Author's response to reviews

Title: Frequency of apnea, bradycardia, and desaturations following first
diphtheria-tetanus-pertussis-inactivated polio-Haemophilus influenzae type B immunization in hospitalized
preterm infants

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Author’s response to reviews:

Dear editor,

Thank-you for agreeing to review a revised version of our manuscript. We have addressed the comments of
the reviewers’ as follows:

Referee #2

General

The authors have revised the manuscript by making a more elaborate description of the characteristics of
the control group, which was criticized in my previous report. It is now more clear that the some of the
assumed differences according to the previous version between the two populations are nonexistent, since
the children in the "control" group were still in neonatal intensive care unit. In my previous report, I also
suggested using the child itself as a control, where the frequencies 72 hours pre and post vaccination would
be compared. The authors suggest that since

multiple factors (sepsis, hypothermia, worsening of a cardiac lesion, or increased observation because of
change of nursing staff) can attribute to the apparent increase in adverse events, the use of control group of
approximately the same age is justified. They also note that this is supported by the fact that an increase of
adverse events were observed for 25% of the infants in the control group

in observation period #2 compared to #1. The way how the adverse events were recorded is also clarified
and the possible bias caused by it is discussed.

In spite of these clarifications, two major concerns still arise from this response

1. The choice of the control group

2. Definition of an adverse event

1. The two populations from which the "case" and "control" groups are collected may not differ that much as
could have been assumed from the previous version. However, there is one serious problem distinguishing
these children that, in the context of current evaluation, seriously underminds this comparison. I elaborated
in the previous report that the setting in this study is clearly not a case-controlled study. Therefore, all
references to case-controlled studies should be removed and

different names for the groups should be used. The more appropriate wording that points out the
differences in these two groups is the vaccinated and the unvaccinated group. The "control" group is the
unvaccinated group, where also children that have received some other vaccination during the
time in question were excluded. When the vaccination coverage is high, the unvaccinated typically
represent a very different group of children, and thus the direct comparison between the vaccinated and
unvaccinated is likely to be biased. Therefore, the standard practice in the analysis of vaccine
adverse event studies is that the adverse events are evaluated only for the vaccinated, where different periods with respect to the vaccination are compared (see, for example, Farrington et al, 1996, and references therein). This approach was also suggested in my previous report. If the authors insist on using the unvaccinated as a control group, an elaborate discussion should be included where the reasons for deviating from well-founded and clearly established way of analysis are stated. In my mind, the current response cannot be seen as adequate; see further considerations below.

We agree with the referee that the unimmunized infants are not perfect controls for the immunized infants. However, since they were matched for the factors that contribute most to adverse cardiorespiratory events in this population (chronologic and gestational age), we feel it is still accurate to refer to them as "controls".

The referee has the legitimate concern that when looking for adverse events related to immunization, unimmunized children may not be appropriate controls as they may be more or less prone to these adverse events related to the reasons why they were not immunized. We appreciate the reference that was sent to us, suggesting that using the patient as their own control is a good method of looking for such events when appropriate controls do not exist. However, in our study, almost all control infants were eventually immunized - just the chronologic age at the time of immunization varied by at least 7 days in the cases versus controls for a wide variety of reasons. Because immunization is often arranged just prior to discharge, if there was a systemic bias, it would be towards the case infants being "more stable" and less likely to have adverse cardiorespiratory events. This is now clarified near the end of the discussion. The problem with using infants as their own control as was done in multiple previous studies is that the adverse events that we are looking for (apnea, bradycardia, and desaturation) are very common events in this population. There remains the possibility that the incidence of these events increases in infants of this age (possibly related to oxygen being weaned, bottle-feeding being introduced, or the infant being out of the incubator for longer periods of time) such that comparing the pre and post-immunization incidence of events is still not totally valid in the absence of a control group. We therefore think the data from the control infants should remain in the paper.

