Author's response to reviews

Title: Predictors of Fatality in Pandemic Influenza A (H1N1) Virus Infection and Impact of Early Neuraminidase Inhibitors

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Author's response to reviews: see over
Response to the Comments

Dear editor,

1. The data was re-analyzed, by considering the comments of the reviewers, accordingly, non-confirmed patients were excluded. The analysis was limited to laboratory confirmed patients.

2. The number of tables was reduced to 3.

3. The number of figures was reduced to 1.

4. The paper was re-written.

Now, we feel more confident with our study, we thank to you and to the reviewers for this productive comments.

1. Statistical tests: In addition to the points raised by reviewer 1, I have other questions regarding the many p values in table 1 and 4. For variables that are dichotomous it is OK. For categorical variables did the authors have done first a global test to test that the distribution is different between the 2 groups compared? If this test is significant, then a test for each category can be done in comparison to a defined reference (the reference should be indicated in the table). In addition for some categorical variables, for instance age in table 1, there is a p value in front of each age category, which indicate that a defined reference has not been used (for example, the age group 14-24 years). In contrast, in table 4, for the variable chest X Ray, there is only one p value!

So it is therefore impossible for the reader to understand clearly how the statistical tests were performed. This needs to be clarified.

Response: All the parameters were revised accordingly, and now all the variables are dichotomous. Each variable was tested for the association with fatality.

2) In figure 2, the box H1N1 cases should be labeled ?H1N1 suspected cases?

Response: This was revised.

3) Clinically, an important information is missing on the characteristics of cases that were admitted in the ICU, in particular, how many of them had an ARDS and how they were take care of?

Response: Among H1N1 confirmed patients 28 out of 241 (12%) were supported by invasive mechanic ventilation at ICU, and depicted in Table 2.

4) It seemed that there are some results that appear in the discussion and were not presented in the result section.

Response: Results and discussion sections were re-written.

Reviewer’s report

Version: 4 Date: 30 May 2012

Reviewer: julien poissy
Reviewer’s report:

Major compulsory revisions:

1) About methods: only patients #14 years old were included. It can be a problem for the interpretation of the results, notably for the repartition of age and the impact on mortality. Why this choice? In the US study published by Skarbinski J et al, 34% of the patients were <18 years old, and only 8% of the patients were >65 years old. This should be discussed and explained.

   Response: This study was performed in Infectious Diseases Departments and Clinics, which included the adult the age group. In order to get precise clinical data, all the admitted patients to these clinics were studied. The authors are Infectious Diseases specialist of adult age group.

2) About statistical analysis: the criteria used to include the independent variables in the multivariate model are not described. Does it mean that only early use of neuraminidase inhibitors, bacterial co-infection, having a chronic disease, gender and age>65 years were included? Why the others significant variables in univariate analysis were not included? Why not have included all the variables with p<0.2 or 0.1 as often done. This could have changed the results and should be specified.

   Response: We avoided putting intermediate and collinear parameters to the model. For instance, we did not put laboratory findings and mechanic ventilation, because the patients who needs mechanic ventilation is more severe, and closer to fatality. These were intermediate variables. We preferred inclusion of independent variables.

3) Organisation of the results section: this section is disorganized. It should be better to have a first part describing the characteristics of the population studied, then a part describing all the variables associated with fatality in univariate modal. These variables could be pooled in one table, not in several. Then the results of the multivariate model could be presented.

   Response: The results were revised accordingly. All the univariate analysis was described in Table 1. Multivariate analysis was described in Table 3.

4) Questions concerning the results: There are a lot of variables in tables 1-2-3 and 4 statistically associated with fatality, but not explained in the text, and not discussed in the discussion. For example, there is more males in the group fatality than in the group survival, and this data is not underlined. Moreover, all these variables should probably be included in the multivariate model. In the third chapter, the first sentence is not clear and gives the impression that there is 24% of mortality in the group >65 years old, whereas the mortality in the group<65 years old is 11%. In fact, there is 24% of patients of more than 65 years in the fatal group, vs 11% in the survival group. It should be better to compare the effective percentage of mortality between the two groups. Moreover, it could be of interest to perform an analysis stratified on this age.

   Response: All the tables and results were revised.

5) What about the mortality in the patients hospitalized in intensive care? What are the characteristics of these patients? Were there under mechanical ventilation?
Response: Nineteen out of 22 fatal cases (86%) were in ICU, where as 13 out of 219 (6%) survived cases were in ICU (p<0.001). This sentence was inserted to results section.

