Reviewer’s report

Title: Age distribution of influenza morbidity and mortality: a comparative analysis between seasonal influenza epidemics and the H1N1 pandemic.

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Reviewer: James Fielding

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This paper has used influenza morbidity and mortality data from two seasonal influenza epidemics of H1N1 and H3N2 in the USA and France and compared them by age group against morbidity and mortality data collected during the H1N1 (2009) pandemic in the USA, Mexico and New Zealand. There are several critical methodological and interpretive flaws in the study that make this paper unsuitable for publication in its current form. These are addressed below in the relevant sections of the assessment criteria.

1. Is the question posed by the authors well defined?

The question posed by the authors is straightforward and clear: how do age-specific morbidity and mortality rates compare between seasonal and pandemic influenza? It is a pertinent question given the left shift of the age distribution of pandemic influenza (H1N1) 2009 observed by countries all around the world.

2. Are the methods appropriate and well described?

In my view, the methods have several critical flaws and are insufficiently described. Firstly, the authors have indicated that they selected two “typical” influenza seasons to provide summary measures of morbidity and mortality for seasonal influenza. However, there is no explanation as to how a “typical” influenza was defined. For example, was it based on a median or mean of morbidity and/or mortality rates over a given time period? What were the thresholds for defining whether a season was dominant H1N1 or H3N2? Were influenza seasons considered in which type B influenza was predominant?

Secondly, whilst the authors used US and French data to establish ‘typical’ morbidity and mortality for seasonal influenza, the comparators for pandemic H1N1 (2009) influenza include Mexico and New Zealand, yet exclude France. Whilst the authors have attempted to control for population differences using age standardisation, this will not control for differential ascertainment of illness or death due to influenza (or influenza-like illness) between seasonal epidemics and pandemics, as well as between countries. Case definitions, nature of surveillance, testing practices, coding practices and influenza awareness are all important and variable factors in case ascertainment from year to year in one country, let alone between countries and between seasonal epidemics and a pandemic. The inclusion of New Zealand and Mexico morbidity and mortality
ratios for pandemic influenza comparison against seasonal ratios for the USA and France presents obvious limitations given the different nature of their health systems (and thus presumably influenza/ILI ascertainment) as well as their influenza seasons because of climate (Mexico) and geography (New Zealand as a southern hemisphere country, which experienced only one pandemic wave compared to the USA and Europe which experienced two). It is thus unclear to me why the authors have not compared seasonal influenza morbidity and mortality ratios in the USA and France directly against the respective pandemic influenza morbidity and mortality ratios in the USA (included in paper) and France (not included in paper) to minimise these inter-country biases.

Other aspects of the methods are insufficiently described, in particular the time periods for which the influenza and ILI data were analysed (only the years are listed) and the case definitions for influenza-like illness and confirmed influenza that were used for each surveillance system/data source. Furthermore, the authors state that “ILI was confirmed virologically in the US” but confirmed virologically for what? Influenza? RSV? Other respiratory viruses? Does this mean that the reported US rates are based on all ILI or those ILI that were laboratory confirmed – and for which virus(es)?

All queries raised in this section are major compulsory revisions.

3. Are the data sound?

The mortality data are presumed to be sound. The morbidity data are also presumed to be sound but as described in the previous section, it would be helpful for these to be described in greater detail (influenza and ILI case definitions, a better specified time period of analysis, and the extent of virological confirmation). References should also be provided for the census populations and all-cause mortality denominator data that were used. These are major compulsory revisions.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?

The study has used data from a variety of external, publicly available sources. The authors should ensure the census and mortality data are properly referenced as discussed in the previous section.

5. Are the discussion and conclusions well balanced and adequately supported by the data?

In general, the discussion and conclusions are poor, but much of this is a consequence of the flaws in the methodology described above. The authors suggest that the age-related risk of infection did not differ between pandemic (H1N1) 2009 and seasonal influenza epidemics, however I believe too few influenza seasons (and in only a handful of countries that, with the exception of the US, are not able to be directly compared to one another over time) have been analysed to make such a sweeping generalisation. On a slightly more technical note, the data do not necessarily indicate risk of infection (with the exception of the US virological confirmed data) because the study has used clinical
presentation data. The limited comparisons also mean the statement that mortality rates differed strongly between seasonal and pandemic influenza is too broad and as such I don’t think the conclusion that the results should help define vaccination priorities or treatment option by age group can be made with much confidence. Thus the discussion requires major compulsory revisions in the context of those made to the methods.

6. Are the limitations of the work clearly stated?

Several important limitations, particularly with respect the methodological flaws described above, have not been addressed. These include the validity of comparing seasonal and pandemic influenza rates from different countries and the use of only four seasons to represent "typical" seasonal influenza – is there some sort of sensitivity analysis that might incorporate the high variability of influenza seasons? A further limitation of the study that has been briefly discussed by the authors is that the study has assumed no age-associated bias in ascertainment of morbidity and mortality. However, further justification is required for this assumption because in my view there is a strong likelihood that this bias does exist within the data sources used for the study. If the authors feel the existing comparisons are valid, an appropriate explanation or defence needs to be included in the discussion. These are major compulsory revisions.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?

The paper only makes scant reference to the observed younger age distribution of pandemic (H1N1) 2009 compared to seasonal influenza. However this was a widely noted phenomenon and there are certainly published papers that discuss this observation, even if the differences are not analysed and compared to the extent which the authors have done in this manuscript. Thus the background would benefit from some examples and references to published surveillance data that note the age shift. This is a major compulsory revision.

The text in the background section of the manuscript also suggests that “little attention has been given to how morbidity differs across age between pandemic and seasonal influenza epidemics”. Whilst this may apply to pandemic (H1N1) 2009 influenza the authors need to make this explicit because I believe that the differing age distributions of the pandemics of 1918-19, 1957 and 1968 compared to seasonal influenza have been well studied. This is a minor essential revision. The background would also benefit by reference to such studies (discretionary revision).

8. Do the title and abstract accurately convey what has been found?

The title succinctly describes the content of the paper and notwithstanding the paper’s important limitations described above, the abstract is a good representation of the paper’s findings. However, if the authors choose to address the paper’s problems and resubmit for publication, the abstract will have to be modified accordingly to reflect the additional content.

9. Is the writing acceptable?
In general the manuscript has been written succinctly and clearly. However, several sentences could be reworded for greater clarity: Methods section, second sentence under the “Indices” subheading “We derived standardized on age measures to allow…”; the figure legends should more clearly state the variables shown in the charts e.g. “Relative illness rate by 5-year age group, influenza season and country”.

There is also a typo in the methods section under “Pandemic data” subheading: “US Centers for Disease Control”.

These suggestions are discretionary revisions.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

I declare that I have no competing interests