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High-dose influenza vaccination in older adults: Reconciling trial evidence for policy

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Seasonal influenza remains a major cause of morbidity and mortality worldwide, with older populations accounting for a disproportionate share of severe outcomes, including hospitalization and death.[1] Although vaccination has long been the cornerstone of influenza prevention, standard-dose vaccines often underperform in this demographic. This reduced protection is widely attributed to immunosenescence, along with a high burden of chronic comorbidities that further compromise vaccine-induced immunity.[2] In response to these challenges, high-dose vaccines—formulated with significantly more hemagglutinin antigen—were designed. Preceding studies have confirmed that these high-dose influenza vaccines demonstrate superior immunogenicity and offer better protection against laboratory-confirmed flu.[3] Whether these immunologic advantages can translate into meaningful reductions in severe clinical outcomes, however, remains uncertain.

Two major, population-scale randomized trials published in The New England Journal of Medicine offer vital, albeit complex, answers to this question. Conducted independently in Spain and Denmark, the GALFLU and DANFLU-2 studies used nationwide health registries and existing vaccination delivery systems to evaluate the real-world effectiveness of high-dose compared with standard-dose influenza vaccines in older populations.[4,5] Rather than limiting evaluation to immunogenicity or laboratory-confirmed infection, these trials place greater emphasis on outcomes with direct clinical and policy relevance.

In the GALFLU trial, community-dwelling adults aged 65 to 79 years were recruited in the Galician region of Spain. Enrollment took place over two consecutive influenza seasons. More than 130,000 participant-seasons were randomized to receive either a high-dose or a standard-dose influenza vaccine. Hospitalization for influenza or pneumonia was defined as the primary composite endpoint. The analysis showed lower event rates among recipients of the high-dose vaccine, corresponding to a relative vaccine effectiveness of 24.2%.[4,5] Hospitalizations specifically attributed to influenza were reduced by approximately one third in the high-dose group. In addition, rates of serious adverse events were similar in the two groups, indicating no evident safety difference associated with high-dose vaccination in this population.

The DANFLU-2 trial took place in Denmark across three influenza seasons. The study enrolled over 330,000 adults aged 65 years or older and reported a different primary outcome. Specifically, the composite endpoint of influenza- or pneumonia-related hospitalization was not significantly reduced.[5] At the same time, the trial did identify a substantial reduction in hospitalizations for laboratory-confirmed influenza in the high-dose group, amounting to 43.6%. Reductions in cardiorespiratory hospitalizations were also observed, although these effects were more modest. This reflects the fact that hospitalizations

