TB. We believe this would not be an optimal approach. At community level, TB symptoms are common and non-specific, meaning that the positive predictive value of a TB symptom screen is very low, and the uncertainty in TB prevalence indirectly estimated in this way would be very high.

3. Which pro-poor strategies could be feasible in this setting?

In the Discussion, we highlighted potentially feasibly TB/HIV-specific “pro-poor” strategies that might be considered for implementation by National TB Programmes:

“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. This could include expanding or relocating primary health care centres with comprehensive TB and HIV services,[18] periodic mobile TB screening camps,[19] or targeted community-wide active case-finding interventions.[20, 21]”

Additional strategies that might be considered include: reduction of poverty through stimulation of economic development; improving housing quality; reducing air pollution; and improved working conditions; although these require much broader societal development interventions, and may not be amenable to change by National TB Programmes. To emphasise these points, we have added an additional sentence to the Discussion:

“There may also be a potential impact from wider development interventions, not specific to TB.”
4. Consider including a flow diagram showing how many areas in total, out of which how many were included in the analysis, and for those included, how many cases according to the NTP. Also, how many cases excluded and were they different from those included?

Thank you for this suggestion. We have added additional text to the Methods to describe how community health worker catchment areas were included in the study:

“To estimate population denominators for the study, we defined boundaries around 315 CHW catchment areas, excluding business and industrial areas and the most affluent areas of the city. Through community engagement activities, and with the support of the Blantyre District Health Officer, we provided training in census enumeration to CHWs in Blantyre. Between 10 October 2015 and 30 December 2015, CHWs, accompanied by study Research Assistants, undertook a circumferential walk around their catchment area to record sets of boundary coordinates using global positioning satellites devices. Where there was overlap between two contiguous CHW catchment areas, the circumferential walks were repeated and boundaries revised to ensure that no areas overlapped.”

We are not able to provide an estimate for the number of community health worker catchment areas that were not included, as we didn’t undertake geospatial mapping activities (CHW boundary definition, high resolution annotation with CHW points of interest – as described on Page 7, Paragraph 1) and census activities in these areas. We therefore feel that adding a flow diagram would not provide substantial useful information to readers.

5. According to the analysis, only 3723/7788 possible participants were included - comment on why the other 50% was not included (i.e. are they not from Blantyre? why were they not captured in ePAL?)

We thank the Reviewer for this helpful comment. To add greater clarity to these data and their description, we have made revisions to Table 1, to the Methods (Page 6, Paragraph 2,):

“To estimate population denominators for the study, we defined boundaries around 315 CHW catchment areas, excluding business and industrial areas and the most affluent areas of the city.”

Page 9, Paragraph 1:

“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. We compared the characteristics of TB cases that resided within and outside of study CHW catchment areas using proportions and means.”
“Between January 2015 and December 2017, 7799 TB cases were registered for TB treatment at the 18 TB registration clinic. Overall, 6077 (78%) registering TB cases were captured by the enhanced TB surveillance 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.

Characteristics of CHW-resident and non-resident TB cases were broadly similar, but with some important differences (Table 1). Overall, 62% (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 >97% 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%).”

In total, 6077 of 7799 (80%) of all TB cases registering in the city were successfully captured by the enhanced surveillance system, and 3723 were classified as being resident within a CHW catchment area that had been mapped in detail as part of the ePAL system.

To provide greater understanding of differences between CHW-resident and non-CHW resident cases, in the new version of Table 1, we compare cases’ characteristics across these strata. As was to be expected from our concentration of mapping activities within the poorest neighbourhoods of the city, there were differences between the groups; these are likely because non-CHW resident cases were systematically different to CHW cases, both in terms of their socio-demographic characteristics and their access to TB diagnosis. We have expanded upon the Limitations section in the Discussion to emphasise these points (Page 19, Paragraph 2):

“Overall we successfully recorded clinical, demographic data from 78% (6077/7799) of all registering TB cases at all 18 health facilities in urban Blantyre. We additionally completed microbiological surveillance by sputum culture from 71% of captured cases, and geolocated 70% of all TB cases registered at city health centres. 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.”

