Reviewer’s report

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

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Reviewer: Stefano Merler

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In this manuscript an analysis of cost effectiveness of mitigation measures for influenza pandemics is performed. The analysis is based on an individual based model developed at the scale of a small city and accounts for several kinds of possible interventions (including social distancing, e.g. school closure, antiviral treatment and prophylaxis and mass vaccination).

In my opinion model parametrization and underlying assumptions are sources of major concern. I have so many concerns about structure of the underlying transmission model, model parametrization and model validation that I have to say that the analysis does not support, quantitatively, author's claims. In particular, the force of infection to which individuals are exposed is not modeled in a suitable way and the procedure used to seed the infection in the considered city is fully arbitrary (and not representative of real world epidemics). More in detail:

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.

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.

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.

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.

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).

5) Finally, it is difficult to evaluate what is really new in this paper with respect to previous publications by the same authors


**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests