Author's response to reviews

Title: Age-prioritized use of antivirals during an influenza pandemic

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Author's response to reviews:

Dear Editor,

we submit the revised version of the paper:

Title: Age-prioritized use of antivirals during an influenza pandemic

Authors: Stefano Merler, Marco Ajelli and Caterina Rizzo

The paper has been modified according to the Reviewer's and Editor's comments that certainly contributed to improve the manuscript.

Reviewer 1:

1. The authors assume R0 to be in the range 1.4-2.0. Larger values of R0 have been estimated (e.g., see summary Table on R0 values for the 1918 influenza pandemic in Chowell & Nishiura, 2008). Suggest to extend their R0 range of values to include a higher R0 value of about 3.

As suggested, the paper now include results for R0=3.

We added the following sentence in the methods:

Since values of R0 much larger than 2 were observed in some cities during the 1918-19 Spanish influenza (see [17] for a review), we also considered a scenario characterized by R0 = 3.

Section Results (and Figures 2, 3, 4 and the new Fig. 5) was significantly modified to take into account the new results for R0=3.

We modified our conclusions. In fact, if R0 is about 3 the number of antivirals required for treatment is about 35% of the population. The following sentence replaced the previous statement throughout the paper:

Our results strongly suggest that governments stockpile sufficient influenza antiviral drugs to treat approximately 25% of their populations, under the assumption that R0 is not much larger than 2.
2. The authors do not make any explicit assumptions on the age-specific clinical and mortality rates. Rather the resulting age-patterns presented in figure 2 are emerging from their simulation results, which is quite interesting to make this comparison. The authors compare resulting age-specific fraction of clinical cases with that of the 1918 influenza pandemic. I suggest considering two explicit age-specific assumptions on patterns of morbidity/hospitalization and mortality rates. The first assumption could follow that of the typical influenza profile where infants and seniors have the highest hospitalization/mortality rates. Perhaps this could be parametrized using epidemiological data from Italy. The second assumption could resemble that of pandemics where a clear age-shift in mortality towards younger populations has been documented (see for example Olson et al, Andreasen et al) and could affect the prioritization of antiviral medications when the objective is to reduce the number of severe cases and/or deaths. I believe the incorporation of these assumptions together with the variation of R0 intensities could inform interventions strategies for epidemic and pandemic influenza.

Subsection "Excess mortality" was added to the Methods:

Though it is not possible to predict death rates in future pandemics (reliable estimates are not available yet for the ongoing A(H1N1) influenza outbreak), it is important to assess the effects of antiviral treatment and prophylaxis under different assumptions on age-specific case fatality rates. We used results presented in [18] on the lethal 1918-19 influenza pandemic in Copenhagen (scenario EM1918), where deaths occurred primarily among young persons, and in [19] on the mild 1969-70 influenza pandemic in Italy (scenario EM1969), where deaths occurred primarily among elderly (as during inter-pandemic seasons), to estimate age-specific case fatality rates. Basically, we assumed that the estimated age-specific excess mortality rates as reported in [18] were associated to an epidemic with R0 = 2 (authors report estimates of R0 in 2.2-2.4 for the Summer wave and R0 about 1.2 for the Fall wave, due to preexisting immunity in the population) and we estimated age-specific case fatality rates (for symptomatic individuals) in such a way that the age-specific excess mortality rates as obtained by running simulations with R0 = 2 comply with the values reported in [18]. The resulting age-specific case fatality rates were used to estimate age-specific excess mortality in all the considered transmission scenarios. Similarly for the data on the 1969-70 influenza pandemic in Italy, where we assumed R0 = 1.4 (estimated value: 1.3-1.6 [20]).

Moreover, we added the following sentence in subsection "Prioritizing antiviral treatment and prophylaxis":

We assumed that treatment with antivirals is associated with a significant reduction in mortality (70%) [8,9].

Fig. 2 now includes the expected excess mortality by assuming different patterns of case fatality rates by age and by varying R0.
Fig. 5 shows the effects of the age-prioritized use of antivirals under different assumptions on age-specific case fatality.

Section results now includes results on excess mortality reduction.

