Author’s response to reviews

Title: ICU-treated influenza A(H1N1) pdm09 infections more severe post pandemic than during 2009 pandemic: a retrospective analysis

Authors:

Pekka Ylipalosaari (pekka.ylipalosaari@ppshp.fi; pylipalo@gmail.com)
Tero Ala-Kokko (tero.ala-kokko@ppshp.fi)
Jouko Laurila (jouko.laurila@ppshp.fi)
Lauri Ahvenjärvi (lauri.ahvenjarvi@ppshp.fi)
Hannu Syrjälä (hannu.syrjala@ppshp.fi)

Version: 1 Date: 28 Aug 2017

Author’s response to reviews:

August 18, 2017

Dear Editor,

Thank you very much for your letter concerning our manuscript entitled “ICU-treated postpandemic influenza A(H1N1) pdm09 infections more severe than during 2009 pandemic: a retrospective analysis” written by Pekka Ylipalosaari, MD, PhD; , Tero I Ala-Kokko, MD, PhD; , Jouko Laurila, MD, PhD;, Lauri Ahvenjärvi, MD, PhD; and , Hannu Syrjälä, MD, PhD.

We have read the referees’ comments carefully and revised the manuscript according to their valuable and constructive criticism. The changes are described on separate sheets, in the form of comments for the reviewers, while corresponding revisions have been made to the text itself. The language of the revised manuscript has been checked.

Please find enclosed the revised version of our manuscript INFD-D-17-00367. We hope that our revised manuscript, which has clearly improved thanks to the suggestions made by the referees, will be accepted for publication in BMC Infectious Diseases.

Sincerely,

Dr Pekka Ylipalosaari
Corresponding Author
Comments for the reviewer 1

If the authors consider it appropriate, the name of the virus should be changed to influenza A (H1N1) pdm09.

The name of the virus has been changed as suggested to influenza A (H1N1) pdm09.

Recent studies have questioned whether pregnancy confers an increased risk for severe influenza disease.

We agree. This was nicely shown in a recent article (Paño-Pardo et al. Antiviral therapy 2012;17(4):719-28.). Because we did not have any pregnant patients this topic was only shortly mentioned in introduction section.

Have the authors calculated the sample size?

We did not calculate the sample size, because all influenza A (H1N1) pdm09 cases treated in our ICU since the pandemic were included in this study.

How were co-morbidities defined?

Co-morbidities were defined as follows: We selected those chronic diseases that had been diagnosed earlier and on which data were available in patient files.

What was the time of administration of influenza vaccine, last year?

In Finland, voluntary seasonal influenza vaccination, which is free of charge, is available for risk groups from October to December.

What was the time from hospital admission to antiviral administrations.

Unfortunately we had only the data of the patient being on antiviral treatment on ICU admission, which are presented in table 1. During postpandemic period almost all patients were admitted directly to ICU. In the discussion we write as follows: During seasonal influenza epidemics, we initiate antiviral treatment for all of our ICU patients with respiratory symptoms. Antiviral treatment is halted, if the PCR for influenza yields a negative result.

References 2 and 10 are the same.

The reference 10 has been deleted.

Comments for the reviewer 2

This study compares influenza A(H1N1) virus infections treated in ICU during pandemic and postpandemic periods. Although being a single center study with quite a low patient number, this
study includes more postpandemic periods than previous studies. Mainly the manuscript is fluent and compact, but several, mostly minor issues needs to be corrected or commented.

Abstract: The abstract does not include results or conclusions of vaccination rate, although it was one of the objectives of the study and reported and discussed in the main text.

The following sentence has been added to the abstract: During 2015-16, only 18 % of the ICU-treated patients had received seasonal influenza vaccination.

References in background and discussion: Row 55: ref 5,6: should it be 5 and 10. Ref 6 reports results from a small single center Turkish study during only pandemic period 2009-2010.

These sentences have been corrected as suggested by referee

Check also row 163.

The following sentence has been added in parenthesis “26% among pandemic patients”.

Check also references on row 181. E.g. ref 23: morbidity and mortality greater during the initial season, is the severity of ICU patients reported?

The exact severity scores of ICU patients were not reported. We deleted this reference, because the information relevant to this manuscript was rather complex.

Abstract, Methods, first sentence: add missing word.

Retrospective analysis of prospectively collected data in 2009–2016. Data are expressed as median (25th–75th percentile) or number (percentile).

Abstract, Methods: Data expressed as median (25th-75th percentile): However, percentiles are not reported for APACHE II, SAPS II and SOFA score. Percentiles for APACHE II and SAPS II are also missing in text on page 6.

Missing percentiles have been added both in the abstract and result sections.

According to data registration, data is expressed as median (25th-75th percentile). In text and tables 1-3 data is also expressed as number (%) and as mean (range) in table 4.

Misleading sentence has been corrected as follows: Values for continuous and ordinal variables are expressed as median (25th–75th percentile) or as number (%). Table 4 did not have values expressed as means (range) and “as means (range)” has been deleted from the footnote of table 4.

See also below comment table 4.