We have additionally updated the Abstract to reflect the changes.
We hope that these additional analyse and interpretation provides readers with greater understanding and clarity.

6. Were any dwellings excluded and why?

As described in the Methods, we undertook a comprehensive door-to-door survey of all dwellings within selected community health worker catchment areas. Fieldworkers undertaking the census were instructed to not enumerate any dwellings that were derelict or abandoned. Five per cent of enumerated households were randomly selected, revisited and re enumerated by a separate Research Assistant team for quality control purposes. We believe that the quality and completeness of the census were high.

We have added additional text to the Methods (Page 6, Paragraph 3):

“We defined a dwelling to be a physical structure within which members of one or more households had slept in the previous week. We excluded dwellings that were derelict or abandoned.”

7. Why were 55% of cases not bacteriologically confirmed? Does this reflect on the quality of the NTP? Could the stratification according to smear status therefore not be valid, i.e. is there a possibility that many smear positive cases were not diagnosed as smear positive? Why were there so many missing results?

In all regions and most countries globally, only a moderate fraction of notified TB cases are microbiologically confirmed. E.g. see data here from WHO 2017 Global Tuberculosis Report (http://www.who.int/tb/publications/global_report/gtbr2017_annex4.pdf?ua=1)

<table>
<thead>
<tr>
<th>Region</th>
<th>Cases notified</th>
<th>% bacteriologically confirmed among pulmonary TB cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>African Region</td>
<td>1,273,560</td>
<td>66%</td>
</tr>
<tr>
<td>Region of the Americas</td>
<td>222,750</td>
<td>78%</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>514,449</td>
<td>53%</td>
</tr>
<tr>
<td>European Region</td>
<td>253,154</td>
<td>64%</td>
</tr>
</tbody>
</table>
South-East Asia Region  2,709,953  61%
Western Pacific Region  1,374,059  38%

There are many reasons for different regions, countries and populations having low percentages of notified cases being bacteriological confirmed. These include: limitations in availability and accuracy of TB diagnostics, quality of care and diagnostics provided, TB screening algorithms used within health systems, availability of high-quality reference laboratories; and TB programme and health system financing and resourcing. We have added text to this Discussion to clarify this point:

“Overall, 58% of notified TB cases initiated on TB treatment by the National TB Programme in study health facilities were microbiologically confirmed by the study laboratory, reflecting the programmatic and diagnostic challenges in confirming TB disease in low-resource settings.”

8. Was any validation done on the ePAL/Mapbook data? I.e. did the researchers physically visit any of the dwellings to confirm the application's accuracy and consistency?

Thank you. Yes, the precursor to ePALS (the Mapbook), was validated in Blantyre previously (MacPherson et al. American Journal of Epidemiology, 2014). Additionally, the ePALS system has been validated as part of the doctoral thesis of Dr Rebecca Harris, London School of Hygiene and Tropical Medicine. Accuracy was high. We now have included a reference to the published thesis of Dr Harris.

9. Table 1: normally missing data are included in the column percentages.

We thank the reviewer for this helpful suggestion. We have rerun our analysis to include missing categories within column percentages. Although for most variables with small numbers of missing values, this results in very little change, for other variables, readers may be confused.

To give a specific example, take the variable “Clinic registration sputum smear status”, for the CHW resident group:

<table>
<thead>
<tr>
<th>Missing/Not done</th>
<th>CHW resident (N=3723)</th>
<th>Valid percentage</th>
<th>Percentage including missing values</th>
</tr>
</thead>
<tbody>
<tr>
<td>2087</td>
<td>56.1%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Smear-negative  618  
   37.8%  16.6%  
Smear-positive  1018  
   62.2%  27.3%  

By reporting only column percentages including missing values, the interpretation of the results changes substantially. We believe that we wish to report – and that readers will wish to know – the percentage of sputum smear samples that were smear positive (62.2%), as opposed to the percentage of all participants that had a smear positive result regardless of whether a smear was done or not. We think that the valid percentage interpretation has greater epidemiological and programmatic relevance. As an additional benefit, the number of missing values remains available for readers to interrogate. We request that the Reviewer and Editor permit us to keep this table presentation as is currently. However, should the Reviewer and Editor feel strongly about this point, we would be very happy to report both the valid percentages as well as percentages including missing values, although we worry that this would add considerable complexity to the table.

