Author's response to reviews

Title: Comparative age distribution of influenza morbidity and mortality during seasonal influenza epidemics and the 2009 H1N1 pandemic.

Authors:

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Fabrice Carrat (carrat@u707.jussieu.fr)

Version: 4 Date: 22 April 2010

Author's response to reviews: see over
Age distribution of influenza morbidity and mortality: a comparative analysis between seasonal influenza epidemics and the H1N1 pandemic.
Magali Lemaitre and Fabrice Carrat

Dear Ms Rajabi,

Thank you for your interest in our work. We are pleased to submit a revised manuscript to BMC Infectious Diseases. We have taken into account all associate editors comments and those of the four reviewers, and we reply to all points raised by each reviewer, particularly by Dr Fielding:

- We changed the title and the abstract
- We have clarified the background and aims of this study.
- We completely rechecked the Methods section as suggested by the 4 reviewers: data source, Influenza-like illness definition, indexes definition.
- We removed analysis based on Mexico and New Zealand data and we performed the analysis to compare seasonal and pandemic data in France and in the US.
- We changed the Discussion section accordingly given the new analysis and following the reviewers’ advice.
- We have added the references suggested by Dr Libster

Please find following our reply to the reviewers.

We look forward to hearing from you.
Sincerely yours,

F Carrat, M Lemaitre
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.

2.1 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?

Authors:
2.1: “Typical” is not actually appropriate: the seasonal epidemics selected for this study are characterized by the circulation of only one influenza subtype nationwide. These seasonal epidemics were identified from published data (US: Glezen WP, et al. Age distribution of patients with medically-attended illnesses caused by sequential variants of influenza A/H1N1: comparison to age-specific infection rates, 1978-1989. Am J Epidemiol. 1991 Feb 1;133(3):296-304., Monto AS, et al. Medical practice-based influenza surveillance: viral prevalence and assessment of morbidity. American Journal of Epidemiology. 1995;141(6):502-6) or from surveillance networks (France: GROG: http://www.grog.org/ since 1984). We selected the 1978-79 US seasonal epidemic and the 1988-89 French seasonal epidemic, during which only the H1N1 subtype was identified. Seasonal epidemics observed in France and in the US in 1989-90, characterized by only the circulation of subtype A/H3N2, were also selected. Epidemics characterized by the circulation of a type B virus would certainly be very interesting to study, but here we focused on type A virus, for comparison with the 2009 pandemic. We have clarified the relevant paragraph.

2.2 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.

Authors:
2.2: We thank the reviewer for this very pertinent remark. Indeed, we cannot deny the existence of a differential bias related to different ascertainment of influenza-like illness or death between countries. When we started this work, no French morbidity and mortality data were available. These data have now been published, and we have repeated the analysis to compare seasonal and pandemic data for France and the US. We have removed analysis based on the New Zealand and Mexico data.

The source of data was the same for all the French seasonal epidemics and pandemics, namely the Sentinels system, a French nationwide network of general practitioners who report, in real time, the number of medical visits for ILI. The definition of ILI has been the same since the network was created (1984). The source of data was different for the US. We agree that surveillance methods were variable between the countries, but using the ILI age distribution and not ILI incidence rates reduces the risk of bias.

2.3 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.

Authors:

2.3: In this analysis, we used epidemic periods either reported in the US (Monto AS, Ohmit SE, Margulies JA, Talsma AN: Medical practice-based influenza surveillance: viral prevalence and the assessment of morbidity. *Am J Epidemiol* 1995, 141(6):502-506) or defined by sentinel systems for France (http://websenti.u707.jussieu.fr/sentiweb/).

The seasonal H1N1 epidemic periods were December 1978 to February 1979 in the US, and December 1988 to February 1989 in France, and the seasonal epidemic periods were January to March 1990 in the US and December 1989 to February 1990 in France.

The pandemic period corresponds to the first wave in the US, as defined by the CDC (from April 15, 2009 to July 24, 2009 (http://www.cdc.gov/h1n1flu/surveillanceqa.htm). The pandemic period was September 2009 to January 2010 in France, as defined by the Sentinels network (http://websenti.u707.jussieu.fr/sentiweb/).

