Effectiveness of high-dose versus standard-dose influenza vaccine in immunosuppressed older adults

A prespecified analysis of FLUNITY-HD

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- I have no personal disclosures
- The DANFLU-2 & GALFLU trials received funding from Sanofi

Background



Immunosuppressed older adults

↑ Risk of severe influenza-related complications[1-3]

↓ Vaccine response[1,4,5]

[1] Kunisaki KM et al. *Lancet Infect Dis* 2009
[2] Greffe S et al. *Influenza Other Respir Viruses* 2023
[3] Collins JP et al. *Clin Infect Dis* 2020
[4] Kimball J et al. *J Infect Dis* 2021
[5] Hall VG et al. *N Engl J Med* 2025

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High-dose influenza vaccine

↑ Protection vs standard-dose against lab-confirmed influenza in the general older population[6,7]

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[6] DiazGranados CA et al. *N Engl J Med* 2014
[7] Skaarup KG et al. *J Infect* 2024

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Knowledge gap

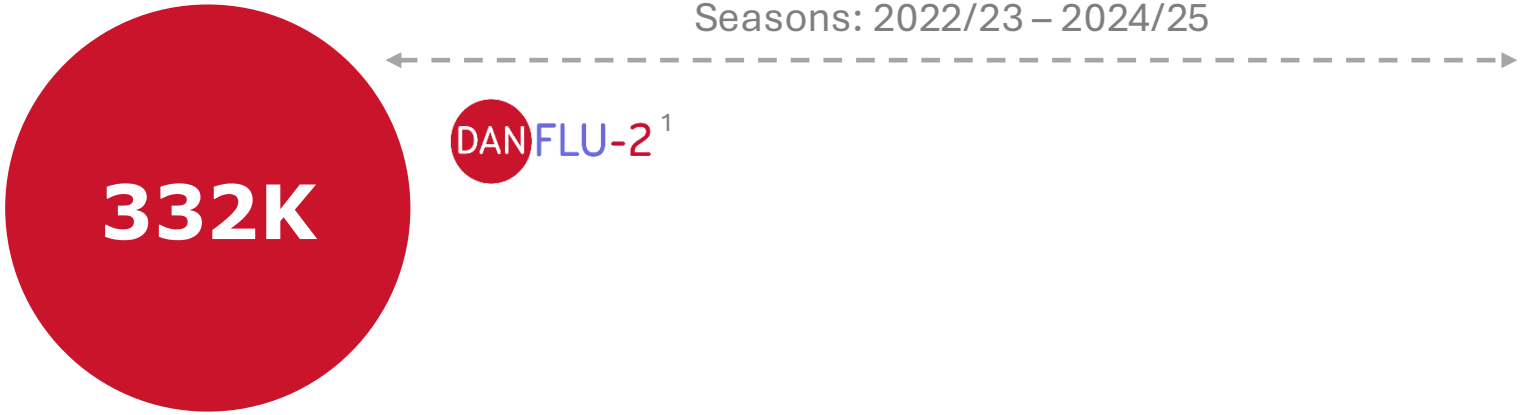
Limited evidence in immunosuppressed populations

[1] Kunisaki KM et al. *Lancet Infect Dis* 2009
[2] Greffe S et al. *Influenza Other Respir Viruses* 2023
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Objective

To assess the relative effectiveness of high-dose versus standard-dose influenza vaccine in older adults according to immunosuppression status

