Author's response to reviews

Title: The Value of Radiographic Findings for the Progression of Pandemic 2009 Influenza A/H1N1 Virus Infection

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Philippa Harris, PhD
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RE: Manuscript reference number: 3688456847264303, MAJOR

Dear Dr. Harris:

Our manuscript, “The Value of Radiographic Findings for the Progression of Pandemic 2009 Influenza A/H1N1 Virus Infection,” has been revised according to the suggestions of the Editor and Reviewers. An item-by-item explanation of our responses to each query appears below. Please note that we paraphrased each of the Reviewers’ questions and suggestions in our responses.

Editor:

1. Please clarify whether the review board at the National Center for Child Health and Development actually approved this study and include this information in the methods section.

This study was approved by the relevant institutional review board and was performed in compliance with the guidelines set forth by the Institutional Review Board at the National Center for Child Health and Development. We have added text to clarify this, in the Methods (page 9, line 10-13).

2. Please clarify why you obtained consent for patients for a retrospective study (i.e. are all patients at the hospital asked if their data can be used for further research purposes?). Please include this information in the methods section.
We obtained consent from patients and/or their parents because all patients who were hospitalized were asked and agreed to sign the relevant consent form so that their data could be used in future research. We have added this information to the Methods (page 9, line 9-10).

Reviewer: Dr. Jung Sook Yeom

A. Major compulsory revisions

Thus, the authors should delete “no study focusing on chest radiographs” from the Abstract. The authors should refer to the previous studies and emphasize the originality of the present study in the Introduction or Discussion.

As suggested, we have deleted the indicated sentence and added some of the new references (references 17-19). These studies describe chest radiography findings associated with disease progression of A/H1N1 infection in adults and children; however, they do not include information on antiviral use. In Japan, neuraminidase inhibitors have been frequently prescribed, and we hypothesized that such treatment affects disease outcome. Thus, we investigated factors associated with rapid disease progression among children admitted for A/H1N1 infection, focusing on initial chest radiographic findings in the context of neuraminidase inhibitor use. We have added text to clarify our study goal, in the Abstract (page 4, line 7-8) and Introduction (page 6, line 13-19). In addition, minor editing was done in the Abstract.

2. Definitions of terms are obscure. Please define: (1) indications for PICU admission; (2) vital signs (maximal body temperature, respiratory rate, or SpO2 either during hospitalization or the initial findings); (3) the meaning of oxygen demand; and (4) definition of consolidation and ground-glass opacity.
We have added detailed definitions of the relevant terms: (1) to (3) (Page 8, line 6-11), and (4) (Page 8, line 14-17).

3. The present study does not describe the extent or pattern of consolidation, which may be more important than the consolidation itself. More detail about consolidation in Group 3 should be provided.

As suggested, we further investigated the extent and distribution of consolidation in Group 3 and subdivided that group into those with consolidation of ≤ 25% (20/64, 31%) and 25-50% (44/64, 69%). Greater consolidation was associated with worse clinical outcomes; i.e., more frequent PICU admission and MV. Furthermore, we classified the distribution of consolidation as unilateral (26/64, 41%) and bilateral (38/64, 59%); however, no significant differences were observed between these groups. We added text to the Methods (page 8, 15-16), and the data are described in the Results (page 12, line 18 – page 13, line 7) and Discussion (page 15, line 12-14).

4. The Results and Discussion are too long and are not well-organized. Please state concisely the main point of this study. The authors should carefully reconsider what is the main purpose of the study, and the results that will appeal to readers.

The main purpose of this study was to investigate factors associated with rapid disease progression among children admitted for A/H1N1 infection, with particular focus on initial chest radiographs of children who received neuraminidase inhibitors. As suggested, we shortened and reorganized the Results and Discussion. The first two paragraphs of the Discussion have been deleted.

5. Secondary bacterial infection will have affected both the clinical course and radiological findings. However, the majority of patients who had consolidation on initial chest radiograph received antibiotics without microbiological evaluation, which may be one of the major limitations of this study. Please mention this in the Discussion.

We have added this limitation in the Discussion (Page 19, line 2-5).

B. Minor essential revisions
1. Methods Statistical analysis: describe inclusion criteria for the logistic regression.
The inclusion criteria for the logistic regression have been added to the Methods (Page 9, line 3-5).

2. Results (1) The classification of chest radiographs in Groups 3 and 4 is confused. Please clarify the inclusion criteria for Groups 3 and 4.
(2) Please delete the detailed information on antibiotics from “secondary bacterial infection and treatment”.

(1) To avoid confusion between groups 3 and 4, we have clarified the relevant group definitions, in the Results (Page 11, line 2-5).
(2) We have deleted the detailed information on antibiotics from the Results.

C. Discretionary revisions
1. I recommend describing the clinical or pathophysiological difference between consolidation and ground glass in the Discussion.

As suggested, we have added text to describe the clinical and pathophysiological differences between consolidation and ground glass opacity, to the Discussion (Page 18, line 2-13).

Reviewer: Dr. Seem Jain

1. Abstract:
* More info is needed in the methods about how you grouped patients (including the fact that normal are included in the no consolidation group) and in order to do so, would cut the background down which is a bit long anyway and not completely related to the analysis at hand.

We have added information on the patient groups and shortened the background section (Page 4, line 3-14).

2. Introduction:
* While it is true that novel swine-origin influenza A infection first circulated in Mexico, it was first reported from the US, where it was first detected by PCR. See reference:
We have clarified our description of the enrolled patients. All enrolled patients were laboratory confirmed using a rapid test or had a history of close contact with family members or friends who had received a laboratory-confirmed diagnosis of influenza infection. This information has been added to the Methods (Page 7, line 5-7).

