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High-Dose vs. Standard-Dose Influenza Vaccine in Chronic Kidney Disease:

A prespecified FLUNITY-HD Subgroup Analysis

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for the DANFLU-2 Study Group and the GALFLU Trial Team

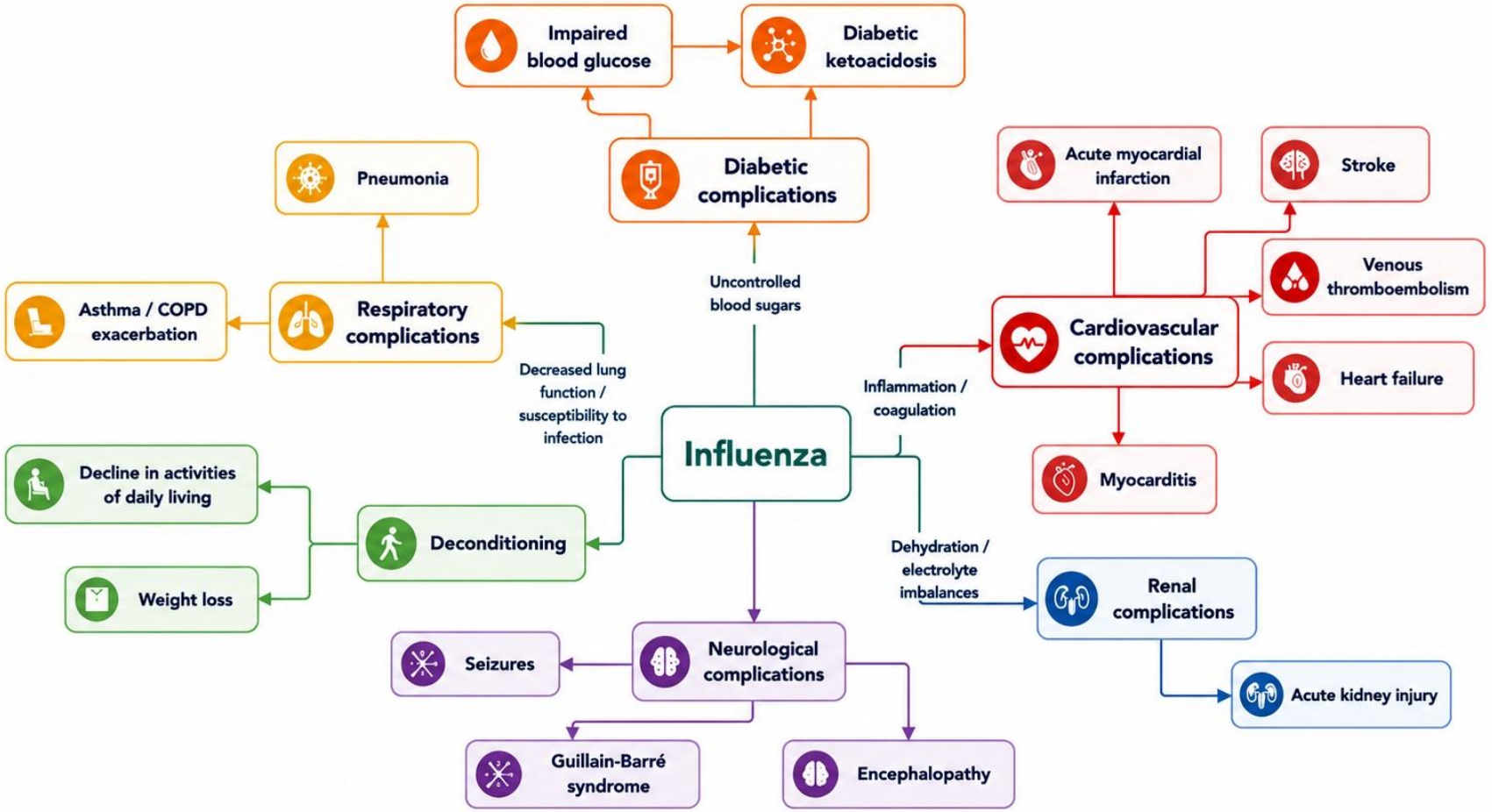
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Disclosures

- **CTCPR,** Copenhagen University Hospital - Herlev-Gentofte sponsored the **FLUNITY-HD** pooled analysis.
- **DANFLU-2, GALFLU,** and **FLUNITY-HD** were funded by **Sanofi** who participated in the study design and protocol development phase, but had no responsibilities in trial conduct, data collection, or data analysis.
- PhD scholarship supported by the Danish Cardiovascular Academy, which is funded by the Novo Nordisk Foundation, grant number NNF20SA0067242 and The Danish Heart Foundation.

