International Journal of Infectious Diseases 161 (2025) 108100

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Relative effectiveness of the high-dose versus standard-dose influenza vaccines for the prevention of laboratory-confirmed influenza among Italian older adults during three recent seasons

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ARTICLE INFO

Article history:
Received 23 August 2025
Revised 30 September 2025
Accepted 30 September 2025

Keywords:
Influenza
Vaccination
High-dose influenza vaccine
Vaccine effectiveness
Older adults

ABSTRACT

Objectives: This study aimed to assess the relative vaccine effectiveness (rVE) of high-dose (HD-IIV) versus standard-dose (SD-IIV) inactivated influenza vaccines against laboratory-confirmed influenza among older adults in Liguria (Italy), Europe's oldest region.

Methods: An integrated analysis of inpatient and outpatient data collected between the 2022/2023 and 2024/2025 seasons was performed using a test-negative approach. Adults aged ≥60 years vaccinated with either HD-IIV or SD-IIV and molecularly tested for influenza were eligible. For the base-case, rVE was estimated through conditional logistic regression. Alternative approaches, including the inverse probability of treatment weighting (IPTW), were used in sensitivity analyses.

Results: Among 1238 vaccinated older adults included in the analysis, influenza positivity prevalence was lower ($P = 0.022$) in HD-IIV (6.6%; 46/693) than SD-IIV (10.3%; 56/545) recipients. rVE of HD-IIV versus SD-IIV was 29% (95% CI: −22%, 59%) among subjects aged ≥60 years. Among adults aged ≥80 years, for whom HD-IIV was preferentially recommended, HD-IIV was more effective than SD-IIV by 54% (95% CI: 10%, 76%). IPTW-derived estimates were similar in both ≥60-year-olds (32%; 95% CI: −20%, 61%) and ≥80-year-olds (53%; 95% CI: 7%, 77%).

Conclusions: Italian older adults, especially the oldest old, vaccinated with HD-IIV experienced fewer influenza episodes than those immunized with SD-IIV.

Introduction

Older age is a well-known risk factor for severe outcomes following influenza infection: the estimated average annual rates (per 100,000 people) of influenza-associated respiratory excess mortality rates are 0.1-6.4 for individuals younger than 65 years, 2.9-44.0 for adults aged 65-75 years, and 17.9-223.5 for those aged ≥75 years [1]. Multimorbidity and frailty, whose prevalence increases with age, further contribute to poor influenza outcomes. The increased risk of serious influenza-related complications is also driven by deleterious changes in immune competence, known as immunosenescence [2].

Annual immunization with inactivated influenza vaccines (IIVs), whose primary goal is to protect high-risk groups against severe influenza-related disease and death, is recommended for all older adults [3]. However, despite proven population-level benefits, vaccine effectiveness (VE) of IIVs in older adults is typically lower than in younger age groups, especially against influenza A (H3N2) [3,4]. Immunosenescence is associated not only with more severe infection but also with a significant decrease in IIV-induced humoral response, which correlates with VE. A quantitative review [5] reported that compared with young adults, the odds of both seroconversion and seroprotection toward three IIV antigens in the elderly were reduced by 41-76%.

Increasing the antigen content or adding adjuvants can both enhance immune response in older adults, which may lead to a

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https://doi.org/10.1016/j.ijid.2025.108100

better protection against disease [6]. Three "enhanced" seasonal IIVs are currently licensed, including egg-based high-dose non-adjuvanted (HD-IIV), egg-based standard-dose MF59-adjuvanted (aIIV), and recombinant high-dose non-adjuvanted IIVs. Several countries, including the US [7] and Italy [8], have recently issued preferential recommendations for the use of enhanced IIVs in older adults.

