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BRICOUT Hélène - Oral presentation : O-048

A Nationwide Retrospective Cohort Study To Assess The Relative Vaccine Effectiveness Of High-Dose Compared To Standard Dose Influenza Vaccines In 65+ Adults In France During The 2022-2023 Season

CONFLICT OF INTEREST DISCLOSURE

I have the following potential conflict of interest to report
- I’m a Sanofi employee

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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 influenza vaccine was shown to offer improved protection against influenza-related hospitalizations vs SD in older adults in a 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 in community setting

- Exploratory : in nursing home setting

1. Diaz Granados C.A. et al. *N Engl J Med.* 2014; 371:635-645.
2. Bricout H et al. *Clinical Microbiology and Infection*. 2024 Aug;S1198743X24004105.

Methods

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:* 1 Sept 2022 to June 30, 2023

Study Treatment

- HD or SD

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

Methods – 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 residual bias due to unmeasured confounders using hospitalizations for UTI, Erysipelas and Cataract as negative control outcomes

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

Flowchart

8,229,537 individuals aged 65+ with either a HD or a SD between 01/09/2022 and 31/03/2023

7,914,298 individuals aged ≥65 years living in the community and **receiving an influenza vaccine** during 2022/23 season in France

976,211 received HD — **6,938,087** received SD

315,239 individuals aged ≥65 years living in nursing home and **receiving an influenza vaccine** during 2022/23 season in France

123,720 received HD — **191,519** received SD

7,676,621 were included in the matching procedure after applying exclusion criteria*

941,996 received HD — 6,734,625 received SD

7,676,621 were included in the matching procedure after applying exclusion criteria*

121,147 received HD — 187,477 received SD

After matching 1:4, the analysis population was:

405,385 received HD — 1,621,540 received SD

After matching 1:1, the analysis population was:

76,858 received HD — 76,858 received SD

* living in overseas departments, study outcome between season beginning and vaccination date +14 days, missing data on region or deprivation index, 21/22 influenza vaccines received or vaccinated twice during the season

Baseline characteristics: Matched population in community

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

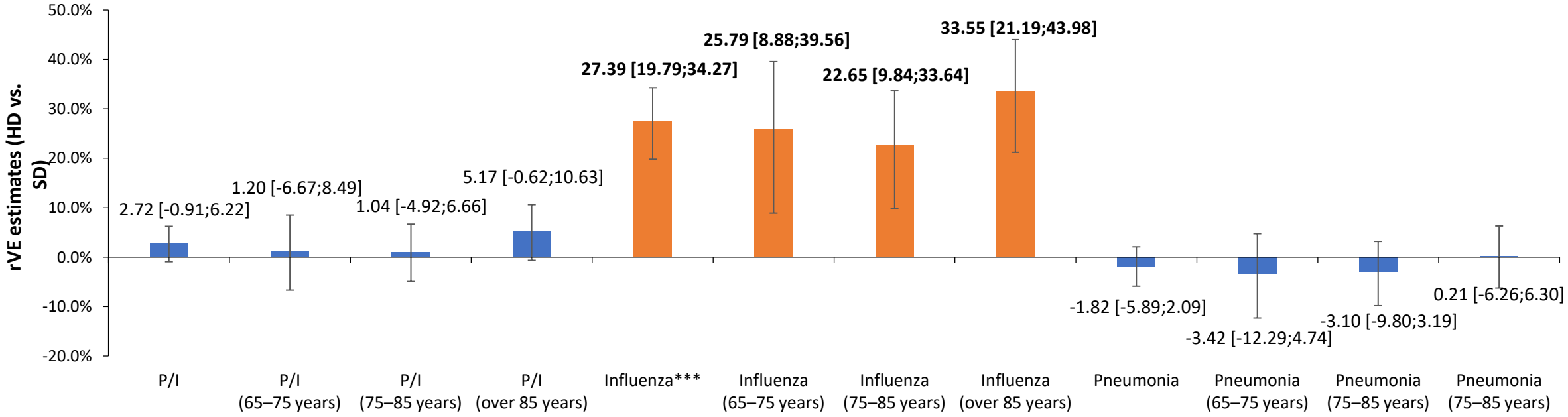
- Presented with less favourable outcomes
- Had a higher prevalence of comorbidities
- Had more comorbidities

