Author's response to reviews

Title: Social factors related to the clinical severity of influenza cases in Spain during the a (h1n1) 2009 virus pandemic

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

Please find enclosed the revised version of the manuscript entitled “Social factors related to the clinical evolution of influenza cases in Spain during the A(H1N1)2009 virus pandemic” which we enclose as a new submission for consideration for publication in BMC Public Health. The manuscript has been revised taking into account the comments of the reviewers to a previous version (original version), which I enclose again with the revised manuscript, as requested, together with the identification number of the original manuscript, as requested in your Email. A detailed response to the reviewers’ comments is enclosed below.

Yours sincerely,

José María Mayoral

Reviewer 1

Methodological issues (Major Compulsory Revisions)
1. How cases and controls were selected was not fully described. Did the hospitalized cases comprise all who were hospitalized at the participating centers from July 2009-February 2010 – or were they a subset? If the latter, what method was used to selected them?

We now state” Hospitalized cases were defined as all patients admitted during the study period due to influenza-like illness, respiratory infection (including pneumonia), septic shock or multiple organ failure in whom pandemic influenza virus A (H1N1) 2009 infection was confirmed. Nosocomial cases were excluded.”

And:

“For each hospitalized case, one control was identified among patients attended by primary health care clinics and emergency units due to influenza-like illness or respiratory infection in whom A (H1N1) 2009 infection was confirmed using the same diagnostic techniques as for cases. Controls were matched with cases according to age (±6 months in patients aged 0-2 years; ±3 years in patients aged 3-17 years and ±5 years in patients aged > 17 years), date of hospitalization of the case (±21 days) and province of residence of the case. If there was more than one exact match, the control selected was the first patient attended in an outpatient centre from the same province as the hospitalized case whose sample was laboratory confirmed.”

2. For controls, it is unclear what clinics or diagnostic laboratories were used to identify them – were they the same ones used for the cases? Were the cases, in essence, the subset of the control population that were hospitalized? If so, this should be stated in the paper. In addition, it would be very helpful to know how many persons at the participating centers were diagnosed with 2009 pandemic strain infection – i.e., the total eligible control pool – from which the cases came. Other control questions: they were matched on age, but what age groups?; on date of hospitalization, but
since controls were not hospitalized, do you mean date of laboratory diagnosis?; and by province of residence – does that also mean by laboratory where diagnosed? If there was more than one exact match, what method was used to determine which control you selected?

We now state “For each hospitalized case, one control was identified among patients attended by primary health care clinics and emergency units due to influenza-like illness or respiratory infection in whom A (H1N1) 2009 infection was confirmed using the same diagnostic techniques as for cases. Controls were matched with cases according to age (±6 months in patients aged 0-2 years; ±3 years in patients aged 3-17 years and ±5 years in patients aged > 17 years), date of hospitalization of the case (±21 days) and province of residence of the case. If there was more than one exact match, the control selected was the first patient attended in an outpatient centre from the same province as the hospitalized case whose sample was laboratory confirmed. “

For outpatient cases of influenza in the context of influenza surveillance, each autonomous community has a reference laboratory and it was this laboratory that confirmed the matched outpatient case If there was more than one exact match, the control was the first patient attended in an outpatient centre from the same province as hospitalized case whose sample was laboratory confirmed.

3. Matching issues. No results are presented to show how well the matches were made. It would be helpful to include in Table 1 the variables on which matching was done as well as the comparative distribution of the study factors. Most importantly, though, results are presented that show that age-group is a very strong and important independent predictor of being hospitalized – yet, matching was done on age. How can this be? Usually one cannot use matching factors in the analysis of outcome except to stratify by them, since they are equally distributed between cases and controls.

We have modified Table 1 to show only the study variables related to matching. With respect to age, we agree with the reviewer. Therefore, we have excluded this variable from the analysis as an independent variable, although it was taken into account in the adjustment for other independent variables.

4. The definition of “overcrowding” is not clear. It is described as “below the fifth percentile of the distribution of square meters available per person in the usual residence.” What distribution is being referred to? The distribution based on responding cases and controls? A national survey or census?

We now state “overcrowding (below the fifth percentile of the distribution of square metres available per person in the normal residence of all study participants)”.

5. “Use of outpatient healthcare services” needs to be defined. Was this a question on a standardized questionnaire or was it something obtained from medical records? Was use of outpatient or emergency services unrelated to influenza or could it have been an early visit for influenza in which a confirmed diagnosis was not made? By how many weeks or months before the influenza diagnosis could one have used these services?

The use of outpatient services (visits to family physician and outpatient emergency visits) was collected in a standardized manner in the study questionnaire. These were standard medical visits, and not services created specifically for the treatment of influenza. In Spain, the first cases of pandemic influenza were reported during April and the first cases included in the study correspond to the month of July, when the incidence of the disease was low and the initial social alarm had diminished.

