Author's response to reviews

Title: Oseltamivir for treatment and prevention of pandemic influenza A/H1N1 virus infection in households, Milwaukee, 2009

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

We hereby resubmit our paper “Oseltamivir for treatment and prevention of pandemic influenza A/H1N1 virus infection in households, Milwaukee, 2009” for publication.

We have addressed the questions raised by the referees and revised the paper accordingly (all changes are underlined). In particular, we put more emphasis on the role of potential biases and also expanded the discussion on how we addressed them through our methodology.

We have also added an Ethics statement into the Methods section.

We wish to thank the referees for their suggestions. We believe that the clarifications and revisions in the latest version have benefited the presentation. Below are the specific responses to the issues raised by the referees.

Reviewer’s report
Title: Oseltamivir for treatment and prevention of pandemic influenza A/H1N1 virus infection in households, Milwaukee, 2009
Version: 1 Date: 22 March 2010
Reviewer: Gerardo Chowell

Reviewer’s report:
Goldstein et al. analyzed the effects of oseltamivir treatment and prophylaxis in the City of Milwaukee by using data on influenza H1N1pdm transmission and oseltamivir usage at the household level. This is an interesting article containing useful data. I have a few comments/suggestions on the description of the data and analysis that the authors could find helpful to revise their manuscript.

1. Please provide more information about the spatial distribution of the participating households in City of Milwaukee.

Response: Initially cases were concentrated on the near south side of Milwaukee which has a large Hispanic population, however in a matter of weeks the epidemic had spread throughout the city. As cases were reviewed in order they were reported these cases would be skewed to those neighborhoods - this is now mentioned in the text.

2. If there is influenza H1N1pdm incidence data available for the City of Milwaukee, it would be interesting to compare it with the incidence data used in this study for 135 households. How does the time line of infection in the study follows City level data?

Response: The cases reviewed for the most part represent all cases reported in chronological order, the only exception would be if there was a delay in the case
report being turned in (this occurs typically because of difficulty in contacting the case). Among the cases present with the Milwaukee Health Department, information on 362 households was entered electronically, where the households were selected as described in the text. Out of those 362 households, 135 households with complete information required for the study were selected. While the cases present with the Milwaukee Health department do represent the chronology of all recorded case, we felt that epidemiological description of the H1N1 outbreak in Milwaukee requires a separate paper.

3. Please provide the start and end of the study period


4. It would be useful to provide more information on how the data was collected. Is there any information on the number of health care centers in the City of Milwaukee that participated in this study? Please consider providing a map with the geographic location of health centers and area where the participating households are located.

Response: Persons meeting the confirmed or probable case definition were reported regardless of provider because of statutory required reporting. Furthermore, during the first wave of the pandemic only 4 providers in the state were capable of doing the appropriate testing all of which provided reports to either Milwaukee or the WI Division of Public Health. Case monitoring (beyond the initial detection) was done through phone interviews – the process is now described in the Methods section.

5. Was oseltamivir available during the entire study period?

Response: Antivirals were available throughout the study period. Later on during the outbreak recommendations on who should be treated did change, but that would not have affected the households included in this study (recommendations changed much later).

6. An interesting related article by Morgan et al. on household level transmission of novel influenza in San Antonio, Texas is available ahead of print: [http://cdc.gov/eid/content/16/4/pdfs/09-1658.pdf](http://cdc.gov/eid/content/16/4/pdfs/09-1658.pdf)

Response: The article above is now cited in our paper, and secondary attack rates are found to be similar in both works.

**Level of interest:** An article of importance in its field  
**Quality of written English:** Acceptable  
**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: Oseltamivir for treatment and prevention of pandemic influenza A/H1N1 virus infection in households, Milwaukee, 2009
Version: 1 Date: 16 March 2010
Reviewer: Andrew C Hayward

Reviewer's report:
Oseltamivir for treatment and prevention of pandemic influenza A/H1N1 virus infection in households, Milwaukee, 2009

Is the question posed by the authors well defined?
The question is whether early use of neuraminidase inhibitors within households reduces secondary spread of pandemic h1n1 in households. The question is well defined. There are a number of subsidiary questions that are less well defined.

