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A Nationwide Retrospective Cohort Study to Assess the Relative Vaccine Effectiveness of High-dose Compared to Standard-dose Influenza Vaccines in France During the 2022-2023 Season

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Background and Objective

Background

- High-Dose (HD) influenza vaccine is an egg-based inactivated vaccine containing 60µg of HA for each strain, i.e. 4-fold HA content of the conventional Standard-Dose (SD) vaccine. In a pivotal randomized controlled trial, HD demonstrated a significant superior rVE of 24.2% (9.7–36.5%) vs SD in preventing laboratory-confirmed influenza[1]
- A high-dose quadrivalent influenza vaccine (HD-QIV) was introduced as an alternative to the standard dose (SD-QIV) for French adults aged ≥65 years during the 2021/22 flu season[2]
- During the 2021/22 season in France, HD-QIV influenza vaccine was shown to offer improved protection against influenza-related hospitalizations vs SD-QIV in older adults in real-world setting (rVE: 23.3% [8.4–35.8%])

Objective

This retrospective cohort study estimated the rVE of HD vs SD against hospitalizations in a real-world setting in France in 2022/2023 season

Methods

Methods (1/2)

Design

- National retrospective cohort study using French health insurance database linked to hospital administrative database (SNDS)

Study Duration

- *Vaccination period: September* 1 2022 to March 31 2023
- *Follow up period:* Vaccination day to June 30 2023

Study Treatment

- HD-QIV or SD-QIV

Study Population

- Adults aged ≥65 years in the community at start of the season

Outcomes*

- **Influenza specific hospitalizations** (ICD-10 discharge codes for influenza)
- **Non-Influenza specific hospitalizations** (ICD-10 discharge codes for pneumonia, P/I, respiratory, cardiovascular, cardiorespiratory)

*Hospitalizations with associated COVID-19 diagnosis code were excluded

Covariates

- Sociodemographic, clinical characteristics at baseline, health care seeking behaviors proxy identified using hospitalizations, medical procedures, or medication dispensing in the past 5 years

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Methods (2/2)

Statistical analysis

HD and SD recipients were matched using a 1:4 propensity score, with an exact constraint on age group, sex, region and week of vaccination

Sensitivity analyses:

- Variations of outcome definition to account for primary/non primary discharge codes position & inclusion of hospitalizations with associated COVID-19 diagnosis
- Restricting analysis to peak influenza season (November 19 2022 to January 22 2023)
- Negative control outcomes analysis: To assess for residual bias due to unmeasured confounders using as negative controls for hospitalizations due to UTI, Erysipelas, Cataract

