Author's response to reviews

Title: Prospective hospital-based case-control study to assess the effectiveness of pandemic influenza A(H1N1) vaccination and risk factors for hospitalization in 2009-2010 using matched hospital and test-negative controls

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Author's response to reviews:

Dear Editorial Team,

We thank the reviewers for their valuable and constructive comments. Please find our reply to their comments and a description of changes to our manuscript below.

Review 1 Dr. van der Sande

Major comments:

1) We agree with Dr. van der Sande that our VE estimate based on the matched design need not be “truer” than that based on the test-negative design. We did not choose two control groups in order to validate the test-negative approach with the case-control-approach. Rather, the hope was that our findings would be strengthened if results were similar with the two approaches. This method is frequently taken in epidemiological studies, although it bears the risk of difficult interpretation of findings if they in fact, differ. In our case, the direction of our findings was similar using the two approaches. However, in the test-negative approach cases and controls differed less regarding influenza-vaccination, which may have been a result of their more similar risk factor profile (overmatching). We have removed the wording “more robust estimates” from the abstract.

2) Our VE estimates are based on the verified influenza cases only – not on ARI, please see. p. 9 under “Data analysis”, second last paragraph. We used the ARI definition for inclusion of potential influenza cases to “capture” as many influenza-positive cases as possible.

3) The reason for inclusion of persons with illness onset up to 10 days prior to hospitalization is similar to 2): We wanted to capture as many H1N1-positive
cases as possible. While a “false”-negative swab is more likely after 7 days, some cases will still be positive, e.g. in the study by De Serres et al. 2010, 42% of patients were still positive on day 8, an in the studies by Lee et al. 2009 and Leekha et al. 57.1% and 54%, respectively, were still positive on day 7. The reviewer's point that 7 days will still misclassify positive patients as negative is well taken; however, a sensitivity analysis using 4 days as the cut-off was already presented in the manuscript (p. 9 and p. 13).

4) Our intention was always to analyse HIV patients separately. We were aware from the outset that one of the participating hospitals specialized in the care of HIV patients and chose to not exclude these from recruitment. However, we planned to exclude them from the main VE analysis as it would not make sense to have a disproportionately high number of HIV patients among our cases or controls compared to the general population. Instead, we planned to perform a separate VE-analysis among HIV-positive patients if a sufficient number could be recruited. Unfortunately, however, the number was insufficient. We have now briefly explained this in the methods section and provided a very short overview of the vaccination status of HIV-positive participants according to their pH1N1-status at the end of the results section and in Table 4 (highlighted).

Minor points:
1. <=10 days was appropriately changed to >= 10 days in the abstract.
2. We disagree that VE results need to precede break through results, as the latter are in effect based on the former.
3. We have split our Table 2 into two tables, see Tables 2 and 3, moved the matching variables to the text, and added structure to the tables to make them easier to read by more clearly grouping variables according to vaccination related variables, risk factors related to underlying illness, health-relevant habits of smoking and alcohol consumption, factors included as possibly relevant to viral transmission, and socioeconomic status.
4. We thank Dr. Van der Sande for pointing out that Fig. 1 was incorrect – “178” was a typographical error, but the number of 94 rather than 119 controls was based on the cut-off for test-negative cases of 4 days rather than 7 days after symptom-onset, which was used in the sensitivity analysis. Thus, we simply erroneously uploaded the wrong figure, and have corrected this.

Review 2: Dr. Van Boven
Points addressed in the section titled “Evaluation”:
1) We have compared persons with ARI who participated in the study with those who have not: Recruited and non-recruited patients did not differ with respect to age and sex distribution, nor regarding the frequency of key symptoms such as fever, cough/sore throat or dyspnoea (first paragraph of results section).

2) As BMC Infectious Diseases is an online journal, we do not think that an online appendix instead of tables in the text is necessary. However, for a clearer presentation, we have split Table 2 into two tables, the first (new Table 2), containing results of the two analyses comparing pH1N1-positive cases with controls, and the second (Table 3) comparing all ARI cases to controls. We have
added some structure to the tables and deleted the first few rows by mentioning age and sex-distributions in the text, making the tables clearer and easier to read. We do feel it is important to present all results, not only significant associations, and believe we have found a good compromise with the two revised tables.

3) We have only minimally shortened the section on the comparison between test positive and negative patients as suggested by the reviewer, because 1) we moved the demographic variables from Table 2 to the text, 2) as investigation of an association with seasonal influenza vaccines was a secondary goal of our study, we felt these results should be mentioned, 3) we felt the remaining text was relevant to the interpretation of the few significant results.

Minor comments
We have addressed all individual minor comments in the text as suggested by the reviewer:

p5: We have spelled out ARI the first time it is mentioned.

p9: We have added the missing bracket in the VE equation.

p10: We have changed “was” to “were”.

p11: ‘and >= 1 hospitalization in the past year’. We have added the MOR to show that this is a negative association

p13: We changed ‘equivalent to’ to ‘yielding’.

p14: ‘A hospital-based case-control study using …’. Clumsy sentence. We rephrased this sentence.

p14: Reviewer’s comment: ‘In a register-based cohort study in Scotland ... VE was 100% (95%CI:-infinity-100%)’. If this is really was this study found then it adds nothing, and should be removed from the discussion and references.

Based on the RR provided in the study, the VE in the Study by Simpson et al. should have been reported as -710-100%. This has been corrected.

p14: ‘were be included’. Typo removed

p14: ‘In addition, vaccination ...’. We rephrased the sentence.

In addition to changes made in response to the reviewer’s comments, we have made minor changes in the wording in a few places and updated the nomenclature of pandemic influenza to influenza A(H1N1)pdm09 according to WHO recommendations. There was an error in the reference manager links of references 17-21 which we have corrected.

Kind regards

Wiebke Hellenbrand on behalf of the authors