10. Was the smear stratification done according to lab smear status or clinic smear status and what is the difference between the two?

For the regression models, TB cases notification rates were stratified on the basis of samples taken as part of study enhanced surveillance activities and tested in the study TB laboratory. We have added text to the methods to clarify this:

“Using the CHW catchment area as the unit of analysis, we undertook two Bayesian conditional autoregression regression modelling analyses with Poisson response distributions [15]: the first to estimate all TB CNRs; and the second to estimate TB CNRs that were microbiologically-confirmed by the study laboratory as part of enhanced surveillance activities.”

11. Were the enhanced surveillance data only for the lab?

We apologise, but we are not clear what the Reviewer means here. In the manuscript, we define enhanced surveillance to include additional research capture from notified TB cases of: demographic characteristics; clinical characteristics; geospatial location of place of residence; and additional microbiological testing in the research TB laboratory of a spot sputum sample taken at TB registration. Should the Reviewer or Editor require further explanation, we would be very happy to provide this.
12. Why was "scanty" a category for the lab smear status but not for the clinic smear status?

The Malawi National TB Programme only records smear results in TB registers as either: Sputum Smear Positive; Sputum Smear Negative; or Not Done. They do not further sub-classify results as “scanty”. However, in the research TB laboratory where enhanced TB surveillance samples were tested, we were able to record scanty results. As we believe this additional categorising provides useful epidemiological data in understanding the microbiological status of notified cases in Blantyre, we have retained this analysis. However, should the Editor or Reviewer feel that this additional detail is not required, we would be very happy to collapse the “scanty” category into the “smear-positive” category for the research laboratory tests.

13. Were other options for "enhanced surveillance" considered, for instance Xpert on all samples instead of culture, which could have given an indication of drug resistance in addition?

Thank you for these helpful points. GeneXpert MTB/Rif was only very rarely used in the study reference TB Laboratory. We have carefully re-reviewed the study datasets. Of the 6077 TB cases notified a total of 32 cases were tested using GeneXpert MTB/Rif, with 12 negative and 20 positive. All GeneXpert MTB/Rif positive cases were additionally sputum culture positive for M. Tuberculosis. Additionally, during the study period, the Malawi National TB Programme was slowly introducing Xpert MTB/Rif to clinics, but coverage was very low overall.

We agree that it would have provided additional useful information to have rifampicin resistance status available for all study samples. However, there are a couple of issues with doing so:

a) The prevalence of multi-drug resistance is very low in Malawi (estimated at 0.4% in a nationally representative MDR-TB prevalence survey – Abouyannis et al, Bull WHO, 2014), meaning that the diagnostic yield would be likely to be extremely low and uncertain. Nevertheless, we are actively considering enhanced surveillance for MDR-TB as part of future studies.

b) TB culture remains more sensitive than GeneXpert MTB/Rif, and is the recognised gold standard confirmatory diagnostic test in community-based studies where the prevalence of disease is low (in Blantyre ~1%). This is especially the case with the newer GeneXpert MTB/Rif Ultra cartridge, which has a lower specificity, and concomitant suboptimal false positive rates.

c) The full economic cost of conducting a GeneXpert MTB-Rif test for a single sputum sample in Malawi is approximately US$28. Across ~4000 cases notified, this would have added US$122,000 to the study budget, which is not feasible with the resources available.
Given these issues, and the fact that GeneXpert MTB/Rif Xpert was only done on a very small number of cases, all of which were culture confirmed, we have removed all mention of Xpert from the manuscript.

14. The higher CNRs in areas with a higher proportion of women: were there more women in certain age groups or other gender issues which might explain the higher rates?

