Author’s response to reviews

Title: Vaccination against 2009 pandemic H1N1 in a population dynamical model of Vancouver, Canada: timing is everything

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Dear BMC Public Health Editors,

Thank you for considering our manuscript. We found the reviews to very insightful and were very happy to improve our paper according to their recommendations. Please find below our responses to individual comments and, where relevant, details on the corresponding changes to the manuscript. The responses are in line, with reviewer comments in italics and our reply in plain text.

Of the many changes and adjustments along recommended lines, the most significant are an expanded introduction and discussion, intended to better situate our contribution to the field; a new 'Initial Conditions' section, to improve the clarity of the content; and simulations for a new vaccination targeting scenario, at the suggestion of the third reviewer. These simulations complement existing simulations by allowing for a general vaccine distribution once immunization of a targeted group (in our case, schoolchildren and their parents, the PC strategy) are complete - a practical option for public health decision-makers in the course of an epidemic. Thus, we have a version of the PC strategy with equivalent population coverage to other scenarios discussed in the manuscript.

Please note that we uploaded a version of the manuscript with “tracked changes” in the 'Additional Materials File' section to make it easier for the Editors to review the revised document."

We thank the Referees for their thoughtful reviews, and feel that the changes we have made accordingly improved our manuscript. We hope that you and the Referees will find our response and edits more than satisfactory. Please do not hesitate to contact the corresponding author if there are any problems with the re-submission. We look forward to hearing from you.

Best regards,
Major compulsory revisions

First, it would be helpful to add a paragraph (in the introduction or discussion) that explains how these results were used in the decisions on vaccination in 2009. Were the strategies as presented here the only real policy options? Were the strategies proposed by the decision makers or by the authors? Which vaccination strategy was chosen for Vancouver?

The results and predictions made by this model were certainly shared, as well with many other analyses, with BC public health decision makers to help them in their decision process back in 2009. Although we recognize the interest of the reviewer in knowing how these and other analyses were used by the BC authorities to help them determine the actual vaccination strategy implemented in BC, we are afraid that we may not be able to share many details of these decision-making procedures in an academic manuscript. As a knowledge translation activity, we are planning to work with policymakers involved in these procedures to draft a separate, policy-oriented manuscript in the future.

However to give the reader some idea of how this model was used, we added the following sentence at the end of the introduction: "This model was used to assist policymakers in evaluating different intervention strategies throughout the Fall (2009) including the impact of vaccination of schoolchildren in addition to the specified target groups, social distancing, as well as assessing the likelihood of observing a third wave in the winter of 2010".

Regarding the vaccination strategy for Vancouver (and BC), as mentioned in the manuscript, here we implemented the actual vaccination coverages observed in BC during the fall of 2009 and compare its efficacy with other alternative strategies. These and many other alternatives were certainly entertained as options by the BC and other Public Health authorities.

Second, it would be essential to add a paragraph to explain how the results relate to other similar results that have already been published. Now the manuscript briefly mentions other work ("the results support the growing modeling literature claiming that the choice of vaccination strategy can have a substantive input on final attack rate.") but it does not mention, cite or discuss any article other than Medlock & Galvani (Science 2009). I would have expected to see references to e.g. Dushoff et al (PlosMed 2007), Wallinga et al (PNAS 2010), Keeling & White (Interface 2010) as these articles might help to explain the outcome that is reported here. The article that is the closest in methods and in results is, as far as I can see, Mylius et al (Vaccine 2008), and the article that opened up this field is Longini (Math Biosci 1978). The point is not to cite all these articles but to specify how this manuscript contributes to the existing literature.

Thank you for the suggestion. Both the introduction and the discussion have been expanded to address this comment.

Third, it would be good to expand the comparison of the model results with observations. Now there is only a check for a qualitative match of the observed age distribution (of reported cases?) and the simulated age distribution (of infecteds?) which provides a check on the right
Figure S8 in the appendix shows the time profile of confirmed cases in BC by age. Our model on the other side predicts the number of actual infections by age (whose time profile for selected parameter values is given in figure 2). Since there is no reliable way to extrapolate from laboratory confirmed cases to actual infection cases, we decided not to make explicit comparisons between the model’s time profile and the observed epidemic. However, as the above mentioned figures show, the observed peak of laboratory confirmed cases and the model's predicted peak of infected cases are quite consistent. The same could be said for the observed and predicted epidemic durations.

Regarding the long natural history of infection assumed (8-12 days), this is what was observed in Canada and elsewhere with long periods of viral shedding after symptoms onset (see Tuite et al, CMAJ 2010 or De Serres et al, EID 2010). We did not explicitly compute our model’s mean generation interval, nevertheless, given the time profile of the epidemic for an R0 of 1.4 (shown in figure 2), which lasts about 60-80 days, it appears to be consistent with the gi values found in the literature.

**Minor essential revisions**

**Background**

*Page 4.* In most regions on this planet there was no “first spring-summer wave”. Please indicate right away that this article focuses on Vancouver in Canada, otherwise the text doesn’t make much sense.

The second sentence now reads “In the Canadian province of British Columbia, Canada it first appeared as a spring-summer wave of low intensity, but resurged as a more substantial and widespread second wave in the fall, as in the rest of Canada and many other countries worldwide [2,3].”

*Page 5.* What is the case definition? Without a case definition it is not clear what is meant by the per-case hospitalization and case fatality rates remain.

The sentence now reads “…but both the per-laboratory confirmed case hospitalization and fatality rates were greatest in older adults, with substantial increase beginning at age 50.”
Methods

Page 5. Please provide the initial conditions for the model on September 1 2009.

We have added a section in the Methods describing the initial conditions. There are also details on these initial conditions given in the text supplement.

Page 6. The latency period of 3 days and infectious period of 7 days suggest a generation interval of 10 days. This differs substantially from most published observations. Please discuss the implications of this assumption.

The published estimates we used were derived in a study performed by a few co-authors, based on laboratory-confirmed reports on pH1N1 with symptom onset between April and June 2009, in Ontario, Canada.

Page 6. Please indicate whether the vaccine is modeled as a leaky vaccine or as an all-or-nothing vaccine.

The first sentence, second paragraph of the ‘Vaccination implementation’ section of methods now reads “All individuals receiving vaccine were assumed to have a reduction in pH1N1 acquisition risk equal to 90% (modeled as a ‘leaky vaccine’).”

Results

Page 8. In comparing simulation results to observations, please indicate the case definition as used in the observations (reported cases?) and the case definition as used in the model (infecteds?)

In the context of our model predictions, we mean to speak of infections, whereas in the context of the data, we mean to speak laboratory-confirmed pH1N1 cases. Since Figure 1 compares proportions only and not raw numbers, the comparison between these two figures (predictions on total number of infections vs data on a subset) is not unfair. We have changed the second sentence of the results to make this distinction more clear:

“In particular, the model predicted that the highest number of infections in the 18-54 age group, followed by the 5-17, 0-4, and ≥55 age groups (Figure 1d), which is similar to what was observed within laboratory-confirmed reported cases.”

Hopefully this change addresses the reviewer's concern.

Discussion

Page 11. “the growing modeling literature”: please make explicit which articles support the findings as reported here.

The discussion has been expanded to address this concern.

Table 1: mortality per 100,000. Does this mean mortality per 100,00 infections or per 100,000 cases?

It means per 100,00 infections; the table now states that explicitly.
Table 3: final attack rates. Does this refer to infection attack rates or clinical attack rates?

This refers to infection attack rates. The table caption now clarifies that point.
REVIEWER 2 – Prof. Gerardo Chowell

Comments

1. The authors model vaccination strategies during the second pandemic wave, but the dependence of this wave on earlier wave(s) of infection is not clearly discussed or described. In particular, the levels of susceptibility across age groups/activity level groups and consequently the reproduction number will be affected by the intensity of earlier waves (R0) and any social distancing interventions during the earlier pandemic period. For instance, recent results indicate that spring and summer waves in Mexico generated significant morbidity levels with high attack rates were observed in Southeastern states of Mexico in the summer, but the subsequent fall pandemic wave had a relatively mild to moderate impact in this region probably due to significant herd immunity levels acquired during the summer wave. It is also possible that early waves generate significant burden on specific populations (e.g., school age children [11]) which could obviously have important effects on targeted vaccination strategies in later waves of infection.

Thank you for your comment. As mentioned in the introduction, we would like to emphasize that there was no significant pH1N1 epidemic in British Columbia until September of 2009 (only a total of about 812 confirmed cases between April and September 2009).

2. Authors assume R0=1.4. What would be the value of R after taking into account background immunity in the population acquired from earlier pandemic waves?

We assume that the reviewer is referring not to the pre-existing immunity thought to exist in individuals exposed to pre-1957 influenza strains, but rather to the 2009 spring-summer wave experienced in many countries including Canada? Some areas, for example England, experienced sizable pH1N1 activity in June and July 2009; as a result the value of R during the Fall wave would certainly be expected to be different. However things were not the same in British Columbia. As stated in the discussion and in the new 'Initial Conditions' section, we assumed that the number of infections in this wave in BC was negligible small compared to the Fall wave. This assumption was supported by both the number of lab-confirmed cases and reported physicians visits. Thus with our assumption that this effect is so small as to be neglected, the value of R is not relevant here.

3. Authors model a vaccination period of 8 weeks and vary this length in a sensitivity analysis. It seems that constant vaccination rates per day were used, but it was not mentioned in the main text.

The supplementary appendix discusses in detail the baseline vaccination rates (decreasing in time) and a sensitivity analysis around this assumption. We point to this more clearly now in the main text. The second sentence of the “Vaccination implementation” section has been changed to:

“Vaccine distribution spanned this roll-out period and resulted in final coverage levels in different age groups (described below). For results shown below, we assumed the daily number of vaccinations gradually decreased throughout the campaign. However using different vaccination rates gave quantitatively and qualitatively similar results; see File S1 for details and
additional information.”
We hope this satisfies the reviewer’s concern.

4. It could mention briefly in the discussion the role of Vaccine distribution rates and the behavior change parameter.

As discussed in the supplementary appendix, alternative time-profiles of vaccine distribution lead to similar results as the baseline. The behaviour change parameter does have a quantitative impact (which is unsurprising: large values for this parameter approximate quarantine) but its qualitative impact is lesser. While studying the impact of behaviour change on epidemic size is a very important issue (that merits a detailed analysis as a complete and separate manuscript), we feel that incorporating a sensitivity analysis on this parameter would not contribute any new knowledge, and distract the reader from our main message. That is, for campaigns initiated late in an epidemic, logistic efforts should be geared towards vaccinating as many people as possible rather than towards maintaining strict targeting strategies.

5. The model is validated using H1N1pdm data. It is not clear from the text the source of the data and how these data was collected. This could be described in a Data section.

The data used in this paper came from private communication with Epidemiology Services at the BC CDC (supplied by a number of co-authors).

6. Authors state that the model predicted incidence across age groups and month – how was the model adjusted to data? Was any optimization process implemented to achieve a fit of the model to data?

The model itself was not adjusted to data. Estimation of the R0 value for the BC pH1N1 epidemic using laboratory confirmed cases lead to an estimate of R0=1.4, consistent with estimates in other provinces and countries. Therefore we used R0=1.4 as baseline and then adjusted the model’s transmission rate (beta) in order to produce a model consistent with the R0 value. The behaviour change parameter is the most uncertain parameter, and was chosen to match authors’ intuition only. Sensitivity of results to this parameter is discussed in the supplement.