Are the methods appropriate and well described?
Non randomised – Observational studies of interventions have the clear disadvantage that those treated and those not treated may vary according to characteristics that may affect the outcome. As a result there are a number of important biases that may have influenced the main finding.

Response: The discussion is now expanded to describe those biases and our efforts to address them in more detail.

Data collection - The methods are based on an observational study of data collected during public health investigations of cases and their contacts in Milwaukee. Standardised data collection forms were used to obtain data on cases and secondary cases however there is minimal information on how these questionnaires were administered e.g. the timing or frequency of data collection from households making it difficult to assess the reliability of the data. There appears to be no system for negative reporting of illness events in household contacts i.e. for reporting that individual members did not have symptoms – thus it is difficult to distinguish an apparently asymptomatic case from one who has not completed an illness report.

Response: Case monitoring (beyond the initial detection) was done through phone interviews – the process is now described in the Methods section. Information on all household contacts was present on case report forms, and their symptoms were recorded – thus lack of symptoms should be interpreted as negative reporting. Each individual tested for H1N1 had a case report form describing him/herself, as well as the whole household. Case report forms from different individuals in the same households were corroborated; households with contradictory information were discarded.

Definition of secondary cases - Fever is used in the definition of ILLI but there is no information on how this is defined – was it self reported subjective feeling of
feverishness or self reported raised temperature based on participant measurement of this with a thermometer? This is important as it substantially affects the sensitivity and specificity of case definitions. The authors refer to these secondary cases as “infections” which is misleading as there may be many asymptomatic infections.

Response: Fever in cases possessing a case report form had a temperature reading in almost all cases. Fever in symptomatic cases frequently had no temperature reading next to it.

Analysis - Two analyses are used one using the household as the unit of analysis (i.e. were there any secondary cases in the household?) and one using individual household members as the unit of analysis. In the latter they have appropriately adjusted for the clustering effect of household. The rationale for having both household and individual level analyses is unclear and the household level analysis adds nothing to the findings except that secondary cases are more likely to occur in large households. As this is simply a reflection of the fact that there are more people to become infected in a large household than a small one it does not imply that transmission risk is higher in large households. I would advise dropping the household level analysis as it adds nothing.

Response: This point is addressed below, following the “Justify or drop the household level analysis” suggestion.

The use of multiple imputation to augment missing age data is not described in the methods section only in the results table.

Response: This is now mentioned in the Methods section.

Are the data sound?
Data completeness - Of the 362 households only 135 had sufficient data to be included in the primary analysis. It is unclear how this may bias results as the factors leading to incomplete data are not clear.

Response: There is a paragraph on inclusion criteria related to data completeness in the discussion.

Estimate of secondary attack rate – the overall secondary attack rate of 13.4% may be an overestimate if (as seems likely) households with secondary cases are more likely to be ascertained and included in the study than households with no secondary cases. This in turn leads to an overestimation of the potential value of oseltamivir treatment.

Response: Our secondary attack rate of 13.4% is very similar to secondary acute respiratory illness rates in [Cauchemez2009] and [Morgan2010] – both stand at
Estimates of effectiveness of oseltamivir - Selection bias may lead to overascertainment of households with secondary cases. This may lead to an artificially high number of secondary events in contacts of those who have never been treated (as treatment and ascertainment of cases for the study are linked) and, if the secondary case is a trigger for considering oseltamivir treatment, an artificially high secondary attack rate in contacts of those who are treated late. This could explain the lower attack rates in contacts of those who were never treated and the main finding that transmission rates are lower if index cases are treated early rather than late.