Study population

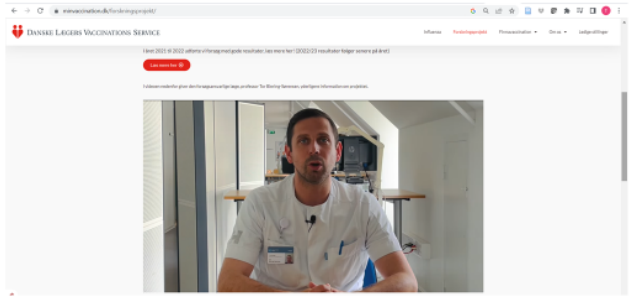


[1] Johansen ND et al. N Engl J Med 2025

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Initial participant data

UNIVERSITY OF COPENHAGEN

REGION H Gentofte Hospital

Center for Pragmatic Randomized Trials

Participant SSN

Baseline characteristics and outcomes



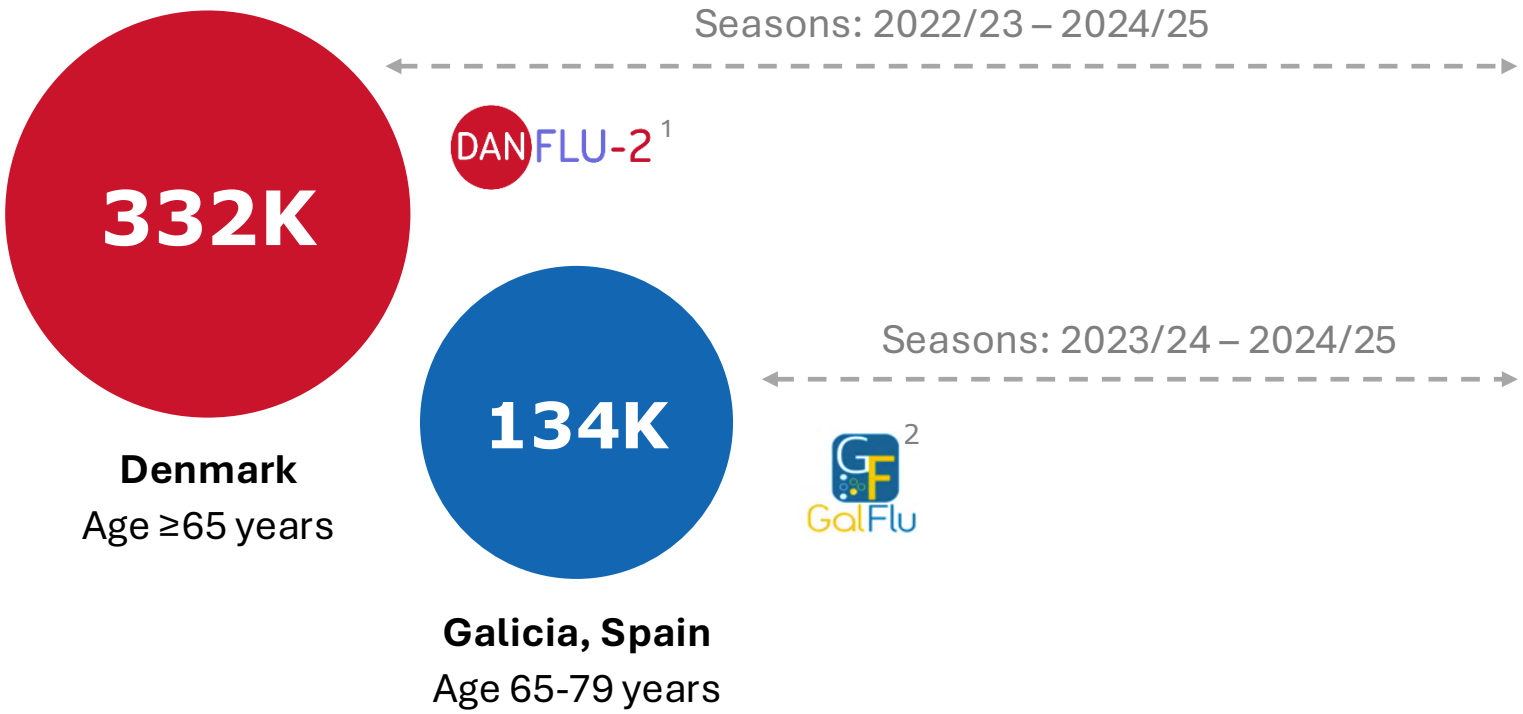
Vaccination clinic network:
- Open year-round – not just for flu vaccination
- Vaccinates >200,000 persons/year and rapidly upscaling
- Inclusion and randomization
- Administration of study drug

- Central trial site
- Study oversight
- Database management
- Nationwide access to all medical records and lab results

Registry data:
- Nationwide tax-funded public health system
- Nationwide registries can be crosslinked using social security numbers (SSN)
- Every hospital contact, death, redeemed prescription is captured in the registries