We apologize for not clearly defining ILI. For the French data, a case of influenza-like illness was defined as fever above 39°C, aches and sore throat. For the US data, a case of influenza-like illness was defined as fever and cough or sore throat. Influenza was not virologically confirmed in the French data. Influenza was confirmed virologically in the US for the H1N1 influenza virus in 1978-79 and for the H3N2 influenza virus in 1989-90.

We used the age distribution of ILI (not virologically confirmed) in France and the age distribution of virologically confirmed influenza in the US.

We have added this information to the Methods section.

3.1 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).

Authors:

3.1: For the US, the morbidity data are sound since we used data for virologically confirmed influenza. Our objective was to compare the age distributions of ILI between pandemic influenza and seasonal epidemics, and not to compare the burden of influenza-related illness (i.e. the cumulative incidence rates) between the US and France. The two data sources are not comparable, as some cases of ILI without virological confirmation could be due to respiratory pathogens other than influenza virus. However, it is worth noting that the age distribution of these two sources of seasonal ILI (one virologically confirmed, the other not) were very similar, indicating that there is no age bias when considering ILI without virological confirmation. The use of ILI without virological confirmation tends to...
overestimate the ILI incidence rate but does not introduce a differential age-related bias if one assumes that the probability of a general practitioner making a wrong diagnosis is same in all age groups. Thus, we believe that the morbidity data for France are also sound.

3.2 References should also be provided for the census populations and all-cause mortality denominator data that were used. These are major compulsory revisions.

Authors:
3.2:
We have specified the data source in Methods:
Census populations:

All-cause mortality data:
- France: Centre d’Épidémiologie sur les causes médicales de décès. Available from: http://www.cephd.vesinet.inserm.fr/

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.

Authors:
We have ensured that the census and mortality data are properly referenced (see answer n°3.2)

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.

Authors:
We agree that this study focused on only a few influenza seasons. However, the age distribution of influenza-like illness and death reported here is very similar to that found in studies of several other influenza seasons (Fox JP, Cooney MK, Hall CE, Foy HM. Influenza virus infections in Seattle families, 1975-1979. II. Pattern of infection in invaded households and relation of age and prior antibody to occurrence of infection and related illness. Am J Epidemiol. 1982 Aug;116(2):228-42, Frank AL, Taber LH, Wells JM. Comparison of infection rats and severity of illness for influenza A subtypes H1N1 and H3N2. J Infect Dis. 1985 Jan;151(1):73-80.). Unlike the incidence of influenza-like illness and death, which can be highly variable from one influenza season to another (even with the same viral subtype), the age distribution of ILI and death is similar for influenza seasons during which the same subtype circulates (Glezen WP, et al. Age distribution of patients with medically-attended illnesses caused by sequential variants of influenza A/H1N1: comparison to age-specific infection rates, 1978-1989. Am J Epidemiol. 1991 Feb 1;133(3):296-304, Fox JP, Cooney MK, Hall CE, Foy HM. Influenza virus infections in Seattle families,

We agree that data do not necessarily indicate risk of infection but correspond to the risk of ILI. However, it is worth noting that the age distribution of these two sources of seasonal ILI (one virologically confirmed, the other not) were very similar. As we have considered the age distribution and not the overall incidence rate, there was no difference between the risk of infection and risk of ILI. We agree that the results should help define vaccination priorities or treatment option by age group can be made with much confidence. We removed this sentence. We concluded that age was an important risk factor of the 2009 H1N1 pandemic.

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.

Authors:
6.
We agree that influenza seasons are highly variable. However, as specified in answers 2 and 5, we now only analyze data for France and the US and we do not use the incidence but the age distribution, which does not differ between seasonal influenza epidemics due to the same subtype.
See reply to comment # 3.1.

We have modified the discussion accordingly.

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).

Authors:
7:
We agree with this comment.
Comparing morbidity
There have been many studies on the age distribution of ILI during seasonal epidemics or pandemics, but to our knowledge, there has been no attempt to compare the two in the same study. Studies of the 1918, 1957 and 1968 pandemics reported age distributions of morbidity similar to those of seasonal epidemics. We have add relevant references (references: Glezen, W.P., Emerging infections: pandemic influenza, Epidemiologic Reviews (1996), pp. 64--76, Taubenberger, J.K. and Morens, D.M., The pathology of influenza virus infections, Annual Reviews (2008)).
Comparing mortality
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.

