Author's response to reviews

Title: Modeling the impact of air, sea, and land travel restrictions supplemented by other interventions on the emergence of a new influenza pandemic virus

Authors:

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

Thank you for your response and the comments on the manuscript from the reviewers, Dr. Deirdre Hollingsworth and Dr. Gianpaolo Scalia Tomba. We have revised the work and are providing a list of changes in response to the comments. According to the comments from Dr. Gianpaolo Scalia Tomba, we agree that the purpose of the manuscript needed better clarification. Thus we have rewritten the entire manuscript including the abstract. In addition, the manuscript was sent to an English editing company recommended by BioMed Central. Since there are many multiple changes in the manuscript after editing, I am sorry the track changes do not follow the precise format from the previous version. However, we hope the revised version is much more readable and will be reconsidered further by BMC Infectious Disease. In the following section, we address the reviewers’ comments point-by-point.

A. Response to the comments of Dr. Deirdre Hollingsworth:

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<tr>
<th>Comment number</th>
<th>Comments and Responses</th>
<th>Track changes / notes</th>
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<tbody>
<tr>
<td>1</td>
<td>This study is carefully performed and written. However, it was not clear to me how the R0s for other countries were estimated (In table 2 of the SI it says they are estimated).</td>
<td>A.1 in Additional File 1</td>
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<td>The R0 for other countries were estimated by the initial growth rate method and is described in page 5 of Additional file 1. We used a linear regression to fit the log(cumulative cases by time). The slope of the growth used to calculate the corresponding R0 was adopted using the equation from Chowell et al., 2004. We used 2 months of daily surveillance data by countries from ECDC for the estimation.</td>
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2. There is also no presentation of data from the Hong Kong epidemic against which to validate the model.

   The Hong Kong H1N1 epidemic data and the median simulated curve from the best-fit model are showed in Additional file 1 Figure 2.

3. The first paragraph seems to be out of date – it refers to a ‘recent’ clinical update from 2010 (reference 1), and an update in Hong Kong from week 29 of the pandemic (reference 2).

   The second paragraph has been re-written to include updated background information.

4. Tables 1, 2 and 3 are difficult to read, and perhaps this information might be better presented as figures.

   As we think Table 1 is not difficult to read, we would like to keep it. However, we agree that Tables 2 and 3 were difficult to read, so we changed them to Figure 5 and 6. Please let us know if presentation is still not clear enough.

5. Are limitations of the work clearly stated? Could do with a little more detail here.

   We revised the limitations section (last paragraph of Discussion section).

6. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? There could be more summary of previous general insights in the introduction.

   Yes, we acknowledged all work in the manuscript. We also thoroughly discussed more previous general insights from other reference in the introduction and the discussion section.

B. Response to the comments of Dr. Gianpaolo Scalia Tomba:

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<td>1</td>
<td>One unclear point about the paper is the purpose of the modeling...</td>
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<td>- If it is mainly about the qualitative effects of travel restrictions, there are too many details and this referee would suggest that the main conclusion, viz. delay in introduction can be obtained, but not much more, is already known;</td>
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- if the purpose is to show that antivirals and hospitalization (removal) can decrease the spread and and/or the peak incidence, then this referee would suggest that this is also known;

- if the purpose is indicating what would have happened in Hong Kong with the A(H1N1) spread in 2009/10 had certain measures been adopted, or how similar future outbreaks could be handled, then the question turns more towards degree of realism of the model, the parameters and the proposed measures…

…

In conclusion, this referee does not find the paper presentable in its present state. In order to become so, the authors must decide on purpose of the paper, discuss the adequacy of assumptions in the light of the stated purpose and finally present results in a clear fashion, once again focusing on relevance for the stated purpose. Only then will it be possible to fairly judge the relevance of the paper to the disease spread modeling community and to health officials interested in countermeasure planning.

We agree to your point that the modeling purpose of the paper could have been clearer. Our topic was changed to ‘Modeling the impact of air, sea, and land travel restrictions supplemented by other interventions on the emergence of a new influenza pandemic virus’. We further sharpened our purpose to evaluate the government strategies dealing with future pandemics by making use of the emergence of 2009 influenza pandemic virus as an example. Strategies comprise: 1) travel restrictions and 2) the use of antivirals and hospitalizations. Vaccination was not evaluated in the study as it took a much longer time to make impact after the virus emerged.