First approved in the United States, HD-IIV has recently become available in Europe. In a pivotal randomized controlled trial (RCT) [9], HD-IIV was 24.2% [95% confidence interval (CI): 9.7%, 36.5%] more efficacious than a standard-dose non-adjuvanted IIV (SD-IIV) in adults aged ≥65 years. Notably, there was also evidence of a higher protection in individuals aged ≥75 years with a relative efficacy of 32.4% [10]. In a meta-analysis [11] with over 45 million adults aged ≥65 years, HD-IIV provided significantly better protection than SD-IIV against influenza-like illness (ILI), influenza-related hospitalizations, cardiovascular, cardiorespiratory, and all-cause hospitalizations. However, most available real-world evidence on the relative VE (rVE) of HD-IIV versus SD-IIV (reviewed in [6,11–13]) is confined to studies conducted in the United States, which used non-laboratory-confirmed influenza proxies of varying specificity.

In terms of mean population age, the Italian region of Liguria is Europe's oldest region. Starting from the 2023/2024 season, the Italian Ministry of Health has preferentially recommended both HD-IIV and aIIV for adults aged ≥65 years [8]. However, in Liguria, recommendations are different: aIIV was recommended for individuals aged 60-79 years, while HD-IIV was recommended for those aged ≥80 years [14–16]. Importantly, these recommendations are not mandatory, and any available IIV can be administered to adults aged ≥60 years. Indeed, a substantial proportion of older adults in Liguria are vaccinated with SD-IIVs [14–16]. Differences in IIV policies and relative usage of single IIVs are likely to affect vaccine effectiveness estimates [6]. While several Italian studies, including Ligurian ones, have demonstrated the benefit of aIIV over SD-IIV [6], data on rVE of HD-IIV versus SD-IIV in preventing laboratory-confirmed influenza among Italian older adults have not been available. Considering also a comparatively high purchase price of HD-IIV, this data gap underscores the need for local rVE estimates. On this background, the objective of this study was to perform an integrated analysis of the rVE of HD-IIV versus SD-IIV in preventing laboratory-confirmed influenza among Ligurian inpatient and outpatient adults aged ≥60 years across three recent influenza seasons.

Methods

Study design and data sources

For this integrated analysis, we combined data from three seasonal inpatient studies [14–16] and one two-season outpatient study [17,18]. We therefore aimed to increase statistical power and generalize findings across multiple seasons. All studies were conducted in Genoa (Liguria, Italy) between mid-October/early November and late April. All patients were tested for influenza using the same real-time polymerase chain reaction (RT-PCR) kit (Allplex Respiratory panel 1; Seegene Inc., Seoul, Korea), which allows distinguishing between virus (sub)types.

A full description of the single seasonal studies can be found elsewhere [14–18]. Briefly, the inpatient studies were conducted in a large tertiary care hospital during the seasons 2022/2023 [14], 2023/2024 [15], and 2024/2025 [16] with the aim to establish absolute VE. The studies had a retrospective test-negative case-control design (TND) and the inclusion criteria were: (i) age ≥18 years; (ii) access to the hospital emergency department (ED) with a subsequent hospitalization; (iii) prescription of an RT-PCR for the detection of influenza virus within 5 days following the ED visit. Patients who either had documented influenza before their ED admission or whose vaccination status was unverifiable were excluded. The three-season pool of subjects eligible for the present study included 3490 hospitalized individuals.

The outpatient study [17,18] was conducted during the 2023/2024 and 2024/2025 seasons with the primary objective to case definitions and burden of respiratory syncytial virus (RSV). In particular, 24 (2023/2024) and 36 (2024/2025) general practitioners (GPs) were randomized 1:1 to enroll outpatients aged ≥50 years seeking care for acute respiratory infection [ARI; defined as sudden onset of ≥1 respiratory symptom (cough, sore throat, shortness of breath, coryza) and GP's judgment of an underlying infection] or ILI [defined as a sudden onset of ≥1 systemic (fever or feverishness, malaise, headache, myalgia) and ≥1 respiratory (cough, sore throat, shortness of breath) symptoms], respectively. Notably, all ILI patients also met the ARI criteria, while 93% of ARI patients also satisfied ILI criteria. Since all patients were also tested for influenza, the study methodologically approaches a classic TND study. Importantly, it has been shown [19] that VE among patients meeting either ARI or ILI criteria varies by only ≤ 2%. For the outpatient study, the pool of adults totaled 1431.

