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

Authors:

  Jackie Lee (JackieLee@cha.ab.ca)
  Joan L Robinson (jr3@ualberta.ca)
  Donald W Spady (dspady@ualberta.ca)

Version: 4  Date: 18 April 2006

Author's response to reviews: see over
Dear Editor,

We appreciate the opportunity to address the concerns of the reviewer and have tried to address each point. We also appreciate the patience of the reviewer and hope we have now understood all the issues. The following explains the changes we have made:

1. case-controlled study
In their most recent reply, the authors argue that the term control group is appropriate, which is OK by me. However, they have ignored the arguments in my two previous reviews regarding the misleading case-control terminology. In this typescript, the authors use the term 'a case' for a child that has been vaccinated. However, the vaccination is the exposure variable in this study. Since 'a case' in medical literature refers to a subject with the disease in question, it is inappropriate to use it to describe the vaccinated. Please remove all references to cases and refer to this particular group as immunized, vaccinated, or something equivalent.

For the remainder of this review, I will use the term 'vaccinated' for the children that are referred to as 'cases' in the typescript.

We agree with the reviewer that our terminology was incorrect, and apologize for misunderstanding the comment in the past. We now use the term “immunized infant” in place of the term “case” or “case infant”.

2. immunization in the control group
On p.10 r.13-17 the authors now state that almost all control infants were already immunized or were eventually immunized (often prior to discharge). The reader is now easily confused: On p.5 r.1-7 the authors state that these control infants were selected during the same follow-up period as the vaccinated, were of same gestational age, and were not yet discharged from NICU. If they fulfilled the eligibility criteria of the vaccinated stated on p.4 r. -3-1, why were they not included in the group of vaccinated? Presumably, these control children that were already immunized were a subgroup of those 60 children that were excluded from the group of vaccinated because of exclusion criteria (p.6 r.-3-1). This implies that at least 64 control infants were vaccinated after discharge. Please provide a specific description of how many of those 60 that were excluded from the group of vaccinated were included in the group of controls, how many control children had their vaccination after discharge, and also how the information regarding their vaccinations after discharge was obtained. The vaccination information is absolutely essential when determining the characteristics of the vaccinated and the control group, and deserves a thorough and detailed description in the typescript.

The reason that we believe it is accurate to state that almost all infants would have received their 2-month immunization is that it is standard practice to immunize all infants who have not yet been discharged at 2 months of age. Instead of relying upon the staff of the NICU to remember this step, a public health nurse visits the NICU frequently to update immunizations. It is exceedingly rare for parents of a perterm infant to refuse to have this immunization given as they have become very
accustomed to much more dramatic interventions if their infant has spent 2 months in NICU. We now clarify this for the reader in “Methods”. Because of this high compliance rate, we had to use the same infants as both immunized infants and as controls (spanning different dates of course) as we would have had almost no controls to choose from if we looked for infants who were in NICU as long as the immunized infants were, yet eventually went home without an immunization. This is now clarified in the manuscript.

---

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

p.4 r.9-11: ‘However, none of these studies included a control group ... so the relationship between the immunizations and these events has not been clearly established.’

If none of these studies included a control group, to what were they compared to? If the comparison was done by using the subject itself as a control, this comparison is actually a preferred way compared to the approach suggested by the authors (as they state on p.10 r.11-12). Therefore if the authors intend to include the statement ‘the relationship has not been clearly established’, this requires a more thorough argumentation.

We now omit the statement as we agree it is controversial.

p.4 r.14: ‘A case controlled retrospective study’

Please delete all references to case controlled studies. The study design in this typescript is a retrospective stratified cohort study.

We made this change as suggested.

p.6 r.10-11: ‘Categorical values were compared by chi-square.’ I can only find one test result on p.7 r.-3. Please modify the sentence by stating specifically that the cellular and acellular vaccines were compared by using this method. Also state that which one (Fisher or chi-square) was used.

Cellular and acellular vaccines were compared by using Chi-square. A p < 0.05 was considered statistically significant. The actual Chi-square value is given in row 5 of page 8.

p.6 r.14: ‘Differences were considered statistically significant for values of p<0.05’ Please include a statement that if the 95% confidence interval of the odds ratio did not include the value one, the difference was considered statistically significant.

This has been done.

p.10 r.7-8: ‘the use of matched controls should decrease the effect of multiple nurses performing the observations’. The authors have not stated that the controls were also matched according to the nurse performing the observations. In other words, if the control child was not observed by the same nurse as the vaccinated,
This possible confounding factor is still present in this study and therefore this sentence should be removed.

This sentence was removed.

Please let us know if further changes are required.

Your sincerely,

Joan Robinson