6) The distinction between rales and ronchus in the table 4 is probably less pertinent than normal versus abnormal lung auscultation. The bilateral involvement in the chest x-ray should be discussed. What about ARDS vs pneumonia? It could be interesting to precise the notion of mechanical ventilation.

Response: The auscultation was revised accordingly. Mechanical ventilation was added to the table.

7) There is a low rate of co-bacterial infections. Is there an explanation? Were they really explored by bacterial systematic samples?

Response: These infections were accepted as nosocomial secondary bacterial infections.

8) What type of nosocomial infections are the infections reported in the 7th chapter. Candida is classified in “bacterial infections”. Candida is a fungus, not a bacterium. These data are too imprecise.

Response: Candida was excluded. All the Gram positive and Gram negative bacterial secondary infections were included.

9) In the 9th chapter, it is noticed that “early” use of neuraminidase inhibitors were found to be protective. Authors have to precise what is “early”. We understand that early is two days, with the sentence in conclusion and table 5. However, is that delay really pertinent? It is usually recommended to start neuraminidase inhibitors within the 48 hours after the onset of the symptoms. It would have been more interesting to have analysed the impact of the delay of initiation of the treatment within these 48 hours. Moreover, in figure 3, authors pooled “late” and “no” oseltamivir. It seems that they consider administration of antiviral treatment after the first 48 hours like no treatment.

Response: By early use of neuraminidase inhibitors, we indicated use of neuraminidase within 48 hours (< 2 days) after onset of symptoms.

10) In figure 3, it is precised fatality due to H3N2 and H1N1. But authors precise that not all suspected hospitalized cases had the laboratory confirmation by PCR. This invalidates the comparison between H3N2 and H1N1, and this figure could be removed.

Response: All the analysis was re-performed based on confirmed cases.

11) In the section discussion: obesity was not found to be associated with fatality whereas several studies found this association in other countries. Authors should have discussed this point. The repartition of age should have also been discussed in comparison with what was noticed in other countries. Indeed, H1N1 pandemic was described to have involved young people, which is unusual.
Response: Our study population was not large. Because of the low power, we couldn’t detect the effect of obesity and pregnancy. This sentence was inserted to discussion: “Lack of association of obesity and pregnancy with fatality could be related to low power of the study.”

12) In the section conclusion: it is proposed to treat and vaccine individuals over 65 years and the individuals with chronic diseases. This is subject to discussion, as in a situation of pandemic it could be discussed to treat everybody, eventually without viral confirmation, to stop the spread of the pandemic, and it was shown that this strategy could be cost effectiveness.

Response: Comment was very well taken and conclusion was revised.

Minor essentials revisions:

1) Statistical analysis: What is the software used? Were the tests two tailed? What is the p value used?

Response: STATA version 11 was used, p value was set as <0.05.

2) Some results are once again given is the discussion with p value, referencing tables... This is redundant with the results section and should be avoided.

Response: The results section was revised.

3) Figure 1 is not really of interest, with a lot of missing data. It should be removed.

Response: Figure 1 was removed.

4) I am not really fluent in english, but I think there is some spelling mistakes in the text that should be corrected.

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

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

Declaration of competing interests: I declare the I have no competing

Reviewer’s report

Title: Predictors of Fatality in Hospitalized Patients with Pandemic Influenza A (H1N1) Virus Infection and Impact of Early Neuraminidase Inhibitors

Version: 4 Date: 23 July 2012

Reviewer: Vittorio sambri

Reviewer’s report:
Major Compulsory Revisions. A major weakness point of the study is that the patients have been basically selected on the bases of epidemiological and clinical data. A small percentage of them have been laboratory confirmed (and the exact percentage have not been reported). The Authors are certainly aware that other flu viruses than the pandemic H1N1sw2009 were circulating contemporarily. As a consequence some of the conclusion of the study (as indicated in the Discussion, i.e. high mortality if age >65 ys; fatality proportion more elevated among not-pregnant women versus those that acquired the H1N1sw2009 during pregnancy) may have been generated by the mixture of H1N1 and "normal flu" viruses infected subject. As a consequence, I suggest that the Authors acquired as much as possible of data about the lab confirmation and they re-analize the population studied divided in two subgroups: lab confirmed and not lab confirmed. This would likely enhance the meaning of these findings. Level of interest: An article of importance in its field

Response: The data was re-analyzed including only confirmed cases.

Quality of written English: Acceptable

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

Declaration of competing interests:

No competing interests to be disclosed