Taylor & Francis
Taylor & Francis Group

Expert Review of Vaccines

ISSN: 1476-0584 (Print) 1744-8395 (Online) Journal homepage: www.tandfonline.com/journals/ierv20

High-dose influenza vaccine: enhanced protection for the elderly

Claudia Maria Trombetta & Emanuele Montomoli

To cite this article: Claudia Maria Trombetta & Emanuele Montomoli (2025) High-dose influenza vaccine: enhanced protection for the elderly, Expert Review of Vaccines, 24:1, 1111-1127, DOI: 10.1080/14760584.2025.2596673

To link to this article: https://doi.org/10.1080/14760584.2025.2596673

Published online: 03 Dec 2025.

EXPERT REVIEW OF VACCINES
2025, VOL. 24, NO. 1, 1111–1127
https://doi.org/10.1080/14760584.2025.2596673

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS Check for updates

High-dose influenza vaccine: enhanced protection for the elderly

Claudia Maria Trombetta[a] and Emanuele Montomoli[a,b]

[a]Department of Molecular and Developmental Medicine, University of Siena, Siena, Italy; [b]VisMederi srl, Strada del Petriccio e Belriguardo, Siena, Italy

ABSTRACT

Introduction: Seasonal influenza causes up to 50 million symptomatic cases and 15,000 – 70,000 deaths annually within the European Union. While influenza affects all age groups, adults aged ≥65 years disproportionately experience high rates of influenza-related hospitalizations and complications. Vaccination remains the cornerstone of influenza prevention and the most effective intervention for reducing morbidity and mortality.

Area covered: This review focuses on the high-dose inactivated influenza vaccine, an enhanced formulation recommended for the immunization of adults aged 60/65 and older. The high dose vaccine contains four times the hemagglutinin antigen compared to the standard dose vaccine, resulting in significantly higher and more sustained antibody responses. This increased immunogenicity is especially pronounced in adults aged ≥75 years and in those with cardiopulmonary diseases or immunocompromised states.

Expert opinion: Expanding the use of the high-dose vaccine to adults aged 50–64 years may proactively address immunosenescence and enhance protection in this population. Moreover, the development of multicomponent vaccines targeting both influenza and COVID-19 within a single formulation could enhance vaccine uptake and streamline immunization programs. Ultimately, the high-dose vaccine has the potential to replace the standard-dose formulation in older adults, thereby optimizing influenza prevention and reducing disease burden.

ARTICLE HISTORY
Received 11 August 2025
Accepted 21 November 2025

KEYWORDS
High-dose vaccine; influenza; elderly; protection; vaccination

1. Introduction

Seasonal influenza is a vaccine-preventable disease that poses a significant public health threat. The European Centre for Disease Prevention and Control estimates that seasonal influenza causes up to 50 million symptomatic cases each year in the European Union/European Economic Area, and 15,000 – 70,000 deaths in European citizens for causes associated with influenza such as increased susceptibility to secondary bacterial infections, cardiovascular events and exacerbations of chronic underlying conditions [1,2]. A statistical model estimated that annual influenza-associated mortality was 3.1 per 100,000 person-years for pneumonia and influenza-related deaths, 13.8 per 100,000 person-years for deaths from underlying respiratory and circulatory conditions, and 19.6 per 100,000 person-years for all-cause mortality [3]. An age-specific Poisson regression model was developed using weekly influenza circulation data. Deaths were stratified into five age groups and influenza - associated deaths estimated separately for influenza A/H1N1, A/H3N2, and B viruses. Viral circulation was represented by the weekly percentage of specimens testing positive for each influenza type and subtype. Weekly age-specific population estimates were used to account for changes in population trend over time. The US populations estimates stratified by age group were sourced from the US Census Bureau. The model developed for this study can incorporate additional factors, such as temperature, that were not included in the previous CDC model but may independently influence winter season mortality. Consequently, the authors consider this new model an advancement in efforts to more accurately quantify the burden of viral respiratory infections on mortality.

The severity and clinical outcomes of influenza depend on the virus, host factors and other factors such as access to care [1]. Although anyone can contract influenza, older adults aged ≥65 years (hereinafter also referred to as the elderly) are at an increased risk of severe illness, hospitalization, and infectious complications due to factors such as immunosenescence, underlying chronic conditions, or a combination of both [4,5]; hospitalization rates for influenza are highest in this age group (309/100,000 person-years; 95% CI, 186.0–1103.7), followed by children aged <1 year (151/100 000; 95% CI, 151–660) [6]. A modeling method estimates that an average of 27,600 respiratory deaths (ranging from 16,200 to 39,000) were associated with seasonal influenza across the 28 EU countries per winter. Of these, 88% occurred among older adults aged ≥65 years, with mortality rates in this age group approximately 35 times higher than subjects under 65 [7].

To date, vaccination remains the most effective method of controlling seasonal influenza infections and the primary strategy for reducing morbidity and mortality caused by influenza. Currently, influenza vaccines contain three influenza viruses (trivalent): subtypes A/H1N1, A/H3N2, and the B/Victoria lineage. Since 2024–2025 influenza season, the B/Yamagata lineage was excluded due to the absence of its detection since March 2020, resulting in a shift from previous quadrivalent to trivalent

CONTACT Claudia Maria Trombetta trombetta@unisi.it Department of Molecular and Developmental Medicine, University of Siena, Via Aldo Moro, 2, Siena 5300, Italy

Article highlights

- The high-dose vaccine elicits stronger anti-neuraminidase antibody responses than the standard-dose vaccine, warranting further investigation in the context of developing a universal vaccine.
- The development of a multicomponent vaccine that provides protection against both influenza and COVID-19 in a single injection could offer a more convenient and effective approach, potentially improving adherence to immunization guidelines and reducing the overall disease burden.

influenza vaccines [8]. Vaccine-induced immune response varies across different age groups with the elderly exhibiting reduced vaccine effectiveness (VE). Immunosenescence has been considered as a key factor that not only makes older adults more susceptible to infectious pathogens but also less responsive to vaccination [9–12]. When the vaccine strains are antigenically well-matched with the circulating viruses, the clinical vaccine efficacy in preventing laboratory-confirmed influenza (LCI) is estimated to be approximately 70%-90% in healthy adults. In contrast, the clinical vaccine efficacy in the elderly seems to be lower, about 17–53%, depending on circulating viruses [13–16]. The wide range of vaccine efficacy may be attributed to various factors such as age, sex, techniques used for diagnosis, location and match or mismatch of seasonal vaccines or circulating viruses, the impact of seasonal influenza infections outside of peaks months, potential interaction with other pathogens, the impact of repeated vaccinations and the immune response including the decline in cellular and humoral immune response associated with aging. A systematic review/meta-analysis [17] estimates the overall seasonal influenza VE at 41% (95% CI, 34–48) for all ages groups against hospitalizations associated with laboratory confirmed influenza virus infection between 2010–11 and 2014–15 influenza seasons. However, VE was lower in the elderly compared to 18–64 age group (37%; 95% CI, 30–44 vs. 51%; 95%CI, 44–58), respectively). Moreover, during seasons with an antigenic mismatch between the vaccine subtype A/H3N2 and circulating viruses, VE against A/H3N2 was close to null in the elderly (43%; 95%CI, 33–53) vs 14% due to circulating strains that are antigenically distinct from the H3N2 component in the vaccine composition, or to adaptations and/or alterations acquired by the vaccine seed viruses during egg-based propagation, which affect their antigenicity. The reason why a poorly matched A/H3N2 vaccine component would offer less protection to the elderly is still unclear. Potential factors may include a more narrow and specific immune response to influenza vaccines and age-related differences in exposure history to A/H3N2 viruses. Over past two decades, high hospitalization rates during A/H3N2-dominated influenza seasons among subjects aged ≥65 have been reported, underscoring how specific dominant circulating strains, such as subtype A/H3N2, may further contribute to high hospitalization levels [18].

Vaccination recommendations differ among countries; however, the World Health Organization (WHO) recommends annual vaccination for pregnant women at any stage of pregnancy, children aged 6 months to 5 years, the elderly, subjects with chronic medical conditions and health workers [19]. In 2003, the World Health Assembly urged Members States to increase influenza vaccination coverage for all high-risk groups and to achieve coverage of 75% among the elderly by 2010. This goal was reaffirmed in 2005 by a European Council recommendation, which called for Member States to increase influenza vaccination in accordance with WHO guidance. Although most Member States recommended vaccination for the elderly, coverage remains low in many countries. Moreover, as reported in the EU Companion Report 2019, none of the 30 EU countries achieved the WHO target of 75% influenza vaccination coverage among older adults. The EU average coverage rate is just 43%, and several countries such as Belgium, Spain, Ireland, have experienced a significant decline in recent years (Table 1) [20–23]. In Italy, vaccination coverage in the last season, 2023–2024, which decreased in all age groups, was 18.9% in the general population and 53.3% in the elderly population [24].

The degree of protection elicited by influenza vaccine depends on a complex interplay between vaccine composition and circulating viruses, the age of vaccine recipients, health status and their previous exposure to influenza, product-specific factors such as formulation [25]. Over the years, various approaches have been implemented to enhance vaccine performance in the elderly, including the addition of adjuvants and, more recently, the increase in the hemagglutinin (HA) quantity, the most abundant and immunogenic protein on the surface of influenza viruses [26].

This review focuses exclusively on the high-dose (HD) inactivated influenza vaccine, an enhanced formulation recommended for the immunization of adults aged 60/65 and older and does not include comparisons between the HD vaccine and other enhanced vaccines.

2. High-dose vaccine

HD vaccine is a split virion, inactivated vaccine containing 60 µg of HA per each virus strains, four times more than the standard dose (SD) (15 µg) [27,28]. The HD inactivated influenza vaccine (Fluzone® High-dose, Sanofi Pasteur) was approved by the Food and Drug Administration (FDA) in December 2009 as a single dose use in subjects aged ≥65 years and was available beginning with the 2010–2011 influenza season in the US. In 2020, the HD vaccine received marketing authorization in 25 European countries (under the name Efluelda®) for use in adults 60 years of age and older. Up to the season 2024–2025 more than 328 million of doses of HD flu vaccine have been distributed worldwide.

2.1. Vaccine immunogenicity

HD influenza vaccines provide superior and sustained immune responses compared to SD vaccines in older adults and high-risk patients, supporting their preferred use for enhanced protection against influenza.

Immunogenicity studies are a key requirement of the regulatory approval process for influenza vaccines. These studies should assess both humoral and cellular immune responses, where feasible and depending on the availability of appropriate reagents. For a new inactivated, non-adjuvanted seasonal influenza vaccine with a manufacturing process comparable to that of an authorized vaccine previously evaluated by EU

Table 1. Influenza vaccination decline, influenza lower respiratory tract infection episodes, hospitalizations, and deaths among all ages by some GBD country, 2017 (adapted from GBD 2017 Influenza Collaborators).

