Reviewer's report

Title: Characterisation of acute respiratory infections at a UK paediatric teaching hospital following the H1N1 pandemic (Observational study assessing the impact of H1N1 on predominant viral pathogens)

Version: 2 Date: 1 April 2014

Reviewer: Nicole Wolter

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Major Compulsory Revisions

1. Materials and Methods, Subjects, first paragraph – authors should provide more detailed information on their definition and identification of cases. What symptoms were used to identify a case of ARI, did these cases include all ARI or only lower respiratory tract infection, was there a cut-off for the duration of symptoms?

2. Materials and Methods, Pathogen detection, first paragraph – the manuscript states that respiratory samples were analysed either by a rapid RSV test or by multiplex PCR testing for ten respiratory viruses. From this it can be assumed that some specimens were only tested for RSV and not for all the respiratory viruses, which would bias the findings towards over-representation of RSV in the study.

3. Results, Pathogens causing ARI – viral aetiology has been described by samples which is incorrect and should instead be described by cases (patients). Although 700 samples were collected, only 645 cases (patients) were included in the study. If a case had two (or more) samples collected and tested and both were positive for the same organism, in this manuscript they would have been treated as two separate incidences of infection. This is incorrect and they should be treated as one infection. To avoid misinterpretation of the data, the authors should describe aetiology by case and not by sample.

4. Discussion – limitations of the study should be mentioned including that data was collected for only one year and therefore did not detect fluctuations in circulating viruses over different time periods, cases were only enrolled from a single site, respiratory bacteria were not detected/targeted. In addition, studies have shown that some respiratory viruses may be detected in asymptomatic patients (controls) and therefore the PCR-detection of a virus on a nasopharyngeal specimen may not necessarily indicate the definitive cause of disease.

Minor Essential Revisions

1. Title – avoid use of abbreviations, such as UK, in the title.

2. Title, and throughout manuscript – H1N1 should be more formally referred to as 2009 H1N1 influenza virus.
3. Abstract, Methods – should include a description of viral testing/detection.

4. Abstract, Conclusions – the statement “H1N1 occurred frequently in otherwise healthy children but was also capable of causing severe disease in those with existing co-morbidities” is not supported by the data in the manuscript. The authors do not show data indicating that H1N1-infected patients with co-morbidities were more likely to have severe disease than H1N1-infected patients without co-morbidities.

5. Background, first two sentences – statements need relevant references.

6. Materials and Methods, Setting and study design, second sentence – no reference is given for the numbers provided for the hospital. Where are these figures taken from, and for which year do the data refer to?

7. Materials and Methods, Subjects, first paragraph – authors should include detail on which co-morbidities were considered.

8. Materials and methods, Pathogen detection, first paragraph – provide details of the manufacturer of swabs and viral transport medium.

9. Materials and Methods, Respiratory virus PCR analysis – provide sufficient details for the “CDC published protocol” so that the reader is able to find the details of the method.

10. Materials and Methods, Respiratory virus PCR analysis – references for methods of PCR-based detection of parainfluenza and some of the other viruses are not provided.

11. Results, Demographics and patient characteristics, second paragraph – the manuscript states that “Mean (IQR) length of stay was 12 (2-11) days. The mean is larger than the IQR, is this correct? See again in results, H1N1 infection, second paragraph.

12. Results, Demographics and patient characteristics, second paragraph – define what was regarded as a “significant co-morbidity”.

13. Figures – Titles of all figures should contain sufficient information to be stand-alone titles that do not require reference to the text. Improve all figure titles accordingly.

14. Figures – abbreviations used in figures should be explained in footnotes.

15. Results, Pathogens causing ARI second paragraph and Table 1 – Text describes the detection rate of various viruses and refers the reader to Table 1. Table 1 shows the pathogens causing co-infections. The text and/or table should be corrected to describe the same data. This is also reflected by the total of 504 positive samples in the text and a total of 401 in table1.

16. Results, Pathogens causing ARI second paragraph - The overall detection rate for each viral pathogen, by case, is not described in the manuscript. In addition the breakdown of positivity by test (Binax or PCR) is not given therefore statements such as “PICU admission was significantly more likely to occur in patients with PCR-negative samples (56%) than those in whom 1 (33%), 2 (35%) or 3 (0%) viruses were detected (p<0.001)” are not interpretable.
17. Results, H1N1 infection, second paragraph – what statistical test was used to compare the mean length of hospital stay between severe and non-severe patients? A statistical comparison of means would require a test such as the student’s t-test, however only the chi-squared test is mentioned in the material and methods.

18. Figure 2 – y-axis needs to be labelled, sample numbers for each bar should be given under each bar together with the label, groups of data should be mutually exclusive (age of 5 years is included in two of the groups) throughout manuscript

19. Results – Prevalence of co-morbidities in patients with H1N1 infection, last paragraph – data and statistics for the overall comparison of co-morbidities amongst patients with and without H1N1 infection should be given to support this statement.

20. Figure 3 – the total number indicated in the legend totals 700, which is the total number of samples tested. Samples cannot be classified as “mild, moderate or severe” and therefore this analysis has been done incorrectly. As stated above, it should be done by case (patient).

21. Figure 3 – this analysis should be done for single infections only and not merely whether the virus was detected or not. For example, rhinovirus is unlikely to cause severe disease on its own, and the severity of disease may be due to the co-infecting pathogen and not necessarily rhinovirus.

22. Discussion, paragraph 7 – It should be specified that NPA samples are an optimal specimen type for diagnosis of viral ARI. NPAs are not necessarily the optimal specimen for diagnosis of ARI in general, as they are not always usefully for bacteria due to bacterial colonisation of the nasopharynx.

Discretionary Revisions

1. Abstract – the study period is stated in the methods and not necessary to repeat in the results.

2. Abstract – abbreviations should be avoided or explained in the abstract.

3. Abstract – when percentages are given, the n/N data should also be given.

4. Background, last sentence – should be written in past tense as study is completed (attempts changed to attempted).

5. Materials and Methods, Setting and study design, first sentence – should be rephrased as a full sentence

6. Materials and Methods, Setting and study design, second sentence – “catchment area of 7.5 million” would be better stated as “catchment area of 7.5 million individuals”

7. Materials and Methods, RSV testing – include the city and company of the manufacturer Alere and in other places where manufacturers are referred to.

8. Materials and Methods, Respiratory virus PCR analysis – virus names should not be capitalised.
9. Materials and Methods, Respiratory virus PCR analysis – details of RNA extraction are not provided

10. Results, throughout – be consistent with use of decimal places, either none, 1 or 2 decimal places throughout the manuscript

11. Results, Types of respiratory sample – the terminology “commonest” should be replaced with “most common”

12. Results, Types of respiratory sample and other parts of manuscript – when percentages are used in the text, the corresponding (n/N) values should be given as well.

13. Results – be consistent with capitalisation of p-value, either “p” or “P”.

14. Results, H1N1 infection, second paragraph – “time spent on PICU” should rather be “time spent in PICU”.

15. Figure 2 – remove decimal place from y-axis labels

16. Throughout text – “PCR-negative” individuals would be better described as “respiratory virus-negative”.

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

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests