Author's response to reviews

Title: Informal social distancing interventions in the case of a severe pandemic to minimize the demand for antiviral treatment from a drug stockpile are not effective.

Authors:

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Version: 2 Date: 8 May 2013

Author's response to reviews: see over
May 8, 2013

Natalie Pafitis, Executive Editor
BMC Public Health
BioMed Central
236 Gray's Inn Road
London WC1X 8HB
United Kingdom

RE: Revision of the research article entitled: “Informal social distancing interventions in the case of a severe pandemic to minimize the demand for antiviral treatment from a drug stockpile are not effective”. MS: 9430164288880312

Dear Dr. Pafitis and Dr. Kwong:

Thank you for the very comprehensive review of my submitted manuscript. I am pleased to submit a revised draft of the manuscript for your consideration.

The reviewers identified several areas for improving the manuscript. Most importantly, we have clarified the objectives of the work and provided a more detailed literature review and description in the introduction and discussion. These modifications allow the work to be considered in the context of existing work and also highlights the major differences between our work and previous models that have been published looking at social distancing measures.

You will find that I have responded to each reviewer comment in the appendix to this letter and I feel that the revision is a much stronger manuscript as a result of the reviewer and editor comments. I look forward to hearing a final decision regarding the acceptance of the revised paper for publication in BMC Public Health.

Sincerely,

Amy Greer, MSc, PhD
Senior Mathematician
Centre for Communicable Diseases and Infection Control
Public Health Agency of Canada
Reviewer's report #1
Title: The Impact of Social Distancing Measures on Antiviral Treatment Demand during a Severe Pandemic
Version: 1 Date: 28 February 2013
Reviewer: Joel Kelso
Reviewer's report:

General Comments
This is a solid modelling paper addressing the question of the magnitude of antiviral drug usage that is likely in an influenza pandemic, given various assumptions about how individuals will curtail their social contact behaviour due to the pandemic. There are a number of (relatively minor) issues I think the author should address; these are listed below.

Major Compulsory Revisions
Comment 1: More explanation is needed on what simulations were done, what combinations of parameter values were simulated, and how these relate to the error bars that appear in Figure. As I understand it, the possible dimensions of variation for the simulation were R0 (three values), pre-existing immunity (3 values), participation in social distancing (3 values), magnitude of behaviour change (3 values), duration of behaviour change (3 values). Of these 5 dimensions, results for full combinations of 4 (all except pre-existing immunity) are given in the Figure (81 data points). Does that mean the error bars relate to pre-existing immunity? Unless I missed it, the error bars are not mentioned anywhere.

Response 1: The reviewer is correct. The error bars represent uncertainty around the pre-existing immunity parameter. The data used to calculate each box plot represents simulations for a single R0 value (as indicated by bar colour) for a range of pre-existing immunity values between 0 and 40% in 5% increments. Therefore, each bar on the box plot represents 9 individual simulation runs. The median (line within the shaded box), 25th and 75th percentile values (top and bottom of shaded box), and upper and lower adjacent values (error bars) proportion of the Canadian population expected to require antiviral treatment (Y-axis). The figure caption has been modified to include this information. In addition, clarification regarding this point has been added to the Methods section of the manuscript.

Minor Essential Revisions
Comment 2: p7 | 156-158: It should be made clear at this point that non-influenza ILLI does not consume antivirals. This is stated in the
conclusion p10-11 l233-235, but on page 7 the statement about "We assume that for ethical reasons, all individuals who present for treatment with respiratory symptoms will be eligible to receive antivirals" may give the impression that non-influenza ILL cases have been taken into account.

Response 2: This is an important point and we have adjusted the text in the Methods section to clarify this.

Comment 3: p1 l9 "Divisionof" -> "Division of"

Response 3: This has been corrected.

Comment 4: Broaden the list of references to other modelling studies that have explicitly considered contact behavioural changes during pandemics. I think it is important to give the reader some context to compare the model of behavioural change used in this paper with other models that have been studied. Some papers are listed at the bottom of this review that may be relevant or contain pointers to relevant research: [Epstein2008,Fenichel2011,Perra2011,Poletti2011].