M.M.L., R.C.H., M.D., R.v.A., and A.C. are full-time employees of Sanofi and may own shares or stock options in the company. C.S.L. has received speaker fees and served on advisory boards for GSK, MSD, Pfizer, Takeda, and Valneva. B.L.C. has received consulting fees from Amgen, Cardurion, Corvia, Myokardia, and Novartis. S.D.S. has received research grants from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, BMS, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lilly, Mesoblast, MyoKardia, National Institutes of Health/National Heart, Lung, and Blood Institute, Neurotronik, Novartis, Novo Nordisk, Respicardia, Sanofi, Theracos, and US2.AI and consulted for Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GSK, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros, and Puretech Health. F.M.-T. has acted as principal investigator for other studies sponsored by AstraZeneca, GlaxoSmithKline, Janssen, Medimmune, Moderna, MSD, Novavax, Novartis, Pfizer, Regeneron, Roche, Sanofi Pasteur, and Seqirus, with honoraria paid to his institution; and has consulting or advisory relationships with GlaxoSmithKline, Janssen, Medimmune, Moderna, MSD, Pfizer, Sanofi Pasteur, and Seqirus. T.B.-S. has received research grants from Bayer, Novartis, Pfizer, Sanofi Pasteur, GSK, Novo Nordisk, AstraZeneca, Boston Scientific, and GE Healthcare; consulting fees from Novo Nordisk, IQVIA, Parexel, Amgen, CSL Seqirus, GSK, and Sanofi Pasteur; and lecture fees from AstraZeneca, Bayer, Novartis, Sanofi Pasteur, GE Healthcare, and GSK. The other authors report no conflicts.

Influenza – The domino effect



Background · Methods · Results · Limitations · Conclusions

Influenza vaccination and cardiovascular risk

Influenza vaccination and cardiovascular risk

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Major Adverse Cardiovascular Events for Influenza Vaccine vs Control

	Influenza Vaccine		Placebo / Control		Risk Ratio
Study	Events	Total	Events	Total	(95% CI)
Govaert et al., 1994	7	927	5	911	1.38 (0.44–4.32)
Gurfinkel et al., 2004	32	145	54	147	0.60 (0.41–0.87)
Ciszewski et al., 2008	16	325	30	333	0.55 (0.30–0.98)
De Villiers et al., 2009	20	1620	20	1622	1.00 (0.54–1.85)
Phrommintikul et al., 2011	20	221	42	218	0.47 (0.29–0.77)
Frøbert et al., 2021	67	1272	91	1260	0.73 (0.54–0.99)
Total	**162**	**4510**	**242**	**4491**	**0.66 (0.53–0.83)**

Adapted from: Berrouzi B, et al. JAMA Network Open. 2022;5(2):e220269.

34%

relative risk reduction

in major cardiovascular events with influenza vaccination vs control

Influenza vaccination and cardiovascular risk

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relative risk reduction

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CARDIOPROTECTIVE THERAPIES IN CKD: RELATIVE RISK REDUCTION FOR CARDIOVASCULAR EVENTS

(For context – only statistically significant outcomes shown)

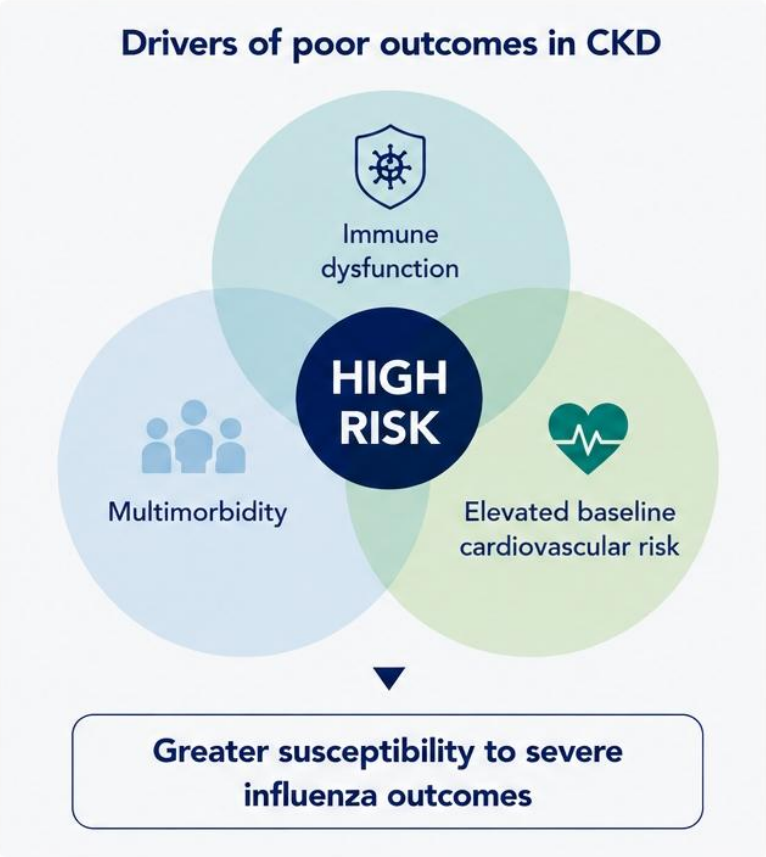
ACEi / ARBs
18–24%
RRR in major cardiovascular events

Statins
15–24%
RRR in major vascular events (Non-dialysis CKD)