Authors:
8:
We have modified the abstract 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.

Authors
9:
We have taken these comments into account.

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
Reviewer's report

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

Version: 1 Date: 12 March 2010

Reviewer: Romina Paula Libster

Reviewer's report:

Major Compulsory Revisions

1) Taking into consideration all the technologic advances in patient care that have lead to improved survival outcomes, comparing the 2009 outbreak information with much earlier time periods is not optimal. Would be important to compare with immediate past outbreaks information.

Authors:

1: Seasonal epidemics are often characterized by co-circulation of two influenza viruses. We focused here on seasonal epidemics characterized by the circulation of only one virus, in order to avoid confusion due to the co-circulation of two subtypes. We selected the 1978-79, 1988-89 and 1989-90 seasonal epidemics, in which the age distribution has been studied. We found no more recent influenza seasons with only one subtype and a known age distribution of ILI, especially for the US.

We agree that technological advances in patient care have led to improved survival. However, this affects incidence rates of morbidity and mortality, whereas we studied the age distribution. The highest attack rate is always observed among young people, and the highest mortality rate is always observed among elderly people.

The paper was probably unclear about the use of age distribution, and the Methods section has been modified accordingly.

2) Are the demographic and epidemiological characteristics of the US and French patients comparable to those from New Zealand and Mexico? What about the comparability of the surveillance systems in these different countries that is used to measure the impact of influenza?

Authors:

2: We thank the reviewer for this remark. Indeed, we cannot deny the existence of a differential bias related to different ascertainment of illness or death due to influenza-like illness between countries. We performed the analysis to compare seasonal and pandemic data for France and the US. When we started this work, no French morbidity and mortality data were available. These data have now been published, and we have thus removed the data for New Zealand and Mexico.

The source of data was the same for all the French seasonal epidemics and pandemics, namely the Sentinels system, a French nationwide network of general practitioners who report, in real time, the number of medical visits for ILI. The definition of ILI has been the same since the network was created (1984). The source of data was different for the US. We agree that surveillance methods were variable between the countries, but using the ILI age distribution and not ILI incidence rates reduces the risk of bias.

3) Have you calculated the estimated population growth when using the 2004/2005 data from the WHO as denominators for the rates? If not, would you be overestimating the morbidity and mortality rates?

Authors:

3: We apologize for not clearly defining indexes. We did not estimate morbidity and mortality rates but only the age distribution of influenza-like illness, population, influenza deaths, and all-cause deaths. There is thus no risk of overestimation.

We estimate the ratios as follows:

Relative Illness Rate (RIR): \( \frac{C_i}{\sum C_i} / \frac{N_i}{\sum N_i} \)

\( C_i \): number of cases of influenza-like illness in a given age group

\( \sum C_i \): Sum of influenza-like illness in all age groups

\( N_i \): Population in a given age group

\( \sum N_i \): Sum of populations in all age groups.
Relative Mortality Rate (RMR): \( \frac{(I_i / \sum I_i)}{(D_i / \sum D_i)} \)

- \( I_i \): number of influenza deaths in a given age group
- \( \sum I_i \): Sum of influenza deaths in all age groups
- \( D_i \): Number of all-cause deaths in a given age group
- \( \sum D_i \): Sum of all-cause deaths in all age groups.

For the RIR estimation, we now use 2008 population data to estimate the age distribution of the population. These data were not available for all-cause deaths. For simplicity, we used 2004/2005 population and mortality data, which corresponded to the most recent year available in the WHO database. We believe that the age distribution of all-cause deaths has not changed much since 2005.

4) How is morbidity defined in this manuscript?

Authors:

Because our objective was to compare the age distribution of illness between pandemics and seasonal epidemics, we used a common indicator for illness. Influenza-like illness is considered the gold standard or morbidity indicator in influenza (e.g. Miller et al. Mortality and morbidity burden associated with A/H1N1pdm influenza virus, PLoS Curr Influenza. 2009 Aug 26: RRN1013; Glezen WP, et al. Age distribution of patients with medically-attended illnesses caused by sequential variants of influenza A/H1N1: comparison to age-specific infection rates, 1978-1989. Am J Epidemiol. 1991 Feb 1;133(3):296-304., Monto AS, et al. Medical practice-based influenza surveillance: viral prevalence and assessment of morbidity. American Journal of Epidemiology. 1995;141(6):502-6), ILI is the most widely used indicator in all influenza surveillance systems.