We now state “and the use of outpatient healthcare services, family physicians or non-hospital emergency units due to influenza symptoms in the 7 days before hospital admission in cases and a medical visit due to influenza symptoms in controls.

6. The definition of “preventive materials” is unclear. This variable is not mentioned in the Methods – it only appears in the Results and Discussion. What standardized question/questions were asked? As background, were standard preventive materials distributed by the national or provincial governments?
Hospitals? How would a person have gotten prevention materials and why would some not have gotten them?

We now state “and information on preventive measures received through various means (health centres, the media, internet, etc.) during the previous year on preventing the spread of influenza”. The study questionnaire contained a standardized question on preventive information received and how it had been received.

In Spain, during the pandemic, there was a national media campaign, including roadside posters and informative booklets which were distributed through health centres. A coordinated national plan was put into action that included recommendations on preventing influenza. Therefore, we believe that this information was distributed in a relatively homogenized way.

What we discuss in the article is that, in spite of these efforts, this information was not received equally by all social sectors and this was a predictive factor for hospitalization for influenza during the pandemic.

7. When was data collection done relative to when diagnosis was done – an average of how many days and with what range? This should be included in the Methods section.

We now state “The median time from hospitalization of cases or taking the sample from outpatient controls until the survey was 99 days (range 0 to 404) for hospitalized cases and 155 days (range 0 to 414) for outpatient controls.”

Results

Minor Essential Revision

1. Table 1 – numbers do not add up to 699 for each variable. Should include the unknowns so reader can readily see how much data is missing.

Table 1 has been changed to present the distribution of variables included in the model and the numbers of matched cases and controls included in the analysis.

Major Compulsory Revision

2. Table 2. The numbers of cases and controls for each variable is very peculiar. First, the numbers for most variables are much smaller than they are in Table 1. No reason is given for this. Second, the numbers for each variable are different. For example, only 540 males and females are included for each of cases and controls, yet there should be data for 699 for each. At the same time, there are 627 cases and 627 controls for which ethnicity is included, 576 of each for education level and 275 for overcrowding. These numbers need to be checked or explained. Without them, it is totally unclear what data set was used to determine the pivotal multivariate results.

These discrepancies have been corrected. Table 1 now shows the characteristics of the cases and controls included in the study, and table 2 shows the results of the multivariate analysis.

Discussion

Minor Essential Revisions

1. 1st paragraph, last 2 sentences. Unclear as written. I think you mean to say “Paradoxically, the virulence of the disease was particularly high among people >=65 years; while incidence in this community was low in this age group, the proportion requiring HOSPITALIZATION was higher. In Spain, IT IS ESTIMATED THAT 2.5% OF ALL CASES OF INFLUENZA ATTENDED BY PRIMARY CARE CENTRES WERE PEOPLE AGED >=65 years compared with 10.6% admitted to the hospital intensive care units.”
This phrase has been corrected.
2. 2nd paragraph, 1st sentence. You stated “We also found that hospitalization was significantly more likely in people aged >=65 years” – but you already stated this. I’d delete it.

This phrase has been deleted
3. 2nd paragraph, last sentence. You say that the risk factors you found were similar to those of seasonal influenza “except for differences related to age and obesity”. However, your study DID find an association with age (also found in studies of seasonal influenza) – and you did not look at obesity, so you can’t say anything about it. I’d delete this sentence.

This has been eliminated
4. 3rd paragraph (pages 5 and 6). The discussion of social inequalities is not very enlightening. In essence, you cite various studies showing that health is related to social inequalities and that overcrowding can predispose to a greater risk of exposure. You then go on to say you found an association with crowding – but you say nothing about how overcrowding could affect the chance of being hospitalized once one has influenza. This is the finding that should be discussed – not risk of exposure.

We agree. We have rewritten the Discussion section.

5. 4th paragraph (page 6) – Your discussion of the finding that non-Caucasians were more likely to have severe influenza seems to imply that it could be because of different use of health services. Yet the available data suggests they are more likely to use health services. More explanation is needed (or some admission that more research is needed to better understand this).

We have rewritten the Discussion section. What we wish to convey is that equal access to health services, both for the indigenous population and for immigrants (especially those from Africa and South America) may have helped to mitigate differences in the presentation of disease severity between different social groups.

6. 5th paragraph (page 6) – your explanation of the finding that persons with higher educational levels who have influenza are less likely to be hospitalized seems to be based on their having more information on avoiding risks and more readily access health services. This seems a little sparse. Can you say more? Could education level also relate to poverty, delayed health care seeking and more advanced disease (e.g., if have underlying asthma, wait too long to treat the asthma exacerbation that influenza induces …)? Could you put it in the context of finding that those hospitalized more frequently (if not readily) accessed health services.

What we wish to convey is that the causal factors are not isolated but interrelated, as shown by various studies on social inequality and the health status. As we state in the manuscript, there are few studies on this subject related to acute infectious disease, and fewer still on the influenza pandemic, even though the social and economic situation played a central role in the 1918 pandemic in Europe, for example.

