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Original Article

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

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ABSTRACT

Objectives: High-dose quadrivalent influenza vaccine (HD-QIV) was introduced during the 2021/2022 influenza season in France for adults aged ≥65 years as an alternative to standard-dose quadrivalent influenza vaccine (SD-QIV). The aim of this study is to estimate the relative vaccine effectiveness of HD-QIV vs. SD-QIV against influenza-related hospitalizations in France.

Methods: Community-dwelling individuals aged ≥65 years with reimbursed influenza vaccine claims during the 2021/2022 influenza season were included in the French national health insurance database. Individuals were followed up from vaccination day to 30 June 2022, nursing home admission or death date. Baseline socio-demographic and health characteristics were identified from medical records over the five previous years. Hospitalizations for influenza and other causes were recorded from 14 days after vaccination until the end of follow-up. HD-QIV and SD-QIV vaccinees were matched using 1:4 propensity score matching with an exact constraint on age group, sex, week of vaccination, and region. Incidence rate ratios were estimated using zero-inflated Poisson or zero-inflated negative binomial regression models.

Results: We matched 405 385 HD-QIV to 1 621 540 SD-QIV vaccinees. HD-QIV was associated with a 23.3% (95% CI, 8.4–35.8) lower rate of influenza hospitalizations compared with SD-QIV (69.5/100 000 person years vs. 90.5/100 000 person years). Post-matching, we observed higher rates in the HD-QIV group for hospitalizations non-specific to influenza and negative control outcomes, suggesting residual confounding by indication.

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Discussion: HD-QIV was associated with lower influenza-related hospitalization rates vs. SD-QIV, consistent with existing evidence, in the context of high SARS-CoV-2 circulation in France and likely prioritization of HD-QIV for older/more comorbid individuals. **Hélène Bricout, *Clin Microbiol Infect* 2024;■:1**

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Introduction

In France, over the past ten seasons (excluding 2020–2021), influenza infection was responsible for more than one million general practitioner visits for influenza-like illness, >20 000 influenza hospitalizations, and ~9000 deaths each season [1]. These surveillance figures are likely to underestimate the true burden of seasonal influenza. The French Agency of Public Health, Santé Publique France, reported that 90% of influenza-related deaths occur in individuals aged ≥ 65 years [2]. Complications leading to hospitalizations and death are greatest among individuals in this age group, which is often more vulnerable because of chronic disease and weakened immune systems. Thus, with the overall aim of reducing the public health burden of influenza, in particular the associated hospitalizations, annual influenza vaccination is recommended and free of charge in France for this age group.

Standard-dose (SD) influenza vaccines are considered to provide suboptimal protection in adults >65 years of age [3], because of immunosenescence [4]. A high-dose (HD) influenza vaccine, with four times the antigen content of a SD vaccine was developed to elicit an improved immune response and improved protection against severe influenza illness, influenza-related hospitalizations, and mortality in this vulnerable population. In a pivotal randomized controlled trial, HD influenza vaccine demonstrated a superior relative vaccine efficacy of 24.2% (95% CI, 9.7–36.5) vs. SD influenza vaccine in preventing laboratory-confirmed influenza in patients older than 65 years [5]. Furthermore, a recent meta-analysis of published evidence of HD vs. SD vaccine efficacy/effectiveness studies showed that HD was associated with a reduction in respiratory-related hospitalizations [6].

HD quadrivalent influenza vaccine (QIV) was introduced in season 2021/2022 in Europe. This study estimated the relative vaccine effectiveness (rVE) of HD-QIV vs. SD-QIV against hospitalizations in community-dwelling adults ≥ 65 years of age during the 2021/2022 influenza season in a real-world setting in France.

