From reviwer2

1) The model is fitted to a dataset representing the first wave of the 2009 pandemic in Hong-Kong. This is a special case of an invasion wave in a tropical setting. It would be important to generalize the findings to other outbreaks, including post-pandemic waves, and other locations. A large amount of serological and epidemiological information exists for the 2009 pandemic and post-pandemic waves in the UK - do the findings extend to these outbreaks as well? What about seasonal strains?

*Ans: I will discuss the future study is to extend the model to seasonal flu to understand whether age specific immune boosting and protection are similar across different seasonal strains. About other regions’ pandemic, to me, the important is not to reconstruct disease for others data but we can indicate the pattern of serological distribution are similar to HK data, then age specific boosting and titre dependent protection are important to incorporate. (cite Dennis E. te Beest et al. Joint modelling of serological and hospitalization data reveals that high levels of pre-existing immunity and school holidays shaped the influenza A pandemic of 2009 in The Netherlands)*

2) I was unconvinced by the comments that the dynamics of models with stratified immunity vs threshold immunity truly differ. Figure 5 indicates there are only subtle changes in Re by the two models -with overlapping CI (as noted in text, Re=1.22 in the stratified model vs 1.19 in the threshold model at the onset of the epidemic, and Re=0.82 in both models near the tail of the epidemic). Further, as noted by the authors, seroprevalence estimates are remarkably similar by the two models.

*We find that the serological model improves the model fit: (1) using Deviance Information Criterion as criteria to estimate the fitness of seroprevalence. DIC is lower when stratified immunity was included (2) The lower RMSE of the reconstructed disease dynamics and the incidence. The seroprevalence estimates are remarkably similar, as in our new figure, it is because seroprevalence would underestimate the cumulative incidence which cannot reflect the true infection rate.*

3) I would have liked to see more formal model comparisons, for instance between the threshold and stratified models, and between different formulations of the stratified model (eg with and without age-dependent Ab boosting, with/without increased susceptibility in children, etc).

*I will add the following simulations*

*model1: threshold (already done)*

*model2:*

*i) full model (10 parameters)*

*ii) without age-dependent protection  (7 parameters)*

*iii) without age-dependent Ab boosting (7 parameters)*

*iii) without increased transmissibility in children (6 parameters)*

*Use DIC to obtain the best fit model. Then reconstruct the disease dynamics use the best fit model.*

4) Some countries (although not Hong-Kong) reported high Ab titers in seniors prior to the pandemic... can't this explain the low attack rates in those age groups? The authors' hypothesis primarily involves differential age mixing and boosting. Is it consistent with the occurrence of recrudescent pandemic waves in the second and third year of A/H1N1 virus circulation, which preferentially affected seniors (as described in the UK, Mexico and elsewhere)?

*I need to do literature survey to see how many countries with low baseline titres in seniors but also show a low incidence.*

[*http://onlinelibrary.wiley.com/doi/10.1111/irv.12074/epdf*](http://onlinelibrary.wiley.com/doi/10.1111/irv.12074/epdf)

*Although some countries show higher Ab titers in seniors, however there are also studies show low pre-existing Ab titres in seniors but still obtain lower incidence. For example, the recorded incidence declined with increasing age in Norwegian population but the baseline or pre-pandemic HAI titres in older group 65-79 were lower than most other age groups. (High prevalence of antibodies to the 2009 pandemic influenza A(H1N1) virus in the Norwegian population following a major epidemic and a large vaccination campaign in autumn 2009 )*

*So, all pre-existing titres, contact mixing, and age specific virulence should be considered. In our study, contact mixing and age specific virulence dominate the low incidence in senior group.*

*About the 2nd and the 3rd waves. Immunisation appears to have contributed to the reduced impact of the pandemic in 2010 (ref* [*http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19788*](http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19788)*).*

*3wave was caused by changes of the virulence (ref).*

*That means other important factors which are not in our study scope here needed to be considered.*

5) Some discussion of the potential role of long-lasting T-cell immunity would be useful.

