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June 17, 2026
Regarding Cai et al., published June 15, 2026

To the Editor of JAMA Internal Medicine:

How large can the grain of salt be?

Cai et al. use inverse probability weighting to reduce confounding thereby aligning the two cohorts (influenza with and without vaccination for COVID-19 in the 2024-2025 season). While this makes sense for most of the variables, the weightings ensnared a relevant and drastic behavior change. Those who were not vaccinated for COVID-19 in the 2024-2025 season and were vaccinated in the 2023-2024 season numbered 201,928, or 29.2% of the unvaccinated cohort. They were upweighted to represent 70.8% of the unvaccinated cohort. Similarly with the 2022-2023 season of 248,890 or 36.0% of the unvaccinated cohort were upweighted to represent 70.1% of the unvaccinated cohort. Lastly, with the 2021-2022 season of 481,454 or 69.7% of the unvaccinated cohort were upweighted to represent 89.9% of the unvaccinated cohort.

This is not a COVID-19 vaccinated vs. unvaccinated comparison in the 2024-2025 season. It is a COVID-19 vaccinated vs. those who chose to suddenly stop COVID-19 vaccination in that season. In upweighting people who suddenly stopped, the authors are underweighting everyone else.

The authors do not report unweighted (or crude) VE, but they can be derived from the numbers presented (95% CI is calculated using the standard Katz logarithm method for risk ratios).

The study utilizes two cohort populations of 690,574 unvaccinated and 349,085 vaccinated.

All three outcomes for all-cause conditions had crude statistical significant negative VE. For all-cause MACE (21,051 unvaccinated and 12,573 vaccinated) the **crude VE is -18.15% (-20.75% to -15.62%)**, the weighted VE is 6.2% (3.8% to 8.9%). For all-cause hospitalization (25,503 unvaccinated and 14,730 vaccinated) the **crude VE is -14.3% (95% CI: -16.6% to -12.0%)**, weighted VE is 6.6% (4.4% to 9.1%). For all-cause death (12,876 unvaccinated and 7,254 vaccinated) the **crude VE is -11.43% (-14.73% to -8.23%)**, the weighted VE is 7.1% (3.9% to 10.5%).

The raw data, before weightings were employed, indicated a negative efficacy for all-cause MACE, all-cause hospitalization, and all-cause mortality. The vaccinated appear more likely to be statistically significantly afflicted by all three all-cause outcomes: MACE, hospitalization, and mortality. When such a disparity exists between crude and weighted VE, extra scrutiny is warranted on how the weighting was performed and reported. That extra scrutiny would take the form of sensitivity analyses. The authors performed 12 different models of sensitivity analyses, and the results clustered around the VE of their reported primary outcome, COVID-19 associated MACE VE of 37.7% (18.2% to 54.9%). The largest deviation of the sensitivity analyses was when the authors enforced the inclusion criteria requiring a 2023-2024 season COVID-19 vaccine, with a VE of 44.5% (12.7% to 66.9%). The VE is inflated when considering those who were vaccinated in the 2023-2024 season, and the main model of the paper more than doubles their weight contribution in the unvaccinated cohort.

It is incumbent upon the authors to re-run primary and secondary outcome analysis without including prior immunizations in the inverse probability weighting, coupled with a thorough explanation as to how negative efficacy turned positive.

Sincerely,

Karl Jablonowski, PhD
Director of Science and Research
Children's Health Defense

postscript

Excluded for submission character limit:
Two outcomes unweighted had a lower, but still statistically significant VE. For COVID-19 associated MACE (295 unvaccinated and 116 vaccinated), the crude VE is 22.2% (3.6% to 37.3%), weighted VE is 37.7% (18.2% to 54.9%). For COVID-19 associated cardiovascular death (96 unvaccinated and 25 vaccinated) the crude VE is 48.5% (20.0% to 66.8%), weighted VE is 57.9% (25.2% to 78.2%).

Three outcomes unweighted were statistically insignificant. For COVID-19 associated myocardial infarction (94 unvaccinated and 43 vaccinated) the crude VE is 9.5% (-29.8% to +36.9%), weighted VE is 38.5% (4.3% to 62.3%). For COVID-19 associated stroke (71 unvaccinated and 28 vaccinated) the crude VE is 22.0% (-20.8% to +49.6%), weighted VE is 30.6% (-24.7% to 64.3%). For COVID-19 associated hospitalization for heart failure (80 unvaccinated and 39 vaccinated) the crude VE is 3.6% (−41.4% to +34.2%), weighted VE is 41.9% (4.1% to 67.5%).