Reviewer's report

Title: Effectiveness of the trivalent influenza vaccine in Navarre, Spain, 2010-2011: a population-based test-negative case-control study

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Reviewer: Heath Kelly

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This study uses the prospective test negative design (TND) variant of the case control study to estimate influenza VE in Navarre, Spain in the influenza season of 2010-11. The study is nested within a larger cohort. The study investigates VE in both inpatients and outpatients, although small numbers of outpatients does not allow a robust VE estimate. Clinical data were obtained from a linked electronic database. Vaccination data were obtained from an online regional register. These linked databases provide high quality data for epidemiological analyses. These investigators have substantial experience with this study design and are affiliated with the European IMOVE collaboration. This experience is reflected in the quality of the paper. My comments are all of a minor nature.

1. In noting that the TND has become widely used, the authors reference the recent meta-analysis led by Osterholm. Only a few observational studies were included in this analysis. An alternative reference might be more appropriate.

2. What do the authors mean by ‘automatic’ reporting of ILI?

3. No detail is provided on the PCR testing.

4. Many investigators include a term in the logistic regression model that accounts for the delay between symptom onset and swabbing of the patient with ILI. This addresses the potential issue of false negative cases if the swabbing is delayed. I note a sensitivity analysis restricted to patients swabbed within 4 days of symptom onset slightly decreases the estimated VE. Was there any reason not to include a term for delay in the model? I also note the comment in the discussion on this issue. Maybe the authors could add a note in the methods.

5. Is there a significant difference – by formal testing - between the effectiveness of the seasonal vaccine and the effectiveness of the combined seasonal and pandemic vaccines? Confidence intervals overlap and the interaction term is not significant.

6. An Australian study which examined the effect of monovalent and seasonal vaccine in the 2010 influenza season could be included in the discussion (Fielding et al, EID).

7. The authors conclude that VE=59% (ref #13) was slightly lower than the VE found in this study. The TND has residual sources of bias, which may be different for different settings (outpatients and inpatients). It is likely that small differences in VE could be explained by residual bias and/or sampling variation. Unless
tested formally for differences in VE (see point 5 above), I believe the authors should not draw conclusions about differences in VE estimates.

8. There is current discussion in the literature about whether a VE of ~60% should be called ‘notable’ as these authors have done, or ‘moderate’ as other authors prefer. See for example ref #4. Will the authors please comment on what they think is a reasonable expectation for the effectiveness of a publicly funded vaccine? For instance, rubella VE is >90%, while measles VE ~90%.

9. There appeared to be 2 lineages of influenza B circulating but the VE estimate for influenza B was very high. Will the authors please comment?

10. There are slight differences in VE estimates for similar categories in Tables 2 and 3. For instance, the VE for pandemic vaccine for all swabbed patients = 44 (-69,82) in Table 2 while in Table 3, VE= 20(-253, 82). I think this is due to the fact that Table 2 estimates include patients who had both vaccines. This would be worth clarifying.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests: no competing interests