Author's response to reviews

Title: Combination Strategies for Pandemic Influenza Response - a Systematic Review of Mathematical Modeling Studies

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Version: 2 Date: 17 October 2009

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

We thank the editors and reviewers for their comprehensive review and invaluable comments on our manuscript. We have revised the manuscript, and have included a point-by-point response to the comments as listed below, with changes underlined in the manuscript.

Reviewer: Antoine Flahault

This is a useful and comprehensive review of papers published in the field of mathematical modelling with regards with mitigation and containment measures against pandemic influenza. This work is well done with regards with methods and well written too. It is obvious that most of material was dedicated to address H5N1 avian flu when H1N1 swine-origin influenza virus (SOI-V) may have different features. There are few additional papers now published which were more focussed on H1N1, with assumptions on parameters more suited to the current strain which could have been listed, although it is always difficult to know to what extent to update such a scientific work. Probably time window could have been extended beyond April 2009, since the work to perform behind seems not too important, and this additional information could be of added value.

We thank the reviewer for the comments, and wish to point out that although most of the studies were performed when the H5N1 avian influenza was of international concern, all of these studies focused on modeling generic influenza pandemics with parameters similar to the 1957, 1968, and in some instances 1918 pandemic. None of the papers used parameters (including Ro, incubation period, infectious period, generation time, case-fatality rates etc) for the H5N1 influenza, because they recognize that it is difficult if not impossible to extrapolate the H5N1 experience of a few hundred isolated cases / clusters of zoonotic infections (for example case fatality rates of >50%) to a pandemic with efficient transmission among humans. To this extent, these existing studies provide a good reflection of the effectiveness of pandemic response measures during pandemics similar to the 1957, 1968, and also the current 2009 pandemic.

We do acknowledge that the Ro for the current pandemic ranges from 1.2 to 1.6 (Fraser 2009) which is similar to estimates of the 1957 and 1968 pandemics (Ferguson 2006). Most of these studies examine the effectiveness of these measures under a range of Ro which includes this range. The reason that higher Ro values of 1.7 and above are mentioned is that the synergistic effectiveness of combination strategies becomes more apparent with increased transmissibility. At very low Ro, stochastic variation may result in the epidemic spontaneously dying off even if no interventions are performed. However, even in such scenarios, response measures will increase the chance of die-offs and reduce morbidity.

We have extended the search to September 2009, and although there are many modeling papers (22 in total) and no papers meet the inclusion criteria (most are methodological papers predicting the Ro of the current pandemic or focusing on individual interventions such as pandemic vaccination in the fall/winter). We believe that this is due to the fact that the existing literature is already comprehensive, and that the current pandemic is
important for real-time data collection to validate existing models, and not to build additional models based on past data.

We have summarized our discussion here in the paper in paragraph 1 of the discussion section on page 15 for greater clarity.

Minor Essential Revisions: For practical purpose, it is essential authors provide more details on length of school closure and work closure when available in papers they reviewed. Unless, it cannot be used for updating preparedness plan as they suggest. They also have to define what they are quoting "social distancing", particularly when they list this item along with others such as school closure, quarantine, work closure which are (for me) included in social distancing.

We thank the reviewer for the important comments and have included details on the length of school and work closures where available. We have also created a box to define the key variables including Ro for greater clarity.

It is important to note that the individual items are not modeled, but the models ascribe a certain effectiveness of these measures in reducing transmission, which is then placed as a variable in the model.

Discretionary Revisions: As I mentioned above, authors could include the few published papers since April, 2009 in this field. They could dedicate a special section discussing difference reported on values of parameters as chosen by authors between H5N1 and H1N1 SOI-V, particularly on R0.

We have done the additional searches are mentioned above. The papers published since April 2009 have already been included in the study. We have discussed the difference in Ro between the 2009 H1N1 pandemic and previous pandemics. However, we have omitted mention of the Ro of H5N1 because none of the studies used such a parameter which is hitherto non-existent.

Authors could emphasise more than they did the fact that they present intervention measures assessed only on the basis of theoretical epidemiology (i.e. mathematical models) and not from clinical evidence. Concerns are raised by many experts in the world, regarding use of universal vaccine strategy, or large use of antivirals, due to the lack of clinical experience or safety concerns. For example, apart from Japan in the 80s, there is no evidence regarding effectiveness and safety of mass use of influenza vaccine in young adults or children. Resistance against Tamiflu in case of large use is also addressed currently as a cause of concern and as a reason for its limitation in use.

This is an important point and we have emphasized this in the paper.

**Which journal?:** Not appropriate for BMC Medicine: an article whose findings are important to those with closely related interests and more suited to BMC Public Health

We acknowledge that while our findings are important for policy makers and healthcare professionals, it may be of greater relevance to those with interests in influenza and
related respiratory disease threats. As this is of core public health importance in the current climate, we hope that a wider audience would be exposed to the usefulness of mathematical models which are starting to proliferate across all diseases. We are happy for the paper to be published in BMC Medicine or BMC Public Health based on the editors’ experience and opinion.
Reviewer: carl heneghan

Reviewer's report:

Title:
It is unclear form the title that this is a systematic review and that it restricted to modelling studies alone

We agree with the reviewer and have revised the title accordingly.

Abstract
The abstract should be written to focus the specific question the review addresses and outline those strategies that are effective and no make statements like several an such as. These are not scientific statements

We have revised the abstract to focus on the effective strategies and removed ambiguous statements.

