A Nationwide Retrospective Cohort Study to Assess the Relative Vaccine Effectiveness of High-dose Compared to Standard Dose Influenza Vaccines in France During the 2021-2022 Season: Results of a Complementary Analysis of DRIVEN Study

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INTRODUCTION

- HD is an egg-based inactivated influenza vaccine containing 60µg of HA for each strain, i.e. 4-fold HA content of a 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]
- In 2021- 2022, the HD vaccine was first introduced under the French national immunization programme as an alternative to SD for adults aged ≥65 years[2]

OBJECTIVE

- This retrospective cohort study estimated the rVE of HD vs SD against influenza-related hospitalizations in a real world setting in France in this first season of use, 2021/2022 season

METHODS

Design

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

Study Treatment

- HD or SD influenza vaccines

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)

Study Duration

- Vaccination period: 1st Sept 2021 to 28th Feb 2022
- Follow up period 1st Sept 2021 to 28th Feb 2022

Study population

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

Covariates

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

Statistical analysis

HD and SD recipients were matched using a 1:4 propensity score, with an exact constraint on selected (age group, sex, region and week of vaccination +/- 1 week) variables

Considering potential remaining confounders in the main analysis[2], **a complementary analysis was done using regression models adjusted for number of comorbidities and vaccine administration at pharmacy to estimate the adjusted incidence rate ratios for HD vs. SD hospitalizations.** The scientific committee suggested this analysis & those 2 variables were selected based on remaining differences between the 2 cohorts after matching (>1% difference post matching, even if not significant).

Sensitivity analyses

- Variations of outcome definition to account for primary/non primary discharge codes position & for COVID involvement in admission
- Restricting analysis to peak influenza season (Feb 28th to May 1st 2022)

Study cohort selection

77,832,853 individuals aged ≥65 years living in the community and **receiving an influenza vaccine during 2021/22 season in** France)

431,643 received HD — **7,401,210** received SD

7,396,968 were included in the matching procedure after applying exclusion criteria (i.e. living in overseas departments, study outcome between season beginning and vaccination date +14 days, missing data on region or deprivation index, 20/21 influenza vaccines received or vaccinated twice during the season)

431,643 received HD — **6,991,233** received SD

After **matching 1:4**, the analysis population was:

405,385 HD recipients (99.9% were successfully matched) — **1,621,540** SD recipients

RESULTS

Description of the population

Unmatched cohorts

- At baseline, HD recipients were older than SD recipients, and had a significantly higher prevalence of most comorbidities of interest and of multiple comorbidities.
- During the follow-up period, they also experienced more severe outcomes post-hospitalization (**Table 1.**)

Table 1. Baseline characteristics

Characteristics	HD	SD
Number of individuals	4,31,643	74,01,210
Age, mean (± STD)	77.4 (7.9)	75.9 (7.7)
Women, n (%)	55.9	54.4
Reasons for end of follow up, n (%)		
Death	2	1.5
End of follow-up	97.7	98.2
Health care seeking behaviors proxy		
All-cause hospitalization in the past 12 months, mean (±STD)	0.1 (±0.8)	0.1 (±0.9)
GP visits in the past 12 months, mean (±STD)	6.2 (±4.8)	5.9 (±4.6)
Influenza vaccination at pharmacy, n (%)	50.5	42.6
Influenza vaccination during the previous season, n (%)	91.3	90.1
COVID-19 vaccinated*, n (%)	93.1	93.6
Pneumococcal vaccination in the previous 5 years, n (%)	11.7	11.4
Medical conditions during the 5 years prior index date, n (%)		
Diabetes	19.7	19.4
COPD/Asthma	11.7	11.5
Cardiovascular diseases	27.7	26
Immunocompromised individuals	18.4	18.1
Number of chronic diseases, n (%)		
None	45.2	47.6
1	32.2	31.4
2	14.4	13.5
3	5.4	5.1
4	1.9	1.7
5	0.6	0.5
6	0.2	0.2

The differences between all the variables for HD and SD vaccines were significant (p<0.0001)

*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)

Matched cohort

- Standard differences showed good balance for all variables included in the matching procedure (i.e. Absolute value of standard difference <0.1)
- After matching, individuals had similar measured characteristics, though in the HD group compared with the SD group, there was an unsignificant trend of:
  - higher prevalence of chronic diseases (i.e. 27.9% cardiovascular diseases for HD vs 26.7% for SD)
  - higher prevalence of multiple chronic diseases (55.0% for HD with at least 1 comorbidity vs 51.8% for SD)
  - higher death rates (1.9% for HD vs 1.6% for SD)

Main analysis and complementary analysis results

- Crude IRR showed a reduction of **23.3% (95%CI: 8.4;35.8)** in influenza hospitalizations rates for HD vs. SD (primary discharge position, excluding COVID-19 code). **Adjustment resulted in a rVE of 24.9% (10.2;37.2)** (**Table 2.**)
- No significant difference between HD and SD was observed on non influenza specific hospitalizations endpoints, except on cardiovascular hospitalizations with a crude rVE = -2.87 (-5.66; -0.16). The results post adjustment showed no significant difference on all non influenza specific hospitalizations endpoints and systematically drove the results in favor of HD up to 3 percentage points
- Post matching there remains evidence of residual bias due to confounding by indication

