Author's response to reviews

Title: Construction of the influenza A virus transmission tree in a college-based population: co-transmission and interactions between influenza A viruses

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Author's response to reviews: see over
Dear Professor Chowell

We appreciate very much the comments and suggestions of two reviewers, and thank you for your encouragement. We have now addressed all the points made by the reviewers (please see the details attached below) and hope the revised manuscript is now suitable for publication in BMC Infectious Diseases.

Look forward to hearing from you in due course.

Yours sincerely

Xu-Sheng Zhang (on behalf of Daniela De Angelis)
Reviewer: Niel Hens

Major essential revisions
- Why did the authors assume one common generation interval distribution for both viruses? Is the empirical evidence in the database consistent with this assumption? This can easily be tested and added to the manuscript.

It is a good suggestion. We have estimated the generation intervals using the available transmission process data and further list a literature to support the one common generation interval distribution assumption. The following are added on page 6 line 124:

“Compared with outbreaks that were involved with one virus and one transmission process [14], …the three different types of infections have similar epidemiological characteristics.”

- The method by Hens et al. (AJE, 2012) relies on assumptions which are outlined in the discussion of that paper. More particularly the assumption about a stationary generation interval distribution should be mentioned here.

Some discussions about this are added before “Conclusion”
“The original method of reconstructing the transmission tree by Hens et al [14] relies on three assumptions… the generation interval distribution has been assumed to be unchanged over different types of infection as well as over the course of the outbreak.”

- Another interesting aspect that has not been studied here and given the limited amount of information is impossible to study is the order in which co-infected individuals were infected by both viruses. Some discussion is welcome.

Yes, we have added the following discussion just before the “Conclusion”:

“Another aspect is how co-infection is generated… therefore no way to investigate the effect of the order in which the two viruses are acquired.”

Minor essential revisions
- lines 79-80: Do the numbers 235 and 191 refer to the wider community or to the two buildings?

To avoid the confusion, the sentence has been rephrased as
“Buildings 1 and 2 (with a total membership of 235 and 191 persons, respectively) are …”

- line 85: Please define clinical patterns more explicitly.

For this, the following was added after the sentence: “and the six co-infected patients showed no more severe symptoms than the singly infected patients.”

- lines 93-96: Significant in what way? What is the null hypothesis tested here?
Here we use “significant” to show the extent of mixing in comparing contacts between two dormitories and these within dormitories. The mixing between students within dormitories should be more or less free which can be regarded as null hypothesis. While contacts between the students from two dormitories are much less so.

- line 115: It’s best to use the same phi throughout equation (1) and the rest of the text.
  Done.

- line 119: Weibull distribution: Is there any impact of the choice of distribution on results? Why the choice for a Weibull distribution?
  We have tried gamma distribution for generation interval, but the results are quite similar as noticed in Hens et al (2012). To clarify it, the following sentence is added “Different distributions such as … to describe the distribution of generation intervals [14].”

- line 125: characteristics
  “Characters” has been replaced by “characteristics”

- line 135: is
  “are” has been replaced by “is”

- line 149-150: Best to add that p=1 here.
  “and $p_{ij}(v,w,\phi, \theta) = 1.$” was now added.

- What happens with ties in dates of symptom onset? Maybe I missed it, but it’s best to explicitly indicate how you tackled that issue.

Sentence 148-149 has been expanded to
“The original numberings of patients in Figure 2 of Liu et al [12] … For convenience of our analysis, the forty patients have been re-indexed in the order of symptom onset as 1, 2, …, 40”

- lines 221-237: It would help to calculate the variance of the different estimates of Re to quantify variability.

The variation of $R_e$ has been given as the 95% confidence intervals. As stated in the text, the values of $R_e$ for H1N1 and co-infection are nearly fixed because the transmission processes involved are almost known and then fixed. However, the value of Re for H3N2 have shown some variation.

- line 229: `can cause’ is best rephrased to specify what was found here.

The sentence has been replaced by the following:
“Although the estimate of $R_t$ for A/H1N1 is in agreement with the usual estimates [16,17], ... reduces susceptibility and hence its spread.”

This also answers the concern of Reviewer #2

- line 237: delete ‘obviously’
Done.

- line 359: should be a non-bold number
  Corrected

**Reviewer:** Michael MW Worobey

The one "minor essential revision" I would recommend is to further comment on the line stating: "These estimates show that A/H1N1 can cause an outbreak on its own but A/H3N2 cannot"

To avoid confusion, this sentence has been replaced by some explanations. See the response to reviewer Niel Hens.

**Other changes**

Three new references have been added.

We spotted a small error in the estimation of model parameter $a$ and $b$ which now has been corrected. This doesn’t affect our conclusion.