For this integrated analysis and in line with the current age indication of HD-IIV in Italy [20], records of individuals aged ≥60 years who had been vaccinated with either HD-IIV or SD-IIV ≥14 days before the swab were extracted from the combined dataset. SD-IIV was defined as any non-adjuvanted, split or subunit, egg-based or cell-based vaccines containing 15 μg of hemagglutinin per vaccine strain. Therefore, subjects aged 18-59 years, unvaccinated individuals, and those immunized with aIIV were excluded. Recombinant IIV has not been commercialized in Italy.

Study endpoint

Cases were defined as individuals who tested positive for influenza, while controls were those who tested negative. The study outcome was rVE defined as the difference in RT-PCR-confirmed influenza between subjects vaccinated with HD-IIV versus SD-IIV and calculated as [1 – odds ratio (OR)] × 100%. For the main analysis, inpatient and outpatient studies were pooled together. A systematic review [21] has not found any heterogeneity, and the pooled difference in VE between inpatient and outpatient studies was only −2% (95% CI: −12%, 10%). However, as inpatients and outpatients may still represent two distinct populations, setting-specific rVE was also estimated.

Vaccination exposure

During the entire study period, influenza vaccination was recommended and offered free-of-charge for all subjects aged ≥60 years. Indeed, the possibility of offering free-of-charge IIV also to adults aged 60-64 years (in addition to the established target of ≥65-year-olds) was first indicated for the 2020/2021 season [8].

Influenza vaccination was verified in the local electronic immunization registry. Recording of vaccine receipt in the registry was mandatory for reimbursement. Exposure misclassification in terms of IIV types was unlikely because the input fields for IIV brand and lot were mandatory. All vaccines were quadrivalent.

Covariates

The following variables were considered as potential confounders: age; sex; presence of co-morbidities (diabetes, cardiovascular, respiratory, renal, hepatic, and immunosuppressive conditions including cancer); calendar month of swab and vaccine

administration; vaccination-to-swab period to account for within-season waning in VE; previous season IIV. Analyses that combined both inpatients and outpatients were also controlled for hospitalization. The variables were collected in a consistent manner: GPs collected the data directly in the outpatient study [17,18], while trained physicians extracted the data from patient files in the inpatient studies [14–16].

Data analysis

Categorical and continuous variables were expressed as proportions and means with standard deviations (SDs) and compared by means of the Fisher's exact and *t* tests, respectively. rVE was evaluated in the entire cohort of inpatients and outpatients aged ≥60 years. Considering the preferential recommendation of HD-IIV for adults aged ≥80 years, we also restricted the dataset to this age group. Additionally, we restricted the dataset to hospitalized adults only. Owing to small numbers, rVE in subjects aged 60-79 years and that in outpatients only could not be assessed. We also performed an exploratory subgroup analysis by season and virus (sub)types. Owing to the paucity of cases, rVE was not assessed for the 2022/2023 season and for influenza B.

In the base-case analysis, rVE was estimated via conditional logistic regression (CLR) with stratification on the month of swab. CLR allows subjects to be compared at risk within the same month and controls for differences in influenza activity over the season [22]. The impact of potential confounders was assessed by increasing number of covariates added as follows. First, a CLR model with no other covariates (referred to as "unadjusted model") was implemented. Second, a parsimoniously adjusted model (CLR with matching on the month of swab and adjusted for age and sex) was assessed, as previously recommended [23]. Third, fully adjusted CLR models with all the covariates listed above were built.

Robustness of the base-case was evaluated in different sensitivity analyses. First, we reapplied unconditional logistic regression, where the calendar period of the swab was modelled as monthly dummies [22]. Second, as fully adjusted models may be at risk of overfitting, especially when the number of events is low, we used the inverse probability of treatment weighting (IPTW) approach, which may effectively control for the indication bias. IPTW was performed as previously described [24,25]. Specifically, weights were calculated from propensity scores, which were derived from a logistic model with the dependent variable of vaccine type and all available baseline pre-vaccination covariates. Stabilized weights were then obtained to reduce α error by multiplying non-stabilized weights by the marginal probability of receiving the actual IIV received. To reduce the impact of outliers, weights >5 were truncated to five. Covariate balance before and after IPTW was assessed via standardized mean differences (SMDs); SMDs < 0.1 were considered to represent negligible imbalances. A univariate logistic model on the weighted population was then run. Additionally, we also evaluated a doubly-robust model that implemented both IPTW and covariate adjustment. In the third sensitivity analysis, we explored unmeasured confounding by assessing rVE in preventing RSV, a negative control outcome [26] tested using the same respiratory panel as influenza (sub)types.

