Author's response to reviews

Title: Influenza pandemic intervention planning using InfluSim: Pharmaceutical and non-pharmaceutical interventions

Authors:

Hans-Peter Duerr (hans-peter.duerr@uni-tuebingen.de)
Stefan O Brockmann (stefan.brockmann@rps.bwl.de)
Isolde Piechotowski (isolde.piechotowski@rps.bwl.de)
Markus Schwehm (markus.schwehm@uni-tuebingen.de)
Martin Eichner (martin.eichner@uni-tuebingen.de)

Version: 2 Date: 19 April 2007

Author's response to reviews: see over
Response to referee reports for the manuscript "Influenza pandemic intervention planning using InfluSim: Pharmaceutical and non-pharmaceutical interventions", by Duerr HP et al. Submitted to BMC Infect Dis

Response to the report of Ruby Siddiqui:

(In the following: comments of the report in size 9 pt, responses in size 12 pt)

General

Dear Ruby Siddiqui,

Thank you very much for your constructive comments which helped to improve the manuscript. Please find below our responses in detail.

We hope that our revision adequately addresses the points raised, and we would be grateful for a rapid response.

Sincerely, Hans-Peter Duerr

---

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. It is hard to evaluate the InfluSim model as it is a 'black box' in this manuscript. A brief description, figure and summary of key parameters and model assumptions are required as well as a description of the profile of infectivity with time since infection (is this what is meant by contagiousness?)

Response: Agreed. We have added an Appendix before the Acknowledgements section, providing a 2 page summary of the InfluSim model as published recently (Eichner M et al. The influenza pandemic preparedness planning tool InfluSim. BMC Infect Dis. 2007). The Appendix provides 2 additional figures: Fig. S1 shows a flowchart of the model structure and Fig. S2 shows the profile of infectivity with time since infection together with the appearance of symptoms over time. We refer to the Appendix in relevant sections of the main text, and have replaced the term "contagiousness" consistently by the term "infectivity".

2. An analyses of the sensitivity of the results to the underlying model assumptions about which there is most uncertainty needs to be performed.

Response: Agreed. Please see concluding paragraph ("Uncertainty in the parameter values") in the Discussion with the newly added Figure 6. Granted?

3. The study appears to make assumptions about the efficacy of face masks and improved hygiene as there is no evidence that such measures would be effective in reducing contact. The assumptions and lack of supporting data need to be made transparent.

Response: We have not made specific assumptions about the efficacy of face masks and improved hygiene in this MS, but consider the reduction of contact rates in general. Thus, various options for how the reduction of contact rates could be achieved are conceivable. Most probably, the misunderstanding was provoked in the original MS by statements in the Methods, in the Background and in the Discussion section ("...the effects of wearing face masks, of improved hygiene...", etc.) which have been deleted. To further clarify this, we added in the Discussion "Since the specific effects of such behavioral changes remain uncertain, we modeled their contribution as a general reduction in contact rates."

4. Was it assumed that only pandemic influenza cases received antivirals or all cases with influenza-likeliness (as is likely in a pandemic scenario)? This will affect overall antiviral effectiveness due to wastage. This needs to be made clear.

Response: InfluSim assumes that all patients who seek medical care (i.e. cases with a severe or an extremely severe course of disease) receive antiviral treatment (see Appendix). It does not consider influenza-like-illness caused by other pathogens. It is correct that treatment of such cases will contribute to deplete the antiviral stockpile,
thus we have extended the appropriate section of the Discussion by adding "Even if the currently stockpiled antiviral drugs will be fully effective against the pandemic strain, their use will not be able to sufficiently prevent the spread of influenza because (i) transmission of the infection may occur before the onset of clinical symptoms, (ii) asymptomatic and moderately sick cases may not be treated, and (iii) the occurrence of cases with influenza-like illness caused by other pathogens may lead to an accelerated depletion of the antiviral stockpile."

5. Why would moderately sick patients be refused anti-viral treatment, even under conditions of unlimited antiviral stocks? This seems highly unlikely in a pandemic situation and should be revised.

Response: Moderately sick cases are defined as patients who develop a rather mild form of disease which does not require visiting a doctor (see Appendix). It is correct that InfluSim assumes antiviral distribution to be restricted to the treatment of cases who seek medical care because they experience a severe or extremely severe course of disease. This is in accordance with the current German policy, as advised by the German Pandemic Preparedness Plan. It is the intention of our paper to examine the effects of limited antiviral stockpiles - a situation which will apply to most countries.

