**Author’s response to reviews**

**Title:** Comparison of indoor contact time data in Zambia and Western Cape, South Africa suggests targeting of interventions to reduce *Mycobacterium tuberculosis* transmission should be informed by local data

**Authors:**

Nicky McCreesh (nicky.mccreesh@lshtm.ac.uk)
Clare Looker (clare_looker@hotmail.com)
Peter Dodd (p.j.dodd@sheffield.ac.uk)
Ian Plumb (idplumb@gmail.com)
Kwame Shanaube (kshanaube@zambart.org.zm)
Monde Muyoyeta (Monde.Muyoyeta@cidrz.org)
Peter Godfrey-Faussett (faussettp@unaids.org)
Elizabeth Corbett (lizcorbett04@gmail.com)
Helen Ayles (helen@zambart.org.zm)
Richard White (richard.white@lshtm.ac.uk)

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**Author’s response to reviews:**

We thank the reviewer for their comments, which have led to improvements in the paper. Please find our point-by-point responses below. We have also made our dataset publicly available with no restrictions in the London School of Hygiene and Tropical Medicine data repository. We have added details of this to the manuscript.

**Editor:**

Please could you also address any concerns about the applicability of this research wrt the transmission of TB

We have responded to the reviewers’ requests for further discussion of the study limitations with respect to how data on numbers of contacts by location translates into infection risk by location. Please see below for the detailed responses to each comment.
and analyse (if possible) whether certain types of participants or communities were likely to have more intense social mixing (and whether this corresponded to local TB incidence).

There are data from an average of only 80 participants who left home the day before the interview in each of the 24 study communities, of who the majority (66%) only visited one type of building. Unfortunately, the study is therefore underpowered to look for differences between individual communities.

Please could the authors clarify if transportation was analysed.

We have added the sentence “Buildings were considered to be enclosed areas with walls and a roof, excluding transport.” (lines 99-100)

Reviewer #1:

This cross sectional study among a stratified random sample of people from Zambia and Western Cape explores the location and duration of contact with others. The manuscript is well written, and the methods are generally clearly described.

Major comments:

1. How did the authors define "building" in the questionnaire? For example, did this refer to open eating areas, or only to dwellings with four walls?

We have added the sentence “Buildings were considered to be enclosed areas with walls and a roof, excluding transport.” (lines 99-100)

2. Are the definitions of building type comparable between these two settings. For example, are churches, hairdressers or workplaces likely to have similar ventilation in these settings? Potential differences could confound the extrapolation of these data to TB transmission risk.

We have added the following text to the discussion:

“There are four main limitations to our study. The first is that no data were collected on building ventilation and crowding. Contacts that occur in close proximity in badly ventilated buildings are likely to be associated with a higher risk of M.tb transmission than contacts in less crowded, better ventilated buildings. The suitability of buildings for transmission may also vary between different settings, and therefore differences in transmission risk in, say, churches between Zambia and South Africa may not be the same as differences in contact time.” (lines 254-259)
3. While this study explores contact among otherwise healthy individuals, the social mixing patterns of symptomatic TB patients may differ. This is difficult to measure, but could potentially reduce the generalisability of this study to TB transmission (for example, sick TB patients may be more likely to stay at home, less likely to work and more likely to be in a clinic environment). This should be noted.

We have added the following text to the discussion:

“Secondly, no data were collected on the prevalence of people with pulmonary and smear positive TB in different building types. While our findings show that few contact hours occur in clinics in either location, this is likely to underestimate the importance of these locations for transmission, as it is very probable that a far higher proportion of contacts in clinics will have TB disease than contacts in other settings. This means, for example, that both adults/youths and children may be exposed to more potentially infective person contact hours on average in clinics than in churches, if prevalences of pulmonary TB in people present at clinics in Zambia are more than five times higher than prevalences in people present in churches. In addition, people attending clinics may be more susceptible to infection and/or progression to disease. The social mixing patterns of people with symptomatic TB may also be different in other ways, for instance people who are very ill may spend less time in bars. This would reduce the contribution of bars to overall transmission.” (lines 264-274)

4. It would be helpful to have validated this method, to establish whether recall bias was a problem (for example by performing a prospective 24 hour diary record of locations visited).

