

Efficacy and effectiveness of high-dose influenza vaccine in older adults by age and seasonal characteristics: an updated systematic review and meta-analysis

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Key Takeaways

This meta-analysis confirms that the protection conferred by HD-IIIV in adults aged ≥65 years is consistently better to SD-IIIV irrespective of age and indicates that broader adoption of HD-IIIV could reduce influenza burden and alleviate strain on healthcare systems

BACKGROUND

- Since its approval in 2009, the high-dose inactivated influenza vaccine (HD-IIIV) has been used in older adults across multiple countries¹
- Evidence from multiple systematic reviews and meta-analyses have shown that HD-IIIV provides greater protection than standard-dose vaccine (SD-IIIV)*, including reduced hospitalisation risk²⁻⁵
- This recent updated analysis include two large, individually randomised pragmatic trials further assessing the relative effectiveness of HD-IIIV versus SD-IIIV* in older adults⁶⁻⁷

OBJECTIVE

Evidence update of previously-conducted systematic literature review (SLR) and meta-analysis of the relative vaccine efficacy/ effectiveness (rVE) of HD-IIIV compared to SD-IIIV against influenza-related outcomes in adults ≥65 years, across the 2009/10-2024/25 influenza seasons and assess the consistency of the results with additional sub-analyses by study design, seasonal and recipient characteristics⁴

METHODS

The methodology for this SLR has been previously published (Lee 2023, Lee 2021)^{3,4}. This updated analysis included additional studies published between January 1, 2023, and September 15, 2025

Key biomedical databases (Embase, MEDLINE All, Cochrane CENTRAL & CDSR via Ovid platform)

Inclusion Criteria

- Randomised or observational studies evaluating the efficacy or effectiveness of HD-IIIV vs. SD-IIIV against probable/laboratory-confirmed influenza-like illness (ILI), emergency department (ED) visits, and a range of hospitalisations potentially attributable to influenza in adults ≥65 years