Country	Reference	Vaccination decline	Deaths (95% UI)	Deaths per 100 000 (95% UI)	Hospitalizations (95% UI)	Hospitalizations per 100 000 (95% UI)	Episodes (95% UI)	Incidence per 100 000 (95% UI)
Belgium	[21]	From 64% (2004) to 58% (2018)	<1000 (<1000 to 1000)	3.2 (2.0 to 4.8)	10 000 (4000 to 22,000)	86.6 (36.7 to 190.6)	19,000 (14000 to 27,000)	171.6 (120.4 to 234.9)
Ireland	[21]	From 64% (2004) to 58% (2017)	<1000 (<1000 to<1000)	1.8 (1.1 to 2.7)	2000 (1000 to 5000)	42.4 (15.9 to 104.0)	6000 (4000 to 7000)	113.5 (80.2 to 153.4)
Italy	[20,21]	From 19.1% (2008–2009) to 15.8% (2018–2019)	<1000 (<1000 to 1000)	0.8 (0.5 to 1.2)	17,000 (7000 to 37 000)	28.2 (11.7 to 61.7)	38,000 (27000 to 52,000)	63.4 (44.5 to 85.1)
Spain	[21]	From 65% (2008) to 56% (2017)	1000 (<1000 to 1000)	1.6 (1.0 to 2.3)	17,000 (7000 to 41 000)	37.7 (14.4 to 89.2)	42,000 (30000 to 56,000)	91.1 (65.0 to 120.7)

UI: 95% uncertainty interval.

regulatory authorities, approval may be supported by comparative safety and immunogenicity studies in selected population subgroups. Traditionally, the immunogenicity of influenza vaccines is evaluated using two primary assays: the hemagglutination inhibition (HAI) assay, which measures antibodies against the HA, and the single radial hemolysis (SRH) assay (as EMA guidelines). The SRH assay is a serological technique based on the passive hemolysis of red blood cells, mediated by the complement system and induced by the formation of antibody – antigen complexes. The resulting 'areas of haemolysis' are directly proportional to the concentration of anti-influenza antibodies present in the serum samples [29]. The enhanced immunogenicity of the trivalent HD influenza vaccine compared to the SD vaccine, with only minimal increased reactogenicity, was demonstrated in phase I and II studies involving ambulatory, medically stable subjects aged ≥65 years [30,31]. These findings were further validated and expanded in a multicenter, randomized, double-blind controlled phase III trial involving subjects ≥65 years of age, living in the community and medically stable, who were randomly selected to receive either the HD (2576 subjects) or SD (1275 subjects) vaccine [32]. Starting from similar pre-vaccination geometric mean titers (GMTs), measured by HAI assay, the HD vaccine induced significantly higher levels of serum antibody response 28-day post vaccination compared to the SD vaccine. Specifically, HAI GMTs were higher in the HD vaccine group for all three influenza strains. In terms of GMT ratio and seroconvertion rates (defined as an increase in HAI titer from <1:10 to ≥1:40 or a ≥ 4-fold increase from pre-vaccination titer ≥1:10), the HD vaccine met superiority criteria for both A strains and noninferiority for the B strain. Given that older adults generally develop lower post-vaccination antibody titers than healthy younger adults and are more susceptible to influenza infection [33], these data provide evidence of the superior protective benefits of the HD vaccine in this age group. Furthermore, this phase III study demonstrated improved immunogenicity in subjects aged ≥75 years and those with a history of cardiopulmonary disease, both of whom are at higher risk of influenza-related complications. The secondary endpoint, which evaluated the rate of seroprotection (defined as an HAI titer ≥1:40), showed higher seroprotection rates for all three strains in the HD vaccine group compared to the SD vaccine group. Other phase III-IV studies [34,35] further proven the HD superior immune response compared to SD in terms of post-vaccination HAI titers, seroconversion and/or seroprotection rates. Tsang et al. [36] conducted a randomized, controlled multicenter, phase II study with the secondary objective focusing on the HD vaccine in older adults compared to SD vaccine in both the same age group and in younger adults (18–49 years of age). Despite similar pre-vaccination GMTs between the older adult in HD and SD groups, post-vaccination GMTs and seroconversion rates were all significantly higher in the HD group for all three strains, as observed in a previous study [32]; seroprotection rates were significantly higher for the A/H1N1 and B strains in the HD group. Post-vaccination GMTs in older adults receiving the HD vaccine were also significantly higher than those in younger adults receiving the SD vaccine for the A/H3N2 strain, but significantly lower for the A/H1N1 and

B strains. Seroconversion rates in older adults receiving the HD vaccine were significantly higher for A/H1N1, not significantly different for A/H3N2, and significantly lower for B strain compared to younger adults receiving the SD vaccine. Overall, both the HD vaccine in older adults and the SD intramuscular vaccine in younger adults elicited comparable antibody response, and for some measures even greater for the HD vaccine. Given that A/H3N2 viruses tend to be most severe in the elderly and are associated with high hospitalization rates and hospital dissemination [18,37], these data on A/H3N2 antibody response may represent a crucial aspect of the HD vaccine.

Another phase IIIb/IV study [38], a supplemental analysis of the original study [35], evaluated the immunogenicity of HD vaccine compared to SD vaccine across specific age groups (65–74 years and ≥75 years) and high-risk comorbid and frailty conditions (≥1 high-risk comorbidity, ≥2 high-risk comorbidities, ≥ 3 frailty conditions) over two years (2011 and 2012). The HD vaccine was associated with significantly higher GMTs compared to the SD vaccine for all strains and across all subgroups included in the analysis. Notably, immunocompromised subjects are at a significantly risk of severe illness and complications from influenza infection. Consequently, immunization is strongly recommended for transplant patients, individuals undergoing immunosuppressive therapy, and others with immunodeficiency. However, these populations are likely to have reduced and non-protective immune responses to the SD vaccine. Caldera et al. [39] reviewed various strategies aimed at enhancing influenza vaccine immunogenicity in immunocompromised subjects. Their analysis revealed that trivalent HD vaccine demonstrated the most success in improving immune response, while maintaining a good safety profile and acceptable reactogenicity in clinical trials. In most cases, HAI GMT ratios of trivalent HD comparing to SD against the vaccine strains were greater than 1.0, suggesting stronger immune responses with HD in these immunocompromised patients. Accordingly, some scientific societies recommended the HD influenza vaccine as a preferred option for immunocompromised patients. Three studies have assessed the HD immunogenicity in HIV-infected adults over 18 years, solid-organ transplant recipients aged 18 and above, and oncology patients younger than 65 years [40–42]. All three studies consistently found that the HD vaccine elicited improved immunogenicity and seroconversion [41,42] compared to the SD in these populations, suggesting that the HD vaccine may be the preferred option for these groups.

As mentioned earlier, starting with the 2024–2025 influenza season, all influenza vaccines are trivalent. However, in the previous decade the WHO recommended the inclusion of both B lineages, resulting in a quadrivalent vaccine. Chang et al. [43] conducted a phase III randomized clinical trial aimed to evaluate the immunogenicity of a quadrivalent HD vaccine formulation compared to the licensed trivalent HD and SD vaccines in adults aged 65 and older. The study found that the quadrivalent HD vaccine induced HAI antibody responses that were non-inferior to those elicited by the trivalent HD vaccine for the three shared strains and superior responses for the additional B-lineage. Furthermore, despite the higher antigen dose in the vaccine, the inclusion of a second B lineage enhanced immunogenicity against the added strain without compromising the immune response to the other strains. Other studies have also shown the highly immunogenicity of quadrivalent HD vaccine compared to the quadrivalent SD vaccine in older adults [44–46]. Pepin et al. [47] further evaluated the immunogenicity of the quadrivalent HD vaccine compared to the SD vaccine in healthy subjects aged 60 years and older. In this study, the HD vaccine demonstrated an enhanced immune response over the SD vaccine, as evidenced by higher GMTs for all four influenza strains 28 days post-vaccination in both the 60–64 and ≥65 age groups. Specifically, GMTs were higher in the 60–64 age group compared to those aged ≥65 years.

Residents of long-term care facilities (LTCFs) are more susceptible to seasonal influenza outbreaks, which can be explosive, with high mortality [48]. A French study [49] estimated that exposure to influenza increased the risk of hospitalization in residents of LTCFs (9.2% of the residents exposed vs. 7.4% of the residents not exposed. All the residents included with follow-up data were considered exposed to influenza if at least one case of influenza-like infection was reported in their LTCF during the influenza epidemic period) (relative risk (RR), 95% CI = 1.24, 1.05–1.47), including hospitalizations due to respiratory causes (2.2% vs 1.5%) (RR, 95% CI = 1.43, 0.99–2.08). Moreover, influenza exposure raised the all-cause risk of death (5.8% vs. 4.3%) (RR, 95% CI = 1.36, 1.10–1.70) and death from respiratory causes (1.5% vs 0.6%) (RR, 95% CI = 2.77, 1.55–4.91), despite high levels of influenza vaccination (93% of residents) [48,49]. Nace et al. [50] conducted the first randomized controlled trial to compare the HD to SD vaccines in frail, elderly residents of LTCFs over two influenza seasons, 2011–2012 and 2012–2013. At day 30 post-vaccination, GMTs were significantly higher in the HD group compared to the SD group for all influenza strains, except for the A/H1N1 virus in 2012–2013, where noninferiority was met. The authors hypothesized that this could be due to the fact that 26% of the participants in this study were involved in both seasons, which featured the same A/H1N1 strains. Overall, these findings suggest that the HD vaccine induced superior antibody responses in frail, older residents of LTCFs. In both seasons, the HD group showed higher seroconversion rates for all influenza strains, and significantly higher seroprotection rates for the A/H3N2 and B strains. At day 180 (6 months after vaccination), GMTs remained significantly higher in the HD group compared to the SD group for the A/H3N2 strain in both years. Seroprotection was significantly higher in the HD group for influenza A strains during the 2011–2012 season, but there was no difference in the 2012–2013 season. Notably, in this study, antibody titers showed minimal change between 1 and 6 months, which is particularly significant considering that the duration of immunity is known to decline in elderly subjects by 6 months after vaccination.

The key studies covered in this section are summarized in Table 2.

2.2. Vaccine efficacy/effectiveness

HD influenza vaccine demonstrates superior efficacy and VE compared to SD vaccines in individuals aged 65 and older,

Table 2. Summary of the key studies included in the vaccine immunogenicity section.

