Author's response to reviews

Title: Vaccination strategies for future influenza pandemics: a severity-based cost effectiveness analysis

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Version: 2 Date: 29 January 2013

Author's response to reviews: see over
Vaccination strategies for future influenza pandemics: a severity-based cost effectiveness analysis

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manuscript reference number: 1377699006829014

Overview of Changes to Revised Manuscript: January 2013

We thank both reviewers for their helpful and insightful comments. As a result of these we have made certain changes to the manuscript:

1. We have added details on epidemic outcomes i.e. the location of infection and age-specific attack rates, which show that the transmission mechanism underlying the simulation model faithfully reproduces empirical data on pandemic spread, particularly the location in which transmission occurs.
2. We have clarified the infection seeding mechanism to state its role in instigating an epidemic in the modelled community.
3. We have added details describing our use of 2009 age-specific attack rate data to derive age-specific susceptibility parameters. In addition, we add a sensitivity analysis looking at an alternative assumption where all age groups have similar susceptibility.
4. We have re-calculated our reported $R_0$ values for the different pandemic scenarios, using the early exponential growth rate of the pandemic, rather than assuming that $R_0$ is equal to $R_{rand}$.
5. We have added text to the introduction section to highlight the novel results which are presented in this paper, in particular how the effectiveness and cost effectiveness of vaccination-based interventions depends on the severity of the pandemic and on the time period required develop and produce a vaccine.
6. A comment on the generalizability of results based on the the Australian-based community model to other developed countries has been added to the discussion section.
7. Additional details of the policy of school closure (whether all schools close simultaneously; or if schools close individually, being based on case numbers in the school) have been added.
8. A comment on the feasibility of sustaining social distancing interventions for the six months until vaccine deployment has been added to the discussion section.
Detailed Responses to Reviewer’s Comments

(page numbers given below refer to the revised manuscript)

Reviewer #1:

1.1) Authors use a single transmission rate for all modeled settings (such as households, schools, etc.); then they model the force of infection to which individuals are exposed by arbitrarily defining the number of contacts per unit of time that individuals have in each setting (except for households). Until a much deeper knowledge on contact patterns of individuals will become available, the best option is to consider homogeneous mixing in each setting so that each individual can potentially infect all the other individuals sharing the same environment. This means that in the equation regulating the force of infection one should divide by N, where N represents the number of individuals in a given environment at a given time. Please note that the same holds also for contacts in the general community. Clearly, this implies to consider a different transmission rate within households, schools, workplaces and in the general community.

The reviewer is correct that in order to model different transmission rates for different settings, the force of infection experienced by each individual must differ in each setting. We achieve this in our model by adjusting contact parameters to obtain location-specific ratios of transmission, and have calibrated these parameters to match published transmission location data, see below.

Our transmission function, which appears on page 13 of the manuscript, is based on pair-wise contact between two individuals, one who is infectious and one who is susceptible. Our “force of infection” parameter $\beta$ adjusts the probability of transmission to reflect alternative attack rates (cf. reproduction number). The differential transmission referred to by the reviewer is captured by adjusting contact parameters, that is, who is in contact with whom, for contact in schools, large workplaces and in the wider community. Text describing this feature in additional detail has been added to the paper, see below.

Following the reviewer’s comment on the description of the transmission model, we have expanded the methods section of the manuscript, giving an outline of the contact and transmission mechanism used, specifically stating the data sets used to calibrate the model to produce location and age specific transmission rates. The following text has been added on page 12:

The number of contacts made by each individual each day in school, work and community settings were adjusted to reproduce the proportion of cases occurring in different settings as reported by empirical studies, specifically
40% of infections occurred in households, 30% in schools and workplaces, and 30% in the wider community [1-3]. Contacts within schools and workplaces occurred in fixed-size mixing groups of maximum size 10; within mixing groups contact was assumed to be homogeneous. Community contacts occurred between randomly selected individuals, weighted toward pairs of individuals with nearby households. The mixing group sizes, and location-specific distribution of where infection occurs, are given in Additional File 1, in Tables S1.1 and S1.2 respectively.