SGLT2 inhibitors
23%
RRR in all cardiovascular events

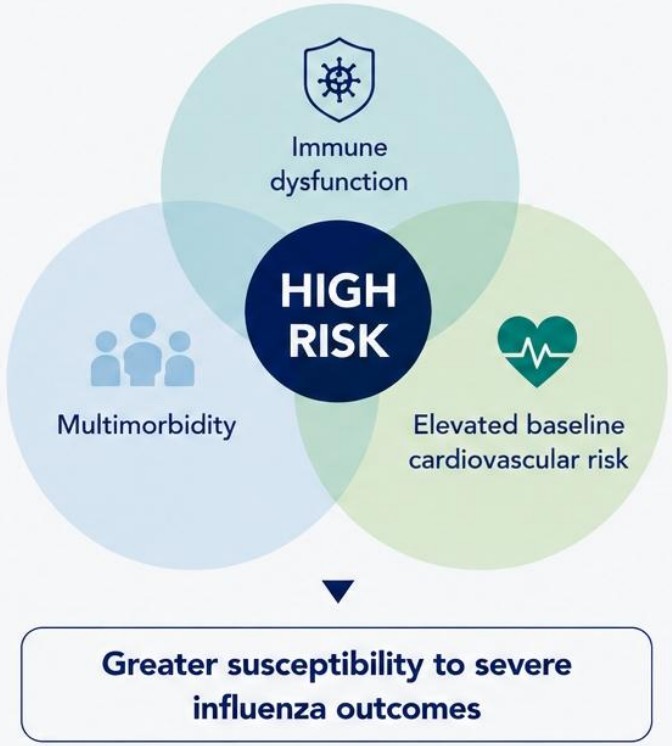
① Berrouzi B, et al. *JAMA Network Open*. 2022;5(2):e220269.
② Ren W, et al. *BMC Nephrol*. 2024;25:402.
③ Navaneethan SD, et al. *Lancet Diabetes Endocrinol*. 2016;4(12):952–965.

Increased vulnerability to influenza among people with CKD



Increased vulnerability to influenza among people with CKD

Drivers of poor outcomes in CKD

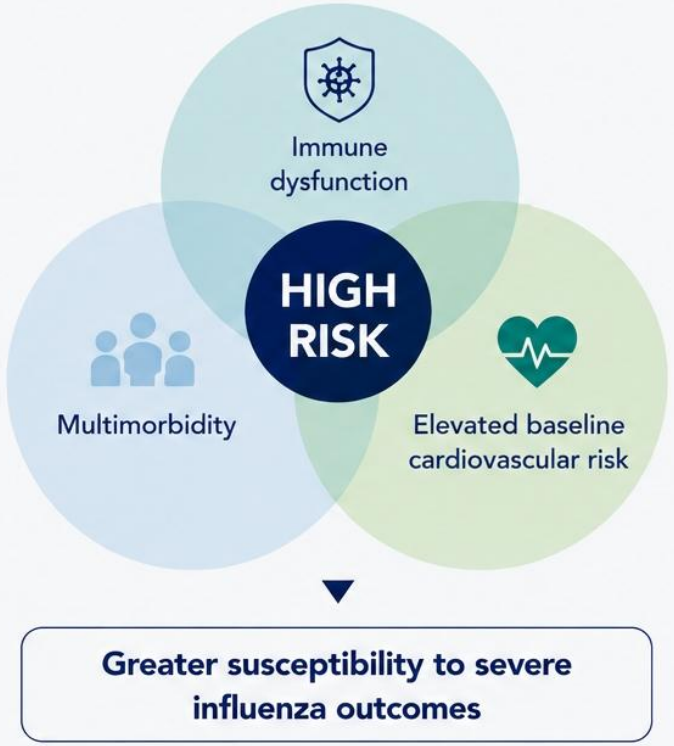


Infections drive mortality in CKD

Leading cause of death.

Increased vulnerability to influenza among people with CKD

Drivers of poor outcomes in CKD



Infections drive mortality in CKD

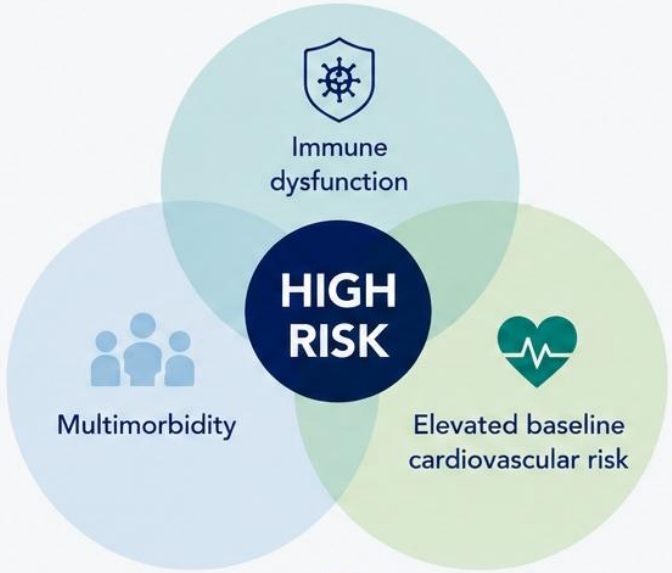
Leading cause of death.

Reduced vaccine responsiveness

Weaker responses to standard vaccines.

Increased vulnerability to influenza among people with CKD

Drivers of poor outcomes in CKD



Greater susceptibility to severe influenza outcomes

Infections drive mortality in CKD

Leading cause of death.