The paragraphs of abstract, background, result, and discussion were rewritten based on our refined ideas. We hope the revisions made the purpose of modeling clearer.

2

… the flow of travellers to Hong Kong must be composed of locals returning from somewhere and non-locals visiting HK. How can 90% or 99% "import restrictions" be practically implemented, in particular towards locals returning home? The returning locals are interesting also because their contact pattern and thus potential of spread should be more extensive than for visitors, although no data, as far as this referee knows, is available on the pattern of contact of visitors to a country…

In the manuscript, the model did not account for the risks of local residents returning from elsewhere. I agree that it is a very interesting
question, but we were not able to quantify the risk of infections for the local Hong Kong travelers because of limited data; moreover, we did not have proper understanding on the pattern of their contacts. Thus it is difficult to address how 90% or 99% would be practically implemented at this stage of research without further data.

Also, although outbound passengers may become infected during their time abroad, they have nonetheless escaped from local infections. Our estimated R0 of Hong Kong was 1.4 and it was closed to the median of R0s among other countries (Additional File 1, Table 2). The similar disease transmission intensity would unlikely lead to a big difference of risk of infections between those with outbound travelling and those staying locally, provided that the periods of H1N1pdm of different countries were not far apart from each other.

The limitation in the last paragraph has been revised.

3 …what would one do with screened positive individuals at the border?

Thank you for raising a very good question. During the pandemic, the screened positive individuals at entry border points would be taken to hospital for further examination in Hong Kong. Confirmed cases would be advised for voluntary quarantine. In the manuscript, we assumed all screened positive individuals would be willing to undergo voluntary quarantine. The probability of disease transmission would likely be zero and the current results would not be affected.

However, in reality, we believe some screened individuals would refuse to the voluntary quarantine. Some would choose other more friendly measures such as wearing surgical mask, and others would not comply with any advice. These situations would lower the sensitivity for screening symptomatic cases for quarantine. As different levels of screening sensitivity have been tested, we believed the model in the manuscript justified this issue. We also added this point in the discussion section.

4 … if there are uncertainties about several parameters, then the most reasonable choice is the vary them all together according to some experimental plan and to collect results (requires choosing some endpoints and, in the case of this stochastic model, maybe some summary statistics...) and then present results as ranges or clouds... This would be better than varying them one at the time, since choices of values may interact in various ways...

We agree with your comment. A multivariate sensitivity analysis section
that varied several parameters together was performed.

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<th>…from a modeling point of view, why use a chain-binomial formulation instead of a continuous one (by the way, this referee found no information about the choice of \Delta t; one could assume that it is 1 day, but then the discrete formulation, compared to the short time scale of E and I periods, might not be very appropriate...).</th>
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| 6 | This referee found it quite difficult to interpret the results given in the Results section of the paper, probably because of the many combinations of parameter values and interventions (see previous point about presentation of results...).

Main points to be answered would be:
- Is the inclusion in the model of different external countries and various modes of entering the country useful? Does it make a difference, compared to a simpler modeling of incoming travelers?

We revised the manuscript and summarized the results again to clarify our interpretation of results. Compared to the simpler models of incoming travelers, we now give more details on the impact of travel | B.5 in Additional File 1 |
restrictions. Some main points drawn:

1. If travel restrictions were to be imposed, the route that is best connected to the source areas--such as the air travel from the Americas/Mexico to Hong Kong--is the most effective route for epidemic delay of the infectious disease at the early stage. This is in addition to suspending travels from large, high-density cities [Hufnagel, et al. 2004].

2. Once the pandemic has spread to other countries for a period of time, the strong land connection to China would have an impact on import transmissions. Due to this, reduction of land travel simultaneous to air travel restrictions would greatly defer the epidemic.

3. Compared with other studies that only studied air travel [Cooper, et al. 2006; Ferguson, et al. 2005], the results in our study were more apparent. We found that if a rigorous restriction on all transport modes is combined with the uses of antivirals and hospitalization, the delays (peak appearing after the 10th month) are possible to allow vaccine production (i.e. beyond the minimum nine months following the first global import to Hong Kong).