Table 2. Hospitalization outcomes

Study Outcomes	Main analysis			Complementary analysis*		
	IRR HD vs SD (95% CI)	arVE % (95% CI)	*P*-value	aIRR HD vs SD	arVE % (95% CI)	*P*-value
Influenza hospitalizations	**0.77 (0.64;0.92)**	**23.29 (8.38;35.77)**	**0.0034**	**0.75 (0.63;0.90)**	**24.91 (10.19;37.21)**	**0.0017**
Pneumonia hospitalizations	1.03 (0.97;1.09)	-3.03 (-9.37;2.95)	0.328	1.00 (0.94;1.06)	0.22 (-5.95;6.03)	0.9434
Pneumonia and/or influenza hospitalizations	1.00 (0.94;1.06)	0.10 (-5.73;5.61)	0.972	0.97 (0.92;1.03)	3.08 (-2.61;8.45)	0.2824
Respiratory hospitalizations	1.02 (0.97;1.08)	-2.40 (-7.86;2.79)	0.3719	0.99 (0.94;1.04)	1.04 (-4.25;6.07)	0.6938
Cardiovascular hospitalizations	**1.03 (1.00;1.06)**	**-2.87 (-5.66;-0.16)**	**0.0376**	1.00 (0.98;1.03)	-0.13 (-2.83;2.50)	0.9237
Cardio-respiratory hospitalizations	**1.02 (1.00;1.05)**	**-2.42 (-4.97;0.06)**	**0.0557**	1.00 (0.97;1.02)	0.36 (-2.09;2.76)	0.769

*Adjustment for number of comorbidities and vaccine administration at pharmacy

Sensitivity analysis

Influenza specific hospitalization

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

Table 3. Influenza specific hospitalization outcomes

Influenza specific hospitalization	Main analysis		Complementary analysis*	
	rVE (95% CI)	*P*-value	arVE (95% CI)	*P*-value
Main analysis	**23.29% (8.38;35.77)**	**0.003**	**24.91 [10.19;37.21]**	**0.0017**
Primary/non-primary discharge position	**21.43% (9.28;31.96)**	0.001	**23.89 [12.01;34.16]**	0.0002
Outcomes with a COVID-19 code	**23.61% (8.88;35.96)**	0.003	**25.32 [10.79;37.49]**	0.0013
During peak of the season	**27.38% (11.05;40.70)**	0.002	**29.52 [13.53;42.56]**	0.0008

*Adjustment for number of comorbidities and vaccine administration at pharmacy

Non Influenza specific hospitalization

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

Discussion

Strengths

- **Large study:** 8 millions of people aged
- ≥65years vaccinated, all HD doses reimbursed captured (405,735 doses)
- PCR testing against influenza was widely used, improving **specificity of influenza coding** during hospital discharge record coding3
- The observed HD rVE on influenza hospitalizations in this observational context is **in line with findings from randomized controlled trials & meta-analysis**

Limitations

- **Confounding by indication:** HD prioritized to older/with multiple comorbidities individuals (SFGG recommended)
- **Remaining unmeasured confounding cannot be ruled out** due to observational nature of the analysis
- **Epidemiological pattern:** atypical viral epidemiology in 21/22 & SARS-CoV2 co circulation

CONCLUSION

- HD influenza vaccine was associated with **23.3% (95% CI: 8.4–35.8) fewer hospital admissions** due to influenza compared to SD in real word setting
- These findings provide further evidence of the important clinical benefit of HD 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]
- In the complementary analysis, **adjustment results trends were in favor of unmeasured residual confounders,** potentially led by **HD being dispensed to frailer individuals** for the first season of use

ABBREVIATIONS

aIRR, adjusted incidence ratio rate; arVE, adjusted relative vaccine efficacy; CI: confidence interval; COPD: chronic obstructive pulmonry disease; GP: general practitioner; ; HA: hemagglutination; HD: high dose inactivated influenza vaccineICD, international classification of disease; IRR, incidence ratio rate; PCR: polymerase chain reaction; P/I: pneumonia and/or influenza; rVE: relative vaccine efficacy; SD: standard dose influenza vaccine; SFGG: Société Française de Gériatrie et Gérontologie; SNDS: Système National des Données de Santé; STD, standard deviation

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CONFLICTS OF INTEREST

- HB, MCL, MD, RCH and AC are Sanofi employees and may hold shares in the company
- OL reports to be a principal investigator in vaccine trials sponsored by Sanofi, MSD, Pfizer, GSK, Moderna. She received financial support for travel to medical congress and personal fees for participation in advisory boards for Sanofi, MSD, Pfizer, and GSK
- AM reports to have participated in an advisory committee organized by Sanofi and to be a member of the scientific board of the GEIG and of the POSTHER study (Herpes Zoster Study, GSK)
- LW has received consulting fees from HEVA, IQVIA and Pfizer for works outside the submitted work
- NA, BG and FR are HEVA employees, which received funding from Sanofi to run the study
- JG reports to have participated in advisory committees organized by GSK, MSD, Pfizer, and Sanofi
- PC reports to have participated in advisory committees organized by Sanofi and being a consultant for Sanofi
- GG reports to have participated in advisory committees organized by Astellas, AstraZeneca, BioMerieux, 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

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