Author's response to reviews

Title: Planning for the next influenza H1N1 season: a modelling study

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Author's response to reviews: see over
Reviewer: Gerardo Chowell
Reviewer's report:
Planning for the next influenza H1N1 season: a modelling study
In this article the authors employ a previously developed mathematical model by their team (BMC Med 2006, 4:26) to estimate the age-specific attack rate of the 2009 H1N1 influenza pandemic, the degree of pre- and post- pandemic immunity among children, young adult and senior populations. The authors also explore the possible impact of the next influenza pandemic season based on varying rates of vaccination and cross protective immunity. This is an interesting paper on a timely topic. The uncertainty in the different epidemiological parameters justifies the approach that the authors have undertaken. However, I have a few comments that should be addressed prior to publication

Authors: we thank the reviewer for his comments.

1. The authors should briefly describe their individual based mathematical model in the methods section besides citing ref 20. The underlying network structures should be clearly described.

Authors: We have added a short paragraph (page 8, lines 12 to 19) to describe how the model was structured and the interested reader can find more details on the underlying network structures in our paper published in BMC Medicine. However, in order to remain concise and because the main objectives of our work were centered on epidemiological findings and prediction of the next pandemic season rather than on modeling issues, we feel that a more complete description would be out of the scope of this paper.

2. A very sensitive aspect of individual based models is the underlying social contact structure that is assumed. Research in the area of epidemics on networks (mostly lead by the physicist community) has increased our understanding of the impact of epidemic/spreading processes on different network structures. For example, epidemics on scale free networks spread very quickly due to the presence of hubs, the highly connected nodes in the network. Research by Vespignani and others has shown that it is possible to generate epidemics on scale free networks with a infectious disease of very low transmissibility. Hence, this may explain their low estimate of the reproductive number.

We thank the reviewer for this comment. We agree that heterogeneity of scale-free connectivity patterns favors epidemic spreading, not only by suppressing the epidemic threshold, but also by accelerating the virus propagation in the population (Pastor Satorras R, Vespignani A, Phys Rev Lett 2001; 86:3200-3203). We have added two sentences in the discussion (page 17, lines 9 to 15) indicating that the network structure might be one explanation for the low value of the "reproductive number".

3. Related to previous point, the authors should elaborate on how the characteristics of the social networks used in their model could affect their results. For example, the authors could compare their results with those obtained
assuming other types of network structures in schools and work places (e.g.,
structures with higher clustering coefficients; assuming Erdos-Renyi or a
Watts-Strogatz 'small world' graph)

Authors: See response to previous comment and the paragraph and new references
added in the discussion. However, we believe that a more formal comparison with
other types of random networks is beyond the scope of this paper

4. Finally please clarify whether each stochastic realization included regeneration
of the underlying population network structure

New networks were generated at each simulation, for all calculations (including
reproductive numbers). We have added a sentence in the manuscript (page 8, line 24).
Reviewer: Junling Ma
Reviewer’s report:
In the manuscript “Planning for the next influenza H1N1 season: a modelling study” by Carrat et al., the authors use a sophisticated individual based model to explain the observed epidemic curve for influenza like illness (ILI) during the 2009 pH1N1 influenza pandemic using French national surveillance data. The research questions are the attack rates and pre-exposure cross-resistance levels in different age groups, and the possibility of a second season caused by the mutants of the pandemic strain depending on different levels of cross-resistance to the mutant strain. These questions are all important in preparing for a possible second season of pH1N1 influenza.

Authors: we thank the reviewer for her comments.

Major Compulsory Revisions
However, the estimated effective reproduction number presented in this manuscript is 1.05, which is substantially lower than other estimations of the pandemic in Mexico and other countries (ranging from 1.6-2, see, for example, Fraser et al., (2009, Science), Nishiura et al, (2009, Euro Surveill), Nishiura et al, (2009, J. NZ Med. Assoc.)) and more close to seasonal influenza. Note that in all these published estimations, the population is treated as fully susceptible, so in fact they estimated the effective reproduction number if pre-exposure resistance exists.

The authors need justify this discrepancy. Clarify a few points below may help us justify the results. Some of these information may be provided in supplementary material.
1. If the effective reproduction number is so low, which is comparable with that of seasonal influenza, how does the French pandemic curve (exponential growth rate and final size) compare with those of other seasonal influenza?

We provide an explanation for the low reproductive number calculated from our random graph - based on comments from another reviewer - see discussion. We also compare our value with the reproductive number estimated using the growth rate of the epidemic curve on the same data (1.18). The estimated number was lower than those observed over 25 seasonal influenza epidemics. We have added these data in the discussion (page16 last line, to page 1, line 6)

2. Is the data used in this research the same as in Fuhrman et al, (2010, Eurosurveillance)? Does it suffer the same change in surveillance as shown in the mentioned paper?