Statistical analysis was performed in R, v. 4.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

In all, 1238 adults aged ≥60 years who had received either HD-IIV (N = 693) or SD-IIV (N = 545) at least 14 days before the swab were identified. Three-quarters (78.1%) of enrollees came from inpatient studies. Participants were, on average, 81.1 years old, with a slight majority (52.1%) being female. Most (87.2%) had ≥1 co-morbidity, primarily cardiovascular disease (74.2%), respiratory conditions (27.0%), and diabetes (18.7%). Previous season vaccination was recorded in 85.5% of subjects.

A total of 102 (8.2%) influenza cases were detected, of which all but two (98.0%) belonged to type A. Within influenza A, both A(H1N1)pdm09 (52.0%) and A(H3N2) (48.0%) were almost equally distributed. Cases and controls were comparable in terms of sex and prevalence of co-morbidities (Table 1). However, cases were on average two years younger (79.2 vs 81.3 years) and had a shorter vaccination-to-swab period (10.1 vs 11.9 weeks). Influenza detection rate was higher during the 2024/2025 season.

Influenza positivity was significantly lower among older adults vaccinated with HD-IIV (6.6%) than in those vaccinated with SD-IIV (10.3%). When stratified by setting, age group, and virus (sub)type, HD-IIV users tended to register fewer influenza cases than SD-IIV users. However, several comparisons were uninformative because of small numbers (Supplementary Table S1).

HD-IIV and SD-IIV recipients differed for most variables considered (Supplementary Table S2). Particularly, subjects immunized with HD-IIV were on average 10 years older (85.6 vs 75.5 years) and had more co-morbidities (90.5% vs 83.1%). The relative proportion of HD-IIV users increased from season to season, and HD-IIV administration took place earlier during the season.

In the entire cohort, rVE of HD-IIV versus SD-IIV estimated via unadjusted CLR model was 40% (95% CI: 7%, 61%). When parsimoniously (28%; 95% CI: −20%, 57%) or fully (29%; 95% CI: −22%, 59%) adjusted, the estimate turned not statistically significant. In the oldest old subgroup (≥80 years), rVE was higher with a fully adjusted estimate of 54% (95% CI: 10%, 76%). Fully adjusted rVE among inpatients only was 33% (95% CI: −24%, 63%) and 57% (95% CI: 13%, 79%) among adults aged ≥60 and ≥80 years, respectively (Figure 1).

We conducted an exploratory analysis to assess whether age group (≥80 vs 60-79 years) modified the effect of IIV type on influenza detection. Though none of the effects proved statistically significant, there was some trend toward lower odds of influenza among the oldest old. Particularly, the adjusted CRL-based ORs were 0.70 (95% CI: 0.22, 2.20) for the interaction term between the IIV type and age group, and 0.80 (95% CI: 0.30, 2.16) and 1.00 (95% CI: 0.52, 1.91) for the main effects of IIV type and age group, respectively.

The base-case results were robust across all sensitivity analyses. Specifically, rVE estimated via unconditional logistic regression consistently remained within a 2% range of the base-case (Supplementary Table S3).

Application of the IPTW procedure in the second sensitivity analysis enabled a better balance for all pre-vaccination covariates considered (Supplementary Figure S1). However, post-weighting SMDs for age (0.16) and vaccination month (0.20) were still slightly imbalanced. rVE estimated via IPTW (with or without double adjustment) consistently fell within a 3% margin of the base-case results (Table 2).