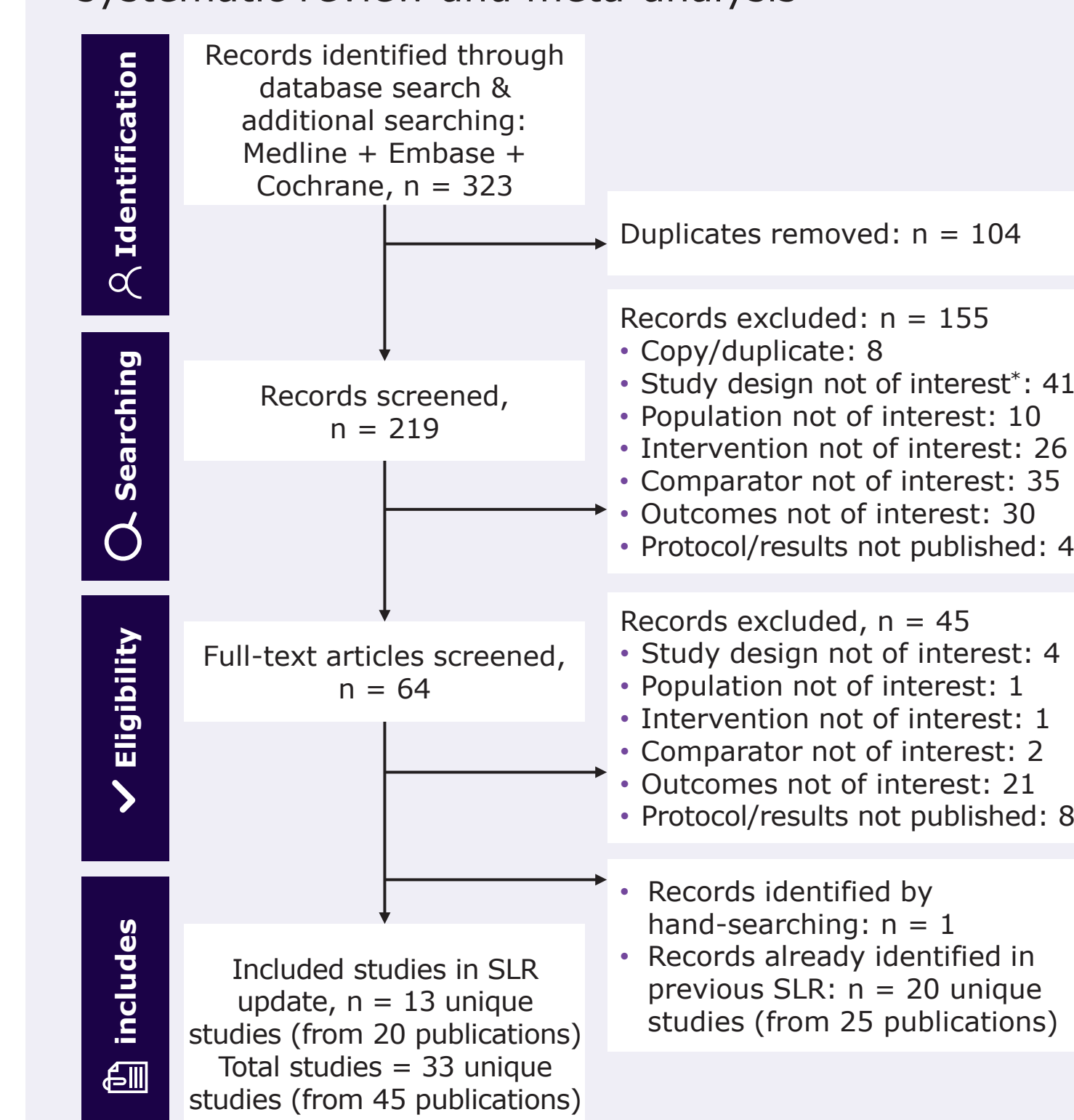
Exclusion Criteria

- Studies with individuals aged <65 years
 - Pandemic/avian/swine influenza vaccines monovalent or bivalent influenza vaccines
 - Experimental vaccines and cell-based or adjuvanted influenza vaccines
 - Studies reporting evidence only on immunogenicity

Analysis

- Effect estimate (i.e., odds ratio [OR] relative risk [RR]) for each clinical outcome was collected from identified studies
- Pooled ORs across multiple studies and influenza seasons was calculated using a random-effects model with DerSimonian-Laird estimators, and rVE was estimated for the pooled estimates with 95% confidence intervals (CIs) in R (v4.3.2)
- Study heterogeneity was assessed using I²
- Publication bias was assessed using funnel plots, and quality of individual studies assessed by Downs and Black critical appraisal tool

Figure 1: Flowchart of studies included in the systematic review and meta-analysis



*Includes Review / Single arm trials / Case series / Case reports / Editorial / Letter / Note / Commentary PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

*SD-IIIV, egg-based unadjuvanted standard-dose inactivated influenza vaccine

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RESULTS

Based on the feasibility, twenty-nine studies (7 randomised, 22 observational) covering 15 Influenza seasons and >85 million vaccinated individuals were included in this updated analysis

Table 1: Summary of updated HD-IIIV Efficacy/Effectiveness Publications

Author (Year)	Study Design	Study Location	Influenza Seasons	Study Population	Study Outcomes
Randomised Studies*					
Johansen, 2025 (NCT05517174)	Phase IV, pragmatic, open-label, registry-based RCT	Denmark	2022-23, 2023-24; 2024-25	Healthy adults ≥65 • HD: 166,218 ; SD: 166,220	• Hospital admission for Influenza or pneumonia, laboratory confirmed Influenza, Influenza ICD coded, cardiorespiratory diseases, pneumonia and cardiovascular diseases • All-cause Hospitalisation
Pardo-Seco, 2025 (NCT06141655)	Phase IV, pragmatic, open-label, registry-based RCT	Spain	2023-24, 2024-25	Community-dwelling adults; 65 to 79 years • HD: 67, 093; SD: 66,789	• Hospital admission for Influenza or pneumonia, laboratory confirmed Influenza, Influenza ICD coded, cardiorespiratory diseases, cardiovascular diseases, cardiorespiratory and pneumonia • All-cause Hospitalisation
Palmu, 2024 (NCT04137887)	Phase IIIb-IV, pragmatic, open-label, registry-based RCT	Finland	2019-20	Healthy adults ≥65 • HD: 16,549; SD: 16,544	• Hospitalisation for Influenza ICD coded, respiratory diseases, cardiorespiratory, P/L, pneumonia, cardiovascular diseases • All-cause Hospitalisation
Observational Studies					
Bricout, 2024	Retrospective Cohort Study	France	2021-22	Individuals living in the community in France; ≥65 years • HD: 4,05,385; SD: 16,21,540	• Hospitalisation for Influenza ICD coded, respiratory diseases, cardiovascular diseases, and influenza or pneumonia
Bricout, 2024a	Retrospective Cohort Study	France	2022-23	Individuals living in the community in France; ≥65 years • HD: 6,75,412; SD: 27,01,648	• Hospitalisation for Influenza ICD coded, respiratory diseases, cardiorespiratory, pneumonia, and influenza or pneumonia
Domnich, 2024	Test-negative case-control	Italy	2023-24	Adult inpatients with prescription of a RT-PCR test for influenza virus detection; ≥18 years • HD: 282; SD: 162; Adjuvanted: 140	• Hospitalisation for laboratory confirmed Influenza
Emborg, 2025	Test-negative case-control	Denmark	2024-25	Individuals tested for influenza A or B; ≥65 years • HD: 1408; SD: 4010; Adjuvanted: 15,197	• Probable or laboratory-confirmed ILI • Hospitalisation for laboratory confirmed Influenza
Imran, 2024	Retrospective cohort study	US	2019-20	Healthy adults ≥65 • HD: 24,48,403; SD: 7,67,725; Adjuvanted: 10,83,466	• Hospitalisation for Influenza ICD coded, pneumonia, respiratory and cardiorespiratory diseases
Ku, 2024	Retrospective cohort study	US	2022-23	Healthy adults ≥65 • HD: 3,70,543; SD: 69,006; SD cell-based: 32,062; Adjuvanted: 23,508	• Hospitalisation for laboratory confirmed Influenza, pneumonia and cardiorespiratory diseases • Influenza-related medical encounters
Najafzadeh, 2024	Retrospective Cohort Study	US	2016-17, 2017-18, 2018-19	Medicare beneficiaries ≥65 • HD: 53,393; SD: 53,393	• Hospitalisation for cardiorespiratory diseases
Yaron, 2025	Retrospective Cohort Study	Israel	2022-23, 2023-24	CHS members who received influenza vaccine; ≥65 years • 2022-23 - HD: 8728; SD: 403065 2023-24 - HD: 8063; SD: 377126	• Hospitalisation for Influenza ICD coded

