Author's response to reviews

Title: Occurrence of AH1N1 viral infection and clinical features in symptomatic patients who received medical care during the 2009 influenza pandemic in central Mexico

Authors:

JUAN P CASTILLO-PALENCIA (jpcastillopalencia@hotmail.com)
LUCIE LAFLAMME (Lucie.Laflamme@ki.se)
JOEL MONARREZ-ESPINO (Joel.Monarrez-Espino@ki.se)

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Author's response to reviews: see over
Dear Editor:

We hereby submit the revised version of the manuscript: “A study of the occurrence of AH1N1 viral infection and the clinical features of symptomatic patients who received medical care during the 2009 influenza pandemic in central Mexico” (reference number 1221865616749065).

All suggestions made by the reviewers were attended when writing this revised version. Here we present a detailed description of the changes done:

**Reviewer 1**

The objective of the study is clearly stated and accomplished, but the occurrence of AH1N1 viral infection and the clinical features of symptomatic patients is already known in many countries, including Mexico. Hence the conclusion of this manuscript is not a new finding.

**Response**

We acknowledged in the manuscript that both the occurrence and the clinical features of AH1N1 viral infection have been previously reported. However, as we pointed out in the Discussion, the value of our study lies in the size of the study population, the inclusion of individuals of all ages, and the stratified analyses by age group based on the observed distribution of confirmed cases of AH1N1. In fact, these merits were emphasized by Reviewer 2 (“Despite other studies had previously investigated a similar issue, strengths of this research are the use of regional surveillance data, the very large sample of subjects tested, the analysis of both hospitalized subjects and outpatients, and the inclusion of both adult and pediatric patients. For these reasons, results are quite interesting and can be useful both for epidemiological purposes and for clinical management of patients with respiratory infections”).

To further highlight the strengths of the study, we now mention the inclusion of “both hospitalized subjects and outpatients” as stated by reviewer 2, so that the paragraph in the Discussion now reads: “A second strength relates to the inclusion of both hospitalized subjects and outpatients of all ages” (third sentence, last paragraph, page 12).
Reviewer 2

1. Pag 2, Abstract: the sentence “Age in years was positively associated with the having the virus in those aged 0-14 years, but negatively in persons aged 15 years or more (0.97-0.98)” is unclear. Please reformulate, for example as follow (if this is the correct significance): “Most positive cases were aged 5-14 years and, in this subgroup, older age was positively associated with A H1N1 infection (95% CI 1.05-1.1); conversely, in patients aged 15 years or more, older age was negatively associated with the infection (95% CI 0.97-0.98)”.

Response: We believe that the wording proposed by the reviewer is better and have therefore changed the sentence accordingly.

2. Pag 7, statistical analyses: infection rate is defined as “Infected cases confirmed by laboratory / Total number of persons screened”. However, not all patients screened had an available laboratory result (764 missing). Hence, infection rate should be defined as “Infected cases confirmed by laboratory / Total number of persons tested (with available laboratory result)” and results corrected accordingly in the “results” section and in table 1 (infection rate: 2767 / 6158 x 100 = 44.9%).

Response: We appreciate the reviewer’s accurate observation. We have now modified the definition in the “Statistical analyses” sub-headline (last paragraph, page 7) and in Table 1, and changed the estimate in the Results section (first sentence, page 7) and Table 1 accordingly. The corresponding change was also done in the abstract.

3. Pag 9, results line 1-4: authors compare hospitalization and mortality rates of the studied population to the same rates observed in Mexico, Canada and USA, but do not provide a statistical comparison; please test for statistically significant differences (for example by using Chi Square test) and provides p values.

Nearly all rates were statistically different (p<0.05 using Chi-square tests) across the geographic areas for the indicators presented: For infection, the comparison was possible only between the USA and SLP (p<0.0001); for hospitalization, all the available rates (Canada, USA, Mexico and SLP) were statistically different from each other (p<0.0001); and for mortality, the only rates that showed a non-statistically p-values (>0.05) were those for Canada vs. Mexico (0.06), Canada vs. SLP (0.76), and Mexico vs. SLP (0.50).

Given the impact of the sample size, whereby very large samples lead to statistical significant differences between rather small rate differences, not to mention the fact that data comes from different reporting systems, we doubt of the value of these comparisons to draw meaningful conclusions. For instance, while a difference of 1.5 percent points for the hospitalization rates between Canada and the USA (15.7 vs. 14.2%) is highly significant statistically (p<0.0001), from the public health perspective
these rates are quite similar. The same could be said for the infection rates between
the USA and SLP (42.7 vs. 44.9%).

However, in attention to the reviewer’s comment we have decided to include a brief
sentence in the Result section indicating that all rates presented were statistically
different, except for the mortality rates between Canada, Mexico and SLP (end of first
paragraph, page 9).

4. Pag 9, results line 5: the authors refer to figure 1 for age distribution. However from
figure it is not clear the exact number (%) of patients in groups aged 0-14 and >15.
Please describe it in the text and also report the percentage of male/female in the two
age groups.

As requested by the reviewer, the following paragraph was inserted in the Result
section when referring to Figure 1 (second paragraph, page 9): “From the 2767
patients with AH1N1 infection, 1409 (50.9%) were aged 0-14 years (731 males,
51.9%; 678 females, 48.1%), and 1358 (49.1%) were ≥15 years old (598 males,
44%; 760 females, 56%).”

5. Pag 10, discussion: authors state that divergent hospitalization rates in different
geographical areas seems to be related to different criteria used for hospitalization.
However, it cannot be fully excluded a different viral pathogenicity and/or clinical
severity of the infection in different areas. Indeed, mortality rate in USA is higher than
that reported in the studied population (is this difference statistically significant?
Please test with chi square test as suggested above). This alternative hypothesis
should be briefly discussed.

