Reviewer's report

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

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Reviewer: Jukka Jokinen

Reviewer's report:

General

The authors have set up a task to study the relationship between adverse cardiorespiratory events and the first DTP-IPV-Hib immunization to preterm infants. In order to explore the causal relationship between an event of interest and the exposure in pre-specified population, a random sample of that population is needed. However, when the event is rare or difficult to measure, the required size of the sample can become so large that the study becomes unfeasible. In these situations, case-control methodology can be applied. The idea in case-control studies is to pick all (or a random sample of) cases with the event of interest and compare their rate of exposure with that of a suitable group of controls (i.e. subjects without the event of interest). Case-control studies are relatively quick and inexpensive, but particular care and effort is required in finding a suitable control group so that potential confounders would be taken into account.

The authors in this paper claim to be the first to conduct a case-controlled trial to study the rate of exposure (i.e. vaccination) in preterm infants with and without the event of interest (i.e. adverse cardiorespiratory event). However, the authors have obscurely defined as "a case" a subject that have received the exposure, i.e. the vaccination, and as "a control" a subject that have not received the exposure. Thus the study setting is clearly not a case-control study, and conclusions derived from this comparison are unclear and hard to follow. The "cases" are collected from a population of infants whose gestational age is less than 32 weeks, have received DTP-IPV-Hib vaccination prior to discharge from neonatal intensive care unit, and have been on a cardiorespiratory monitor for at least 3 days before and after vaccination. The "controls", however, are collected from a population of infants that have the same gestational and postnatal age, have been (apparently) discharged from hospital after birth, but have been hospitalized again for some reason at the postnatal age when the "cases" have received their vaccination.

The authors claim that because they have matched the "controls" according to the gestational and postnatal age of the "cases", the difference in the number of cardiorespiratory events in these two groups is attributed to the vaccination. As is clear from the descriptions above, the two groups are samples from very different populations, and numerous other reasons and open questions arise that may also attribute to the differences between these two groups. What kind of children are those who are still in intensive care at the age of approximately 10 weeks and are in cardiorespiratory monitor? What are the reasons for the monitoring? On the other hand, what possible reasons one can think of how these children differ from those that have been discharged and hospitalized again at the age of ~10 weeks? And why have they been hospitalized?

Another crucial point in these kind of assessments is the definition of the event of interest, since it can have a huge impact in the analysis. The authors define that an adverse cardiorespiratory event has occurred if 1) there are no apneic or bradycardic events 3 days prior vaccination, and two or more events occur within 3 days post
vaccination, or 2) there is 25% increase in the number of apneic or bradycardic events 3 days post vaccination compared to 3 days prior. This definition is clear for the "cases" but how is the event defined for controls that have not received vaccination? In addition, no clear description is given whether these "control" children have been in cardiorespiratory monitor for six days or whether the event of interest was recorded by a study nurse rather than the monitor. If monitor was not used, it is plausible that some events may have been missed, which causes further bias into the evaluation.

In summary, what the authors see as the strength of the study, i.e. use of the "control" group, I see as the major weakness of this study. On the basis of the considerations above, I conclude that the results regarding the effect of DTP-IPV-Hib vaccination on cardiorespiratory adverse events derived in this study do not adequately address the study hypotheses set by the authors. However, the study hypothesis set by the authors regarding the effect of whole-cell and acellular pertussis vaccine is very insightful, may be of interest for the readers of this journal, and in my mind, could be more adequately addressed using the data already available; see Major revisions below.

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

When determining the effect of the exposure on an event of interest, the essential goal is to try to make all other possible confounding factors as equivalent as possible. The exposure in this study is the vaccination. The most efficient way of controlling the potential confounders is to use the subject itself as a control: if the only notable change in the child's status during the six-day monitoring is the vaccination, the best way to find out the effect of the vaccination is to compare the number of apneic and bradycardic events pre and post vaccination *within* the child. This can be achieved by taking the difference (or a ratio) of the events pre- and post vaccination for each child. If the average difference is zero (or ratio is 1), no apparent change has occurred. The differences can subsequently be compared between groups of infants receiving whole-cell and acellular pertussis vaccine. In my mind, in order to make this manuscript a useful contribution, the authors should make a major revision, and analyse their "cases" by using this type of approach. For this evaluation, the use of the "control" group, as defined by the authors, is needless, and should be excluded from the analysis.

An important question to be addressed in this type of analysis is how the events are recorded: if it is through observation of study nurses, there is a potential danger of bias, since it is plausible that the infants are more closely monitored after the vaccination. Also, the rate of events could be adjusted by the length of the follow-up in order to include such infants that have been discharged before 3 days post vaccination. Statistical expertise in collection of the data and subsequent analysis is advised.

As the authors correctly note in their discussion, it is instructive to keep in mind the population under study when making the conclusions, that is, preterm infants in neonatal intensive care and in cardiorespiratory monitoring during the time of vaccination. Thus when making conclusions and possible recommendations, it should be emphasized that the effect, or lack of it, is observed in infants with such characteristics, and generalizability of the results to other populations is questionable. In other words, this study can find out whether it is advisable to vaccinate preterm infants who are still in neonatal intensive care after approximately 10 weeks from birth, and are in a cardiorespiratory monitor during the time of planned vaccination.

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

Not applicable until major revisions have been addressed.
Discretionary Revisions (which the author can choose to ignore)

Same as above.

**What next?**: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Level of interest**: An article whose findings are important to those with closely related research interests

**Quality of written English**: Acceptable

**Statistical review**: No

**Declaration of competing interests**: I declare that I have no competing interests