Were continuous parameters normally distributed and suitable for analysis with Student's t-test?
Normal distribution is not a mandatory assumption for t-test. More important assumption is the approximate equality of variances, which was formally checked by Levene’s test. However, Mann-Whitney U-test was added in to the statistical method since between group comparisons between SOFA sub scores are ordinal scale variables.

The section of data registration and statistical analysis has been corrected as follows: Between-group comparisons were made with Student’s t test (continuous variables), Mann-Whitney U-test (ordinal variables) or Fisher exact test (categorical variables).

Use score, scale, point or index consistently throughout abstract, main text, figures and tables, according to the original scoring systems.

This has been corrected as suggested

Sentences on rows 53-55 and 152-155 are not fluent.

These sentences have been corrected as follows:

Comparisons of ICU-admitted patients from the 2009 pandemic and the successive waves showed that the patients treated during the second and third waves were older and often had more comorbidities than the patients during the pandemic [5,6].

This was surprising because the vaccine strain was identical with the H1N1 virus circulating in the community [19].

Row 114: The list of most commonly detected bacteria includes 21 of 22 mixed influenza and bacterial infections. Why not as well report all detected bacteria. Or is there an error in the number of patients.

We critically re-evaluated microbial findings of respiratory specimens. We excluded the names of microbes. As corrected table 2 shows, there were more mixed bacterial infections among pandemic patients: 7 (43.8) vs. 9 (15); p=0.033. This finding has been added into result section and also shortly discussed.

What is the relevance of reporting pneumococcal antigen-positive urine (table 2)?

This information has been deleted.

Discussion: Row 156 Patients had several underlying diseases. Does this mean that each patient had several underlying diseases?

The misleading word “several” has been deleted. Some patients had more than one chronic underlying disease, which has been added into footnote of the table 1.

According to study parameters severity of underlying diseases was collected.
The misleading sentence in the study parameters has now been corrected as follows: The following information was collected for all study participants: age; gender; underlying diseases and organ dysfunction on admission as assessed by the Acute Physiology and Chronic Health Evaluation (APACHE II) [7], Sequential Organ Failure Assessment (SOFA) [8], and Simplified Acute Physiology Score (SAPS II) [9].

Underlying diseases are not reported or referred to in results section.

Underlying diseases have been referred to in result section as follows: As Table 1 shows the proportion of patients with epilepsy and other neurological diseases was lower during the postpandemic period than during the pandemic period: 5 (8.3%) vs. 6 (37.5%), respectively (p = 0.009). Postpandemic patients had statistically more often cardiovascular diseases: 24 (40%) vs. 1 (6.3%), p = 0.015.

Data can be found in table 1, but without disease severity. Row 160: according to table 1, the mortality discussed here refers to ICU mortality.

The comment on miss-information of disease severity, please see the comment above. The missing word “ICU” has been added.

However, in results only 6 month mortality is reported and in study parameters only hospital mortality and 6 month mortality were recorded. Why not 6 month mortality instead of 180 day mortality in table 1?

As suggested, in table 1 there is now 6-month mortality instead of 180-day mortality.

Row 163-164: patients…began?

This sentence was clarified as follows: For more than 75% of patients during both periods antiviral treatment was started in the emergency room or in the ward before ICU admission; for the remaining patients antiviral treatment was started on ICU admission.

Row 177: most of them had disabilities. Which disabilities? Where are the disabilities reported?

The word disability has been replaced by the more exact word: chronic underlying disease. Moreover, most of them had chronic underlying diseases (please see table 1).

List of abbreviations: Is ARDS or CDC used in text?

Unnecessary abbreviations have been deleted.

Several other unlisted abbreviations are used.

We have added other unlisted abbreviations in the text.

Table 1: 6 month mortality as in results and study parameters.
180-day mortality has been changed into 6-month mortality.

Abbreviations TISS, BMI, LOS and SAPS II missing.

These abbreviations have been added.

Table 3: PaO2/FiO2 could be included in clinical data (table 2).

According to the reviewer’s suggestion, this ratio has been included in table 2.

Median PaO2/FiO2 quite high. However, 4 postpandemic patients were treated with ECMO.

We agree. However, during the pandemic period the hypoxia of all influenza patients were treated successfully by conservative treatment of hypoxia.

What was the indication for ECMO?

The following sentence has been added into the result section: During postpandemic period four patients with severe ARDS needed ECMO treatment, because conservative treatment of hypoxia was unsuccessful (Table 4).

Is the number of ARDS patients available?

We calculated the number of ARDS patients by Berlin criteria (The ARDS Definition Task Force. Acute Respiratory Distress Syndrome. The Berlin Definition. JAMA. 2012;307(23):2526–2533. doi:10.1001/jama.2012.5669), and the results are reported in table 2 and result section.

Table 4: Which values are median and which mean?

All values are medians and an erroneous expression as mean (range) has been deleted.

Is the duration of ventilation in hours?

The missing word - hours - has been added.

Abbreviation SOFA missing.

SOFA has been now explained: Sequential Organ Failure Assessment

Figures 1 and 2: axis labels missing:

Axis labels have been added.