7. Authors found that timing of start of vaccination campaign plays a major role on the final morbidity and mortality outcomes. This is in line with prior studies (see Chowell et al. Plos One 2009).

We have added a citation to this paper and comments in the introduction and discussion.
Major Revision

1. How the Parent and Child (PC) strategy is formulated is crucial since the more interesting results of the paper emerge from that strategy. However, the rationale for many aspects of the PC strategy is not clear to me. For instance, why would the vaccine not be given to children under 5 years of age, as Table 2 states? Also, since the strategy presumably should not target 30-39-year-olds without children, why does the strategy include the entire 30-39 age class? It seems like it would be easy to estimate what percentage of individuals aged 30-39 in Vancouver/BC/Canada have children and then to only vaccinate that proportion of that age class. The same goes for 20-29 and 40-49 year-olds. A third thing that confused me about the PC strategy is that it does not allow for any other individuals to be vaccinated, even though the vaccine coverage is lower than AC or UC and hence vaccine would presumably still be available once all parents and children received it. This would amount to individuals outside the PC classes actually being refused the vaccine. Many Canadian jurisdictions in the 2009 pandemic practiced sequencing whereby high-priority groups received the vaccine first but the vaccine was later made available to everyone. Hence, a more realistic way to formulate the PC strategy would be to allow other groups to be vaccinated once the target coverage had been reached in PC groups, such that the eventual coverage matches the 47% of the UC and AC strategies. This would be particularly interesting in light of Figure 2 showing that the 5-17 age class was the first to be “hit” by the pandemic. Hence, my major revision to suggest is that the authors should either (1) rethink and reformulate the PC strategy in response to the above comments, and/or (2) keep the PC strategy as is but also add a fourth sequencing strategy (such as 0-17 and 65+ year-olds first and then everyone else). As I mentioned in my opening, I think the paper is a valuable addition to the literature as it currently stands, but clearing up these questions around the PC strategy would make it considerably more useful for evaluating the 2009 pandemic and preparing for future pandemics, and hopefully with all the modelling machinery in place it will not create too much extra work to run these additional vaccine coverage scenarios.

This is an excellent point. We chose the PC strategy to be school-children and adults aged 30 to 39 years since that is the optimal distribution as predicted Medlock & Galvani (2009) which was highly cited and discussed at the time of the pH1N1 epidemic; we therefore hesitate to re-formulate it. However the reviewer's comment about coverage is one we are happy to expand upon. We have included a fourth targeting scenario called “PC+.” That scenario presents a sequence of strategies. First, we use the PC strategy with vaccination rate to match the UC/AC strategies (so the 36% coverage is achieved at the same time, approximately 38 days). At that point we allow for vaccinations to be available to the public, for the remaining duration (18 days or near 2.5 weeks) which we represent by the AC coverages, scaled proportionally down in order to create an overall population coverage of 47%. The timing and coverage were selected for fair comparison with the AC and UC strategies.

Unsurprisingly with its higher coverage, the PC+ strategy improves upon the PC strategy in terms of both attack rate and mortality reductions. Interestingly we also find that, in contrast to the PC strategy, the PC+ strategy offers the best mortality reduction across all campaign initiation times. This is likely due to a combination of the PC coverage being attained sooner and limited protection of the most vulnerable populations, aged 0-4 and 55+.
Minor Revisions:
2. Abstract: the abstract describes the model as a city level contact network model that captures transmission network dynamics. This implies it is a true network model but actually it is a compartmental model that has been parameterized with contact network data (which the authors do make clear elsewhere). Information is lost when using contact network data to parameterize a compartmental model and so it is important to be clear that this is actually a compartmental model, parameterized with contact network data. Wording should be changed to reflect this.

The abstract now states “We adapted a city-level contact network model to study different campaigns on influenza morbidity and mortality.” rather than “We applied a...” We hope that that change, in combination with the Abstract's Methods statement, “We modeled different distribution strategies initiated between July and November 2009 using a compartmental epidemic model that includes age structure and transmission network dynamics.” satisfies the reviewer's concern.

