COVID-19, Flu Vaccine Coadministration May Lower MACE Risk in Older Adults

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Major adverse cardiovascular events (MACE) remain a significant concern following COVID-19 infection, particularly in older populations. Previous data established a link between COVID-19 vaccination and a reduced risk of these cardiac complications. The critical question for the 2024-2025 season was whether the updated COVID-19 vaccine, alongside influenza vaccination, would maintain this protective effect amidst evolving viral variants and widespread population immunity.

KEY TAKEAWAYS

- The Pivot: The 2024-2025 COVID-19 vaccine, when coadministered with an influenza vaccine, continued to reduce MACE risk in older adults.
- The Data: Coadministration reduced MACE risk by 24% (HR 0.76; 95% CI, 0.71-0.81; PThe Action: Clinicians should continue to recommend coadministration of COVID-19 and influenza vaccines to eligible older adults, emphasizing the cardiovascular benefits.

The persistent threat of major adverse cardiovascular events (MACE) following COVID-19 infection has prompted ongoing investigation into vaccine efficacy beyond acute respiratory illness. Early evidence suggested that COVID-19 vaccination offered a protective effect against these cardiac sequelae. But with the continuous evolution of SARS-CoV-2 variants and a population largely exposed to the virus or prior vaccination, the sustained benefit of updated vaccines, particularly when coadministered with influenza shots, required fresh scrutiny.1

A study published in JAMA Internal Medicine addressed this directly, examining the 2024-2025 COVID-19 vaccine and its association with MACE among US veterans.1 The investigators, led by Ziyad Al-Aly, a clinical epidemiologist at Washington University School of Medicine in St. Louis, analyzed a large cohort of veterans aged 65 years and older. The study population comprised individuals who received either the 2024-2025 COVID-19 vaccine coadministered with an influenza vaccine, or an influenza vaccine alone, between September 1, 2024, and March 31, 2025. This design allowed for a direct comparison of MACE incidence in a real-world, high-risk population.1

What the trial actually measured

The primary endpoint for this observational cohort study was the incidence of MACE, defined as a composite of myocardial infarction, stroke, or all-cause mortality, occurring within 90 days of vaccination. The study included 1,245,678 US veterans aged 65 years and older. Of these, 622,839 received coadministration of the 2024-2025 COVID-19 vaccine and an influenza vaccine, while 622,839 received only the influenza vaccine. The researchers used propensity score matching to balance baseline characteristics between the two groups, including demographics, comorbidities, and

prior healthcare utilization, which is critical for minimizing confounding in observational studies.1

The data showed a significant reduction in MACE risk for those receiving both vaccines. Coadministration of the 2024-2025 COVID-19 vaccine with an influenza vaccine reduced the risk of MACE by 24% (HR 0.76; 95% CI, 0.71-0.81; P3.2 fewer MACE events per 1,000 vaccinated individuals in the coadministration group over the 90-day follow-up period.1

Breaking down the composite endpoint, the coadministration group saw a 20% reduction in myocardial infarction (HR 0.80; 95% CI, 0.73-0.88; P28% reduction in stroke (HR 0.72; 95% CI, 0.65-0.80; P25% reduction in all-cause mortality (HR 0.75; 95% CI, 0.69-0.82; P1

The study also explored the timing of vaccination, finding that earlier vaccination within the season correlated with a slightly greater protective effect, although the difference was not statistically significant. This suggests that the benefit is largely independent of the exact timing within the vaccination window, as long as vaccination occurs. Safety profiles were largely similar between the two groups, with no new or unexpected adverse events reported with coadministration beyond those typically associated with each vaccine individually. This is an important consideration for public health campaigns promoting combined vaccination strategies.1

The open-label, observational design is the obvious caveat. While propensity score matching helps mitigate confounding, it cannot account for all unmeasured confounders. For example, individuals who opt for coadministration might inherently have different health-seeking behaviors or baseline health statuses not fully captured by administrative data. The study population, consisting solely of US veterans, limits generalizability to broader civilian populations, particularly those with different demographic profiles or healthcare access. Still, the large sample size and rigorous statistical methods lend considerable weight to the findings.1

The mechanism behind the observed cardiovascular protection is likely multifactorial. COVID-19 infection itself is known to induce systemic inflammation, endothelial dysfunction, and hypercoagulability, all of which contribute to MACE risk. Vaccination may mitigate these pro-thrombotic and pro-inflammatory states, thereby reducing the downstream cardiovascular complications. The coadministration with influenza vaccine might offer synergistic protection, as influenza infection also carries a known risk for cardiovascular events, particularly in older adults.1

CLINICAL IMPLICATIONS

The sustained reduction in major adverse cardiovascular events with coadministration of COVID-19 and influenza vaccines is a clear win for public health. For clinicians, this means continuing to advocate for both vaccines, especially in older adults. The data provides a tangible, quantifiable benefit beyond preventing respiratory illness, offering a compelling argument for patient adherence.

The consistent hazard ratios across myocardial infarction, stroke, and all-cause mortality suggest a broad protective effect. This is not merely about avoiding a severe COVID-19 case; it is about mitigating the systemic cardiovascular damage that the virus can inflict. The message to patients should be unequivocal: these vaccines are cardiac protective, not just respiratory shields.

While the study was observational and focused on veterans, the sheer scale of the cohort and the rigorous matching procedures make the findings difficult to ignore. The cardiovascular benefits of vaccination are becoming increasingly clear, moving beyond the initial focus on acute infection. This should inform future guideline updates and public health messaging, emphasizing the dual protection offered by these

> coadministered vaccines.
> The next step is to see if these benefits extend to younger populations or those with specific cardiovascular risk factors not fully represented in the veteran cohort. Further research could also explore the long-term durability of this cardiovascular protection beyond 90 days. For now, the evidence supports a straightforward clinical recommendation.

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REFERENCES

1. 1. Cai M, Xie Y, Al-Aly Z. 2024-2025 COVID-19 Vaccine and Major Adverse Cardiovascular Events Among US Veterans. JAMA Intern Med 2026.

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