[1] Johansen ND et al. N Engl J Med 2025

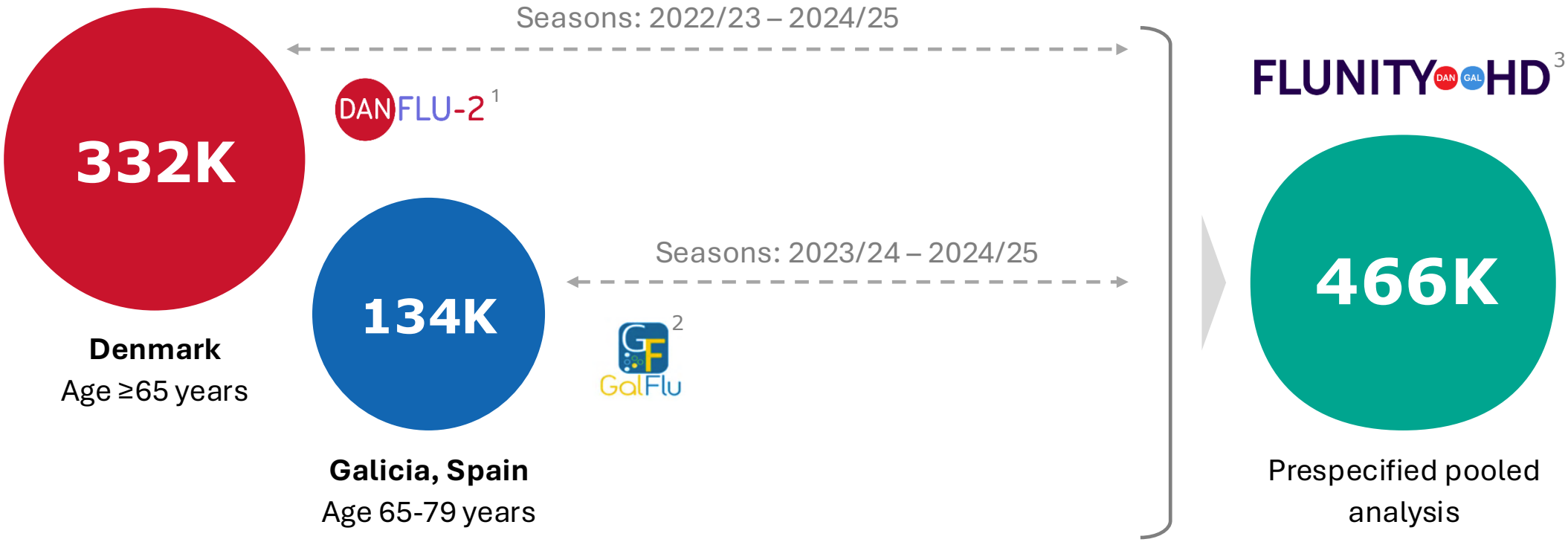
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[1] Johansen ND et al. N Engl J Med 2025

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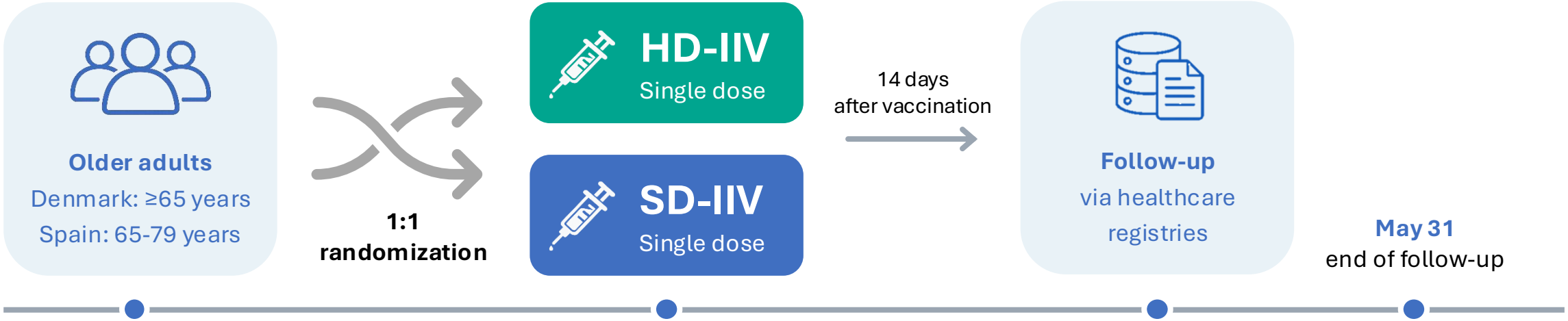


[1] Johansen ND et al. N Engl J Med 2025

[2] Pardo-Seco J et al. N Engl J Med 2025

[3] Johansen ND et al. Lancet 2025

Study design



Trials required participants to attend **only one physical visit** for randomization and vaccination