Thanks for raising this important issue. In our multivariable models, we adjusted for the proportion of catchment area residents that were aged 15 years or older, as well as for the adult male-to-female ratio. We were very interested to find a correlation between lower male to female ratios and high case notification rates. In the Discussion, we speculated around potential reasons for this, including the possibility that neighbourhoods with the highest male-to-female ratios were concentrated in the densely populated central areas of the cities. Our previous qualitative studies in these neighbourhoods (referenced in the manuscript) have shown that highly mobile young men may not be able to prioritise care-seeking for TB because of fatalistic health seeking behaviour and intense pressure of work.

Following the Reviewer’s suggestion, we have done further exploratory analysis of these data. In the census of approximately ~750,000 people, we did not record the age of catchment area residents, but instead categorised them as either infants, toddlers, children, or adults, so we can’t further disaggregate within age groups. We have however examined the correlation between adult male-to-female ratios and the proportion of catchment area residents that were aged 15 years or older. These results are shown below.

This graph shows no clear correlation, and without further supporting data we are reluctant to speculate further about the nature of this relationship.

15. Page 2, line 26: rather use "catchment area" CNRs instead of "neighbourhood" CNRs?

Thank you. We have made this change.

16. Page 5, line 56: the "head of dwelling" was interviewed rather than the "head of household"?

No, head of household is more appropriate here. In the Methods, we set out the following definitions, which are standard in census activities:

“We defined a dwelling to be a physical structure within which members of one or more households had slept in the previous week. We defined a household to be a person living alone or
a group of people living together who shared meals together, and who may have been related or unrelated.”

As there could be more than one household per dwelling, we interviewed the head of each household.

17. Page 7, line 42: Xpert is not mentioned in the tables - should this be corrected?

Please see response to Reviewer 1, Point 13 above, which addresses these issues in detail.

18. Page 16, line 49: "greater diagnostic barriers are likely to be reflected by a higher proportion of smear positive patients…” - but in an area with a high HIV prevalence, this might not be the case?

Although at the individual patient level it is well recognised that there is a correlation between HIV-positivity (mediated by CD4 cell count) and sputum smear-negativity, we are not aware of robust evidence suggesting that this relationship holds at the population level. On the other hand, higher programmatic smear positivity rates among notified cases are indicative of delays and barriers to diagnosis. We have added a sentence to the discussion to address these issues.

“...The household enumeration data was limited to basic data on age and sex, and so we are unable to estimate correlations with important intermediary determinants – notably HIV prevalence, the relationship with sputum smear positivity rates at the population level remains uncertain without detailed HIV prevalence data – and relied on data from the Worldpop Project for estimating neighbourhood-level poverty.”

Responses to Reviewer 2’s comments

1. I have severally read the manuscript. The authors reviewed the literature well and provided adequate justification for the study. The Methods is appropriate and the Results interesting. The study demonstrated what is available in the literature: poverty and distance from health facility as risk factors of not-diagnosing TB in a resource limited setting.

Thank you for these comments.
2. However, from a programmatic perspective, I feel there is a need to better highlight the implications of their study findings. I have a few suggestions to further improve the manuscript.

1) In the Discussion Section, there is a need to assess how the enhanced citywide tuberculosis surveillance contributed to TB case detection from the study area. OR compared to baseline, what fraction of TB cases could have been detected using the routine TB programme?

Thank you for these comments. The enhanced surveillance programme was not an intervention, but rather a set of surveillance activities integrated within routine National TB Programme registration systems and designed to improve knowledge about TB epidemiology and care under routine programmatic conditions. As such, we don’t think that the enhanced surveillance activities will have resulted in any change in TB case notifications or detection.

As discussed in our response to Reviewer 1, Point 2, to estimate the prevalence of undiagnosed TB in Blantyre, a citywide TB prevalence survey would have to be carried out. We have not done this yet, but plan to do so later in 2019. TB prevalence surveys require extremely large sample sizes and are very expensive.

3. Secondly, given the intervention, there is a need to assess the possible cost effectiveness of the intervention. Most studies in low and middle income countries that assessed impact of community/population screening/surveillance to improve TB case detection have been found not to be cost-effective. A note on cost effectiveness of this intervention will be informative in proposing this strategy for the TB control programme.