Antiviral treatment of patients with mild or moderate disease not only poses problems of diagnostics, but also leads to an extremely quick depletion of antiviral stockpile in most countries. Although this strategy would certainly delay the pandemic wave by several weeks, it would also deprive severe cases of receiving appropriate treatment. We would like to refrain from a revision of this point.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. Define 'partial isolation'

Response: This term was misleading and has been removed throughout the paper. We now refer only to "isolation" which we define in the Methods section and in the Appendix, where it says: "Isolation of cases reduces their contact rates. Contacts are not necessarily reduced by 100%, but between 0 and 100%, as specified by the user. ..."

2. Clarify whether contact reduction also includes partial isolation

Response: To make this more explicit, we have added to the legend of Fig. 4 "... if contact reduction measures are implemented additionally to the isolation of cases", and to the legend of Fig. 5 "...and contact reduction measures are implemented additionally to the isolation of cases"

3. Give an idea in the text of the numbers of cases involved when epidemic peaks are reduced or the timings involved when peaks are delayed.

Response: We have provided in several places of the Results section statements like "..., protracts the peak of the epidemic by about one week" or "The peak of the epidemic is protracted by about 1 day for every percent of contact reduction...". This information about the timing of the epidemic is complemented with the section "Cumulative number of infections and outpatients" within the Results section. We would like to keep these crude numbers to avoid the spurious impression that a model can predict peaks or case numbers with unrealistically high precision. We feel that an increased reporting of detailed model output would be misleading (cf. also the topic "sensitivity analyses" above, see Major Compulsory Revisions, point 2).
4. The results section is misleading to non-modellers as no detail is given on the InfluSim model and model assumptions so the stated incidence, consultations and hospitalisations cannot be applied to all countries.

Response: In the revision, this should be clarified by the Appendix.

5. The manuscript (Fig. 2) seems to indicate that mitigation is equivalent to delay of the epidemic peak. The main aim of antiviral stockpiling is to reduce the number of cases (and deaths) i.e. an individual-level effect. Reduction in transmission (and therefore a delay in the peak) is secondary. In fact, as a delay of months is highly unlikely, a reduction in cases is the most important result.

Response: Agreed. This applies already to Fig. 1 and, therefore, we have complemented the first paragraph of the results section with: “This example furthermore shows that the mitigation of the epidemic is not necessarily associated with a significant reduction in the number of infections. For information on the proportions of infected people and outpatients see the legends to the Figures.”

6. Is the effect of antivirals on individual outcome considered (Fig. 3)? It appears that only the effect of antivirals on delaying the epidemic peak is considered here.

Response: Yes. Antivirals reduce the remaining duration of the disease, the degree of contagiousness, and the probability of hospitalization and death of each patient who receives antiviral treatment (see Appendix).

7. Why is an exponential distribution used to model the period between symptom onset and seeking medical help?

Response: Using an exponentially distributed waiting time allows for incorporating variability in the behaviour of patients without introducing more equations in the model. It seems reasonable that most patients seek medical help soon after onset of symptoms and only few wait for more than two days.

8. How will antivirals be distributed? If patients attend health centres, is their increased exposure to infection at health centres? Is this included in the model?

Response: No. We have not incorporated specific transmission sites (health care centres etc.).

9. The word ‘predictions’ should not be used when referring to infectious disease models (Discussion)

Response: Agreed. Has been removed throughout the MS.

10. The ‘wide distribution’ and ‘high prevalence’ of infection are not the problem for antiviral effectiveness, rather the high number of antiviral courses required (Discussion)

Response: Changed into "Under a high prevalence of infection in phase 6, a wide distribution requires an enormous number of antiviral courses; with available stockpiles, it will be virtually impossible to locally contain the pandemic with targeted antiviral prophylaxis."

11. We do not know whether stockpiled antivirals will be sufficient to prevent the spread of influenza (Discussion)

Response: Merging the two sentences with "because" should make this clearer: "Even if ... prevent the spread of influenza because transmission of the infection ... who may not be treated."

12. Transmission of influenza before the onset of symptoms is an assumption. There is little data to support this (Discussion)

Response: That's why we say "may occur", referring to the paper of Hayden et al. 1998; J Clin Invest.