As mentioned above (point 3), all hospitalization rates differed statistically (p<0.0001)
from each other mainly due to the large samples compared. While it is true that
differences in pathogenicity and/or clinical severity of the infections across study
areas cannot be completely ruled, we believe that the differences observed are much
more likely due to differences in the hospitalization criteria used, especially
considering the lack of standardization routines at the hospitals during the first
months of the pandemic. In fact, the suggestion of reviewer 1 conflicts with the
opinion of reviewer 3, who also thinks that comparisons are difficult, as “different
reporting system” and “different criteria of hospitalization” were used. For this reason,
we decided to modify the sentence in concern, so that it now reads: “While different
viral pathogenicity and/or clinical severity cannot be completely ruled out, it seems
that hospitalization criteria varied considerably across geographic areas, as indicated
by the relatively large variation observed” (first paragraph, page 11).

6. Pag 12, discussion: an interesting finding is that “seasonal vaccination against
influenza was related to protective odds for infection in the adult population”. This
result is intriguing but should be better discussed. Other reports have previously
investigated this issue, some suggesting a partial protection (Fabbiani M et al. J Med
Virol 2011; Orellano PW et al Vaccine 2010; Johns MC et al. PLOS One 2010) while
others not (Kelly H et al. Euro Surveill 2009; Larrauri A et al. Gac Sanit. 2011; Hardelid P et al. Euro Surveill 2011). These studies should be cited and eventually briefly discussed. Ref. 31 refers to a study performed before pandemic influenza A H1N1 spread and does not appear to add relevant information to the discussion.

The references mentioned and few others were included in the revised version when contextualizing and discussing the protective effect of seasonal vaccination found as suggested by the reviewer. The paragraph in concern now reads: “The protective odds for infection found with seasonal vaccination against influenza in the adult population add to the controversy on this topic, as previous studies have reported protection (31-35), no effect (36-40), and even increased risk of infection (41). While the potential cross-reactive protection of seasonal influenza vaccines through humoral and cell-mediated immune responses (42-43) needs further investigation, an upcoming review to assess the protection offered by influenza vaccines against circulating influenza A or B viruses that are not antigenically well-matched to vaccine strains will help elucidating this issue (44)” (last paragraph, page 12).

Also, reference 31 and the brief description written in the original text were deleted as suggested by the reviewer.

**Discretionary revisions**

1. Title: In my opinion, the title seems a little redundant. At the discretion of authors, it could be shortened as follow: “Occurrence of AH1N1 viral infection and clinical features in symptomatic patients who received medical care during the 2009 influenza pandemic in central Mexico”.

   The title was shortened as proposed by the reviewer so that it now reads: “Occurrence of AH1N1 viral infection and clinical features in symptomatic patients who received medical care during the 2009 influenza pandemic in central Mexico”.

2. In the abstract and throughout the manuscript the terms “OR” and/or “95% CI” in parenthesis are often omitted; please always indicate for a better comprehension.

   We made the requested change in the Abstract, and tried to make it clearer in other parts of the manuscript when referring to the OR and 95% CI, but avoiding repeating these were unnecessary.

3) Pag 4, line 4: correct “stain” to strain.

   This typographical error was corrected

4. Table 2 and 3: please include a column showing p values for crude or adjusted OR (at least for variables showing a statistically significant association).
We included the p-values in Table 3 as suggested by the reviewer, but decided not to do so in Table 2 due to space limitations and to avoid presenting a crowded table.

Reviewer 3

A lot of papers have been published on clinical features of H1N1 in 2009. More work should be done to investigate the change of H1N1 during the post-pandemic period. What is most reliable to distinguish influenza and other respiratory diseases is the seasonal onset, clinical features are similar between them. Have you ever compared H1N1 with seasonal influenza? What is the difference of clinical features between them?

Response: In this revised version we have made reference in the Discussion section to the infection, hospitalization, and mortality rates of seasonal influenza in SLP stratifying the information by age group (0-14 and ≥15 years) so that it reads: “The infection, hospitalization, and mortality rates can be compared with those of seasonal influenza in SLP during the same period, which were 5.3% (0-14y 3.7%, ≥15y 4.8%), 9.6% (0-14y 4.9%, ≥15y 12.5%), and 1.8% (0-14y 0.9%, ≥15y 2.4%), respectively (26). While the seasonal infection rate contrasts with the much higher rate seen for AH1N1 (44.9%), the mortality rate is nearly 2.5 times higher (1.7 vs. 0.7%), pointing to the high infectivity, but low lethality of this virus, as previously observed (2, 6).” (second paragraph, page 11).

We have also contrasted the clinical features between seasonal and AH1N1 influenza infections as suggested by the reviewer as follows: “Compared with confirmed cases of seasonal influenza in SLP during the same period, those with AH1N1 infection aged ≥15 years showed significantly (p<0.05) higher proportions of cough, clear rhinorrhea, nasal congestion, sore throat, malaise, chills, and myalgia (ranging from 8.3 to 16.4% higher), but had lower proportion of dyspnea (5.3% less), however, among those aged 0-14 years, the proportions were significantly higher only for cough (8.3%) and clear rhinorrhea (8.7%) (26)” (second paragraph, page 14).

Table 1: The incidence, hospitalization and death ratio was not comparable between different countries based on different reporting system, different criteria of hospitalization.

Response: Yes, we had acknowledged this in the Discussion section.

We hope that this second revised version is now suitable for publication. In case of questions or doubts, please do not hesitate to contact us.

With best regards,

Joel Monárrez-Espino, MD, PhD
Corresponding author on behalf of co-authors