Reviewer's report

Title: Antiviral prophylaxis during pandemic influenza may increase drug resistance

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This study evaluates the potential impact of pre-exposure prophylaxis (combined with treatment and social distancing) on the emergence and spread of drug-resistance in the population during an influenza pandemic. While the subject of study is timely and critical for development of effective pandemic responses, the novelty of the work is largely faded by several recent studies that have thoroughly discussed strategic use of antiviral drugs in the context of drug resistance. Some of the relevant studies are:


A) Major Compulsory Revisions

A1) Methods

- The authors should consider a range of reproduction numbers R0 for the drug-sensitive strain. This should lead to qualitatively similar results, but the emergence and spread of resistance is more likely for lower R0 under high pressure of drugs. This has been discussed in reference [1] above and reference [5] of the paper where non-pharmaceutical measures are combined with an antiviral strategy.

- The current paper’s assumptions about antiviral mitigation effect are inconsistent with recent meta-analysis of antiviral effectiveness (Halloran et al, AJE 2006, DOI: 10.1093/aje/kwj362). The problem lies in the double counting of reductions in infectiousness. The impact of antivirals can be modelled as
reduction in infectiousness from the point of treatment, but no reduction in
duration, or a reduction in duration of infectiousness but no reduction in
infectiousness per day, or some combination of both. The key point is that the
overall impact has to match the reduction in secondary attack rates seen in
household studies (see the Halloran paper). The figure of a 60% reduction in
absolute infectiousness used by Longini/Germann/Ferguson and others is
consistent with trial data, but only if one assumes no reduction in the duration of
infectiousness. The authors should perhaps remove the shortened infectious
period for treated sensitive infections and consider a reduction in infectiousness
estimated in household studies.

• Early treatment reduces contagiousness, but also results in a longer time for
selection in favour of pre-existing resistant mutants, and therefore, affects the
dynamics of resistance in a complex manner (See references [1,3,5] above).

• Without considering compensatory mutations or further replication and mutation
of the virus in multiple hosts, it is relatively strong assumptions for a resistant
virus to evolve with 80%#100% transmission fitness. As has been discussed in
the literature, resistant viruses may initially emerge with impaired fitness (see

• It is assumed that 50% of prophylaxed individuals with asymptomatic infection
acquire immunity upon recovery. Is the remaining not immune or partially
immune; the authors may consult reference [4] above for some discussion on this
point.

A2) Results

• Regardless of the outcome, is 10% or higher (20%) prophylaxis coverage
feasible over the entire course of a pandemic wave (3 to 4 months as predicted
here)?

• It is hard to believe that simulations yield similar profiles for the spread of
resistance when fitness of resistant strain is significantly lower than 80% (for
example, when fitness is between 20% and 40%), even with high prophylaxis
coverage.

A3) Uncertainty analyses

• What percentage is “few people” referring to for prophylaxis?

• Is the work loss estimated per 100,000 inhabitants or per person? It seems that
this is different for unknown parameters in (a) and (b).

A4) Quick calculation formula

• There is a discussion on the fitness of resistance based on a range of
reproduction numbers in reference [4] of the paper. Can the authors provide a
range of fitness within which resistance spread is likely to occur?

• Drug-resistance could still be a big problem even when remains less than , but
sufficiently close. This is due to the creation of a large number of resistant infections, and therefore depletion of drug-stockpile without having the desired mitigation effects. One would be interested to know when drug-resistance takes over, and this depends on several factors including the time at which the resistant strain with high fitness comparable to that of the sensitive strain emerges. This has been partially discussed in reference [3] above.

- Last paragraph: the dominance of resistance is due to the fact that the spread of the sensitive infection is significantly reduced through high coverage of prophylaxis. There is an in-depth discussion on this point in reference [6] of the paper.

A5) Discussion

- Reference [6] of the paper is a modelling approach to evaluate the impact of prophylaxis on the spread of drug-resistance, and not a surveillance or data driven study. Also reference [7] is based on a mathematical model that considers the use of M2 ion channel and not neuraminidase inhibitors. These studies provide no evidence for circulation of H1N1 resistant viruses to oseltamivir.

- Can the authors provide supporting documents for the portion of resistant infections to neuraminidase inhibitors between 4% and 70%?

- “…, the fitness of the current resistant strain must indeed be very high.” This may not be an accurate statement, as the spread of resistance may have been resulted from the accumulation of drug-resistance over several seasonal influenza.

- The spread of resistance in the population for a fitness above 80% has been shown in several previous studies (see for example, references [1,3] above, and references [4,5] in the paper).

- Prophylaxis coverage of 10% to 20% seems to be significantly large, and to some extent infeasible. Restricting prophylaxis to healthcare workers and first responders (that constitutes about 1%#5% of the population) is also considered to be large, and requires prohibitively large stockpiles.

- It would be interesting to compare the results when post-exposure prophylaxis is taken place, as the prophylaxis coverage would decrease significantly, and therefore induce a much lower selection pressure (since prophylaxis is given for a short period of time to those who have been exposed to the disease).

A6) Conclusion

- Conclusion is generally masked by previous studies. The authors may consult the recent study (reference [2] above) that evaluates the impact of multi-drug strategies on the emergence of drug-resistance and mitigation of the pandemic.

A7) Figure 2

- Does the grey curve include the portion that develops drug-resistance during
treatment, but initially was infected by the sensitive strain? How do these portions differ: direct transmission versus resistance development?

A8) Supplementary material

• What is the value of effective reproduction number Re with isolation, treatment and prophylaxis?

• Can the authors explain how they get the numbers in expression for f(t)?

• Regarding the reduced duration or level of infectiousness, see the second comment in Methods.

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B) Minor Essential Revisions

• First statement in background: these studies also considered a combination of targeted prophylaxis and social distancing measures.

• “… spread are essential” should read “… spread is essential”

• In methods: “… allows to prophylactically treat …” should read “… allows for prophylaxis of …”

• Remove “do” between “virus and “no longer”, there is one more place that “do” should be removed.

• Use “prophylaxis” in place of “prophylactic antiviral medication” throughout the paper.

• “Fifty percent … become immune …” should read “Fifty percent … becomes immune …”

• “… work loss for people who receive …” should read “… work loss for people who received …”

• In results: It is difficult to understand what this statement is trying to convey: “As patients infected with the resistant strain … if no prophylactic medication is given”. Please clarify or reword it.

• In uncertainty analyses: Use “baseline” in place of “default”. What is “practically” referred to?

• In quick calculation: “(s=0)” should read “(s=1)”.

• In Supplementary Material: “R0=sRe” should read “sR0=Re”

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

Quality of written English: Needs some language corrections before being
published

**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.