	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, %	55.01	55.01	0
Patients with at least one LTD (long-term disease) status, %	50.50	49.16	0.0105
Reasons for end of follow-up, %			
Death	1.83	1.68	
End of follow-up	97.68	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, %	48.38	48.12	0.0051
Influenza vaccination during the previous season, %	91.94	91.74	
COVID vaccinated, %	97.39	97.46	
Pneumococcal vaccination in the previous 5 years, %	12.26	11.99	
Events occurring during the 5 years prior index date, %			
Diabetes	21.02	20.65	0.009
COPD/Asthma	12.18	11.87	0.0093
Cardiovascular diseases	27.90	27.13	0.0173
Immunocompromised subjects	19.03	18.47	0.0142
Medical diseases or conditions reported during the 5 years preceding the index date, %			0.0228
None	44.83	46.27	
1	32.20	31.43	
2	14.48	14.06	
3	5.67	5.49	
4	1.99	1.93	
5	0.62	0.61	
6+	0.21	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)

HD was associated less influenza hospitalizations vs SD in community

- In the matched cohorts, HD was associated with **27.39% (95% CI: 19.79–34.27)** relative reduction in influenza hospitalizations (main diagnosis position, COVID19 excluded) vs SD
- This **benefit is largely conserved in all age groups**, even in the 85+ with a rVE of 33.55%
- No significant difference between HD and SD was observed on P&I and pneumonia hospitalisations respectively



Blue: non-significant results, Orange: in favor of HD, bold***: significant results (AFTER Bonferroni-Holm correction); *= *p*-value<0.05 / **=*p*-value<0.01 / ***=*p*-value<0.001