3. Abstract: results are described in terms of morbidity, but morbidity is never defined.

We now implicitly define morbidity as the number of infections, in the introduction.

4. Page 4: “The commencement of this second wave... depending in part upon prior first wave experience, demographic and environmental factors”. Is this speculation/expert opinion or is there a reference the authors could cite supporting the dependence on these three factors?

It is speculation/expert opinion. We have added the word “likely” to make this more clear.

5. Page 7: please be more explicit about what type of sensitivity analysis was conducted. It sounds like a univariate analysis.

It was in fact a multivariate sensitivity analysis. We performed simulations trying every parameter set on a multi-dimensional grid, with equal probability for each parameter set. The section “Sensitivity of results to transmission parameters for pH1N1” now contains the following passage clarifying that point:
“Varying epidemiological parameters changed the cumulative attack rate in the presence of the Actual Coverage strategy in predictable ways. This is clear from Figure 6 (see Figure S7 for results in the absence of vaccination), where we show a sensitivity analysis on the cumulative attack rate for a given R0. To generate the shaded areas, we ran simulations for parameter combinations from the ranges given in Table 1 with each combination given equal weight. We observed in particular that...”

6. Table 1 reports ranges for some parameter values. Please clarify how these are used in the analysis.

The ranges were used in the sensitivity analysis. See previous response.
7. For Vancouver, would there be grounds to include in the sensitivity analysis pre-existing immunity for those younger than 55 years? There may have been some due to previous H1N1 vaccines or the spring wave, naturally.

Thank you for the suggestion. This is related to comment #2 from the second reviewer. As stated in the discussion and in the new “Initial Conditions” section, we assumed that the population was completely susceptible at the start of the epidemic. That is, that the number of infections during the spring wave in BC was negligibly small (a total of about 812 confirmed cases) compared to the Fall wave. This assumption was supported by both the number of lab-confirmed cases and reported physicians visits and hospitalization from the April-Aug 2009 period (BCCDC influenza surveillance report). With regards to previous H1N1 vaccines: it is our understanding that at best only very limited cross-protection was offered by previous seasonal flu vaccines or H1N1 infection. If this were not the case, one would have expected a much less pronounced influenza activity due to the cumulative vaccine coverage rates from previous years (seasonal flu annual coverage rates in BC for the “target groups”, i.e., community-dwelling adults, ≥65 years of age; high-risk adults 12-64 yos; staff of long-term care facilities; staff of acute-care facilities; and residents of long-term care facilities are about 70%, 50%, 65%, 45% and 90%, respectively; source: Immunization in British Columbia 2008 available at: http://www.bccdc.ca/NR/rdonlyres/4F2E7994-8A4A-4F2E-9E3E-FFFB7BAD0B1E/0/2008AnnualReportFINALcolour28OCT2010.pdf). Also, initial studies of the pre-existing immunity in the population against pH1N1 showed that this was negligible for individuals younger than 55. We therefore argue that our results would not be impacted by including negligible pre-existing immunity in adults younger than 55.

8. Discussion: It would be interesting to add a comment on how specific the results may be to the contact patterns in Vancouver. For instance, with a large Asian population, I suppose that intergenerational households are common and thus herd protection effects from a PC strategy would be more significant than for a place like Winnipeg or Halifax for example.

Thank you for the suggestion. We do not have detail international demographic data to compare the population structures; as far as interaction patterns within different Canadian jurisdictions are concerned, our analyses (unpublished) suggest that while different urban demographic structures might impact the initial pattern of spread of a respiratory pathogen during an early stage of an epidemic, this issue is less pronounced when disease transmission become rampant. Detailed analysis of this phenomenon deserves a stand-alone publication and we plan to publish these results in the near future.

9. References: The URL references may not be formatted according to BMC guidelines, which probably requires things like accession dates and document titles.

Thank you for the comment. We will make sure that all the references are in the right format at the time of publication.