Reviewer's report

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

Version: 1 Date: 27 March 2007

Reviewer: Ruby Siddiqui

Reviewer's report:

General
The issues discussed in this study are both new and well defined. This study is important and comes at a time that public health agencies are debating pandemic influenza control measures and refining pandemic influenza contingency plans. The authors highlight that intervention measures should not be considered in isolation but instead combined to both reduce and delay the peak of a pandemic wave. This will in turn reduce the burden on public health services and buy time for vaccine development respectively. The Duerr et al manuscript is of a high calibre, the figures and tables are clear and describe the findings well and the discussion and conclusions are generally well balanced and adequately supported by the data.

I do, however, have some important concerns that I feel need to be addressed before this work can be published. The main concern is that this manuscript is intended for the BMC: Infectious Diseases readership which includes clinicians, patients, policymakers, the media and members of the general public. It should therefore be a self-contained manuscript and should not rely so heavily on referring to the previous manuscript that describes the deterministic model of pandemic influenza called InfluSim (Eichner et al, 2007). While it is reasonable to omit the technical details of the model, I believe that Duerr et al should include as a minimum a basic description of the InfluSim model, key model parameters and model assumptions (perhaps in an additional figure). Without these it really is impossible to make sense of the paper. A second major concern is that the manuscript entirely lacks sensitivity analyses to the key biological assumptions. This is highly unusual for any modelling study where there is as much uncertainty concerning epidemiological or biological assumptions as there is here, and without such analyses readers can have no way to assess how robust the results are to the key uncertainties. I believe there is also a significant danger that without such sensitivity analysis naïve readers (i.e. those unfamiliar with modelling and the profound uncertainties associated with influenza transmission) may believe the results rather too much. Since many of the assumptions of the model are unsupported by data (for example, the assumption that transmission occurs before onset of symptoms, the assumption that asymptomatics can transmit) the tentative nature of the findings needs to be emphasized more and the results couched in much more circumspect language.

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

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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'
2. Clarify whether contact reduction also includes partial isolation
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.
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.
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.
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.
7. Why is an exponential distribution used to model the period between symptom onset and seeking medical help?
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?
9. The word ‘predictions’ should not be used when referring to infectious disease models (Discussion)
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)
11. We do not know whether stockpiled antivirals will be sufficient to prevent the spread of influenza (Discussion)
12. Transmission of influenza before the onset of symptoms is an assumption. There is little data to support this (Discussion)

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?
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?
15. What consultation/hospitalisation/case fatality rates were used for the scenario in this manuscript?
16. Was it assumed that all severely ill patients were hospitalised (and therefore all deaths occurred in hospital)?
17. Were the relative contagiousness values assumed? Define contagiousness.
18. Was it assumed all cases received antivirals within 48 hours?

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

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I have no competing interests but I recently joined the modelling team at the Health Protection Agency that is involved with the large EU-funded SARSControl collaboration. I have not met or had any contact with any of the authors of this manuscript.