Author's response to reviews

Title: Analysis of the effectiveness of interventions used during the 2009 H1N1 influenza pandemic

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Version: 3 Date: 24 February 2010

Author’s response to reviews: see over
Analysis of the effectiveness of interventions used during the 2009 H1N1 influenza pandemic

Possible new title as suggested by reviewer Rachitos:

Aggressive antiviral deployment and extended school closure improves on interventions used during the 2009 H1N1 influenza pandemic

Response to Reviewers’ Reports

We would like to thank the editors and reviewers for their attention to our manuscript. Detailed responses to each reviewers’ comments are given below along with detail of corresponding changes to the manuscript.

Note that reference numbers given here correspond to those in the revised manuscript.

Referee 1 (Hatzakis)
1. The reviewer noted that there have been other studies about the impact of interventions on influenza spread, and that we should clearly stress the novel content of this analysis.

   The novel content of this analysis is that we have narrowed our focus to a set of intervention scenarios that are highly likely to be used in future pandemics (or in resurgent waves of the current pandemic) – namely, those that were actually used in 2009. Furthermore, we have concentrated on epidemics with reproduction number and serial interval estimated from the 2009 pandemic.

   We have added sentences to this effect to paragraph 3 of the background section.

2. The reviewer pointed out three additional influenza intervention modelling studies that included an antiviral component. We have updated the “related work” section of the discussion to include these references. We have found the Sypsa and Hatzakis study has comparable results, and that these were our study and other comparable studies. The Yasuda study is similar but does not have a directly comparable intervention scenario. The Halloran study, includes several assumptions that are not relevant to the 2009 pandemic: lowest $R_0$ considered was 1.7, diagnosis ratio was 60% or 80%, all scenarios included additional social distancing (workplace and community) that was not widespread in 2009; they also they did not consider T or T+H+E; for did they report AV stockpile requirements. A statement to this effect now appears in the paper.
3. Our assumed latent and infectious periods do give a generation time consistent with estimates of influenza A/H1N1. We have added comments to this effect where the durations are given and in the results section that describes the no-intervention epidemic outcomes.

4. The 30% AVEs figure was introduced by Longini et al in [26] (reference numbers used here correspond to those in the revised manuscript), which stated that no direct estimates were available but that 30% could be inferred from neuraminidase household trial data from 1998-1999. Yang et al [38] presented a maximum likelihood estimate based on that trial data plus an additional trial in 2000-2001, and found AVEs to be 85%. We have added a reference to a recent estimates of AVEs given in [40]. We assume that the modelling studies mentioned by the referee were conducted before this publication (although the 85% figure appears in a 2004 technical report) and used the earlier estimate. The Halloran 2008 [27] study is based on the same simulation models used in earlier Ferguson et al [20], Longini et al [21] and Germann et al [22] studies and have presumably inherited the 30% AVEs estimate. We have added a comment to this effect in methods section where antiviral efficacy is described.

5. The school closure methods section has been updated to clarify the details of the school closure; and suggested addition made to the discussion section.

6. As suggested, we have tightened up the reference section to make it more concise in the area indicated.

7. Table 4 has been removed.

8. The methods section describing the age-specific susceptibility parameters has been expanded to state that our no-intervention epidemic has an age-specific attack rate with higher rates in children compared to adults; and a comment has been added to the discussion stating that school closure would be less effective if this were not the case.


10. This formula has been moved to the methods section as suggested.

11. Corrected.

12. Figures have been updated as suggested.

13. The laboratory confirmed cases and death statistics have been updated.

14. We have moved the comment about the estimated $R_0$ of the 2009 pandemic to methods section, and extended it to state that there have been both higher and lower estimates of $R_0$ (giving references), indicating that our choice of 1.5 as being representative of the pandemic is still reasonable.

15. 4 weeks is probably longer than anyone would consider mandating home isolation for school contacts of diagnosed individuals; however we wanted to examine interventions similar to those actually used in a systematic way, so we included the same range as for the other school interventions (1-4 weeks).