We apologize for not clearly defining ILI. For the French data, a case of influenza-like illness was defined as fever above 39°C, aches and sore throat. For the US data, a case of influenza-like illness was defined as fever and cough or sore throat. Influenza was not virologically confirmed in the French data. Influenza was confirmed virologically in the US for the H1N1 influenza virus in 1978-79 and for the H3N2 influenza virus in 1989-90.

We used the age distribution of ILI (not virologically confirmed) in France and the age distribution of virologically confirmed influenza in the US.

We have added this information to the Methods section.

5) If ILI was not laboratory-confirmed, both the Morbidity and Mortality rates would likely be overestimated? Please comment.

Authors:

As specified in comment #3, we did not use the morbidity and mortality incidence rates but rather the age distribution of influenza-like illness and influenza deaths.

Age distribution of ILI:

Our objective was to compare the age distributions of ILI between pandemic and seasonal influenza, not to compare the burden of influenza-related illness (i.e. the cumulative incidence rates) between the US and France. The two data sources are not comparable, as some cases of ILI without virological confirmation can be attributed to respiratory pathogens other than influenza virus. However, it is worth noting that the age distribution in these two data sources for seasonal ILI (one virologically confirmed, the other not) was very similar, indicating that there was no age bias for ILI without virological confirmation. The use of ILI without virological confirmation tends to overestimate the ILI incidence rate but does not introduce a differential age-related bias if one assumes that the probability of a general practitioner making a wrong diagnosis is same in all age groups.

Age distribution of deaths:

Influenza was identified with codes 470 to 474 of the International Classification of Diseases (ICD) 8th revision before 1979, and code 487 of the 9th revision thereafter. Influenza deaths were not confirmed virologically, but this is the best indicator of influenza deaths.

6) The methods used to calculate the morbidity and mortality rates in the various populations should be clearly outlined (number of subjects in the numerator and in the denominator). Could you clarify?

Authors:
6: Please see the reply to comment # 3.

7) In the background statement “A shift of mortality toward younger age groups...” needs greater support with references from the literature. Please comment.
Authors:
We have clarified the relevant sentence.

8) The methods are not well detailed. Surveillance methods may vary with both site and time. Could you revise?
Authors:
8 Please see the replies to comments # 2 and 5.
In this analysis, we used epidemic periods stated in published reports for the US (Monto AS, Ohmit SE, Margulies JA, Talsma AN: Medical practice-based influenza surveillance: viral prevalence and the assessment of morbidity, Am J Epidemiol 1995, 141(6):502-506) and defined by sentinel systems in France (http://websenti.u707.jussieu.fr/sentiweb/).
The seasonal H1N1 epidemic periods were December 1978 to February 1979 in the US, and December 1988 to February 1989 in France, while the seasonal epidemic periods were January to March 1990 in the US and December 1989 to February 1990 in France.
The pandemic period corresponds to the first wave in the US, as defined by the CDC (from April 15, 2009 to July 24, 2009 [http://www.cdc.gov/h1n1flu/surveillanceqa.htm]).
The pandemic period was September 2009 to January 2010 in France, as defined by the Sentinel network (http://websenti.u707.jussieu.fr/sentiweb/).
We agree that influenza seasons are highly variable. However, as specified in answer 2, we now focus only on France and the US, and do not use the incidence but the age distribution, which does not differ between seasonal influenza epidemics due to a given subtype.
We have revised the Methods section.

We have added this information and clarified the Methods section.

9) In the methods, were the ICD used to identify influenza laboratory confirmed? Please, clarify.
Authors:
9: Please see reply to comment # 5.

10) The authors may consider adding these additional references and commenting on them in the Discussion.
We thank the reviewer for these references, which we have added and discussed.

Minor Essential Revisions
1) It would be important to use a consistent term throughout the manuscript for the Pandemic influenza (H1N1) virus.
   Authors:
   1:
   We now use “pandemic influenza (H1N1) virus” throughout.