The following text has been added on page 13:

Age-based susceptibility $Susc(I_s)$ was calibrated to reproduce age-specific infection rates observed in the 2009 pandemic [4]. Figure S1.1 appearing in an additional file [see Additional File 1] gives the age-specific distribution of infections for the three pandemic scenarios. An alternative age-based susceptibility profile, where all age groups were equally susceptible, was used in a sensitivity analysis.

These additional details have also been added to the extended simulation model description appearing in Additional File 1.

The Ferguson model which the reviewer refers to assumes uniform mixing, with each individual contacting every other within a location. In this model the force of infection contributed by each infected individual is proportional to a location-dependent factor divided by $N$ (where $N$ is the population of the location). In our model each 1-to-1 contact with an infected individual contributes a constant force of infection that does not depend on $N$ – however the number of contacts is not $N$, but a fixed smaller contact group size value (with maximum 10) dependent on the location type. The chosen school and workplace mixing group sizes are both (1) plausible, because not every child in a school or person in a large workplace will mix equally with all other individuals in the location, and (2) give appropriate location-specific transmission ratios, as described in the added text above.

Note that our model does meet the appropriate comment made by the reviewer with respect to homogeneous mixing; in each location (e.g. school or workplace) a fixed contact group is established and contact within that group is assumed to be homogeneous. This is mentioned in the added text appearing above.

1.2) Moreover, to properly parametrize the model, authors have to compare the fraction of infections generated in the different settings with available estimates (see for instance Ferguson et al, Nature 442:448-452, 2006; Cauchemez et al, Nature 452:750-754, 2008; Cauchemez et al, PNAS 108:2825-2830, 2011; Cauchemez et
al, Stat Med 23:3469-3487, 2004). My feeling is that, because of this rather "arbitrary" model parametrization, these proportions (which are crucial in determining epidemic dynamics, age distribution of cases and effectiveness of interventions) as resulting from the analysis of model simulations would not be in agreement with empirical estimates. I invite authors to provide estimates about proportion of cases by setting and age distribution of cases and to compare them with available empirical estimates.

As stated in (1.1) above, we agree completely with the reviewer regarding the fraction of transmissions occurring in different locations. The contact model parameterisation was not arbitrary; the model was in fact parameterised specifically to reproduce location- and age- specific proportions of infections. In addition to expanding the description of the model parameterisation process as outlined above, a new figure (Figure S1.1) and a new Table (Table S1.2) have been included in Additional file 1, giving the age and location distribution of infection occurrence, for the three pandemic scenarios.

2) Timing and number of arrivals of the first tens/hundreds of cases is crucial in determining timing of local epidemics (and thus to evaluate intervention policies based on mass vaccination). However, in this study importation of cases is made in a fully arbitrary and unrealistic way. Human mobility at Australian and international scale should be considered for estimating the number of travelers arriving (for instance daily) in Albany, coupled to a model (at least a very simple one) of the "global" influenza dynamics to obtain more reliable estimates of infected imported cases over time. See for instance Ferguson et al, Nature 442:448-452, 2006.

We agree about the crucial importance of the relative timing of the arrival of the first cases and the timing of the instigation of intervention measures. We also agree with the reviewer that the representation of case importation that we have adopted is somewhat artificial. However it should be noted that the intent of our seeding model of imported infections was not to simulate the interaction of the global pandemic with the local community, but rather to simulate influenza transmission from the point where imported cases would establish a local epidemic in the community.

The seeding assumption of 1 case per day was chosen to reliably begin a local epidemic in every stochastic simulation. Analysis of the low transmissibility scenario shows that seeding at this rate for 7 days results in a sustained epidemic in >97% of the simulation runs and 100% with two weeks of seeding, with higher percentages for the higher transmissibility scenarios. Seeding at this rate is continued throughout the simulation in order to capture the case where an epidemic may be initially suppressed by a rigorous intervention strategy, but may subsequently break out if intervention measures are relaxed.
The fact that simulations begin from the arrival of the first and subsequent cases in the local community has been more clearly explained in the manuscript. The following text has been added to the “Three pandemic scenarios” methods subsection on page 7.

Each simulation is assumed to begin when the first and subsequent cases arrive in the local community. After this point in time, one randomly located infected individual is seeded into the population each day, for the duration of the epidemic. Analysis shows that this rapidly triggers a local epidemic; within two weeks in the low-transmissibility scenario, and within one week for the higher transmissibility scenarios.