Methods

Study design and data sources

This was an observational retrospective cohort study, based on French national administrative healthcare data, designed to describe the characteristics of individuals who received a seasonal influenza vaccine in the community between 1 September 2021 and 28 February 2022, and to assess the rVE of HD-QIV compared with SD-QIV. The study used data from the National Health Data System (Système National Des Données de Santé [SNDS]), which is part of the National Health Insurance system (Supplementary Method 1). The SNDS encompasses anonymous, individual-level data on all healthcare claims for >99% of the population residing in France, regardless of the insurance scheme, i.e. close to 65 million people [7–10].

Ethical approval and consent to participate

The data supporting the study findings are part of the National Health Data System (SNDS) and are available from the Health Data Hub (<https://www.health-data-hub.fr/>). Restrictions apply to the availability of these data containing potentially identifying and sensitive patient information. Special permission to access these data for this study was granted by the ethical and scientific committee for health research, studies, and evaluations (Comité Ethique et Scientifique pour les Recherches, les Etudes et les Evaluations dans le domaine de la Santé) and the French data protection authority (Comité National de l'Informatique et des Libertés [CNIL]). The study protocol obtained two consecutive authorizations from the French data protection authority CNIL (initial authorization: Decision No. DR-2022-049; substantial modifications authorization: Decision DR-2023-013).

Informed consent was not required for the use of anonymized secondary data, as mentioned in the Social Security Code, Article L161-28-1. All methods were performed in accordance with CNIL regulations and with the REporting of studies Conducted using Observational Routinely-collected Data guidelines.

Study population and study period

All individuals aged ≥ 65 years, living in the community and having received an influenza vaccine dispensed between 1 September 2021 and 28 February 2022 (the official end of the French influenza vaccination campaign) were included. They were followed from vaccine dispensing (index date) up until 30 June 2022, or up to admission to medico-social housing, nursing homes, or death.

Variables of interest

Exposure

We used pharmacy dispensing records as a proxy for influenza vaccination (Supplementary Method 1). Vaccine type was classified by medication codes (Table S1).

Outcomes

Primary outcomes were hospitalizations for influenza, pneumonia, respiratory disease, cardiovascular disease, and cardiorespiratory disease (either cardiovascular or respiratory). Hospitalizations were ascertained by their International Classification of Diseases ICD-10 discharge diagnosis code (Table S2) and were collected from 14 days after the index date (start of vaccine protection) to end of follow-up. Hospitalizations with a COVID-19-associated discharge diagnosis code were excluded from this primary analysis. Given that the Programme de médicalisation des systèmes d'information hospital administrative database is maintained for reimbursement purposes, we used both primary ICD-10 discharge diagnosis codes and non-primary diagnosis codes to identify the study outcomes for the analysis. Given the primary diagnosis code should be the main determinant for hospitalization

[11], we reported primary analyses based on the primary ICD-10 discharge code. However, because the choice of coding in Programme de médicalisation des systèmes d'information could potentially be impacted by the level of severity of the outcome and linked to it, by the level of reimbursement that can be claimed by the hospital, we also conducted an analysis with the outcomes of interest coded with both primary or non-primary discharge codes.

Covariates

A fixed 5-year pre-index date period was used to capture baseline demographics, comorbidities/medical history, and previous treatments and vaccinations (Table S3) [12].

Statistical methods

Propensity score matching

Because the study relied on a retrospective database analysis with routine treatment allocation (no randomization), treatment selection or indication bias could exist. To adjust for potential confounding, every HD-QIV vaccinee was matched to four SD-QIV vaccinees using a propensity score, with an exact constraint on sex, age groups (65 to 75/75 to 85 and over 85 years of age), geographical region, and week of dispensing of the vaccine. The propensity score was computed using a logistic regression model including socio-demographic variables, health behaviour proxies, and comorbidities (Supplementary Method 2). An inverse probability of treatment weighting stability was also conducted as a stability analysis on top of the propensity score main analysis (Supplementary Method 3).

Main analysis

To estimate the association between vaccination with HD-QIV or SD-QIV and hospitalization, Poisson models, negative binomial models and their zero-inflated counterparts were used to estimate incidence rate ratios (IRR) with corresponding 95% CI [13]. The model with the lowest Akaike information criterion was chosen (Table S4) [14]. The models included an offset for the log of the follow-up time, which allows a rate model to be computed. The rVE was computed as $([1 - \text{IRR}] * 100)$, with corresponding 95% CIs by Taylor series variance approximation [15,16].

