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

Authors:

Iván Martínez-Baz (imartinba@navarra.es)
Víctor Martinez-Artola (vmartind@navarra.es)
Gabriel Reina (gabi@unav.es)
Marcela Guevara (mguevare@navarra.es)
Manuel García Cenoz (mgcenoz@navarra.es)
Julio Morán (jmoranpi@navarra.es)
Fátima Irisarri (firisarz@navarra.es)
Maite Arriazu (marriazb@navarra.es)
Esther Albéniz (ealbenim@navarra.es)
Jesús Castilla (jcastilc@navarra.es)

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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 *BMC Public Health* as a Research Article. The manuscript has been revised following the reviewer's comments. The response to reviewer 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. When reading the manuscript again, I wondered if the authors haven’t overstated the benefits of the TND in the introduction. Certainly a viral endpoint is to be preferred in VE studies, but this endpoint, together with the application of the TND, will not eliminate bias. The TND is a design in evolution and the nuances of its biases are not yet completely understood. The authors might consider a minor re-wording.

We have reworded these two sentences to modulate the message:
“Studies looking at poorly specified outcomes tend to underestimate the effect of the intervention [6], whereas those that analyze virologically-confirmed cases reduce this problem [4,9]. A design that compares confirmed influenza cases with test-negative controls tends to improve the comparability and is easy to carry out, thus this type of study has come to be widely used [4,9-14].”

2. I don’t believe ref#4 (a meta-analysis, mostly of RCTS) in the last paragraph of the discussion is the appropriate reference for the comment on selection bias in the TND.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.

The reviewer is right. There was a mistake in this reference. The right reference is #6.