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# Relative effectiveness (rVE) of the high-dose vs. standard-dose influenza vaccines in the French National health data system (SNDS) for people aged 65+ living in community, obtained using two approaches based on the propensity score

## CONTEXT

The High-dose (HD) vaccine is an inactivated influenza vaccine containing 60 µg of haemaglutinnin (HA) per strain, i.e. four times more HA than a standard-dose (SD) vaccine. In a pivotal randomised controlled trial, the HD vaccine demonstrated a 24.2% (9.7-36.5%) superior relative vaccine efficacy compared with the SD vaccine for the prevention of laboratory-confirmed influenza cases[1].

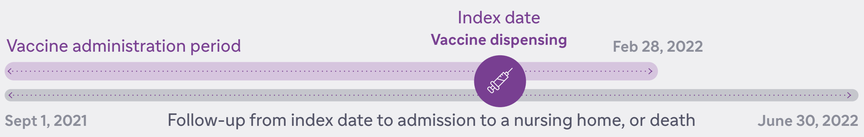
In 2021-2022, the HD vaccine was introduced for the first time as part of the French national vaccination programme as an alternative to the SD vaccine for adults aged ≥ 65 years[2].

This retrospective cohort study estimated the rVE of the HD vaccine compared with the SD vaccine against influenza-related hospitalisations in a real-life setting in France.

## METHODS

### Study design and period

Nationwide retrospective cohort study on the SNDS.




### Study population

Adults aged ≥65 years residing in community at the time of HD or SD influenza vaccine dispensing.

### Outcomes

Collected from index date + 14 days:

- Influenza-related hospitalisations (ICD-10 discharge codes in main diagnosis, excluding stays with COVID-19 codes).
- Non-influenza specific hospitalisations (ICD-10 discharge codes for pneumonia, P/I, respiratory disease, cardiovascular disease, and cardiorespiratory disease).

### Covariables

Sociodemographics, comorbidities and medical history, healthcare resource use, identified through hospitalisation, medical procedure, and/or drugs dispensings during the 5 years preceding index date.