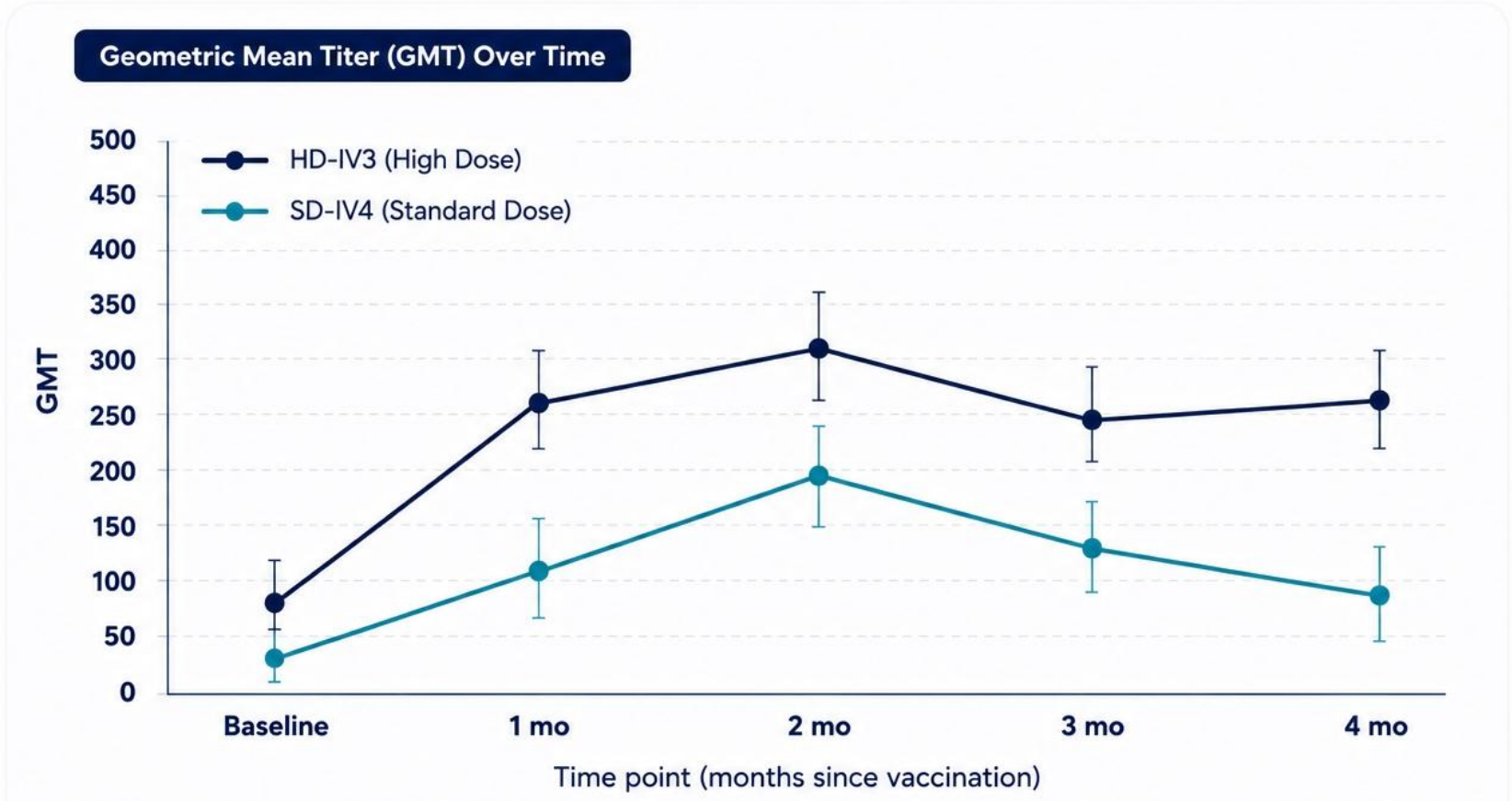
Reduced vaccine responsiveness

Weaker responses to standard vaccines.

Opportunity for effective prevention

Evaluate strategies, including enhanced vaccines.

Superior and more sustained antibody responses for high-dose vs standard-dose influenza vaccine in hemodialysis patients