Definition of immunosuppression

IMMUNOSUPPRESSIVE CONDITIONS



- Hematologic disease
- Solid organ transplant
- HSCT
- Primary immunodeficiency
- HIV

and/or

IMMUNOSUPPRESSIVE TREATMENT

- Chemotherapy
- Immunosuppressive agents
- Systemic glucocorticoids



- Not mutually exclusive
- Based on registry data (ICD-10 codes, procedure codes, ATC codes)

Outcomes

PRIMARY ENDPOINT

Hospitalization for pneumonia or influenza

Defined by ICD-10 codes

SECONDARY ENDPOINTS

- Cardio-respiratory hospitalization
- Lab-confirmed influenza hospitalization
- All-cause hospitalization
- All-cause mortality



Analysis

- Relative vaccine effectiveness (rVE) and absolute risk reduction (ARR)
- Stratified by immunosuppression status with test for interaction adjusted for trial and season

RESULTS

Baseline characteristics

STUDY POPULATTION

Total population
466,320

Mean age
73.3 years

Female
48.0%

With immunosuppression
27,065 (5.8%)

WITH IMMUNOSUPPRESSION

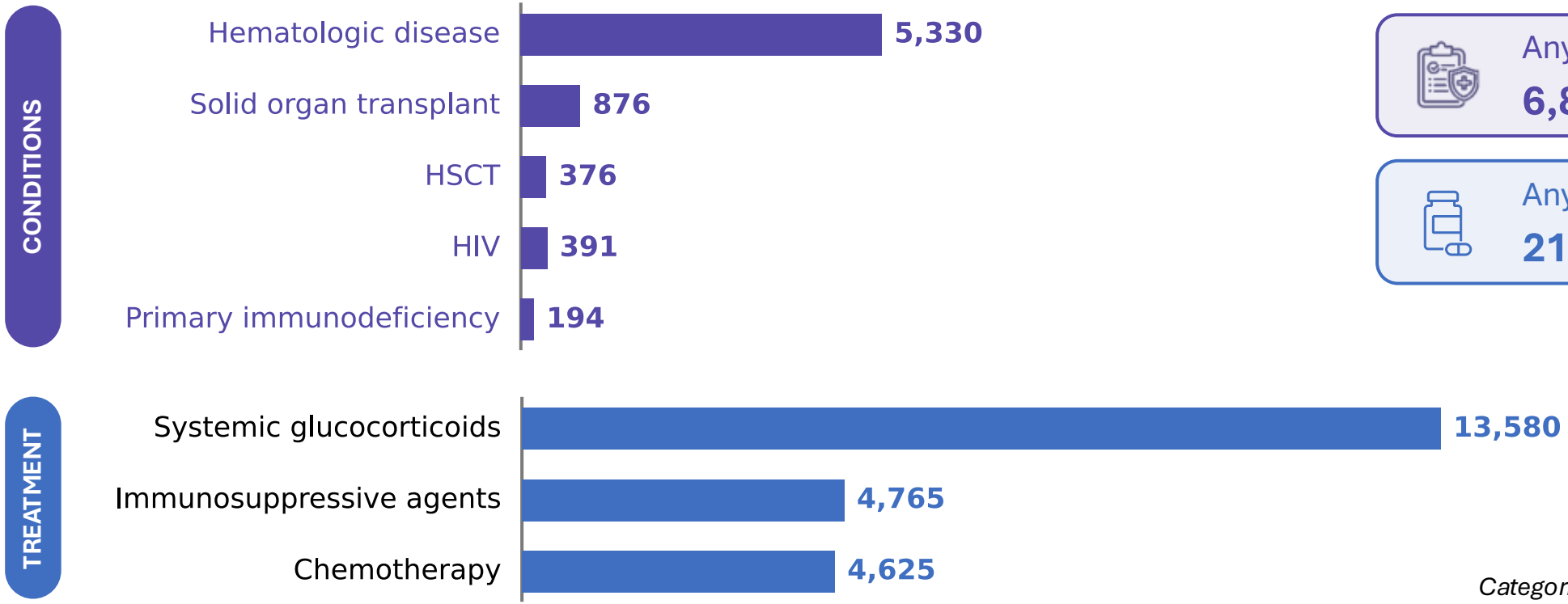
- **Similar age and sex distribution**
- **More comorbidities**

  Cancer: **32.4% vs 11.0%**
  Chronic kidney disease: **14.5% vs 10.1%**
  Chronic lung disease: **12.6% vs 6.5%**