There were 63 RSV cases that were similarly (P = 0.99) distributed among HD-IIV (5.1%; 35/693) and SD-IIV (5.1%; 28/545) recipients. Unadjusted, parsimoniously adjusted and fully adjusted CLR-based ORs were 1.04 (95% CI: 0.62, 1.76), 1.13 (95% CI: 0.61, 2.10) and 1.17 (95% CI: 0.60, 2.26), respectively. The distribution of RSV detections was also comparable (P = 0.85) among subjects immunized with either HD-IIV (5.2%; 32/617) or SD-IIV (4.5%; 9/201). The unadjusted, parsimoniously adjusted, and fully adjusted regression approaches produced similar, non-significant CLR-based ORs of 1.38 (95% CI: 0.62, 3.04), 1.32 (95% CI: 0.60, 2.93), and 1.25 (95% CI: 0.54, 2.87), respectively.

In an explanatory subgroup analysis by virus type A subtype and season (Table 3), there was a trend toward a greater rVE of HD-IIV versus SD-IIV against A(H1N1)pdm09 and, consequently,

Table 1
Characteristics of cases and controls; Genoa (Italy), 2022/2023-2024/2025 seasons.

Variable	Level	Cases (N = 102), n (%)	Controls (N = 1136), n (%)	P value
Sex	Male	50 (49.0)	543 (47.8)	0.84
	Female	52 (51.0)	593 (52.2)	
Age, years	Mean (SD)	79.2 (9.7)	81.3 (9.3)	0.042
	60-79	41 (40.2)	379 (33.4)	0.19
	≥80	61 (59.8)	757 (66.6)	
Setting	Inpatient	69 (67.6)	898 (79.0)	0.012
	Outpatient	33 (32.4)	239 (21.0)	
Season	2022/2023	5 (4.9)	109 (9.6)	0.045
	2023/2024	32 (31.4)	263 (23.2)	
	2024/2025	65 (63.7)	480 (42.3)	
Presence of co-morbidities	Any	89 (87.3)	991 (87.2)	0.88
	Cardiovascular	77 (75.5)	842 (74.1)	0.81
	Respiratory	22 (21.6)	312 (27.5)	0.24
	Diabetes	16 (15.7)	215 (18.9)	0.51
	Renal	11 (10.8)	165 (14.5)	0.37
	Hepatic	5 (4.9)	26 (2.3)	0.17
	Cancer/ immunosuppression	13 (12.7)	212 (18.7)	0.18
Vaccine type	HD-IIV	46 (45.1)	647 (57.0)	0.022
	SD-IIV	56 (54.9)	490 (43.1)	
Month of vaccination	October	31 (30.4)	319 (28.1)	0.13
	November	57 (55.9)	368 (32.4)	
	December or later	14 (13.7)	99 (8.7)	
Time since vaccination, weeks	Mean (SD)	10.1 (4.3)	11.9 (6.0)	< 0.001
Previous season vaccination	Yes	85 (83.3)	973 (85.7)	0.56
	No	17 (16.7)	163 (14.3)	

HD-IIV, high-dose inactivated influenza vaccine; SD, standard deviation; SD-IIV, standard-dose inactivated influenza vaccine.