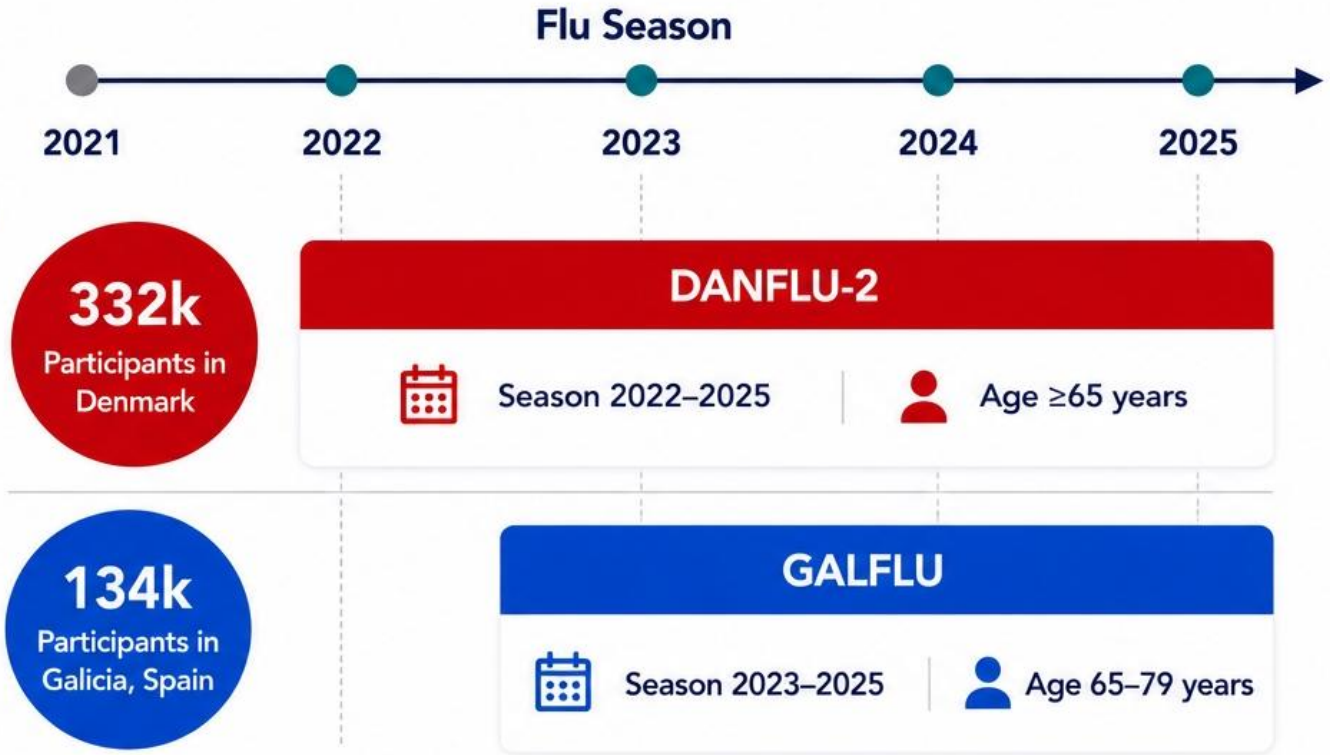


Manley HJ, et al. *AM J Kidney Dis*. 2022.

FLUNITY-HD: a pre-specified pooled analysis of DANFLU-2 and GALFLU against severe outcomes

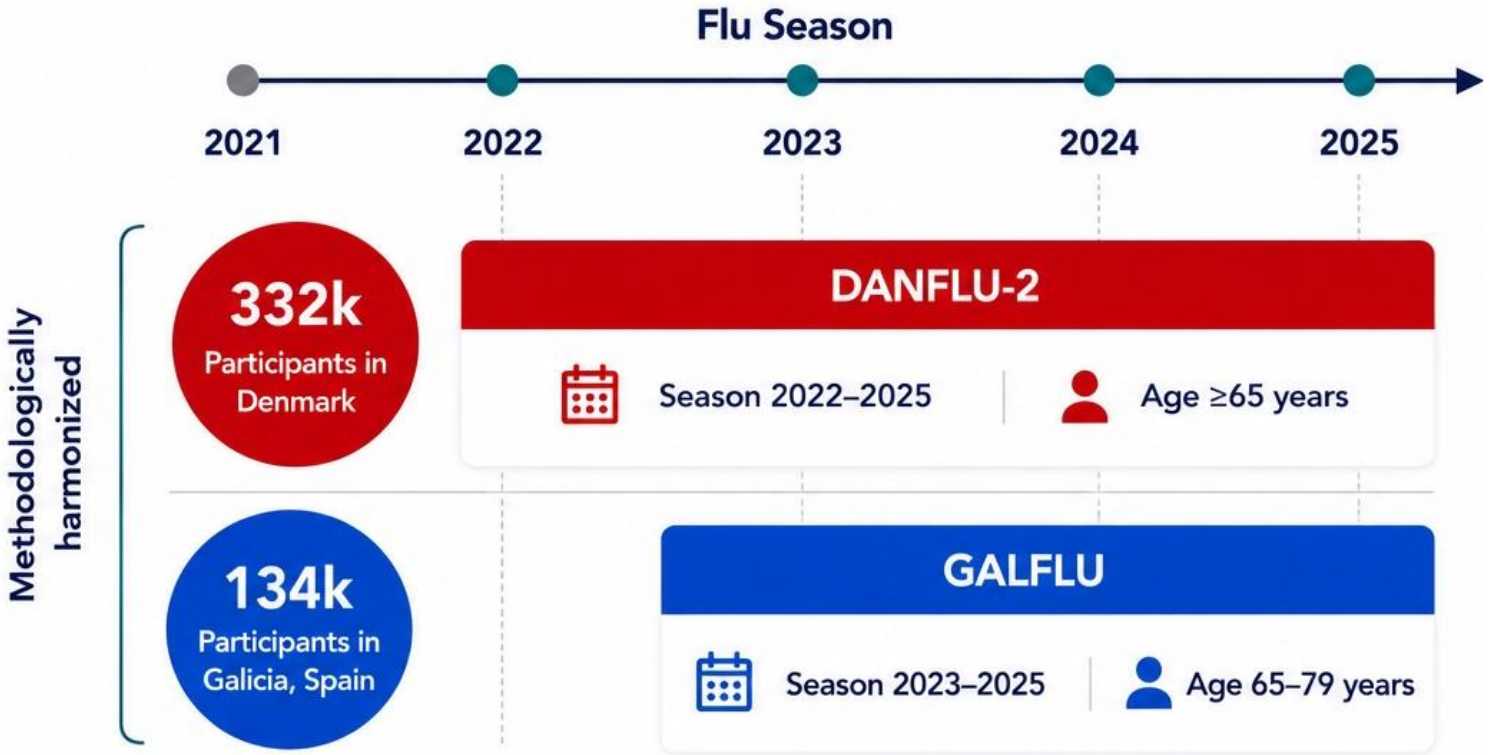
Johansen ND, et al. *N Eng J Med*. 2025. Pardo-Seco J, et al. *N Eng J Med*. 2025

FLUNITY-HD: a pre-specified pooled analysis of DANFLU-2 and GALFLU against severe outcomes