Response 4: We have added significantly more in depth review of the literature in the introduction of the paper to place our model and its purpose within the context of existing models that consider behavioral changes in the population.

Comment 5: Add the final attack rate (and/or infection rate) corresponding to each of the three (R0) transmissibility scenarios in Table 1.

Response 5: This is an excellent addition that was an oversight on our part. We have added the infection attack rates to Table 1 as calculated in the absence of any public health interventions.

Discretionary Revisions
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Comment 6: Reference could be made to other modelling studies that have estimated antiviral usage for scenarios that combine AV treatment and social distancing interventions e.g. [Ferguson2006 Supporting Info, Halder2010].

Response 6: In response to this comment, we have addressed this point in the introduction of the paper by briefly discussing the existing models that look at social
Comment 7: Can a more specific comment be made on the public health planning consequences of the results? Looking at the overall results, the message that I would take away is that you can’t expect behavioural changes to significantly reduce demand for AVs during a pandemic - unless you can get most people to make major reductions in their contact behaviour, for at least three months.

Response 7: This is an important take-home message and one that perhaps has not been highlighted sufficiently in the manuscript. Additional text to highlight the public health planning implications of the model results has been added to the conclusions section of the manuscript.

Comment 8: If I understand correctly, the main outcome quantity of the model is "cases seeking medical attention". This is taken as a measure of the quantity of antiviral drugs used for treatment; but it is also a measure of any usage of health care resources that stem from (or occurs proportionally to) an instance of "medical attention sought". This is implied in the abstract and conclusion, in which antiviral drugs are mentioned as an instance of "limited health care resources", but it could be made explicit by adding a sentence of two in the discussion. I think it makes sense to present the results mainly in terms of antiviral usage, but the results are a little more general and it would be a shame if that point were missed.

Response 8: This is an excellent suggestion and several sentences have been added to the Discussion section of the manuscript to highlight this point.

Comment 9: Even if for a severe pandemic, it might be the case that "social distancing fatigue" occurs in less than 3 months. Presenting simulation results for, say 4 or 8 weeks (and possibly dropping the 16-week results) would give a more comprehensive picture.

Response 9: Since the reviewer has indicated that this is a discretionary revision we have decided not to add in additional simulation results for shorter durations of social distancing than the existing scenarios in order to return the manuscript revisions within the allotted time given by the editor. We have added a comment related to the potential impact of shorter simulations to the Discussion section.

Comment 10: In the figures, change the "Distancing" column heading to
"Participation" would be clearer. The caption is good, but just looking at the figure, it's a little hard to interpret "Distancing" vs "Reduction in Contacts".

Response 10: This is an excellent suggestion. The heading text has been changed to say "participation".

Comment 11: p4 l79 "may become stretch thin" -> "may become thinly stretched"

Response 11: This has been corrected.

Comment 12: The statement "even the largest stockpile is unlikely to contain enough treatment courses to treat more than 25% of a population" (on page 4 line 82-85) needs further support with references (or, failing that, personal communication from a senior Canadian public health official?).

Response 12: A reference to Annex E of the Canadian Pandemic Influenza Plan for the Healthcare Sector has been added to provide support for this statement.

Comment 13: Method details and model parameters from [9] and the Tuite et al 2010 CMAJ paper could be included in an Additional File. The model is nice and concise, would only take up a few pages, and would make the paper more self-contained.

Response 13: I would be happy to include the documents from Tuite et al. 2009 and Tuite et al. 2010 as a supplementary file if the editors feel that it would be useful.

Comment 14: A comment could be made in the discussion about the importance of reserving a supply of AVs for hospitalized cases and other small, vulnerable groups e.g. pregnant women. AVs used in these circumstances would be much more effective at preventing deaths per-dose, and the results show that if they're not reserved, the general AV supply is likely to be used up. I assume hospitals hold their own reserves, but I don't know the situation for other vulnerable groups.

Response 14: This is also an important point. Some text has been added to the limitations section of the manuscript to address this point.