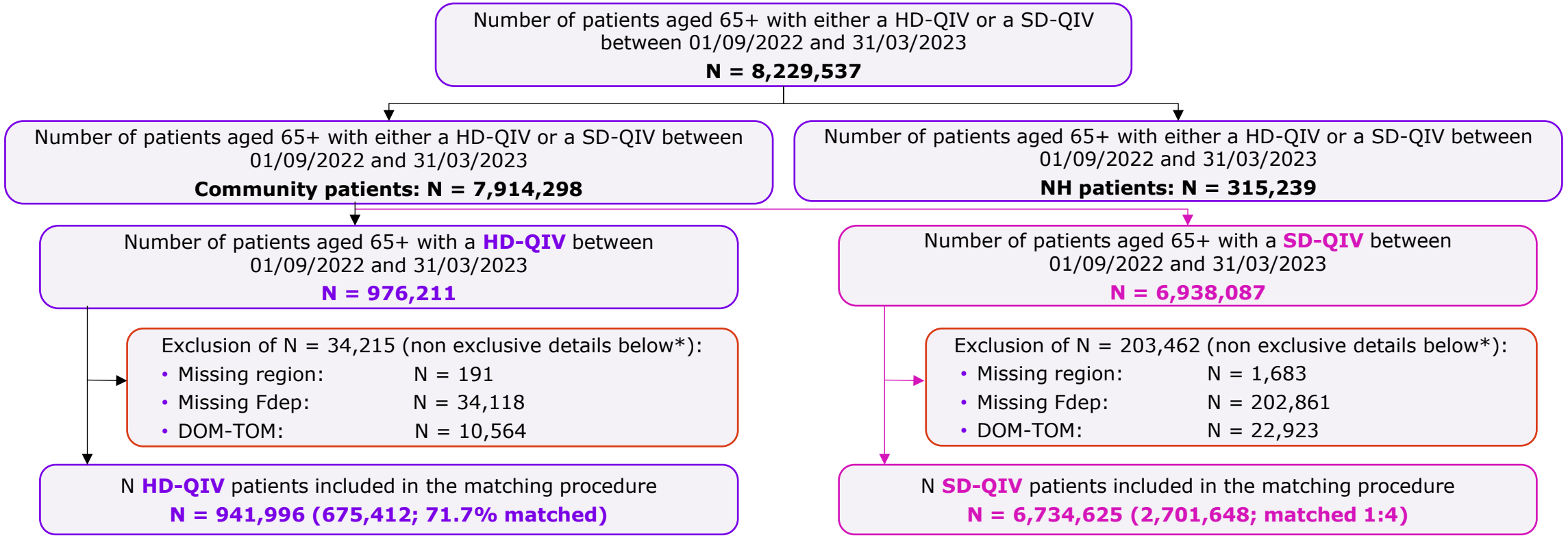
Stability analysis: To perform rVE analyses using classical logistic regression on all variables included in the propensity score

Results

Results

- A total of 976,211 individuals received HD-QIV and 6,938,087 SD-QIV of which 675,412 HD-QIV vaccinees were matched to 2,701,648 SD-QIV vaccinees in 1:4 ratio

Figure 1. Flowchart of study cohort



Regarding the exclusions, the details are non-exclusive: i.e. a patient could have been excluded for a missing Fdep and residing in the DOM-TOM

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Baseline characteristics: Matched population – Community 2022/2023 (1/2)

Overall, HD-QIV and SD-QIV recipients were well-balanced, though HD recipients differed marginally:

- Had a higher proportion of women
- Presented with less favourable outcomes
- Were more frequently vaccinated at pharmacies
- Had a higher prevalence of comorbidities
- Had more comorbidities

Table 1. Baseline characteristics – matched population

	HD-QIV N = 675,412	SD-QIV N = 2,701,648	Std Differences
Baseline characteristics			
Age, mean (± STD)	76.83 (7.68)	76.78 (7.73)	0.0066
Sex, N **women** (%)	371,550 (55.01)	1,486,200 (55.01)	0
Patients with at least one LTD (long-term disease) status, N (%)	341,113 (50.50)	1,328,099 (49.16)	0.0105
Reasons for end of follow-up, n (%)			
Death	12,354 (1.83)	45,393 (1.68)	
End of follow-up	659,715 (97.68)	2,643,553 (97.85)	
Health care seeking behaviors proxy			
All-cause hospitalization in the past 12 months (proxy for health status), mean (STD)	0.14 (0.99)	0.13 (0.99)	0.0043
General practitioner (GP) visits in the past 12 months (proxy for health status), mean (STD)	5.80 (4.42)	5.73 (4.38)	0.0153
Influenza vaccination at pharmacy, n (%)	326,738 (48.38)	1,300,091 (48.12)	0.0051
Influenza vaccination during the previous season, n (%)	620,982 (91.94)	2,478,557 (91.74)	
COVID vaccinated, n (%)	657,801 (97.39)	2,632,920 (97.46)	
Pneumococcal vaccination in the previous 5 years, n (%)	82,789 (12.26)	323,832 (11.99)	
Events occurring during the 5 years prior index date, N (%)			
Diabetes	141,985 (21.02)	558,016 (20.65)	0.009
Obesity and/or history of obesity surgery	55,830 (8.27)	216,516 (8.01)	0.0092
Undernourishment/or history of undernourishment	40,626 (6.01)	157,605 (5.83)	0.0077
COPD/Asthma	82,238 (12.18)	320,773 (11.87)	0.0093
Dementia	18,039 (2.67)	67,799 (2.51)	0.0102
Cardiovascular diseases	188,455 (27.90)	732,952 (27.13)	0.0173
Immunocompromised subjects	128,518 (19.03)	499,107 (18.47)	0.0142
Chronic liver disease	10,683 (1.58)	41,777 (1.55)	0.0028
Terminal chronic kidney failure	3,242 (0.48)	12,553 (0.46)	0.0022
Medical diseases or conditions reported during the 5 years preceding the index date, n (%)			0.0228
None	302,797 (44.83)	1,250,066 (46.27)	
1	217,462 (32.20)	849,080 (31.43)	
2	97,773 (14.48)	379,766 (14.06)	
3	38,282 (5.67)	148,363 (5.49)	
4	13,458 (1.99)	52,144 (1.93)	
5	4,200 (0.62)	16,419 (0.61)	
6+	1,440 (0.21)	5,810 (0.22)	