2) The conclusion “Possibly because younger people have never previously encountered this viral subtype” should be moved to the discussion since it is speculative and should be replaced with a statement that summarizes the conclusion of your work.
   Authors:
   2:
   We have modified the text accordingly.

Level of interest: An article of importance in its field
Quality of written English: Not suitable for publication unless extensively edited
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
I declare that I have no competing interests
Reviewer's report
Title: Age distribution of influenza morbidity and mortality: a comparative analysis between seasonal influenza epidemics and the H1N1 pandemic.
Version: 1 Date: 1 March 2010
Reviewer: Dora Claire Pearce
Reviewer's report:
General comments: This paper is very topical and identified an important difference between age-related mortality patterns associated with H1N1 pandemic influenza and seasonal influenza, not evident for morbidity, with relevance for implementation of control strategies in future pandemics. The authors utilize available data sources to advantage, and use appropriate methods to conduct a robust statistical analysis, the title of the paper clearly conveying its content. Study objectives are clearly stated, and the discussion and conclusions are insightful and well supported by the data, which is well represented in the figures.

We thank the reviewer for these general comments.

Minor Essential Revisions:
1. Abstract: Please clarify the sentence describing the findings in relation to mortality in the results section of the abstract.
   Authors: 1:
   We have modified the abstract accordingly.

2. Methods: Please describe age categories used in the analysis in the methods section. These appear to differ between data sources in the figures and reporting in the Results section, and it would strengthen the manuscript if the authors discussed likely impacts on comparisons if these do indeed differ.
   Authors: 2:
   Indeed, the age groups available for the US were broader than those for France. We used 5-year age groups for France and 20-year age groups for the US. The Relative Illness Rate (RIR) and Relative Mortality Rate (RMR) were calculated with these original age groups in each country (see figure). For purposes of comparison, we then aggregated the French data to obtain the same age groups as in the US.

3. Statistical analysis: Please specify the hypotheses being tested with the Kruskall-Wallis and the Friedman tests, outlining the comparisons being made.
   Authors: 3:
   We have modified the Methods section, and used only the Kruskall-Wallis test to compare RIR (respectively RMR) by age group between seasonal and pandemic influenza.

4. Results: Please indicate the statistical tests to which the quoted p-values correspond.
   Authors: 4:
   All p values were obtained with the Kruskal-Wallis test.

5. Discussion: Paragraph 2; first sentence: for consistency throughout the manuscript it would be preferable to use "ILI" rather than "flu-like illness".
   Authors: 5:
   We have replaced 'flu-like illness" by ILI.

6. Please specify at what age people are considered to be “elderly” in relation to the age patterns for morbidity and mortality in figures 1 and 2.
   Authors: 6:
   People over 65 are considered “elderly” in this study, as now stated in the article.
7. It would be helpful to include a discussion of the possible limitations of the study due to the use of morbidity data based on medical visits for ILI in France versus virologically confirmed cases in the US.

Authors:

Our objective was to compare the age distributions of ILI between pandemic influenza and seasonal epidemics, and not to compare the burden of influenza-related illness (i.e. the cumulative incidence rates) between the US and France. The two data sources are not comparable, as some cases of ILI without virological confirmation could be due to respiratory pathogens other than influenza virus. However, it is worth noting that the age distribution of these two sources of seasonal ILI (one virologically confirmed, the other not) were very similar, indicating that there is no age bias when considering ILI without virological confirmation. The use of ILI without virological confirmation tends to overestimate the ILI incidence rate but does not introduce a differential age-related bias if one assumes that the probability of a general practitioner making a wrong diagnosis is same in all age groups.

We have added this paragraph to the Discussion.

Discretionary revisions:

1. The term "age-standardized measures" may be preferable to "standardized on age measures".
2. In their discussion, the authors may wish to expand on suggested links between the observed age-related risk of infection, age-to-age contact rates, and published surveys of contacts.
3. Expansion of the discussion to include variation in virulence between the viruses included in the analysis in relation to mortality patterns observed would be relevant to the conclusions drawn from the study.
4. Clarification of what is meant by “inappropriate” immune responses would be of interest.