We did not implement a case-finding intervention in this study, but rather undertook enhanced surveillance of TB notifications integrated with the routine National TB Programme. We thank the Reviewer for the suggestion, but struggle to see how a cost-effectiveness analysis would possible or meaningful here.

4. What proportion of TB cases remains undetected in the intervention site?

As discussed in response to Reviewer 1, Point 2, and Reviewer 2 Point 1, we do not know this. Without conducting a large and very expensive TB prevalence study, it would be difficult to estimate the prevalence of undiagnosed TB.
Responses to Reviewer 3’s comments

1. It is difficult for the reader to differentiate between procedures that are part of routine patient care and study specific procedures. I understand the presented analyses include TB data from a new surveillance system (implemented at TB clinics) and TB data that were reported by patients or documented during TB work-up, both routine patient care data (including culture?). Did study specific procedures relate to geolocation only? The manuscript should more clearly present the framework and a consistent wording should be used/defined (e.g. routine and enhanced surveillance is mentioned probably meaning the same).

Thank you for this suggestion. We have added additional text to the methods to clarify these issues (see Page 6, Paragraphs 1 and 2):

“At all health facilities in the city, patients are investigated for TB by health workers, usually with an initial symptom screen and subsequent examination of a diagnostic sample, most commonly sputum smear microscopy. Once a decision to initiate TB treatment has been made by a health worker – either on the basis of a positive microbiological sample, or on clinical decision – the patient is referred to their nearest TB registration clinic, which will usually be located within the same health facility. Here, Ministry of Health TB Officers initiate TB treatment, and register the patient using the National TB Register, recording demographic and clinical characteristics. In this study, we implemented enhanced TB surveillance at the point of TB registration.”

Additionally, please see response to Reviewer 1, Point 10 above for further explanation.

2. A more detailed characterization of the 18 health facilities where TB cases are registered and the general flow of TB cases should be provided. Are presumptive TB cases presenting to these health facilities for diagnostic TB work-up? Or are these health facilities only registering TB patients who have been diagnosed with TB elsewhere? Are patients diagnosed with TB elsewhere all referred to these facilities for registration and medication? Are these health facilities the only points of care where TB medication is provided/available? How is inpatient TB care linked to the registration facilities? How high do you estimate TB related mortality, i.e. may there be a substantial number of patients who died during inpatient care and before registration? Please include respective information.

Thank you for these helpful comments. To add additional clarity, we have modified the Methods section to describe in greater detail the TB care-seeking and diagnostic process in Blantyre:

“At all health facilities in the city, patients are investigated for TB by health workers, usually with an initial symptom screen and subsequent examination of a diagnostic sample, most commonly sputum smear microscopy. Once a decision to initiate TB treatment has been made by
a health worker – either on the basis of a positive microbiological sample, or on clinical decision – the patient is referred to their nearest TB registration clinic, which will usually be located within the same health facility. Here, Ministry of Health TB Officers initiate TB treatment, and register the patient using the National TB Register, recording demographic and clinical characteristics. In this study, we implemented enhanced TB surveillance at the point of TB registration.”

We additionally thank the Reviewer for the suggestion to further explore TB case fatality ratios, and investigate whether pre-treatment case fatality ratios may provide further useful information. As explained above, and is standard in most National TB Programmes, TB cases are notified at the point at which they initiate anti-tuberculosis treatment. Thus, the TB case notification rate is necessarily defined as the number of TB cases notified (and hence who have started treatment) per 100,000 population.

In this study, we implemented enhanced surveillance of TB case notifications into routine National TB programme activities. We struggle to see how we could collect any information about pre-notification mortality. To do so, one would have to implement an enhanced surveillance system for all presumptive TB cases (i.e. people attending health centres and hospitals with symptoms of TB). In Blantyre and elsewhere in sub-Saharan Africa, ~30% of adults attending primary care have cough, and ~60% have either cough, or fever, or weight loss, or night sweats. The study population in Blantyre was about ~750,000 people, and attendance rates at the 18 health facilities in the city are likely to be high. To implement an enhanced surveillance programme for all presumptive TB cases would clearly be an impossible task.