Sensitivity analyses

We performed a number of sensitivity analyses. First, outcomes were restricted to those occurring within a 9-week interval encompassing the 4 weeks before and after peak incidence week (as defined by *Santé Publique France*), coinciding with 28 February to 1 May 2022 [17,18]. This was intended to increase the specificity of the hospitalization of interest, as the probability of miscoding influenza hospitalizations should be lower during peak influenza activity; and the probability of being hospitalized for respiratory/cardiovascular events because of influenza should be higher. Second, the impact of using different outcome definitions (primary discharge code vs. any primary or non-primary discharge diagnosis code) was explored. Third, given the high SARS-CoV2 circulation and its high level of surveillance, individuals with outcomes of interest that also included a COVID-19 discharge ICD-10 code were examined, as COVID-19 infection may have been frequently coded and may have played a role in some of the hospitalizations, especially in hospitalizations that were non-specific to influenza. Finally, negative control outcomes (outcomes sharing the same potential sources of bias as the primary outcome but cannot plausibly be related to the exposure of interest) were analysed to check for unmeasured confounding by examining the effect of HD-QIV vs. SD-QIV on hospitalizations that were unrelated to influenza, its

complications, or influenza vaccination (i.e. urinary tract infection, cataract surgery, or erysipelas).

Results

The eligible individuals' identification process is shown in Fig. 1. We matched 405 385 HD-QIV vaccinees with 1 621 540 SD-QIV vaccinees at a 1:4 ratio. The 350 HD-QIV vaccinees who did not achieve a 1:4 matching ratio (0.08%) were excluded from the analysis, and their characteristics are summarized in Table S5.

Baseline characteristics of the HD-QIV and SD-QIV cohorts before matching and after matching are described in Table 1, Table S6, Supplementary Result 1, and propensity scores detailed results (Fig. S2, Table S7). After matching, characteristics were similar between the cohorts (Fig. S2). However, figures for HD-QIV displayed marginally higher prevalence, albeit not statistically significant for any comorbidity.

Hospitalization rates with influenza as the primary ICD-10 discharge code were 69.5 per 100 000 person years (PY) and 90.5 per 100 000 PY for HD-QIV and SD-QIV recipients, respectively, translating to an rVE of 23.3% (95% CI, 8.4–35.8) (Table 2). In the sensitivity analysis restricting outcomes to the peak influenza period, the influenza hospitalization rates were 52.6 per 100 000 PY and 72.4 per 100 000 PY for HD-QIV and SD-QIV, respectively, with a rVE point estimate of 27.4% (95% CI, 11.1–40.7). In the sensitivity analysis including influenza hospitalizations with a COVID-19 code, influenza hospitalization rates for HD-QIV and SD-QIV were 70.3 per 100 000 PY and 92.0 per 100 000 PY, respectively, yielding an rVE of 23.6% (95% CI, 8.9–36.0), similar to the main analysis. Inverse probability of treatment weighting results were consistent with the main analysis (Table S8).

For the hospitalization non-specific to influenza, we observed marginally higher hospitalization rates in HD-QIV than in SD-QIV recipients (Table 3). In the sensitivity analysis restricted to the epidemic peak, the IRR suggested lower rates of non-influenza-specific hospitalizations in the HD vs. SD group, but these differences were not statistically significant (Table 4). When alternative outcome definitions were used, using primary or non-primary diagnosis, similar results were observed, with an IRR of 0.79 (95% CI, 0.68–0.91) for influenza hospitalizations, and IRRs above 1 for the non-influenza-specific hospitalization (Table S9). The sensitivity analysis of non-influenza-specific hospitalizations including outcomes with a COVID-19 code showed an IRR slightly above 1 (Table S10).