Authors:

We have modified the text accordingly.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I declare that I have no competing interests.
Reviewer's report
Title: Age distribution of influenza morbidity and mortality: a comparative analysis between seasonal influenza epidemics and the H1N1 pandemic.
Version: 1 Date: 4 March 2010
Reviewer: Anne A Mazick
Reviewer's report:
Major Compulsory Revisions

Background:
1) The background is very brief, is lacking a sufficient introduction into the subject as well as a clear statement of the aim and the objective of the manuscript.
Remark: The assessment of age specific morbidity in pandemic compared with seasonal influenza epidemics is subject of many surveillance reports and publications of the pandemics epidemiological characteristics.

Authors:
1: We have clarified the background and aims of this study.
Comparing Morbidity
There have been many studies either on the age distribution of ILI seasonal epidemics or on the age distribution of ILI during pandemics. However, to our knowledge, there has been no attempt to compare both in the same study. Studies of 1918 and 1957, 1968 pandemics reported age distribution morbidity similar to those reported seasonal epidemics. We have added references in the text (references: Glezen, W.P., Emerging infections: pandemic influenza, Epidemiologic Reviews (1996), pp. 64–76, Taubenberger, J.K. and Morens, D.M., The pathology of influenza virus infections, Annual Reviews (2008)).
Comparing mortality

Methods:
2) Definitions of seasonal influenza epidemic periods and the 2009 H1N1 pandemic period are lacking.
Authors:
2: We agree that we did not clearly define the seasonal influenza periods and the 2009 H1N1 pandemic period.
We used epidemic periods either reported in the US (Monto AS, Ohmit SE, Margulies JA, Talsma AN: Medical practice-based influenza surveillance: viral prevalence and the assessment of morbidity. Am J Epidemiol 1995, 141(6):502-506) or defined by sentinel systems for France (http://websenti.u707.jussieu.fr/sentiweb/).
The seasonal H1N1 epidemic periods were December 1978 to February 1979 in the US, and December 1988 to February 1989 in France, and the seasonal epidemic periods were January to March 1990 in the US and December 1989 to February 1990 in France.
The pandemic period corresponds to the first wave in the US, as defined by the CDC (from April 15, 2009 to July 24, 2009 (http://www.cdc.gov/h1n1flu/surveillanceqa.htm).
The pandemic period was September 2009 to January 2010 in France, as defined by the Sentinels network (http://websenti.u707.jussieu.fr/sentiweb/).
We added this information to the Methods.

3) Seasonal epidemic data:
3.1) No selection criteria for influenza epidemics included in the study were given, it was only stated that “typical” epidemics were selected. This is not adequate and the reader is left wondering what a “typical” epidemic consists of.
Authors:
3.1: “Typical” is not actually appropriate: the seasonal epidemics selected for this study are characterized by the circulation of only one influenza subtype nationwide. These seasonal epidemics were identified from published data (US: Glezen WP, et al. Age distribution of patients with medically-attended

3.2) The seasonal epidemics chosen to compare to the H1N1 pandemic in 2009 date back between 20 and 30 years. Therefore the populations compared in this study may have different underlying levels of immunity to influenza viruses as well as the systems to collect morbidity data may be very different. Both factors may limit the comparability of the data here presented.

Authors:

3.2
Seasonal epidemics are often characterized by co-circulation of two influenza viruses. We focused here on seasonal epidemics characterized by the circulation of only one virus, in order to avoid confusion due to the co-circulation of two subtypes. We selected the 1978-79, 1988-89 and 1989-90 seasonal epidemics, in which the age distribution has been studied. We found no more recent influenza seasons with only one subtype and a known age distribution of ILI, especially for the US. The source of data was the same for all the French seasonal epidemics and pandemics, namely the Sentinels system, a French nationwide network of general practitioners who report, in real time, the number of medical visits for ILI. The definition of ILI has been the same since the network was created (1984). The source of data was different for the US. We agree that surveillance methods were variable between the countries, but using the ILI age distribution and not ILI incidence rates reduces the risk of bias. Technological advances in patient care have led to improved survival. However, this affects incidence rates of influenza morbidity and mortality, whereas we studied the age distribution. The highest attack rate is always observed among young people, and the highest mortality rate is always observed among elderly people.

