Author's response to reviews

Title: Influenza-attributable deaths in south-eastern France (1999 to 2010): mortality predictions were undependable.

Authors:

Simon-Djamel THIBERVILLE (djamt@yahoo.fr)
Jean GAUDART (jean.gaudart@univ-amu.fr)
Didier RAOULT (didier.raoult@univ-amu.fr)
Remi N CHARREL (remi.charrel@univ-amu.fr)

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

Thank you for evaluating our article.

We carefully considered the comments of the reviewers and have modified our manuscript accordingly.

We submit 2 versions, one with the correction highlighted in blue and one final version.

We also provide below a point-by-point response to the reviewer’s comments.

We hope that you will now find the revised version of the manuscript enclosed suitable for publication.

**Version:** 2  **Date:** 11 February 2015

**Reviewer:** Bayad Abdalrahman

**Reviewer’s report:**

All comments are minor essential before publication:

**Presentation:**

It is not well presented and not easy to read. The authors need to articulate their views in a coherent way. The article also needs some work on the language side of things.

**Examples:**

Please be consistent in expressing the name of the virus as (Influenza virus A (H1N1)) such as in line 64 and 77. **We corrected the name of the virus consistently through the manuscript.**

Please make it clear when you talk about seasonal influenza or pandemic influenza. For example in line 83 “we estimated the influenza-attributable deaths”. I assume this is for seasonal influenza? **The sentence has been corrected as suggested.**

Reference to data sources should be quoted at the end of the article such as lines 89, 93, and 97. **We quoted the references at the end of the manuscript accordingly.**

**Methods:**

This section is not clear to me, for example, the authors mentioned mortality data were used but it is not clear if this data was about all deaths from all causes across all age groups or influenza related deaths.

**We added on the methods section the definition of the causes of deaths used:**

Line 97-99: “The file contained gender, age at death grouped in 5 year ranges, week of death, and cause of death using the four digit International Classification of Diseases (ICD) code (10th revision).”

And on Line 130-132: “The dependent variables were the weekly deaths from all non-violent causes (all codes except ICD9: 800-999, ICD10: S/T), from respiratory diseases (ICD9: 460-519, ICD10: J), and from cardiovascular diseases (ICD9: 390-459, ICD10: I).”

**Discussion section:**

Line 174: I am not sure the word “drastically” has been used appropriately. Line 214-215: **We deleted drastically according to this comment.**
“others causes”…should be other cause, without “S”. We corrected the sentence according to this comment.

Line 217: I believe you wanted to say front page or front line publications? Please check language appropriateness. We corrected the sentence according to this comment.

Conclusion section:

In line 226, can you please clarify what is pdm? Also, it would be nice to see the virus name’s format consistently the same (influenza virus A (H1N1)). The acronym A(H1N1)2009 has been used throughout the revised version to name the 2009 pandemic virus.
Reviewer’s report:

The authors aim to show that influenza-attributable deaths caused by the A(H1N1)2009 pandemic in the South-East of France were much lower than expected.

To this end, they used a methodology previously established by Redlberger-Frity et al. applying it to an Austrian cohort. It is therefore not surprising that their results seem to follow the Redlberger-Frity et al. hypothesis; the authors support the idea that influenza A(H1N1)2009 had a much smaller impact than initially predicted.

Major Compulsory Revisions

1. Abstract, Background

The authors need to clearly state the objective/hypothesis of the study, which is not 100% transparent to the reader.

A statement of purpose should be included at the end of the Introduction Section similar to a sentence in the beginning of the Abstract, but to be completed to state the actual hypothesis:

Abstract L29: “we aimed to estimate the influenza-attributable deaths during the periods form 1999 to 2010... in order to corroborate the hypothesis that...”

The sentence should continue with one (or both) of the following:

a) … influenza-attributable deaths caused by influenza A(H1N1)2009 viruses were much lower than initially expected (then specify expectation including reference or citation!)

b) .... in South-Eastern France primarily affected young people

The sentence has been modified as suggested.