Negative control outcomes analysis showed IRRs of 1.03 (95% CI, 0.98–1.07), 1.00 (95% CI, 0.98–1.02) and 1.05 (95% CI, 0.96–1.16) for urinary tract infection, cataract, and erysipelas hospitalizations, respectively. Although none were statistically significant, the rates were higher in HD-QIV vs. SD-QIV recipients for the three different negative control outcomes considered (Table S11), which may suggest residual unmeasured confounders.

Discussion

In this study, HD-QIV was associated with 23.3% (95% CI, 8.4–35.8) fewer hospital admissions because of influenza compared with SD-QIV, a finding that was consistent across sensitivity analyses. This finding is in the same direction as the literature, with an rVE against influenza hospitalization of HD vs. SD influenza vaccines estimated at 11.7% (95% CI, 7.0–16.1) in a recently updated meta-analysis [6], and a large Danish pragmatic Randomized Controlled Trial (RCT) in 2021/2022 with an observed rVE of 64.4% (95% CI, 24.4–84.6) for hospitalizations for pneumonia and/or influenza in HD-QIV recipients vs. SD-QIV recipients [19]. No differences or non-significant trends in favour of HD-QIV vs. SD-QIV

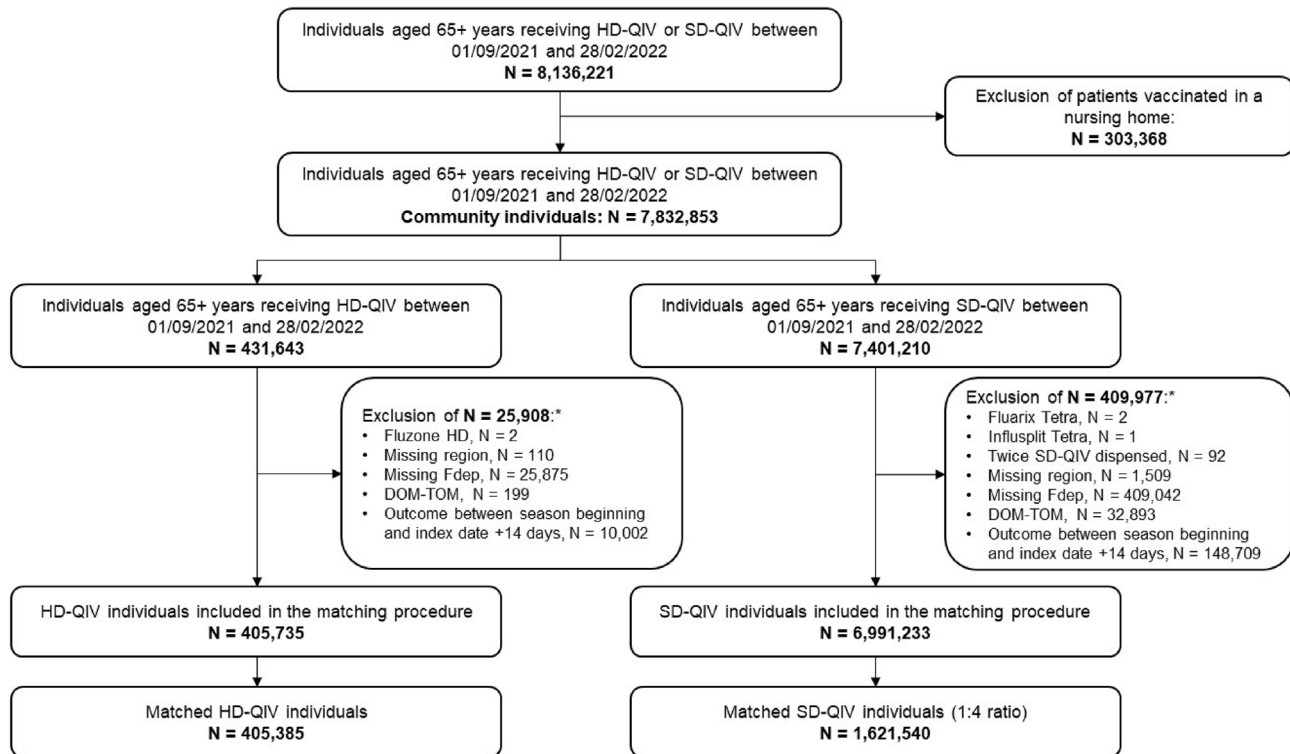


Fig. 1. Flowchart for community SD-QIV and HD-QIV recipients aged ≥ 65 y during the 2021/2022 season in France. *Individuals were excluded if they experienced an outcome related to hospitalization from the start of the influenza season up to 14 d after the index date. Individuals receiving multiple influenza vaccines in the same season, those who were vaccinated with a Northern Hemisphere (NH) 2020/2021 formulation, those living in French overseas departments, and individuals for whom information on region and/or deprivation index were not available were also excluded. More than one exclusion criterion may have been applied to a single patient; e.g. an excluded patient may both have a missing FDep and be residing in the DROM-COM. DOM-TOM, French overseas departments and territories; FDep, French social deprivation index; HD, high-dose; QIV, quadrivalent influenza vaccine; SD, standard dose.

were observed for hospitalizations that were non-specific to influenza (defined by primary ICD-10 discharge codes). We also observed a non-significant trend towards higher rates of negative control outcomes in HD-QIV recipients, suggesting that, despite matching on several measurable baseline characteristics, residual confounding by indication (i.e. in the case of HD-QIV being preferentially administered to more vulnerable individuals and individuals with higher levels of comorbidity) and residual unmeasured confounding may have remained. Indeed, although the two cohorts were matched on baseline characteristics, we still observed a slight trend towards a