We would further need to be able to ascertain mortality outcomes from all people attending health centres or hospitals with symptoms of TB. Malawi has no system of vital registration, so this would also be an impossible task.

Currently, we feel that any further analysis of TB case fatality ratios after TB treatment has been initiated would be better suited to a future study. This would also be a considerable task, as the outcomes of all notified TB cases would have to be ascertained during 6-12 months of follow-up.

3. The term "city-wide surveillance" is used repeatedly but parts of the city have been excluded from the analyses. Information on how catchment areas were chosen for inclusion should be specified in the methods section and also information on the (estimated) total population of Blantyre (percent coverage by the study) should be provided. Almost 25 percent of registered TB cases where not included in the analyses because patients were not residing within included catchment areas, this may be an important source of bias and this challenges the term "city-wide".
Thank you for these comments. As described in response to Reviewer 1, Point 4 above, our enhanced surveillance system excluded business and industrial areas, and the most affluent neighbourhoods of the city. As recommended, we have added additional text to the manuscript (Page 5, Paragraph 2) to provide greater clarity:

“To estimate population denominators for the study, we defined boundaries around 315 CHW catchment areas, excluding business and industrial areas and the most affluent areas of the city.”

4. It remains unclear if "adults" were defined as patients older than 15 years for all aspects of the analyses; this should be clarified. As not specified in the manuscript I assume that population denominators included individuals aged younger than 15 years but enumerators for CNRs excluded patients aged older than 15 years. Please clarify. If denominators did not exclude individuals aged younger than 15 years (who accounted for up to 55% of the population in some catchment areas) this may be a source of bias as poorer populations may have more children accounting for lower CNRs.

Thank you. We have added additional text to clarify that case notification rates included all notified cases (of any age) within the numerators, and all residents (of any age) within the denominators:

“Using census denominators, we estimated CHW catchment area TB case notification rates (CNRs) per 100,000 residents per year, and disaggregated by TB microbiological status (smear-positive or culture-positive for M. tuberculosis on study enhanced surveillance sample vs. all TB cases).”

Please note also that in our multivariable models, we adjusted for the proportion of catchment area residents that were aged 15 years or over.

5. The abstract should include the number of TB registration clinics and the approximate coverage of the city population by the analyses.

Thank you. We have included the number of TB registration clinics in the Abstract. We regret that we are not able to include the approximate coverage of the city, as any such figure would be speculative: we can’t provide population denominator estimates for areas of the city that we did not map or undertake census activities in.

6. The abstract should include mention that CNRs referred to adult/>15y old population only.
Case notification rates are estimated as the number of notified cases per 100,000 residents, regardless of age. We have therefore not changed the abstract.

7. The abstract mentions TB surveillance at all public and private TB treatment registration centres. In the manuscript there is no further mention of "private" facilities, please clarify.

Thank you. Enhanced TB surveillance was implemented at one public and two private hospitals, 13 public and one private primary health care centres, and one prison clinic. We have added text to the Methods to describe this (Page 6, Paragraph 2).

8. Reference 10 appears to refer to the TB surveillance program but not to the stated HIV prevalence of 20% in Blantyre, please add a reference for HIV prevalence.

Reference 10 is:

This National Survey provides estimates for HIV prevalence for Blantyre.

9. The last sentence of the introduction section reads very vague: "… we aimed … to identify the most important and modifiable barriers …". What potential barriers where identified / thought of prior to the study?

Thank you. We have modified this sentence to add greater clarity:

“We report on the implementation and evaluation of an enhanced citywide TB surveillance programme in Blantyre, Malawi, where nearly one-in-five adults are HIV positive. [10] We aimed to use high-quality spatially-resolved surveillance data to support public health practitioners and policymakers to identify the most important and modifiable barriers to TB diagnosis and treatment. We hypothesised that neighbourhood characteristics such as poverty rates, age and sex structure, and distance from TB registration clinics might be correlated with TB case notification rates, and so guide the implementation of interventions to improve access to TB diagnosis and prevention.”