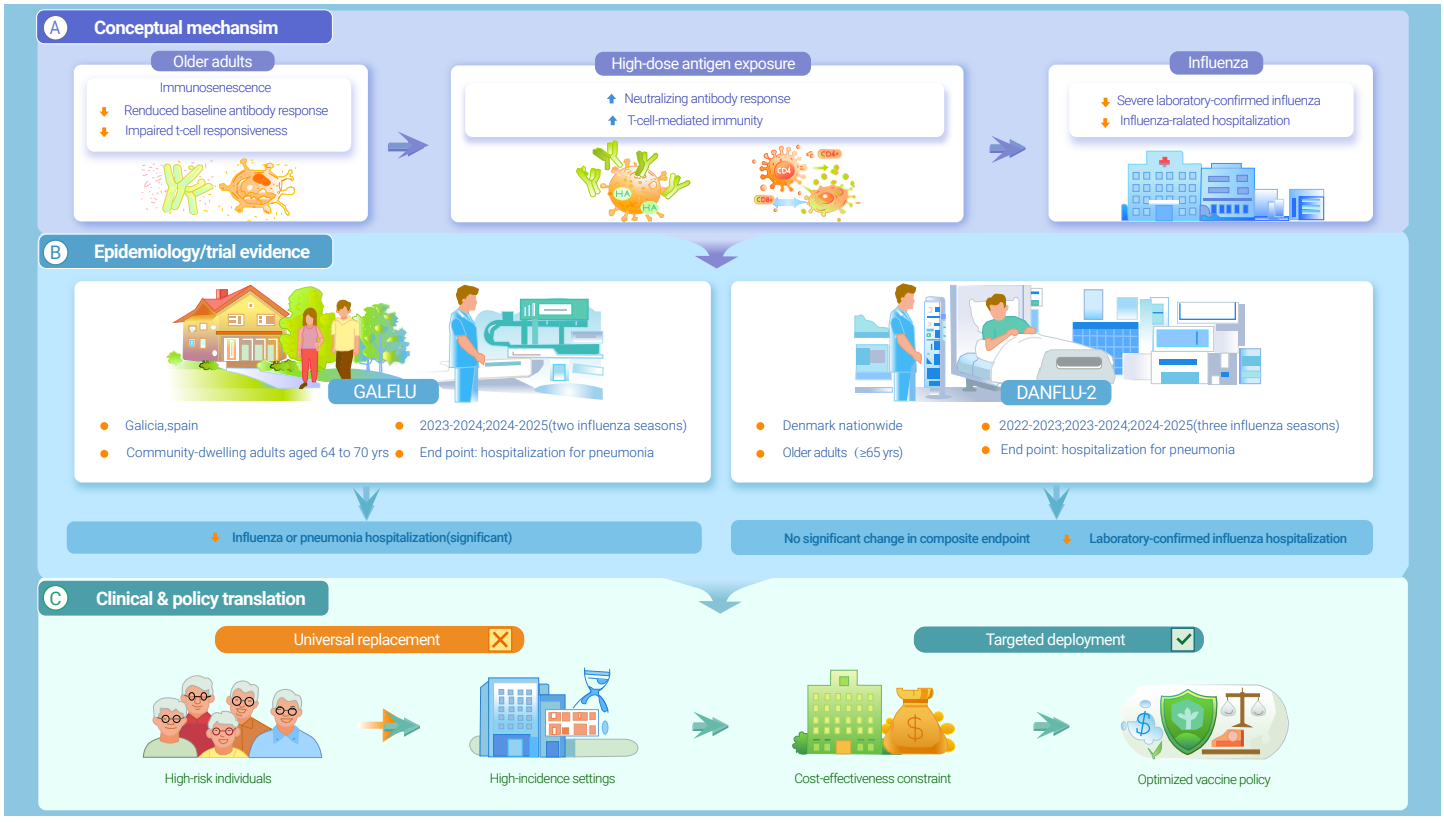

Figure 1. Conceptual framework linking immunosenescence, trial evidence, and policy implications of high-dose influenza vaccination in older adults.

for laboratory-confirmed influenza constituted only a subset of the broader composite endpoint, which also included pneumonia admissions driven by heterogeneous etiologies. Adverse event rates were comparable between the two vaccine groups, as also observed in GALFLU. In other words, no additional safety signals emerged with the high-dose formulation.

At first glance, the results of GALFLU and DANFLU-2 do not fully align. A more detailed look helps reconcile these differences. When interpreted through transnational and epidemiological reasoning, the findings point to a consistent underlying signal. In both trials, high-dose vaccination was associated with fewer cases of laboratory-confirmed severe influenza. This endpoint is most closely aligned with the biological action of vaccination, as laboratory confirmation—typically through highly specific methods such as RT-PCR—directly identifies influenza virus infection and therefore more precisely captures vaccine-mediated immune protection.[4,5] By contrast, broader composite outcomes introduce substantial etiologic heterogeneity. Pneumonia may arise from bacterial infection, aspiration, chronic lung disease exacerbation, or non-influenza viral pathogens, while all-cause hospitalization reflects an even wider spectrum of clinical events. Because many of these pathways are only indirectly related—or unrelated—to influenza infection, inclusion of such outcomes can attenuate the measurable impact of influenza-specific vaccination strategies.

Moreover, differences in primary outcomes between GALFLU and DANFLU-2 likely reflect variation in the clinical and health system settings of the two studies. Baseline hospitalization rates differed substantially between the two settings. In Denmark, comparatively lower event rates would constrain the absolute risk reduction achievable through vaccination, even if relative effectiveness were similar. Also, influenza vaccination coverage among adults aged ≥ 65 years differs regionally, with uptake in Denmark around 75% in recent seasons compared with approximately 65% in Spain, potentially influencing the incremental advantage of switching to high-dose formulations. Patterns of healthcare utilization and admission thresholds further shape measured outcomes. Finally, seasonal variation in circulating strains and transmission intensity—factors known to influence vaccine effectiveness, may further modulate observed protection.

Methodologically, both GALFLU and DANFLU-2 illustrate the value of registry-based randomization in pragmatic trial settings. In both studies, randomization was integrated into routine vaccination programs. Outcomes were identified using comprehensive administrative health data, which allowed the trials to be conducted at a scale and with a level of external validity rarely achievable in conventional randomized studies.[4,5] This approach is well suited to influenza, where severe outcomes are uncommon and context dependent. While well suited to large-scale evaluation, this design offers limited resolution at the biological level. This limitation does not preclude biologic plausibility. Although immunologic correlates were not directly examined, higher antigen exposure may plausibly augment immune responses relevant to protection. As illustrated in Figure 1, increased antigen exposure may partially offset immunosenescence, enhancing antibody and T-cell–mediated responses and thereby strengthening protection against severe influenza.

Taken together, GALFLU and DANFLU-2 indicate that the benefit of high-dose influenza vaccination in older adults is relatively specific: reductions are most consistent for severe, laboratory-confirmed influenza, whereas broader outcomes such as pneumonia or all-cause hospitalization are more sensitive to baseline risk and contextual factors. This distinction is critical for policy interpretation. Rather than signaling inconsistency, differences between trials underscore how endpoint definition and epidemiologic background shape measured effectiveness.

The central question posed at the outset—whether enhanced immunogenicity translates into meaningful clinical benefit—can therefore be answered in the affirmative, albeit with contextual qualification. The remaining challenge is not to demonstrate efficacy, but to define strategy. Clarifying correlates of protection, refining risk stratification, and evaluating cost-effectiveness across healthcare systems will be essential. In an aging population, the focus must shift from proof of benefit to precision in deployment.

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AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.