Author's response to reviews

Title: Relationship between the population incidence of febrile convulsions in young children in Sydney, Australia and seasonal epidemics of influenza and respiratory syncytial virus, 2003-2010: a time series analysis

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Author's response to reviews: see over
Dear Dr McVernon, Dr Widgren and Professor Wong,

Thank you for reading and reviewing our manuscript.

I am writing to submit the attached revised manuscript with the new title: 
Relationship between the population incidence of febrile convulsions in young children in Sydney, Australia and seasonal epidemics of influenza and respiratory syncytial virus, 2003-2010: a time series analysis.

The following is a detailed point by point response to your comments:

Dr Widgren (all changes highlighted in yellow in the manuscript)

1. Add the methods used for assessing the correlation into the abstract.

   A short description of the updated method has been added (page 2, lines 13-14).

2. Emphasize the time correlation between ED for ILI and febrile convulsions in the abstract.

   This has been done (page 3, lines 2-3).

3. Expand on the benefit of these findings in the conclusions.

   This has been done (page 3, lines 11-14).

4. The title is ambiguous, what relationship is under investigation? Consider: “Relationship between the population incidence of febrile convulsions in children and the seasonal epidemics of common respiratory viruses…” etc.

   The revised title is: “Relationship between the population incidence of febrile convulsions in young children in Sydney, Australia and seasonal epidemics of influenza and respiratory syncytial virus, 2003-2010: a time series analysis.”

5. Clearly state the aim and objectives of the study in the text.

   The aims have been revised (page2, lines 5-9).

6. The use of Emergency department presentation of bronchiolitis and influenza-like illness as proxies for RSV and influenza-infections respectively are used without much discussion. A reference is given to a previous paper from one of the authors, investigating the relationship between virus circulation and ED presentations of these syndromes in the same region during an overlapping time period. This is a strength and should be highlighted.

   The new statistical analysis has been based on the methods used in the paper by Schindeler et al (see page 9, lines 16-17). We have included further explanation of the relationship between the syndromes and virus circulation (see page 8 lines 15-
a. The specificity of the use of these proxies needs to be discussed in the manuscript.

The limitations of these proxies have been described page 18, line 15 – page 19, line 3).

7. The main analysis, investigating the relationship between the time-series, was carried out visually. However, the reader has little chance of carrying out the same exercise as the graph of ED presentations of ILI has a scale that makes it difficult to judge the shape, size or timing of other seasons than the 2009 pandemic season.

Figure 1 has been revised to meet the requirements of the statistical analysis and the axes have been labelled more clearly. We have chosen not to alter the scale of the ILI series as that would reduce the visual impact of the changed relationship between ED ILI and ED convulsions in 2009.

8. There are several statistical methods to compare time-series data, as described e.g. in reference nr 23 (Schindeler). Why was this not applied here?

The original descriptive analysis was designed to show how routinely collected data could be used to rapidly examine the relationships between syndromes. However, as advised we have now conducted a statistical analysis using the same method as. Schindeler et al (see page 9, lines 16-17).

9. The method for calculating excess is not the most commonly used for time-series. Why not use a baseline approach?

The excess calculation has now been abandoned in favour of the statistical measure of relationship.

10. Importantly, focus the discussion around the aim of the study, whether it was to investigate the time relation between (proxies for) respiratory virus circulation and febrile convulsions, to estimate the excess in febrile convulsions due to the same viruses or to respond to concerns about convulsions due to vaccination.

The discussion has been refocused. There are two aims of the study, to determine if influenza and/or RSV are associated with febrile convulsions and to estimate their contribution. The feasibility of such an analysis for rapid surveillance of febrile convulsions is a secondary aim. Influenza vaccination associated febrile convulsions has been discussed as a motivator of the study only.

11. There is a lack of relationship between the magnitudes of the peaks in the time-series. This is an important limitation and needs to be addressed. The point made on magnitude of epidemics and its correlation to circulating strains in paragraph 4 in the discussion is not clear.
The information on circulating strains has been reworded (page 20, lines 7-13). We tested the relationship between ILI and convulsions in 2009 and found a weaker association (page 20 lines 15-16).

12. Paragraphs 5 and 6 of the discussion: Is the message that the impact of the pandemic was a falsely high number of ED presentations for both convulsions and ILI? Please explain for readers not familiar with the NSW setting.

The relationship between ED ILI and ED convulsions was shown to be weaker in 2009 (page 19 lines 20-21).

The observed population rates of ED convulsions and ambulance fitting and convulsions during 2009 is likely to be accurate due to the unmistakeable nature of convulsion symptoms (page 20 lines 1-3).

13. Have you investigated the relationship between RSV/bronchiolitis peaks and febrile convulsions with a time-lag?

The new statistical analysis included a lag analysis of +/- 2 weeks for both syndromes (see Table 1).