Major Compulsory Revision

7. Discussion of limitations. It is unclear what is intended when the authors cite “However, we found that hospitalized patients more frequently attended primary care clinics and emergency units before disease onset” or by “It is worth emphasizing that people who had received preventive information had fewer hospitalizations” Neither seems to be a limitation by itself – but each becomes a limitation that should be stated. Among the limitations that are not stated but should be: 1) asked about whether received “preventive information”, but did not ask whether the information received discussed what to do if developed influenza symptoms and whether they followed that advice – thus, unclear what was being measured; 2) the meaning of the finding that those more likely to be hospitalized were more likely to have recently used healthcare is unclear. Don’t know whether this is a marker of having more severe underlying disease or a marker that they more readily access health care; 3) do not know if the control
group was truly representative of the population of people who became infected with influenza or whether they were a distinct subset with their own “risk factors” for seeking health care and getting a diagnosis in the first place. They may be intrinsically different that those who were hospitalized, who may be more representative of the general population in that they had no choice to seek health care.

These results, which are discussed in the manuscript, suggest that access to outpatient health services is what might be expected from a public health system with universal coverage, i.e., that health services are most used by those with severe disease. A paradoxical finding would have been to find that hospitalized patients consulted health services less during the days previous to hospitalization. Such findings would have seriously put into doubt the role of the health system during the pandemic. Therefore, our finding is that the health services act as one more determinant of collective health, as shown by various conceptual models such as Lalonde (1974), Daahlgren and Whitehead (1991), Evans (2001), OMS (2005), Barton (2006).

Cases and controls included in the study were asked whether they had received preventive information, but were not asked whether they had followed the advice given and to what degree. This is a limitation of the study. However, given the large differences between those did or did not receive information, we suggest the differences could have been even greater among those patients who followed the advice given to the letter.

What we wish to convey is that the causal factors are not isolated but interrelated, as shown by various studies on social inequality and the health status. As we state in the manuscript, there are few studies on this subject related to acute infectious disease, and fewer still on the influenza pandemic, even though the social and economic situation played a central role in the 1918 pandemic in Europe, for example.

The control group is not representative of the general population or of the infected population. It represents the infected population who presented symptoms of influenza and visited their family physician about these symptoms. We believe this does not invalidate the utility of using this group to examine the hypothesis of the study.

Reviewer 2

Reviewer Report on SOCIAL FACTORS RELATED TO THE CLINICAL EVOLUTION OF INFuenza CASES IN SPAIN DURING THE A (H1N1) 2009 VIRUS PANDEMIC

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

The authors may wish to investigate interactions between education and prior preventative information to assess whether those with more (or less) schooling have different associations with hospitalization depending on whether they received preventative information. It may be that such information will benefit those with less education more – a type of substitution – or benefit those with more education more – a type of complementarity.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

There is some awkward English and typos that should be corrected. In Methods: “For each hospitalized case, one control was identified among patients attended by primary health care clinics and emergency units….in whom A (H1N1) 2009 infection was confirmed.” The word “not” should be between was and confirmed. Age is missing from Table 1 and should be added.

The manuscript has been revised and errors corrected,
Age has been added to Table 1

Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)
The set-up of the research question in the Introduction could be more specific. It is stated that "objective material conditions and available individual and social resources influence the health status, regardless of the health problems presented. This paradigm has been widely studied, especially in the context of chronic disease." What is the name of this paradigm in the literature, what types of variables are shown to be important and what are the mechanisms for their importance? Why specifically is it “more difficult” to apply to infectious diseases? Please also explain further “the atypical profile of severe cases reported” for H1N1.

The data collection seems to be thorough with a wide range of recruitment of respondents by region. In the Methods section, the number of cases excluded due to refusals/failure to answer the questionnaire should be included. Please report a response rate for the study.

The authors should explain further the data collected (and used in the analysis). For example, “the information received through various means during the previous year on preventing the spread of influenza” is unclear – what specifically was measured? What are terms such as “comorbidity or risk factor” used in the tables referring to exactly? What is the reference period for use of outpatient or emergency services (e.g. in the past month or past year)? It is stated that the “variables of interest” are education, overcrowding, ethnicity and use of health care. Please explain the rationale for focusing on these 3 variables.

We have revised the Introduction section in order to clarify these points. We now state in greater detail the profile of patients affected by the pandemic virus. We have included information on the number of non-responses in the Results section.

The questionnaire used included a standardized question on preventive information received and how it was received. In Spain, during the pandemic, there was a national media campaign, including roadside posters and informative booklets which were distributed through health centres. A coordinated national plan was put into action that included recommendations on preventing influenza. Therefore, we believe that this information was distributed in a relatively homogenized way.

In the Methods section, we now specify the risk factors and comorbidity to which we refer.

In the Methods section, we now specify the reference period for the use of outpatient and emergency services.

With respect to the variables of interest, we now specify in the Methods section that these were “social” variables of interest, which were used to collect information in the study questionnaire.