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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Version: 3 Date: 17 November 2012

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 *BMC Public Health* as a Research Article. The manuscript has been revised following the reviewers' 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,
Response to reviewer 1

1. For the sake of completeness, I suggest the authors report the VE against hospitalisation, even though the estimate is not conventionally statistically significant. The point estimate will be instructive, given that the estimates presented in the revised manuscript suggest the VE against hospitalisation for laboratory confirmed influenza will be lower than the VE against influenza treated in the community. This finding, initially counterintuitive, has been reported previously.

Done. We now include the estimates of VE against hospitalization in table 2.

2. I am still struggling a little with the model. Will the authors please clarify? In one model the exposure is receipt of seasonal influenza and monovalent pandemic vaccine, but the model with only seasonal vaccine as the exposure includes monovalent vaccine receipt as covariate. Is this correct? Does any model in Table 2 include seasonal vaccine only? That is, are patients who have received pandemic vaccine excluded?

The footnote in table 2 now explains more clearly the variables in each model.

In methods, last paragraph, we say: “All adjusted analyses include both vaccines, except the analysis of influenza B, since the pandemic vaccine did not include this virus.”

Patients who had received the pandemic vaccine were not excluded from any analysis.

As pointed out by reviewer 2, the treatment of previous vaccination in these models is complicated, given that previous vaccination is such a reliable predictor of current vaccination. These are not independent terms in the model. I note Table 3 has results for the vaccines separately. I think these are important results. It appears as if pandemic vaccine effectiveness by itself is waning. This has also been reported previously, as has the apparent increased protection from both vaccines – presumably a boosting effect. However I acknowledge there can be residual discussion about terms to be included in the model. Will the authors please make a theoretical case for the model they have adopted? Which covariates are likely to be genuine confounders?

Tables 2 and 3 present two different points of view of the effects of both vaccines. In methods we say “The effects of the 2010-2011 seasonal vaccine and the monovalent A(H1N1)pdm09 vaccine were evaluated as independent variables in one model, and as a combined variable (unvaccinated, only seasonal vaccine, only pandemic vaccine, or both vaccines) in a different model.”

We have included in the analysis the most common recognized confounders. For some specific analysis we did not include some covariates that were not applicable or not appropriate: when evaluating the influenza vaccine effectiveness against influenza B virus, we did not include monovalent A(H1N1)pdm09 influenza vaccination, and when considering only patients in primary care, or only hospitalized patients, we did not include the health care setting. This has been clarified in the footnote of table 2.
3. I am confused by one of the results. VE> 50 years = 69%, VE<50 years = 73%. I would have expected an all age VE to be somewhere between these estimates but all estimates were <67%.

We have double-checked the analysis and these results are right. These findings may be explained simply by random variation since the difference in the point estimates is small and the confidence intervals are wide and overlap.
Response to reviewer 2

I have reviewed the comments made by Prof. Heath Kelly and also the one I made to the first version of the manuscript. I've read carefully the answer of the authors and the changes they have made in their manuscript. The author's have included in their resubmitted version most of both reviewers comments. However, given their results on the null effect of the pandemic vaccine, on the absence of interaction between past and current vaccine, and, finally, the strong correlation with previous and current vaccination, authors (and readers) should be suspicious of the 20 points improvement on influenza vaccine effectiveness when both, current and previous vaccine, are considered as one unique exposure. This is surely due to bias due to background and unknown population characteristics.

In fact the population included is a mix of low risk, high-risk and no risk at all; of targeted for influenza subjects and people that were vaccinated because they choose to. This unequal study base is clearly shown in the age distribution of cases and controls, the majority in the 15 to 44 age group, a group at extremely low risk for mild or severe influenza, and the mix of outpatient and hospitalized patients, with disproportionate different numbers. I would advise against presenting a biased result as relevant as is done in table 3 of the manuscript. Nevertheless, this is a decision up to the authors.

The authors have modulated their discussion and their conclusions, and I would advise potential readers to opt for the caution in interpretation comments in the discussion.

We aimed to evaluate the trivalent influenza vaccine effectiveness, and our conclusions focus on this vaccine. However, we consider it important to adjust for the effect of the pandemic vaccine, since some authors have reported a residual effect [ref. 11, 12]. We did not find any statistically significant effect of the pandemic vaccine, and we did not make any conclusions about this. People who received both vaccines did not show a significantly higher effectiveness as compared to people who only received the seasonal vaccine.

Table 3 now shows the analysis for the target population for vaccination (high-risk population); the effectiveness remains higher in people who had received both vaccines, but this difference is not statistically significant.

In the discussion we say: “Our results concerning a possible residual effect of monovalent influenza A(H1N1)pdm09 vaccination in the previous season were not conclusive. As in other studies, a greater protective effect was observed with both vaccines than with seasonal vaccine alone [11,12], but in our study this difference was not statistically significant. Since this was a new virus with which most of the population had had no previous contact, dual vaccination may have helped to achieve a better immune response [19-21]. However, this finding could be due to biases since previous receipt of the pandemic vaccine may be an indicator of health-seeking behaviours.”