14. More than a two-week sample should be used for representativeness for ED triage data.

Given the increased complexity of the study and in the interests of timeliness and brevity, this data has now been removed from the study.

15. Explain how this ED triage data is related to the ED data.

Please see 14.

16. Give the numbers of non-febrile convulsions in the ED triage data. Can these be considered noise of constant size? The implication of a difference between season and non-seasons should be discussed

Please see 14.

17. Add the representativeness of the laboratory data for the region of the eight laboratories you received virological data from.

The inclusion of the statistical analysis has rendered this data redundant, so in the interests of timeliness and brevity, it has now been removed from the study.

18. In figure 3, could you also indicate the percentage of laboratory samples positive for influenza over the years, in addition to the number of positive samples? This would make the difference between the 2009 pandemic season and remaining seasons easier to interpret.
19. As you point out weekly virological data would of course be much more informative. Were these not available?

Weekly virological data was not available for the whole time series. The inclusion of the statistical analysis has rendered this data redundant, so in the interests of timeliness and brevity, it has now been removed from the study.

20. Please, look through the abbreviations. Not all are explained.

All abbreviations are now explained.

21. (Background) It would be interesting to know the population of NSW.

This information has been added (page 5, lines 17-19).

22. (Background) A peak incidence does not occur at a certain age, it would rather be” peak incidence is seen in 18-month old children”

This has been changed (page 4, lines 4-5).

23. (Background) Clarify that it is incidence through the age of 4 that is described in the Sillinpää study.

This has been changed (page 4, line 6).

24. Clarify in the methods what “almost all ED services” means with regards to public hospitals in NSW.

This has been clarified (page 7 lines 6-8 and page 8 line 1).

25. Clarify in the methods whether also the data on ED presentations of influenza-like illness and bronchiolitis were restricted to the Sydney region.

Please see 24.

26. There are results in the methods section. These should be moved.

This has been done. Discussion of the Year2009 indicator serves only to explain its use in the Methods (page 10, lines 14-18).

27. Influenza activity is said to have been higher than usual in 2003, 2007 and 2009. Please give a reference.

References have been added (page 12, lines 12-13). The explanation has also been clarified (page 20, lines 7-13).

28. Figure 1 shows convulsions only for 0-5 y.o. but the legend mentions two age groups.
This was a typographical error that has been corrected.

29. Label the graphs and their scales better and amend the ILI ED figure as above.

Figure 1. has been revised to meet the requirements of the statistical analysis and the axes have been labelled more clearly. We have chosen not to alter the scale of the ILI series as that would reduce the visual impact of the changed relationship between ED ILI and ED convulsions in 2009. Figure 2. and Figure 3. have been rendered redundant by the statistical analysis and have been replaced with the observed versus predicted population rates.

30. Instead of figure 2, show the time-series with three-week rolling average to determine threshold between epidemic and non-epidemic periods. This would make the method (if it is to be kept) used clearer and give the magnitude of the excess figures some perspective.

Please see 29.

Professor Wong (all changes highlighted in red in the manuscript)

1. The data had been retrospectively retrieved from 2 administrative sources in the NSW Emergency Department, with only provisional diagnosis of convulsions and only proxy measures for influenza-like illness or bronchiolitis were obtained. The authors should explain the reliability of these data eg type of febrile convulsion- simple, atypical, recurrent

We chose to study population level de-identified syndromic surveillance data, as such we can report only on the provisional diagnosis based on the primary symptom of seizure. We are unable to calculate the number of simple, atypical or recurrent seizures or any subsequent sequelae (page 18, lines 19-21).

2. Any underlying neurodevelopmental disorders in this cohort to explain for the proneness of febrile seizures

Please see 1.

3. For influenza related febrile seizures, subsequent development of influenza encephalopathy can ensue. Can the authors report the number of influenza encephalopathy in this cohort?

Please see 1.

4. What was the routine microbiological workup for common viruses in the ED setting in Australia for those presenting with the provisional diagnosis of convulsions as this can affect the incidences.

We are unable to report this data without re-identifying each record and linking to a separate database.
5. The risk of fever precipitated convulsion is high for those with underlying epilepsy or neurodisabilities, can the authors report for this cohort?

Please see 1.

6. Other viruses can also be associated with a higher risk of febrile convulsion in infants eg HH6. Can the authors explain for the possibility of other viruses being a contributory factor in this cohort rather than influenza?

Specific mention of the connection between HH6 and febrile convulsions has been added (page 5, line 1). Current literature (van Zeijl et al 2004) linked the incidence of febrile convulsions to seasonal epidemics of influenza. Our new statistical analysis supports this conclusion.

Thank you once again for considering our manuscript.

Yours sincerely

Ben Polkinghorne