- **Balanced randomization**

  HD-IIV: **13,522 (50.0%)**
  SD-IIV: **13,543 (50.0%)**

Composition of immunosuppression



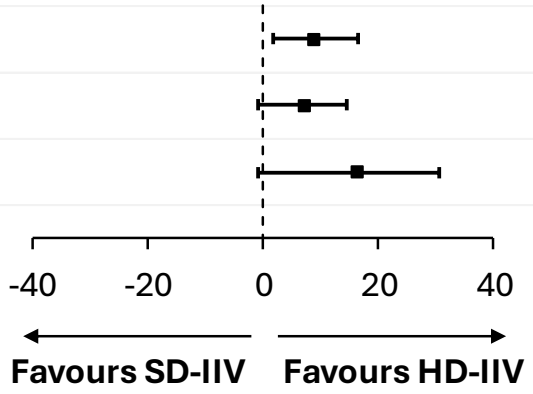
Any condition
6,889 (25%)

Any treatment
21,601 (80%)

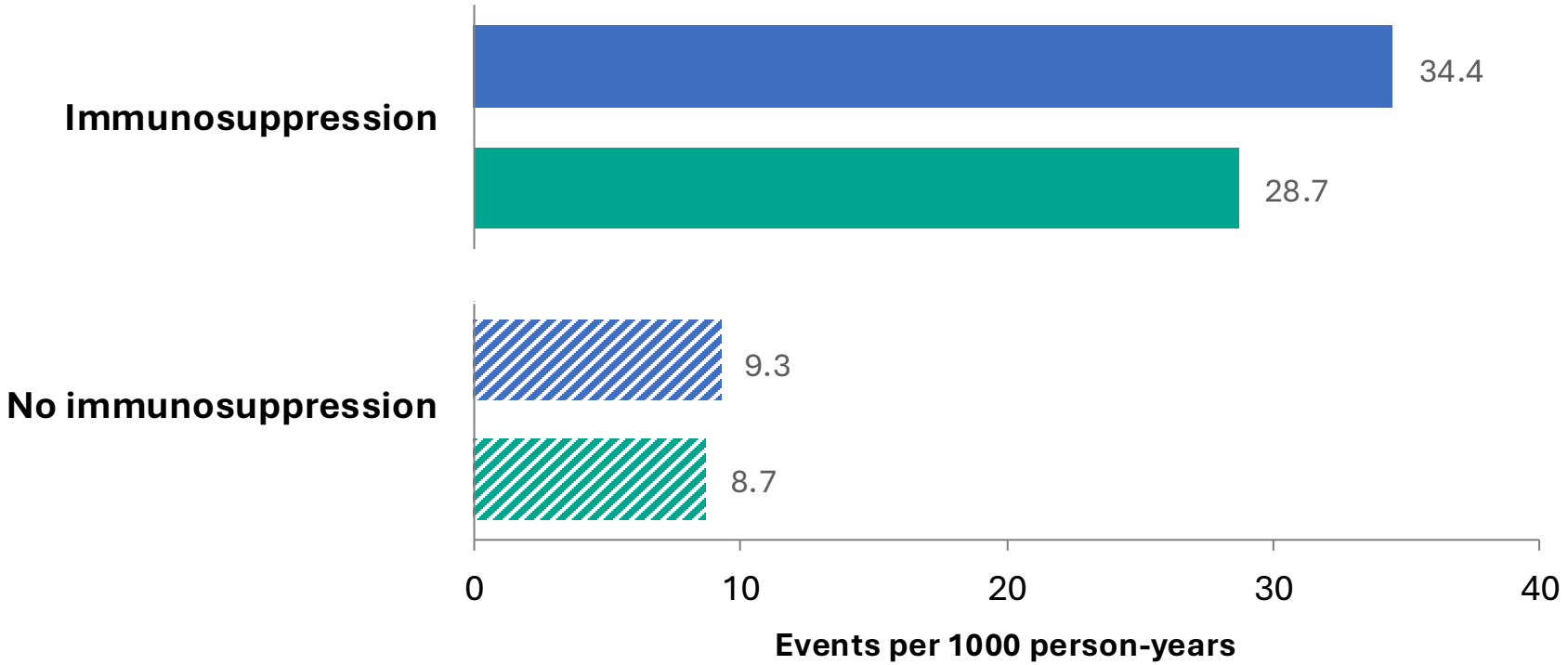
Categories not mutually exclusive

Primary endpoint

Outcome	No. of events		Crude rVE (95% CI)	*p*- value for interaction
	HD-IIV	SD-IIV		
Hospitalization for pneumonia or influenza				0.30
Overall	1,312	1,437	8.8 (1.7 to 16.5)	
No immunosuppression	1,100	1,183	7.2 (-0.9 to 14.6)	
With immunosuppression	212	254	16.4 (-0.7 to 30.7)	