*In relation to this, it is not entirely clear but for the laboratory diagnosis, was only a rapid test used? I am not familiar with this assay but rapids are known to have many false negatives so again unclear as to whether you missed many cases because of this. It would be best to understand the sensitivity of the assay you used. Most other studies used PCR to determine H1N1 status so this is a serious methods issue that needs to be clarified in order to put the findings in perspective and if only used rapids, this needs to be included in the limitations.
In the current study, only a rapid test was used for laboratory diagnosis. Although rapid tests result in false negatives, we used the ESPLINE Influenza A&B-N (FUJIREBIO INC., Tokyo, Japan) rapid diagnostic kit. According to the package insert for this product, the sensitivity of this assay against influenza A is high (96.8%). We have added this information to the Methods (Page 7, line 9-11). We did not perform PCR to confirm diagnoses. This is indeed a limitation of our study and we now describe it as such, in the Discussion (Page 19, line 5-6).

* In the last line under subjects, you state that 7 patients were excluded because they had a diagnosis other than influenza. Were these lab confirmed patients? If so, it is not clear to me why you would exclude them. Please clarify.

They were laboratory-confirmed cases; however, chest radiographs were not obtained for them. Thus, their exclusion from the study. This has been added to the Methods (Page 7, line 11-16).

* Under data collection, how was flu-like symptoms defined? You mention fever but a full definition should be included.

We defined flu-like symptoms as fever ≥38°C, cough, headache, chills, myalgia, malaise, anorexia, nausea, vomiting, and diarrhea. We have added this definition to the Methods (Page 8, line 4-5) (reference 22).

3. Results:
* What is plastic bronchitis? Please explain.

Plastic bronchitis is characterized by bronchial casts typically containing fibrin exudates with varying numbers of inflammatory cells in the large airways. We have included this explanation in the Results (Page 10, line 13-14).

* How was pneumonia defined? Was this based on clinical judgment?

Yes, pneumonia was diagnosed based on clinical judgment. This has been added to the Methods (Page 8, line 11-12).
* My main concern is in 3rd paragraph (and also mentioned above)- why did you keep the normal group in your analyses? If your hypothesis (as stated in your introduction) is to determine if infiltrates are correlated with severity, than including patients with normal findings, will bias you towards that. Most of your results are also intuitive if you use normal as your referent, so makes it a bit less interesting. It also informs your multivariate analysis. It may be that not including the normal would not change your results but this analysis should be done and may be the better one to present. If they are the same, you could also say that you did it both ways. But this does need to be addressed.

We included the normal group in our analyses because several patients rapidly deteriorated despite having normal findings on initial chest radiographs. Some of these patients had abnormal findings, including consolidation and ground-glass opacity, on subsequent chest radiographs. As suggested, we also performed the analyses excluding patients with normal chest radiograph, which showed the significance of consolidation pattern on initial chest radiograph. These data has been included in the Results (Page 14, line 15– Page 15, line 7).

* In addition, there is no mention of infiltrates in any of your radiograph grouping definitions. Where are these patients included?

We have included infiltrates in the definitions used for radiograph grouping. This description has been added to the Results (Page 10, line 17 – Page 11, line 5).

* What is aerodermaectasia? Please clarify.

Aerodermaectasia is another term for subcutaneous emphysema. For clarity, we changed the term to subcutaneous emphysema in the manuscript (Page 11, line 5).

4. Discussion:
* First paragraph mentions “the presence of pulmonary infiltrates on chest radiographs representing alveolar damage is directly correlation with disease severity...” However, you never include infiltrates in your groupings of radiographs in the results. Are infiltrates meant to be synonymous with consolidation? If so, that should be stated but also that is not really the correct way as radiologists (and also in epidemiological
studies that involve radiographs) infiltrates are considered a distinct entity from consolidation.

No, we did not intend infiltrates to be regarded as completely interchangeable with consolidation. For example, we distinguish hilar infiltrates from consolidation. To avoid confusion, we have added the relevant description to the definitions of the radiography groups (Page 10, line 17 – Page 11, line 5).

* At the end of the 2nd paragraph, you state “these were distinct characteristics of the 2009 A/H1N1 influenza infection compared to other seasonal influenza infections.” However, your analysis does not include seasonal infections and in addition, your discussion does not explain this statement either. Would delete or describe the differences using the literature more thoroughly.

We agree and have deleted the indicated text.

* You discuss oxygen demand in your discussion but you never define this in your methods or results. This does need definition as different clinicians and in different countries could view this differently.

We have added a definition of oxygen demand (Page 8, line 8-11).

* The discussion is a bit long and reviews a lot of the overall H1N1 pandemic data but could use more focus towards the radiographic findings and approach that the analysis is supposed to be geared to.

We have deleted the second and third paragraphs of the Discussion and now focus on the radiograph findings.

5. Tables:
* In Table 1, would remind people of the groupings of 1, 2, 3, and 4. Is the SpO2 adjusted for the FiO2? How is O2 demand on admission or during admission defined? This should be included in the methods. What does time to onset mean – in relation to the chest x-ray or admit or what? You include antibiotic use and while antiviral use was very high, it would be good to include it in this table. These comments apply to table 2 as well and are very important.
SpO₂ was not adjusted for the FiO₂. The definition of oxygen demand on admission and during hospitalization was added to the Methods (Page 8, line 11-14). Time to onset means time from onset of illness; thus, we corrected the term in Tables 1 and 2. Finally, we now include antiviral use in conjunction with antibiotic use in Table 2.

* It seems like Table 3 and 4 could be combined somehow.

We have combined Tables 3 and 4.

We thank the editor and reviewers for their many constructive comments on our manuscript and hope you will find the revised manuscript acceptable for publication in *BMC Infectious Diseases*.

Thank you very much for your time and consideration.

Sincerely,

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