marginally higher prevalence of chronic diseases. Despite this potential residual confounding biased against the HD-QIV vaccine, a high value for rVE against influenza hospitalization was still observed and was robust to the sensitivity analyses. Furthermore, our findings support previously published data showing improved protection provided by HD-QIV compared with SD-QIV in elderly individuals in a randomized setting [5].

Limitations of our study include potential bias in the distribution of the HD-QIV vaccine during the first year of its release in France. The French Geriatric Scientific Society (*Société Française de Gériatrie et Gérologie*) recommends the preferential use of HD-QIV for all adults aged ≥ 65 years [20]; however, to support supply management during this first year after its release, the *Société Française de Gériatrie et Gérologie* recommended prioritization of HD-QIV for at-risk seniors, i.e. older and/or with multiple comorbidities for the first year of use [1]. The slightly higher hospitalization rates for negative control outcomes and

for some non-influenza-specific outcomes (based on primary and non-primary discharge codes) in the HD-QIV recipients in our study supported this 2021/2022 recommendation being implemented in practice, as do the baseline characteristics before matching (HD-QIV vaccinees were older and had more comorbidities than SD-QIV vaccinees). The limitations linked to the use of administrative databases for research purposes also applied to our study, i.e. ICD codes may not be reliable because coding can be impacted by practices and is not done for research purposes, and we may not have captured all relevant health characteristics of the study individuals. This limits the ability of our matching techniques to adjust for confounding, as without robust estimators of frailty or severity level for the comorbidity it is difficult to adjust for these confounding factors, which may lead to an underestimation of vaccine effectiveness. Other unmeasured confounders missing from administrative databases could have impacted our findings if they were unbalanced between HD-QIV and SD-QIV recipients; for example, frequency of contact with children and the proportion living alone (social isolation). In addition, although we used the pharmacy dispensing date as a proxy for the vaccination date, $\sim 50\%$ of those in the study were not vaccinated at the pharmacy (no pharmacy vaccination date recorded). However, sensitivity analyses using the first medical encounter within 2 weeks of pharmacy collection instead of pharmacy dispensing data did not alter the study findings (data not shown). From a statistical viewpoint, the current results were interpreted with the same unadjusted level of type I error (alpha