Influsim model (M. Eichner et al, 2007)

13. How were individuals divided into their respective risk groups? Was this risk to infection? Risk of severe illness?

Response: The subdivision of the age classes in groups with or without increased risk follows the German Pandemic Preparedness Plan. People with increased risk...
are as likely as others to acquire the infection, but are under higher risk of developing an extremely severe course of disease which may necessitate hospitalization and even become life-threatening. As we focus in this paper on the number of outpatients (rather than on hospitalizations and deaths), these features are not relevant here.

14. How was clinical severity defined? (e.g. what was the clinical difference between very sick and extremely sick individuals?) How would this definition be implemented in a health-care setting?

Response: This feature has now been clarified in the Appendix: Very sick and extremely sick patients seek medical help (i.e. become outpatients) and may be offered antiviral treatment. Extremely sick patients only differ from the other very sick patients by the fact that they need hospitalization (unless it can be averted by antiviral treatment). Again, as the paper does not concentrate on hospitalizations, the distinction of extremely sick patients is not really relevant here. To avoid a lengthy paper, such detailed information can be looked up in the Appendix or in the preceding paper.

15. What consultation/hospitalisation/case fatality rates were used for the scenario in this manuscript?

Response: All very sick and extremely sick patients (i.e. one third of all people acquiring an infection) seek medical help and become "outpatients" (see Appendix, Natural history of disease). A small fraction of these need hospitalization and may die from the disease. As the paper does not concentrate on hospitalizations and deaths, these fractions are not really relevant for the results here. A full description of these parameters is given in our previous InfluSim paper.

16. Was it assumed that all severely ill patients were hospitalised (and therefore all deaths occurred in hospital)?

Response: No, please see above.

17. Were the relative contagiousness values assumed? Define contagiousness.

Response: The term "contagiousness" has been consistently replaced by "infectivity", which is now illustrated in the Appendix, Fig S2.

18. Was it assumed all cases received antivirals within 48 hours?

Response: Not exactly. All cases who seek medical help within 48 hours after onset of symptoms are given antiviral treatment if this intervention is chosen at that time and if antiviral drugs are still available. See also response to major revision number 7.

Discretionary Revisions (which the author can choose to ignore)

1. All social distancing measures (including school closures and cancellation of mass gatherings as well as partial isolation and protective behaviour) should be included in the same paper.

Response: Sorry, this would clearly be beyond the scope of this paper.

2. Is this study only applicable to countries that can afford to stockpile or have been able to stockpile antivirals?

Response: Fig. 4 addresses intervention by contact reduction alone without antivirals and thus should be able to address this issue for countries that cannot afford extensive stockpiling. The optimal use of very small amounts of antiviral drugs is also addressed in fig. 3, showing that even 1% of antivirals can be efficient if used timely.

3. Could this model be extended to evaluate the economic burden and health benefit impact of pandemic influenza and the cost-effectiveness of alternate interventions (costs and QALYs)?

Response: Yes, InfluSim already allows calculating the costs of hospitalizations, outpatient visits and interventions, estimating the work loss due to influenza sickness.
Response to the report of Bram M Palache:
(In the following: comments of the report in size 9 pt, responses in size 12 pt)

Dear Bram M Palache,

Thank you very much for your positive report. Please find below our response to your comment. We hope that it is adequately considered in the revised manuscript, and we would be grateful for a rapid response.

Sincerely, Hans-Peter Duerr

General

-------------------------------------------------------------------------------

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

-------------------------------------------------------------------------------

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

In light of pre-and clinical research findings on cross reactivity between various H5N1 avian influenza strains on candidate pandemic vaccines, the article should discuss these findings in light of their findings for the need of early intervention if a pandemic would emerge to have the greatest impact. The authors only discuss pandemic vaccines, which will not be available within months after the onset of the pandemic. The possible role for pre-pandemic vaccines and its potential impact on the pandemic should at least be discussed in light of the latest information on H5N1 prototype vaccines.

Response: Agreed. In the Discussion we have added to the paragraph "Optimizing interventions": Vaccinating a small fraction of the population with a pre-pandemic vaccine would have a similar effect on the course of the epidemic as reducing the basic reproduction number by the percentage of immunized individuals (e.g. by 10%). The effect of varying $R_0$ and other influential parameters is examined in the following sensitivity analyses.

-------------------------------------------------------------------------------