Primary endpoint – absolute rate reduction



ARR (95% CI)
per 1000 PY

Immunosuppression
5.7 (-0.1 to 11.4)

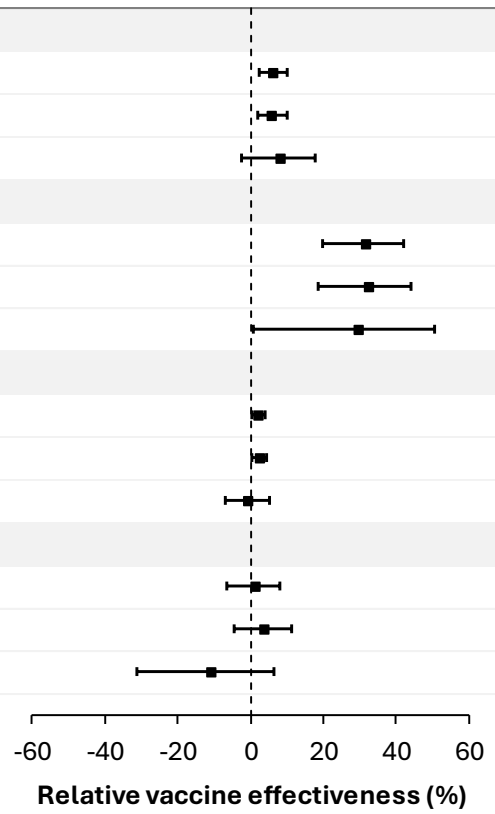
No immunosuppression
0.7 (-0.1 to 1.4)

SD-IIV HD-IIV

Internal

Secondary endpoints

Outcome	No. of events (IR per 1000 PY) HD-IIV	SD-IIV	Absolute rate reduction per 1000 PY (95% CI)	rVE, % (95%)	*p* for interaction
Cardio-respiratory hospitalization					0.70
Overall	4,720 (35.4)	5,033 (37.8)	2.4 (1.0 to 3.9)	6.3 (2.5 to 10.0)	
No immunosuppression	4,102 (32.5)	4,359 (34.6)	2.1 (0.7 to 3.5)	6.0 (1.9 to 10.0)	
With immunosuppression	618 (85.1)	674 (92.7)	7.6 (-2.1 to 17.3)	8.2 (-2.6 to 17.8)	
Lab-confirmed influenza hospitalization					0.83
Overall	249 (1.9)	365 (2.7)	0.9 (0.5 to 1.2)	31.9 (19.7 to 42.2)	
No immunosuppression	190 (1.5)	281 (2.2)	0.7 (0.4 to 1.1)	32.5 (18.5 to 44.1)	
With immunosuppression	59 (8.0)	84 (11.4)	3.4 (0.2 to 6.6)	29.7 (0.7 to 50.4)	
All-cause hospitalization					0.25
Overall	19,921 (154.6)	20,348 (158.3)	3.6 (0.6 to 6.7)	2.2 (0.3 to 4.1)	
No immunosuppression	17,665 (144.8)	18,103 (148.7)	3.9 (0.9 to 7.0)	2.6 (0.5 to 4.6)	
With immunosuppression	2,256 (331.7)	2,245 (329.5)	-2.2 (-21.5 to 17.1)	-0.6 (-6.7 to 5.1)	
All-cause mortality					0.12
Overall	1,421 (10.5)	1,437 (10.7)	0.1 (-0.6 to 0.9)	1.2 (-6.3 to 8.3)	
No immunosuppression	1,129 (8.9)	1,173 (9.2)	0.4 (-0.4 to 1.1)	3.9 (-4.4 to 11.5)	
With immunosuppression	292 (39.3)	264 (35.4)	-3.9 (-10.1 to 2.3)	-10.8 (31.3 to 6.5)	



Strengths and limitations

STRENGTHS

- Large, harmonized, individually randomized trial
- Broad, real-world population
- Near-complete follow-up
- Consistent results across trials and subgroup

LIMITATIONS

- Open-label design
- Heterogeneous immunosuppressed population
- Registry-based data
- Secondary analysis

CONCLUSION

HD-IIV provided a modest but significant reduction in hospitalization for influenza or pneumonia vs SD-IIV, with no effect modification by immunosuppression.

Immunosuppressed participants had markedly higher absolute risk, with potentially greater absolute benefit.

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