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: Joan Puig-Barberà

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

The authors estimate the effectiveness of the trivalent influenza vaccine in preventing outpatient illness and hospitalizations from laboratory-confirmed influenza in the 2010-2011 season by means of a nested test-negative case-control study. The vaccination status of laboratory-confirmed influenza cases is compared with that of test-negative controls, after adjusting for major known confounders.

Discretionary Revisions

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?

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?

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?
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.

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.

b) Epidemiological week should be used for adjustment.

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

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:

'I declare that I have no competing interests'