Intro
Consider changing promulgated to made public – keeps the English simple and easy to understand

We agree and have made the English across the paper as simple as possible.

Line 8 paragraph refer o these strategies without defining what these strategies Are

We have listed the strategies in the introduction.

The aim of this paper should be more explicit at the end of the introduction
Issues should include: what are the components of a combination strategy and the quantitative impact in terms of what outcome

We agree and have included the suggestion.

METHODS
The search strategy is limited by the search of only one database – this means the likelihood of missing papers is high why is this

We disagree with the reviewer on the point that the likelihood of missing papers is high. Our opinion is that Pubmed contains sufficient articles and search engines, and almost all important healthcare modeling papers (even those from snowball searches) are represented in the database. Such searches of Pubmed databases have been used in previous reviews in this journal (Lee 2009)

In addition, we have performed extensive snowball searches of the referenced papers which have only identified one additional paper which was in Pubmed database but due to the title and content of the paper, was not identified by the search. As the number of modeling papers is relatively small, it is evident from our search and also from prior experience that authors tend to cite similar papers of interest and there is substantial overlap and coverage.

Results
The paper would be enhanced with a good comprehensive description of what
each of the interventions is. This would be useful in a BOX ie social distancing comprises ...........................................

We agree with the reviewer and have created a box to include the interventions mentioned in the review. At the same time, we have indicated in the tables exactly what each study refers to because the basket of items under social distancing differs.

The concept of Ro should be outlined in the methods

We are aware that some readers may not be familiar with the concept of Ro and have outlined this in the methods.

The results should consistently refer to the influenza strain studied

As mentioned above, modeling studies so not refer to specific influenza strains or pandemics, but rather adopt the general parameters that are reasonable for pandemic influenza. Many of these parameters such as Ro, incubation and infectious periods are estimated from epidemiological and clinical studies and there is no data on specific strains. What the models represent is a set of assumptions based on existing data to predict what may occur in hypothetical situations with hopefully some realism. As such, we have mentioned the Ro (the most commonly used modeling term to represent the transmissibility of the virus) instead of the strain which is not meaningful for future predictions.

Do the modelling studies present confidence intervals and p values without these, results are of no value, if they don’t you should state this explicitly in the methods

Confidence intervals or ranges are presented in some modeling studies on the impact of the strategy itself (for example on the attack rates and days to the pandemic’s peak). We have summarized these values in Tables 1 and 2 where directly available. However, most of the comparisons are the imputed effectiveness between strategies and confidence intervals are not provided or available in these studies.

The p-value or significance of an intervention is applicable to case-control or cohort studies in estimating outcomes from real data. As the scenarios generated by mathematical models are hypothetical (the data is used only to fit the model but there is no real data on the outcomes to compare with), tests of significance are not applicable.

To make more of this paper I would consider re organizing it by influenza type
For H5N1 the following factors significantly decreased transmission......................
For H1N1...........
For seasonal influenza.............etc

As mentioned above, the models do not refer to a strain of influenza and are not meant to be an extrapolation of clinical studies. None of the papers use H5N1 specific parameters when modeling human pandemic influenza. As such, there is no data from the studies or basis to organize it by influenza type or strain.
Also consider organizing the results into high and low Ro results which may help the reader to understand the impact
I.e. At high Ro rates the following components were effective..................

The Ro provides a reflection if the transmissibility of the virus and the models use different Ro values as their assumptions. Each model explores different strategies and all of these are relevant across all Ro. It is only the relative impact that changes with Ro and we have presented the relative impact where available.

It is however not possible or meaningful to say that at high or low Ro, some components are more effective than others if the comparisons do not indicate so. In addition, each model also uses different assumptions and input parameters, and as mentioned in the discussion, we caution against trying to compare different models in the same way one would compare randomized-control trials through a meta-analaysis. We have instead represented the Ro used in the various studies in a separate column in Tables 1 and 2 for readers to compare.

Discussion
There needs to be a comprehensive discussion around the limitations of modelling approaches of the review and the findings

We have added a limitations section in page 19, with the main limitation being that models are only a suggestion of what may happen. There are many unknowns which can only be confirmed through clinical or epidemiological studies. That is also one of the findings from this study which is the importance of performing clinical or epidemiological studies in-situ to validate the models.

Also the modelling studies need to be discuses in the light of other study type e.g. antivirals are pretty useless at preventing transmission in RCT studies.

We have included this in the limitations.

Editors comments

Which combinations of interventions are more effective than others?
Under what conditions?

We are attempted to show the combinations of interventions that are more effective compared to others within the same study. As modeling studies are unique with different assumptions and conditions, it is not possible to compare the findings between studies to determine relative effectiveness. We have made the paper clearer where comparisons between combinations are mentioned.

What can results from these modeling studies tell policy makers that they dont already know?

We agree with the editor, and have included further discussion on this issue. Most policies on pandemic influenza are designed based on limited scientific evidence and
mostly on “expert opinion” or “best practices”. Modeling studies provide suggestions on the effectiveness of these policies given the impossibility in performing observational trials during a pandemic.

Given the global interest and discussion on influenza and the lack of evidence on the effectiveness of strategies against influenza, our paper presents an important modeling aspect to assist healthcare workers, public health professionals, and decision makers on the importance of combination strategies against influenza. We hope that you will consider our paper for publication, and look forward to hearing from you soon.

Regards,
Vernon Lee
On behalf of the authors

References:

