Author's response to reviews

Title: The spatial distribution of leprosy cases during 15 years in a leprosy control program in Bangladesh, an observational study

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Author's response to reviews: see over
Response to the comments of reviewers for the manuscript entitled “The spatial distribution of leprosy cases during 15 years of a leprosy control program in Bangladesh, an observational study”

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Dear Dr. Graham,

On behalf of the authors, I would like to thank you for your decision to allow us to submit revisions of both manuscripts without combining them. Although we appreciate the arguments of the reviewers to combine the papers, we believe that the key messages of the research will be clearer in two separate publications.

The copy edit agency suggested to a small change in the title, *i.e.* “15 years of a leprosy control program” instead of “15 years in a leprosy control program”. We have followed this suggestion.

In this letter, we would like to address the comments of the reviewers, and indicate the revisions to the manuscript.

**Reviewer 1:** Alexandre Alcaïs

We thank the reviewer for his kind remarks.

**Reviewer 2:** Aparna Pandey

**Abstract:**

These study aims to identify spatial pattern of leprosy occurrence whereas in the results the have reported the occurrence of spatio-temporal clusters.

We have clarified the description of the aim of the study by changing sentence:

“We studied the distribution of leprosy cases detected by a control program to identify spatial and spatio-temporal patterns of occurrence and to search for environmental risk factors for leprosy.”

What do authors mean by geographic risk factors? Does it mean environmental risk factor?

In the first sentence of the abstract, we mention the “geographic nature” of risk factors. With this, we mean that the distribution over an area of certain risk factors is influenced by the geography of the area. An example is the proximity to a river. The position of the riverbed is a geographic feature, while the risk might be constituted by environmental factors associated with a better survival of *M. leprae* outside the body.

We clarified this by changing the first sentence of the abstract in:

“An uneven spatial distribution of leprosy can be caused by the influence of geography on the distribution of risk factors over the area, or by population characteristics that are heterogeneously distributed over the area.”

The term proximity to town is very vague? What does it really mean and how it is measured? Is it distance of from the center of town or particular point? It needs to be defined precisely.

We have clarified this point in the abstract by changing “town” in “town-center”. Also in the material sections we have added that we measure from the town center.

To clarify “proximity”, we changed the last sentence of the results section of the abstract in:

“The overall risk of leprosy in the district was not associated with roads, rivers and leprosy clinics. The risk was highest within 1 kilometer of town centers and decreased with distance to town centers.”

**Background**

Most of literature quoted indicated geographic difference due to difference in socioeconomic conditions of host. These cases are more from the areas with prevailing poor socio-economic conditions. It’s a well-known fact at the leprosy is a disease of Poverty. Then what are new authors want to tell.
This study adds to the understanding of the epidemiology of leprosy by reporting on the situation in Bangladesh, rather than Brazil (South-America) and Malawi (Africa), which are countries with different geography, environments, cultures, population densities and levels of poverty. To our knowledge we are the first to report this kind of data from a long-running control program, in combination with the spatial and spatio-temporal patterns associated to it.

Proximity to water may have different meaning in district of Malawi than in a locality of Bangladesh where environment is general humid. It’s doesn’t carry much meaning.

We agree that the proximity to water in a locality such as Bangladesh has a different meaning than in Malawi. However, it is of importance to mention these findings, as we later on do not find the relationship. We added the following sentence to the paragraph:

“In a locality with many rivers and other bodies of water, such as northwest Bangladesh, the relationship between leprosy and open water might be quite different.”

Difference in accessibility of health care has also been reported as a factor. Authors have mention it’s never been reported. This type of statement to be better avoided.

Unfortunately, we were not able to find any international papers on the relation of leprosy to the proximity of health services. However, we agree that this statement is somewhat presumptuous, and removed the statement.

Material and methods
The reviewer understood our methods, but the section was not clear enough. We have added sub-sections, rearranged the text, and changed parts of this section. We hope that our new rearranged and copy-edited material and methods section is now less confusing.