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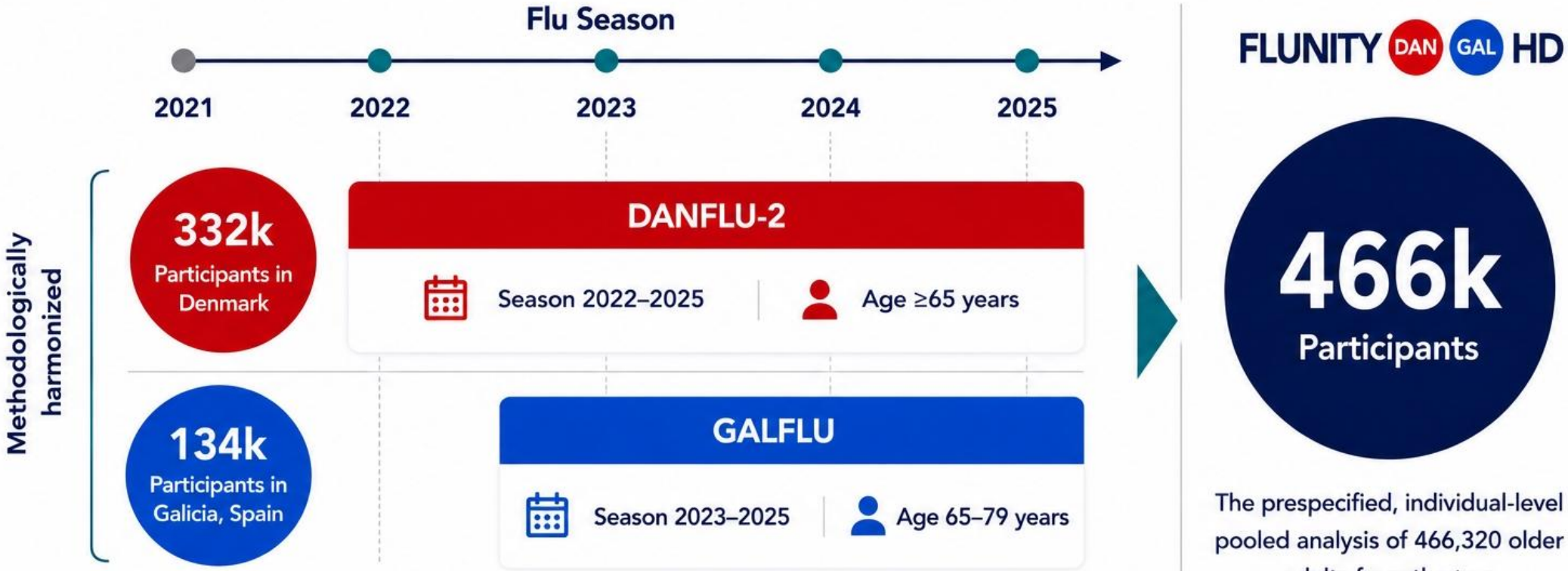
FLUNITY-HD: a pre-specified pooled analysis of DANFLU-2 and GALFLU against severe outcomes



GALFLU was designed based on the DANFLU-2 protocol, with *a priori* intention of pooling with DANFLU-2 to enhance statistical power, external validity, and thereby generalisability of the results

Johansen ND, et al. *N Eng J Med*. 2025. Pardo-Seco J, et al. *N Eng J Med*. 2025

FLUNITY-HD: a pre-specified pooled analysis of DANFLU-2 and GALFLU against severe outcomes



The prespecified, individual-level pooled analysis of 466,320 older adults from the two harmonized studies

GALFLU was designed based on the DANFLU-2 protocol, with *a priori* intention of pooling with DANFLU-2 to enhance statistical power, external validity, and thereby generalisability of the results

Background | Methods | Results | Limitations | Conclusions

FLUNITY-HD outcomes

FLUNITY-HD outcomes

01



Primary endpoint

- Hospitalization for influenza or pneumonia

FLUNITY-HD outcomes

01



Primary endpoint

- Hospitalization for influenza or pneumonia

02



Key secondary endpoints (tested hierarchically)

- Hospitalization for any cardio-respiratory disease
- Laboratory-confirmed influenza hospitalization
- All-cause hospitalization
- All-cause mortality

FLUNITY-HD outcomes

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01



Primary endpoint

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02



Key secondary endpoints (tested hierarchically)

- Hospitalization for any cardio-respiratory disease
- Laboratory-confirmed influenza hospitalization
- All-cause hospitalization
- All-cause mortality

03



Additional secondary endpoints

- Hospitalization for influenza
- Hospitalization for pneumonia

FLUNITY-HD outcomes

01



Primary endpoint

- Hospitalization for influenza or pneumonia

02



Key secondary endpoints (tested hierarchically)

- Hospitalization for any cardio-respiratory disease
- Laboratory-confirmed influenza hospitalization
- All-cause hospitalization
- All-cause mortality

03



Additional secondary endpoints

- Hospitalization for influenza
- Hospitalization for pneumonia

Passively collected through national registries

Additional exploratory FLUNITY-HD outcomes

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01



Cardiovascular hospitalization

02



Heart failure hospitalization

Passively collected through national registries

FLUNITY-HD main results

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Summary: HD-IIV vs SD-IIV demonstrated superior protection across key clinical end points

Background — Methods — Results — Limitations — Conclusions

Johansen ND, et al. Lancet 2025.

