Reviewer's report

Title: Published sequences do not support transfer of oseltamivir resistance mutations from avian to human influenza A virus strains

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Reviewer: Vanessa Escuret

Reviewer's report:

This work is a demonstration using published NA sequences that there is no transfer of oseltamivir resistance mutations from avian to human influenza strains. This work is a demonstration of what was assumed and is beyond the question of oseltalmivir mutation transfer. Indeed, NA from avian and human influenza viruses remain phylogenetically distant.

Minor essential revisions

In the Abstract, line 35:
In 2007/2008 the isolation of human influenza viruses bearing a « H275Y » mutation (N1 numbering) was not due to selection pressure as they were isolated in patients without oseltamivir treatment. The sentence « The results indicate that resistance in influenza viruses infecting humans is due to selection pressure… » should be modified or suppressed.

Introduction, page 3, line 61: the authors should add the A(H7N9) as an avian influenza virus able to infect humans and add corresponding references.

Materials and Methods: Avian and human influenza virus N1 and N2 genes studied:
There are very few avian N1 (only 4) and N2 (only 1) bearing an oseltamivir resistance mutation. As a consequence is-it possible to deduce statistically significant results from these data?

Results line 107: « traditional » should be changed as this term is not appropriate and authors should change this term by « seasonal influenza viruses circulating before the A(H1N1)pdm09 ».

Results line 113: The authors should better define the origin of the 92 human N1 sequences bearing a « H274Y » mutation as most of these strains were probably isolated in 2007 or 2008 (probably designed by the dark yellow box in figure 1) when there was emergence of A(H1N1) viruses bearing this mutation in patients who did not received any oseltamivir treatment.

Results, page 6, lines 136 to 138:
There was a confusion between avian and human sources in this sentence. The sentence should be modified as follows: « One N2 sequence from a human source was found among the N2 sequences from avian in cluster A (fig 2), whereas altogether 17 N2 sequences from avian were found among the N2 sequences with human source (cluster B).»
Results, page 7, line 149: « I total… » should be changed by « In total »

Supplementary figures 1 and 2: may be interesting as they refer to other mutations but are difficult to understand without any legends. Whose figure S1 or S2 concerns N1 or N2? Legends should be added.

Figure 2 legend: the reference to the dark yellow box should not be mentioned in this legend (as it is useful only for figure 1 legend).

Authors should not insert references in the Results section: there is a mix with discussion of the results. Line 124 (ref 15), line 126 (ref 9), line 146 (ref 16), line 156 (ref 17), line 160 (ref 13), line 161 (ref 14), line 165 (ref 18). The authors must comment the results and cite these references only in the Discussion section.

Discussion:

It would be interesting to add data concerning oseltamivir consumption according to countries and whether there is a detection of pollution by oseltamivir more important in these regions?

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

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

V.E. received a travel grant from Roche Pharmaceuticals to attend the Fourth European Scientific Working Group on Influenza (ESWI) Influenza Conference and declares potential conflict of interests with Sanofi-Pasteur (intervention in symposium).