3.3) Apart from the US which was included in both the seasonal and epidemic analysis, different countries were used for the comparison (France and US for seasonal data; New Zealand, Mexico and Us for pandemic data.) No explanation was given why these countries were chosen nor was described how comparing data from different countries may influence the results.

Authors:

3.3: We thank the reviewer for this very pertinent remark. Indeed, we cannot deny the existence of a differential bias related to different ascertainment of influenza-like illness or death between countries. When we started this work, no French morbidity and mortality data were available. These data have now been published, and we have repeated the analysis to compare seasonal and pandemic data for France and the US. We have removed the New Zealand and Mexico data.

Please see reply to comment # 3.2.

4) Morbidity data

4.1) A description about the nature of the pandemic morbidity data (and also mortality data) is lacking. Where they clinical illness or laboratory confirmed influenza? How were these data collected and where the morbidity data of the seasonal influenza collected in a similar and comparable manner?

4.2) For the morbidity data during seasonal epidemics: It is not clear what “ILI was confirmed virologically” means: Laboratory confirmed influenza?”

Authors:

4.
We apologize for the lack of data description. The age distribution of ILI and deaths in the US was collected from the Centers for Disease Control and Prevention (Centers for Disease Control and Prevention [http://www.cdc.gov/h1n1flu/surveillanceqa.htm]). Influenza-related morbidity and mortality were virologically confirmed.
For France, the age distribution of ILI was collected from the sentinel system (Réseau Sentinelles [http://websenti.u707.jussieu.fr/sentiweb/]) and the age distribution of deaths was collected from Institut de Veille Sanitaire (Institut de Veille Sanitaire [http://www.invs.sante.fr/surveillance/grippe_dossier/points_grippe/grippe_230310/tableau_deces_grippe_a_h1n1_230310.pdf]).

For the French morbidity data, a case of influenza-like illness was defined as fever above 39°C, aches and sore throat. For the US morbidity data, a case of influenza-like illness was defined as fever and cough or sore throat. Influenza was not virologically confirmed in the French data. Influenza was confirmed virologically in the US for the H1N1 influenza virus in 1978-79 and for the H3N2 influenza virus in 1989-90.

We used the age distribution of ILI (not virologically confirmed) in France and the age distribution of virologically confirmed influenza in the US.

Age distribution of ILI:

Our objective was to compare the age distributions of ILI between pandemic and seasonal influenza, not to compare the burden of influenza-related illness (i.e. the cumulative incidence rates) between the US and France. The two data sources are not comparable, as some cases of ILI without virological confirmation can be attributed to respiratory pathogens other than influenza virus. However, it is worth noting that the age distribution in these two data sources for seasonal ILI (one virologically confirmed, the other not) was very similar, indicating that there was no age bias for ILI without virological confirmation. The use of ILI without virological confirmation tends to overestimate the ILI incidence rate but does not introduce a differential age-related bias if one assumes that the probability of a general practitioner making a wrong diagnosis is same in all age groups.

Age distribution of deaths:

Influenza was identified with codes 470 to 474 of the International Classification of Diseases (ICD) 8th revision before 1979, and code 487 of the 9th revision thereafter. Influenza deaths were not confirmed virologically, but this is the best indicator of influenza deaths.

We have added these informations to the manuscript.

5) Population data and all-cause mortality data.

5.1) No reference to the used population data and all-cause mortality data is given for the seasonal epidemics.

Authors

5.1

We apologize for the lack of references, and now specify the data source in the Methods:

Census populations:


All-cause mortality data:

- France: Centre d’Epidémiologie sur les causes médicales de décès. Available from: http://www.cephid.vesinet.inserm.fr/

5.2) For the pandemic, 5 year old population data and all-cause mortality data were used. These data may change significantly over the period of 5 years especially if stratified into small age groups, leading potentially to an erroneous denominator for the analysis of pandemic data. To limit that, if data from 2009 were not available, why were not data from 2008 used?

Authors:

5.2

2008 data all-cause deaths were not available. For simplicity, we used 2004/2005 population and mortality data, which corresponded to the most recent year available in the WHO database. The age distribution of all-causes deaths might have changed for very old people, but as people over 65 years were considered “elderly” for this study, we believe that the age distribution of all-cause deaths has not changed much.