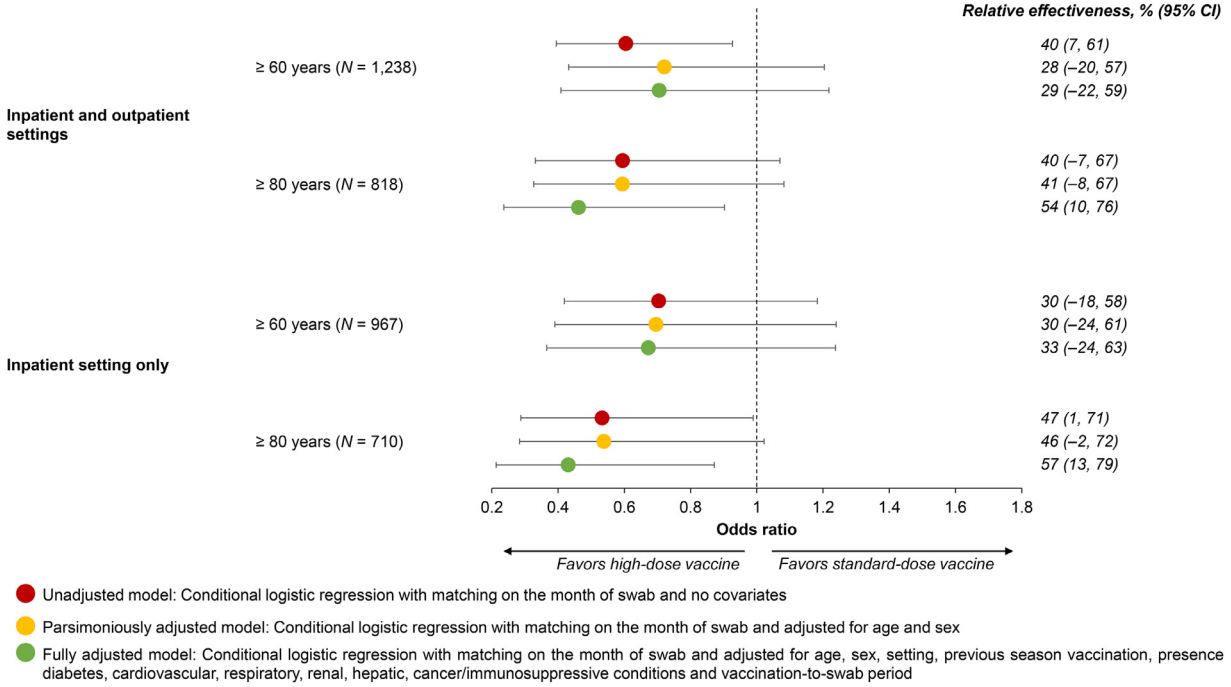

Figure 1. Relative effectiveness of the high-dose (HD-IIV) versus standard-dose (SD-IIV) influenza vaccines against laboratory-confirmed influenza in older adults; Genoa (Italy), 2022/2023-2024/2025 seasons.
Abbreviation: CI, confidence interval.

during the A(H1N1)pdm09 dominant 2023/2024 season. However, owing to small numbers, the obtained estimates were associated with large uncertainty.

Discussion

In this integrated analysis, Italian older adults vaccinated with HD-IIV tended to report fewer laboratory-confirmed influenza episodes than their counterparts vaccinated with SD-IIV. This benefit was particularly evident in the oldest old, where the observed rVE consistently indicated a meaningful effect, regardless of the modeling strategy employed. Liguria, currently the oldest region in Europe by mean population age, implements a unique IIV policy. This policy preferentially recommends HD-IIV for all individuals aged ≥80 years and institutionalized subjects. Our findings, which span three seasons with diverse

Table 2
Relative effectiveness of the high-dose versus standard-dose influenza vaccines against laboratory-confirmed influenza in older adults: sensitivity analysis by applying the inverse probability of treatment weighting approach.

Setting	Age, years	*N*	Relative effectiveness HD-IIV vs SD-IIV, % (95% CI)	
			IPTW weights only	Doubly adjusted
Inpatient and outpatient	≥60	1238	32 (−20, 61)	28 (−33, 61)
	≥80	818	53 (7, 77)	57 (16, 78)
Inpatient only	≥60	967	31 (−33, 64)	31 (−38, 65)
	≥80	710	54 (8, 77)	59 (16, 80)

CI, confidence interval; HD-IIV, high-dose inactivated influenza vaccine; IPTW, inverse probability of treatment weighting; SD-IIV, standard-dose inactivated influenza vaccine.

Table 3
Relative effectiveness of the high-dose versus standard-dose influenza vaccines against laboratory-confirmed influenza in adults aged ≥60 years: exploratory subgroup analysis by influenza A subtype and season.

