Author’s response to reviews

Title: Frequency of apnea and bradycardia 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 referees as follows:

Referee #1
As suggested, we changed the terminology to make it clear that the control infants received no immunization during the study period as we agree this was confusing. Instead of referring to the pre-immunization and post-immunization period in controls, we now refer to these times as observation period #1 and observation period #2.

Referee #2
The referee questions the choice of controls in this study. The problem appears to be that the original version of the paper did not clarify that both cases and controls were infants of the same gestational age who had not ever been discharged from the neonatal intensive care unit. Most of these infants would have been born at 23-28 weeks gestation so had not been discharged as they were still on oxygen, still having adverse cardiorespiratory events, or still not feeding well. We now clarify that the controls had not yet been discharged which should make it clearer to the reader that the case and control infants should be at roughly equivalent risk for new onset of adverse cardiorespiratory events.

The reviewer suggests that it would be more valid to use each infant as its own control, comparing the incidence of adverse cardiorespiratory events in the 72 hours post-immunization to the 72 hours pre-immunization. To some extent this data is already reported in the manuscript, with 37.6% of case infants having an increase in adverse events. However, the reason why we think that interpretation of this data is clarified by the addition of a control group is that multiple factors can result in an apparent increase in adverse cardiorespiratory events in this fragile population (sepsis, hypothermia, worsening of a cardiac lesion, or increased observation because of a change in nursing staff) such that an increase in events post-immunization would not necessarily be an effect of the immunization. This is validated by the fact that we found a significant incidence of increase in adverse cardiorespiratory events in the control group at an equivalent age (24.8%).

As explained to referee #1, the terminology has been changed to clarify that controls were observed for 6 days at an equivalent chronologic age to cases, and the terms "pre-immunization" and "post-immunization" are no longer used for controls as they do not apply. It is now clarified in the manuscript that both cases and controls were on a cardiorespiratory monitor during the study period.

We agree with the referee that it is plausible that the increase in adverse cardiorespiratory events in the cases was related to increased concern on the part of the nurse, and mention this in the discussion. It is unfortunate that adverse events are recorded only by observation, but it would not be practical to perform more detailed monitoring (such as is done in sleep studies) for an immunization study.

We would be happy to consider any further suggested changes.

Yours sincerely,
Joan L. Robinson