FLUNITY-HD main results

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Summary: HD-IIV vs SD-IIV demonstrated superior protection across key clinical end points

Across
3 seasons
2 geographical areas
5 epidemiological patterns

466k participants

LCI hospitalization	Hospitalization for pneumonia or influenza	Hospitalization for any cardio-respiratory disease	All-cause hospitalizations
31.9% (19.7 to 42.2)	**8.8%** (1.7 to 15.5)	**6.3%** (2.5 to 10.0)	**2.2%** (0.3 to 4.1)

rVE (95% CI) for HD-IIV vs SD-IIV

Background — Methods — Results — Limitations — Conclusions

FLUNITY-HD main results

HD-IIV vs SD-IIV: rVE across key clinical and exploratory endpoints

Secondary endpoints

All-cause mortality

1.2%
(-6.3 to 8.3)

Hospitalization for influenza

39.6%
(26.4 to 50.5)

Hospitalization for pneumonia

2.3%
(-6.0 to 10.0)

rVE (95% CI) for HD-IIV vs SD-IIV

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FLUNITY-HD main results

HD-IIV vs SD-IIV: rVE across key clinical and exploratory endpoints

Secondary endpoints

All-cause mortality	Hospitalization for influenza	Hospitalization for pneumonia
1.2% (-6.3 to 8.3)	39.6% (26.4 to 50.5)	2.3% (-6.0 to 10.0)

rVE (95% CI) for HD-IIV vs SD-IIV

Selected exploratory endpoints

Hospitalization for heart failure	Hospitalization for CVD
21.3% (7.4 to 33.2)	6.6% (1.6 to 11.4)

rVE (95% CI) for HD-IIV vs SD-IIV

Johansen ND, et al. Lancet 2025.

FLUNITY-HD: CKD subgroup analysis

FLUNITY-HD: CKD subgroup analysis

CKD definition in FLUNITY-HD

Prevalent CKD defined by laboratory values

- Sustained kidney impairment: **eGFR <60 ml/min/1.73²**
- Markers of kidney damage: **uACR >30 mg/g**
- Markers of kidney damage: **Urine albumin >20 mg/L**

On ≥2 occasions more than 3 months apart

FLUNITY-HD: CKD subgroup analysis

CKD definition in FLUNITY-HD

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eGFR <60 ml/min/1.73²	uACR >30 mg/g	Urine albumin >20 mg/L

On ≥2 occasions more than 3 months apart

02

ICD-10 codes retrieved from registries

- Primary or secondary diagnosis consistent with CKD, including codes for dialysis or kidney transplant.

Vestergaard SV, et al. *Clin J Am Soc Nephrol.* 2021

FLUNITY-HD: CKD subgroup analysis

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CKD definition in FLUNITY-HD

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On ≥2 occasions more than 3 months apart

02

ICD-10 codes retrieved from registries

- Primary or secondary diagnosis consistent with CKD, including codes for dialysis or kidney transplant.

03

Exclusion based on lab timing

- eGFR <60 ml/min/1.73² measured only the day before or during a hospitalization was considered non-CKD.

Baseline characteristics among participants with CKD

Baseline characteristics among participants with CKD

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Selected baseline characteristics by randomization group

Baseline characteristic	HD-IIV N=24,062	SD-IIV N=24,195
Age, mean years (SD)	76.1 (6.2)	76.1 (6.3)
Female sex, n (%)	9,086 (37.8)	9,190 (38.0)
Diabetes mellitus, n (%)	8,458 (35.2)	8,433 (34.9)
Influenza vaccine in previous season, n (%)	23,557 (97.9)	23,695 (97.9)
COVID-19 vaccine in current season, n (%)	22,471 (96.4)	22,613 (96.3)
Heart failure, n (%)	2,417 (10.0)	2,410 (10.0)
Chronic CVD, n (%)	11,478 (47.7)	11,443 (47.3)
Immunosuppressed, n (%)	2,146 (8.9)	2,074 (8.6)
Chronic lung disease, n (%)	2,960 (12.3)	2,924 (12.1)

Well-balanced characteristics across randomization groups

Baseline characteristics across CKD status

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Baseline characteristic	CKD N = 48,257	No CKD N=418,054
Age, mean years (SD)	76.1 (6.2)	73.0 (5.2)
Female sex, n (%)	18,276 (37.9)	212,655 (50.9)
Diabetes mellitus, n (%)	16,891 (35.0)	48,090 (11.5)
Influenza vaccine in previous season, n (%)	47,252 (97.9)	401,493 (96.0)
COVID-19 vaccine in current season, n (%)	45,084 (96.4)	275,784 (96.5)
Heart failure, n (%)	4,827 (9.2)	8,206 (2.0)
Chronic CVD, n (%)	22,921 (47.5)	84,779 (20.3)
Immunosuppressed, n (%)	4,220 (8.7)	20,396 (4.9)
Chronic lung disease, n (%)	5,884 (12.2)	26,092 (6.2)

Higher comorbidities among people with CKD vs no CKD

PRIMARY ENDPOINT

HD-IIV vs SD-IIV: Hospitalization for pneumonia or influenza

Population	HD-IIV	SD-IIV
	no./total no.	
All participants	1,312/233,311 (0.6%)	1,437/233,009 (0.6%)
CKD	328/24,062 (1.4%)	396/24,195 (1.6%)
No CKD	984/209,247 (0.5%)	1,041/208,807 (0.5%)

PRIMARY ENDPOINT

HD-IIV vs SD-IIV: Hospitalization for pneumonia or influenza

Population	HD-IIV	SD-IIV	rVE (95% CI)	NNV	P for interaction
	no./total no.				
					0.15
All participants	1,312/233,311 (0.6%)	1,437/233,009 (0.6%)	8.8% (1.7 - 15.4)	1,839 (1049 - 9756)	
CKD	328/24,062 (1.4%)	396/24,195 (1.6%)			
No CKD	984/209,247 (0.5%)	1,041/208,807 (0.5%)			

