High-dose influenza vaccine in older adults by age and seasonal characteristics: Systematic review and meta-analysis update[1]

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Literature search: Up to 30 April 2023

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KEY TAKEAWAYS[1]

- HD-IIV continued to demonstrate better protection against influenza and associated serious outcomes, compared with the SD-IIV, irrespective of age, study type or setting, or characteristics of the influenza season, in a meta-analysis of efficacy/effectiveness data covering 12 seasons and including >45 million adults ≥65 years of age
- Data from this updated meta-analysis of randomized and observational studies add to the pool of evidence of HD-IIV relative to SD-IIV against severe influenza outcomes in adults aged ≥65 years

BACKGROUND

- Older adults (aged ≥65 years) are more vulnerable to influenza and influenza-associated complications compared with other age groups;[1–3] they also tend to be less responsive to SD-IIV than younger adults, this can be attributed to aging which causes immunosenescence[4,5]
  - To address this, the HD-IIV vaccine was developed, containing 60µg of HA per strain (roughly **4x** the amount of HA compared with SD-IIV)[2]
- In a systematic review and meta-analysis (literature search cutoff: 31 May 2020) based on 15 studies across 10 consecutive seasons, HD-IIV demonstrated better protection over SD-IIV in reducing influenza infection and associated complications[2]

OBJECTIVES[1]

- To update the systematic review and meta-analysis from 2020 with the latest available efficacy/effectiveness data of HD-IIV compared with SD-IIV in preventing clinical outcomes associated with influenza, from randomized and observational studies in adults ≥65 years of age

Primary objectives

To estimate pooled rVE against lab confirmed or probable **influenza-like illness (ILI) visits,** including hospitalizations due to influenza, pneumonia, cardiorespiratory, cardiovascular, and all cause admissions; and hospitalizations/ER visits due to influenza or pneumonia. The new outcomes in this updated analysis were hospitalizations/ER visits and CV hospitalizations

Secondary objectives

To estimate stratified rVE by:

- Age
- A/H3N2- or A/H1N1-predominant seasons
- Antigenically-matched or mismatched seasons

Sensitivity analysis of rVE by study type

STUDY CONDUCT[1]

Study Design

Systematic review and meta-analysis

of 21 published randomized and observational studies (six new studies beyond the 2020 analysis)

Participants

>45 million individuals

aged ≥65 years (including >29 million HD-IIV recipients)

Seasons

12 influenza seasons

Across influenza seasons (2009/2010 to 2019/2020, 2021/2022)

Literature search up to 30 April 2023[a]

[a]Inclusion criteria for publications included primary research studies conducted in adults aged ≥65 years that included HD-IIV and SD-IIV interventions and reported on the rVE against clinical outcomes.

Abbreviations: CV: cardiovascular; ER: emergency room; HA: hemagglutinin; HD-IIV: high-dose inactivated influenza vaccine; rVE: relative vaccine efficacy/effectiveness; SD-IIV: standard-dose inactivated influenza vaccine. **Disclosures:** Sanofi funded this study. Authors JKHL, GKLL, JKY, MML, and SIS are Sanofi employees.

References: 1. Lee JKH, et al. *Vaccine: X.* 2023;14:100327. doi: 10.1016/j.jvacx.2023.100327; 2. Lee JKH, et al. *Vaccine.* 2021;39 Suppl 1:A24–A35. doi: 10.1016/j.vaccine.2020.09.004; 3. CDC. FluView Interactive. Available at: https://www.cdc.gov/flu/weekly/fluviewinteractive.htm. Accessed 12 June 2023; 4. Tsang P, et al. *Vaccine.* 2014;32(21):2507–17. doi: 10.1016/j.vaccine.2013.09.074; 5. Weinberger B, et al. *Clin Microbiol Infect.* 2012;18 Suppl 5:100–8. doi: 10.1111/j.1469-0691.2012.03944.x; 6. ACIP. Available at: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-06-22-23/03-influenza-grohskopf-508.pdf. Accessed 12 June 2023; 7. ECDC. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/seasonal-influenza-vaccines-systematic-review-efficacy.pdf. Accessed 12 June 2023; 8. NACI. Available at: https://www.canada.ca/en/public-health/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2022-48/issue-9-september-2022/summary-national-advisory-committee-immunization-naci-seasonal-influenza-vaccine-statement-2022-2023.html. Accessed 12 June 2023; 9. ATAGI. Available at: https://www.health.gov.au/sites/default/files/2023-03/atagi-advice-on-seasonal-influenza-vaccines-in-2023.pdf. Accessed 12 June 2023; 10. Pérez-Rubio A, et al. *Rev Esp Quimioter.* 2021;32(6):631–638; 11. Clinicaltrials.gov. DANFLU-2, NCT05517174. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT05517174. Accessed 12 June 2023.

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RESULTS: HD-IIV VS SD-IIV[1]

POOLED rVE BY SEASON CHARACTERISTICS

	Primary objective	Predominant circulating strain[a]		Antigenic similarity with predominant circulating strain[b]	
Outcome rVE % (95% CI); n; p-value	**All seasons**	**A/H3N2-dominant seasons**	**A/H1N1-dominant seasons**	**Matched seasons**	**Mismatched seasons**
Influenza-like illness[c]	**14.3** (4.2, 23.3); n=11; p=0.007	**16.3** (2.5, 28.2); n=7; p=0.022	8.0 (-3.7, 18.4); n=4; p=0.170	20.4 (-10.7, 42.7); n=4; p=0.175	**13.7** (0.0, 25.5); n=7; p=0.050
Hospitalization + ER visit					
Influenza[d]	**10.4** (6.8, 13.9); n=13; p<0.001	**10.3** (5.4, 15.0); n=8; p<0.001	**11.0** (3.8, 17.6); n=5; p=0.003	**11.0** (3.8, 17.6); n=5; p=0.003	**10.3** (5.4, 15.0); n=8; p<0.001
Pneumonia[e]	4.4 (-0.1, 8.6); n=5; p=0.053	2.2 (-2.8, 6.9); n=3; p=0.384	8.4 (-0.7, 16.7); n=2; p=0.069	8.4 (-0.7, 16.7); n=2; p=0.069	2.2 (-2.8, 6.9); n=3; p=0.384
Hospitalization					
Influenza[d]	**11.2** (7.4, 14.8); n=11; p<0.001	**13.7** (7.0, 20.0); n=7; p<0.001	**7.2** (3.3, 11.0); n=4; p<0.001	**7.2** (3.3, 11.0); n=4; p<0.001	**13.7** (7.0, 20.0); n=7; p<0.001
Pneumonia[e]	**27.8** (12.5, 40.5); n=5 p<0.001	**39.9** (19.3, 55.3); n=2; p<0.001	**19.1** (5.0, 31.2); n=2; p=0.010	**28.7** (6.0, 45.9); n=3; p=0.016	–
Pneumonia/influenza[f]	**14.4** (6.8, 20.6); n=8; p<0.001	**13.7** (5.3, 21.4); n=6; p=0.002	**19.6** (3.0, 33.4); n=2; p=0.023	**13.5** (5.0, 21.3); n=5; p=0.002	19.3 (-0.3, 35.1); n=3; p=0.053
Respiratory	**14.7** (8.5, 20.4); n=7; p<0.001	**16.6** (8.4, 24.1); n=5; p<0.001	**10.3** (1.9, 17.9); n=2; p=0.018	**9.9** (4.5, 14.9); n=5; p<0.001	**21.3** (15.6, 26.7); n=3; p<0.001
Cardiovascular	**12.8** (10.2, 15.3); n=9; p<0.001	**12.8** (10.0, 15.6); n=7; p<0.001	**12.6** (5.8, 18.9); n=2; p<0.001	**12.5** (8.4, 16.4); n=5; p<0.001	**12.6** (8.6, 16.4); n=4; p<0.001
Cardiorespiratory	**16.7** (13.8, 19.5); n=9; p<0.001	**17.6** (14.2, 20.9); n=7; p<0.001	**14.1** (3.7, 23.4); n=2; p=0.009	**15.6** (11.8, 19.2); n=5; p<0.001	**18.4** (13.8, 22.9); n=4; p<0.001
All-cause	**8.2** (5.5, 10.8); n=12; p<0.001	**8.0** (4.4, 11.6); n=9; p<0.001	**8.9** (5.4, 12.2); n=3; p<0.001	**6.1** (3.6, 8.4); n=7; p<0.001	**12.6** (7.8, 17.2); n=5; p<0.001

POOLED rVE BY STUDY DESIGN[g]

Outcome rVE % (95% CI); n; p-value	RCTs	Observational studies
Influenza-like illness[c]	**24.1** (10.0, 36.1); n=3; p=0.002	11.1 (-0.1, 21.0); n=8; p=0.051
Hospitalization + ER visit		
Influenza[d]	–	**10.4** (6.8, 13.9); n=13; p<0.001
Pneumonia[e]	–	4.4 (-0.1, 8.6); n=5; p=0.053
Hospitalization		
Influenza[d]	–	**11.2** (7.4, 14.8); n=11; p<0.001
Pneumonia[e]	**27.8** (12.5, 40.5); n=4; p<0.001	–
Pneumonia/influenza[f]	–	**13.4** (7.3, 19.2); n=7; p<0.001
Respiratory	19.6 (-12.8, 42.8); n=2; p=0.207	**14.8** (7.6, 21.5); n=5; p<0.001
Cardiovascular	7.8 (-2.5, 17.0); n=4; p=0.132	**13.2** (10.5, 15.8); n=5; p<0.001
Cardiorespiratory	**12.2** (5.6, 18.3); n=4; p<0.001	**17.9** (14.7, 21.0); n=5; p<0.001
All-cause	**10.6** (2.7, 17.8); n=5; p=0.009	**7.8** (5.3, 10.3); n=7; p<0.001

SUBGROUP ANALYSIS BY AGE

Influenza-like illness

- The rVE (95% CI) was **21.1%** (12.4, 28.9; n=2; p<0.001) in those aged 65–74 years and **24.8%** (12.3, 35.6; n=3; p<0.001) among those aged ≥75 years

Hospitalization

- The rVE (95% CI) was **8.7%** (1.5, 15.2; n=7; p=0.018) in those aged 65–74 years, **12.2%** (7.3, 16.9; n=13; p<0.001) in those aged ≥75 years, and **16.0%** (9.8, 21.8; n=6; p<0.001) in those aged ≥85 years; a similar trend was observed for influenza-related hospitalization/ER visit

[a]Based on US CDC national surveillance data; [b]Based on US CDC data on viral antigenic characterization comparing reference vaccine strains with circulating viruses; [c]Probable/ laboratory confirmed influenza-like illness; [d]ICD-9-CM 487 coded hospitalizations; [e]ICD-9-CM 480–486 coded hospitalizations; [f]ICD-9-CM 480–488 coded hospitalizations; [g]Individual-level randomized and cluster-randomized studies. Results in bold where p≤0.05.

LIMITATIONS[1]

- There was statistical heterogeneity observed in several of the pooled rVE estimates
- The observational studies may have been impacted by unmeasured confounders (e.g., selection bias, health-seeking behaviour)

CONCLUSIONS[1]

- HD-IIV was consistently more effective than SD-IIV at reducing influenza-associated clinical outcomes in people aged ≥65 years, irrespective of age, study type or setting, or influenza season characteristics: demonstration through 5 randomized studies and confirmation of data in real-world by observational studies
  - These data are consistent with previous studies which have been assessed by health authorities through GRADE analysis[2,6–10]
- Large-scale randomized real-world studies are ongoing and have been designed to further demonstrate the public health benefits of quadrivalent HD-IIV compared with quadrivalent SD-IIV[11]

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