Author's response to reviews

Title: Selection bias: neighbourhood controls and controls selected from those presenting to a health unit in a case control study of efficacy of BCG revaccination

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Author's response to reviews:

We thank the referees for their comments. We addressed the comments as indicated in the response below and believe this is a much clearer version.

Response to Reviewer's comments
Title: Selection bias: neighborhood controls and controls selected from those presenting to a health unit in a case control study of efficacy of BCG revaccination.
Reviewer: Joanna Stewart
General

Major Compulsory Revisions

Reply from authors:
We judge from her comments that we did not make it sufficiently clear in the paper that HU controls and neighborhood controls were effectively matched by age of birth (as they were matched to the age group of cases at the time of the recruitment of the cases). The fact that neighborhood controls are born slightly later than HU controls is just chance variation, given the width of the age groups used for matching. We edited the text of the paper to make this much clearer. We also made it clear that the neighborhood controls had two additional years in which they could have been vaccinated, and that we looked at the ages of vaccination in neighborhood controls that had a vaccination card and found that none were vaccinated in the two years before recruitment. Finally the reviewer asks about the ORs for vaccination and age in the two control groups in table 4. We decided that in this case the OR was not very informative, and we removed age from table 4 and present the vaccine coverage by age in the two control groups in the text. We thank the reviewer for the comment, as we think this is better. We expect that the referee did not really mean that the data is uninterpretable! but we expanded the discussion of the limitations.

Results
Reply from authors: On reflection we decided to remove the p values, as the table is meant to show the distribution rather than test for significance.

2. Continued:
Reply from authors: We agree it is not necessary to present table 2 separately, but decided data from table 2 would be better in the text.

Reply from authors: We respectfully disagree. We think one of the objectives of the study is to demonstrate how robust the OR is to control for each of the variables in the study, to establish that the difference in vaccination in the two control groups does not come from these characteristic of the population, and therefore we think that showing this in details is necessary to make this point.
Reply from authors: To explore the degree of mobility in the study population we analyzed replies to two questions from the questionnaire. The proportion not born in Recife was about 10% in cases, in neighborhood controls and in HU controls. The proportion that moved to Recife in the previous 2 years was available only for cases and HU controls; this was under 1% in both groups. So it is clear that this is a remarkably stable population and changes in the population in the two years between recruitment of HU and neighborhood controls were unlikely to be responsible for the lower vaccine coverage in population controls. We included this in the text of the paper.

Reply from authors: We made clear in discussion and abstract that we are only excluding confounding factors from the measured variables.

5. Typos: Reply from authors: thanks for identifying these!

Not essential points:
Reply from authors: The change in VE - which we did not present in this paper is actually very small: from -1% in the unmatched analysis, -3% in the matched analysis and 8% in the adjusted analysis.

7. Reply from authors: We included this in the methods section.

Reviewer: Phillip Hill

Authors reply: It was certainly not our intention to hide the process, and indeed we reported the history of the two case control studies in the text; but we amended the text to make this even clearer. The reason we did not publish the two results initially was that we judged that the reason for the difference when the two sets of controls were used was interesting and informative enough to warrant further investigation and reporting: this is what we report in this paper.

Major compulsory

Reply from authors: We shortened the introduction which is now much clearer. Thanks for the suggestion.

Reply from authors: done

Maybe we did not make it sufficiently clear in the paper that HU controls and neighborhood controls were effectively matched by age of birth (as they were matched to the age group of cases at the time of the recruitment of the cases). The fact that neighborhood controls are born slightly later than HU controls is just chance variation, given the width of the age groups used for matching. We edited the text of the paper to make this clearer page 8, para1. We also made it clear that the neighborhood controls had two additional years in which they could have been vaccinated, and that we looked at the ages of vaccination in neighborhood controls that had a vaccination card and found that none were vaccinated in the two years before recruitment.

Reply from authors: The reason that more HU controls were females is that a higher proportion of HU users are female. There were almost no refusers, and most exclusions were a result of subjects having more no BCG scar.

Reply from authors: We think the only comparison with the RCT that is appropriate is to compare the estimated VE; we now present this in the text.

Reply from authors: Done

Reply from authors: The information from table 2 is now included in the text.

Reply from authors: We considered his suggestion and understand why he made it but decided to decline as removing the second line for binary variables will also remove the number of subjects in the category and put the burden on having to calculate this on the readers

Reply from authors: In fact table 4 had a mixture of p values and Confidence intervals and we decided to keep confidence intervals and remove p values as CIs are more informative.

Reply from authors: We respectfully disagree. We think one of the objectives of the study is to demonstrate how robust the OR is to control for each of the variables in the study, to establish that the difference in vaccination in the two control groups does not come from these characteristic of the population, and therefore we think that showing this in details is necessary to make this point.
Reply from authors: Relevant aspects of the control of tuberculosis in Brazil are: that notification is compulsory, treatment is done exclusively by the tuberculosis control programme, and medicines are released for individual cases only, and only after they are notified, all treatment is free. We expect very few cases of tuberculosis escape detection. As we recruited from all notified cases, we expect it is unlikely that cases were biased in relation to BCG. This paper does not aim to discuss all aspects of case control studies of tuberculosis in developing countries but rather to focus on design and potential for bias in the selection of users of health units.

The socio economic questions used are those used in the Brazilian census and are the result of long years of experience. In a separate case control study investigating the association between socio economic factors and tuberculosis - in preparation for submission- we found they predict tuberculosis well; this has also been shown in other studies (e.g. Souza,WV et al. The use of socio economic factors in mapping tuberculosis in risk areas in a city in Northeastern Brazil. Pan Am J Public Health 2000;8 (6) 403-10.)