Remarkably, we found that antiviral treatment provided to some age-classes (basically, those characterized by high case fatality rates) can result in a large reduction of the excess mortality, though the cumulative number of cases is not largely decreased. We added the following paragraph in the Conclusions:

In countries where the number of antivirals stockpiled is well below 25% of the population, treatment of elderly should be considered as a priority if age-specific case fatality rate were similar to that estimated for the 1969-70 influenza pandemic in Italy, where deaths occurred primarily among elder persons. On the contrary, treatment of adults should be considered as a priority if age-specific case fatality rate were similar to that estimated for the 1918-19 influenza pandemic in Copenhagen, where deaths occurred primarily among adult persons.

3. Another characteristic feature of pandemics is that they typically appear in a series of waves often unexpectedly in Spring-Summer season. Please discuss how the appearance of a series of pandemic waves could affect your conclusions.

We added the following paragraph in the Discussion:

A characteristic feature of pandemics is to appear in a series of waves. Results presented in this work could be considered fairly unrealistic if waves were determined by virus mutations resulting in the elimination (even partial) of acquired immunity in the population. In fact, a much larger cumulative attack rate would be expected during a series of wave in which acquired immunity is lost at the end of each wave. On the contrary, no substantial differences, but for the timing of the epidemic spread, would be expected if waves were determined by factors that do not contribute to increase the effective reproductive number (e.g. school closure in the Summer period or spontaneous behavioural changes of the population in response to the epidemic [36]).

Editor:

1. The age-specific prioritization may have ethical impacts; could this be alluded to in the discussion.

We added the following paragraph in the Discussion:

However, our strategies of age prioritization could have important ethical impacts that should be taken into account. Recently, the WHO has developed specific guidelines to take into account ethical considerations in developing a public health response to pandemic influenza [27]. As regards age-based prioritization, it is stated that ``the goal of reducing overall disease burden might also provide a rationale for favouring younger persons, even if the fair innings argument is not
accepted". However, "age-based prioritization criteria should be adopted only after wide public consultation".

2. In the discussion too, I would like a mention on page 11 of the example of the spread of oseltamivir resistant H1 N1 in the winter 07/08 as an example how things could potentially go during an epidemic.

We added the following paragraph in the discussion:

In fact, our results should also consider the possibility of the emergence of an antiviral resistant strain as observed in the last two influenza seasons for influenza A(H1N1) strain [32]. The circulation of transmissible oseltamivir-resistant virus may preclude the use of oseltamivir for post-exposure prophylactic treatment of close contacts. However, certain countries have differentiated their stockpile acquiring also zanamivir which is particularly relevant in light of emerging resistance to oseltamivir. This implies that additional antiviral reserve capacity is required and this is likely to come primarily from zanamivir [32].

3. Could the authors elaborate a little bit regarding the adverse consequences of treatment delay. All those involved in pandemic planning are discussing whether care should be given using the existing infrastructure of care delivery (e.g. in Switzerland, visit to the GP and drug delivery by pharmacies), or whether ad hoc structure (dedicated outpatients clinics) should be set up where patient could have at the same time a visit and receive directly the drug.

We added the following paragraph in the Discussion:

Antiviral drugs must be given early in the course of infection to reduce symptoms (maximum 48 hours) and before any prospect of knowing the sensitivity of the virus [33,34]. Viral loads begin to decrease 24-48 hours after he onset of symptoms and late antiviral therapy is unhelpful [35]. This critical aspect may have important implications on infrastructure for care delivery. Since health systems may be overwhelmed during a pandemic, new care services able to provide the usual health care services (such as drug delivery in hospital or in pharmacies or directly at home) should be considered in order to timely distribute antivirals to cases and close contacts. Also, monitoring systems able to detect adverse events should be considered. However, this aspects are directly related to the organization of the health care system, and should be tailored on the basis of the different resources available.

4. Formally, the table are difficult to read : could the key to policies be made easier to read (by codes like in figures 3 and 4 ?

The only additional information contained in the Tables (with respect to Fig. 3 and 4) was the standard deviation of all estimated values. We decided to drop all the Tables and we added subsection "Realizations and results variability" in the Results (which contains all the relevant information):
Results presented in this section were obtained by averaging over 15 simulations for each transmission scenario considered (but for the baseline simulations which were based on 100 simulations). This certainly represents a number large enough to guarantee the stability of the results. Specifically, only the timing of the initial cases is highly variable (however, this is due to the high stochasticity of the epidemic in its initial phase). On the contrary, the epidemiological indicators depending on the whole course of the epidemic are very stable: standard deviations are less than 0.02% of the population for the cumulative attack rates, less than 6 days for the peak day and less than 0.04% of the population for the peak daily case incidence.