Author’s response to reviews

Title: Estimation of outbreak severity and transmissibility: Influenza A(H1N1)pdm09 in households

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Author’s response to reviews: see over
Author's covering letter for initial submission

Title: Estimation of outbreak severity and transmissibility: Influenza A(H1N1)pdm09 in households

Authors:

Version: 1 Date: 14 August 2012

Comments: see over
14 August 2012

Dear Sir / Madam,

Please find attached our revised manuscript “Estimation of outbreak severity and transmissibility: Influenza A(H1N1)pdm09 in households.”

We would like to thank the editorial staff and reviewers for their constructive comments, and our response to these follows below.

Yours sincerely,

Thomas House (Corresponding Author).
We would like to thank both reviewers for their constructive reviews. We agree that the suggested changes will improve the paper, and have made them in red in the main text. We also insert our comments here, in italics, beneath the specific requests.

Reviewer's report 1:

This paper estimates influenza transmission parameters in the context of a spectrum of health outcomes from uninfected, through subclinical, to lab-confirmed, and including other respiratory infections. This is a valuable approach that allows more detailed exploration of typical study data, and is clearly explained – I particularly like Figure 1 as a graphical representation of the underlying model. The authors also conduct a review of published estimates of influenza transmission parameters. I’d like to see this review connected more clearly to the main focus of the paper, and would appreciate some more detail and discussion of a few of the findings as outlined below.

Discretionary Revisions:

1) The authors have undertaken a thorough review of papers estimating household transmission parameters for influenza, but at present, this review seems disconnected from the main statistical analysis. It does not appear to be mentioned anywhere in the Methods or Results and Discussion sections, and is only alluded to briefly in the Conclusions. I think the paper can stand alone without this review, but if the authors see it as providing valuable context, then more effort should be made to integrate it into the main text.

We see the review as providing important context to other researchers, but sympathise with the point made by the reviewer that it is not integrated into the main text, and so now provide the review as Additional File 1.

2) To me, the most surprising finding of this analysis is the estimate for p, the proportion of swabs from H1N1 positive cases that were found to be negative by PCR. The authors estimate that 42% of cases of H1N1 did not return a positive swab. Although there are a number of rapid tests that show low sensitivity, RT-PCR is often taken as the gold standard in influenza testing. The authors discuss some data-related factors that could explain this low estimate – e.g. swabs taken too late, or in individuals with mild illness – but I think it is also important that they discuss any model assumptions that might lead to errors in this estimate. For example, does the model of other respiratory infections (estimated as the baseline prevalence, s) allow for these other infections to be transmitted within the household? Could the estimates of k include some infections other than influenza? I realise that a thorough testing of alternate models goes far beyond the scope of this paper, but some discussion of the possible impact of the underlying assumptions would be valuable here.

The simulation study given in the Technical Appendix (Additional File 2) shows that the model provides accurate parameter estimates. We agree that other respiratory infections could in general be a major source of bias; we have made it more clear in the text that the levels of these were sufficiently low in Birmingham at the time that the effect should be negligible. Asymptomatics could be a significant source of bias if they are entirely without even the most minor symptoms, and this is now stated in the paper. We also note the existing discussion of possible bias in the paragraph before the section on “Statistical Analysis”.

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3) The relationship between household size and transmission rates is a complicated one that is not well understood. In their systematic review of pH1N1, Lim et al. (reference 24) found that “secondary infection risk was variously observed to increase with household size or not to be associated with household size”. The one study they identified that showed a decline in secondary infection risk with household size was the Cauchemez study (reference 20), which Lim et al. noted has a “broader definition of household contact”. In this context, it would be helpful to know what definition was used for household contacts in the data analysed in this paper. The authors’ observation that they expect transmission probabilities to “decline swiftly as household size increases” seems a bit strong given this variability in findings.

*We agree that our original statement was too strong, and the discussion in the Conclusions has been modified. Our definition of household contacts (which is the standard, narrow one) is also now present in the Methods section.*

Finally, I am very intrigued by the finding of heterogeneity in individual infectiousness. I hope the authors have an opportunity to explore this in further work – particularly in relation to the age of cases and contacts.

*We appreciate the reviewer’s positive comments, and also hope to address these issues in future.*

**Reviewer's report 2:**

Authors use mathematical and statistical modeling to estimate heterogeneity in transmissibility at the household level by using epidemiological data that includes different case definitions. For this purpose, authors use data collected during the early phase of the 2009 A/H1N1 influenza pandemic in Birmingham, UK. The paper is well written and the methodology presented is novel in that it uses multiple layer epidemiological data that goes beyond the estimation of secondary attack rates at the household level. It provides a framework to estimate household level transmissibility according to household size. Furthermore, authors carry out a systematic and useful review of studies of household level A/H1N1 data during the 2009 A/H1N1 influenza pandemic. I only have a few comments on the data analyzed, interpretation of results, and the limitations of methodology presented.

1. Epidemiological data are based on notifications to the UK Health Protection Agency by general practitioners. Could you please provide more details on the network of general practitioners that provided notifications during 2009 A/H1N1 influenza pandemic (e.g., representativeness of general population)
2. Given that data employed are based on disease notifications, data may be representative of most severe cases? Perhaps this should be discussed as a limitation.

*We have added discussion of the representativeness of the data on the basis of geography and severity in the ‘Data Collection’ section – stating that the testing was done on the basis of clinical suspicion, and our methodology for dealing with case ascertainment, should mean that severity bias is not highly significant. We have stated that while the sample is geographically representative, there is still some possibility of differential reporting.*

3. Did all possible cases and their contacts received antiviral medication for treatment/prophylaxis? Some statistics on treatment administration could be provided if available. Please explain how antiviral treatment (and time of start of treatment relative to onset of symptoms) could have affected your results given that methodology employed does not seem to have taken into account this pharmaceutical intervention.
We have added discussion in the Conclusions – as we state there, given the complexities of transmission it is hard to do more than conjecture without doing a full analysis, but we would expect that inclusion of treatment time as a covariate would lead, for later and earlier antiviral administration respectively, to a higher and lower estimate of transmission probability than our existing $T_n$ estimates. These higher and lower estimates are likely to lead to similar population averages compared to our results – i.e. our model could be more sophisticated but we do not expect systematic bias.