Effectiveness of High-dose Influenza Vaccine Against Hospitalizations in Older Adults (FLUNITY-HD): An Individual Level Pooled Analysis

Authors: Johansen ND, Modin D, Pardo-Seco J, Rodriguez-Tenreiro-Sánchez C, Loiacono MM, Harris RC, Dufournet M, van Aalst R, Chit A, Larsen CS, Larsen L, Wiese L, Dalager-Pedersen M, Claggett BL, Janstrup KH, Duran-Parrondo C, Piñeiro-Sotelo M, Cribeiro-González M, Conde-Pájaro M, Mirás-Carballal S, González-Pérez JM, Solomon SD, Sivapalan P, Martel CJ, Jensen JUS, Martinón-Torres F, Biering-Sørensen T; DANFLU-2 Study Group; GALFLU Trial Team

Journal: Lancet (Published: October 17, 2025)

Summary

FLUNITY-HD is the **largest individually randomized influenza vaccine effectiveness study,** with approximately half a million older adults over **3 seasons and 2 geographical areas,** that assessed the relative vaccine effectiveness (rVE) of high-dose inactivated influenza vaccine (HD-IIV) vs standard-dose inactivated influenza vaccine (SD-IIV) against **hospitalization**

HD-IIV demonstrated superior protection vs SD-IIV against influenza or pneumonia hospitalizations, cardio-respiratory hospitalizations, laboratory-confirmed influenza hospitalizations, and all-cause hospitalizations

BACKGROUND

The superior efficacy of HD-IIV over SD-IIV in preventing laboratory-confirmed influenza cases has been previously demonstrated in an individually randomized clinical trial[1,2]

Evidence from individually randomized, sufficiently powered studies assessing HD-IIV's effectiveness in prevention of influenza related hospitalizations and mortality has been limited[3]

FLUNITY-HD is a prespecified pooled analysis of ***two methodologically-harmonized***, pragmatic, individually randomized trials assessing the rVE of HD-IIV vs SD-IIV against severe clinical outcomes such as hospitalization

DANFLU-2, conducted in Denmark

GALFLU, conducted in Galicia (Spain) and designed based on DANFLU-2 with a priori intention of pooling the 2 trials to increase statistical power and generalizability

OBJECTIVE

To assess the rVE of HD-IIV vs SD-IIV against hospitalizations in a prespecified, individual-level pooled analysis of more than 466,000 older adults from both pragmatic trials (DANFLU-2 and GALFLU)

STUDY METHODS[1]

Study design
Pre-specified, individual-level pooled analysis of all data from two methodologically harmonized, individually randomized pragmatic trials: DANFLU-2 and GALFLU

Vaccines
HD-IIV: quadrivalent formula, 60µg HA per strain
SD-IIV: quadrivalent formula, 15µg HA per strain*
Co-administration with other seasonal vaccines permitted

Study duration:
DANFLU-2: Across 3 influenza seasons (2022-2025)
GALFLU: 2 influenza seasons (2023-2025)

Inclusion criteria
DANFLU-2: ≥65 years
GALFLU: Community dwelling older adults aged 65-79 years

Data collection
Both trials used routine healthcare databases through national registries as primary data source

DANFLU-2 332,438

GalFlu 133,882

Conducted in *2 geographic areas and across 3 seasons* maximized *statistical power and generalizability*

A *prespecified, individual-level pooled analysis* across all trial data

FLUNITY-HD

Participants 466,320 individually randomized (1:1) older adults

OUTCOMES

Primary end point
hospitalization for influenza or pneumonia (statistically powered)

Secondary end points
Secondary endpoints **were tested hierarchically**: cardio-respiratory hospitalization (statistically powered), laboratory-confirmed influenza (LCI) hospitalization, all-cause hospitalization, all-cause mortality, hospitalization for influenza (ICD-10), and hospitalization for pneumonia

Endpoints are based on international classification of disease (ICD) -10 codes except laboratory-confirmed influenza hospitalization and all-cause death

Statistical analysis

- The pooled analysis was prespecified to ensure sufficient statistical power to assess the rVE of HD-IIV vs SD-IIV against hospitalization for influenza or pneumonia
- Primary and secondary objectives were tested (via a hierarchical testing sequence) for statistical significance (one-sided alpha = 0.025) ***with superiority pre-defined in the protocol as 95% confidence interval lower bound greater than zero***

*The SD-IIV used are the standard of care in the populations and geography under study and are licensed by the EMA

References: 1. Johansen NK, et al. Effectiveness of high-dose influenza vaccine against hospitalizations in older adults (FLUNITY-HD): an individual-level pooled analysis, *Lancet*, 10.1016/S0140-6736(25)01742-8 . **2. DiazGrandos Ca**, et al. Efficacy of high-dose vesrsus standard-dose influenza vaccine in older adults, *NEJM*, 10.1056/NEJMoa1315727; **3. Lee J**, et al. High-dose influenza vaccine in older adults by age and seasonal characteristics: systematic review and meta-analysis update, *Vaccine X*, 10.1016/j.jvacx.2023.100327

MAT-US-2513932 - V1.0 -P - 17 October 2026

RESULTS

Participants and main baseline characteristics

Participants were individually randomized in this analysis[1]

466,320

- HD-IIV (n = 233,311)
- SD-IIV (n = 233,009)

Baseline Characteristics were balanced across HD-IIV and SD-IIV groups in the pooled dataset[1]