10. What was the procedure if the head of a household was not present when the CHWs came for the interview? Please clarify.
Thank you. Three attempts were made to interview the head of the household. When the head of the household could not be interviewed, the next most senior household member was interviewed. We have added text to the Methods to describe this (Page 5, Paragraph 4).

“We defined a household to be a person living alone or a group of people living together who shared meals together, and who may have been related or unrelated. The head of each household (or, in their absence, the next most senior household member) was interviewed using a structured census questionnaire that recorded the number of households and people residing within the dwelling.”

11. Xpert status is mentioned as a collected variable but Xpert findings are not presented as results, please clarify.

Thank you. Please see detailed response to Reviewer 1, Point 13 above.

12. The ratio of sputum smear positive to smear negative as a marker for late presentation - is this a valid marker in a population with such a high HIV prevalence / co-infection rate and a cohort with more than a third of patients being diagnosed with EPTB? Please comment.

As noted in above in response to Reviewer 1, Point 18, although at the individual patient level it is well recognised that there is a correlation between HIV-positivity (mediated by CD4 cell count) and sputum smear-negativity, we are not aware of robust evidence suggesting that this relationship holds at the population level. On the other hand, population delay in care-seeking and health system quality are recognised to be associated with higher smear-positivity rates (i.e. the fraction of notified cases that are sputum smear positive).

13. How were re-treatment cases handled at TB registration? Were patients counted twice or was there a procedure to exclude multiple registrations of same patients? Adding information on the proportion of re-treatment cases to Table 1 would be valuable.

We have re-examined the study datasets. In total, 17/6077 patients (0.3%) were registered as retreatment TB cases during the study period. In our analysis, retreatment cases were handled as new registration episodes. As this was a very rare event, we have not done any further analysis of this group, but would be willing to do so if the Reviewer and Editor felt it would add further strength to the key messages of the manuscript.
14. What is the rational for comparing the 3723 cases resident in CHW catchment areas with the 286 cases not living in CHW catchment areas (Table 1)? Would it not make more sense to compare the resident cases to all 4065 (7788 - 3723) cases captured by ePAL but not resident in a catchment area? Please clarify.

Thank you. Please see response to Reviewer 1, Point 5, which responds to these issues in detail.

15. Why where sputum microcopy and culture not performed in around a quarter of cases? Was there an algorithm in place e.g. that patients who had started TB treatment during a preceding defined period would not need to provide a sputum? Please clarify.

Please see response to Reviewer 1, Point 7, which responds to this issue in detail. Additionally, we note that our enhanced TB surveillance activities were integrated within the National TB Programme, and we implemented by TB Officers within study health facilities. As described in Page 8, Paragraph 2, TB Officers undertook collection of an additional sputum sample at the point of TB registration:

“TB Officers asked all registering adult TB cases (regardless of TB category or classification) to submit a single sputum sample for smear and culture. Sputum samples were collected daily from each registration centre, and transported in cooler boxes to the TB Research Laboratory at the College of Medicine, University of Malawi for fluorescence microscopy and MGIT culture. Patients with positive results requiring additional clinical input were traced and linked to care.”

There are a number of reasons why ascertainment of sputum status with enhanced surveillance samples was not complete: children and younger adults generally cannot produce satisfactory sputum samples; extrapulmonary TB cases may not have respiratory symptoms, and might struggle to produce a sputum sample; and National TB Programme Officers, although trained and supported by the study, may not have been able to complete sputum collection for all registering cases. We emphasised these points in the Results:

“Sputum samples taken for TB culture as part of enhanced TB surveillance activities were successfully collected and reported for 71% (4306/6077) of cases overall, and 73% (2170/3723) of CHW catchment area-resident cases.”