2. Methods

Is there a specific reason why the authors did not calculate the number of life years lost? This calculation would be very insightful to be presented and discussed. Calculation of life years lost would provide additional detail regarding the overall effect of Influenza A(H1N1)2009 disease on a population level. Due to the fact that the age groups affected during the pandemic differed from previous seasons/epidemics, the effect on the population of losing the young versus losing elderly people are different (long term losses versus short term losses).

This calculation would also provide stronger evidence for the final point in the discussion regarding the overall number of deaths during the 2009-2010 season compared to previous ones (see comments L.225-226).

Actually, the annual life tables at the regional level from 1999 to 2010 are not publicly available. Even if the number of years lost was not possible at this stage, we presume that our estimations of attributable deaths by age group can be interpreted on the light of the reviewer perspective.

Conclusion

The fact that the age group most affected by the Influenza H1N1pdm(2009) viruses included children and young adults, does not mean that the virus was not serious. It seems that older adults and the elderly were more likely to be vaccinated and/or protected naturally.

We agree with this comment and this subject was developed in the first part of the discussion, on line 187-197.

The statistical approach (attributable death) use in this article was based on the number of death and the
number of ILI. Thus, the number of death due to influenza could not be underestimate except if the number of ILI was under diagnosed.

Among those not immunized against the new strain, the death rate increased in all the 3 age groups incl. those younger than 55 years of age, (from an average of -0.035 to 0.28; an average of 0 to 0.58; and an average of 0.31 to 0.62). A simple estimate of the increase in number of deaths in each age group should give a rough estimate of the pandemic strength adjusted by age.

We agree with this comment but as we discuss in the last section we found negative attributable deaths in each age group during pandemic and seasonal periods. Consequently, the increases in number of deaths were difficult to depict clearly on a graph. Moreover we thought that the figure 1 was sufficient to represent the pandemic strength adjusted by age.

3. Conclusion (2)

A statement should be added to the effect that vaccination past exposure to antigenetically related viruses are both important when estimating/modeling the disease impact of a new viral threat. The A(H1N1)2009 pandemic could have had serious consequences, had the age group of the elderly not been partially immune to the virus. Using an effective vaccine in the children on the other hand, could have major impact on preventing spread of pandemic viruses – including to other risk groups, such as the elderly. These comments have been included at the end of the discussion

Discretionary Revisions

4. Methods

Even though the authors use the same procedure and statistical approach derived from a previously published study, the statistical methods used should be explained in more detail. This would allow the reader to follow the reasoning without having to have the initial paper by Redlberger-Fritz et al. at hand (incl. readership in low-resource settings). Basic information which statistical package was used and how excess death rates were calculated, should be included.

We modified the statistical section in depth according with this comment, as follow:

“In order to compare our results with published data, we used the same statistical model used by Redlsperger-Fritz [8]. General linear models (glm) were used to estimate the expected number of deaths according to a Poisson distribution model. The population log was used as an offset. Cofactors were the total number of RSV, the epidemic weeks (dummy variable), and the sinusoidal transformation of time. The attributable number of deaths ADj for epidemic weeks j were estimated as following:

\[ AD_j = D_j(1-exp\{-\theta_j\}) \]

Where, for the epidemic week j, D was the number of deaths and \(\theta\) the associated parameter estimated by the glm. The dependent variables were the weekly deaths from all non-violent causes (all codes except ICD9: 800-999, ICD10: S/T), from respiratory diseases (ICD9: 460-519, ICD10: J), and from cardiovascular diseases (ICD9: 390-459, ICD10: I). To assess the excess mortality by age group, we used 4 age groups (0-24, 25-44, 45-64 and > 65 year-old).

All statistics were provided by using the R software (version R3.1.0; http://www.r-project.org/).”

Minor Essential Revisions

L 47. The authors should specify what is meant by the term “global”. After reading it seems to become clear that the “total n” in the study is the population in the PACA region of South-East France (which is represented in the study given their sampling design). We corrected the manuscript according to this
L49. “same approach of an Austrian study”. suggest: “same approach as in a previously published study using an Austrian population sample”. We corrected the manuscript according to this comment.