Author, Year (NCT number)	Reference	Study design	Study location	Influenza seasons	Study population	Study outcomes	Additional information
Falsey et al., 2009 (NCT00391053)	[32]	Multicenter, randomized, double-blind, controlled phase III trial	United States	2006–2007	Adults ≥65 years of age HD: 2,575 SD: 1,262	• Seroconversion • HAI GMTs	Study included in the summary of product characteristics [72].
DiazGranados et al., 2014 (NCT01427309)	[35]	Phase IIIb – IV, multicenter, randomized, double-blind, active-controlled trial	United States Canada	2011–2012 2012–2013	Adults ≥65 years of age HD: 15,991 SD: 15,998	• Seroconversion • HAI GMTs	Study included in the summary of product characteristics [72].
Nace et al., 2015 (NCT01654224)	[50]	Single-blinded, randomized, controlled trial	United States	2011–2012 2012–2013	Frail adults ≥65 years of age HD: 94 SD: 102	• GMTs	
Tsang et al., 2013 [31] (NCT00551031)	[36]	Randomized, controlled, phase II trial	United States	2007–2008	Adults ≥65 years of age HD: 635 ID: 635 SD: 319 Adults 18–49 years of age SD: 186	• HAI GMTs	
Chang et al., 2019 (NCT03282240)	[43]	Randomized, modified double-blind, active-controlled, multi-center trial	United States	2017–2018	Adults ≥65 years of age IV4-HD: 1,777 IIV3-HD1: 443 IIV3-HD2: 450	• HAI GMTs • Seroconversion	Study included in the summary of product characteristics [72].
Pepin et al., 2021 [42] (NCT04024228)	[47]	Phase III, randomized, modified double-blind, active-controlled trial	European Union	2019–2020	Adults 60–64 years of age HD: 378 SD: 379 Adults ≥65 years of age HD: 394 SD: 382	• Superior immunogenicity of IIV4-HD, relative to IIV4-SD	Study included in the summary of product characteristics [72].

GMTs: geometric mean titers; HAI: hemagglutination inhibition assay; HD: high-dose; ID: intradermal; IIV4-HD: high-dose quadrivalent inactivated influenza vaccine; IIV3-HD1: high-dose trivalent inactivated influenza vaccine containing the Victoria-lineage B strain; IIV3-HD2: high-dose trivalent inactivated influenza vaccine containing the Yamagata-lineage B strain; IIV4-SD: standard-dose quadrivalent influenza vaccine.

significantly reducing the incidence of LCI, hospitalizations, and influenza-related complications across varying influenza seasons and patient subgroups.

Influenza vaccine performance is evaluated by efficacy (measured in randomized controlled trials [RCTs]) and VE, assessed in real-world observational studies. Regulatory authorities, such as the FDA in the U.S.A. and EMA in Europe, require strong evidence of vaccine efficacy, which is essential for vaccine approval. Efficacy refers to the vaccine's ability to reduce the risk of infection and subsequent disease under ideal circumstances, typically measured through RCTs. These trials assess various outcomes, including LCI, influenza-related illnesses (e.g. medically attended influenza), influenza-associated hospitalizations, and influenza-related deaths. In contrast, VE measures how well the vaccine reduces disease outcomes (e.g. disease incidence, hospital admission) among subjects vaccinated in 'real-world' conditions. VE is typically evaluated through observational studies [14].

The HD vaccine is the only licensed influenza vaccine to have shown greater efficacy compared to a SD vaccine in preventing LCI in a RCT [51]. The study [35], conducted over two years (year 1: 2011–2012, year 2: 2012–2013; both influenza seasons characterized by A/H3N2 as the predominant virus), included a total of 31,989 subjects aged 65 and older. Notably, the total sample size required to provide 80% power to demonstrate the superior efficacy of HD vaccine was 30,000 participants, assuming a 30% relative vaccine efficacy and a 2% influenza incidence for the SD group. The primary endpoint was the occurrence of LCI, caused by any influenza viral types or subtypes, at least 14 days after vaccination, in association with protocol-defined influenza-like illness (PD-ILI). This endpoint was met by a total of 529 participants, 228 (1.4%) in the HD group and 301 (1.9%) in the SD group, with a relative efficacy of HD to SD of 24.2%. This indicates that administering the HD vaccine (alternatively to SD vaccine) may prevent approximately one-quarter of all breakthrough influenza illness and over a third of those caused by strains similar to the vaccine. While this study did not provide direct data to estimate absolute efficacy, it can be inferred considering estimates external to the study of the absolute efficacy of SD vaccines. Previous studies have suggested that inactivated vaccines similar to trivalent SD offer approximately 50% protection against influenza in older adults. Assuming 50% absolute efficacy for SD in the elderly, the HD absolute efficacy would be estimated at 62%, a level of protection similar to that reported in SD vaccines in younger adults. These findings are consistent with the aforementioned study [36], which showed comparable antibody

response for both the HD vaccine in older adults and the SD intramuscular vaccine in younger adults. Therefore, vaccination with the HD vaccine provides additional protection against influenza for a large number of subjects compared to the SD vaccine. The findings of this RCT are even more compelling when considered in the context of the influenza seasons involved. The first season, 2011–2012, experienced low influenza activity and a moderate-to-good match between the vaccine and circulating strains, while the second season, 2012–2013, was characterized by high influenza activity and a mismatch between the circulating strains and vaccine strains. Despite these significant differences, the HD vaccine demonstrated to be more efficacious than the SD in preventing LCI. Supplemental analyses performed on the original study provided additional data [38,52]. The HD vaccine demonstrated borderline significant overall VE over the SD for the prevention of all-cause hospitalization (6.9%; 95%CI, 0.5–12.8). However, the most significant reduction in disease was observed for serious pneumonia, which occurred 39.8% (95%CI, 19.3–55.1) less frequently among HD recipients than among SD recipients when combining data from both seasons. The relative VE (rVE) was 46.4% (95%CI, 15.9–65.8) in the first season and 34.3% (95% CI, 3.1- −55.4) in the second season. Additional data on serious cardio-respiratory events, congestive heart failure, and other respiratory events were also provided. For serious cardio-respiratory events, the combined HD rVE (calculated as (1 − RR) × 100 [52]) was 17.7% (95%CI, 6.6–27.4), indicating that the HD was significantly more effective than SD in preventing serious cardio-respiratory events possibly related to influenza, most of which involved hospitalizations. For congestive heart failure, the combined rVE was 24.0% (95% CI, −7.2–46.1). For other respiratory events, a rVE of 34.0% (95%CI, −3.8–58.1) was reported. Considering the varying features of the influenza seasons mentioned earlier, rates of serious events were consistently lower with HD vaccine compared to the SD vaccine in both study years for three of the seven pre-selected serious cardio-respiratory event categories, as well as for the aggregate occurrence of any serious event possibly related to influenza. Overall, these supplemental analyses suggest that, compared to SD, HD reduces the risk of serious adverse events related to influenza infection [38]. The other supplemental analyses were conducted to explore the efficacy of HD vs SD vaccines against laboratory-confirmed, PD-ILI by age groups (65–74 years and ≥75 years), and high-risk comorbid and frailty conditions. There was a noted increase in the HD vaccine efficacy compared to the SD against PD-ILI with advancing age: 19.7% (95% CI, 0.4%-35.4%) for subjects 65–74 years, and 32.4% (95% CI, 8.1%-50.6%) for those aged 75 years and older [38]. Notably, the analysis of participants with one, two, or three or more baseline frailty conditions consistently favored HD over SD. The relative efficacy point estimates ranged between 16.0% and 27.5% against any influenza strain, regardless of its similarity to the vaccine, and from 8.3% to 49.6% against strains antigenically similar to the vaccine components. Overall, the HD vaccine appears to offer benefits over the SD vaccine for all adults aged 65 and older, regardless of age, presence of comorbidities, or frailty-associated conditions. These findings further support the inclusion of the HD vaccine in vaccination programs targeting older adults and individuals with baseline frailty conditions. These data align with a retrospective cohort analysis [53] of beneficiaries aged 65 years and older who received HD or SD vaccines in community pharmacies during the 2012–2013 influenza season. The HD vaccine was 22% (95% CI, 15–29) more effective than the SD in preventing probable influenza infection (rapid influenza test followed by oseltamivir treatment) across all beneficiaries. Furthermore, there was a 36% (95% CI, 13–54) reduction in infection among subjects aged 85 years and older, although the difference in rVE between the two groups was not statistically significant. This study presented, for the first time, relevant information on the reduction of influenza-related hospital admissions in HD compared to SD vaccine recipients, with a rVE of 22% (95% CI, 16–27) in all beneficiaries, consistent with findings from another study (rVE of 23.3%, 95%CI, 8.4–35.8) [54]. In the same influenza season, the HD vaccine was shown to be 36.4% (95% CI, 9.0%–56%) more effective in reducing post-influenza deaths [55], a season characterized by the circulation of A/H3N2 virus. As mentioned above, when this subtype predominates, there tends to be a higher rate of hospitalizations and severe complications. In the following season, the HD VE was not confirmed for reducing post-influenza deaths, showing to be minimal and not statistically significant. However, it remains relevant in reducing the rate of influenza-related hospitalizations (12%, 95% CI, 4.9–19.9). The reduced or absent VE of the HD vaccine during the 2013–2014 season could be attributed to several factors, including differences in the subjects who received the HD vaccine by season, variations in the circulation patterns of specific influenza viruses by season, and differences in the antigenic similarity between the vaccine and circulating viruses by season. Moreover, the authors speculated that this season was predominately characterized by the A/H1N1 virus, which accounted for 90% of influenza A detections. Data from a previous trial [35] suggested that the HD vaccine had greater relative efficacy against the A/H3N2 virus compared to A/H1N1, although this difference was not statistically significant. Therefore, it remains uncertain whether the findings of this study reflect a difference in comparative effectiveness by A subtype viruses.

Lee and colleagues conducted three systematic reviews and meta-analysis over multiple influenza seasons (2009–2010 to 2021–2022, excluding the 2020–2021 season), with varying sample sizes, to evaluate the HD VE across different endpoints [56–58]. The first systematic review and meta-analysis included clinically relevant outcomes from both randomized and observational studies spanning six influenza seasons [56]. They found that the HD vaccine was more effective than SD in preventing probable or laboratory-confirmed ILI (rVE = 19.5%; 95% CI, 8.6–29.0), hospitalized cases of influenza (rVE = 17.8%; 95% CI, 8.1–26.5), pneumonia (rVE = 24.3%; 95% CI, 13.9–33.4) and cardiorespiratory events (rVE = 18.2%; 95% CI, 6.8–28.1) in adults ≥65. Additionally, it was more effective in reducing hospital admission in older adults living in both the community setting or in LTCFs (rVE = 9.1%, 95% CI, 2.4–15.3). The pooled rVE estimates indicated a moderate, though statistically non-significant, impact of HD versus SD on death following hospital admission or emergency department visit for influenza (rVE = 22.2%; 95% CI, −18.2–48.8). Limited benefit was found for all-cause mortality (rVE = 2.5%; 95% CI, −5.2–-9.5). The updated review over 10 influenza seasons not only

