Author's response to reviews


Authors:

Annick D Lenglet (annick@thelenglets.com)
Victoria Hernando (vhermando@isci.es)
Pilar Rodrigo (mrodrigo@aragon.es)
Amparo Larrauri (alarrauri@isci.es)
Juan DM Donado (idonado@isci.es)
Salvador de Mateo (smateo@isci.es)

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

Thank you for sending us our manuscript entitled “Impact of flu on hospital based morbidity during 4 flu seasons in Spain, 2000-2004”. We are grateful to both reviewers for the careful revision of the manuscript and the insightful comments and questions posed. We have taken careful consideration of each of the comments made and have, where possible, tried to clarify, change or add more information. Please find below our replies to each of the two reviewers comments and queries. Also, find enclosed the revised manuscript for this article.

We appreciate your revision of the new version of this manuscript and look forward to hearing from you.

On behalf of all the authors,
Victoria Hernando
National Centre for Epidemiology, Public Health Institute Carlos III
Tlf: +34 91 822 26 08
Fax: +34 91387 78 16
e-mail: vfernando@isciii.es
**Reviewer 1 – Douglas M Fleming**

**General Comments**

1. Though we agree with the reviewer that our study only included 3 epidemic periods of influenza (and 4 winter seasons) and therefore generalising the results to other winters is not advisable, we feel that sufficient other bibliography (included in the references) supports many of the main findings of our study. We have therefore tried to limit generalised comments about this finding in the text. However, we do think, that various other studies have also found that H3N2 is a more virulent strain of influenza compared to H1N1, and that excess morbidity can be expected in seasons where the former is the dominant influenza strain circulating.

2. It is correct that the database which we have used does not collect any information on influenza vaccination status of those persons that are admitted to hospital. If this information had been available in the sources of data which we have used, we agree with the reviewer that the results would have been additionally interesting. However, we assume that the hospital admissions should be representative of the whole population (including vaccinated and non vaccinated persons). We therefore think that the recommendation on vaccination in target groups is still a valid one. For some addition information, we have included some other references which demonstrated the low influenza vaccine coverage in vulnerable groups in Spain.

3. We agree with the reviewer that the delay seen in hospitalisations is very clear in 2 out of the three seasons with a flu epidemic. We have added this as a result in the manuscript and also in the discussion.

**Major Compulsory Revisions**

- Page 3 paragraph 4: please see our comments in the General section part 1.
- Page 4 Methods paragraph 1: we thank the reviewer for this observation. The objective of this study was to study the potential pathologies that can result from complications with influenza infection. Acute bronchitis is not listed as a complication from influenza. Please refer to: Mandell, Douglas, Bennett, Section on Complications of Influenza in the Chapter on Influenza Virus, in Infectious Disease, Principles and practice. It is for this reason that we chose not to include ICD9 code 466 in the study.
- Page 4 Methods, paragraph 2: unfortunately we have not had the opportunity to measure the impact of the flu epidemics on overall circulatory disease. We appreciate the reviewers suggestion and will try to include this possible outcome of influenza infection in any future studies we conduct on the subject.
- Page 4 Methods, paragraph 3: as the objective of the study was to conduct an evaluation of the impact of influenza on hospital morbidity at the national level, we have not broken the analysis down to regional level. We have tried to clarify the functioning of the sentinel influenza surveillance network further in the methods section of the new manuscript. Even though Spain is divided into regions, the sentinel influenza network physicians report to a regional and national level each week. In our experience, though there might be a slight difference in the time at which influenza epidemics start, the wave of influenza throughout Spain is very equal in all the regions and the delay is minimal. As we have studied the impact of the national epidemic period, and we have also included hospital admissions at the national level, we continue to think that the
method for estimating national excess hospital morbidity due to influenza remains a valid approach.

- Page 7 Discussion, paragraph 1: though we agree with the reviewer that there is a second part to the main conclusion (having to do with the delay in hospitalisations and the epidemic period), we still think that our study has shown, that in the epidemic periods which we studied, flu did have an impact (delayed, but an impact nonetheless) on flu-associated hospital morbidity.

- Paragraph 2: we agree with the reviewer that the exact role of other respiratory viruses in the current study has not be sufficiently clarified and merits further study. Interestingly, in our experience, RSV epidemics tend to precede influenza epidemics in Spain (in contract to findings in other countries).

Reviewer 2 – William C Thompson

Major Compulsory Revisions
1. We thank the reviewer for his compliment.
2. We have tried to clarify the way that hospitalisations were calculated in the study and have avoided using the term ‘rates’ when speaking of excess hospital morbidity.
3. Please see point 2 above and the methods sections where we have to further clarify the calculations which we conducted.
4. We appreciate greatly the mentioning of the two additional articles which we had not yet included in the bibliography. We have read each of them with great interest and have included them as further support to our finding that the seasons where H3N2 is the dominant serotype circulating, an increased level of excess morbidity is encountered. The difficulty in comparing rates between each of the articles mentioned is that the studies use different methodologies to estimate the excess hospital based morbidity as well as how to define what an ‘epidemic’ and ‘non-epidemic’ period is. However, all of the studies included in our reference list appear to agree on the point that epidemics where H3N2 is the dominant circulating type, the estimated hospital excess morbidity is higher.