*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)

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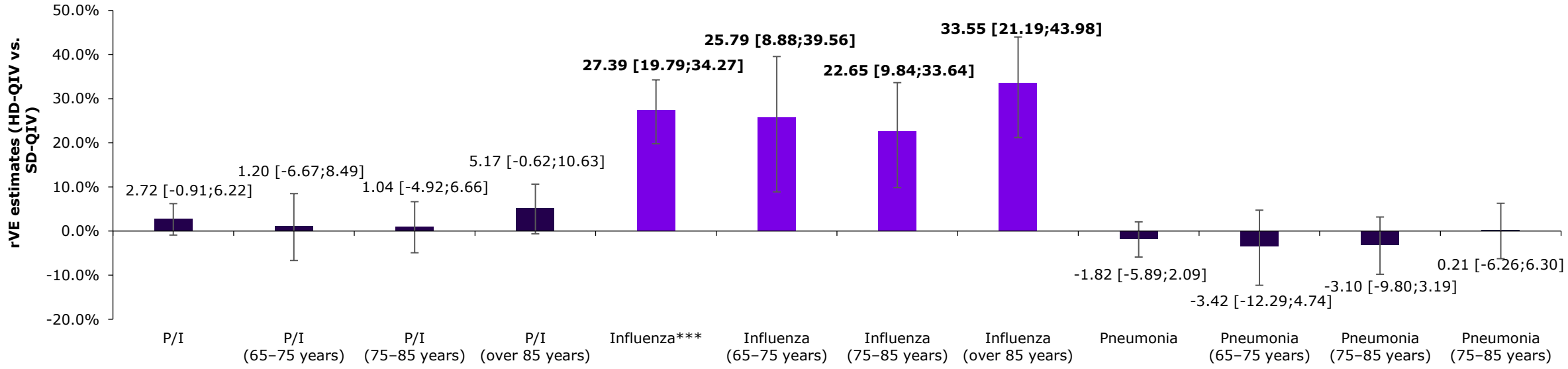
Results

Main analysis and complementary analysis results

- Crude IRR showed a HD-QIV was associated with **27.39%** (95% CI: 19.79−34.27) relative reduction in influenza hospitalizations vs SD-QIV
- No significant difference between HD-QIV and SD-QIV was observed on non influenza specific hospitalizations endpoints, except on cardiovascular hospitalizations with a crude rVE = **-**2.93 (95% CI: **-**5.07;-0.83). The results post adjustment showed significant difference on all non influenza specific hospitalizations endpoints and systematically drove the results in favour of HD up to 3 percentage points
- Higher outcome rates in HD recipients, even after matching, suggests some residual bias due to unmeasured confounding

Figure 2. Relative vaccine effectiveness (rVE) of HD compared to SD in matched cohort



Miracle purple: non-significant results, Chasing purple: in favor of HD, bold***: significant results (AFTER Bonferroni): *= *p*-value<0.05 / **=*p*-value<0.01 / ***=*p*-value<0.001