Comment 15: In the model, antiviral treatment does not decrease transmission, whereas in fact they might (see Yang reference below). This model simplification is probably fine and is correctly stated on page 7 lines 158-160. However, it could also be noted in the "limitations" section
of the discussion, along with a brief comment on the possible consequences. 
It is possible that reduced transmission due to antiviral treatment
leads to a lower attack rate, and in turn to lower antiviral usage. 
This self-limiting effect of antiviral usage may be very small for
a treatment-only strategy (as opposed to prophylactic strategies,
where it could be significant, see [Arinampathy2010,Kelso2010]),
but might be worth mentioning. (also, sorry, I know its probably a perfectly fine
approximation in this context, but exponentially distributed gestation periods made me
giggle).

Response 15: *It is true that this model does not consider the possibility that antiviral
treatment decreases transmission by reducing the infectiousness of treated individuals. 
After discussions with a variety of Canadian clinicians about this assumption we decided
that for antiviral planning purposes, using an assumption which was essentially a
“worst-case” scenario was reasonable. However, this is an assumption and there is
evidence that infectiousness is reduced in individuals receiving treatment within 48 hours
of symptom onset. In order to clarify that this is an important assumption of the model,
进一步 details and references to relevant literature have been added into the limitations
section of the manuscript.*

Level of interest: An article whose findings are important to those with closely
related research interests
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a
statistician.
Declaration of competing interests:
I declare that I have no competing interests

Reviewer's report #2
Title: The Impact of Social Distancing Measures on Antiviral Treatment Demand
during a Severe Pandemic
Version: 1 Date: 2 April 2013
Reviewer: Nedialko Dimitrov
Reviewer's report:
Overall
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I recommend a major revision of this manuscript before it is accepted for
publication. I find this paper to be well written and in line with what generally is
published these days in the area of infectious disease modeling, especially of
influenza. However, I find the paper lacking in a critical aspect: it does not do a
sufficiently in-depth literature review to place the paper’s results in context and highlight its contributions. As a reader, I am left unclear on what is new in the manuscript. Much of the discussion and conclusion is full of relatively weak statements that are otherwise well known, whose purpose seems to be to be mainly guard against criticism from reviewers. I understand the authors in writing such statements, but I'd like to see a stronger manuscript with clearly stated contributions and novel take-aways for the reader, placed in context of previous research. More specific comments on individual sentences and paragraphs in the manuscript follow.

Specific comments
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Comment 1: An example of a weak statement in the paper is the first sentence of the abstract: "In the case of a severe pandemic... _it is likely_ that _some_ of the population _may_..." There are three weakening insertions in one sentence here. I suggest exchanging this sentence and other similar statements throughout the paper with factual statements and citations. For example "ABC show (a study reference) that during the XYZ epidemic a fraction of the population willingly reduced their number of daily contacts."

Response 1: We have taken the comment of this reviewer into consideration and changed both the first sentence of the abstract as well as similar sentences throughout the manuscript in order to improve the quality of the text.

Comment 2: The results section of the abstract is a little too vague to be useful to the reader. For example "With short periods of social distancing (12 weeks or less)"-- this is good, because the authors gave specifics--"the effect is relatively small"--this is vague and not useful--"unless the proportion of people involved and the magnitude of the behaviour change is large"--also vague and not useful. I suggest altering all similarly vague statements throughout the paper with specifics on what the manuscript’s model shows. Consider rewriting this, as an example: "If social distancing measures last for 12 weeks or less, XYZ specific result with numbers"

Response 2: We have clarified the text throughout the manuscript to address this comment and we feel that the changes better reflect the quantitative results. We have also focused on presenting the updated results in the context of the research question which has also been clarified as requested by the reviewer.

Comment 3: It is not clear from the abstract, or from the rest of the paper, what is novel about the results of the manuscript. The conclusions of the abstract state: "Our results demonstrate that the magnitude and duration of social distancing
behaviours adopted by the population during a severe pandemic can have a significant impact on the need for antiviral drugs." What is new in this statement?