After the beginning of a sustained local epidemic, any subsequent variation in the amount of seeding has very little effect on the progress of the local epidemic, as the number of imported cases is much smaller than those generated by the local epidemic. Our analysis shows that for the low transmissibility scenario, even if the seeding rate is increased to 5 infections per day, after 7 days the number of infections generated from the self-sustained local epidemic is twice the number of imported infections, and by 14 days local infections outnumber imported infections by a factor of 8.

Given the importance of the timing of intervention strategies relative to the start of the local epidemic, we felt that a further point required clarification in the manuscript. Social distancing and antiviral interventions are assumed to be triggered shortly after the arrival of the pandemic in the local community. This is achieved in the simulation model through triggering the activation of interventions after a certain number of cases have been diagnosed in the community. This feature is described in the extended methods description appearing in Additional File 1, but was not initially included in the main manuscript. We have now added the following text to the “Antiviral drug and social distancing” methods subsection on page 9.

Antiviral drug and social distancing interventions were initiated when specific threshold numbers of symptomatic individuals were diagnosed in the community, and this triggered health authorities to activate the intervention response. This threshold was taken to be 0.1% of the population. It was assumed that 50% of all symptomatic individuals were diagnosed, and that this diagnosis occurred at the time symptoms appeared. This intervention activation threshold occurs 13, 9 and 7 days after the simulation start in the mild, moderate and extreme pandemics respectively.

3) I cannot see any detail about how the authors model age-specific susceptibility to infection by age. I took a look at the supporting text of Milne et al, PLOS ONE
3:e4005, 2008, but the description of what was done there does not fully convince me. If I am not wrong, the authors fit seroprevalence data on seasonal influenza with their model. First of all, do the data account for both a baseline pre-epidemic and a post-epidemic seroprevalence? Second, did the authors use the same model (based on arbitrary assumptions, see comment 1 of this review) for fitting the data? Third, why did the authors use "old" seasonal data instead of more recent 2009 pandemic data for which estimates are already available in the literature (see the studies focusing on Mexico: Fraser et al, Science 324:1557--1561, 2009; US Cauchemez et al, N Eng J Med 361:2619-2627, 2009; and Europe Merler et al, PLOS Comput Biol 7:e1002205, 2011)? My major concern, however, is that differential susceptibility to infection is not necessarily a feature common to all (and thus future) influenza pandemics. At the moment, it seems an ad hoc assumption to adjust the age distribution of cases.

We thank the reviewer for making this point. In fact, we used age-specific infection data from European 2009 data to derive the age-specific susceptibility, following our earlier work in [5], and had erroneously stated in Additional File 1 that we used seasonal influenza age-specific seroprevalence data to derive age-specific susceptibility parameters. We have now amended the “influenza transmission model” methods subsection on page 11, as described in (1.1) above.

Firstly, the 2009 data used was post-epidemic (laboratory confirmed) A/H1N1 2009 infection rates in different age groups. This was used to derive age-specific susceptibility factors that gave rise to the same (observed) ratios of infections between different age groups under the “mild” pandemic scenario.

Secondly, in both the 2008 publication and this paper we generated age-specific infection rates by adjusting the susceptibility parameters Susc of the transmission probability function presented on page 13 of the manuscript. In the 2008 publication, Susc was calibrate using seasonal influenza data; in this paper 2009 pandemic data was used. Taken together, the contact model calibration described above along with the age-specific susceptibility parameterisation gives baseline epidemic characteristics consistent with observed characteristics of the 2009 pandemic.

Thirdly, as stated above, we did use 2009 data and not older seasonal influenza data.