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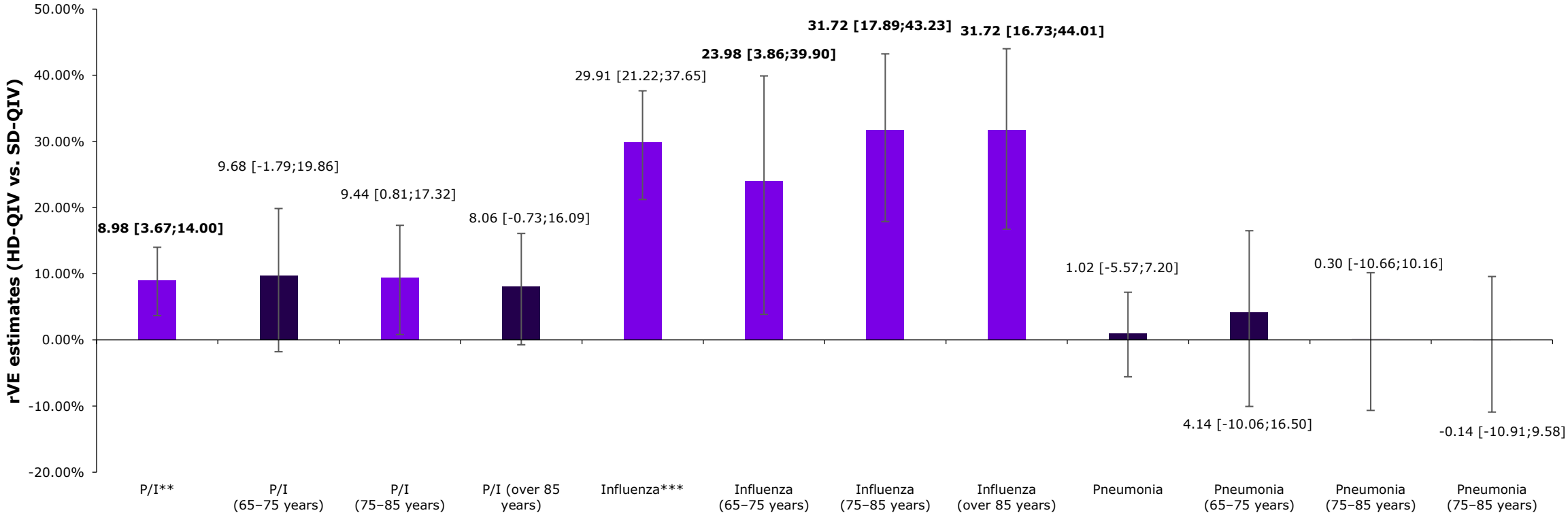
Sensitivity analysis (1/2)

Figure 3. Sensitivity analysis: Season peak (W47 to W03) P/I, Influenza, Pneumonia by age groups



Deep purple: non significant results, Chasing purple: in favor of HD, turquoise: in favor of SD, bold***: significant results (AFTER Bonferroni): *= *p*-value<0.05 / **=*p*-value<0.01 / ***=*p*-value<0.001

Sensitivity analysis (2/2)

Influenza specific hospitalization

Results were robust to all sensitivity analysis with HD associated with fewer influenza hospitalizations

Non influenza specific hospitalizations

Results were sensitive to the outcome definition & time horizon (peak) indicative of confounding

