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, MINOR

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:

*Please also ensure that your revised manuscript conforms to the journal style.*

We have revised the manuscript according to the BMC journal style. We have changed the authors’ information and a reference list formatted to the BMC journal style.

Reviewer: Dr. Jung Sook Yeom

*When the time of vital signs was? Initial vital signs on admission? This is certainly important because body temperature was defined as an independent factor associated with the clinical course of the patients.*
In the same perspective, I could not fully understand the interpretation of "why the body temperature is lower in patients who required MV" in Discussion section. ("This may be related to the fact that the body temperature of patients hospitalized in the PICU—antipyretics or anesthetics in preparation for MV") What does that mean?

The authors should be clarified the time of vital signs and be cautious interpretations of its meanings.

The vital signs analyzed were taken when the patients admitted to our institution. This was clarified in the text (page 7, last paragraph) and the Tables (Tables 1 and 2). When the patients were transferred from outside facilities to our institution, they had already received antipyretics or anesthetics in preparation for mechanical ventilation. These treatments might contribute to lower the body temperature when they were transferred and admitted to our institution at the time of measuring vital signs

*Definition of "consolidation" and "GGO" should be described in clinical aspect in Methods section. This would better set up the reader to understand the implication of the results with regard to "group 3 vs group 2+4"

As described in the response to the other Reviewer, we have changed “GGO” to “reticulonodularity or diffuse haziness of the lungs”. We have described the definitions of consolidation and reticulonodularity or diffuse haziness of the lungs separately in the Methods section (page 8, line 15 – page 9, line 2).

*The description of "clinical implication of consolidation and GGO" in Discussion section was obscure. In my opinion, it should be mentioned in Discussion section "how does antiviral therapy influence clinical course of patients, focused on initial chest radiographic findings". It would be more suitable to the goals of the manuscript.

We have added the description of the impact of antiviral on clinical course of patients focusing on initial chest radiographic findings in Discussion section (page 19, line 15 – page 20, line 6).
* It seems to me that a case was considered if 1) lab confirmed by rapid methods 2) contact of a laboratory-confirmed case. I will reiterate that being a contact alone is not the same as being a laboratory-confirmed case and for that reason, you cannot lump them together. Can you explain your rationale for this approach a bit more? In your results, you know state that only 68% were cases based on laboratory testing. What does your data look like if you concentrate only on the 139 patients with known influenza? This is a really important issue as patients can have findings consistent with pneumonia on chest x-ray that are due to multiple infectious etiologies but also non-infectious causes as well.

The cases were defined as patients who had a history of close contact (within 1-5 days) with family members and/or friends with laboratory-confirmed influenza or those who had received a diagnosis of influenza at our institution. Because A/H1N1 spread rapidly in the community during the study period and there was no other dominant infections recorded at the same time, it would be appropriate to make a diagnosis of A/H1N1 with close contacts who were laboratory confirmed with influenza-like symptoms and signs with an appropriate incubation period.

* Given some of your response to the comments, I think you need to be more clear in your methods that you looked at serial chest x-rays when available but only did the analysis based on the initial chest x-ray.

As you suggested, we have added the description regarding the analyses based on the initial chest radiographic findings (page 8, line 12–13).

* In my experience, GGO are usually made on CT scans and not on chest x-rays. I worry about misclassification here. Group 4 could also be considered infiltrate.

We have revised the description of radiological findings based on the description of an authoritative radiology textbook (Leonard E. Swischuk, Emergency imaging of the acutely ill or injured child 3rd edition, Williams and Wilkins). As the Reviewer suggested, GGO are the findings usually made on CT scans. Instead, “reticulonodularity or diffuse haziness of the lungs” is more appropriate term to describe the chest X-ray findings.
* I am still concerned about your inclusion of normal chest x-rays in your analysis. I appreciate your adding these results in towards the end of your discussion. They are much more compelling than the results including group 1 as when you present it with group 1, it just seems intuitive that all your findings will be skewed towards consolidation. I understand some of your reasoning for this but how many patients with normal films actually had changed chest x-rays later in the clinical course? If you choose to include this in the analysis, then you should include this all in your methods and also need to state how many normal films changed later in your course such that you felt strongly to include them in your analysis.

We agree with your concern, however, the serial chest X-ray information in patients with normal findings was not available, because most of the patients with normal findings on initial chest radiographs took chest radiographs only once on admission. We have added this description in the Method section (page 8, line 12–13)

* When you talk about clinical characteristics such as respiratory rate, heart rate, and temperature – are these all initial findings on admission? Please clarify.

All the vital signs were measured on admission. We have clarified the timing obtaining the vital signs (Table 1, and Table 2).

* On page 17, 2nd full paragraph, when you state, “Reviewing the chest radiographic findings in patients with A/H1N1 infection demonstrated...” it is not clear that is referring not to your study but something published in the literature already. You did reference but would be better if you could add language making this clearer. You do the same thing on page 18, “in children with A/H1N1 infections, abnormal chest radiographic findings were uncommon...”

We have revised the sentences according to the Reviewer’s suggestions (page 17, line 13, and page 18, line 6–9).
* You spend a lot of time in your discussion talking about studies that analyzed chest radiographic progression but you don’t include your own results in this matter. Do you data on progression of chest radiographs that you could include in your paper?

As mentioned, we have shortened the discussion regarding the studies that analyzed chest radiographic progression, and mainly focused on initial chest radiographic findings (Page 18, 1st paragraph). Unfortunately, the main objective of this study was to investigate factors associated with rapid disease progression among children admitted for A/H1N1 infection, focusing on initial chest radiographs. Therefore, data on progression of chest radiographs during the hospitalization were not evaluated in this study.

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

Thank you very much for your consideration.

Sincerely,

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