Author’s response to reviews

Title: Risk of seizures after immunization in children with epilepsy: A risk interval analysis

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Author’s response to reviews:

We thank the reviewers for their detailed and helpful comments on our manuscript. We also thank the editor for the opportunity to revise and resubmit our manuscript for reconsideration by BMC Pediatrics. Our point-by-point response to the editor's and reviewers' comments is below.

Technical Comments:
- tables should be in proper place

Response: In the initial submission, the tables were embedded in the text as per the author guidelines. The tables have now been moved to the end of the manuscript file, after the figure legend (pages 20-22).

Editor Comments:

Please address the reviewers' concerns which can be found below.

An editorial note regarding the review report by reviewer 1:

one of the concerns raised states: "The study would be much crisper if the inclusion criteria were modified to include ONLY pts who had vaccinations - ie include only those pts who could be assessed both during the risk period (after vaccination) and non risk period. Thus, the analysis should be limited only to those who had immunization records available AND had a vaccine during the study period. The extra data on pts who never had vaccines, or had no vaccine records available is not relevant to the study and is distracting."
Please note that we do not require you to re-analyse your data and rewrite your manuscript according to this comment. We do however ask you to include a comment to the reviewer explaining the set-up of your study as presented in this manuscript.

Reviewer reports:

Elaine C Wirrell (Reviewer 1): This paper is a retrospective study on the risk of seizures after vaccination in children<7 yrs.

The paper is of interest but could be improved with a few modifications.

1. The study would be much crisper if the inclusion criteria were modified to include ONLY pts who had vaccinations - ie include only those pts who could be assessed both during the risk period (after vaccination) and non risk period. Thus, the analysis should be limited only to those who had immunization records available AND had a vaccine during the study period. The extra data on pts who never had vaccines, or had no vaccine records available is not relevant to the study and is distracting.

Response: We agreed with the reviewer’s comment that the data on patients with immunizations during the study period could be presented more clearly and that some extraneous information was presented in the initial manuscript, which has been removed (see below). Only patients who received immunizations during the study period were included in the risk interval analysis to determine the incidence of seizure during the risk and non-risk (i.e., control) periods. The total N of 147 in the title for Table 3 (page 22) was an error and has been corrected to: N=80. Baseline characteristics of patients whose immunization records were and were not available were presented to demonstrate the representativeness of those who consented to the overall population of children with epilepsy in Nova Scotia, Canada. However, we recognized that this may not haven been the most relevant comparison. Therefore, we have revised the paper to present the characteristics of the participants included in the risk interval analysis (i.e., participants with immunization visits) more clearly. As there were some important differences between children with immunization visits, those without immunization visits and children without available records that affected the interpretation of the results (e.g., younger age at diagnosis and higher frequency of seizure events), we felt it was important to present those data as well. The revisions are detailed below:

a) The abstract was modified to include only the number of seizures and immunization events in children with immunizations (page 2, lines 42-45): “…of whom 80 (54%) had one or more immunizations between the epilepsy diagnosis date and age 7 years. These 80 children had 161 immunization visits and 197 medically attended seizures.” We also reported the seizure frequency of children with immunization visits separately from other groups (page 2, lines 45-47): “Children with immunizations had more seizures than either those with no immunizations or those with no records (mean 2.5 versus 0.7 versus 0.9, p<0.001).”
b) The text in the methods section was modified (page 7, lines 125 and 129): “…and number of seizure events were compared among children with and without immunization visits and those whose records were unavailable”, and we used ANOVA rather than t-tests for the 3-way comparisons of continuous variables.

c) The results section has been modified (page 8, lines 157-162): “Children with immunization events were diagnosed at a younger mean age (2.1 years versus 4.0 years versus 3.1 years, p<0.001) and had more seizure events during the observation period (mean events per subject=2.5 versus 0.7 versus 0.9, p<0.001) than either children with no immunization events or children whose records were unavailable.” The discussion was modified similarly (page 12, lines 248-250): “Children with immunization events experienced more seizure events than those without immunization events or whose records were not available.”

d) Table 1 (page 20) has been modified to present the characteristics of children with immunization events versus those with no immunization events versus those whose records were not available.

e) We removed the description of types of healthcare encounters for all eligible subjects and focused only on the types of healthcare encounters among participants with immunization events (see page 9, lines 178-183): “Children with immunization visits had a total of 197 healthcare encounters for seizure during the study period. The majority of encounters were telephone calls to the neurologist (131/197; 66%), followed by ED visits (31/197; 16%), hospitalizations (20/197; 10%), and unscheduled outpatient visits (15/197; 8%). The number of seizure events was similar across all four seasons, ranging from 54 events in winter (27%) to 43 events in summer (22%). The mean age at the time of the seizure event was 3.5 years (standard deviation=1.7).”

f) In Table 2 (page 21), the title was shortened to: “Immunizations administered after epilepsy diagnosis”, the denominator (N) under “Number of immunization visits per subject) was changed to 80 from 147 and the number of subjects with 0 immunization visits was removed.