What do authors mean by sentences like the is more concentration on voluntary reported cases, where as in analysis section it is mentioned that they have tested for clustering of each mode of reporting separately. Moreover more than 50% of cases included have been detected by active means i.e. contact tracing, school survey, village survey etc.

In the main text of the article, we wanted to focus (we wrote “concentrate”) on the voluntary reported cases, as these give a better picture of the “true incidence”, even if more than 50% of the cases are found by active case finding.

Results
Tables are not clear. Titles are not clear eg. Table 1 tile is shows the clusters characteristics and leprosy situation. Similarly in Table 2 as Title4 unduly long. Why mode of detection is mentioned when authors have only depicted voluntary reported cases. Time periods also not uniform.

We do not share the opinion that the title of table 1 is not clear or too long, as it exactly indicates the contents of the table. We see that the title of table 2 slipped our attention, as it contains the title used in a previous version of the manuscript. We have removed and edited the title.

The time periods do not have to be uniform. The method used searches for spatio-temporal clusters in flexible time and space. We did not mention this in the methods section and therefore added the sentence:

“Both the circular base (the area) and the height of the cylinder (the time period) are flexible”.

Discussion
Nothing is explained properly

We do not understand what the reviewer means with this remark. We sum up several possible explanations for our findings, but we are not in a position to state that one explanation is better than another.
Explanations given for temporal associations are very confusing. Why increased awareness is restricted to one particular period? Was an IEC campaign undertaken during that time?

No IEC was undertaken, but the organization of DBLM expanded their control activities over the district in the period from 1993 onwards, which indeed explains the detection peak in the years afterwards. We did not mention this in the discussion and therefore added:

“The detection increased dramatically in the years 1992 to 1994 due to improved organization in the leprosy control program. The most likely cluster was found prior to this period, showing that the spatio-temporal clusters both need a spatial and a temporal component, i.e. the analysis corrects for pure temporal clusters.”

Higher proportion of MB missing cases also needs explanation

We have discussed this issue as follows:

“We retrospectively traced back patients; therefore, a proportion of the cases could not be found. The demographic characteristics, including age and sex, were not different from the included patients. The missing cases, however, contained proportionally more MB cases. The reason for this is not clear, but this difference is not likely to introduce a bias in our analysis, as there is no evidence to expect that MB cases were distributed differently than PB cases.”

We could speculate on the reasons, but as we do not have any evidence or data to back these, so this would solely remain speculation.

Concentration of leprosy cases in or near urban area is not a new phenomenon. Migratory patients also play a role in it. Now urban leprosy control is posing much greater problem in India. Authors should reanalyse the cases and look for rural urban / periurban differences. This will help in drawing attention of the programme planners for mobilising the resources more effectively.

We are happy that the reviewer agrees with our main conclusion. We agree completely that urban leprosy is an increasing problem and want to draw attention of all stakeholders in leprosy control. We think that with this paper we are already pointing towards this problem.

A new study would indeed added more to our understanding of leprosy epidemiology, but would involve many other techniques, the choice for a proper control group etc. This study is in itself important, as it can be used to increase understanding for many other researchers without doing a new study of these subjects.

Reviewer 3: W.C.S. Smith

We thank this reviewer for his kind summary of our paper.

Major compulsory:

1. In the methods section a temporal cluster is defined as period in which cases detection is exceptional high but this is not quantified and needs to be specified so that the reader understands what” exceptional high” means. Similarly a geographic cluster is defined as a high excess proportion but this again needs to be specified.

In both instances, the null-hypothesis is that all cases are distributed over time or/and over space randomly. In the spatio-temporal analyses, the same likelihood function with a Poisson assumption is used as for pure spatial or temporal analyses. In the spatio-temporal analyses, the expected number of cases if all space and time locations were independent. The expected cases in a certain time-space location is conditioned of the time-location and the space-location. An exceptionally high case detection is thus a case detection that (for spatio-temporal clustering) is higher than in surrounding areas based upon the expected case detection which is calculated by the average case detection in that area over the whole study period, and the average case detection in the whole area in that specific time frame.