L49, please specify the term “excess respiratory mortality (as opposed to “excess mortality”). What is the baseline rate of “respiratory mortality” in South-East6 France? How is this data gathered? Does this include all age groups and respiratory disease or specific ones? Are there statistical data (publications or public health figures) which could be referenced?

We added in text within the method section the definition used to classify the death from all non-violent causes (non violent mortality), from respiratory diseases (respiratory mortality) and from cardiovascular disease (cardiovascular mortality).

Line 130-132: “The dependent variables were the weekly deaths from all non-violent causes (all codes except ICD9: 800-999, ICD10: S/T), from respiratory diseases (ICD9: 460-519, ICD10: J), and from cardiovascular diseases (ICD9: 390-459, ICD10: I).”

In the abstract section, the term excess respiratory mortality refers to the all age groups analysis.

L50. Thus, (comma): corrected
L51 As direct result, (comma), corrected
L52. Saved, corrected

L51-53. The sentence goes back and forth. Rephrase so that there is some order in the sentence. We modified the manuscript according to this comment.

L133- “where as” is “whereas”, corrected

L157-159. How were the groups divided? Please explain this somewhere.

We added on line 133 : “To assess the excess mortality by age group, we used 4 age groups (0-24, 25-44, 45-64 and > 65 year-old).”

L187. We considered it interesting to analyze the excess… We corrected the manuscript according to this comment.

L192. Prevented, corrected

L190-192. The meaning of this sentence is unclear. Rephrasing this sentence would be advisable, for example: “Pre-existing exposure to closely related viruses prior to 1957 may have provided cross-reactive immunity during the A(H1N1)2009 outbreak in the same way influenza vaccination may reduce the incidence of influenza-related complications”. We clarified the text according to this comment.

L.199. The sentence is not complete, please specify which mortality rate(s) the “lower mortality” is compared to

To clarify this sentence, we added on line 218: “… compared to the previous seasonal mortality”
L215. Suggested citation. INSERM CepiDc? We added the reference according to this suggestion.

L217. “none could forecast” or “none could have forecasted” We corrected the sentence according to this comment.

L219. “Was” suggest replacing by “had been” We corrected the sentence according to this comment.

L219.” In the global population” should be “for the general population” We corrected the sentence according to this comment.

L224. -The authors seem to overuse the term “global”. recommend to substituting by specific terms or “general” or “total” as applicable. We modified the overuse of the term “global” throughout the article.

“The global assessment of the situation” is an overly generalist phrase. Its coverage should be substantially reduced. Example: “The assessment of this study” is … “according to our observations”…. Or directly “The 2009 influenza pandemic…” We corrected the manuscript by using the last suggestion.

L.225. “has corresponded” is misused. Should be substituted by “has resulted in a reduction of the ….”. We corrected the text according to this comment.

L.225-226. This sentence repeats what was already stated in 224-225. It may be deleted. If the authors want to go into more detail, they should mention that the reduction in deathrates during he pandemic season occurred exclusively in the elderly population. As this age group accounts for the biggest share of deaths in the population studied, the overall number of deaths caused by the A(H1N1)2009 pandemic in the PACA population resulted in a smaller death toll compared to seasonal/ epidemic years (see previous comments in Methods, second paragraph). We corrected the text according to this comment.

L.230. Consistency in headings: Colon in/out? We corrected the manuscript according to this comment.

L.242. References style is different from all the previous heading styles. We corrected the style according to this comment.

Figure1. Y axis: Excess mortality per 100,000 inhabitants,

Figure1. X axis tags. Should not cover the figure itself. Tags should be under the bars.

We corrected the Figure according to this comment.

References:
Ref 1,4: The references for online resources are incomplete and need to be revised to include author names, access dates and titles etc., We corrected the references according to this comment.

Ref. 4. Should be cited following the newspapers citation format., We corrected the references according to this comment.