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Effectiveness of high-dose versus standard-dose influenza vaccine in older adults according to age and sex: A prespecified analysis of the FLUNITY-HD study

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Take Home message

Our age and sex interaction results did not suggest clinically meaningful heterogeneity across sex and prespecified 5-year age strata in comparing HD-IIV vs. SD-IIV.

OBJECTIVE

The relative vaccine effectiveness (rVE) of HD-IIV versus SD-IIV according to age and sex had not been explored in depth.

BACKGROUND

The FLUNITY-HD study, a prespecified pooled analysis of **466,320** individually randomized older adults, previously demonstrated superior protection of high-dose inactivated influenza vaccine (HD-IIV) compared with standard-dose inactivated influenza vaccine (SD-IIV) against hospitalization outcomes among adults aged ≥65 years (1).

METHODS

This prespecified analysis pooled data from two methodologically harmonized, individually randomized trials in which participants were assigned to receive HD-IIV or SD-IIV.

Primary endpoint:

Hospitalizations for influenza or pneumonia

Secondary endpoints:

Cardiorespiratory hospitalization, laboratory-confirmed influenza hospitalizations, all-cause hospitalizations, pneumonia hospitalization and mortality

Figure 1: Risk Ratio (HD-IIV vs SD-IIV) of Endpoints by Sex

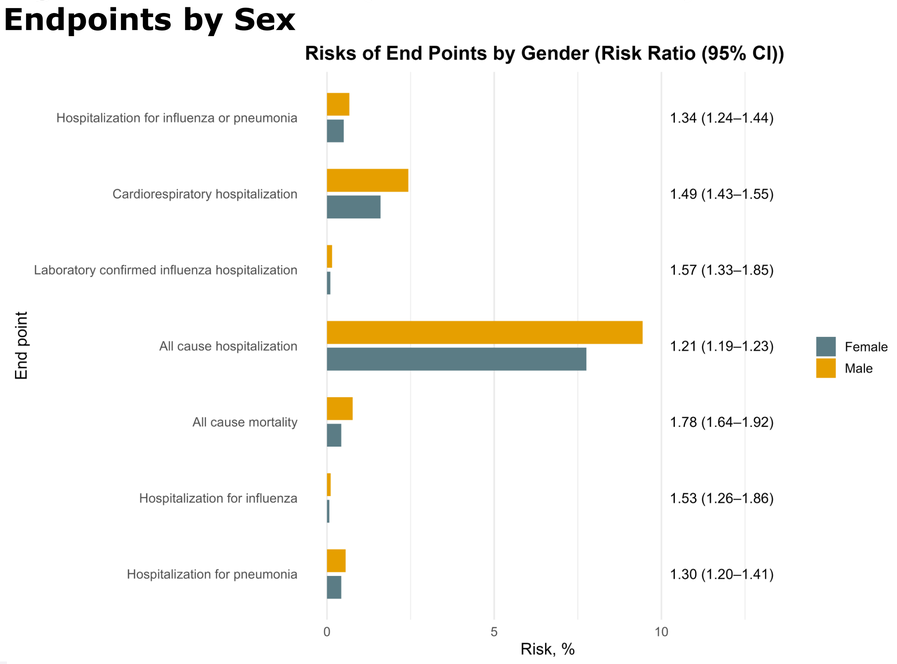
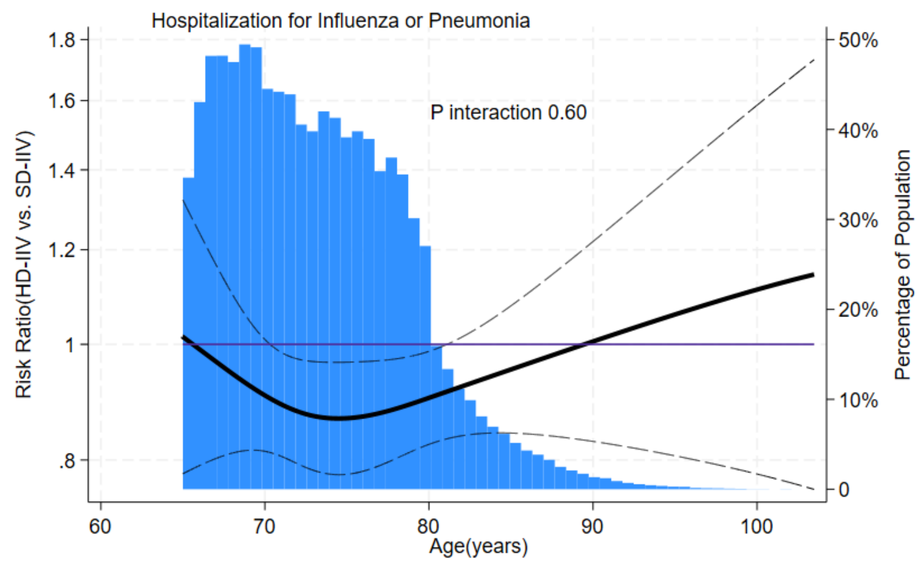


