Author's response to reviews

Title: Human influenza A H5N1 in Indonesia health care service-associated delays in treatment initiation

Authors:

Wiku Adisasmito WA (wiku.adisasmito@ui.ac.id)
Dewi Nur Aisyah DNA (dewi.aisyah.ui@gmail.com)
Tjandra Yoga Aditama TYA (doctjand@yahoo.com)
Rita Kusriastuti RK (ritakus@yahoo.com)
Trihono N/A TH (trihono1954@yahoo.com)
Agus Suwandono AS (suwandon049@gmail.com)
Ondri Dwi Sampurno ODS (ondri@litbang.depkes.go.id)
Prasenohadi N/A PH (praseno@gmail.com)
Nurshanty A Sapada NS (sapada_rspiss@yahoo.com)
MJN Mamahit MNJM (makentur@yahoo.com)
Anna Swenson ASW (aswenson@outcome.com)
Nancy A Dreyer ND (ndreyer@outcome.com)
Richard Coker RC (richard.coker@lshtm.ac.uk)

Version: 2 Date: 20 February 2013

Author's response to reviews: see over
Dear Dr Daniel Barnett,

Many thanks to you and the reviewers for the constructive and encouraging comments on our manuscript entitled “Human influenza A H5N1 in Indonesia health care service-associated delays in treatment initiation”.

After careful consideration of all comments we have now revised the manuscript accordingly. Please see the attached revised manuscript and response to reviewers’ comments. We hope the manuscript is now acceptable for publication in BMC Public Health.

Yours faithfully,

Prof. Wiku Adisasmito
(Corresponding author)
**Reviewer 1**

<table>
<thead>
<tr>
<th><strong>Background</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Comments</td>
<td>Regarding the last sentence “this is the first analysis of health service barriers to care for human H5N1 cases,” it may be just from Indonesia, but other country.</td>
</tr>
<tr>
<td>Revision</td>
<td><em>We have been unable, despite an extensive search, to locate any other papers that address health service barriers and human H5N1 cases either in Indonesia or elsewhere.</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Methods</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Comment 1</td>
<td>The authors said that subjects included 74% of all reported H5N1 human cases in Indonesia between September 2005 and December 2010. Authors excluded 26% of total cases due to administration hurdles. The selection of subjects needs to be a little bit clearer.</td>
</tr>
<tr>
<td>Revision</td>
<td><em>Case records on 27% of cases previously reported to WHO could not be retrieved. We have clarified this issue.</em></td>
</tr>
<tr>
<td>Comment 2</td>
<td>I was surprised that the median number of first access to healthcare from symptom onset was 0.0 (range, 0-7) among the study subjects. How this kind of early seeking healthcare behavior came from? Is this the normal behavior for people in Indonesia? Were the subjects included the people in the rural area? Even people who live in rural, do they easy to access to healthcare?</td>
</tr>
<tr>
<td>Revision</td>
<td><em>This was a surprise to us too and suggests, as we point out, that delays in treatment are principally a function of health services rather than delays in patients seeking care. We found no difference in this even where rural settings were concerned suggesting that public awareness of H5N1 and the need for early presentation is well-established. We have addressed this issue in the discussion section more clearly.</em></td>
</tr>
<tr>
<td>Comment 3</td>
<td>Authors concluded the differentia on among healthcare provider refer to the delayed treatment. The conclusion was clear; however, authors included “others (nurse and midwife)” for this evaluation (Tables 2, 3). Do nurse and midwife have authorization for prescribing drugs? Or, just the places for first presentation of healthcare for the patients? Cleared description need to include in this evaluation of this study.</td>
</tr>
</tbody>
</table>
Revision | Due to uneven physician distributions across Indonesia, patients in rural/remote area usually receive medications from nurses or midwives.

Comment 4 | There are many papers that previously discussed about the relationship between delayed antiviral treatment and mortality for H5N1 patients. Authors need to be included more references other than the papers from Indonesia.

Revision | We have included a reference from a global registry that draws on data from numerous countries (ref 3) rather than numerous country studies (these are included in this reference).

**Figure**

Comment | Page 11, Line 10
I cannot see Figure 2 in this manuscript.

Revision | Corrected in the attached

**Reviewer 2**

**Background**

Comment 1 | Overall the background is well written and understandable, although it is a bit too brief and do not highlight the gaps of knowledge that lead to the study, and why the expected results are of interest. This part should be located just before the declaration of the purpose of the study.

Page 4 of 22
Line 10: In the paragraph "We recently reported ... after symptoms onset", what do you means with "case fatality rates are still improved"? Do the fatality rates increase or decrease when the treatment is delayed?

Revision | We agree regarding extending the background and have added the following sentences: Given the very high mortality rates associated with H5N1 infection in Indonesia and the known association with delays in initiating treatment, it is important to determine whether delays occur across the country or whether some provinces experience longer delays than others, and whether delays are the result of patients delaying seeking health care or whether delays in the health care service itself are important.

We have clarified the section on treatment delay and earlier research to make it more clear: We recently reported the impact of treatment on the clinical course of influenza H5N1 and showed that though treatment with oseltamivir within 48 hours offers significant
benefits in terms of survival, the benefits of treatment persist in terms of reduced case fatality rates, though to a lesser extent, even if treatment is delayed up to 6 to 8 days after symptom onset

Comment 2
Page 4 of 22
Line 4: “By 21 February 2012, 586 cases have been reported.”, if possible state the whole period of reference (e.g. "From XXXX to YYY...")

