Reviewer's report

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

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Reviewer: Andrew C Hayward

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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.

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.

Definition of secondary cases - Fever is used in the definition of ILI 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.

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.

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

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.

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.

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.

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.

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.

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.
Specify whether fever was based on thermometer readings or subjective feeling
of fever.
Include the use of multiple imputation to augment age data in the methods
section.
Justify or drop the household level analysis.

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. 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.

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

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