### Statistical analyses

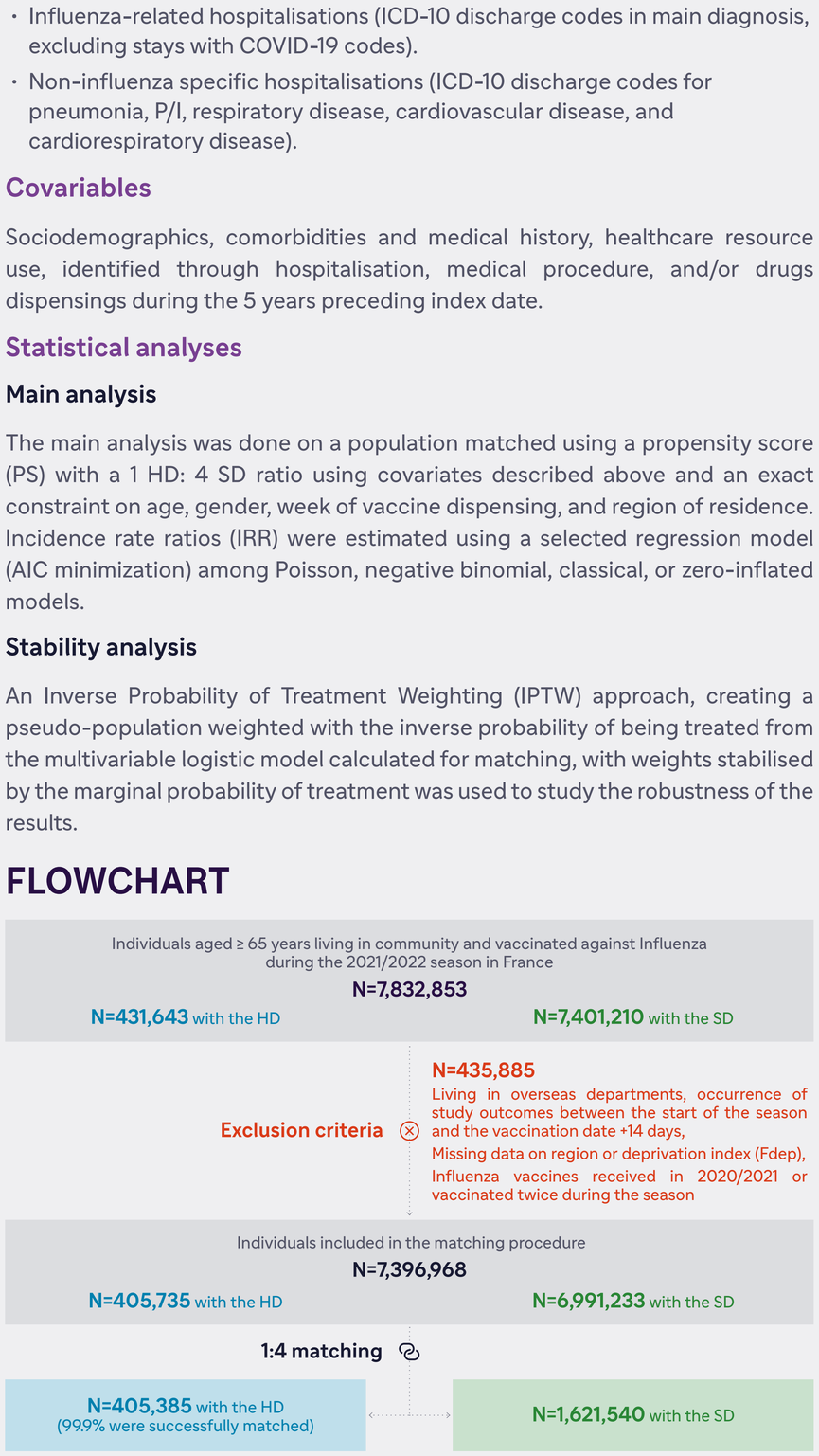
#### Main analysis

The main analysis was done on a population matched using a propensity score (PS) with a 1 HD: 4 SD ratio using covariates described above and an exact constraint on age, gender, week of vaccine dispensing, and region of residence. Incidence rate ratios (IRR) were estimated using a selected regression model (AIC minimization) among Poisson, negative binomial, classical, or zero-inflated models.

#### Stability analysis

An Inverse Probability of Treatment Weighting (IPTW) approach, creating a pseudo-population weighted with the inverse probability of being treated from the multivariable logistic model calculated for matching, with weights stabilised by the marginal probability of treatment was used to study the robustness of the results.

## FLOWCHART




## RESULTS

### Population characteristics

#### Unmatched cohorts

At inclusion, HD vaccinees were older than SD vaccinees and had a significantly higher prevalence of most comorbidities of interest and multiple comorbidities. Death was the reason for the end of follow-up in 2% of HDs and 1.5% of SDs.

**The differences between HD and SD were systematically significant, whatever the variable (p<.001).**

| | HD vaccines | SD vaccines |
|---|---|---|
| **in the last 12 months* | N=431,643 | N=7,401,210 |
| Age, Mean (SD) | 77.4 (±7.9) | 75.9 (±7.7) |
| Women | 55.9% | 54.4% |
| Death | 2.0% | 1.5% |
| Other end of follow-up motive | 98.0% | 98.5% |
| Number of all-cause hospitalisations*, mean (SD) | 0.1 (±0.8) | 0.1 (±0.9) |
| Number of visit to a GP*, mean (SD) | 6.2 (±4.8) | 5.9 (±4.6) |
| Influenza vaccination by a community pharmacist | 50.5% | 42.6% |
| Influenza vaccine dispensing (season 2020/2021) | 91.3% | 90.1% |
| COVID-19 vaccination | 93.1% | 93.6% |
| Pneumococcus vaccine dispensing in the last 5 years | 11.7% | 11.4% |
| Diabetes | 19.7% | 19.4% |
| COPD/Asthma | 11.7% | 11.5% |
| Cardiovascular diseases | 27.7% | 26.0% |
| Immunodepression | 18.4% | 18.1% |
| Number of chronic condition | | |
| 1 | 45.2% | 47.6% |
| 2 | 32.2% | 31.4% |
| 3 | 14.4% | 13.5% |
| 4 | 5.4% | 5.1% |
| 5 | 1.9% | 1.7% |
| 6 | 0.6% | 0.5% |
| 7 | 0.2% | 0.2% |

#### Matched cohorts

After matching, the individuals had similar measured characteristics. The standardised differences showed good balance for all the variables included in the matching procedure (i.e. absolute value of the standardised difference <0.1).

In the HD group compared to the SD group, there was a non-significant trend for:

- Higher prevalence of chronic diseases (e.g. 27.9% cardiovascular diseases in HD vs 26.7% in SD).
- Higher prevalence of multiple chronic diseases (55.0% of HD with at least one comorbidity vs 51.8% of SD)
- Higher mortality rate (1.9% for HD vs 1.6% for SD).