2. Why did so many families not allow release of vaccine records? Was this because families were not contactable, or because they actually refused release. How many times did the authors try to contact them.

Response: The study team sent letters to all parents informing them of the study and then called them up to 5 times at different times of the day and left up to 2 messages. This detail has been added to the methods (page 6, lines 99-100): “The study team attempted to contact caregivers by telephone up to five times, calling at different times of the day and leaving up to two messages.” The reasons why we did not obtain consent to release immunization records are now described in Figure 1 (see page 8, line 152 and figure legend on page 19). The most common reason for not providing consent was that the family was unable to be contacted by telephone (76 subjects), followed by refusal to participate (44 subjects).
3. The authors may miss some seizures as not all families will call with every sz. However, would likely have detected more severe seizures or seizure clusters that were out of the ordinary

Response: We agree with the reviewer’s comment. The under-ascertainment of seizures is described as a limitation on page 12, lines 252-254.

4. Table 3 - is this based on 80 pts who had vaccines, as opposed to 147?

Response: Yes, Table 3 (page 22) is based on 80 patients who had vaccines. The total N in the title has been corrected to 80, as indicated in the response to comment 1 above.

Bernd Neubauer (Reviewer 2): "There were 302 children with epilepsy who were eligible for the study. Immunization records were retrieved on 147 patients (49%)."

1. This is a low number! Why did not more parents consent? Is there a possible explanation? Were all parents contacted? Were some just unavailable?

Response: We thank the reviewer for this comment. All parents were contacted by mail and then by telephone up to 5 times. Failure to reach families was the most common reason why consent was not obtained. Further detail on how parents were contacted and the reasons why immunization records were not obtained are described in the methods (page 6, lines 99-100) and Figure 1, respectively, as discussed in our response to reviewer 1’s comment 2 above.

2. "Children whose immunization records were available had more seizures than those without records (mean 1.7 versus 0.9, p=0.002)."

Please comment.

Response: We retrieved information on seizure events from all eligible children. We have now reported the mean number of seizure events for children with immunization visits, with no immunization visits and with no immunization records in Table 1 and in the results (page 8), as detailed in our response to comment 1 from reviewer 1. This finding suggests that the risk interval analysis was biased toward children with more frequent seizures, which is a limitation, as discussed on page 12, lines 248-251: “Children with immunization visits experienced more seizure events than those without immunization events or whose records were not available, which would be expected to lead to an overestimation of the risk of post-immunization seizure.” Because this bias would be expected to lead to an overestimation of the risk, the probability that we missed a true increased risk of post-immunization seizure (i.e., type II error) is reduced.

3. "We conducted a retrospective cohort study of children diagnosed with epilepsy before 7 years of age who lived in Nova Scotia, Canada and were followed by the IWK Health Centre Neurology Service between January 2010 and December 2014."
Please give numbers how many % of children with epilepsy this will cover in the given Population.

Response: A previous population-based study of epilepsy in Nova Scotia reported that 95% of children with epilepsy in the province were followed by the IWK Neurology Service (Camfield et al, Epilepsia, 1996, 37:19-23). We modified the Methods (page 5, line 89-90) to: “...the IWK Neurology Service follows approximately 95% of children with epilepsy in Nova Scotia, Canada” and cited the above paper (reference 18).

4. "...33% had unclassified epilepsy" This seems to be a high rate. Please comment.

Response: The relatively high proportion of children with unclassified epilepsy may be explained by the fact that epilepsy type was extracted from medical record by non-expert coders and the epilepsy syndrome was not always clearly recorded in the medical record. In addition, in some children who were recently diagnosed with epilepsy, a specific epilepsy syndrome may not yet have been determined.

5. "Ascertainment of healthcare encounters for seizure may have been incomplete if some telephone calls to the neurologist were not documented or if some emergency visits and admissions to hospitals outside of the IWK were not reported to the neurologist. This could have led to an underestimation of the risk of post-immunization seizure."

True! One more reason for an underestimation might be that parents might be warned by their physician or health care provider that seizures may have to be expected after immunizations. They might be prepared how to respond in such case.... Some parents therefore might find it unnecessary to report single or short seizures and handle it without phone call etc.. It would be interesting to inquire those participants who did not document a postvac. seizure by phone.

Response: We agree with the reviewer that it is possible that parents may have been less likely to report seizures immediately after vaccination if they were pre-warned about a potential risk of seizure after vaccination. This was included as a limitation (page 12, line 254-255): “In addition, if parents were warned that seizures could occur after immunization, they may have been less likely to report post-immunization seizures.” Pre-warning parents may be less likely to affect reporting of seizures occurring more than a few days post-immunization (e.g., during the risk period for febrile seizures after live vaccines). It is important to note that children with immunization visits were the group with the highest frequency of reported seizure events, making it less likely that under-ascertainment significantly altered the results. We did not ask parents if their child had a post-immunization seizure so as to avoid introducing recall bias.