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:**

We thank Professor Van der Sande for her additional constructive comments.

We have now included a more in-depth discussion of our control selection and possible biases. In addition, we investigated whether more frequent outpatient physician visits by hospital as compared to test-negative controls might explain their higher vaccination coverage. However, a similar proportion of test negative and hospital controls saw a physician at least once (73% vs. 72%, p=0.90) in the past year, while more test-negative than hospital controls saw a physician >3 times (53% vs. 38%, p=0.11).

We do not wish to claim a relative strength of the use of hospital controls over test-negative controls; rather, we described the results obtained, looked for potential biases to explain them, and pointed out that – while non-significant in the test-negative analysis both estimates are in a similar direction. We feel it is legitimate to discuss the greater possibility of overmatching for certain health risks, including vaccination probability, when using test-negative as compared to hospital controls.

While Dr. van der Sande’s comment that “the hospital controls could not have any ARI, therefore, the chance of having an actual influenza infection could have been artificially minimised” is in principle well-taken, it is standard practice to exclude potential controls with a past history of the disease in question. Failure to do this would obviously lead to an underestimate of etiological effects. For this reason, we excluded patients with a history of laboratory-confirmed pH1N1-infection as well as patients with a history of ARI-symptoms, but only in conjunction with fever (see methods). Thus hospital controls could have symptoms of ARI as long as they did not have fever. As pointed out in the methods, we chose hospital controls with only acute diagnoses or minor elective
procedures, and therefore assume their potential risk of H1N1 exposure was uninfluenced by their impending hospitalisation.

We feel we have honestly pointed out the limitations of our study, as also underlined in the initial comments of the second reviewer – the most important of which is low power due to the late start and the low vaccination coverage achieved in Berlin. We agree with the reviewer that pooling would not solve methodological problems – however, since the major limitation of our study was not, in our view, methodological, but rather, insufficient power, pooling with similar studies could lead to better estimates in the future. We have tried to make this clearer in our concluding remarks.

Minor comments:

1. We have deleted the duplicate “influenza” as suggested.

2. We deleted “highly” before “effective” in the first sentence of the discussion.

3. We also deleted the reference to the Scottish study (Simpson et al.), as correspondence with the authors since submission of our first revision confirmed that these estimates were very unstable.

4. We cited other studies that investigated the same vaccine as in our study – pandemrix. The citation suggested by Professor Van der Sande (Steens et al.) used a different vaccine. We have added further studies, however, that have since been published (H.-D. Emborg, et al. Effectiveness of vaccine against pandemic influenza A/H1N1 among people with underlying chronic diseases: cohort study, Denmark, 2009-10. BMJ 344, 2012. and A. Ortvqvist, et al. Effectiveness of an Adjuvanted Monovalent Vaccine Against the 2009 Pandemic Strain of Influenza A(H1N1)v in Stockholm County, Sweden. Clin.Infect.Dis. 52 (10):1203-1211, 2011.)

We hope that these revisions are now satisfactory. Please note that we did not feel that our methods section needs to be revised, as implied by the editorial comment in the e-mail sent to us on Feb. 21, 2012. This was not suggested by either reviewer. Instead, one of the reviewers asked to provide a more detailed discussion on the two different methodological approaches in the discussion section.

Kind regards

Wiebke Hellenbrand on behalf of the authors