Virus	Season	Relative effectiveness HD-IIV vs SD-IIV, % (95% CI)	
		Unadjusted[a]	Adjusted[b]
A(H1N1)pdm09	All	44 (1, 68)	38 (−26, 70)
A(H3N2)	All	34 (−22, 64)	24 (−69, 66)
A and B	2023/2024	62 (18, 82)	60 (−2, 84)
A and B	2024/2025	27 (−25, 58)	24 (−56, 63)

CI, confidence interval; HD-IIV, high-dose inactivated influenza vaccine; SD-IIV, standard-dose inactivated influenza vaccine.

[a] Estimated via conditional logistic regression model with matching on the month of swab and no covariates.

[b] Estimated via conditional logistic regression model with matching on the month of swab and adjusted for age, sex, setting, previous season vaccination, presence of ≥1 co-morbidity and vaccination-to-swab period.

influenza epidemiology, corroborate the appropriateness of this policy.

In the overall population aged ≥60 years, rVE of HD-IIV versus SD-IIV was 29% (95% CI: −22%, 59%). This point estimate is in line with the relative efficacy of 24.2% (95% CI: 9.7%, 36.5%) reported in the pivotal RCT [9]. As witnessed by the available systematic reviews [6,11–13], HD-IIV boasts numerous randomized and non-randomized rVE studies, which consistently found that HD-IIV offers an improved protection over SD-IIV. For instance, among randomized studies, a rVE of up to 64.4% has been reported [13]. However, single primary studies showed a substantial variation in the observed effect sizes and most studies used less specific, non-laboratory-confirmed endpoints. Specificity of the outcome plays a crucial role in interpreting and comparing VE of two IIVs from different studies [27]. Therefore, it is worth primarily comparing our findings to the few available observational studies with laboratory-confirmed endpoints. In a US hospital-based TND study conducted during the seasons 2015/2016 and 2016/2017 [26], rVE of HD-IIV versus SD-IIV in adults aged ≥65 years was 27% (95% CI: −1%, 48%) in the entire population including unvaccinated individuals, and 22% (95% CI: −10%, 44%) when the dataset was restricted to vaccinees only. In a larger study of a similar design spanning four influenza seasons (from 2015/2016 to 2018/2019) [28], the pooled IPTW-adjusted rVE of HD-IIV versus SD-IIV was 18% (95% CI: 0%, 33%). rVE based on multivariable logistic regression was lower (7%; 95% CI: −16%, 26%). Apart from the adjustment strategy, rVE estimates differed substantially for virus subtypes and seasons. In another US single-season (2016/2017) retrospective matched cohort study [29], compared to SD-IIV, HD-IIV reduced hospitalizations for RT-PCR-confirmed influenza by 30.7% (95% CI: 8%, 48%). Importantly, those authors warned that unmatched or overly simple matched rVE studies may substantially underestimate rVE: the unmatched rVE was −8.5% (95% CI: −22%, 7%).

When restricted to the older population of ≥80 years, HD-IIV was more effective than SD-IIV by 54% and the 95% CI (10%, 76%) excluded the null. Analogous estimates emerged when the dataset was limited to hospitalized patients. In the pivotal efficacy RCT [10], relative efficacy in adults aged ≥75 years (32.4%; 95% CI: 8.1%, 50.6%) was higher than in those aged 65-74 years (19.7%; 95% CI: 0.4%, 35.4%). In a US retrospective cohort study carried out during the 2010/2011 season, Richardson et al. [30]. found a significant interaction ($P = 0.002$) between age and vaccine type, suggesting that the effect of HD-IIV versus SD-IIV was modified by age. Specifically, while rVE of HD-IIV versus SD-IIV against hospitalization for influenza or pneumonia in subjects aged ≥85 years was 48% (95% CI: 8%, 71%), no benefit was found in both 65-74- (rVE −16%; 95% CI: −88%, 29%) and 75-84-year-olds (rVE −44%; 95% CI: −152%, 18%). The incremental benefit of HD-IIV in the oldest old could be explained by a substantially lower immunogenicity of SD-IIV in this age subgroup. Indeed, compared to subjects aged <75 years, individuals aged ≥75 years are less likely to seroconvert by 39-68% [5]. In a nutshell, the currently available evidence (reviewed in [6,11–13]) conveys a general trend toward benefits of using HD-IIV in older adults. However, the magnitude of this benefit varies and seemingly depends on a variety of factors, such as study design, including the presence of randomization and endpoint specificity, age and other characteristics of vaccinees, as well as season-specific influenza epidemiology. In this regard, pluriannual aggregated analyses may offer useful insights into the "average" effect.

