Reviewer's report

Title: Antiviral prophylaxis during pandemic influenza may increase drug resistance

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Reviewer: Helmut Uphoff

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General comments:
Congratulation to the Authors for this interesting and relevant article. Simulation tools are adapted and used to timely address the important question of resistance with regards to pandemic planning just when a surprising fitness in conjunction with resistance against Oseltamivir has been observed in seasonal Influenza A/H1N1. The option models or simulations provide to test hypothesis and the consequences of certain assumptions has been used in a timely and elegant manner. The results are interesting and potentially of great importance for planning strategies to mitigate Influenza epidemics or a pandemic by medication and or prophylaxis. The problems addressed and the methods used are well described and retraceable due to free access to the model used (InfluSim).

The assumptions made and model parameters are in a plausible range even though some are challengeable like e.g. the amount of de novo evolving resistance combined with fitness, the time frame of its evolution during the illness, the duration of prophylactic treatment or the sensitivity of 50% against sensitive strains in people with prophylaxis.

The manuscript adheres to relevant standards of reporting and data deposition. Discussion and Conclusions are supported by the data but discussion is strongly focused on the results of the study. More emphasis may be put on relations and contradictions with other studies or assumptions e.g it would be of interest to know the authors idea how the contradiction of their results to the citations 5 and 6 may be explained (last sentence of the discussion).

Even though the idea that the model itself, its suitability for the situation simulated and the assumptions made are sources for limitations may be common, it would be helpful to give the reader some more guidance in this respect.

The acknowledgement looks sound and sufficient to me and the title and abstract convey what has been found. The writing is fine from my perspective but as a non native speaker with the same language background as the authors this may be biased.

Comments in more detail:

Abstract:
Results: What is the idea of the first sentence? 40% of 2.5 = 1?

Second sentence: if I understood properly - in the simulation resistance occurred at a random time after infection and treatment coincided, which would mean: beginning with infection for the people with prophylaxis? Is this in line with the sentence: Although….passing on is unlikely,…?

Conclusions: What had been modeled was mitigation strategy and hence conclusions may be more clearly be adhered to that (compare background).

Background: As mitigation strategy had been modeled, the problem of containment at the place of emergence - with may be limited adaption of the virus to the new host - or the containment of first outbreaks may be seen in its specific context rather.

Regarding the resistance in H1N1 it is interesting to note that a clear link to the use of Oseltamivir could not be established yet and that it is uncertain to which extent the resistance derived from “ongoing spontaneous” de novo mutations.

As the resistance has been observed against Oseltamivir and the resistance situation is slightly different with other NI it may be better to stick to discuss resistance in general in order to avoid further discussions regarding resistance mechanisms – which is not in the focus of this paper.

Method:
Redundancies with the legends of the figures may give the opportunity to cut.

The assumptions of resistance and fitness in 4.1% of treated children and 0.32% of treated adults seems challengeable as well as the random time point between treatment and the end of Contagiousness. One could assume that due to internal selection processes resistance may be less frequent in the beginning.

It is not clearly stated if the same assumptions are made for prophylactically treated persons which would mean that they could spread resistant viruses from a random time just after infection to the end of contagiousness – making them to a relevant source.

Results:
The rapid takeover of resistant strains despite relative low percentages of people under prophylaxis is surprising. It would be interesting to see the fraction of de novo resistance particularly in the beginning of the epidemic when particularly children may be affected.

It is not very understandable how exactly the grey bar in Fig.3c should be interpreted “The expected work loss without prophylaxis is depicted…”

The lower and upper borders of the grey line in the graph (2.2-2.4) partly correspond to the values mentioned in the text 2.1 to 2.4.

What is ESW? – text at the y axis of the graph Fig3c.

It is not clearly explained from the text that the grey line stands for average
workdays lost in the total adult population (when no prophylaxis is given) and the other lines stand for average work days lost specifically in people getting prophylaxis (but then the 0 in the x axis is misleading?)

Uncertainty analysis:
a) How can the low sensitivity of treatment failures and Hospitalisation to changes of susceptibility from 0 to100% be explained with respect to the Hypothesis that prophylaxis is a major factor for selection pressure. How does the sensitivity of the proportions of sensitive and resistant strains (Figures 2) look like?

The influence of variations of the susceptibility on the work loss for the scenario 0 susceptibility with 0 illness in the so protected is plausible (with literally no resistance around. But when prophylaxis does not work at all (100% susceptibility for all strains) a work loss like in a scenario without prophylaxis appears plausible (2.1 days). This would be expected independently of the proportion of people treated prophylactically.

This factor of the sensitivity analysis should be double checked.

Quick calculation formula:
Helpful and indicate the simplification due to the deterministic model.

Discussion:
It may be reconsidered if the wording NI-resistance is of any advantage. The model gives an impression for any resistance – under certain assumptions that primarily derive from Oseltamivir use. The resistance situation and probabilities of occurrence are probably different between NI-medications. Further discussions of this topic may be avoided by generally mentioning the modeled type of resistance and its assumed frequency against any medication or prophylaxis.

Fitness here is a rather theoretical relative value, which may not easily be established or measured in nature. Nevertheless the spread of current resistant H1N1 variants may even be due to a selection advantage of these strains independent from resistance.

Even though the risk of the emergence of a resistant strain is given for containment strategies as well, the simulation here is adapted to mitigation strategies. For containment additional considerations must be included as well, and the chances for containment have to be seen in relation to the risk of creating resistance – which would emerge anyway soon after treatment numbers increase (with the modeled likelihood of de novo emergence).

In the discussion in particular for findings with potential impact on planning strategies more emphasis may be put on limitations of the method and assumptions used.

In particular differences (and their possible source) between other authors
findings as mentioned in the last sentence of the discussion may be discussed more intensely.

Conclusions:
The clues are of particular relevance in case of vaccine shortness.

Figures:
Fig2 I would prefer to see assumption 1 and 6 adjacent to each other because they both stand for the “generation” or “input” of resistance in the simulation.

Fig 3 just mentioning the single nonresistant in the legend without the other factor for the “generation” of resistance in the simulation may be somewhat misleading.

Supplementary data:
Very helpful

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 declare that i have no competing interests