Revision
We have modified the sentence to read: By 21st February 2012, 586 cumulative cases have been reported globally

Methods

Comment 1
I strongly suggest to reorganize the Methods and Statistical Analysis section, as data used are not clearly defined methods are not well explained. Moreover, some of the information provided here are repeated throughout the section.

Revision
We have restructured and clarified these sections and removed duplication

Comment 2
You should declare the amount of data you retrieved from the Ministry of Health and from literature.

Page 5 of 22
- It is not clear whether you recorded all of the symptoms for each case or only the predominant one
- What do you mean with “outcome information”? Should this provide information on the fatality rate?

Revision
All data were collected from provincial & district health office clinical records as mentioned in Methods section. As these clinical records also reported and jointly collected by the Ministry of Health, we validated the data with the Ministry of Health data.

All data on symptoms and signs that was documented were analysed. We have made this clear in the manuscript. Data was not restricted to one ‘predominant’ symptom.

Outcome information is the data describing the patient’s clinical including death outcome

Comment 3
Page 5 of 22
- lines 6 and following: “All cases had laboratory confirmation of infection... ......Health”, you have already explained that in the preceding phrase.
- lines 9-10: I would rather write “likely
source of exposure” than simply “exposure”.
- lines 16-17: These two lines could be merged with the description of the data included in the registry you created (lines 9-10), to avoid repetitions and ease the reading

Revision

We have deleted the duplication noted here. We agree and have added ‘likely source of exposure’

Statistical Analysis

Comment 1

If I understand correctly, you analyzed the differences in the various time intervals grouped by single factors (i.e. Presence of a single symptoms, or location of first presentation to provider). I do not think that this is the best way to analyze your data, as you would lose the effect of the presence of multiple factors. I would rather suggest to use an alternative method, such as a GLM. In such a way you would be able to consider all of the factors, and to include interactions between terms.

Revision

We considered simultaneously adjustment for multiple factors; however, due to the wide variability in missing data (since data were collected using available from existing records), the sample size was too small to conduct a multivariate analysis.

Comment 2

- lines 2-3: I would delete the phrase “All analyses reflect data as reported”, and begin directly with "Cases with missing data."
- It is not clear what you consider here as "time intervals of interest". I think it would be better to define what "time intervals" are earlier in the Method paragraph, right after you describe the data sources.

Revision

We have modified this section to read: Cases with missing data on either the time intervals of interest or the exposure (including cases where the exposure was coded as “not known or not documented”) were excluded from analyses. The denominator for each analysis is the number of cases with non-missing values for the relevant variable. Since time intervals were not normally distributed, nonparametric statistical tests were used.

Results

Comment 1

Please clarify in this section and/or in the Methods the actual numbers you are working
on, and why you are excluding some of the cases from the analyses. i.e. you obtained data for 124 cases of which 114 had information on the symptoms onset date and time to presentation, 94 had data on the time period to viral testing... etc...
Moreover, how many of the virologically tested cases had also date of symptoms onset? And what about the treated?

Revision

In the methods section we clarify that only cases with non-missing data are included in each analysis. The "n" for each analysis is included in the relevant table, and has been added to the text where it was not included previously.

Comment 2

Page 7 of 22
lines 9 and following: The numbers differ from the ones reported in table 2. In table 2 you report that 65 ouf of 118 cases (and not 65%) first presented to a local physician office, same for the 25/124 to the emergency room. Moreover you should specify that the total number of cases you are considering here is 118 and not 124 (and please explain why).

Revision

Corrected in the attached.

Comment 3

Page 9 of 22
Are the 30 symptoms reported on presentation the predominant symptoms (i.e. only one predominant symptom was recorded)? If more than one symptoms were recorded per case, I suppose that the time intervals to virological tests and to treatment did not depend on just the predominant symptom, but on a combination of symptoms. I think the authors should consider this possibility in the discussion.

Revision

Addressed under comment 2 in methods above. And in the manuscript.

Discussion

Comment 1

Page 11 of 22
- lines 9-10: In your opinion why the fatality rates were lower for cases presenting to rural health centres and public health services?
- Line 10: Please replace “figure 2” with “table 2”.
- Line 20: I do not understand why you are saying that 65.52% of the cases presented to a physician's office. In table 2, you report 65 cases on 118 being presented to a physician (i.e. 55%).

Revision

- We too were intrigued by this
association. One possibility is that patients with an obviously poor prognosis may have been referred to higher level health facilities without being formally admitted to rural health centres or public health centres.

- Corrected in the attached
- Corrected in the attached

**Tables**

<table>
<thead>
<tr>
<th>Comment 1</th>
<th>Table 2. Why did you report 107/124 and not 107/118, since your population of reference here is 118 (sum of N) and not 124...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revision</td>
<td>We have updated the table in the attached.</td>
</tr>
<tr>
<td>Comment 2</td>
<td>Table 3. Please report in the main text the totals you have put in the table.</td>
</tr>
<tr>
<td>Revision</td>
<td>Corrected as attached</td>
</tr>
</tbody>
</table>