Author's response to reviews

**Title:** Effectiveness of a MF-59TM-adjuvanted pandemic influenza vaccine to prevent 2009 influenza A/H1N1-related hospitalisation; a matched case-control study

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**Author's response to reviews:** see over
Dear editor,

Please find attached our revised manuscript ‘Effectiveness of a MF-59TM-adjuvanted pandemic influenza vaccine to prevent 2009 influenza A/H1N1-related hospitalisation; a matched case-control study’ with manuscript number MS 1515886902508337. We have changed and added information to the manuscript according to the suggestions of the associate editor and reviewer. Furthermore, we adapted some text for clarification or consistency (all marked as track changes). We hope that you accept the manuscript for publication in BMC Infectious Diseases.

In the letter below we answer the comments and questions of the reviewer and editor point-by-point.

In anticipation of your response,

Yours sincerely,

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Associate Editor's comments:

1) Authors should explain better who were the patients who were swabbed and had laboratory confirmation. Did they perform a throat swab in all hospitalized cases?

*In the Netherlands, all patients hospitalised for suspected pH1N1 infection should have been swabbed and tested for pH1N1 infection. The instructions at the national level were to perform a nose and a throat swab combined in one transport medium.*

We added information on the swabbing instructions to the method section. See also the answer below to comment 1) of the reviewer.

2) Page 6 ?Study population?: The data sources for cases and controls was different as control data were carried out by a general practitioners (GPs) network, but what is the representativeness of the GPs included in the study? Are there any difference in data collections among the two data sources (the Municipal Health Services and the surveillance database)?

*Controls were derived from the IPCI database, which consists of electronic patient records of about 500 GPs from all over the Netherlands. In the Netherlands, nearly all people are registered with a GP. In total, about 5% of all Dutch inhabitants are included in the IPCI database. The GP patient population of IPCI is representative of the Dutch population regarding sex and age, except for a slight under representation of the elderly population that is under care of medical practitioners in nursing homes. There was a nationwide mandatory notification system of hospital admissions for pH1N1 infection. As discussed in the manuscript, we expect that our notified cases and GP-controls originate from the same, general population. We extended the information on the generalisability in the method section.*

*Furthermore, the reviewer is right that differences exist between the 2 data sources that gave rise to the cases and controls. An important difference is that data of cases was self-reported, while data of controls was extracted from electronic patient records. We have elaborated on this issue in the discussion part.*

3) Page 6, line 27 Authors should explain what they mean with ?calendar date?. What are they referring to?

*To match controls with cases we took care that eligible controls were alive and present for at least 1 year in the database at the index date (that is, day of disease onset of the corresponding case). We added this information in the method section.*
4) Page 7: Exposure definition? Authors should explain better the exposure definition when the exact date of vaccination was unavailable.

We have changed the text on exposure definition.

5) Page 10: As Authors report in ?Discussion? session the use of different data sources could limit this study because of differences in the quality and level of information. In cases, vaccination status was ?self reported?: how were these data validated? Is it possible to recover GP registered data that were incomplete?

Only if vaccination status was missing, hospital physicians were contacted by the municipal health service again and were asked to provide vaccination data if possible. If information could not be obtained through the patient (self-reported; e.g. patient was already discharged), hospital physicians were asked to contact the GP of the patient. Although a lot of effort was put into retrieving all vaccination dates, it was not possible to recover all dates as the GP of hospitalised patients was not always known (therefore registered data could not be retrieved). Patients could not be contacted after discharge because data were part of routine surveillance and no consent for further inquiries was obtained. We added additional information about recovering missing data in the method section.

Reviewers comments:

1) Could you explain briefly (even if there is a reference) what were the criteria for hospitalised cases to be swabbed? What is the representativeness of swabbed patients? Who entered the data for hospitalized cases. As the data source for cases and controls was different, it would be important to clearly show the differences in data collection, variables definition (e.g. chronic diseases?), data validation.

In the Netherlands, all patients hospitalised for suspected pH1N1 should have been swabbed and tested for pH1N1 infection. There were no additional selection criteria for testing (see also the answer to question 1 of the associate editor). Whether to test or not was a decision of the attending physician. After laboratory confirmation, the attending physician and the laboratory had the legal requirement to contact the Municipal Health Service (MHS). The MHS notifies the case by entering the reported data into the national password-secured web-based routine surveillance database. The researchers had access to this data base and checked the entered data. Missing data were retrieved by the MHS through the hospital physician; before discharge the hospital physician would ask the patient directly, while after discharge, GPs were contacted if the GP of the patient was known. This information is added in the method section. Furthermore, a reference (van ’t Klooster et al. 2010) is added in which more information is provided about the notification system.
Data of controls pertaining to underlying medical conditions, vaccination status, date of vaccination, pregnancy and hospitalisation with confirmed or suspected pH1N1 infection were extracted using algorithms based on International Classification of Primary Care (ICPC) codes or open text fields. As we already elaborated on in the discussion, the level of the available data differed indeed between the cases and controls (see also the answer to comment 2 of the associate editor). For cases, data on chronic diseases was available at aggregated level (pulmonary disease, cardiac disease, diabetes mellitus, chronic kidney failure, cancer and immunocompromised condition). For controls, data on chronic diseases were extracted from the IPCI database using ICPC codes as well as free text terms and was therefore available at disease-level. To make the information of the groups comparable, we aggregated the data of controls to the same level as was available for cases. Information on vaccination status and date of vaccination were extracted from IPCI using algorithms based on ICPC code and open text fields including brands and batch-code. We added this information in the method section.