confirmed the findings from the previous one but also provided new insights into the HD efficacy/effectiveness based on characteristics of each influenza season [57]. It reported reductions in mortality due to pneumonia/influenza (rVE = 39.9%, 95% CI, 18.6–55.6%) and cardiorespiratory causes (rVE = 27.7%, 95% CI, 13.2–32.0%). Similar pooled rVE estimates were observed in both matched and mismatched seasons, as well as in seasons where A/H3N2 or A/H1N1 viruses predominated. The prevention of hospitalization in mismatched seasons may be attributed to cross-reactive T cell responses, which protects against serious complications from all influenza A/H3N2 strains, even when strain specific antibodies fail to prevent infection [59,60]. The most recent review and meta-analysis, covering 12 influenza seasons, further supported the previous findings and provided new outcomes on hospitalization/emergency room (ER) visit and cardiovascular hospitalization, with the HD vaccine offering better protection than the SD (rVE = 10.4%, 95% CI, 6.8%-13.9%; rVE = 12.8%, 95% CI, 10.2%-15%) [58]. Regarding influenza-related hospitalizations/ER visits, the HD vaccine was more effective than SD vaccine during matched and mismatched seasons, as well as during A/H3N2 and A/H1N1 dominant seasons. The analysis of subgroups by age (65–74 years, ≥ 75 years, ≥ 85 years) revealed that HD provided better protection than SD against ILI in subjects aged 65–74 years and ≥75 years. Specifically, the rVE of HD compared to SD against ILI was 21.1% (95% CI, 12.4%-28.9%;) in the 65–74 age group, increasing to 24.8% (95% CI; 12.3%-35.6%) in those aged ≥75 years. For influenza related hospitalizations, the rVE was 8.7% (95% CI; 1.5%- 5.2%) among subjects aged 65–74 years, with a notable increase observed with advancing age: 12.2% (95% CI; 7.3%-16.9%;) in those aged 75 years, and 16.0% (95% CI; 9.8%-21.8%) in those aged ≥85 years. Furthermore, HD vaccination was associated with improved protection against hospitalization/ER visits in those aged ≥75 years and ≥85 years, but not in those aged 65–74 years. Overall, these reviews consistently support the enhanced protection offered by the HD vaccine compared to the SD vaccine in adults aged ≥65 years, with increasing benefit observed in the older age groups.

Gravenstein et colleagues [61] conducted the first randomized, prospective study in a population of long-stay nursing home residents (92,269 residents across 823 recruited nursing homes) to assess the effect of the HD versus SD vaccine on hospital admissions related to respiratory infections during the 2013–2014 influenza season. The study found a 12.7% relative reduction in the incidence of hospital admissions for respiratory illness among residents in HD vaccine facilities and a 20.9% relative reduction in hospital admissions for pneumonia, despite the predominance of the A/H1N1 virus during the 2013–2014 influenza season.

The DANFLU-1 trial is a pragmatic, open-label, active-controlled randomized trial designed to assess the feasibility of randomizing a representative sample of Danish citizens aged 65–79 to receive either HD or SD quadrivalent influenza vaccines during the 2021–2022 influenza season. Conducted within a registry-based framework using existing vaccination infrastructure, the study serves as a pilot trial for a potential future fully powered trial [62]. Indeed, nationwide healthcare databases offer the opportunity to combine the gold standard of individual randomization, thereby providing unbiased results from which causal conclusions can be inferred, with real-world, representative patient populations and pragmatic data collection. This approach integrates rigorous randomization of treatment allocation with existing data-collection platforms, enabling efficient collection of baseline and follow-up information while significantly reducing complexity and costs. The study yielded valuable insights, particularly for designing future fully powered vaccine trials, as well as for trials exploring other interventions. A post-hoc analysis of DANFLU-1 trial [63] found that the HD vaccine was associated with a reduction in the incidence rates of hospitalizations due to pneumonia or influenza and all-cause hospitalizations, compared to the SD vaccine. These trends were evident regardless of influenza circulation levels. An exploratory subgroup analysis of the all-cause hospitalizations outcome suggested increased rVE of the HD versus SD in subjects without chronic cardiovascular (CV) disease as compared to those with (no chronic CV disease: 427 vs. 531 events, incidence rate ratio (IRR) 0.79 (95% CI, 0.67–0.92); chronic CV disease: 220 versus 211 events, IRR 1.11 (95% CI, 0.88–1.39). The data showing a reduced incidence of hospitalization for influenza and pneumonia align with another study [64], which also found a reduction in all-cause mortality in favor of the HD vaccine. A further analysis was conducted on 12,477 participants related to DANFLU-1 trial, of whom 2540 (20.4%) had chronic CV disease, 275 (2.2%) heart failure (HF), 962 (7.7%) ischemic heart disease (IHD), and 878 (7.0%) atrial fibrillation [65]. In this study, the HD vaccine, compared to SD, was associated with a reduced incidence of hospitalizations for pneumonia or influenza and all-cause mortality, irrespective of chronic CV disease, HF, IHD and atrial fibrillation. However, the presence of chronic CV disease modified the rVE of HD compared to SD for all-cause hospitalizations. Additionally, in patients with chronic CV disease, a secondary exploratory analysis found that time since latest all-cause hospitalization prior to randomization might influence the rVE of HD compared to SD against all-cause hospitalizations. The superior performance of HD compared to SD vaccines in reducing the risk of first and recurrent hospitalization for pneumonia and influenza, as well as recurrent all-cause hospitalizations or all cause-mortality, was also observed in subjects with chronic kidney disease [66]. Another study conducted over three influenza seasons in patients with high-risk CV disease found that the HD trivalent vaccine did not significantly reduce all-cause mortality or hospitalizations for cardiac or pulmonary causes when compared to SD vaccine [67]. The comparison between HD and SD vaccines favored HD in lowering the risk of the first occurrence of all-cause death or hospitalization for pneumonia and influenza also in subjects with diabetes [68]. Moreover, the HD vaccine was associated with a reduction in the rate of all-cause hospitalizations, regardless of diabetes status.

The key studies covered in this section are summarized in Table 3.

Table 3. Summary of the key studies included in the vaccine efficacy/effectiveness section.

Author, Year (NCT number)	Reference	Study design	Study location	Influenza Seasons	Study population	Study endpoint	Outcomes	Vaccine efficacy/effectivess	Additional information
DiazGranados et al. 2014 (NCT01427309)	[35]	Phase IIIb – IV, multicenter, randomized, double-blind, active-controlled trial	United States Canada	2011–2012 2012–2013	Adults ≥65 years of age HD: 15,991 SD: 15,998	• Laboratory-confirmed influenza	Pneumonia within 30 days of specified illness: PD-ILI, laboratory-confirmed, caused by any viral types/subtypes (regardless of similarity to the vaccine) HD 3 (0.19)* - SD 7 (0.44)* (RR 0.43) Hospitalizations within 30 days of specified illness: PD-ILI, laboratory-confirmed, caused by any viral types/subtypes (regardless of similarity to the vaccine) HD 6 (0.38)* - SD 10 (0.63)* (RR 0.60)	Relative efficacy IIV3-HD vs IIV3-SD 24.2%	Study included in the summary of product characteristics [72]
DiazGranados et al. 2015	[38]	Phase IIIb – IV, multicenter, randomized, double-blind, active-controlled trial	United States Canada	2011–2012 2012–2013	Adults ≥65 years of age (stratified 65–74 years and ≥75 years), high-risk comorbid conditions HD: 15,990 SD: 15,993	• Culture- or PCR-confirmed influenza PD-ILI caused by any influenza viral type/subtype	Not available	Relative efficacy IIV-HD vs IIV-SD 19.7% (65–74 years) and 32.4% (≥75 years)	
Gravenstein et al. 2017	[61]	Single-blind, pragmatic, comparative effectiveness, cluster-randomized trial	United States	2013–2014	Adults ≥65 years of age and long-stay residents	• Hospital admissions related to pulmonary and influenza-like conditions • All-cause hospital admissions	Not available	Comparative effectiveness of HD in reducing respiratory-related hospital admissions vs SD 12.7%	Study included in the summary of product characteristics [72]
Izurieta et al. 2015	[53]	Retrospective cohort study	United States	2012–2013	Medicare beneficiaries ≥65 years of age HD: 929,730 SD: 1.615,545	• Probable influenza infection • Hospital or emergency department visit	Rapid influenza diagnostic test followed by oseltamivir treatment outcome was more common in the SD recipients (1·30 outcomes per 10 000 person-weeks) than in the HD recipients(1.01 outcomes per 10,000 person-weeks), corresponding to a risk difference of 0.29 (95% CI 0.19–0.38)	Relative vaccine effectiveness of HD in preventing probable influenza infection vs SD 22%	

(*Continued*)

Table 3. (Continued).

Author, Year (NCT number)	Reference	Study design	Study location	Influenza Seasons	Study population	Study endpoint	Outcomes	Vaccine efficacy/effectivess	Additional information
Shay et al. 2017	[55]	Data collected from Medicare administrative files	United States	2012–2013 2013–2014	Adults ≥65 years of age HD SD	• Post-influenza death	Across both seasons, 83 postinfluenza deaths occurred in the HD group during 30,079,255 person-weeks of observation (rate, 0.028/10000 person-weeks), and 162 deaths in the SD group during 42,696,182 person-weeks (rate, 0.038/10000 person-weeks), representing a risk difference of −0.01/10000 person-weeks (95% CI, −.019 to −.002), and an incidence rate ratio of 0.73 (95% CI, .59–.95)	Comparative effectiveness 24%; in 2012–2013, HD was 36.4% more effective in reducing mortality; in 2013–2014, it was 2.5%.	
Johansen et al. 2024 (NCT05048589)	[63]	Post-hoc analysis of a pragmatic, registry-based, open-label, active controlled, randomized trial (DANFLU-1)	Denmark	2021–2022	Adults aged 65 - 79 years	• Hospitalizations for pneumonia or influenza, respiratory hospitalizations, cardio-respiratory hospitalizations, cardiovascular hospitalizations, • All-cause hospitalizations, and all-cause death	Not available	Relative effectiveness of QIV-HD vs QIV-SD against recurrent outcomes: hospitalizations for pneumonia or influenza (10 vs. 33 events, IRR 0.30) and all cause hospitalizations (647 vs. 742 events, IRR 0.87)	
Christensen et al. 2024	[65]	Prespecified analysis of a pragmatic, open-label, randomized feasibility trial (DANFLU-1)	Denmark	2021–2022	Adults aged 65 - 79 years with cardiovascular disease QIV-HD QIV-SD	• Hospitalizations due to pneumonia or influenza, respiratory disease, cardio-respiratory disease, cardiovascular disease, all causes, and all-cause mortality	Not available	Relative effectiveness of QIV-HD vs. QIV-SD against hospitalizations for pneumonia or influenza 3 (**IR PY 4) vs 7 (IR PY 8.8) and all-cause mortality 5 (**IR PY 6.7) vs 14 (**IR PY 17.7) according to the presence of chronic cardiovascular disease at baseline	
Lee et al. 2018	[56]	Systematic review	Not available	2009–2010 2010–2011 2011–2012 2012–2013 2013–2014 2015–2016	Adults ≥65 years of age HD SD	• Assess the relative vaccine efficacy or effectiveness of HD-IIV3 against probable/ laboratory-confirmed ILI, hospital admissions, and death	Not available	Pooled relative vaccine efficacy or effectiveness of HD-IIV3 vs SD-IIV3 19.5% against ILI, 9.1% preventing all-cause hospital admissions, 17.8% cardiorespiratory events, 24.3% pneumonia, 18.2% cardiorespiratory events, 22.2% against post-influenza mortality, 2.5% against all-cause mortality	

(*Continued*)

Table 3. (Continued).