16. The triggering community case threshold has been added to the description of the “all schools closure” intervention.
17. Additional details of behaviour of treated individuals and the timing of treatment initiation have been added to the antiviral intervention descriptions in the methods section.

18. Prophylaxis was assumed to begin at the same time as treatment of the diagnosed case, this detail has been added as above.

19. A comment stating that the listed no-intervention epidemic characteristics apply to epidemic spread within a community with the structure of our modelled community has been added to the beginning of the results section.

20. A comment has been added about the Japanese experience in May 2009 when school closure successfully contained an early outbreak, delaying the progress of the pandemic in Japan by perhaps 6 weeks [33].

21. As part of our response to comment 2 above, the Sypsa and Hatzakis [47] paper has been included in the “related research” section. We note that the results of this paper falls in with the comparable individual-based model study, having unmitigated epidemics in the 30%-35% range, and simulating the treatment plus household prophylaxis intervention, and gratifyingly the results are similar to the other comparable studies.

22. Reference added as suggested.

23. A comment about the large number of antiviral courses used for sustained prophylaxis strategies possibly leading to antiviral resistance has been added to the discussion.

24. This similarity in antiviral usage for the T+H+E strategy with and without school closure at $R_0 = 1.6$ is indeed correct. With extended prophylaxis, the pattern of antiviral usage is quite complex. Although increasing $R_0$ increases infections and antiviral use, it actually lowers the ratio of prophylactic courses per infection – there is a saturation effect where a greater number of numbers of infections occur in contact groups (hubs and households) where an infection, diagnosis and prophylaxis has already occurred. While interesting we think that including this commentary would unnecessarily complicate the manuscript.

Referee 2 (Rachiotis)

1. While we think the original title is appropriate, we propose the following alternative title that could be used if the editors agree with the reviewer that the paper’s most significant implications should be reflected in the title:

“Aggressive antiviral deployment and extended school closure improves on interventions used during the 2009 H1N1 influenza pandemic”

2. It would indeed be feasible to enlarge the current study to include additional non-pharmaceutical interventions, and several previous modelling studies have done so (eg [17] [20] [22] [23] [49]) - including our own previous studies using the same simulation model used here [7] [8]. However we feel that these additional results would detract from the main focus of this paper, which was to model interventions that actually occurred. While workplace closures, household quarantine and so forth occurred in several locations, these interventions were a much less common response than school closure.
and antiviral usage. We could simulate additional non-pharmaceutical interventions; however, unlike the observed combination of school closures and antivirals, these simulations would be much more speculative as to the combinations and operational details of simulations, and so would add little to the existing modelling results while making the manuscript more complex.

3. The referee makes a good point: the reason we have not modelled other non-pharmaceutical interventions is not because we believe they are ineffective or unimportant; on the contrary, combinations of rigorous social distancing interventions may be the only way to arrest the spread of a highly transmissible, highly pathogenic influenza strain while vaccines are developed [8] [30]. We have added a comment to this effect in the discussion.

4. It is true that the scale of use of antivirals required by the sustained prophylactic strategies shown to be effective in our paper is much larger than occurred in practise in 2009, and may lead to a higher probability of antiviral resistance. We have added a comment to this effect in the discussion section (as for Referee 1 comment 24).

5. Our assumption has generally been that while vaccination is the ideal solution to a pandemic, vaccines would not be available soon enough and that antivirals and non-pharmaceutical interventions would have to be employed as a stopgap or alternative. However the referee makes an interesting point that antivirals seem to be more acceptable to the public even now that a vaccine is available. This may be true also for school closure, although we feel that the same factors that lead to low acceptance of vaccination (the lack of perception of a deadly threat) also make school closure unpalatable, and the acceptance of school closure in 2009 was due to uncertainty of the nature of the pandemic.

Minor essential revisions have been made as suggested. With regards to dates for URL references (numbers 5,6,7 in manuscript) – the BMC Public Health reference format specifies no date in the format for URL references, which should appear:

Title [url]