The reviewer’s main comment that the particular age-specific infection profile used in this study need not be a feature of a future pandemic is a valid concern. We have responded to this by conducting an additional sensitivity analysis where we assume that all age groups are equally susceptible, which might be the case if a truly novel influenza strain causes the next influenza pandemic. We now report on the outcome
of this sensitivity analysis (it does not change any of the studies findings) in the “sensitivity analysis” results subsection on page 22:

In the main results it was assumed that individual susceptibility to infection differed by age, resulting in age-specific infection rates similar to the 2009 pandemic, where 18-24 years olds had the highest attack rates while those 25 years and older had the lowest [4]. Previous pandemics have exhibited different age-specific attack rate profiles. The 1957 pandemic resembled seasonal influenza with the highest attack rates in children, while the 1968 pandemic had similar attack rates in all age groups [6]. The sensitivity of the results to an alternative assumption that all age groups would be equally susceptible was examined. The result was a shift in the burden of illness to older age groups, and as a result, slightly fewer life years were saved by interventions. However the shift of illness to older age groups also reduced the death-related productivity losses, resulting in slightly lower total pandemic costs and slightly improved cost effectiveness of interventions.

4) The definition of R0 used by the authors (and that I found in their paper Milne et al, PLOS ONE 3:e4005, 2008) is not satisfactory. It has been shown in the literature that averaging over the infections generated by the first (randomly chosen) infectious individual in a fully susceptible population leads to a poor estimate of R0. If the authors read carefully the reference they cite (that should support their hypothesis that R0 is similar to Rrand), they will find that Ferguson et al found the relation "R0 approx Rrand +0.2", which is a poor approximation for typical R0 influenza values (with R0 in 1.2-2). Using a definition of R0 based on the doubling time (or growth rate) of the epidemic looks much more appropriate (I recall that this is the method used in the mentioned study by Ferguson et al).

The reviewer correctly comments that the R\text{rand} approximation to R0 used is not appropriate for the lower-transmissibility pandemic scenarios used in this study, and we thank him for this useful observation. We have now calculated R0 values based on the early epidemic growth rate, following the method outlined in [ref from Nilimesh] and have updated the reported R0 values appearing in the manuscript accordingly. We found the largest discrepancy between R\text{rand} and the alternative calculation of R0 to be for the mild pandemic scenario, which has an R0 value of 1.5 rather than 1.2 as approximated by R\text{rand}. We have now briefly described the derivation of the reported R0 values in the “Influenza transmission model” methods subsection on page 13, as follows.

The R0 values for the three pandemic scenarios were calculated by fitting an exponential growth curve to the daily incidence in the early stages of the pandemic, using the daily incidence and serial interval distribution recorded from 40 randomly seeded simulations, following the method described in [7].
5) Finally, it is difficult to evaluate what is really new in this paper with respect to previous publications by the same authors:

The current manuscript makes significant advances with respect to these previous publications. Most importantly, none of these previous papers considers vaccination as an intervention, nor do they include an economic analysis of vaccination-based intervention measures. Moreover, and to our knowledge, no previous study has specifically addressed the issue of what plausible intervention strategies could be used to manage the delay between the arrival of a pandemic in a community and the availability of an effective vaccine, and how the cost effectiveness of these strategies depends on pandemic severity. We have now expanded the introduction to emphasise the novelty of the results, see response to Reviewer 2, (1).
Reviewer #2

1) The end of the intro could better delineate why this study is different from the many previous efforts to model intervention strategies for pandemic influenza. Is it because there is an explicit effort to integrate a transmission/severity model with cost effectiveness metrics?

*We thank the reviewer for making this observation. We consider that major advance made in this study is the examination of plausible pandemic mitigation strategies that explicitly address the timing “gap” between the arrival of the pandemic in a community and the availability of an effective vaccine. Moreover, we determine the effect which pandemic severity has on the effectiveness and cost effectiveness of interventions. We have revised the final paragraph of the introduction (page 5) to clarify the novel contributions of this study, as follows.*

No previous studies explicitly address the realistic combination of rapidly activated social distancing and antiviral interventions together with vaccination, which is needed to deal with the probable 6-month delay in vaccine availability. This modelling study directly addresses this scenario, and seeks to quantify the cost effectiveness of a plausible range of combined social distancing, antiviral and vaccination intervention strategies. Furthermore, this study determines the effect which pandemic severity has on the cost effectiveness of intervention strategies. Pandemic severity is a key factor in the assessment of alternative intervention strategies, as strategies that are considered too costly and socially disruptive for mild pandemics similar to the 2009 pandemic may be optimal for severe pandemics with high mortality rates.

2) The model is based on the population structure and activities of a medium-size Australian city. Are results sensitive to the specific network considered here, and/or is this network pretty similar to those modeled after US or other developed cities?

