Reviewer's report

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

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Reviewer: Ruby Siddiqui

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'Influenza pandemic intervention planning using InfluSim: Pharmaceutical and non-pharmaceutical interventions'
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Submitted to BMC Infectious Diseases

Peer review by M. Ruby Siddiqui

Response to revised manuscript, June 2007

The authors have addressed all the major comments and although I have made some suggestions to further improve the manuscript I will defer to the BMC Infectious Diseases editors to request or decline these additional revisions

Previous Major Compulsory Revisions (which 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?)
The authors have improved this section by including a figure and brief description of the model in an Appendix. However the manuscript consistently refers to the 'standard set of InfluSim parameters' but do not summarise these parameters in the manuscript. It is quite difficult to make sense of the results section without these key parameters and I feel it would greatly improve the readability of the manuscript if these could be tabulated.

2. An analyses of the sensitivity of the results to the underlying model assumptions about which there is most uncertainty needs to be performed.
Exploring the impact of uncertainty of the key parameters is usually a major part of the Results section of modelling papers rather than an addition to the Discussion. It is not clear why this paper should be different, unless the intention is merely to provide a quick demonstration of one possible outcome of the model, rather than to provide a serious evaluation of possible interventions. However, the aim of the paper does appear to be to provide a serious evaluation of possible interventions. Since very large uncertainty in parameter values does exist (including the efficacy of antivirals), the sensitivity analysis should be fundamental to the conclusions of this study and I do think it should appear in the Results section rather than in a separate publication. In my opinion, if this could be added, it would greatly improve the quality and utility of the paper. For Figure 6, an indication of the values of the varied parameters for the extreme peaks would be useful. Also it’s ambiguous how the efficacy of antivirals on the infectious period and infectiousness were used in this model. A formula should be given.

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.
The authors have attempted to clarify this section by removing any reference to face masks and improved hygiene. However the reader is left uncertain about how ‘contact reduction’ might occur and must wait until the Discussion in the sentence starting ‘For Figure 5 we assumed that contact reduction measures...’ Therefore a sentence such as: 'In the scenarios presented below, we assume that everybody in the population avoids a given percentage of contacts (e.g. by improved hygiene, wearing masks, or behavioural changes)...’ should be added to the Methods section. Also it’s not clear why different base-case contact reduction rates are used (10% in Fig. 1 but 20% in Fig 5)?
4. Was it assumed that only pandemic influenza cases received antivirals or all cases with influenza-like illness (as is likely in a pandemic scenario)? This will affect overall antiviral effectiveness due to wastage. This needs to be made clear
The authors address this point adequately

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. Although moderately sick cases are not treated in the InfluSim model they are highly likely to seek medical attention (and antiviral treatment) in a pandemic situation. This would further deplete limited stocks and should be mentioned in the Discussion

Previous 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’
The authors address this point adequately

2. Clarify whether contact reduction also includes partial isolation
The authors address this point adequately

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.
The authors address this point adequately

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
The authors address this point adequately but a summary of key parameters is required

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.
The authors address this point adequately

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.
The authors address this point adequately

7. Why is an exponential distribution used to model the period between symptom onset and seeking medical help?
The authors address this point adequately

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?
Mention in Discussion. Also how realistic is an early initiation of contact reduction and antiviral distribution?

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

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)
The authors address this point adequately

11. We do not know whether stockpiled antivirals will be sufficient to prevent the spread of influenza (Discussion)
…their use may not be able to sufficiently prevent the spread of influenza because…

12. Transmission of influenza before the onset of symptoms is an assumption. There is little data to support this (Discussion)
…(i) transmission of the infection may occur before the onset of clinical symptoms (as assumed in the InfluSim model)…

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?
The authors address this point adequately

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?
The authors address this point adequately

15. What consultation/hospitalisation/case fatality rates were used for the scenario in this manuscript? The first paragraph of the results section refers to consultations, hospitalisations and deaths so the rates need to be provided in a summary of key parameters

16. Was it assumed that all severely ill patients were hospitalised (and therefore all deaths occurred in hospital)?
The authors address this point adequately

17. Were the relative contagiousness values assumed? Define contagiousness.
The authors address this point adequately

18. Was it assumed all cases received antivirals within 48 hours?
The authors address this point adequately

Previous Discretionary Revisions (which are recommendations for improvement but 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
The authors address this point adequately

2. Is this study only applicable to countries that can afford to stockpile or have been able to stockpile antivirals?
The authors address this point adequately

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)?
The authors address this point adequately