We used data from the French General Practitioner (GP) Sentinel network as was indicated in the original manuscript, and we provided a reference describing how influenza like illness is surveyed by this network. We have added two sentences to briefly describe the sentinel network and to indicate that no change in surveillance occurred due to the H1N1 pandemic (page 6, first para).
3. Clarify the model used for fitting. I suspect it is an epidemic model on a contact network, with constant per-link transmission rate and degree distributions. If so, does it consider network clustering? As including clustering may greatly change the outcome of an epidemic.

We briefly described the model used (page 8 lines 12 to 19). Please note that a detailed description of the model - including how graphs are mixed to generate the contact pattern has been published in a previous paper. We acknowledge that clustering was present in the simulated network (for the reviewer's information, the mean local clustering coefficient was 0.20 (SD 0.02))

We did not assume a constant per link transmission probability - see next reply.

4. How many parameters are estimated? In the manuscript two are mentioned, namely, the pre-exposure resistance levels in younger and elder adults. But how are transmission rates and initial conditions determined?

We now provide details on how transmission rates were parameterized. Rather than assuming that infectivity was constant from the end of the latent period until recovery, we modeled it as a function depending on the time elapsed from infection. We assumed the kinetics of infectivity had a gamma density function form with alpha =5.2 and beta=1, and the function was truncated at ten days. The infectivity kinetics was assumed identical for children and adults and was scaled to adjust the proportion of the population infected by pandemic H1N1 (particularly the children population which was assumed lacking pre-exposure immunity).

We have added a description of how infectivity was handled in the revised manuscript (page 9, first para).

Regarding initial conditions: all simulations started with a single infectious individual, with varying pre and post exposure resistance levels in adults - other parameters were given in the manuscript.

5. Specify the statistical method used in fitting. How are confidence intervals computed?

We indicated in the manuscript that goodness-of-fit was optimized by minimising the difference by age group between the observed and average rates in simulated outbreaks. In fact we simply determined pre-exposure immunity levels (as well as the scaling factor for infectivity) using a gridding method - running the model by varying the parameters until a satisfactory solution was obtained. Note that the proportion of infected persons calculated from the observed data (e.g. 18.1% overall (95%CI 12.2%-23.9%)) matched the simulated corresponding proportion 'at optimum' (18.3%, IQR (17.2%-20.7%)) - idem in all age groups. Since there was a substantial degree of uncertainty on the data to be fitted and many fixed parameters of the model (e.g. infectivity of asymptomatic infected persons, effectiveness of antiviral treatments to reduce infectivity,..) are speculative, we feel that a more complex method for optimizing model parameters would be in itself a subject of research.

Confidence limits were calculated with the delta method as was indicated, taking into account uncertainty on the different surveillance measures used for estimating the final epidemic size across age groups. However, since no measure of uncertainty was obtained for pre-exposure protection levels, we arbitrarily assumed that pre-exposure immunity could vary between +5% and -5% of the values obtained in the
fitted model in order to calculate post-exposure immunity confidence intervals with the delta method.

6. The authors seem to use nonlinear least square regression. If it is true, this method treats the error at each observation independently identically distributed. On the other hand, in an epidemic, the variance of error grows with the mean. So the least square method tends to bias towards the peak and final size, and generally yields unreliable approximation of the exponential growth phase. The exponential growth phase is more dependent on R0. In contrary, the peak and final size are not good indicators of R0 as changing the reporting ratio may change the estimation significantly. The authors should use more appropriate statistical methods such as minimum chi-square or maximum likelihood methods.

We fully agree with the comment but our approach was to calibrate our model to fit the final size of the proportion of infected subjects in each age group. We have included a calculation of R based on the initial growth phase in the discussion, based on a linear approximation of the solution of an SEIR model (page 17, first para). We obtained value of 1.18 for the reproductive number. Note that for this calculation, we hypothesized a ratio of an infectious period to the generation time of 0.61 (therefore a mean latent period of 1 day - but the calculation with a 0.5 mean latent period gave similar results). Note also that we applied the same calculations on seasonal epidemics observed in the sentinel network and the average R value was 1.49 with a range between 1.23-1.98. A paper is currently in preparation on this topic and is the reason why we provide an alternative reference analyzing the same data with a quite similar methodology and reporting R values on seasonal epidemics of 1.3 (SD=0.07). Therefore the initial growth rate of the first pandemic H1N1 season in France was the lowest ever observed in 26 years of active influenza-like illness surveillance.

Minor Essential Revisions
1. State that the surveillance data is aggregated weekly.
We indicate that weekly surveillance data was used (page 6, first para)
2. In figure 2, plot the average of the simulated curves, which is used to approximate the observed epidemic curve (blue) in fitting.
The simulated curves are not synchronous, and the shape of the curve averaged by unit time would be flattened compared with the observed and simulated curves. - This would give the impression that the epidemic is longer and less intense than the individual epidemics. For this reason, plotting the average curve would not be useful and was not included in the paper.