And provided further interpretation in the Limitations paragraph of the Discussion:

“TB cultures were not done on 27% of CHW resident TB patients who did not submit sputum, including 17% of pulmonary TB cases: this is likely to include a bias against less gravely ill patients too sick to produce sputum, or started on TB treatment out-of-hours while inpatients. Overall, 58% of notified TB cases initiated on TB treatment by the National TB Programme in study health facilities were microbiologically confirmed by the study laboratory, reflecting the programmatic and diagnostic challenges in confirming TB disease in low-resource settings.”
16. HIV prevalence is high, but there is no distribution analysis for HIV status per catchment area; please comment.

Thanks for raising this issue. We believe there are two possible interpretations of the Reviewer’s comment, and so have attempted to respond to both here:

i. Paraphrasing Reviewer’s comment: “Were potentially associations between TB case notification rates and catchment area HIV prevalences investigated?”

No – estimating catchment area HIV prevalences would require an extremely large and very expensive citywide HIV prevalence survey. This has not yet been done in Blantyre, although we plan to do in 2019 as part of a community cluster-randomised trial.

ii. Paraphrasing Reviewer’s comment: “What was the range of HIV prevalence among notified TB cases across community health worker catchment areas?”

The HIV prevalence among notified TB cases overall was 67% (as reported in Table 1), and ranged from 0% to 100% across community health worker catchment areas. We don’t feel these ranges provide useful additional information to readers, and so have not added to the manuscript.

17. Page 16, line 11: "… had higher TB CNRs …" should this not be "lower TB CNRs"; please check.

Thanks – we have checked carefully. The current wording in the manuscript is correct. Please see Figure 3 and Table 2; as the adult male:female ratio reduces, the TB case notification rates increase.

18. Page 16, starting line 18 to the end of the paragraph: "Areas in Blantyre …" it remains unclear to the reader if this would translate into higher rates of undiagnosed TB i.e. lower CNRs or if you suggest that these young men present late and thereby contribute to higher CNRs because of longer infectiousness. Same for the last sentence of the paragraph, please clarify the assumed/derived hypotheses in terms of CNRs.

Thank you. We have modified this paragraph to provide additional clarity:

“Although we cannot speculate about the causal nature of the relationship between neighbourhood sex ratios and TB case notification rates, if confirmed by prevalence survey data,
this suggests that lower case notification rates may, in part, be driven by male barrier to TB diagnosis.”

Please note that, contrary to the Reviewer’s comment, lower case notification rates do not necessarily imply higher rates of undiagnosed prevalent TB attributable to delayed care-seeking among men. As we Discussion in Page 17, Paragraph 2, any such correlation remains speculative until confirmed by TB prevalence surveys. We did however adjust for community-level risk factors that might be important determinants of poor access to diagnosis, and believe that this interesting finding deserves further investigation.

19. Paragraph on strengths and limitations: "...93% were successfully recorded and geolocated..." This statement appears limited by the high rate of missing sputum data; please comment.

Thank you. For detailed discussion about sputum data under programmatic conditions, please see response to Reviewer 1, Point 7 above.

20. Discussion of distance remains rather abstract as absolute measures for distance are not discussed (the only scale for distance in meters is provided in supplemental Table 1). For a better and more pragmatic understanding of the distance variable examples of "far" vs. "close" in absolute meters or kilometers would be helpful.

Posterior probability distributions for the correlation between distance from the nearest TB registration clinic and TB case notification rates are provided in Table 2 in the manuscript, giving the adjusted relative rate TB case notification rates per log10 increase in distance in metres.

We additionally translate these estimates to intuitively understandable metrics when we state:

“For Analysis 1 and 2, the TB case notification rate halved for every 3.2-fold (95% CI: 2.24-5.21) and 3.5-fold (95% CI: 2.28-6.86) increase in distance respectively.”

We are extremely reluctant to dichotomise the continuous variable of distance from clinic in metres to two categories (“far” or “close”) as suggested. Not only would any such categorisation be completely arbitrary, it would not stand up to any rationale statistical or causal scrutiny: there is no plausible reason that we can think of to suggest that, at any specified distance threshold, TB case notification rates would suddenly, and dramatically take a step down or up. Nor that at distances before and before and after such a threshold, TB case notification rates would be constant. For a discussion of these issues, please see: Royston P, Altman DG and Saurbrei W.