Mean age (in years) – 73.3 ± 5.4

48.9% had a chronic condition

23.1% had a history of cardiovascular disease

70.9% received concomitant COVID-19 vaccination

Primary and Secondary Endpoints[1]

Primary endpoint: The incidence of *hospitalization for influenza or pneumonia* was *significantly lower* in the HD-IIV group compared with the SD-IIV group with a *rVE of 8.8%* (95% CI: 1.7 to 15.5)

Secondary endpoints: HD-IIV *significantly reduced cardio-respiratory hospitalizations, LCI hospitalizations* and *all-cause hospitalizations* compared to SD-IIV with no difference in all-cause mortality

Endpoints	HD-IIV n = 233,311 no. (%)	SD-IIV n = 233,009 no. (%)	rVE % (95% CI)	One-Sided P Value	Number Needed to Vaccinate (95% CI)
Primary endpoint					
Hospitalization for pneumonia or influenza	1,312 (0.56)	1,437 (0.62)	*8.8* (1.7 to 15.5)	0.008	**1,839** (1,049 to 9,756)
Secondary endpoints					
Hospitalization for any cardio-respiratory disease	4,720 (2.02)	5,033 (2.16)	*6.3* (2.5 to 10.0)	<0.001	**730** (463 to 1,832)
Laboratory-confirmed influenza hospitalization	249 (0.11)	365 (0.16)	*31.9* (19.7 to 42.2)	<0.001	**2003** (1,511 to 3,233)
All-cause hospitalization	19,921 (8.54)	20,348 (8.73)	*2.2* (0.3 to 4.1)	0.012	**515** (278 to 3,929)
All-cause mortality	1,421 (0.61)	1,437 (0.62)	1.2 (-6.3 to 8.3)	0.38	-
Hospitalization for influenza	164 (0.07)	271 (0.12)	39.6 (26.4 to 50.5)	NA	-
Hospitalization for pneumonia	1,161 (0.50)	1,187 (0.51)	2.3 (-6.0 to 10.0)	NA	-

Purple endpoints were tested using a prespecified hierarchical testing sequence, whereby testing only continued down the hierarchy if the endpoint tested achieved statistical significance

Sub-group analysis: Results for the primary endpoint consistently favored HD-IIV in subgroup analyses including across major prespecified subgroups of age, sex, and comorbidities

Both groups exhibited similar rates of serious adverse events

STRENGTHS

- **Largest individually randomized influenza vaccine effectiveness study**: analyzing nearly 500K older adults across two geographical areas over three seasons, providing comprehensive effectiveness data
- **Pre-specified powered hierarchical testing:** Controlled testing showed HD-IIV's superior rVE vs SD-IIV
- **Pooled analysis strength:** Prospective methodological harmonization minimized heterogeneity while maximizing generalizability and limiting bias

LIMITATIONS

- **Open-label:** The trial was open-label; **however**, pre-specified definitions and assessment of severe outcomes likely **minimized** any potential **associated bias**
- **Did not employ systematic influenza testing**
- Reliance on routine healthcare data may have introduced imprecision into the underlying trial data
- Potential for heterogeneity between the trials, considering differences in regions, local epidemiology, enrollment ages, and local healthcare practices, despite harmonization of study protocols and end points. On analysis, no statistically significant heterogeneity was detected

CONCLUSIONS

HD-IIV demonstrated superior protection against hospitalizations for - influenza or pneumonia, cardio-respiratory diseases, laboratory-confirmed influenza, and all-cause vs SD-IIV in older adults

Flunity-HD is the *first study of its kind* that assessed the benefits of the HD influenza vaccine against severe outcomes compared to SD in an individually randomized setting, covering two geographic areas and three seasons

HD-IIV demonstrated superior protection against hospitalizations for - influenza or pneumonia, cardio-respiratory diseases, laboratory-confirmed influenza, and all-cause vs SD-IIV in older adults

HD-IIV showed *2.2% lower all-cause hospitalization* rates vs SD-IIV, meaning that vaccinating *515* older adults with HD-IIV instead of SD-IIV could prevent one all-cause hospitalization, suggesting potential for reducing healthcare burden at the population level

Abbreviations: CI: confidence interval; COVID-19: coronavirus disease 2019; EMA: European Medicines Agency; HA: hemagglutinin; HD-IIV: high-dose inactivated influenza vaccine; ICD: international classification of disease; LCI: laboratory-confirmed influenza; NA: not applicable; rVE: relative vaccine efficacy; SD-IIV: egg-based unadjuvanted inactivated influenza standard-dose vaccine

References: 1. Johansen NK, et al. Effectiveness of high-dose influenza vaccine against hospitalizations in older adults (FLUNITY-HD): an individual-level pooled analysis, *Lancet*, 10.1016/S0140-6736(25)01742-8. **2. DiazGrandos Ca**, et al. Efficacy of high-dosevesrsus standard-dose influenza vaccine in older adults, *NEJM*, 10.1056/NEJMoa1315727; **3. Lee J**, et al. High-dose influenza vaccine in older adults by age and seasonal characteristics: systematic review and meta-analysis update, *Vaccine X*, 10.1016/j.jvacx.2023.100327

The study was sponsored by Sanofi

Sanofi Science

Use the QR code to access the microsite

Access the publication

MAT-US-2513932 - V1.0 -P - 17 October 2026