Table 1
Baseline cohort characteristics – after matching

Characteristics	HD-QIV	SD-QIV
Number of individuals	405 385	1 621 540
Age, mean (\pm STD)	77.4 (7.4)	77.3 (7.9)
65–75 y, n (%)	172 071 (42.4)	688 284 (42.4)
75–85 y, n (%)	161 258 (39.8)	645 032 (39.8)
Over 85 y of age, n (%)	72 056 (17.8)	288 224 (17.8)
Women, n (%)	227 755 (56.2)	911 020 (56.2)
Reasons for end of follow-up, n (%)		
Admission into a medico-social housing (other than NH)	35 (0.0)	121 (0.0)
Admission into NH	1416 (0.3)	5178 (0.3)
Death	7605 (1.9)	26 608 (1.6)
End of follow-up	396 329 (97.8)	1 589 633 (98.0)
Health care seeking behaviours proxy		
All-cause hospitalization in the past 12 mo, mean (STD)	0.1 (0.9)	0.1 (0.8)
GP visits in the past 12 mo, mean (STD)	6.2 (4.8)	6.1 (4.6)
Influenza vaccination at pharmacy, n (%)	205 005 (50.6)	834 196 (51.4)
Influenza vaccination during the previous season, n (%)	369 734 (91.2)	1 490 257 (91.9)
COVID-19 vaccinated ^a , n (%)	391 967 (96.7)	1 571 018 (96.9)
Pneumococcal vaccination in the previous 5 y, n (%)	47 432 (11.7)	179 405 (11.1)
Medical conditions during the 5 y before index date, n (%)		
Diabetes	80 454 (19.9)	309 552 (19.1)
Obesity and/or history of obesity surgery	34 503 (8.5)	129 287 (8.0)
Undernourishment/or history of undernourishment	27 848 (6.9)	100 485 (6.2)
Chronic respiratory diseases	48 102 (11.9)	177 592 (11.0)
Dementia	13 607 (3.4)	46 906 (2.9)
Cardiovascular diseases	113 066 (27.9)	432 428 (26.7)
Immunocompromised individuals	75 142 (18.5)	285 269 (17.6)
Chronic liver disease	6525 (1.6)	24 125 (1.5)
Terminal chronic kidney failure	1692 (0.4)	6303 (0.4)
Number of chronic diseases, n (%)		
None	182 213 (45.0)	781 010 (48.2)
1	130 086 (32.1)	494 610 (30.5)
2	59 146 (14.6)	218 801 (13.5)
3	22 584 (5.6)	84 959 (5.2)
4	7981 (2.0)	29 673 (1.8)
5	2536 (0.6)	9206 (0.6)
6	839 (0.2)	3281 (0.2)
Precariousness index (FDep99), n (%)		
Q1, Individuals living in a low-poverty municipality	77 989 (19.2)	313 265 (19.3)
Q2	79 443 (19.6)	318 652 (19.7)
Q3	85 160 (21.0)	340 820 (21.0)
Q4	79 318 (19.6)	315 693 (19.5)
Q5, Individuals living in a highly disadvantaged municipality	83 475 (20.6)	333 110 (20.5)

FDep, French social deprivation index; GP, general practitioners; HD, high-dose; NH, nursing home; QIV, quadrivalent influenza vaccine; SD, standard dose; STD, standard deviation.

Standard differences showed good balance for all variables included in the matching procedure (i.e. absolute value of std. diff <0.1).

^a COVID-19 vaccinated is a variable identified as such within the database. It reflects the COVID-19 vaccination status of each patient at index date following current guidelines (it can refer to a single dose, two, or three, depending on the individual's eligibility).