We address these points in the updated discussion section.

Ref:

7 …Since I presume that 99% limitation of incoming passengers is unrealistic, do lower levels make any difference?

We varied the level of travel restrictions (90% and 99%) based on some previous findings [Tomba, et al. 2008; Hollingsworth, et al. 2006; Epstein 2007]. According to their results, travel restrictions less than or equal to 90% showed little impact on epidemic delay. In our study, even though 90% restrictions of all means of transports could defer peak times for several weeks, only rigorous 99% restrictions were able to defer the peak for a long period of time--vaccine production required. Therefore, we assert that lower levels of restrictions (<90%) may well have an impact but not great enough for preparations for future influenza pandemics.
We admitted that a stringent policy for travels reduction (i.e. 99% limitation of incoming passengers) have been undoubtedly unrealistic to date. However, more severe diseases such as SARS and influenza A (H1N1) successively emerged in the society in recent years, affecting a wider range of age groups more severely compared to epidemics in the past. It is highly probable that a more lethal virus may emerge in the near future that will require stricter policies. Thus our study offers officials a better understanding of how to possible impacts of imposing future strategy towards emerging and infectious disease (i.e. travel restrictions in addition to other effective control measures).

Nevertheless, in which specific scenarios we can obtain a benefit from the interventions is not as straightforward to predict, as factoring such factors as economical impacts would be significant. We will not discuss at length this issue in our manuscript, as it is beyond the boundary of our research purpose, but in further research we will try to perform more comprehensive cost benefit analysis. We added this point in the last paragraph of Discussion section.

Ref:

8 Antivirals and hospitalization are applied to a rather small percentage of infecteds, but the effect on final AR is quite large... How comes?

We applied the use of antivirals and hospitalization to 18% infected subjects in total. In the model settings, we assumed the antiviral would reduce 60% infectiousness for the individuals and both interventions would reduce the average infectious period by 1.5 days. The probabilities of disease transmission from those individuals were thus reduced. In comparison to a previous study [Halder, et al. 2010] with similar model setting, the effect of antivirals and hospitalization to final AR in our study may be quite large (6.5% vs 21%). The main reason is that our model did not assume any disease transmission from asymptomatic individuals. Halder, et al. assumed a 50% antivirals’ coverage of symptomatic cases, but there was not any coverage on asymptomatic...
individuals. The percentage of the infected receiving antivirals would not be as large as in our study.

On the other hand, our assumed length of infectious period was comparatively short (2.9 days vs 3.75 days by calculation). So when antivirals and hospitalization were imposed on the infectious subjects through our model, there were fewer disease transmissions than that of Halder, et al. The antivirals and hospitalization consequently showed a larger AR reduction in our study even for a small percentage of infected.

We assessed the effect of these treatments by varying the length of infectious period reductions and fraction of infectiousness reduction in the multivariate sensitivity analysis section. The results showed they would provide moderate deviation on the daily incidence but would not substantially affect our main findings.

Ref:
Nilimesh Halder, Joel K Kelso and George J Milne. Analysis of the effectiveness of interventions used during the 2009 A/H1N1 influenza pandemic. *BMC Public Health* 2010, 10:168

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<th>Finally, in the rest of the world, the reason for wanting to delay spread was that vaccines were slow in arriving and being deployed... Why are there no vaccines in this scenario?</th>
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<td>For a new influenza pandemic (for example, a likely one may be Avian H5N1 influenza), we can forecast that scientist and officials could potentially spend more than half a year developing and adequately procuring vaccination into practice—which is an estimate based on previous pandemic experience [Stohr, et al. 2010]. In accordance with the Hong Kong SAR Government [Hong Kong Information Services Department, 2009], they implemented the H1N1 vaccination programme about nine months after the first global onset case, during which the peak time of H1N1pdm passed. Public health officials thus require other strategies to protect people during the first few months of a pandemic. These could include travel restrictions, the use of antiviral drugs, and hospitalizations. This was the main reasoning we did not include impact of vaccinations in the study.</td>
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B.9 in manuscript
Based on our revised manuscript in response to reviewer comments, we hope very much that you will find this manuscript acceptable for publication in *BMC Infectious Disease*. Thank you for your time and further consideration.

Yours sincerely,

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