Author's response to reviews

Title: Seasonal influenza risk in hospital healthcare workers is determined by household rather than occupational exposures: results from a prospective cohort study in Berlin, Germany.

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Author's response to reviews: see over
First of all thank you to the reviewers for reviewing our manuscript and for their thoughtful comments and suggestions. We would like to answer to the reviewers’ comments as follows:

**Reviewer:** Helen C Maltezou  
**Reviewer’s report:**
This is an interesting topic investigated, given the influenza pandemic that emerged the last months. However there are several aspects that need to be addressed:
1. Abstract, page 2, Background, 2nd sentence: please replace “clients” with “patients”.
   **Done**
2. Abstract, page 2, results: Immunization is not a risk factor but a protective factor, that is why the OR is < 0.50.
   I have removed “risk” and given OR for all listed exposures here.
3. All over the text, when there are more than 1 HCW, please use HCWs.
   **Done**
4. Background: For risk factors for nosocomial influenza and the rational for vaccination of HCWs, please read and include in the reference list the following comprehensive review article on this topic: Maltezou, Nosocomial influenza: new concepts and practice, Curr Opin Infect Dis, 2008.  
   **Referenced.**
5. Methods, page 5: It is not clear how and who was enrolled in the study as a non-HCW worker. This is very important, given the fact that non-HCWs have a significant comparable to HCWs) influenza vaccination rate and similar rates of influenza infection. There are mainly elderly? Persons with underlying diseases ? Please clarify their profession (you may present it at the first paragraph of the Results section).
   The study specifically looked at occupational exposure so only persons aged 16 to 65 were included (age comparison is in table 1). I have improved documentation on the characteristics of non-HCW in the methods, including occupation. Most were scientific staff, administrators or students.
6. Methods, page 5: are there any data regarding the profession category of HCWs? It would be interesting to see if HCWs working in pediatric departments on in the Emergency Departments have higher rates of infection. We did look at risk by department and by number of child contacts, but found no significant effects. There is, however, an association when HCW have 7 or more daily child contacts at work (RR=1.75; p=0.11) which is shown in table 3 which might need further exploration in a more focused study.
7. Methods, page 6, first paragraph: please specify the reference laboratory (name, and city).
   **Done- it is in the same institution that led the study, the RKI.**
   “Blood samples were refrigerated, then transported within three days to the national reference laboratory for influenza at the Robert Koch Institute in Berlin”
8. Inclusion and exclusion criteria, page 6: in continuation with the above comments, please provide here a clear definition of a non-HCW.

Inserted: “Non-HCW were those working or studying at the study sites, or attending the blood donation centres, who did not fit the definition of HCW.”

9. Methods, page 9, role of the funding body: please move this paragraph at the end of the text.

Done.

10. Results: There are data that are duplicated or overpresented. Please delete appropriately. Also, there is no need to duplicate data already presented in tables (page 11). Most probably you do not need to give, and discuss the findings of the univariate analysis. Overall, you need to decrease the Results section by one third to a half.

Edited.

11. Discussion: please decrease the number of words by one third to a half. Some editing, but also some additions due to reviewers’ comments.

12. Discussion, page 13: There are various factors that may partially explain the similar rate of infection among HCWs, compared with non-HCWs: first the fact that 40% of them are vaccinated, which translates to protection (as also found by the statistical analysis), possible use of masks during caring for infected patients, also isolation – cohorting of infected patients. These aspects should be discussed.

The statistical analysis adjusts for the role of immunisation, but HCW status is still not a significant risk factor. I have added isolation as an infection control measure that might reduce the risk of infection in HCW (discussion).

“Also, infection control measures such as use of personal protective equipment and individual or cohort isolation might have reduced the risks of infection in HCWs.”

Regarding PPE, we asked HCW if they had close contact with patients suffering from suspected respiratory infections, and if so, how often they work using protective facemasks. 159/250 had had such close contact, of whom 3/159 never wore a facemask and 39/159 said they “always” wore one in this situation.

13. Discussion: throughout this section there are numbers appearing within the text. Do they represent references? Please correct.

