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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Version: 5 Date: 15 December 2006

Author's response to reviews: see over
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

3. At what age were children usually being vaccinated? There is comment in the results that age is associated with vaccination in both groups but in fact the odds ratios for vaccination across age are very different in the 2 groups. Is this because of a decline in vaccination rate in the 7-9 year olds over the 2 years and the movement of the 7-9 year olds into the 10-14 year olds by the time the neighbourhood controls were selected? Presumably including year of birth additionally to matching on age attempted to overcome this but the influence of age is not linear (see OR’s). Also there is confounding with group – all later birthdates will be controls, all earlier cases. This change in the odds ratios I believe needs to be investigated and discussed further in the paper as, as it stands, one interpretation is that the change in vaccination rates from the time the cases occurred to the time the neighbourhood controls were selected could be rendering the controls non comparable with the cases, despite the authors dismissing this in the discussion. At the least the discussion needs to acknowledge that because of this time difference for neighbourhood controls, and because of the different population of people attending a clinic, neither set of controls is in fact valid and the difference in estimates formed using them exemplifies that if you do not choose controls which are in fact a random sample of the population from which the cases came the data is uninterpretable.

1. It is not clear what the effect of the time delay was. Please could this be elucidated. Was the age matching done on the age that the controls were at selection and the cases at time of illness? If the controls were selected 2 years after the cases (I assume the first set of controls were selected at the same time as the cases occurred?) then you would expect the neighbourhood controls to be born 2 years later but the text says they were one year later.

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: This result could be included in Table 1 rather than having a separate table.

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 form 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:

6. Results – the adjusted VE for neighbourhood controls changes quite a lot from the crude one – this is correct is it, and its direction is correct?

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. Although the abstract states that the results of the RCT are used as a comparison, the results of this study are not given in this paper. Although it does not necessarily follow that the fact that a study produces the same results as the RCT means the controls are not biased, if the RCT is to be used as a gold standard it would be informative to quote it.

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

8. While there is mention that if cases are all registered with a HU then a random sample of controls registered with the same HU’s would be appropriate this point could be made clearer, and be followed by the point that it is not appropriate to select from a subgroup which may not be representative, such as those who have attended clinics. In the present case of clinic attendees it is very obvious that there is a reason why the way in which they differ from a sample from the appropriate population would be likely to bias the result. However any sample which is not taken from the population from which the cases come runs this danger, irrespective of whether or not it is obvious. Therefore it would be good to use these examples as illustration of the problem of incorrect controls concluding that if a case control study is to be conducted the method of control selection must always aim to produce a random sample of the population from which the cases are drawn.

Reply from authors: Yes, this is the main message of the paper and we made it much clearer in the many changes we made to the text.
Reviewer: Phillip Hill

The published case control study that was referred to enrolled neighbourhood controls and not health unit controls. Therefore the authors at least appear to have got this mixed up in the introduction/methods. This does beg the question as to what the authors were trying to do with this study. Playing devil’s advocate for a second: it appears that what actually may have happened was that they initially did a case control study using health unit controls and didn’t publish those results as they were so different from the RCT results. Perhaps they then proceeded to do a study with neighbourhood controls to see if they would be more like the RCT results and published that study instead. It would be important to hear from the investigators what actually happened. Why did they not present their initial case control results with a good discussion of why they might be biased, or at least wait till they had results from both sets of controls before publishing them?

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

I think the intro is too long and much of this could wait until the discussion for comparison with the present results.

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

It is of note that the confidence intervals around the efficacy estimates using the two groups of controls actually overlap with each other-this is not pointed out by the authors and should be mentioned I would have thought. One cannot say for certain that the efficacy estimates are actually different.

Reply from authors: done

Why were the controls an average of 1 year older than the cases when the control selection was actually 2 years later?

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.

P values should be either the actual p value or whatever the journal requires when < . E.g. < 0.0001

Reply from authors: Done

Table 2 is really too small an amount of information to warrant being a table.

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

Table 3. When a variable is binary, just one component could be mentioned in the table eg. Proportion male n(%), rather than give both results, as one can be easily deduced from the other.

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

Table 4-p values should be shown.
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.

Table 5-I personally think this table can go to text as the results are uniform.

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.

With respect to BCG vaccination. Since it is done at health facilities, one would be concerned that individuals that are more likely to attend the facility to receive their vaccination may also be more likely to attend if they have symptoms of any disease. So, facility controls may be over-represented with respect to BCG scar and this does seem the case in this study. However, TB cases may also be over-represented with respect to BCG scar.

One would expect a paper such as this to have a more full discussion of the design issues if it is really to help us understand the issues around case control studies in TB in developing countries better.

It would be helpful to have more detail on the local health system—what are health units in relation to other providers in the community and the hospital who provides TB treatment—i.e., what are the providers of treatment?

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.

There should probably be some discussion about the usefulness of the socio-economic surrogates mentioned—i.e., there is no guarantee that anyone is getting this right in developing country research.

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.)