Table 2
Relative vaccine effectiveness and sensitivity analysis against influenza hospitalizations

Vaccine group	Hospitalization rate per 100 000 person years (95% CI)	IRR HD-QIV vs. SD-QIV (95% CI)	rVE (95% CI)	p value
HD-QIV	69.47 (59.64–80.92)	0.77 [0.64–0.92]	23.29 [8.38–35.77]	0.003
SD-QIV	90.53 (84.68–96.78)			
<i>Sensitivity analysis including influenza hospitalizations with a COVID-19 code</i>				
HD-QIV	70.31 (60.42–81.83)	0.76 [0.64–0.91]	23.61 [8.88–35.96]	0.003
SD-QIV	92.00 (86.10–98.29)			
<i>Sensitivity analysis during the peak of the season</i>				
HD-QIV	52.63 (44.17–62.71)	0.73 [0.59–0.89]	27.38 [11.05–40.70]	0.002
SD-QIV	72.36 (67.15–77.97)			

HD, high-dose; QIV, quadrivalent influenza vaccine; rVE, relative vaccine effectiveness; SD, standard dose.

risk) despite the multiplicity of outcomes tested. A *post hoc* alpha adjustment was performed on the main analysis (primary discharge code and without COVID-19) using the Bonferroni–Holm method. Key findings remained unchanged, with HD-QIV significantly associated with fewer influenza hospitalizations compared with SD-QIV, and no significant association was found for all the other non-influenza-specific hospitalizations. Finally, the atypical viral epidemiology (late influenza peak in April 2022, moderate intensity influenza epidemic, and SARS-CoV-2 co-circulation) [21] in the 2021/2022 season may have also contributed to the low to no effect observed for non-influenza-specific hospitalizations. In this context of a moderate influenza season, influenza contributes less to these broader outcomes (e.g. pneumonia, respiratory, or cardiovascular hospitalizations), therefore diluting the effect of influenza vaccines in preventing these potentially influenza-associated complications, leading to potential underestimation of rVE.

The strengths of our study are the large sample size and our ability to capture all HD-QIV vaccines provided free of charge at pharmacies in the community setting in France, giving a comprehensive overview of vaccine effectiveness. We set the level of statistical significance for our analysis at 5%, but considering the very large sample size, we should interpret with caution any small effect sizes found to be significant [22,23]. Additionally, increased use of PCR testing for influenza and other respiratory viruses during the COVID-19 pandemic [24,25] likely improved the specificity of influenza coding at hospital discharge, allowing for more accurate identification of influenza cases for the influenza hospitalization. This may have also reduced the use of broader codes (i.e. those related to non-influenza-specific outcomes) in the hospital administrative database compared with before COVID-19. These strengths increased the validity and reliability of our findings for influenza hospitalizations, as laboratory-confirmed influenza hospitalization is generally the most specific vaccine effectiveness endpoint [26,27].

Future research should focus on applying previously described techniques to better adjust for confounding [28,29]. Additional research is warranted in subsequent years of HD-QIV use in France, though such research should proceed with caution, as PCR testing practices in hospitals is not likely to regress post-COVID-19 pandemic and broader hospitalization endpoints may continue to be impacted by the observed ‘triple epidemic’ of influenza, SARS-CoV-2 and Respiratory Syncytial Virus (RSV) viruses co-circulating during winter, as observed during the 2022/2023 season in France, causing a substantial burden on hospitals.

In conclusion, HD-QIV was associated with a 23.3% (95% CI, 8.4–35.8) lower rate of influenza hospitalizations compared with SD-QIV. This first assessment of HD-QIV in France provides an overview of its performance in real-world settings. These critical findings build on existing evidence and provide further evidence of the important clinical benefit of HD-QIV [6].

Table 3
Non-influenza specific post vaccination outcome rates identified in primary diagnosis, excluding COVID-19 codes