In addition, the authors claim that since there are multiple factors that can attribute to the increased frequency of adverse events in time, the use of control group is justified. However, the ages of 55 children in the unvaccinated group are adjusted up to +/- 7 days from the age of the vaccinated, thus representing more variability than possible comparison between pre and post vaccination ages +/- 3 days.

We agree it would have been ideal to use a shorter window period (3 days versus 7 days) in choosing ages for controls versus cases. However, we had great difficulty finding controls for some of the infants even with using this longer window and had to exclude 8 infants as no control could be identified. Although 4 days makes a huge difference in the incidence of cardiorespiratory events in preterm infants in the first few days of life, the effect should be much smaller at a mean age of 74 days. We now clarify in the text that a shorter window period would have been ideal.

It is also hard to see how the multiple factors stated in the reply would more likely be increased in the age of ~10 weeks+3 days compared to ~10 weeks-3 days. The stated support for this claim is that 25% of the unvaccinated experienced increase in adverse events during period #2. However, this is based on asymmetric definition of an adverse event; see concern 2.

2. The definition of an adverse event has been defined as 1 if there is an increase during observation period #2 compared to observation period #1, and zero otherwise. This definition is asymmetric, i.e. only focused on increase during period #2. For example, in the unvaccinated group, 25% of children experienced increase during period #2. The reader is left wondering what is the proportion out of 75% of children that have experienced increase during period #1 compared to period #2. This is the reason why, in the previous report, I suggested using a difference (or a ratio) of events as the response variable. This would account for changes also in another direction. This asymmetry of the measure is also the reason why using the unvaccinated group as a control cannot be justified from the 25% increase in one direction only.
As suggested, we now report both the incidence of an increase in adverse cardiorespiratory events and the incidence of a reduction in adverse cardiorespiratory events in the case infants. We agree that this strengthens our paper. In obtaining the data to complete this analysis, minor corrections were made in the other data.

Furthermore, as was stated in my previous report, if the adverse events were recorded only by observation, an increased concern after vaccination by the study nurses is likely to cause an increased charting of adverse events during the post-vaccination period. The authors now confirm that the recording was indeed done only by observation. The authors also seem to agree on this possible bias but state in the discussion that the use of matched controls should decrease this as a confounding factor. However, since the "control". i.e. the unvaccinated group did not receive the vaccination, there is no reason why there would be an increased concern during period #2 for these children, and therefore the unvaccinated (control) group cannot remove this as a confounding factor. As the authors state in their report, a more detailed monitoring would be impractical, and therefore this source of bias cannot be removed.

We agree with the referee that use of controls would not eliminate bias if the nurses expected more adverse cardiorespiratory events in the cases, and now clarify this point in the discussion. However, we also add the information that there seemed to be limited awareness amongst nurses or physicians that infants who had been recently immunized could be at risk for these events.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

In summary, since the 1) comparison between the vaccinated and unvaccinated, as well as 2) comparison between pre- and post-vaccination periods present apparent and clearly established sources of bias, most of the currently hypothesized effects of the vaccination cannot be adequately addressed from these data. Therefore, I cannot but to conclude that these data is only suitable for comparison of the effects of whole-cell and acellular pertussis vaccination, where the bias due to vaccination is removed by discarding the unvaccinated (i.e. "control") group from the analysis (as I suggested in my previous report), and the asymmetry from the definition of adverse event is removed by taking into account the changes into another direction (either by using difference or ratio, or similar definition also into another direction). As was stated in General discussion, the apparent bias caused by increased charting cannot be removed, but the bias will most likely be the same for children with whole-cell and acellular pertussis vaccinations. Therefore the absolute increase is rather meaningless number from these data, but the difference in the increase between

the whole-cell and acellular pertussis vaccines can provide answers about the differences of these two vaccinations.

As explained above, we think our study adds to the literature on the risk and severity of adverse cardiorespiratory events following immunization of preterm infants and think that we have chosen a valid control group.

Yours sincerely,

Joan L. Robinson