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

**Version:** 2  **Date:** 2 February 2012

**Reviewer:** Marianne A.B. van der Sande

**Reviewer's report:**

The authors have now clarified that the reasons for including an alternative control group (non-ARI hospitalisations) was to try and confirm the estimates from the test-negative approach. Indeed, in the absence of a golden standard, using different methods to estimate the ‘true’ VE could be an option to strengthen confidence in the outcomes. An underlying assumption is that such methods have similar validity. However, for a case-control analysis, selection of proper controls is key: controls should come from the same population as the cases and represent those at risk for becoming a case (here: influenza); one well-selected control group being considered better than two or more. The hospital controls could not have any ARI, therefore, the change of having an actual influenza infection could have been artificially minimised, potentially inflating the VE estimates and biasing risk factor estimates.

Therefore, on methodological grounds, it could be argued that the test-negative approach is more valid.

Indeed, as the power of the study would only be sufficient for a high VE, it is not surprising that the high estimate of the alternative method had CI not including 0% VE, and the lower estimate not; again this does not prove (or disprove) its validity. Thus, I still feel the authors need to justify the underlying validity of their alternative approach prior to embracing its outcomes.

I would really suggest the authors include a methodological discussion of the merits of their two approaches, rather than rely on a post hoc convenience assessment. The claimed strengths of the alternative method (significant VE, risk factors) are not necessarily strengths of the method. Both the abstract and the discussion still overstate the implications and ignore methodological restrictions. Pooling does not solve such limitations, nor will more studies with yet more estimates, without a sound methodological basis. In the discussion.

**Minor comments:**

In replacing the old pandemic name with the new official name, the text now often has it as pandemic influenza influenza A(H1N1)pdm09, please remove duplicate influenza.

The first sentence of the discussion still claims "high effectiveness". Suggest deleting "high" (in accordance with the last para of the discussion). Also, it would
be better to not just cite studies which observed a high VE against hospitalisation, but also studies which estimated a much more modest VE (e.g. Steens et al using a matched case-control approach observed 19% VE against hospitalisation, and 49% if restricted to those with underlying medical conditions; BMC ID 2011:11:196).

**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'