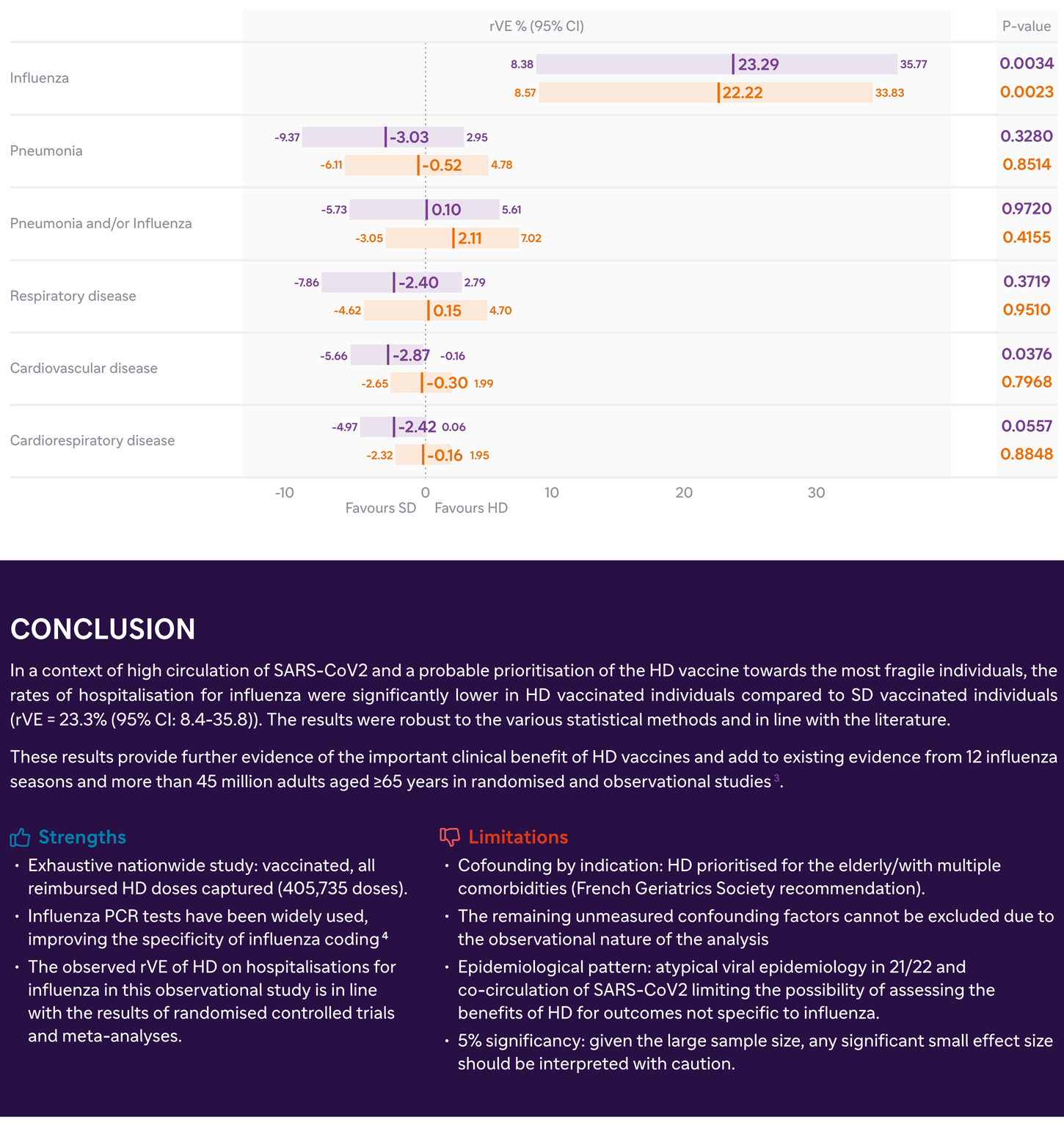
#### IPTW

The characteristics of the weighted pseudo-populations were comparable (463,665 HD and 6,923,992 SD), i.e. the standardised differences showed a good balance for all the variables included in the weighting (absolute value of the standardised difference <0.1).

### Endpoints

HD vaccination was associated with a 23.3% (8.4%;35.8%) reduction in hospital admissions for influenza compared with SD vaccinees in the main analysis (PS matching). The IPTW method led to an estimated rVE of 22.2% (8.6%;33.9%) for the prevention of hospitalisations for influenza. No significant difference between HD and SD was observed for hospitalisations not specific to influenza, except for cardiovascular hospitalisations, with an rVE of -2.9% (-5.7;-0.2%). The results using the IPTW method did not show any significant difference for non-influenza-specific hospitalisations.

**Relative vaccine effectiveness of HD vs. SD on hospitalisations**




## CONCLUSION

In a context of high circulation of SARS-CoV2 and a probable prioritisation of the HD vaccine towards the most fragile individuals, the rates of hospitalisation for influenza were significantly lower in HD vaccinated individuals compared to SD vaccinated individuals (rVE = 23.3% (95% CI: 8.4-35.8)). The results were robust to the various statistical methods and in line with the literature.

These results provide further evidence of the important clinical benefit of HD vaccines and add to existing evidence from 12 influenza seasons and more than 45 million adults aged ≥65 years in randomised and observational studies[3].

### Strengths

- Exhaustive nationwide study: vaccinated, all reimbursed HD doses captured (405,735 doses).
- Influenza PCR tests have been widely used, improving the specificity of influenza coding[4]
- The observed rVE of HD on hospitalisations for influenza in this observational study is in line with the results of randomised controlled trials and meta-analyses.

### Limitations

- Cofounding by indication: HD prioritised for the elderly/with multiple comorbidities (French Geriatrics Society recommendation).
- The remaining unmeasured confounding factors cannot be excluded due to the observational nature of the analysis
- Epidemiological pattern: atypical viral epidemiology in 21/22 and co-circulation of SARS-CoV2 limiting the possibility of assessing the benefits of HD for outcomes not specific to influenza.
- 5% significancy: given the large sample size, any significant small effect size should be interpreted with caution.

**References**

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