Corrected

14. Please, in the Discussion refer to the Curr Opin Infect Dise paper mentioned above.

Reviewer: JEROME SALOMON

Reviewer's report:

1) Major Compulsory Revisions : none

2) Minor essential revisions :

- please explain and discuss significant differences observed between the two groups in terms of sex ratio, immunisation, smoking and use of public transport; impact on your analysis and conclusion?
Inserted into discussion:
“Although there were differences between the two comparison groups with respect to sex, recent immunisation, smoking and use of public transport, the logistic regression methods should have adjusted for these where they had an effect on the outcome (in particular immunisation). The lower average age and higher proportion of females in the HCW group is likely to be due to recruitment among trainee nurses in the larger hospitals.”

- You should discuss more deeply the quite important losses during study (1044 participants recruited but only 736 available for analysis of SCII).

Sentence added to results comparing excluded participants, and to discussion.
Results: “Those not included in the study were of younger age (38 vs 34, p<0.01 Kruskall-Wallis) and were more likely to be HCW at recruitment (42% vs 34%, p<0.01), but there were no significant differences in sex, current immunisation, smoking status, car ownership or use of public transport in excluded versus non-excluded participants.”

Discussion:
“Loss of recruited participants, mostly due to losses to follow up (despite repeated attempts to contact) and to the timing of vaccination, reduced the effective power of the study and may have worsened selection bias, although excluded participants did not differ significantly with respect to variables found to influence the outcome.”

- In terms of household contacts, could you give some more details about children's mean age, school, regular use of public transport? Unfortunately we only asked about broad age groups <16 and >=16, and didn’t ask further questions about household contacts themselves.

- Selection bias could be more developed and detailed
Have added some sentences to the discussion.
“It is possible that HCWs with a higher number of patient contacts and, therefore in theory a higher risk of influenza, would be less likely to participate due to pressure of work. Alternatively, HCWs who were concerned about their higher risk of influenza may have protected themselves better and may have been more likely than other HCWs to participate, which would tend to decrease the relative risk in this group.”

- The power of the study could be too low and the size of the population not sufficient to detect a relative risk of 1,7...
Please use a more cautious title "could be" or "seems" determined ...
We acknowledge this lack of power and have amended the title.

What is your real independence from BGW (of course very concerned by results)?
I was aware of the possible influence of the funding body from the start of the study, and coming from outside the German healthcare system, I had no conflicts of interest here- nor did my co-authors. The BGW did influence the question that was asked but not the way that it was addressed, as stated in the paper.
Could you find any references about car ownership and influenza or airborne transmission?
There is evidence for intra-car transmission of SARS (the reference is cited),
but we could find no papers linking car ownership itself with influenza or other
respiratory pathogens.

Do you think this study could be done during this pandemic period and could
you give any comment about your results, HCW and pandemic situation?
It would be very interesting to repeat this study during a pandemic for
comparison. We were initially reluctant to extrapolate to the current situation,
but I have now added a paragraph on this.
“What significance does this study have for the current H1N1v pandemic? As
pandemic influenza should result in a higher attack rate than seasonal
influenza, the prevalence of influenza in hospital inpatients and staff is likely to
be higher than for seasonal influenza, so increasing the risk of exposure and
infection for HCWs compared to that described here. For the same reasons,
the risk in HCWs and non-HCWs from their household contacts would also be
higher than for seasonal influenza. Therefore even if a repeat study during
pandemic conditions identified a significant occupational risk for HCWs,
household exposures might still be more strongly associated with influenza
infection.”

Do you have any information about hygiene measures taken, use of personal
protective equipment?
We asked HCW if they had close contact with patients suffering from
suspected respiratory infections, and if so, how often they work with protective
facemasks. 159/250 had had such close contact, of whom 3/159 never wore a
facemask and 39/159 said they “always” wore one in this situation.

3) Discretionary revisions:
please verify your references in the text (not correctly integrated page 14 and
after) check your references (page 19 to 22) : long title, short title of periodics,
use vancouver presentation.
Reformatted.