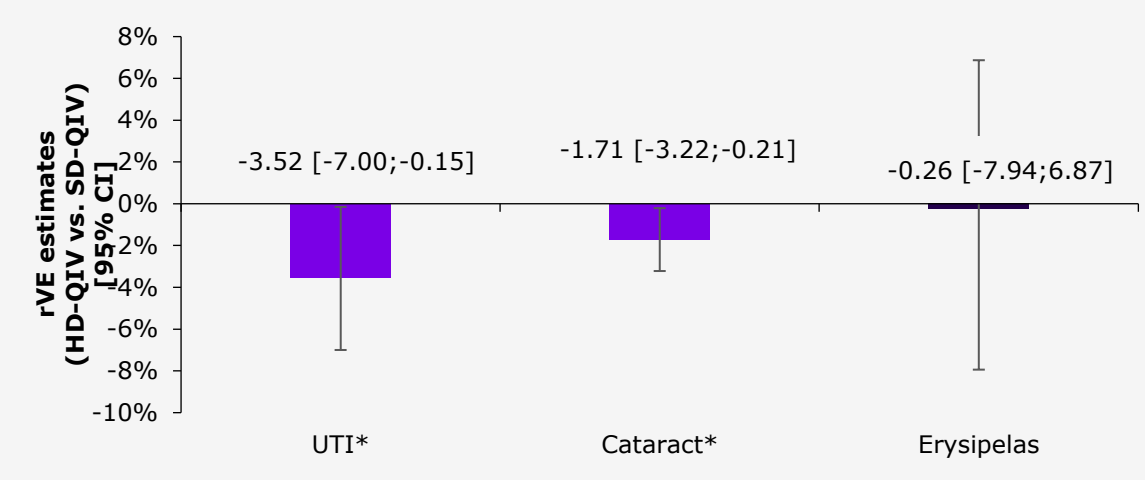
Negative control outcomes

Non-significant differences; point estimates all trending in same direction indicating that the possibility of residual confounding cannot be excluded

Table 2. Influenza specific hospitalization outcomes

Influenza specific hospitalization	rVE (95%CI)	*p*-value
Main analysis	27.39 [19.79;34.27]	<0.0001
Primary/non-primary discharge position	19.07 [12.37;25.27]	<0.0001
Outcomes with a COVID-19 code	27.14 [19.57;33.99]	<0.0001
During peak of the season	29.91 [21.22;37.65]	<0.0001

Figure 4. Negative control outcomes



Deep purple: non-significant results, Chasing purple: in favor of HD; bold***: significant results (AFTER Bonferroni): *= p-value<0.05 / **=p-value<0.01 / ***=p-value<0.001

Discussion

Discussion

Limitations[2]

Confounding by indication: HD prioritized for older/with multiple comorbidities individuals (SFGG reco)

Remaining unmeasured confounding cannot be ruled out: Negative control outcomes analysis results, database observational studies

Epidemiology: Long and severe 22/23 season & SARS-CoV2 co circulation

5% α risk: Considering the **large sample**, any significant small effect sizes to be interpreted with caution

Strengths[2]

Large study: 8 millions aged ≥65 years were vaccinated, all HD-QIV doses reimbursed captured (405,735 doses)

PCR testing against influenza was widely used, improving **specificity of influenza coding** during hospital discharge record coding[3]

The observed HD-QIV rVE on influenza hospitalizations in this observational context is **in line with findings from RCTs & meta-analysis**

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Conclusion

Conclusion

- HD-QIV showed a superior clinical benefit on the reduction of influenza hospitalizations compared to SD-QIV in real-world setting. Results are consistent with 2021/22 analysis[2]
- In a context of triple epidemic and long epidemic during 2022/23 winter, the use of a differentiated vaccine adapted to adults ≥65 years could help reduce respiratory infections related burden
- These findings provide further evidence of the important clinical benefit of high dose vaccines and add on to existing evidence across 12 influenza seasons & over 45 million in adults aged ≥65 years in both randomized and observational studies[4]

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Abbreviations, References, Funding and Acknowledgements

Abbreviation:
CI, confidence interval; DOM-TOM, French overseas departments and territories; Fdep, French social deprivation index; HD-QIV, High dose-quadrivalent influenza vaccine; ICD, international classification of disease; IRR, incidence ratio; HA, hemagglutinin; PCR: polymerase chain reaction; P/I, pneumonia and influenza; rVE, relative vaccine effectiveness; RCTs: randomized control trials; SD-QIV, standard dose-quadrivalent influenza vaccine; SFGG, Société Française de Gériatrie et Gérontologie; SNDS, Système National des Données de Santé, STD, standard deviation; UTI, urinary tract infections

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Thank You

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