6) Indexes used

Relative illness rate and relative mortality rate
I am not familiar with these indices and have not seen them in the published literature. It is essential to add an explanation of the indices and their interpretation /limitations, as well as why there where chosen instead of more commonly used indicators.

Authors:
6.
We thank the reviewer for this useful comment.

We estimated the ratios as follows:
Relative Illness Rate (RIR): \( \frac{C_i / \sum C_i}{N_i / \sum N_i} \)
- \( C_i \): number of cases of influenza-like illness in a given age group
- \( \sum C_i \): Sum of influenza-like illness in all age groups
- \( N_i \): Population in a given age group
- \( \sum N_i \): Sum of population in all age groups.

Relative Mortality Rate (RMR): \( \frac{I_i / \sum I_i}{D_i / \sum D_i} \)
- \( I_i \): number of influenza deaths in a given age group
- \( \sum I_i \): Sum of influenza deaths in all age groups
- \( D_i \): Number of all-cause deaths in a given age group
- \( \sum D_i \): Sum of all-cause deaths in all age groups.

We now describe how these indices were estimated in the Methods.

As reported ILI incidence rates for the 2009 H1N1 pandemic are unreliable, we chose to analyze the age distribution of ILI. For consistency, we used a similar method to analyze mortality data. However, it should be pointed out that the calculated relative illness and death rates do not provide information on the morbidity or mortality burden of influenza in the general population.

We have added this paragraph to the manuscript.

Results
7) Only the indices are presented, no underlying crude morbidity or mortality data or other indicators. Confidence intervals for all RIR and RMR would help to identify significant differences between epidemics and pandemic. It may be possible to add them to the graphs.

Given the uncertainties about the methodology the results section will need to be reviewed again at a more advanced stage of the manuscript.

We preferred not to present confidence intervals on the figures to allow a better readability given the number of curves for the seasonal epidemic graph.

Authors:
7:
Now that we have modified the Methods, and our comparison between seasonal and pandemic influenza is based on the same countries, we believe the results are sound. Our findings should be of interest to health authorities during future influenza outbreaks.

Discussion
8) How do the results fit in with the epidemiological characteristics of the H1N1 pandemic published elsewhere?

Authors:
8:

9) The authors consider incidence data for the H1N1 pandemic are unreliable, but fail to explain why and why they think flu-like illness data are more accurate.

Authors:
9:
We consider that incidence data for the H1N1 pandemic are unreliable, owing for example to the difference between morbidity rates based on virologically confirmed and unconfirmed data. We do not consider that ILI data are more accurate, but that the age distribution of ILI is more accurate.

Moreover, the data source was the same for all the French seasonal epidemics and the pandemic, namely the Sentinels system, which is a French nationwide network of general practitioners who report, in real time, the number of medical visits for ILI. The definition of ILI has been the same since the network was created (1984). The data source was different for the US. We agree that the surveillance methods were variable between the countries, but the risk of bias is reduced by using the ILI age distribution and not the ILI incidence rate.

We have modified the discussion as follows:
As reported ILI incidence rates for the 2009 H1N1 pandemic are unreliable, we chose to analyze the age distribution of ILI. For consistency, we used a similar method to analyze mortality data. However, it should be pointed out that the calculated relative illness and death rates do not provide information on the morbidity or mortality burden of influenza in the general population.

10) Although the authors assume that there is no age-related reporting bias, there will certainly be some. Interesting to discuss would also be if this bias differs between seasonal and pandemic influenza.

Authors:
Our objective was to compare the age distribution of ILI between pandemic influenza and seasonal epidemics, and not to compare the burden of influenza-related illness (i.e. cumulative incidence rates) between the US and France. The two data sources are not comparable, as some cases of ILI without virological confirmation can be attributed to respiratory pathogens other than influenza virus. However, it is worth noting that the age distributions in these two data sources on seasonal ILI (one virologically confirmed, the other not) were very similar, indicating a lack of age bias when considering ILI without virological confirmation. The use of ILI without virological confirmation tends to overestimate the ILI incidence rate but does not introduce a differential age-related bias if one assumes that the probability of a general practitioner making a wrong diagnosis is same in all age groups.

- Minor Essential Revisions
  11) The titles of the figures are missing
  We have added titles of the figures.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
I declare that I have no competing interests