PRIMARY ENDPOINT

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CKD	328/24,062 (1.4%)	396/24,195 (1.6%)	16.7% (3.3 - 28.3)	693 (395 – 3,676)	
No CKD	984/209,247 (0.5%)	1,041/208,807 (0.5%)	5.7% (-3.0 - 13.6)	2,275 (1,298 – 12,068)	

Consistent rVE of HD-IIV vs SD-IIV on secondary outcomes across CKD status

Endpoint	HD-IIV (n = 24,062)	SD-IIV (n = 24,195)	rVE (95% CI)			NNV	P for interaction
	no.		CKD	No CKD	All participants		
Cardiorespiratory hospitalization	1,033 (4.3%)	1,135 (4.7%)	**8.5% (0.3 - 16.0)**	**5.6% (1.2 – 9.8)**	**6.3% (2.5 - 10.0)**	**336 (213 – 844)**	**0.53**
LCI hospitalization	49 (0.2%)	88 (0.4%)	**44.0% (19.7 - 61.4)**	**27.9% (13.3 – 40.2)**	**31.8% (19.7 - 42.2)**	**625 (448 - 1395)**	**0.21**
All-cause hospitalization	3,847 (16.0%)	3,897 (16.1%)	**0.7% (-3.8 - 5.1)**	**2.5% (0.3 – 4.6)**	**2.3% (0.3 - 4.1)**	**279 (151 – 2,130)**	**0.43**

Consistent rVE of HD-IIV vs SD-IIV on secondary outcomes across CKD status

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	no.		CKD	All participants		
Cardiorespiratory hospitalization	1,033 (4.3%)	1,135 (4.7%)	**8.5%** (0.3 - 16.0)	**6.3%** (2.5 - 10.0)	**336** (213 – 844)	**0.53**
LCI hospitalization	49 (0.2%)	88 (0.4%)	**44.0%** (19.7 - 61.4)	**31.8%** (19.7 - 42.2)	**625** (448 - 1395)	**0.21**
All-cause hospitalization	3,847 (16.0%)	3,897 (16.1%)	**0.7%** (-3.8 - 5.1)	**2.3%** (0.3 - 4.1)	**279** (151 – 2,130)	**0.43**
All-cause mortality	442 (1.8%)	410 (1.7%)	**-8.4%** (-24.3 - 5.4)	**1.2%** (-6.3 - 8.3)	**4,754** (712 - ∞)	**0.48**
Pneumonia hospitalization	311 (1.3%)	340 (1.4%)	**8.2%** (-7.6 - 21.4)	**2.3%** (-6.0 - 10.0)	**887** (333 - ∞)	**0.36**

Consistent rVE of HD-IIV vs SD-IIV on secondary outcomes across CKD status

Endpoint	HD-IIV (n = 24,062)	SD-IIV (n = 24,195)	rVE (95% CI)		NNV	P for interaction
	No.		CKD	All participants		
Cardiorespiratory hospitalization	1,033 (4.3%)	1,135 (4.7%)	**8.5%** (0.3 - 16.0)	**6.3%** (2.5 - 10.0)	**336** (213 – 844)	**0.53**
LCI hospitalization	49 (0.2%)	88 (0.4%)	**44.0%** (19.7 - 61.4)	**31.8%** (19.7 - 42.2)	**625** (448 - 1395)	**0.21**
All-cause hospitalization	3,847 (16.0%)	3,897 (16.1%)	**0.7%** (-3.8 - 5.1)	**2.3%** (0.3 - 4.1)	**279** (151 – 2,130)	**0.43**
All-cause mortality	442 (1.8%)	410 (1.7%)	**-8.4%** (-24.3 - 5.4)	**1.2%** (-6.3 - 8.3)	**4,754** (712 - ∞)	**0.48**
Pneumonia hospitalization	311 (1.3%)	340 (1.4%)	**8.2%** (-7.6 - 21.4)	**2.3%** (-6.0 - 10.0)	**887** (333 - ∞)	**0.36**
Influenza hospitalization	20 (0.08%)	63 (0.3%)	**68.1%** (46.2 - 81.7)	**39.6%** (26.3 - 50.5)	**564** (470 - 826)	**0.005**

Consistent rVE of HD-IIV vs SD-IIV on exploratory outcomes across CKD status

Endpoint	HD-IIV (n = 24,062)	SD-IIV (n = 24,195)	rVE (95% CI)		NNV	P for interaction
	no.		CKD	All participants		
Cardiovascular hospitalization	593 (2.46%)	611 (2.53%)	**2.4%** **(-9.4 - 13.0)**	**6.6%** **(1.6 - 11.5)**	**596** **(346 – 2,509)**	**0.38**
Heart failure hospitalization	111 (0.46)	115 (0.48)	**2.9%** **(-27.1 - 25.9)**	**21.3%** **(7.4 - 33.2)**	**986** **(633 – 2,849)**	**0.048**

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The trial was not powered for subgroup analysis

Although the CKD subgroup analysis was prespecified, the trials were not specifically powered to detect differential treatment effects across subgroups.

Conclusions



- HD-IIV provided **greater protection** than SD-IIV against a wide range of hospitalization outcomes, with consistent findings regardless of preexisting CKD.

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- HD-IIV provided greater protection than SD-IIV against a wide range of hospitalization outcomes, with consistent findings regardless of preexisting CKD.



- Benefits were particularly pronounced for influenza-related and cardiorespiratory hospitalization outcomes among individuals with CKD, supporting HD-IIV as a potentially important preventive strategy in this high-risk population.