Author, Year (NCT number)	Reference	Study design	Study location	Influenza Seasons	Study population	Study endpoint	Outcomes	Vaccine efficacy/effectivess	Additional information
Lee et al. 2021	[57]	Systematic review and meta-analysis	Not available	2009–2010 2010–2011 2011–2012 2012–2013 2013–2014 2014–2015 2015–2016 2016–2017 2017–2018 2018–2019	Adults ≥65 years of age HD SD	• Assess the relative vaccine efficacy/ effectiveness of HD-IIV3 against probable/ laboratory-confirmed ILI, hospital admissions, and death	Not available	Relative vaccine efficacy/effectiveness of HD-IIV3 vs SD-IIV3 39.9% at preventing pneumonia/influenza mortality and 27.7% cardiorespiratory mortality	
Lee et al. 2023	[58]	Meta-analysis	Not available	2009–2010 2010–2011 2011–2012 2012–2013 2013–2014 2014–2015 2015–2016 2016–2017 2017–2018 2018–2019 2019–2020 2021–2022	Adults ≥65 years of age HD SD	• Estimate pooled relative vaccine effectiveness of HD-IIV versus SD-IIV	Not available	Relative vaccine effectiveness of HD-IIV3 vs SD-IIV3 10.4% against influenza related hospitalizations/ emergency room visits and 12.8% cardiovascular related hospitalizations	

HD: high-dose; SD: standard-dose; IIV3-HD: high-dose, trivalent inactivated influenza vaccine; IIV3-SD: standard-dose, trivalent inactivated influenza vaccine; QIV-HD: quadrivalent influenza vaccine high-dose; QIV-SD: quadrivalent influenza vaccine standard-dose; PD-ILI = Protocol-defined Influenza-like-illness; *Rate = events per 1,000 subject-seasons; RR: Relative Risk; IRR: incidence rate ratios; **IR: (incidence rate per 1000 person-years (PY).

2.3. Vaccine safety

Although the HD influenza vaccine contains a greater amount of HA antigen than the SD vaccine, multiple randomized controlled trials and systematic reviews demonstrate that the HD influenza vaccine maintains a favorable safety profile with no significant increase in serious adverse events compared to the SD vaccine in adults aged 60 or 65 years and older. While local and systemic reactogenicity, such as injection-site pain, headache, and myalgia, is more frequent with the HD vaccine, these effects are generally mild and transient. Enhanced surveillance studies further confirm its consistent safety across diverse populations, including at-risk groups, supporting its continued use without major safety concerns. However, reducing both local and systemic reactogenicity could improve vaccine uptake, as even minor adverse events may decrease the likelihood of individuals getting vaccinated annually.

Despite the higher dose of HA in the HD vaccine, no safety concerns have been reported. DiazGranados et colleagues [35] in a RCT showed that the relative risk of experiencing at least one serious adverse event with the HD, compared to the SD, was 0.92 (95% CI, 0.85 - 0.99) in subjects 65 years of age and older. Studies consistently indicate that the HD vaccine is generally well tolerated, though more solicited reactions than the SD were reported in people aged 60/65 years or older [32,43,47]. For instance, within 7 days following vaccination, the most frequently reported solicited injection-site reaction was pain [47]. In the 60–64 age group, 51.7% of individuals in the HD group experienced pain compared to 23.6% in the SD group. In the ≥65 age group, pain was reported by 39.4% of those in the HD group and 18.3% in the SD group. Regarding solicited systemic reactions in the 60–64 age group, the most common were myalgia (31.0%) and headache (30.2%) in the HD group, compared to headache (19.9%) in the SD group, while in the ≥65 age group were myalgia (21.6%) in the SD group and headache (17.3%) in SD group. A systematic review [69], assessing the safety of the HD vaccine in subjects aged 18 years and older across 24 studies (19 RCTs and 5 non-randomized studies), concluded that HD vaccine was associated with increased rates of local and systemic adverse events compared to SD. These adverse events included combined local reactions, pain at injection site, swelling, induration, headache, chills and malaise. Specifically, serious adverse events were reported in 4 studies and were considered potentially related to the administration of the HD influenza vaccine (for examples small-fiber neuropathy, cranial-nerve VI palsy, Crohn's disease). The HD vaccine showed a significantly higher frequency of combined local reactions (RR = 1.40, 95% CI, 1.20–1.64), pain (RR = 1.56, 95% CI, 1.26–1.93), swelling (RR = 2.20, 95% CI, 1.12–4.32) and induration (RR = 1.63, 95% CI 1.10–2.39). Additionally, the vaccine was also associated with a significantly higher frequency of headache (RR = 1.35, 95% CI, 1.02–1.77), chills (RR = 1.73, 95% CI, 1.07–2.81) and malaise (RR = 1.28, 95% CI, 1.08–1.51). However, there were no significant differences between the two vaccine groups in terms of combined systemic reactions, fever, myalgia, diarrhea and fatigue. The safety profile was also evaluated in at-risk populations, including subjects with malignancy, rheumatoid arthritis, hematopoietic stem cell transplant (HSCT) recipients, transplant recipients and those undergoing oncological interventions. Overall, no significant safety concerns were raised. In some cases, no significant differences were found in the incidence of new onset immune-related adverse events following vaccination with both vaccines in subjects with malignancy or undergoing oncological treatment, as well as in local or systemic reactions in solid-organ transplant recipients. For HSCT subjects, there were no differences in systemic reactions between the two groups, although the HD vaccine was associated with a significantly higher frequency of combined local reactions in HD group compared to SD.

The Enhanced Passive Safety Surveillance (EPSS), introduced by the EMA in 2014, aims to improve early detection of vaccine-related adverse drug reactions (ADRs) through near real-time spontaneous reporting. It supports early identification of clinically relevant safety signals before peak influenza vaccination periods, encouraging reporting by both patients and healthcare providers [70]. Two EPSS studies conducted in Germany and Finland during the 2021–2022 and 2022–2023 influenza seasons assessed adverse events following immunization (AEFI) within seven days post-vaccination for both HD and SD influenza vaccines [70,71]. In Germany, the HD vaccine was introduced in 2021 and preferentially recommended over other influenza vaccines for adults aged 60 years and older. In contrast, in Finland, the SD vaccine is recommended for individuals aged 65 years and older, children aged 6 months to 6 years, pregnant women, and individuals with underlying health conditions. In Germany, vaccinee reporting rates were lower in 2022–2023 than in 2021–2022, with consistent trends across both seasons. Most new AEFI reported were already listed in the Summary of Product Characteristics (SmPC). In Finland, aggregate reporting rates remained stable, though local reactions like erythema and swelling were slightly higher in 2022–2023. Ten newly reported AEFI were not in the SmPC but did not raise safety concerns [70,71]. Overall, both studies confirmed the consistent and well-established safety profile of split-virion influenza vaccines.

The key studies covered in this section are summarized in Table 4.

3. Conclusions

Seasonal vaccination remains the most effective public health strategy for reducing morbidity and mortality associated with influenza. Factors such as lower VE, predominant viral subtypes, degree of vaccine mismatch and poor antibody response in the elderly contribute to a higher disease burden in older adults.

Our review supports existing literature evidence on the HD vaccine, an enhanced formulation containing four times the HA content of a SD vaccine. This vaccine has been shown to elicit significantly stronger antibody responses in the elderly and to be more efficacious than the SD in preventing LCI and influenza-related hospitalizations [72]. Additionally, it reduces the risk of serious adverse events related to influenza infection and offers benefits over the SD vaccine for all adults aged 65 and older, regardless of age, presence of comorbidities, or frailty-associated conditions. Furthermore, the HD vaccine is associated with an

Table 4. Summary of the key studies included in the vaccine safety section.

Author, Year (NCT number)	Reference	Study design	Study location	Influenza seasons	Study Population	Study Endpoint	Outcomes	Additional information
DiazGranados et al. 2014 (NCT01427309)	[35]	Phase IIIb – IV, multicenter, randomized, double-blind, active-controlled trial	United States Canada	2011–2012 2012–2013	Adults ≥65 years of age HD: 15,991 SD: 15,998	• Serious adverse events	Relative risk for having at least one serious advent events with IIV3-HD compared to IIV3-SD was 0.92	Study included in the summary of product characteristics [72].
Gandhi-Banga et al. 2023	[70]	Enhanced passive safety surveillance	Germany Finland	2021–2022	Adults ≥60 years of age HD-IIV4 (Germany): 903 Subjects aged ≥6 months SD-IIV4 (Finland): 1000	• Reporting rate of suspected adverse drug reactions occurring ≤7 days post-vaccination		
De Avila Machado et al. 2024	[71]	Enhanced passive safety surveillance	Germany Finland	2022–2023	Adults aged ≥60 years of age (Germany) HD-IIV4: 1041 Subjects ≥13 years of age (Finland) SD-IIV4:971	• Reporting rate of suspected adverse events following immunization occurring ≤7 days post-vaccination • Estimating the vaccinee reporting rate occurring ≤7 days post-vaccination according to pre-defined age groups (≥6 months to < 6 years, ≥6 to < 13 years, ≥13 to < 18 years, ≥18 to ≤65 years and > 65 years) with the SD-IIV4 vaccine in Finland • Estimating the vaccinee reporting rate for serious suspected adverse events followingimmunization over the entire follow-up period in Finland and Germany • Comparing the vaccinee reporting rate of suspected adverse events following immunization observed during the current EPSS with the rates reported during EPSS in the 2021/22 season in each country and with the rates reported in the Summary of Product Characteristics for each vaccine		

HD-IIV4: high-dose – quadrivalent inactivated split-virion influenza vaccines; SD-IIV4: standard dose – quadrivalent inactivated split-virion influenza vaccines; IIV3-HD : high-dose trivalent inactivated influenza vaccine; IIV3-SD: standard-dose trivalent inactivated influenza vaccine; Enhanced Passive Safety Surveillance.

increase in the number of subjects to be protected after vaccination. Another important aspect not considered in this review is the cost-effectiveness and public health impact of using HD influenza vaccine. A study conducted among older adults in Japan found that switching from SD to HD is a favorable strategy from the healthcare payer perspective [73]. When considering only the vaccine effective against influenza hospitalizations, administering HD vaccine instead of SD over an influenza season in older adults aged ≥65 years resulted in a greater reduction in influenza cases, influenza-related hospitalizations and deaths, and outpatient and outpatient/emergency department visits, making it a cost-effective approach. When broader outcomes were considered, including pneumonia and influenza, respiratory and cardiorespiratory hospitalizations possibly related to influenza, the HD vaccine led to even greater reductions in hospitalizations, bed occupancy days (alleviating the burden on hospitals), and subsequent deaths compared to SD. Additionally, the HD vaccination was found to be a cost-saving strategy when considering the cardiorespiratory hospitalization. Other studies [74,75] support these findings, reinforcing that the

switch to HD influenza vaccine is a cost-effective intervention, particularly in seasons with higher disease burden.

