Author's response to reviews

Title: The spatial distribution of leprosy in four villages 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 in four villages 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 our studies will be clearer in two separate publications.

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

**Reviewer 1: Alexandre Alcaïs**

*Is it possible to provide an estimate of the posterior power of their approach based on the differences observed?*

While writing this manuscript, we asked ourselves the same question. From the current study however, we could not distinguish between the possibilities that leprosy does not cluster within village level or that this clustering is too moderate to detect with the number of observations in this study. Therefore, we are not able to answer this question.

*The reason and implementation of the Monte Carlo p-values should be given in the statistical section*

In the statistical section, we changed the sentence:

“The groups were scanned with the spatial scan statistic for high prevalence clusters of cases. The scan is performed for pure spatial data. Clusters were tested against a Poisson model [10].”

into:

“The groups were scanned using spatial scan statistic to detect high prevalence clusters of cases. The scans were performed for purely spatial data, and imposed circular windows with flexible radii on all of the locations in the area. The number of cases within a window was assumed to follow a Poisson distribution under the null hypothesis. For each window, the likelihood was calculated for the observed cases and the expected cases under the null hypothesis. The window with the highest likelihood constituted the most likely cluster. The distribution of the maximum likelihood was determined by many random replications of the dataset under the null hypothesis. The \( p \) value was then calculated by comparing the rank of the maximum likelihood of the real dataset with the ranks of the maximum likelihoods of the random datasets [10]. The analyses were performed with SatScan version 7.0 [11].”

*An overall map of the region*

We have added Figure 1 containing a detailed map of the Nilphamari district, Bangladesh.

*There is a clear excess of PB cases. Is that a common feature in the region? If not could the authors given an explanation.*

The percentage of PB cases detected in this region has indeed been high; around 80% in the last 15 years. Furthermore, the percentage of PB cases found during surveys is always higher than among voluntary reported cases. During surveys cases are often identified that would otherwise remain undetected.
We added to the results section:
"The proportion of PB cases was not unexpected, given that the proportion of PB cases among the total cases detected in this district was approximately 0.8. During surveys, such as the one used in this study, the proportion of PB cases is higher than among voluntarily reported cases, because many less-severe cases can remain otherwise undetected."

Reviewer 2: Aparna Pandey

Introduction
It is not clear, what authors mean with exposure:

In this first sentence, we tried to make a general statement and therefore do not explicitly state what we mean with exposure. Exposure to an infectious agent, such as *M. leprae*, can indeed be prolonged contact with a patient. However, not only the duration of contact, but also contact intensity may attribute to the level of exposure to infection. We use the term “exposure” in its most general context.

*The objectives of the study are not explicitly stated. How the areas with high incidence will be identified is not mentioned.*

We changed the last paragraph of the introduction into:
“We believe that identifying neighborhoods or areas with many previously undetected cases will improve efforts to find new cases. Here, we report on the spatial distribution of prevalent cases and cases that were found during two follow-up surveys with two-year intervals in four villages within a highly endemic area. We attempted to identify spatial clusters of leprosy cases within these four villages using a spatial scan statistic [11].”

The exact method of identifying high incidence or high prevalence areas is described in the methods section.

Material and methods
Contacts of leprosy patients (COLEP) needs to be defined and how they were chosen? What is meant by 20 groups of 1000 persons is not clear. What is about 1000 people were examined? Sequencing of sentences is not proper, it is more confusing.

We changed the material and methods in such a way, that we hope that it becomes more clear. COLEP is a study conducted in the same area. We make use of data gathered for a specific part of this larger field trial. We removed further references to the larger COLEP trial, as it was confusing.

*It is also not very clear whether the study subjects were the same as those included for chemoprophylaxis, then what is use of undertaking the study at all.*

The subjects included in this study were not part of the trial.

*How the follow up was undertaken in not mentioned. The reference quoted is still in press.*

We changed the sentence containing this reference into the following:
“The inhabitants who participated in the first survey were visited in the same months in 2004–2005 and 2006–2007, if they still lived in the same area. So that our results may be thoroughly understood, we have provided a summary of our survey methods. A more extensive description of the survey can be found elsewhere [6].”

The reference has now been published and full reference is provided.
Statistical Analysis

ANNI needs to be defined.

ANNI stands for Average Nearest Neighbor Index, which is a method to measure the amount of aggregation of point data. An index of 1 indicates a strong aggregated spatial distribution compared to random spatial distribution of the data. This was already described in the statistics section.

How it was determined that the deceased persons didn’t have leprosy it is not clear.

We changed the sentence in the results section:

“As far as we could determine, none of the deceased people had experienced clinical leprosy.”

into:

“As far as we could determine either by registration at the clinics or by asking relatives, none of the deceased people had experienced clinical leprosy.”

Results

Just mention of mean age is insufficient.

We added the proportion children under age 15 in the text, which was on average 0.54.

In table and text it is not clear which group belongs to high exposure and which to high prevalence.

At the start of the current study, we had only information on the number of cases during intake and the seroprevalence of each village. We did not try to make a distinction between high exposure and high prevalence, but by using the information of high number of cases during intake and high seroprevalence related to risk of leprosy, we tried to maximize the probability of finding a cluster of prevalent or newly detected cases during the surveys.

Cases at intake  How the term case has been used for those who got RFT? As per standard definition after RFT, the treated person no more remains a case.

We agree with the reviewer and removed the term case for persons released from treatment.

What efforts have been made to minimize bias, because more than one fourth (265 out of 1000) of the population is lost to follow-up

The loss to follow-up was less severe than the reviewer suggests. The total study population consisted of 4123 persons, giving a loss to follow up of 6%. We asked the population or relatives, whether they knew if these people have had experienced leprosy. Furthermore, we tried to minimize bias by asking the population or relatives, where the migrated people had lived during the take in. Further details concerning persons lost to follow-up are unfortunately not available. However, our general opinion is that a bias that would substantially change our findings, could only occur when the prevalence of leprosy among the people that migrated would have been extremely high, as compared to the overall population. This is not likely.

Discussion & conclusion

Explanations of the findings are not given. Whatever explanations are given have been contradicted (1st para). In fact discussion needs rewritten.

Our discussion has been edited to improve the clarity of our arguments.
We do not agree with the reviewer that we contradict our own explanations. We discuss two equally likely explanations of our results. Independent of which of these explanations – no clustering at this level or too moderate clustering to detect it – is true, the overall conclusion remains that spatial clustering of leprosy at this level is of less importance.
In the conclusion authors need to report their own findings. Rather they have mentioned other studies.

We agree and added text to the discussion, which was removed in the conclusion section.

**Other general comments**

*Language needs correction throughout*

The manuscript has been copy-edited by a professional bureau in the USA.

*Terms prevalence and incidence have been used interchangeable quite often in the text. Rather for leprosy the term “case reporting” should be used.*

We have tried to be more precise in the use of terms throughout the revised manuscript. The term case reporting is indeed often a more precise indication in leprosy epidemiology. We have also used the term previously undetected prevalence to indicate that the proportion of cases among the population were detected by active case finding rather than through voluntary reporting.

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

On behalf of the authors,

With kind regards,

Egil Fischer