Is table 4 really meaning anything important?
If, due to the lack of power which you note above and other factors, we have
missed a true but modest association between being a HCW and influenza,
the risk of reported respiratory infection might be a more sensitive measure of
overall respiratory infection risk of which influenza should be a subset.
However the text does summarise the table adequately so I have removed
Table 4 and replaced it with one requested by another reviewer.

Reviewer: Sirenda Vong
Reviewer’s report:
Reviewer’s report
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essential clarifications that need to be provided by the authors.

- Major Compulsory Revisions
  1) The whole basis of the study is the selection on controls. It was unclear to me as to who these controls were. Little information was provided by the authors. Could they expand? Age, gender, occupation, methods of selection ..etc. Were all of them selected among non-health care personnel working in the selected sites or among people attending these sites during the time when the study was enrolling?

  Age and sex of controls and HCW are summarised in table 1. The methods of recruitment are described in the methods. We approached as many people as we could, including nearly all the employees at one administrative centre, but participation was voluntary. Controls were enrolled from those employed at the study sites rather than those attending them, apart from the blood donation centres (see addition to methods text). I have also added the names of the administrative centres. There were a variety of occupations in control participants, with scientific staff, students and administrators being the most common.

  2) In the laboratory investigations section: the rational for SCII case definition is unclear. I can understand why titer of 5 and 10 could be considered alike. However, what is the reason why the authors would assume this? Does this mean that a titer of 20 could be considered positive assuming a four fold rise from a baseline titer of 5? I would advice the authors to show the data regarding the titer levels in geometric means, median and range among cases and controls. Sentence should have read “Titres below 10 were given the value 5” and there is precedent for this method of calculation (ref). A titre of 20 would not be sufficient for a titre rise: the definition of SCII given is :” SCII was defined as a fourfold or greater titre rise between pre- and post-season samples, with a postseason titre of at least 40. “

  We repeated analyses using geometric means and other ways of modelling titres as continuous variables, but as we were studying infection risk (with infection being an all or nothing event) rather than immunity we used SCII as a dichotomous outcome. A planned paper on vaccine efficacy will elaborate more on the actual titres. Adding geometric mean, median and range for pre and post-season titres for the four variants in the two study groups would require an additional (complex) table, whose contents would reflect vaccination status as well as serological influenza infection.

- Minor Essential Revisions
  1) The definitions of SCII in the abstract and the methods section don’t match Corrected.

  2) Again in the abstract, the authors stated logistic regression model to perform multivariate analysis while it was not clear to me what the authors used when reading the stat analysis section. Was it a fixed or random effect model or a log regression model accounting for clusters?
The main model was standard logistic regression, without any group-level terms. A multilevel, fixed-effects model using xtlogit (to account for clustering by study site) was also performed but was not significantly different to the standard model (see results).

3) In the multivariate analysis paragraph of the results, the authors stated rho and Chi2 test for p value while the methods section reads the use of the log-likelihood ratio test.
I've amended the results. The “Chi2” usage reflected the name used in the STATA output here which states it as “chibar2”, although the test statistic is derived from a likelihood ratio method.

4) It’d be useful to tell us which statistical software and which generalized linear model was used for the analysis particularly for the two-level multivariate analysis
Now referenced and included- STATA release 10, standard logistic regression (logistic) for main model and random-effects model (xtlogit) for group level model.

- Discretionary Revisions
1) The assumption that health care workers are at higher risk of being infected by influenza viruses in hospitals are commonly heard; before this study I have never heard of any national advisory boards that recommended vaccination among health care workers based on higher risks in health care settings. Apart from Germany, could the authors expand on this and name other EU countries that recommend vaccination also relying on this basis?
I agree, and searched for such citations in other EU countries without success- hence only Germany being cited.

2) Please provide references on kinetics of antibodies to explain persistent titers of >40 at 2-3 months after point of infection.
There is evidence of antibody response persistence at 4 months and beyond following vaccination, but we could not find similar evidence regarding natural infection.
3) Sorry to be picky but I’m used to having sentences in English beginning with letters, not numbers
Corrections made.

4) A table displaying serological results by type of infections (ARI, ILI..) and cases/controls would help
Now included as table 2, replacing old table 4 which is summarised in the text.