Taken together, these literature findings underscore the benefits of the HD vaccine for the elderly, which is included among the recommended options for this age groups in most countries. It is important to note, however, that this review focuses exclusively on the HD vaccine and does not cover other enhanced vaccines or alternative vaccination improvements currently available.

4. Expert opinion

This review summarizes the current literature on the enhanced immunogenicity of the HD influenza vaccine in individuals aged 65 and older. Notably, evidence indicates increased immunogenicity with advancing age, in frail individuals and those with underlying risk conditions, populations highly vulnerable to severe influenza outcomes. A study has shown that, in addition to higher HAI antibody titers, the HD vaccine elicits stronger neutralizing and anti-neuraminidase (NA) antibody responses than the SD vaccine [76]. Specifically, the HD vaccine contains eight times the NA activity of the SD vaccine and induced a significantly higher frequency of antibody responses, as well as higher mean postvaccination anti-NA titers against the N1 and N2 of the A/H1N1 and A/H3N2 viruses included in the vaccines compared to the SD vaccine. These findings warrant further investigation, especially considering the potential future availability of vaccines that include standardized NA content. Currently licensed influenza vaccines primarily target HA immunity with standardized content, but there are no such standards for NA content. Consequently, NA levels can vary between vaccines and manufacturing processes, and the full extent of NA-based protection remains unclear [77]. Notably, quantification of the total NA content in six recently available commercial influenza vaccines revealed that the highest NA content was observed in the HD vaccine [78]. However, current estimates suggest that seasonal inactivated influenza vaccines result in only approximately 30% seroconvertion against NA in humans. A straightforward step toward developing a universal influenza vaccine would be to enhance seasonal vaccines by increasing their ability to elicit robust antibody responses to NA, regardless of whether broadly protective NA epitopes can be specifically targeted [79]. However, the development of a truly universal vaccine may require broader recognition of NA subtypes. In addition, more intensive research is needed, particularly focused on the continued isolation and characterization of NA-specific human monoclonal antibodies from different individuals, as has previously been done for HA. These efforts may support a deeper characterization of the immunodominance hierarchy of NA epitopes, the identification of common molecular patterns in NA-specific antibody responses across individuals and potentially uncover additional broadly protective epitopes [79]. Recent preclinical studies indicate that targeting both HA and NA would lead to better antiviral activity and improved protection compared to targeting HA alone. This dual targeting could help mitigate reduced vaccine efficacy caused by HA drift and the resulting mismatch in vaccine formulations. Emerging evidence also shows that NA induces protective antibodies that often exhibit increased breadth of recognition across strains. Human studies suggest that NA inhibition antibody titers independently correlate with protection and may even serve as a more reliable predictor of protection or reduced disease severity than HAI antibody titers [77].

The recent COVID-19 pandemic has reinforced the importance of vaccination as the most crucial tool for controlling infectious diseases. The coadministration of influenza and COVID-19 vaccines is currently endorsed by the WHO and national health authorities. However, despite the availability of vaccines, uptake for both influenza and COVID-19 remains suboptimal. Given the annual circulation and continuous evolution of influenza viruses and SARS-CoV-2, there is a continued need to enhance vaccine coverage. A multicomponent vaccine that provides protection against both diseases in a single injection may offer a more convenient and effective solution, potentially improving adherence to immunization guidelines and reducing the overall disease burden. Various strategies are being explored to advance the development of a combined vaccine. One approach is the mRNA platform, which may offer great advantages including the elimination of potential virus egg-adaptation, rapid production timelines, flexibility to update vaccine composition as needed, and the ability to induce broad immunity and robust T-cell responses for the influenza component. An alternative approach involves developing a vaccine based on a recombinant protein combined with an adjuvant [80].

Another current strategy involves combination vaccine candidates that incorporate already licensed vaccines to protect against both influenza and COVID-19. The FDA has granted Fast Track designation to two such candidates designed for individuals aged 50 and older. Both candidates combine two established vaccines with proven efficacy demonstrated through RCTs and favorable tolerability profiles. The first candidate pairs a HD influenza protein-based trivalent vaccine with an adjuvanted recombinant COVID-19 vaccine; placebo will be co-administered in the HD vaccine alone, adjuvanted recombinant COVID-19 vaccine alone, and combined vaccine study groups [81]. The second combines a recombinant protein-based trivalent influenza vaccine with the same adjuvanted recombinant COVID-19 vaccine; placebo will be co-administered in the recombinant alone, adjuvanted recombinant COVID-19 vaccine alone, and combined vaccine study groups [82]. These combinations aim to leverage the advantages of both influenza vaccines, which have shown superior protection against influenza infections in older adults compared to SD influenza vaccines in pivotal clinical trials. Moreover, real-world evidence has demonstrated their significant and consistent reductions in flu-related hospitalizations. The COVID-19 vaccine used in these combinations has exhibited a better tolerability profile than currently available mRNA COVID-19 vaccines when administered as a booster dose. It has also demonstrated high efficacy as a primary vaccination in two pivotal phase III studies. To evaluate the safety and immunogenicity of these combination candidates, two separate phase I/II parallel, randomized, modified double-blind, multi-arm studies have been initiated [83]. However, the development of a combined vaccine may present technical challenges and potential limitations. One critical aspect to be

considered is the phenomenon observed with repeated influenza vaccinations, where diminished immune response and reduced VE have been documented over time. This raises an important consideration for future combination vaccine strategies involving COVID-19: repeated administration in a combination vaccine format may similarly lead to reduced immunogenicity. Therefore, further research is essential to validate this hypothesis and to optimize combination vaccine strategies to effectively address evolving viral threats. Antigenic interference is another significant challenge. This may occur when the immune response to one antigen affects the response to another, potentially reducing the overall efficacy and safety of combination vaccines compared to standalone formulations. Minimizing such antigen interference is critical to ensuring that the immune responses are comparable to those elicited by individual vaccines. Compatibility issues may also arise from the key components or additives such as adjuvants. Additionally, identifying robust correlates of protection remains a pressing need. Ongoing research is necessary to establish new correlates and to better understand the mechanisms that underpin durable and broadly protective immunity. From a technical perspective, combination vaccines require the separate production of multiple antigens, each with its own specific manufacturing and quality control requirements. These antigens must then be integrated into a single formulation, making the production process significantly more complex than that of a single-antigen vaccine. A further concern is the interdependence of antigen supply: a delay or failure in the production of one antigen can halt the entire manufacturing process, leading to supply chain disruptions. This complexity also limits the number of manufacturers capable of large-scale production, increasing the risk of global shortages [84,85].

In the coming years, the use of the HD influenza vaccine in older adults is expected to continue growing each influenza season, gradually replacing SD vaccines within this population. As of the 2024–2025 season, over 328 million doses of the HD influenza vaccine have been distributed worldwide. This figure is likely to grow further in the next years as additional countries recommend the vaccine. Increased usage will also generate additional data to further support the added benefits of the HD vaccine for older adults [86]. Another important consideration is the potential extension of the HD vaccine to subjects younger than 60 years. Most European countries, currently recommend influenza vaccination for persons aged 65 and older, as well as for high-risk groups. However, countries such as Hungary, Germany, Greece, Italy and Portugal have set the influenza vaccination age threshold at 60 years, while others, including the United States, Canada, and Belgium, recommend vaccination for adults aged 50 and above. Expanding vaccination coverage to include adults aged 50–64 could substantially reduce the annual burden of influenza. Although the risk of severe influenza increases with age, the 50–64 age group still experiences a significant burden of severe disease [87,88]. Vaccinating this population has been demonstrated to be cost-effective [23,89,90]. Evidence suggests that broadening influenza vaccination programs beyond traditional target groups may represent an effective alternative strategy to decrease influenza burden. This approach could lead to higher overall vaccine uptake and be easier to implement compared to risk-based recommendations [91]. A multicenter, modified double-blind, randomized, active-controlled phase II trial demonstrated that the trivalent HD influenza vaccine was more immunogenic than the SD vaccine in adults aged 50–64, while maintaining an acceptable safety profile. Administering this vaccine to the 50–64 age group could help address immunosenescence [92]. Notably, epidemiological data suggest that the initial decline in immune competence begins around age 50 and accelerates after 65–70 [91]. Given the significant burden of influenza in this age group, the HD vaccine may have a substantial public health impact by offering improved protection compared to SD vaccines. However, other enhanced vaccines and alternative vaccination improvements currently available are not addressed in this review.

Author contributions

CRediT: **Claudia Maria Trombetta:** Data curation, Writing – original draft; **Emanuele Montomoli:** Conceptualization.

Declaration of interests

EM is founder and Chief Scientific Officer of VisMederi srl. The authors have no other relevant affilitions or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

1. Seasonal influenza vaccines. 2017 [cited 2025 Jul 25]. Available from: https://www.ecdc.europa.eu/en/seasonal-influenza/prevention-and-control/seasonal-influenza-vaccines
2. Factsheet about seasonal influenza. 2017 [cited 2025 Jul 25]. Available from: https://www.ecdc.europa.eu/en/seasonal-influenza/facts/factsheet
3. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA. 2003;289(2):179–186. doi: 10.1001/jama.289.2.179
4. Flu and Older Adults. *National Institute on Aging*. 2022 [cited 2025 Jul 25]. Available from: https://www.nia.nih.gov/health/flu/flu-and-older-adults
5. Krammer F, Smith GJD, Fouchier RAM, et al. Influenza. Nat Rev Dis Primers. 2018;4(1):3. doi: 10.1038/s41572-018-0002-y
6. Zhou H, Thompson WW, Viboud CG, et al. Hospitalizations associated with influenza and respiratory syncytial virus in the United States, 1993–2008. Clin Infect Dis: An Off Publ Infect Dis Soc Am. 2012;54(10):1427–1436. doi: 10.1093/cid/cis211
7. Paget J, Danielle Iuliano A, Taylor RJ, et al. Estimates of mortality associated with seasonal influenza for the European Union from the GLaMOR project. Vaccine. 2022;40(9):1361–1369. doi: 10.1016/j.vaccine.2021.11.080
8. Recommended composition of influenza virus vaccines for use in the 2024–2025 Northern Hemisphere influenza season. n.d. [cited

