Author's response to reviews

Title: Burden of paediatric influenza in the European Union: a systematic review

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Author's response to reviews: see over
Dear Dr Silvestre,

On behalf of my fellow authors, I am pleased to re-submit the following original article paper entitled ‘Burden of paediatric influenza in the European Union: a systematic review.’ for your consideration for publication in BMC Public Health. We thank you for providing the peer reviewers’ comments on our paper. We have resubmitted the revised manuscript using tracked changes to highlight where we’ve made updates in line with the comments.

Specifically, here are the reviewer comments and the actions taken:
Reviewer 1 (Catherine Weil-Olivier)

Minor Essential Revisions

Comments are inserted in the text

Authors’ action/response: We have edited the text to address the comments in the body:
clarified the aims of the study, edited the list of countries, clarified the methods section (including Figure 1), clarified the section on costs, and added a discussion on antivirals and influenza surveillance in the discussion.

Regarding the reviewer comments about Vesikari and Hoberman studies (on p. 7): these studies did not include the key outcomes of interest (health outcomes and economic outcomes), therefore they were not included in this review.

Regarding the inclusion of the articles: the articles that reported the outcomes of interest (health outcomes and economic outcomes) based on ILI assessment were included in the review, but included in the online appendices and described in the article only to a limited degree (because they are not specific to influenza). We felt that it would be helpful to publish a summary on them because such information may be of interest to clinicians or researchers who study respiratory illness in general. That’s why we report that we selected 53 studies for review (based on the data availability), of these studies, 13 reported culture confirmed influenza.

Discretionary Revisions

1) Abstract:

1.1) Introduction: Alphabetic order for the countries participating.

Authors’ action/response: Corrected

1.2) Methods: any details would be welcome about the meaning of "structured" and the retained 53 publications: are the 53 retained publications all the European data published during the selected years? If not, how were they selected?
**Authors' action/response:** We changed “structured” to “systematic”, which is a more accurate term.

1.3) Representativeness of northern and southern regions of the EU: they are mainly western European countries / regions

**Authors' action/response:** We have changed the wording in the Title, Background, Methods and Discussion to describe the chosen countries as those in “Western Europe”

2) Methods

2.1) P8.§5 : please a full wording is useful for “HRQoL”

**Authors' action/response:** We have dis-abbreviated this and other acronyms at first mentioning.

2.2) Globally, to better understand and rely on the results presented later on, the inclusion / exclusion criteria should be more clearly specified once.

**Authors' action/response:** Please see additions in the Methods section.

3) Results

3.1) Comments are inserted in the text

**Authors' action/response:** Corrected – please see description above.

4) Discussion

4.1) The authors, based on this interesting overview of the European burden of pediatric Influenza, should consider the broad scope of actions against influenza in children without only targeting vaccination policy in this range of age (though the most potentially active prevention by far). The benefit of influenza rapid diagnosis testing at bedside with reliable tests (high specificity and good sensitivity) as an epidemiological tool of screening and guiding clinical decisions, the potential use of antivirals as a useful part of care would prevent this article, sponsored by the vaccine industry to appear so clearly oriented.

**Authors' action/response:** Please see edits in the discussion section.
4.2) Authors should comment on the selection of 9 countries among the 27 Member States in Europe as finally only 5 in 9 of the selected countries reported published studies (Finland, France, Germany, Italy, The Netherlands): authors should justify the inclusion of those not reporting and the exclusion of the other European Member States

**Authors' action/response:** Please see justification provided in the Methods section. We also changed the title.
Reviewer 2 (Susanna Esposito)

The paper of Antonova et al. is interesting and well written, although some minor revisions are required.

1) One of the major limitations is represented by the huge number of Tables and Figures. I think that several of them can be deleted so that the manuscript can be read in an easier way. Please delete Table 4, Fig. 1, Supplemental File 1, Fig. 2, Supplemental file 2, Figure 5 and Figure 6.

Authors’ action/response: Please see the following changes:

- we have simplified Figure 1
- we have removed Figure 6
- we have moved Table 4 to Supplemental files.

We would like to keep the rest of the tables and figures in the manuscript or online (for supplemental materials) because we believe that some readers may be interested in this information.

2) Please clarify who were the two independent reviewers.

Authors’ action/response: Please see edits in the Methods section and an acknowledgment

3) In the discussion, please consider differences in influenza burden according to patient’s age.

Authors’ action/response: Please see paragraph 4 in the discussion section.

4) In the discussion, please consider the importance of influenza as priority for prevention in a period of economic crisis.

Authors’ action/response: Thank you for your suggestion. We believe that economic considerations are an important driver in healthcare in general and in vaccination policy in particular. At the same time we feel that such arguments are outside of the scope of our paper. Furthermore, we sincerely hope that all economic hardship in the EU will soon diminish and would like to avoid “dating” our paper to a time of specific economic circumstances.
5) Please speculate more on what to do in terms of prevention (ie, universal vaccination for who?).

Authors’ action/response: We added discussion points about influenza surveillance and antiviral use in the Discussion section
Reviewer 3 (Pieter L Fraaij)

With interest I read the before mentioned manuscript. Overall this manuscript tries to give insight in the burden of disease of flu in Europe. The authors have done elaborate work to identify papers and the summarized data provide interesting data. I do have however some comments:

1) First of all this paper has its position in a field full of controversy and I feel that the data need to be presented more carefully. For instance the in the background the sentence “many countries……high risk of morality or hospitalization” I am not comfortable with. I do not agree with this high risk form mortality and data in the text by the authors do not reflect it. I would suggest to read the article carefully and rephrase some passages. It may be considered overly biased ‘pro-vaccination’ and thus neglected. In addition data may one may also be interpreted to show that flu does not often cause severe disease (or are groups to small?)

Authors’ action/response: We have reviewed our paper and removed all statements that appeared potentially controversial, including the one you pointed out.

2) Please provide original references in the line ‘……because they have higher viral titers and adults…..’. Are the authors sure that this is the main mechanism for children to be the primary vector of flu transmission? How about preexisting immunity?

Authors’ action/response: We have added a point on pre-existing immunity and a reference for higher titers.

3) I had some problems trying to understand the different numbers in the text and flow chart on numbers of articles included (ie how does the 1,002 relate to the 1,153). I may have overlooked something but that may also happen to other readers. I suggest that both text and flow chard correspond.

Authors’ action/response: We have expanded the explanation in the Methods section and clarified the flow diagram (Figure 1).
This work has not been previously published, nor is it under consideration for publication elsewhere. We feel that this manuscript represents an important contribution to the literature. The findings of this literature review may benefit public health officials, policy makers, healthcare professionals, and the public who have a stake in pediatric influenza policy. It may serve as a knowledge base for the ongoing pediatric influenza vaccination policy debate in Europe.

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Thank you for your consideration of this manuscript, and we very much look forward to your response.

Yours sincerely

Catherine Rycroft

On behalf of co authors