Any modeler, or infectious disease expert knows that if extreme social distancing takes hold for a long period of time, the infection will be wiped out because of the decrease in the reproduction number. On the other hand, if the social distancing is weak, the reproduction number remains about the same, and the epidemic progresses as usual. What is new, in terms of specific numbers or insight, that is offered inside this manuscript?

Response 3: In order to place the manuscript within the proper context, we have included a more in depth literature review in the introduction of the paper as described in the response to reviewer #1. We have also elaborated on the reason why this paper is of importance compared to other papers that use dynamic models to examine the impact of social distancing as described in response to reviewer #1. The objective of this model was to evaluate to what extent it might be possible to rely on informal behavioral changes to decrease antiviral treatment needs during a severe pandemic so that less antivirals would need to be held in the National stockpile since stockpiling for a "worst-case" scenario (e.g. a severe pandemic) is highly cost-prohibitive. We have also added more detail about how stockpile sizes were decided upon in the past which differs from the use of a dynamic model making this work a novel contribution to the literature.

Comment 4: On Page 5, the definition of "differential transmissibility" is unclear. Do the authors mean "there is no difference in transmissibility between asymptomatic and symptomatic individuals?"

Response 4: We have added a sentence to clarify the meaning of differential transmissibility in the methods section. It is the case, that we assume that asymptomatic individuals and symptomatic individuals are equally infectious. Since the purpose of our model is to examine the amount of antiviral that would need to be stockpiled to address hypothetical pandemics of differing severity we made this assumption as a "worst case" scenario for planning purposes.

Comment 5: On page 5, the phrase "The model ran for 12 months" is a little unclear. I presume the authors mean the model captured 12 months of the epidemic, as opposed to "the model used 12 months of super-computer time."

Response 5: Yes, the reviewer is correct in the interpretation of the sentence. We have clarified this point in the text of the manuscript.
Comment 6: On page 6, the sentence "transitions between compartments were the same..." and the entire description of the model parameterization... I suggest the authors construct an appendix with an explicit specification of the entire model, including all model parameters. This is critical for the reproducibility of the results. As the manuscript stands, if I were to give the manuscript to an advanced graduate student, they will not be able to reproduce the model because of lack of detail in the manuscript. I suggest putting this detail in an appendix because it is too tedious in the main body of the paper, but still a requirement for scientific integrity.

Response 6: Where appropriate we have clarified the text in the Methods section to improve the flow and readability as well as the ability to reproduce the model. All model parameters are currently included in Table 1 of the manuscript and we have referred to the original version of the previously published model in the text. This paper also includes significant elaboration on any additional points requiring clarification. As we have indicated in our response to reviewer #1, we would be happy to include a more in depth discussion of the model in an appendix if the editor feels that it is necessary however, we believe that all of the required information has now been clarified in the text.

Comment 7: The paper makes a number of model assumptions that refer possible observations of past influenza epidemics, but it is not clear will hold for future epidemics. For example, the pre-existing immunity assumption on Page 6. Why is it reasonable that for future epidemics we should assume a fraction of those 65 and older have immunity? In addition, why is it reasonable to assume seasonality will result in 2 waves? (also page 6). For seasonality, how is the influenza transmission reduced or increased according to the season in the model? Why is this particular parameterization of seasonality reasonable? The manuscript refers to details of the model, but there is no discussion on why these details are implemented in a reasonable way and should hold for future epidemics--so that the model results are insightful.

Response 7: In order to identify the biological relevance of our model assumptions we have elaborated on these points within the text of the methods section. We have also included additional references in support of these assumptions where necessary.

Comment 8: In page 7, the sentence "We assume high vaccine coverage levels as might be expected for a severe" is missing a word.

Response 8: We apologize for this oversight. The sentence has been updated to contain the word “pandemic” at the end of this sentence.
Comment 9: I am unclear on the meaning of "for ethical reasons, all individuals who present for treatment with respiratory symptoms will be eligible..." Do the authors mean that there is no insurance coverage type consideration in the model? If that is the case, why is it "for ethical reasons?" And I am also unclear how priorities are taken into effect. So, an individual could be eligible for antivirals, but not receive them. When does that happen?