2025 Jul 25]. Available from: https://www.who.int/publications/m/item/recommended-composition-of-influenza-virus-vaccines-for-use-in-the-2024-2025-northern-hemisphere-influenza-season
9. Aiello A, Farzaneh F, Candore G, et al. Immunosenescence and its hallmarks: how to oppose aging strategically? A review of potential options for therapeutic intervention. Front Immunol. 2019;10:10. doi: 10.3389/fimmu.2019.02247
10. Sambhara S, McElhaney JE. Immunosenescence and influenza vaccine efficacy. Vaccines Pandemic Influenza. 2009;333:413–429. doi: 10.1007/978-3-540-92165-3_20
11. Dugan HL, Henry C, Wilson PC. Aging and influenza vaccine-induced immunity. Cell Immunol. 2020;348:103998. doi: 10.1016/j.cellimm.2019.103998
12. Boivin W, Loeb M, Openshaw P, et al. Seasonal influenza vaccination: overcoming immunosenescence with enhanced vaccines. Vaccine: X. 2025;24:100662. doi: 10.1016/j.jvacx.2025.100662
13. Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). n.d. [cited 2025 Jul 25]. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5103a1.htm
14. Trombetta CM, Kistner O, Montomoli E, et al. Influenza viruses and vaccines: the role of vaccine effectiveness studies for evaluation of the benefits of influenza vaccines. Vaccines (Basel). 2022;10(5):714. doi: 10.3390/vaccines10050714
15. Goodwin K, Viboud C, Simonsen L. Antibody response to influenza vaccination in the elderly: a quantitative review. Vaccine. 2006;24(8):1159–1169. doi: 10.1016/j.vaccine.2005.08.105
16. Xiao T, Wei M, Guo X, et al. Immunogenicity and safety of quadrivalent influenza vaccine among young and older adults in Tianjin, China: implication of immunosenescence as a risk factor. Immun Ageing. 2023;20(1):37. doi: 10.1186/s12979-023-00364-6
17. Rondy M, El Omeiri N, Thompson MG, et al. Effectiveness of influenza vaccines in preventing severe influenza illness among adults: a systematic review and meta-analysis of test-negative design case-control studies. J Infect. 2017;75(5):381–394. doi: 10.1016/j.jinf.2017.09.010
18. Langer J, Welch VL, Moran MM, et al. High clinical burden of influenza disease in adults aged ≥ 65 years: can we do better? A systematic literature review. Adv Ther. 2023;40(4):1601–1627. doi: 10.1007/s12325-023-02432-1
19. Influenza (seasonal). n.d. [cited 2025 Jul 25]. Available from: https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal)
20. Ministero della salute - dati coperture vaccinali influenza. n.d. [cited 2025 Oct 10]. Available from: https://www.salute.gov.it/new/it/tema/influenza/dati-coperture-vaccinali-influenza/
21. Troeger CE, Blacker BF, Khalil IA, et al. Mortality, morbidity, and hospitalisations due to influenza lower respiratory tract infections, 2017: an analysis for the Global Burden of Disease Study 2017. Lancet Respir Med. 2019;7(1):69–89. doi: 10.1016/S2213-2600(18)30496-X
22. Managing seasonal vaccination policies and coverage in the European region. n.d. [cited 2025 Jul 25]. Available from: https://www.who.int/europe/activities/managing-seasonal-vaccination-policies-and-coverage-in-the-european-region
23. European Commission. State of health in the EU - companion report 2019 ec.europa.eu/health/state Printed by Imprimerie Centrale in Luxembourg. © European Union; 2019. doi: 10.2875/85326
24. EpiCentro. Coperture della vaccinazione antinfluenzale in Italia. n.d. [cited 2025 Jul 25]. Available from: https://www.epicentro.iss.it/influenza/coperture-vaccinali
25. Influenza immunology evaluation and correlates of protection: a focus on vaccines - PubMed. n.d. [cited 2025 Jul 25]. Available from: https://pubmed.ncbi.nlm.nih.gov/26954563/
26. Monto AS. Moving toward improved influenza vaccines. J Infect Dis. 2017;215(4):500–502. doi: 10.1093/infdis/jiw644
27. Licensure of a high-dose inactivated influenza vaccine for persons aged ≥65 years (fluzone high-dose) and guidance for use — United States, 2010. n.d. [cited 2025 Jul 25]. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5916a2.htm
28. Sanofi to build new facility in Canada to increase global availability of high-dose influenza vaccine. n.d. [cited 2025 Jul 25]. Available from: https://www.sanofi.com/en/media-room/press-releases/2021/2021-03-31-14-05-00-2202566
29. Trombetta CM, Perini D, Vitale L, et al. Validation of single radial haemolysis assay: a reliable method to measure antibodies against influenza viruses. J Immunol Methods. 2015;422:95–101. doi: 10.1016/j.jim.2015.04.009
30. Keitel WA, Atmar RL, Cate TR, et al. Safety of high doses of influenza vaccine and effect on antibody responses in elderly persons. Arch Intern Med. 2006;166(10):1121–1127. doi: 10.1001/archinte.166.10.1121
31. Couch RB, Winokur P, Brady R, et al. Safety and immunogenicity of a high dosage trivalent influenza vaccine among elderly subjects. Vaccine. 2007;25(44):7656–7663. doi: 10.1016/j.vaccine.2007.08.042
32. Falsey AR, Treanor JJ, Tornieporth N, et al. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. J Infect Dis. 2009;200(2):172–180. doi: 10.1086/599790
33. Greenberg DP, Robertson CA, Noss MJ, et al. Safety and immunogenicity of a quadrivalent inactivated influenza vaccine compared to licensed trivalent inactivated influenza vaccines in adults. Vaccine. 2013;31(5):770–776. doi: 10.1016/j.vaccine.2012.11.074
34. DiazGranados CA, Dunning AJ, Jordanov E, et al. High-dose trivalent influenza vaccine compared to standard dose vaccine in elderly adults: safety, immunogenicity and relative efficacy during the 2009–2010 season. Vaccine. 2013;31(6):861–866. doi: 10.1016/j.vaccine.2012.12.013
35. DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. N Engl J Med. 2014;371(7):635–645. doi: 10.1056/NEJMoa1315727
36. Tsang P, Gorse GJ, Strout CB, et al. Immunogenicity and safety of Fluzone(®) intradermal and high-dose influenza vaccines in older adults ≥65 years of age: a randomized, controlled, phase II trial. Vaccine. 2014;32(21):2507–2517. doi: 10.1016/j.vaccine.2013.09.074
37. Rothman E, Olsson O, Christiansen CB, et al. Influenza A subtype H3N2 is associated with an increased risk of hospital dissemination – an observational study over six influenza seasons. J Hosp Infect. 2023;139:134–140. doi: 10.1016/j.jhin.2023.06.024
38. DiazGranados CA, Dunning AJ, Robertson CA, et al. Efficacy and immunogenicity of high-dose influenza vaccine in older adults by age, comorbidities, and frailty. Vaccine. 2015;33(36):4565–4571. doi: 10.1016/j.vaccine.2015.07.003
39. Caldera F, Mercer M, Samson SI, et al. Influenza vaccination in immunocompromised populations: strategies to improve immunogenicity. Vaccine. 2021;39(1):A15–A23. doi: 10.1016/j.vaccine.2020.11.037
40. McKittrick N, Frank I, Jacobson JM, et al. Improved immunogenicity with high-dose seasonal influenza vaccine in HIV-infected persons: a single-center, parallel, randomized trial. Ann Intern Med. 2013;158(1):19–26. doi: 10.7326/0003-4819-158-1-201301010-00005
41. Natori Y, Shiotsuka M, Slomovic J, et al. A double-blind, randomized trial of high-dose vs standard-dose influenza vaccine in adult solid-organ transplant recipients. Clin Infect Dis: An Off Publ Infect Dis Soc Am. 2018;66(11):1698–1704. doi: 10.1093/cid/cix1082
42. Jamshed S, Walsh EE, Dimitroff LJ, et al. Improved immunogenicity of high-dose influenza vaccine compared to standard-dose influenza vaccine in adult oncology patients younger than 65 years receiving chemotherapy: a pilot randomized clinical trial. Vaccine. 2016;34(5):630–635. doi: 10.1016/j.vaccine.2015.12.037
43. Chang L-J, Meng Y, Janosczyk H, et al. Safety and immunogenicity of high-dose quadrivalent influenza vaccine in adults ≥65 years of age: a phase 3 randomized clinical trial. Vaccine. 2019;37(39):5825–5834. doi: 10.1016/j.vaccine.2019.08.016
44. Chen J-Y, Hsieh S-M, Hwang S-J, et al. Immunogenicity and safety of high-dose quadrivalent influenza vaccine in older adults in Taiwan: a phase III, randomized, multi-center study. Vaccine. 2022;40(45):6450–6454. doi: 10.1016/j.vaccine.2022.09.078

