Reviewer’s report

Title: Significant cross reactivity to influenza virus in adults and children following natural exposure during a period of marked antigenic drift

Version: 2

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Reviewer: Feng Liu

Reviewer’s report:

Mandelboim et al. reported their findings to demonstrate significant cross reactive (CR) antibodies to influenza virus in adults and children following natural exposure during a period of marked antigenic drift. The findings bear good scientific merit and will contribute to better understand the mechanism of naturally occurred cross reactive antibody in human population following infection of flu virus. A few points need to be addressed and some revisions/rewarding are necessary before further consideration of publishing.

Major Compulsory Revisions

1. What’s the flu vaccination history of these subjects recruited in this study, especially for those children? The authors emphasized natural flu infection, but they didn’t provide any evidence or statement that those children were not vaccinated yet when they were taken blood draw. This is an important part of experiment design, otherwise the authors cannot say the CR antibodies detected were purely induced by natural flu infection.

2. Results, the second paragraph. The authors can only say “the A/Wyoming virus are antigenically similar to A/Fujian” but NOT the A/California virus. (No. 8, 2005, 80, 65–76 http://www.who.int/wer). In addition, A/Wisconsin/67/05 strain is also NOT antigenically similar to A/Fujian/411/02.

3. Discussion. The fifth paragraph, the authors cannot say “…thus these CR antibodies appear to be protective” because we can only refer to the threshold of HI titer of #40 as an indication of reduction of 50% risk from flu infection. To be cautious, I would suggest to reword the sentence as “…might provide protective function.”

4. Discussion. The first half of sixth paragraph is quite confusing and not clearly delivering the authors’ point to me. Suggest to reword it. In addition, the same as comment 11 above, the authors cannot say “…as our detection assays requires that the generated antibodies will be protective.” Again, suggest to change it as “we use the threshold of HI titer of #40 as a positivity.” Again, the authors need to revise this part.

Minor Essential Revisions

1. The authors should add line numbers cross the manuscript to make tracking easier.

3. In Abstract, Results part, the authors need to clearly state that 13% in 2002 and 29% in 2007 of sera from children shows HI antibodies titers of # 40 against both Panama/1999 and Wisconsin/2005. The current description is confusing.

4. Methods, Sample collection. It’s indicated that samples were collected from children aged 1-17 yr here, but only those from aged 1-3 yr were used in the study, right? Change “age 1-17” into “age 1-17 years”, and the same for age 1-3.

5. Methods, HI assay part. The last sentence, change “…active since 2006.” into “active in 2006-2007 season.”

6. Discussion. The first paragraph, suggest to move “following 4 years of infections” after “…strain A/Panama/2007/99”.

7. Discussion. The third paragraph, change “…2009 swine influenza…” into “…2009 swine origin influenza…”.

8. Discussion. The fourth paragraph, the mortality rate of H5N1 human infection is about 60%, but not 50% (see WHO webpage).

**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:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.