



## **Influenza vaccine effectiveness in older adults: study methods, transparency and impacts on public health**

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## Letter to the Editor

**Influenza vaccine effectiveness in older adults: study methods, transparency and impacts on public health**

Dear Professor Lee,

We re-read the article by Domnich et al. [1] following citation in a recently-published ECDC report [2]. Domnich et al. conducted a post-hoc, test-negative case-control design (TND) study of Italian hospitalizations (using DRIVE [3] data) and estimated relative effectiveness (rVE) of 59.2% for adjuvanted vs unadjuvanted influenza vaccination, which was influential in ECDC conclusions. These results directionally contradict Italian hospitalized results from DRIVE itself which reported lower adjusted VE for adjuvanted than non-adjuvanted vaccine in both 2018/19 (34% [−12–61] for adjuvanted vs 92% [40–99] for Fluarix Tetra) [4] and 2019/2020 (52% [27–68] vs 67% [8–88]) seasons, findings associated with negative, rather than positive, adjuvanted rVE [5]. The reasons for this disparity were discussed by Domnich and colleagues but deserve additional exploration considering their newfound policy relevance.

The underlying hospitalization data were highly confounded, with groups “severely unbalanced” across multiple variables. STROBE guidelines recommend unadjusted estimates be presented alongside confounder-adjusted results to inform the effects of adjustment [6]. We calculate (supplementary appendix) the unadjusted odds ratio (OR) is 1.92, reversing after adjustment to 0.41 (4.7-fold reduction). On the rVE scale, this equates to a change from −92% to +59%. This sizeable adjustment was achieved by an opaque propensity score matching (PSM) method which may be inappropriate in this context [7], derived from nineteen confounding variables without model diagnostics or exploration of intermediate models. This analytic strategy differs from those used by influenza TND networks in Europe [8] and North America [9] including the DRIVE consortium from which these data originated, which recommends clear and parsimonious logistic regression methods [3]. Design decisions are especially critical in observational studies where researchers can test many different methods and models but report only the most impactful results, making replication challenging [10]. Confirmatory analyses of the dataset are needed to describe this risk [11].

We have the following recommendations for the authors:

1. rVE from a parsimonious logistic regression (as in DRIVE) should be presented.
2. The rationale for PSM use, justification for variable selection and statistical diagnostics should be reported.
3. Sensitivity on the treatment of missing data and the role of influential confounders should be presented.
4. Underlying source data and statistical code should be shared to allow independent verification to assess the robustness of the results for policy.

In the absence of powered randomized trials for causal inference, observational studies should be interpreted with care. We thank the authors for their consideration and look forward to clarification.

**Declarations of competing interest**

AC, RH and JN are full-time employees of Sanofi, a company that makes vaccines including against influenza and hold stocks in the company. PC reports consulting fees unrelated to this project from Sanofi. TS reports consulting fees from Sanofi and honoraria for presentations unrelated to this project. TBS has received research grants from Sanofi Pasteur, GSK, Novo Nordisk, AstraZeneca, Boston Scientific and GE Healthcare, consulting fees from Novo Nordisk, IQVIA, Parexel, Amgen, CSL Seqirus, GSK and Sanofi Pasteur, and lecture fees from Bayer, Novartis, Sanofi Pasteur, GE healthcare and GSK.

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**Ethical approval**

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**Author contributions**

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**Supplementary materials**

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.ijid.2024.107103](https://doi.org/10.1016/j.ijid.2024.107103).

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