45. Sanchez L, Matsuoka O, Inoue S, et al. Immunogenicity and safety of high-dose quadrivalent influenza vaccine in Japanese adults ≥65 years of age: a randomized controlled clinical trial. Hum Vaccines Immunotherapeutics. 2020;16(4):858–866. doi: 10.1080/21645515.2019.1677437
46. Sanchez L, Nakama T, Nagai H, et al. Superior immunogenicity of high-dose quadrivalent inactivated influenza vaccine versus standard-dose vaccine in Japanese adults ≥ 60 years of age: results from a phase III, randomized clinical trial. Vaccine. 2023;41(15):2553–2561. doi: 10.1016/j.vaccine.2023.02.071
47. Pepin S, Nicolas J-F, Szymanski H, et al. Immunogenicity and safety of a quadrivalent high-dose inactivated influenza vaccine compared with a standard-dose quadrivalent influenza vaccine in healthy people aged 60 years or older: a randomized phase III trial. Hum Vaccines Immunotherapeutics. 2021;17(12):5475–5486. doi: 10.1080/21645515.2021.1983387
48. Lansbury LE, Brown CS, Nguyen-Van-Tam JS. Influenza in long-term care facilities. Influenza Resp Viruses. 2017;11(5):356–366. doi: 10.1111/irv.12464
49. Gaillat J, Chidiac C, Fagnani F, et al. Morbidity and mortality associated with influenza exposure in long-term care facilities for dependent elderly people. Eur J Clin Microbiol Infect Dis. 2009;28(9):1077–1086. doi: 10.1007/s10096-009-0751-3
50. Nace DA, Lin CJ, Ross TM, et al. Randomized, controlled trial of high-dose influenza vaccine among frail residents of long-term care facilities. J Infect Dis. 2015;211(12):1915–1924. doi: 10.1093/infdis/jiu622
51. Antonelli Incalzi R, Consoli A, Lopalco P, et al. Influenza vaccination for elderly, vulnerable and high-risk subjects: a narrative review and expert opinion. Intern Emerg Med. 2024;19(3):619–640. doi: 10.1007/s11739-023-03456-9
52. DiazGranados CA, Robertson CA, Talbot HK, et al. Prevention of serious events in adults 65 years of age or older: a comparison between high-dose and standard-dose inactivated influenza vaccines. Vaccine. 2015;33(38):4988–4993. doi: 10.1016/j.vaccine.2015.07.006
53. Izurieta HS, Thadani N, Shay DK, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis. Lancet Infect Dis. 2015;15(3):293–300. doi: 10.1016/S1473-3099(14)71087-4
54. Bricout H, Levant M-C, Assi N, et al. The relative effectiveness of a high-dose quadrivalent influenza vaccine versus standard-dose quadrivalent influenza vaccines in older adults in France: a retrospective cohort study during the 2021–2022 influenza season. Clin Microbiol Infect. 2024;30(12):1592–1598. doi: 10.1016/j.cmi.2024.08.012
55. Shay DK, Chillarige Y, Kelman J, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines among US Medicare beneficiaries in preventing postinfluenza deaths during 2012–2013 and 2013–2014. J Infect Dis. 2017;215(4):510–517. doi: 10.1093/infdis/jiw641
56. Lee JKH, Lam GKL, Shin T, et al. Efficacy and effectiveness of high-dose versus standard-dose influenza vaccination for older adults: a systematic review and meta-analysis. Expert Rev Vaccines. 2018;17(5):435–443. doi: 10.1080/14760584.2018.1471989
57. Lee JKH, Lam GKL, Shin T, et al. Efficacy and effectiveness of high-dose influenza vaccine in older adults by circulating strain and antigenic match: an updated systematic review and meta-analysis. Vaccine. 2021;39(1):A24–A35. doi: 10.1016/j.vaccine.2020.09.004
58. Lee JKH, Lam GKL, Yin JK, et al. High-dose influenza vaccine in older adults by age and seasonal characteristics: systematic review and meta-analysis update. Vaccine: X. 2023;14:100327. doi: 10.1016/j.jvacx.2023.100327
59. Sridhar S, Begom S, Bermingham A, et al. Cellular immune correlates of protection against symptomatic pandemic influenza. Nat Med. 2013;19(10):1305–1312. doi: 10.1038/nm.3350
60. Wilkinson TM, Li CKF, Chui CSC, et al. Preexisting influenza-specific CD4+ T cells correlate with disease protection against influenza challenge in humans. Nat Med. 2012;18(2):274–280. doi: 10.1038/nm.2612
61. Gravenstein S, Davidson HE, Taljaard M, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccination on numbers of US nursing home residents admitted to hospital: a cluster-randomised trial. Lancet Respir Med. 2017;5(9):738–746. doi: 10.1016/S2213-2600(17)30235-7
62. Johansen ND, Modin D, Nealon J, et al. Feasibility of randomizing Danish citizens aged 65–79 years to high-dose quadrivalent influenza vaccine vs. standard-dose quadrivalent influenza vaccine in a pragmatic registry-based setting: rationale and design of the DANFLU-1 trial. Pilot Feasibility Stud. 2022;8(1):87. doi: 10.1186/s40814-022-01044-w
63. Johansen ND, Modin D, Skaarup KG, et al. Effectiveness of high-dose versus standard-dose quadrivalent influenza vaccine against recurrent hospitalizations and mortality in relation to influenza circulation: a post-hoc analysis of the DANFLU-1 randomized clinical trial. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 2024;30(11):1453–1459. doi: 10.1016/j.cmi.2024.01.017
64. Johansen ND, Modin D, Nealon J, et al. A pragmatic randomized feasibility trial of influenza vaccines. NEJM Evidence. 2023;2(2):EVIDoa2200206. doi: 10.1056/EVIDoa2200206
65. Christensen J, Johansen ND, Modin D, et al. Relative effectiveness of high-dose versus standard-dose quadrivalent influenza vaccine in older adults with cardiovascular disease: a prespecified analysis of the DANFLU-1 randomized clinical trial. Circ: Cardiovasc Qual Outcomes. 2025;18(2):e011496. doi: 10.1161/CIRCOUTCOMES.124.011496
66. Bartholdy KV, Johansen ND, Janstrup KH, et al. High-dose vs standard-dose influenza vaccine in chronic kidney disease: a secondary analysis of DANFLU-1. J Am Coll Cardiol. 2024;S0735-1097(24):08018–5. doi: 10.1093/eurheartj/ehae666.3272
67. Vardeny O, Kim K, Udell JA, et al. Effect of high-dose trivalent vs standard-dose quadrivalent influenza vaccine on mortality or cardiopulmonary hospitalization in patients with high-risk cardiovascular disease: a randomized clinical trial. JAMA. 2021;325(1):39–49. doi: 10.1001/jama.2020.23649
68. Lassen MCH, Johansen ND, Modin D, et al. Effects of high-dose versus standard-dose quadrivalent influenza vaccine among patients with diabetes: a post-hoc analysis of the DANFLU-1 trial. Diabetes, Obes Metab. 2024;26(5):1821–1829. doi: 10.1111/dom.15498
69. Comber L, Murchu O, Jordan E, et al. Systematic review of the efficacy, effectiveness and safety of high-dose seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in individuals ≥18 years of age. Rev Med Virol. 2023;33(3):e2330. doi: 10.1002/rmv.2330
70. Gandhi-Banga S, Wague S, Shrestha A, et al. Enhanced passive safety surveillance of high-dose and standard-dose quadrivalent inactivated split-virion influenza vaccines in Germany and Finland during the influenza season 2021/22. Influenza Resp Viruses. 2023;17(1):e13071. doi: 10.1111/irv.13071
71. de Machado MAA, Gandhi-Banga S, Gallo S, et al. Enhanced passive safety surveillance of high-dose and standard-dose quadrivalent inactivated split-virion influenza vaccines in Germany and Finland during the 2022/23 influenza season. Hum Vaccines Immunotherapeutics. 2024;20(1):2322196. doi: 10.1080/21645515.2024.2322196
72. Efluelda 60 microgrammi/ha sospensione iniettabile in siringa preriempita. Riassunto delle caratteristiche del prodotto. n.d. Available from: https://medicinali.aifa.gov.it/it/#/it/dettaglio/0000066849
73. de Courville C, Tadera C, Arashiro T, et al. Cost-effectiveness and public health impact of using high dose influenza vaccine in the Japanese older adults. J Med Econ. 2025;28(1):544–555. doi: 10.1080/13696998.2025.2488151
74. Alvarez FP, Allard L, Bianic F, et al. Cost-effectiveness and public health impact of using high dose quadrivalent influenza vaccine in the French older adults population. J Med Econ. 2024;27(1):1300–1307. doi: 10.1080/13696998.2024.2404331

75. van der Pol S, Zeevat F, Postma MJ, et al. Cost-effectiveness of high-dose influenza vaccination in the Netherlands: incorporating the impact on both respiratory and cardiovascular hospitalizations. Vaccine. 2024;42(15):3429–3436. doi: 10.1016/j.vaccine.2024.04.040
76. Cate TR, Rayford Y, Niño D, et al. A high dosage influenza vaccine induced significantly more neuraminidase antibody than standard vaccine among elderly subjects. Vaccine. 2010;28(9):2076–2079. doi: 10.1016/j.vaccine.2009.12.041
77. Cortés G, Ustyugova I, Farrell T, et al. Boosting neuraminidase immunity in the presence of hemagglutinin with the next generation of influenza vaccines. NPJ Vaccines. 2024;9(1):228. doi: 10.1038/s41541-024-01011-x
78. Gao Z, Robinson K, Skowronski DM, et al. Quantification of the total neuraminidase content of recent commercially-available influenza vaccines: introducing a neuraminidase titration reagent. Vaccine. 2020;38(4):715–718. doi: 10.1016/j.vaccine.2019.11.041
79. Wu NC, Ellebedy AH. Targeting neuraminidase: the next frontier for broadly protective influenza vaccines. Trends Immunol. 2024;45(1):11–19. doi: 10.1016/j.it.2023.11.001
80. Huang Y, Shi H, Forgacs D, et al. Flu-COVID combo recombinant protein vaccines elicited protective immune responses against both influenza and SARS-CoV-2 viruses infection. Vaccine. 2024;42(5):1184–1192. doi: 10.1016/j.vaccine.2023.12.084
81. Sanofi. *A phase 1/2, parallel, randomized, modified double-blind, multi-arm study to assess the safety and immunogenicity of a combination vaccine comprised of different recombinant spike antigen levels of a matrix-M adjuvanted recombinant COVID-19 vaccine and high-dose inactivated influenza vaccine in adult participants 50 years of age and older* (Clinical trial registration No. NCT06695117). clinicaltrials.gov. 2025. Available from: https://clinicaltrials.gov/study/NCT06695117
82. Sanofi. *A phase 1/2, parallel, randomized, modified double-blind, multi-arm study to assess the safety and immunogenicity of a combination vaccine comprised of different recombinant spike antigen levels of a matrix-M adjuvanted recombinant COVID-19 vaccine and recombinant influenza vaccine in adult participants 50 years of age and older* (Clinical trial registration No. NCT06695130). clinicaltrials.gov 2025. Available from: https://clinicaltrials.gov/study/NCT06695130
83. Press release: two combination vaccine candidates for prevention of influenza and COVID-19 granted fast track designation in the US. n.d. [cited 2025 Jul 25]. Available from: https://www.sanofi.com/en/media-room/press-releases/2024/2024-12-11-06-00-00-2995072
84. Fatima M, Hong K-J. Innovations, challenges, and future prospects for combination vaccines against human infections. Vaccines (Basel). 2025;13(4):335. doi: 10.3390/vaccines13040335
85. Wang Y, Ma Q, Li M, et al. A decavalent composite mRNA vaccine against both influenza and COVID-19. MBio. 2024;15(9):e0066824. doi: 10.1128/mbio.00668-24
86. Samson SI, Leventhal PS, Salamand C, et al. Immunogenicity of high-dose trivalent inactivated influenza vaccine: a systematic review and meta-analysis. Expert Rev Vaccines. 2019;18(3):295–308. doi: 10.1080/14760584.2019.1575734
87. Torcel-Pagnon L, Coudeville L, Harris RC, et al. The impact of influenza on US working-age adults: exploring the benefits of the recombinant influenza vaccine. Clin Infect Dis. 2025:ciaf200. doi: 10.1093/cid/ciaf200
88. Kim DK, McGeer A, Uleryk E, et al. Burden of severe illness associated with laboratory confirmed influenza in adults aged 50–64 years: a rapid review. Influenza Resp Viruses. 2022;16(4):632–642. doi: 10.1111/irv.12955
89. Aballéa S, Chancellor J, Martin M, et al. The cost-effectiveness of influenza vaccination for people aged 50 to 64 years: an international model. Value Health J Int Soc Pharmacoeconomics Outcomes Res. 2007;10(2):98–116. doi: 10.1111/j.1524-4733.2006.00157.x
90. Béraud G, Mosnier A, Guérin O, et al. Cost-effectiveness analysis of expanding influenza vaccination to adults aged 50 and over in France. Infect Dis Ther. 2025;14(7):1513–1527. doi: 10.1007/s40121-025-01168-5
91. Marchi S, Fallani E, Salvatore M, et al. The burden of influenza and the role of influenza vaccination in adults aged 50–64 years: a summary of available evidence. Hum Vaccines Immunotherapeutics. n.d.;19(2):2257048. doi: 10.1080/21645515.2023.2257048
92. DiazGranados CA, Saway W, Gouaux J, et al. Safety and immunogenicity of high-dose trivalent inactivated influenza vaccine in adults 50–64 years of age. Vaccine. 2015;33(51):7188–7193. doi: 10.1016/j.vaccine.2015.10.131