*As the reviewer points out, the contact structure and behavioural assumptions of our simulation model are based on an Australian context. However, comparing the results of studies that use our simulation model [8-11] to a variety of other individual-based simulation models at a variety of scales (e.g. small community [12], city [13], country [3, 14, 15]) shows that the results of this Australian community model are consistent with these other models, in as far as comparable pandemic and intervention scenarios are being evaluated. We thus believe that the model is broadly representative of developed world cities, and the results are thus applicable to US, European or other developed world populations. A comment to this effect has been added to page 25 in the discussion section of the manuscript.*
3) During the 2009 pandemic, some countries adopted a limited school closure policy, in which each school or local government was free to decide whether the entire school or specific classes needed to be closed, and school activities typically resumed 2-3 wks after the initial cases were identified. Can such a policy be modeled here, which is perhaps more realistic than widespread systematic school closure?

With respect to the policy of school closure i.e. all schools closing at once as opposed to individual schools closing or individual class closures, we chose policies that previous studies suggested were the most effective [10]. For sustained school closure, all schools closed at once; for limited duration school closure, schools closed individually based on occurrence of cases in the school. This methodological detail, which previously appeared in the extended methods section in Additional File 1, has now been added to the methods section of the manuscript on page 10.

For sustained school closure, all schools were closed simultaneously once the intervention trigger threshold was reached. For school closure durations of 2 weeks, which was only used for the mild pandemic scenario, and 8 weeks, which was used for all pandemic scenarios, schools were closed individually as follows: for a primary school the whole school was closed if 1 or more cases were detected in the school; in a high school only the class members of the affected class were isolated (sent home and isolated at home) if no more than 2 cases were diagnosed in a single class; however if there were more than 2 cases diagnosed in the entire high school the school was closed. Note that these school closure policies were only activated after the community-wide diagnosed case threshold was reached; cases occurring in schools before this time did not result in school closure. This policy of triggering school closure based on epidemic progression avoids premature school closure which can reduce the effectiveness of limited duration school closure [10].

So in fact the mild pandemic strategies A2 and A2’ (described in Figure 1), which involve individual schools closing for 2 weeks when cases were detected in the school, is essentially the policy outlined by the reviewer in comment (3). We thank the reviewer for the observation that these strategies were actual strategies employed during the 2009 pandemic, and have included a comment to that effect in the methods section on page 12.

4) For the strategy in which social distancing is sustained or continuous, and vaccine arrives 6 months after the initial case, are we assuming that social distancing will remain in place for 6 months? Perhaps the (lack of) feasibility of such measures should be discussed.

This is correct – as stated on page 10 of the methods section, “sustained” social distancing is assumed to continue until the vaccination campaign is complete (or for
an equivalent duration for strategies without vaccination). The reviewer makes an important point that social distancing of this duration (greater than 6 months) is unprecedented and may be practically impossible. However, the results for the strategies that include sustained social distancing are important because they highlight a significant distinction between moderate and extreme pandemics. We have added a comment addressing the plausibility of sustained social distancing to the discussion section on page 24 as follows.

It should be noted that for the intervention strategies considered in this study, sustained social distancing is assumed to continue until the vaccination campaign is complete (or for an equivalent duration for strategies without vaccination). Social distancing of this duration (greater than 6 months) is unprecedented and may be practically impossible. However, the results for the strategies that include sustained social distancing are important because they highlight a significant distinction between moderate and extreme pandemics. In contrast to mild and moderate pandemics, for extreme pandemics the results demonstrate that even if social distancing cannot be sustained indefinitely, longer periods of social distancing are strictly better than shorter periods, resulting in fewer lives lost and a lower total cost, with or without vaccination. This can be seen by comparing strategies C1, C2 and C3 (also no intervention, C2’ and C3’) in Table 1. This indicates that for extreme pandemics, public health efforts to sustain social distancing for as long as possible are worthwhile for both humanitarian and economic reasons, if a long-term, whole-of-society perspective is taken.

Minor comments: □ Fig 2: is “sustained” SD equivalent to “continuous” SD?

Yes, and we have amended the manuscript to consistently reference the term “sustained”.

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References