*Add a reference talking about the kinetics of the effector CD8 T cell using Empirical data*

[*http://jvi.asm.org/content/75/22/10663.long*](http://jvi.asm.org/content/75/22/10663.long)

6) Some sections of intro and results could use careful proofing. For instance, the notion of "boosting" is introduced on page 10 of results but not previously defined.

Minor comments:

7) The posterior distributions of TP50s look wide (Fig S5)... are they statistically different?

*Will make a note, they are not significantly different because of the credible interval*

8) Fig S5: it would be useful to harmonize the x-axes of each class of parameters to facilitate comparisons across age groups

*Will change*

9) Second sentence at the top of p7 is particularly unclear ("Model titres at T1...")

*I don’t understand why it is not clear. Let’s discuss sometime together.*

10) Second para of p8: Not sure why the predicted seroprevalence at T2, estimated at 20.4%, is considered "slightly lower" than the baseline of 8.9%...

*Rephrase the sentence*

11) Equ 5 could be simplified by replacing I\_alpha with TP50

*Will change*

12) Bottom of p16: sorry if I missed it, but I could not find the boosting terms, AbB\_alpha, in any of the equations

Reviewer1

My biggest problem with the motivation of the work is that incorporating serology into transmission models is not new.

*Will do literature survey to address whether it is new. To me all the current model use the simple threshold or a corrected threshold. That is what we want to compare.*

[*http://www.ncbi.nlm.nih.gov/pubmed/25540241*](http://www.ncbi.nlm.nih.gov/pubmed/25540241)

*We shall make clearer whether the idea of serological model is new. Rephrase in introduction and discussion.*

How was convergence of their metropolis hastings algorithm established? How did the authors handle initial conditions?

*Will do MCMC diagnosis and show the traces*

They make various assumptions regarding functional forms (eg phi), but where is the empirical support for these choices or the exploration of sensitivity?

*Show the following references: http://bmcmedresmethodol.biomedcentral.com/articles/10.1186/1471-2288-10-18#CR25\_421*

[*http://www.sciencedirect.com/science/article/pii/S1045105609000116*](http://www.sciencedirect.com/science/article/pii/S1045105609000116)

[*http://cvi.asm.org/content/15/7/1042*](http://cvi.asm.org/content/15/7/1042)

[*http://apps.who.int/iris/bitstream/10665/84288/1/WHO\_IVB\_13.01\_eng.pdf*](http://apps.who.int/iris/bitstream/10665/84288/1/WHO_IVB_13.01_eng.pdf)

They assert that including births/deaths would not change their results -- what is this based on?

*Will explain it.*

What is the value of omega? Was it assumed, or estimated?

*Will explain it.*

The fitted model predictions show very little variability in comparison with data, probably resulting from the mean field assumption--why is this justified, given that we know the R0 for influenza is typically small?

*I don’t understand*

Here are the outlines for changes of our manuscript.

To be more efficient, before we meet on Wednesday, I will send you an updated version following this outline and use that one we can discuss.

If you have any thoughts you want to add on, please let me know today.

Sean

“The underlying hypothesis is interesting, but I feel that the authors have fallen short of demonstrating the importance of stratified immunity.”

1. I agree we have fallen short of demonstrating the importance of stratified immunity. For the new manuscript, we shall demonstrate the improvement of the new titre model.

* First, make clear what titre model improves the performance than threshold model. Two improvementsç
  + Seroprevalence underestimates the cumulative incidence
  + Peak time delay -> Make a formal model comparison
* Second, make clear what are similar between two models
  + R0 is similar but the main difference is the delay of Re drop to 1.
* Third, make a quantitative comparison. e.g, likelihood ratio test for observing hospital confirmed cases assuming Poisson distribution.

1. We shall make clearer whether the idea of serological model is new. Rephrase in introduction and discussion.
2. Add more references about the uses of serological data
   * To use serological data to infer force of infection (from a book). VZV viruses
3. Our methods, state clear the parameters. Make a table.
4. MCMC diagnosis and the traces

Model1, 1:40

Model2, Titres, age specific boosting, age specific protection, transmissibility

Model3, Titres, boosting, age specific protection, transmissibility

Model4, Titres, age specific boosting, protection, transmissibility