Reviewer’s report

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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Reviewer: Marianne A.B. van der Sande

Reviewer’s report:

The authors set out to assess the effectiveness of pandemic influenza vaccination in protecting against hospitalisation. To do so, they used the test negative approach and a matched control approach, and concluded that a) the matched control approach resulted in more robust estimates, and b) that pooling of data would increase power, and robustness.

I have a few major concerns.

- It is not clear what the authors mean by a more robust estimate. Is this a more precise estimate, that is a narrower confidence interval around the point estimate? Or an estimate which is more close to the true (albeit unknown) vaccine effectiveness? Clearly, the matched design presented by the authors resulted in a narrower CI, but I do not see why this estimate would be truer than the test negative approach. The test negative approach has been widely evaluated and accepted to estimate VE, while its limitations have been acknowledged. The authors should justify why they set out to compare/validate the test-negative approach with a matched case-control design and should discuss the limitations and potential biases of the matched case control design in relation to the limitations of the test-negative design.

- Estimating VE against influenza using ARI rather than the more accepted ILI case definition needs justification and discussion as well. Could this have biased the estimates?

- In the study population it is mentioned that ARI patients were included if symptom onset was no more than 10 days prior to admission. Then, in the data analysis, it is mentioned that anyone with a negative swab within 7 days of symptom onset was considered negative; so why include people with onset between 7 and 10 days? However, 7 days will still misclassify a considerable number of influenza patients as negative. Viral shedding data suggest that only ARI (if ILI not possible) patients with symptom onset no more than 4 days ago should be included.

- The authors excluded HIV-infected patients, not by design, but as an after thought. Would this also have happened if no breakthrough infections had occurred in this group? As HIV-infected people were eligible, they should be included in the primary analysis.
In addition a few minor comments:
- Abstract, methods: vaccination <=10 days before symptom onset is mentioned, this should read >=10 days
- Abstract, results: results about VE should precede data about breakthrough infections.
- The risk factor analysis is a bit overwhelming. Many variables, not always clear what the rationale is, nor if any correction was made for testing such a large number of variables.
- Please check numbers. Fig 1 mentions 178 recruited cases, the results section mentions 177. Table 1 mentions 119 test negative ARI, Fig 1 only mentions 94 such controls.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

'I declare that I have no competing interests'