Hospitalization outcomes	HD-QIV event rate per 100 000 person years	SD-QIV event rate per 100 000 person years	IRR HD-QIV vs. SD-QIV (95% CI)	rVE (95% CI)	p value
Pneumonia	701.02 (668.15–735.52)	681.99 (665.61–698.78)	1.03 (0.97–1.09)	–3.03 [–9.37 to 2.95]	0.3280
Pneumonia and/or influenza	770.49 (735.99–806.61)	772.52 (755.07–790.38)	1.00 (0.94–1.06)	0.10 [–5.73 to 5.61]	0.9720
Respiratory	942.69 (904.45–982.56)	922.91 (903.81–942.41)	1.02 (0.97–1.08)	–2.40 [–7.86 to 2.79]	0.3719
Cardiovascular	4078.98 (3998.56–4161.01)	3966.88 (3927.08–4007.09)	1.03 (1.00–1.06)	–2.87 [5.66 to –0.16]	0.0376
Cardiorespiratory	4858.74 (4770.90–4948.20)	4750.02 (4706.45–4793.99)	1.02 (1.00–1.05)	–2.42 [–4.97 to 0.06]	0.0557

HD, high-dose; IRR, incidence rate ratios; QIV, quadrivalent influenza vaccine; rVE, relative vaccine effectiveness; SD, standard dose.

Table 4
Sensitivity analysis for non-influenza-specific hospitalization outcomes during the peak influenza season

Hospitalization outcomes	HD-QIV event rate per 100 000 person years	SD-QIV event rate per 100 000 person years	IRR HD-QIV vs. SD-QIV (95% CI)	rVE (95% CI)	p value
Pneumonia	190.31	191.34	1.00 (0.89– 1.11)	0.38 [–11.24 to 10.79]	0.9457
Pneumonia and/or influenza	242.94	263.70	0.92 (0.84– 1.02)	7.79 [–1.64 to 16.34]	0.1025
Respiratory	294.72	311.91	0.95 (0.87– 1.03)	5.38 [–3.41 to 13.42]	0.2226
Cardiovascular	1191.53	1185.04	1.01 (0.96–1.05)	–0.51 [–5.18 to 3.96]	0.8267
Cardiorespiratory	1437.41	1451.57	0.99 (0.95–1.03)		0.6435

HD, high-dose; IRR, incidence rate ratios; QIV, quadrivalent influenza vaccine; rVE, relative vaccine effectiveness; SD, standard dose.

Author contributions

H.B., M.-C.L., N.A., B.G., K.M. and F.G.: contributed to the study design, statistical analysis plan, data analysis, and interpretation of results. H.B., R.C.H. and A.C.: contributed to the development of outline and manuscript writing. P.C., A.D., J.G., G.G., O.L. and L.W.: participated in the review of the study analysis plan and critically reviewed the results. N.A.: led the writing of the statistical analysis plan, data management, and ran the analysis. All co-authors reviewed the manuscript and agreed with the content of the manuscript.

Transparency declaration

H.B., M.C.L., R.C.H. and A.C. are Sanofi employees and may hold shares in the company. N.A., B.G. and F.R. are HEVA employees, which received funding from Sanofi to run the study. P.C. reports to have participated in advisory committees organized by Sanofi and being a consultant for Sanofi. J.G. reports to have participated in advisory committees organized by GSK, MSD, Pfizer, and Sanofi. G.G. reports to have participated in advisory committees organized by Astellas, AstraZeneca, BioMérieux, MSD, Pfizer, Sanofi, Sanofi Pasteur, Sanofi Pasteur-MSD, and Vifor, acted as consultant and speaker for these companies, and participated in congresses on invitation by Eisai, MSD, Novartis, Pfizer, Sanofi, and Vifor. O.L. reports to be a principal investigator in vaccine trials sponsored by Sanofi, MSD, Pfizer, GSK, and Moderna. She received financial support for travel to medical congress and personal fees for participation in advisory boards for Sanofi, MSD, Pfizer, and GSK. A.M. reports to have participated as an employee without personal funding to advisory committees organized by Sanofi and Viatrix and to be a member of the influenza group from SFM. She received funding to attend scientific conferences. L.W. received personal fees for participation in advisory boards for Sanofi, Pfizer, and Heva. The manuscript is a part of the QHD00030 study that was fully funded by Sanofi.

Data availability

The data that support the findings of this study are available from the French national health insurance information system, but

restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cmi.2024.08.012>.

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