Has this been done using this method in this, or other settings?

We have added the following sentences to the discussion:

“Finally, data were collected using a retrospective questionnaire, and not directly recorded or collected using prospective diaries. Recall bias is unlikely to be a large problem for this study, as data were collected on locations visited during the day before the interview only. Over short time periods, there is little difference in reported numbers of contacts using retrospective vs prospective study designs[25].” (lines 289-292)

5. Another interesting finding is that over 50% of subjects did not leave their houses - which seems to contrast with molecular epidemiological studies in southern Africa showing that little transmission occurs in the household. The authors may consider noting this discrepancy.

We have added the following text to the discussion:

“There is considerable variation between people in susceptibility to M.tb. infection and TB disease however, and in infectiousness given active disease. Chance contacts between highly susceptible and infectious people may therefore be important to overall transmission, and infection risk may be higher than we have estimated in locations where cumulative numbers of
new contacts are high. This may also help to explain why only a small proportion of people are infected by people living in their own households, despite the large amount of time people spend in their own houses.” (lines 247-253)

Minor comments:

1. The p-values for bars was missing in Table 1

p-values are not shown as we consider the estimates for bars in Western Cape to be unreliable. The reasons for this are given in the discussion. We have made this clearer in the table and table legend.

2. The number of significant figures used in Table 1 vary, and should be uniform.

Numbers in the tables are now all given to two significant figures

Reviewer #4:

This is a well-written, clear manuscript about an interesting approach to better understand the transmission of tuberculosis (TB) in high incidence communities in sub-Saharan Africa. This paper seems to ask the question of where most TB transmission is occurring and is a companion paper to the recently published paper by Dodd et al that addresses the 'Who?'

My major suggestion is to include a few more comments in the section on limitations.

One is the logical paradox of collecting data in households after providing the rationale that most transmission occurs outside of households.

The data we present are on time the respondents spent in other people’s households, not their own. A number of studies show that little transmission occurs between members of the same household in high TB sub-Saharan African settings, but there are far fewer data on the proportion of transmission that occurs within houses between people who are not members of the same household.

Perhaps the surveys did not include members of the population who might be most likely to transmit TB?

The study sample was a stratified random sample of adults living in sampled areas within the 24 high TB prevalence communities that were part of the ZAMSTAR study, and response rates were high (78% of people who were still resident in the community). The probability of inclusion in the study is therefore unlikely to vary greatly between people more or less likely to transmit TB.
The other issue with which I grappled is the lack of coherence with outbreak investigations that have identified a variety of settings where there is a high risk of TB transmission: hospitals (e.g., Bamford, 2010; Sissolak, 2010); prisons (e.g. Henostroza, 2013); mines, bars, and others.

We have expanded the paragraph on outbreak investigations in the introduction:

“Individual outbreaks of M.tb infection have been linked to a wide range of settings, including public transport[8, 9], schools[10], churches[11, 12] and healthcare facilities[13, 14]. These kinds of study provide some information on locations where transmission can occur, but as outbreak investigations are typically only undertaken when unusual patterns of disease are noticed, they give little insight into the types of location where transmission is most common. The potential for zoonotic transmission has been raised in Zambia by others but not addressed here.” (lines 62-67)

It seems that another potential limitation of such survey methods is misclassification or erroneous reporting associated with stigma. Perhaps respondents would be embarrassed to report that they had been visiting a relative in prison or in the hospital, or that they had spent many hours drinking in a bar?

We have added the following sentence to the discussion:

“It is possible that some misreporting occurred through social desirability bias however, and respondents may have under-reported visits to or time spent in bars or clinics, and over-reported visits to churches or workplaces.” (lines 292-295)

However, in spite of these limitations and issues, the authors are to be congratulated on an excellent study and manuscript. The early events of TB transmission have been difficult to study, as TB cases likely progress from a subclinical through minimally symptomatic state before progressing to overt disease that leads them to seek medical attention. Exactly when most transmission occurs is unknown, and studies such as this have the potential to improve our understanding.