Figure 2: Restricted cubic splines with age-primary endpoint



CONCLUSIONS

Among more than 466,000 individually randomized older adults:

HD-IIV demonstrated consistently improved protection against hospitalizations for various causes across age and sex groups, underscoring the potential benefit of HD-IIV over SD-IIV against severe hospitalization outcomes in the spectrum of age within the older adult population in both sexes.

RESULTS

A total of 466,320 individually randomized participants were included in the analysis (233,311 HD-IIV; 233,009 SD-IIV).

Mean age was 73.3 years (SD 5.4); 223,681 **(48.0%) were female.**

HD-IIV provided superior protection (overall rVE 8.8%, 95% CI (1.7 to 15.5), P-value 0.0082) compared with SD-IIV against the primary endpoint of hospitalization for influenza or pneumonia with no effect modification in age and sex.

Number Needed to Vaccinate (NNV) was lower in male and ≥85 years population, as low as 465 and 241 to avert one all-cause hospitalization, respectively.

Figure 3: Outcomes in age groups

Outcome	HD-IIV	SD-IIV	rVE(95%CI)	P-interaction	NNV
Hospitalization for influenza or pneumonia	1312 (0.56)	1437 (0.62)	8.8 (1.7 to 15.5)	0.75	1839 (1041–9488)
Age 65-69	243 (0.31)	258 (0.33)	5.9 (-12.4 to 21.4)		3412 (1937–17666)
Age 70-74	287 (0.40)	318 (0.44)	10.1 (-5.7 to 23.6)		2543 (1444–13168)
Age 75-79	375 (0.62)	439 (0.73)	14.5 (1.7 to 25.7)		1553 (881–8040)
Age 80-84	246 (1.40)	256 (1.40)	4 (-14.7 to 19.7)		775 (440–4015)
Age ≥85	161 (2.39)	166 (2.67)	1.1 (-23.5 to 20.9)		469 (266–2429)
Cardiorespiratory hospitalization	4720 (2.02)	5033 (2.16)	6.3 (2.5 to 10)	0.74	730 (463–1852)
Age 65-69	997 (1.28)	1099 (1.41)	9.4 (1.2 to 16.9)		1119 (705–2820)
Age 70-74	1246 (1.74)	1329 (1.86)	5.9 (-1.6 to 13)		850 (535–2142)
Age 75-79	1433 (2.38)	1526 (2.54)	6.1 (-0.97 to 12.7)		624 (393–1572)
Age 80-84	675 (3.85)	678 (3.87)	0.5 (-10.7 to 10.7)		409 (257–1031)
Age ≥85	369 (5.48)	410 (5.98)	8.2 (-5.8 to 20.5)		265 (167–668)
Laboratory confirmed influenza hospitalizatior	249 (0.11)	365 (0.16)	31.9 (19.7 to 42.2)	0.46	2003 (1481–3173)
Age 65-69	49 (0.06)	75 (0.09)	34.7 (5.2 to 55.4)		3238 (2448–5244)
Age 70-74	58 (0.08)	102 (0.14)	43.3 (21 to 59.6)		2187 (1653–3542)
Age 75-79	87 (0.14)	105 (0.17)	17.1 (-11.1 to 38.3)		1791 (1354–2900)
Age 80-84	39 (0.20)	54 (0.30)	27.8 (-10.9 to 53.4)		1014 (766–1642)
Age ≥85	16 (0.23)	29 (0.42)	43.7 (-6.9 to 71.4)		741 (560–1200)
All cause hospitalization	19921 (8.54)	20348 (8.73)	2.2 (0.3 to 4.1)	0.29	515 (279–3818)
Age 65-69	4863 (6.26)	5005 (6.45)	2.9 (-0.9 to 6.7)		703 (377–5160)
Age 70-74	5589 (7.82)	5768 (8.10)	3.4 (-0.15 to 6.9)		561 (301–4114)
Age 75-79	5788 (9.64)	5898 (9.82)	1.8 (-1.7 to 5.3)		462 (248–3391)
Age 80-84	2462 (14.07)	2384 (13.64)	-3.1 (-9.1 to 2.5)		333 (178–2443)
Age ≥85	1219 (18.11)	1293 (18.85)	3.9 (-3.9 to 11.2)		241 (129–1767)
All cause mortality	1421 (0.61)	1437 (0.62)	1.2 (-6.3 to 8.3)	0.34	
Age 65-69	193 (0.24)	225 (0.29)	14.3 (-4.2 to 29.7)		
Age 70-74	336 (0.47)	314 (0.44)	-6.5 (-24.7 to 8.8)		
Age 75-79	445 (0.74)	433 (0.72)	-2.7 (-17.7 to 10.1)		
Age 80-84	224 (1.28)	246 (1.40)	9 (-9.4 to 24.4)		
Age ≥85	223 (3.31)	219 (3.19)	-3.7 (-25.6 to 14.2)		
Hospitalization for influenza	164 (0.07)	271 (0.12)	39.6 (26.4 to 50.5)	0.51	
Age 65-69	38 (0.04)	46 (0.05)	17.5 (-29.5 to 47.7)		
Age 70-74	39 (0.05)	68 (0.09)	42.8 (14 to 62.4)		
Age 75-79	56 (0.09)	93 (0.15)	39.7 (15.2 to 57.5)		
Age 80-84	21 (0.12)	40 (0.22)	47.5 (8.9 to 70.6)		
Age ≥85	10 (0.14)	24 (0.35)	57.5 (7.8 to 81.8)		
Hospitalization for pneumonia	1161 (0.50)	1187 (0.51)	2.3 (-6 to 10)	0.86	
Age 65-69	207 (0.26)	214 (0.27)	3.4 (-17.4 to 20.6)		
Age 70-74	249 (0.34)	252 (0.35)	1.5 (-17.7 to 20.6)		
Age 75-79	324 (0.53)	350 (0.58)	7.4 (-7.9 to 20.6)		
Age 80-84	228 (1.30)	225 (1.28)	-1.2 (-22.2 to 16.1)		
Age ≥85	153 (2.27)	146 (2.12)	-6.7 (-34.9 to 15.4)		

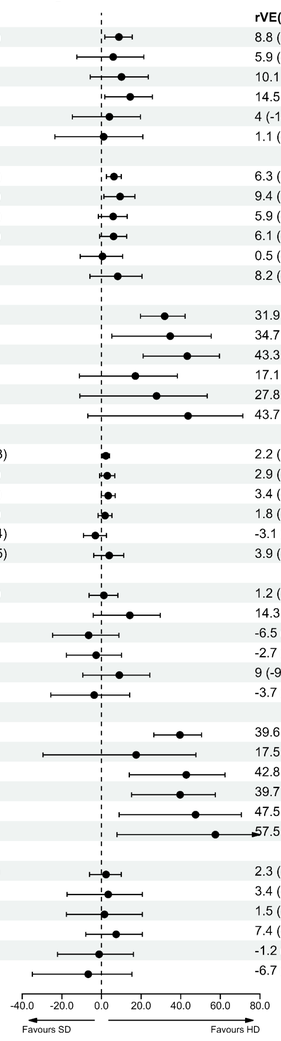
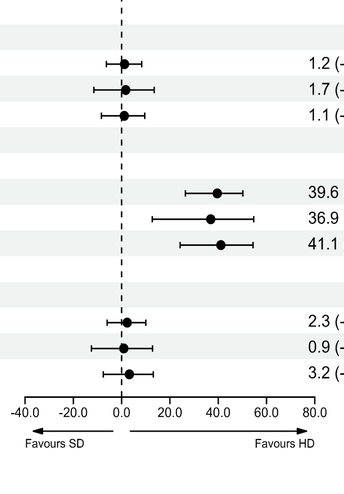