Sensitivity analysis - community

Influenza specific hospitalization

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

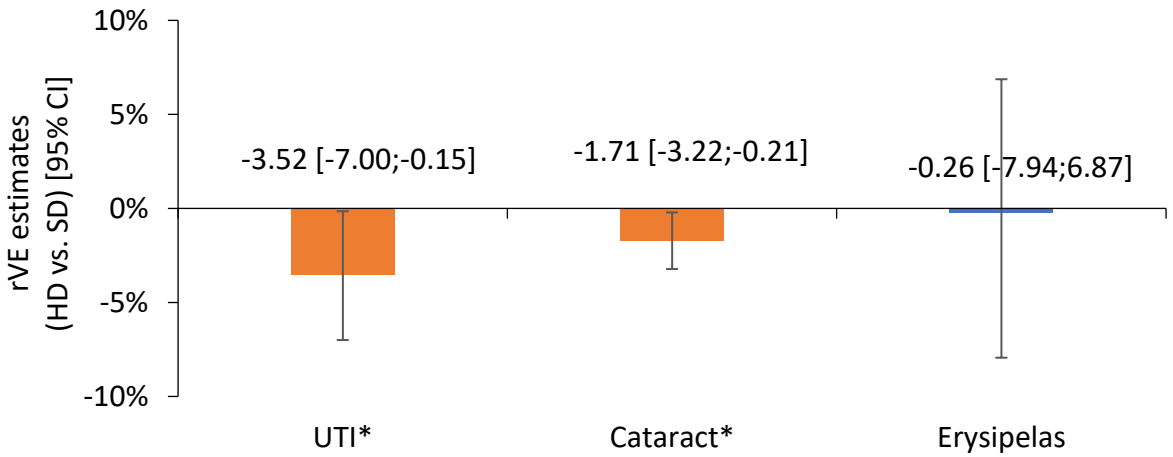
Non influenza specific hospitalizations

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

Negative control outcomes

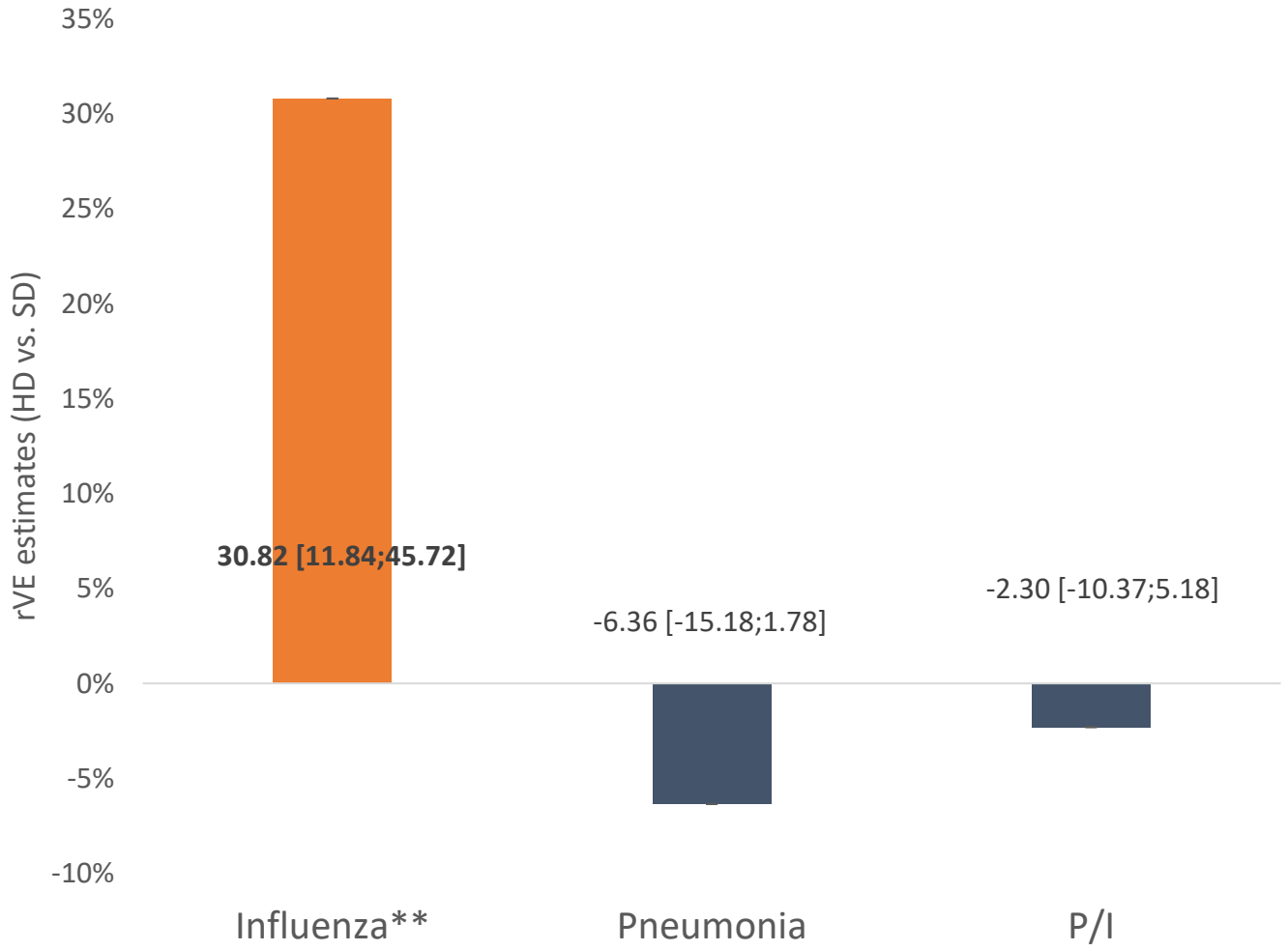
Significant differences likely indicated the presence of residual confounding

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
Primary outcome 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



Exploratory analysis – nursing home setting

- 76,858 HD recipients were matched 1:1 to 76,858 SD.
- In the matched cohorts, the incidences of hospitalization for pneumonia and P&I didn't differ between the two groups.
- HD vaccination was associated with a significant decrease of **30.82% (95%CI 11.84; 45.72; p<0,05)** in hospitalizations for influenza versus SD.



Discussion

Limitations

Confounding by indication: HD prioritized for older/with multiple comorbidities individuals (SFGG reco guideline, pharmacist' choice)

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

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

Large study: ~8 millions aged ≥65 years were vaccinated, all HD doses reimbursed captured (976,211 doses)

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

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

Conclusion

- HD showed a superior clinical benefit on the reduction of influenza hospitalizations compared to SD in a real-world setting, observed in community & nursing home setting, and consistent across age groups. Results are consistent with 2021/22 analysis[1]
- In a context of triple epidemic (Influenza, COVID-19 and RSV) 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[2]

1. Bricout H et al. *Clinical Microbiology and Infection*. 2024 Aug;S1198743X24004105.
2. Lee J.K.H. et al. *Vaccine X*. 2023;14:100327.

Thank you !

Abbreviations, References, Funding

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

References:

1. Diaz Granados C.A. et al. *N Engl J Med.* 2014; 371:635-645.
2. Bricout H et al. *Clinical Microbiology and Infection*. 2024 Aug;S1198743X24004105.
3. HAS. Haute Autorité de Santé - Distinguer la grippe de la COVID-19 : dans quelles situations et avec quels tests ? (has-sante.fr) (Assessed August 2024)
4. Lee J.K.H. et al. *Vaccine X*. 2023;14:100327.

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