As this was not clear in the material and methods we clarified by:
“A temporal cluster is a period in which case detection was higher than expected for cases randomly distributed over the study period. The likelihood that the case detection originated at random during a period was calculated assuming a Poisson distribution of cases among the population.”

And by changing:

“A cluster is found in a geographic area, if the area has a high excess proportion compared with the surrounding areas.”

into

“The likelihood that the case detection in a certain space-time window originated by chance was calculated under the assumption that no space-time interaction exists. The expected cases in a certain area were calculated based upon the number of cases observed at that location during the entire study period and the number of cases in the whole district during that timeframe.”

2. In the results the missing cases are reported to show no bias by sex and age, but they are claimed to be equal rather than not different. The additional tables show that there is a significant difference in the % MB among missing cases but this is not reported in the text.

We corrected our mistake in the inference, and changed the sentence to:

“The percentage males and the birth year were not different for missing and included cases.”

We added the difference in % MB in the text of the results section, as it was already discussed in the discussion section.

3. The last few paragraphs of the results suggest that cases within clusters did not live nearer or further to towns but a few lines later it is noted that case detection is higher nearer to towns. These statements need to be reconciled.

These statements indeed seem to contradict each other, and we did not explain properly. The difference being that we looked at the cases that were a member of a spatio-temporal cluster. The areas (thus only the spatial component of the clusters) is indeed closer to towns. We need to add this.

We changed:

“Furthermore, the cases within a cluster did not live nearer or further to towns, roads, clinics or rivers, for none of the detection modes.”

in:

“Furthermore, the cases within a spatio-temporal cluster did not live nearer or further to towns, roads, clinics or rivers, for none of the detection modes.”

And we added:

“Cases within the same area were not accounted to the spatio-temporal cluster if their diagnosis was outside the timeframe of the cluster.”

Furthermore, it should be noticed that areas with a continuously high detection rate will not be determined to be a spatio-temporal cluster, but rather a spatial cluster. Although this is normally part of the discussion, we spend some sentences on this topic in the results for clarity:

“This seems to contradict the previous finding that cases within spatio-temporal clusters do not live nearer to towns. However, areas with a high incidence of cases throughout the entire study period do not constitute a spatio-temporal cluster. These areas can add to the risk calculated for proximity to towns.”
4. The discussion uses the term outbreak to describe the clusters. This is misleading as it implies an interpretation of the clusters when different explanations need to be considered—particularly whether these are real clusters or an artefact of the operational aspects of leprosy control.

We need to note here that we have put the word outbreak between quotes throughout the paragraph. The definition of an outbreak being the sudden occurrence of disease, often refined to a specific location, is exactly a spatio-temporal cluster. We think that the use of ‘outbreak’—between quotation marks—gives a better visualization for the reader.

Minor essential
5. The claim in the introduction that leprosy distribution in relationship clinic facilities has never been studied is overstating this as programmes regularly do this in planning the location of clinics.

Unfortunately, we were not able find any international papers on the relation of leprosy to the proximity of health services. However, we agree that this statement is somewhat presumptuous, and removed the statement.

6. The patients locations are based upon the location at the time of diagnosis rather than the time of first signs or of original contact, the needs noting.

We added to the material and methods section:

“We note that this is not necessarily the location at which the patient became infected. Another possibility would have been to use location at which the patient lived when the first signs of disease were found. The location where the patient lived during diagnosis, however, could be determined more accurately, and we assume that the difference with the location at which the first signs occurred is not very different on the scale of a whole district.”

7. The issue of education and awareness raising among contacts even without contact surveys will increase case detection in this group. The effect of raising awareness is clearly demonstrated in the figure of case detection between 1989 and 2004

We agree that awareness is higher among contacts even without contact surveys. We think that this is of minor consequence to our findings.

We hope to have adequately answered to issues raised by the reviewers. Furthermore we added a section describing the authors’ contributions.

Yours sincerely,

Egil Fischer