This study suffers from some important limitations. First, a limited number of influenza detections and/or vaccinees in some population strata (i.e., outpatients and HD-IIV recipients aged 60-79 years) prevented us from conducting several subgroup analyses, and those that were performed had wide CIs. Second, hospital-based studies conducted during the 2023/2024 and 2024/2025 seasons did not rely on clinical case definitions, and all patients with a RT-PCR test prescription were assumed to have symptoms attributable to ARI. We had previously realized that the description of symptoms related to the current ED visit and available in medical records were often incomplete and skewed to the most severe symptoms. Absence of a clinical case definition allows for increased sensitivity and pool of eligible patients, but can also introduce selection bias (e.g., asymptomatic screening, differences in RT-PCR test prescription between vaccinated and unvaccinated individuals). We however showed [16] that the absolute VE estimated in patients meeting the ARI case definition is similar to VE estimated in all patients with a RT-PCR test prescription. Moreover, with regard to the present rVE analysis limited to vaccinated subjects only, we have no reasons to believe that the RT-PCR test prescription differed between people immunized with different IIV types. Third, although there was no meaningful difference in RSV detections rates (considered as negative control outcome) between HD-IIV and SD-IIV recipients, we cannot completely rule out some residual confounding. For instance, adjustment for age and presence of co-morbidities only partially reflects the level of frailty. Analogously, granularity of some covariates, such as calendar time,

was low, which may distort results [29]. Finally, although RSV positivity has been previously used as a negative control outcome in a TND rVE study [26], it remains unclear whether its use is optimal in rVE studies. Furthermore, the covariates of age and month of vaccine administration remained slightly unbalanced after IPTW, which reflects the preferential recommendation of HD-IIV in adults aged ≥80 years and earlier vaccination with and/or distribution of HD-IIV doses, respectively.

In conclusion, Italian older adults vaccinated with HD-IIV during the last three influenza seasons tended to have fewer influenza-related GP visits and hospitalizations than their counterparts vaccinated with SD-IIV. The incremental benefit increased with age, resulting in higher effectiveness in the oldest old.

Declaration of competing interest

A.D. provided consultancies and/or received speaker fees from CSL Seqirus, GSK, Sanofi, and SD Biosensor. A.O. provided consultancies and/or received speaker fees from CSL Seqirus, Moderna, Novavax, and SD Biosensor. D.P. provided consultancies for Pfizer and CSL Seqirus and received grants for conducting observational studies from Sanofi, Pfizer, GSK, and Viatris. G.I. provided consultancies and/or received grants for conducting experimental and/or observational studies for GSK, Sanofi, MSD, CSL Seqirus, and Pfizer. A.S. declares no conflicts.

Funding

A part of this integrated analysis (the outpatient study originally conducted to investigate the burden of RSV) was funded by GlaxoSmithKline Biologicals SA (id 221526). GlaxoSmithKline Biologicals SA had no role in the decision to perform or publish this integrated analysis nor in the preparation of the manuscript. The inpatient studies were unfunded.

Ethics approval

Both inpatient (#166/2023, id 13094) and outpatient (#397/2023, id 13354) studies were approved by the Ethics Committee of Liguria Region. The patient's written consent was obtained from all prospectively enrolled outpatients. Informed consent was waived for the retrospective data-linkage inpatient study.

Author contributions

Study concept, design, and interpretation: A.D., A.O., and G.I. Acquisition of data: A.D., A.O., and D.P. Manuscript drafting: A.D. Data analysis: A.D. and A.S. Critical review of manuscript: A.O., A.S., D.P., and G.I. Supervision: G.I. All the authors reviewed and edited the manuscript and were responsible for the decision to submit the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.108100.

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