Validation for pregnancy and hospitalisation was done by hand. As it was not possible to validate all vaccination data of controls, we only included patients from GPs that had consistent and complete registration of vaccinations. See the answer to comment 5) of the associate editor for validation of data of cases.

2) What is the representativeness of the GPs included in the study compared to all GPs? Are they representative of the vaccine coverage of the population giving rise to the cases? Would it be possible to know the number of hospitalized cases among these GPs catchment population and in the rest of GPs? The difference in vaccine coverage?

See also the answer to comment 2 of the associate editor. As the IPCI GP patient population is representative for the Dutch population except for a slight under representation of the elderly population and GPs included in the IPCI database are from all over the Netherlands, it can be assumed that the included population is similar to the population that gave rise to the hospitalised patients (only 11 cases (7%) were older than 70 years). Unfortunately it is not possible to know the number of hospitalised cases for every GP catchment population. Regarding the representativeness of the vaccine coverage; we observed that part of the GPs did not consistently register vaccinations. Therefore, we only included patients who were registered with a GP that had consistent and complete registration of vaccinations. Consistent registration of vaccinations was defined based on the vaccination coverage in the GP practice population aged ≥60 years.

We extended the information on the generalisability in the method section.
3) Time was an important confounding factor during the pandemic in all studies published. In that sense: I don’t understand very clearly the matching by time criteria. You mention “calendar date” but how was it exactly done? Would it be possible to have estimates stratified by time or restricted to the influenza peak?
It would be interesting to see a graph with recruitment of cases and controls by time (index week?)

For the clarification of ‘calendar data’: see comment 2 of the associate editor.

We agree with the reviewer that time could be an important confounding factor during the pandemic. The reviewer suggests that estimates are stratified by time or restricted to the influenza peak. As the influenza peak and the start of the vaccination campaign took place at the same time, no restriction was possible towards the influenza peak, as the sample was too small (too little power) to estimate the VE for only those patients whose day of symptom onset was in December of January.
In the discussion we now elaborate on the limited possibilities to investigate residual confounding by time.

The reviewer suggests to include a graph with recruitment of cases and controls by time. In figure 2, the epicurve is presented for cases. Controls were matched to cases on time. All cases and controls were obtained retrospectively; recruitment therefore took place at the same time. Controls were alive and present in the database at the index date.

4) Exposure
You define a valid vaccination as > 7 days before the index date. Have you tried to stratify according to different delays (8-13, >14)?
For the missing data on vaccination, you can also try imputing data.

As suggested by the reviewer, we added results using >14 days between date of vaccination and day of disease onset to define vaccination as valid in addition to the result of > 7 days. Furthermore, we performed an additional sensitivity analysis in which we imputed the missing delay between disease onset and date of vaccination for those with unknown date of vaccination. No clear correlation was observed between date of symptom onset and the delay between disease onset and date of vaccination except from an upper bound based on the start of the vaccination campaign relative to the start of this study (see figure – A). We therefore sampled from a uniform distribution using this upper bound (for 2 imputed samples see figure – B).

Figure: A shows the distribution of delay between date of vaccination and disease onset as plotted by the date of disease onset for those whose date of vaccination was available. B shows data of 2 different imputed datasets of the
delay between date of vaccination and disease onset as plotted by the date of disease onset for those whose date of vaccination was unavailable.

We added the imputation method and imputed results to the manuscript.

5) How was the matching on chronic diseases done? What was the distribution of chronic diseases among cases and controls?

As described in the answer to comment 1 of the reviewer, for the cases the data on chronic diseases was available at aggregated level and for controls at disease-specific level. We aggregated the data of controls to the same level that was available for cases and subsequently matched on all aggregated diseases (that is, pulmonary disease, cardiac disease, diabetes mellitus, chronic kidney failure, cancer and immunocompromised condition). We matched on age (+/- 12 months), sex, calendar date and all (aggregated) underlying medical conditions. For a few, no control was available with similar underlying medical conditions. Those we matched on age (+/- 12 months), sex, calendar date and at least 1 similar (aggregated) underlying medical condition, or finally, we matched on age and sex and an (undefined) underlying medical condition. One case did not have a matched control (unvaccinated male, 7 years old suffering from renal disease).

Because of the used method, the distribution of chronic diseases among cases and controls was similar.

We extended the information on matching in the method section.

6) Adjustment
- You have adjusted by age, sex, chronic condition and addressed in the restricted analysis frailty bias. Do you know if, even after matching, those variables had some residual confounding effect? Have you adjust for any other potential confounding factor? If data were not available, may be this can be mentioned in the discussion as limitation.

Although we attempted to limit the amount of bias or confounding by matching on important variables, we cannot exclude the presence of residual confounding. With the restricted available data we had only limited possibilities to adjust for other sources of potential confounding than presented in the manuscript. We added this information to the manuscript.