Response 9: Clearly this is an area where confusion lies regarding what we meant by this point. We have changed the text of this section to represent our true intentions. In short, given our current technological limitations (e.g. no reliable point of care test for pandemic influenza) we are assuming that individuals who present to a doctor with respiratory symptoms will be assumed to be a potential pandemic influenza case. Since it may not be possible to distinguish true influenza cases from non-influenza cases which also present with respiratory symptoms (based on case definitions), we assume that doctors will err on the side of caution and prescribe antivirals to these patients without doing any sort of “triage” and therefore these individuals “consume” antivirals from the stockpile. Since we are interested in maximum possible stockpile requirements, we have not considered that antivirals may only be offered to individuals with underlying chronic conditions or some other subset of all infections presenting for care.

Comment 10: I am unclear on the meaning of "We assume no variation in the magnitude of behavior change over each time period examined" occurring on Page 8.

Response 10: What we mean in this case is that we do not include a parameter for the waning of compliance as might be expected in reality. Based on the literature it was not clear what a reasonable parameter should be for the waning of compliance and therefore we did not include this in the model. We have added a sentence in the methods section to clarify this point.

Comment 11: On page 9, the sentence "Clearly, increasing the duration of time that distancing occurs..." made me question why we are looking at antiviral demand? Why not look at simply number of infected individuals? Is the model's antiviral demand simply a group-weighted sum of the number of infected individuals? In other words, 30% of infecteds from group A seek antivirals and 40% of infecteds from group B seek antivirals? Ultimately, doesn’t social distancing simply reduce the effective reproductive number? Why not simply express that reduction, and that way we clearly now how much and for how long that reduction has to hold to wipe the epidemic? It is just not clear what the takeaways are for the reader on antivirals here.
Response 11: I believe that our revisions which more clearly lay out the model context and relevant published literature, combined with a more defined objective and more clear discussion of the model structure and results address this comment. We have also added text to the discussion to more clearly identify the important take-away messages as also identified in comment 13.

Comment 12: On page 10, the phrase "age-specific social distancing" made me ask the question... is the social distancing in the manuscript's model not age-specific? Is it across the board, for all age groups? Why does that make sense? Why would kids social distance themselves as much as adults? Also, what is the purpose of having the age compartments if not to do different social distancing on them? Is it just to have different contact rates from the Mossong study?

Response 12: We have clarified this point in the manuscript. Our model is age structured in order to capture age-specific contact rates as described by Mossong et al. However, the way in which distancing is implemented in the model is not age-specific (as you might expect for a school closure intervention). In the case of a school closure, it is assumed that school aged individuals reduce their contacts but adult contacts remain unchanged. Since we considered more informal social distancing based on individual perceptions related to pandemic severity, we assume that data on stated intentions to distance are likely to apply to all family members (see Bish et al. 2010 and Ibuka et al. 2010). If a parent says that in the case of a severe pandemic they plan to work from home, not attend outside events or take public transit (thereby reducing their contacts significantly), it seems unlikely that they would permit or encourage their children or other family members to engage in behavior that is in opposition to their stated intentions. While this is an assumption of the model it is also a necessary assumption as we felt it was better to use the data collected in published surveys to root our distancing interventions in then make judgment calls about how contact behaviour of children (who were not included in the surveys) would differ from the behaviour reported by adults.

Comment 13: The conclusions section is weak as stated before. I is unclear what is new. I suggest a clear literature review that compares and contrasts this manuscript's Contributions with those of existing manuscripts, in addition to explicitly stating the main takeaways for the reader.

Response 13: The reviewer is correct that this is a key component of the paper that could be significantly improved. This was also a concern for reviewer #1. As a result we have added substantial additional text that uses the existing peer-reviewed literature to place the model in the proper context and we also compare and contrast our results with those of similar previously published papers. We have also added several additional sentences in the discussion section to explicitly state the main take away message from the paper as suggested by the reviewer.
Level of interest: An article of limited interest
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests