Author’s response to reviews

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

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Author’s response to reviews: see over
Dear Sir,

The manuscript entitled "Effectiveness of the trivalent influenza vaccine in Navarre, Spain, 2010-2011: a population-based test-negative case-control study" is hereby resubmitted for consideration by the Editorial Board of the BMC Public Health as a Research Article. The manuscript has been revised following the reviewer’s comments. The response to reviewers is below.

Neither the paper per se nor any part thereof has been published previously or is being submitted to any other journal.

All authors have contributed substantially to the work. The final manuscript has been approved by all authors, and they have taken due care to ensure the integrity of the work.

Thank you for your attention in this matter.

Yours faithfully,
Reviewer 1:

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. Additional references have now been included.

2. What do the authors mean by ‘automatic’ reporting of ILI?
This sentence has been modified.

3. No detail is provided on the PCR testing.
More details have been given in the revised version of the methods section.

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.
The delay in swabbing has been included in all models.

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.
We clarify this result in the text.

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).
The Fielding reference has been included in the discussion (ref. 12)

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.
Corrected

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%.
“Notable” has been replaced by “moderate”.

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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? 
Done. A sentence has been included in the discussion.

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. 
Clarification comments have been included in methods, results and in the footnote of table 3.
Reviewer 2

1) Authors conclusion is that the 2010-2011 seasonal influenza vaccine had a notable protective effect. They consider that this one single season effect supports the recommendation for annual influenza vaccination. Is this inductive conclusion, not supported by the data, tenable? We have eliminated this conclusion in the abstract.

2) No serious case is made in the introduction regarding why outpatient medically attended influenza like illness (MALI) and suspected influenza hospitalization are treated as a single outcome. Selection criteria for inclusion, testing, and study base provenance of MALI and hospitalized patients is surely to differ. Can the authors elaborate the justification for this decision in the introduction, and accordingly comment it in the discussion? In methods we clarify that the surveillance criteria were the same (influenza-like illness definition) for both hospital and primary health care cases. Depending on the severity, influenza-like illness is seen either in primary care or in hospitals. As stated in the objective, our justification is to analyse all influenza cases in a well-defined population. We also present results separately for primary health care patients.

3) Design, variables, confounders, statistical analysis, and specific analysis are appropriate to the research question. But categorization of time at risk and the meaning of pandemic 2009 vaccination should be reconsidered. A three categories time at risk analysis is proposed. Albeit, cases are concentrated on the peek of the season while controls are in the two tails. As no matched analysis was contemplated a more grainy, by epidemiological week, adjustment, or if numbers are scarce, two-week periods, should be a good measure to assure comparability of risk supported by cases and controls. Can it be done and results presented accordingly? We have changed the adjustment to 4-week periods. The study size does not allow adjustment by 2-week periods.

4) It is remarkable that pandemic (monovalent) vaccine is, before adjustment, even more effective than the trivalent vaccine against all influenza cases. Notwithstanding that 33 out of 267 cases were influenza B. Reporting, therefore, effectiveness of the 2009 monovalent vaccine to prevent 2010-2011 influenza cases is questionable with the presented data. Strong correlation is to be expected with previous vaccination. Adding both vaccinations (2009 monovalent and 2010-2011 trivalent) as "being immunized" is misleading as size of "vaccinated" is increased not by protection but by "propensity of being vaccinated". Then, 2009 pandemic vaccination should be treated as a confounder (indicator of health seeking behavior, added to high-risk condition in the young population, or other circumstances). Others, cited in the text, have published this add-on as durable protection and reported it as the effectiveness of having received both vaccines (2009 pandemic plus seasonal trivalent), but this publishing doesn't refute the
argumentation that the meaning of previous vaccination is an indication of propensity to being vaccinated rather than “persistent immune protection”. The authors could take this in consideration. In conclusion this is a challenging paper. And is to be an interesting reading for researchers involved in the field. 

We have expanded our explanation of the findings regarding the effect of the pandemic vaccine. In the discussion we recognise that the pandemic vaccine is a possible confounder and indicator of health-seeking behaviour.

In short, my major concerns are:

a) The use of a mixed outcome that includes two different populations (outpatients plus hospitalized patients) and, in consequence, a combined outcome, with no clear justification. 
Some justification is included in the introduction. Please also see point 2.

b) Epidemiological week should be used for adjustment. 
Done.

c) Pandemic 2009 vaccination is used as a “preventive exposure” and effectiveness is reported when it should be considered a confounder and bias explained. 
Done.