Figure 4: Outcomes in male and female

Outcome	HD-IIV	SD-IIV	rVE(95%)	P-interaction	NNV
Hospitalization for influenza or pneumonia				0.58	
All participants (N = 466,320)	1312 (0.56)	1437 (0.62)	8.8 (1.7 to 15.5)		1839 (1041-9488)
Female (n= 223,681)	541 (0.48)	579 (0.52)	6.5 (-5.2 to 17.0)		2191 (1250-11624)
Male (n=242,639)	771 (0.63)	858 (0.71)	10.4 (1.1 to 18.8)		1601 (913-8494)
Cardiorespiratory hospitalization				0.40	
All participants (N = 466,320)	4720 (2.02)	5033 (2.16)	6.3 (2.5 to 10.0)		730 (463-1852)
Female (n= 223,681)	1820 (1.63)	1904 (1.70)	4.3 (-2.0 to 10.3)		930 (561-2289)
Male (n=242,639)	2900 (2.39)	3129 (2.58)	7.5 (2.7 to 12.1)		612 (370-1508)
Laboratory confirmed influenza hospitalization				0.85	
All participants (N = 466,320)	249 (0.11)	365 (0.16)	31.9 (19.7 to 42.2)		2003 (1481-3173)
Female (n= 223,681)	93 (0.08)	134 (0.12)	30.5 (8.8 to 47.2)		2665 (1966-4266)
Male (n=242,639)	156 (0.13)	231 (0.19)	32.6 (17.1 to 45.4)		1674 (1235-2680)
All cause hospitalization				0.06	
All participants (N = 466,320)	19 921 (8.54)	20 348 (8.73)	2.2 (0.3 to 4.1)		515 (279-3818)
Female (n= 223,681)	8670 (7.75)	8693 (7.77)	0.2 (-2.8 to 3.1)		576 (309-3514)
Male (n=242,639)	11251 (9.26)	11655 (9.62)	3.7 (1.2 to 6.2)		465 (250-2838)
All cause mortality				0.92	
All participants (N = 466,320)	1421 (0.61)	1437 (0.62)	1.2 (-6.3 to 8.3)		
Female (n= 223,681)	483 (0.43)	492 (0.44)	1.7 (-11.5 to 13.5)		
Male (n=242,639)	938 (0.77)	945 (0.78)	1.1 (-8.4 to 9.6)		
Hospitalization for influenza				0.73	
All participants (N = 466,320)	164 (0.07)	271 (0.12)	39.6 (26.4 to 50.2)		
Female (n= 223,681)	63 (0.06)	100 (0.09)	36.9 (12.7 to 54.7)		
Male (n=242,639)	101 (0.08)	171 (0.14)	41.1 (24.2 to 54.4)		
Hospitalization for pneumonia				0.77	
All participants (N = 466,320)	1161 (0.50)	1187 (0.51)	2.3 (-6.0 to 10.0)		
Female (n= 223,681)	483 (0.43)	488 (0.44)	0.9 (-12.5 to 12.8)		
Male (n=242,639)	678 (0.56)	699 (0.58)	3.2 (-7.6 to 13.1)		



REFERENCE: 1. Johansen, N.D., et al., *High-dose influenza vaccine effectiveness against hospitalization in older adults.* New England Journal of Medicine, 2025. **FUNDING STATEMENT:** FLUNITY-HD was funded by Sanofi who participated in the study design, protocol development, and manuscript review phases, but had no responsibilities in trial conduct, data collection, or data analysis.**CONFLICTS OF INTEREST:**NDJ has received speaker fees from Sanofi. MML, RCH, MD, RvA, and AC are full-time employees of Sanofi and may own shares and/or stock options in the company. CSL has received speaker fees and served on advisory boards for GSK, MSD, Pfizer, Takeda, and Valneva. BLC has received consulting fees from Amgen, Cardurion, Corvia, Myokardia, and Novartis. SDS has received research grants from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, BMS, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lilly, Mesoblast, MyoKardia, NIH/NHLBI, Neurotronik, Novartis, Novo Nordisk, Respicardia, Sanofi, Theracos, 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. FM-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. TB-S has received research grants from Moderna, 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 Pfizer, AstraZeneca, Bayer, Novartis, Sanofi Pasteur, GE Healthcare, and GSK. All other authors declare no competing interests.**ACKNOWLEDGEMENTS:** The authors express their sincere appreciation to all study participants, to the Danish and Galician populations, and to the healthcare professionals in Denmark and Galicia for their invaluable support and contribution to the successful execution of the DANFLU-2 and GALFLU trials.