Response: We agree that selection bias may potentially be the main source of bias in the paper. As indicated in the paper, only households where the first symptomatic individual had a case report form (which in particular implies that the first case was tested for H1N1) were included in the study. While this might not have taken care of all the selection bias, this bias is strongly correlated with larger household sizes as noted by the reviewer. Since household size was included in the multivariate analysis on the household level and was found to be positively associated with having at least one secondary case (see Table 2), this should reduce, if not fully eliminate, the extent of the remaining bias.

Statistical power – The main finding that early oseltamivir treatment reduces the risk of secondary transmission compared to late treatment is far from reaching statistical significance. Given the low secondary attack rate the study is underpowered to address this question. Although the finding that early treatment reduces transmission compared to late treatment is biologically plausible both bias and lack of statistical power mean it is not possible to draw robust conclusions on this question from this study.

Response: We indicate in the Abstract that: “Larger randomized trials are needed to confirm this finding statistically.”

Does the manuscript adhere to the relevant standards for reporting and data deposition?
Yes

Are the discussion and conclusions well balanced and adequately supported by the data?
The discussion is up front about the potential biases and lack of statistical power but perhaps does not make it sufficiently clear that the main finding that early treatment is associated with lower transmission than late treatment could very easily be due to bias rather than simply lack of statistical power. The conclusion is appropriately guarded specifying that early oseltamivir treatment “may” reduce transmission and acknowledging that larger studies are needed. It would be
helpful to also point to the need for randomised trials in the conclusion.

Response: The first point is now addressed in the Discussion; the need for randomized trials is mentioned in the Conclusion.

Are limitations of the work clearly stated?
Yes. The authors in particular point to the difficulty of conducting research in a pandemic situation which necessarily has an impact on study quality.

Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
Yes

Do the title and abstract accurately convey what has been found?
Yes

Is the writing acceptable?
Style - on a number of occasions material that is more relevant to the discussion is presented in methods or results.

Major Compulsory Revisions – None
Minor Essential Revisions
Introduction -
None
Methods Section
Include greater detail on the timing and frequency of contacts with households for data collection.

Response: Case monitoring is now described in the Methods section.

Specify whether fever was based on thermometer readings or subjective feeling of fever.

Response: It is now stated in the Methods section:
“Fever in cases possessing a case report form had a temperature reading in the majority of cases; fever in symptomatic cases frequently had no temperature reading next to it.”

Include the use of multiple imputation to augment age data in the methods section.

Response: This is now mentioned in the Methods section.

Justify or drop the household level analysis.
Response: The household analysis addresses the probability of at least one secondary case in a household; individual analysis addresses the individual risk of being a secondary case. We believe that those are different issues which merit different analyses. We have spelled out some of the differences in the Discussion. It was also reassuring that the effect of early Oseltamivir usage by the index case was very similar in both analyses. Finally inclusion of the household level analysis was useful in addressing the potential selection bias mentioned by the reviewer – see the response above on that point.

Results section
Move material that could be considered as discussion out of the methods section into the discussion section.
Discussion section
Make it clear that the secondary attack rate estimate may be biased by overascertainment of households with secondary cases.
Make it clearer that the main finding could be due to bias as well as low statistical power.

Response: It is now stated in the first sentence of the Discussion: “Early oseltamivir use was associated with approximately a 42% reduction in the odds of at least one secondary case in the household, though this finding was not statistically significant and could be impacted somewhat by biases.”
Description of biases and our attempts at addressing them is now expanded in the Discussion.

Remove or downplay the finding that secondary cases were more likely in larger households as this gives a spurious impression that the risk of transmission is affected by household size.

Response: The following is added to the Discussion:
“No association between individual risk of a symptomatic secondary infection and household size was found.”

Conclusions
Make it clear that that randomised studies would be the ideal design to address the question.

Response: This is now mentioned in the Conclusion.

Discretionary Revisions - None

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests: I declare that I have no competing interests'