*Includes individual-level randomized studies; HD, High-dose trivalent influenza vaccine; ICD, International Classification of Diseases; RCT, Randomised controlled trial; SD, Standard-dose trivalent/quadrivalent influenza vaccine

Table 2 (A): Pooled relative vaccine efficacy/effectiveness of HD-IIIV versus SD-IIIV against influenza-related outcomes for all seasons and sub-analyses by age

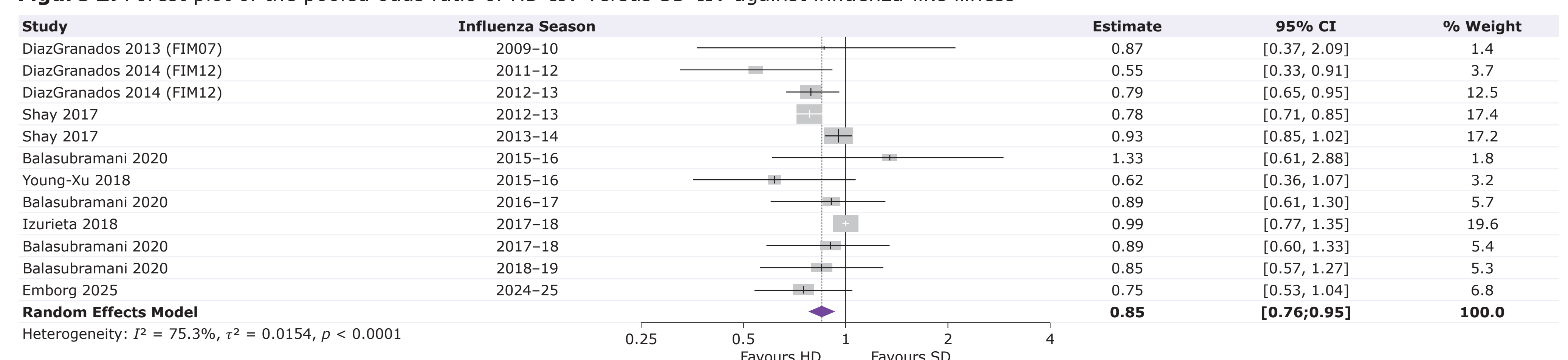
Outcome rVE (95% CI); n; p-value	All Seasons	A/H3N2-dominant Seasons ^a	A/H1N1-dominant Seasons ^a	Matched Seasons ^b	Mismatched Seasons ^b
Probable Influenza-like Illness (ILI)	15% (5 - 24%); n=12; I ² = 75%	16% (3 - 28%); n=7; I ² = 84%	11% (-2 - 22%); n=5; I ² = 9%	18% (1 - 31%); n=6; I ² = 39%	14% (-1 - 27%); n=6; I ² = 85%
Hospitalisation+ER Visit					
Influenza^c	10% (7 - 14%); n=14; I ² = 75%	10% (4 - 15%); n=9; I ² = 81%	12% (5 - 18%); n=5; I ² = 62%	11% (6 - 15%); n=7; I ² = 54%	10% (4 - 16%); n=7; I ² = 85%
Pneumonia^d	6% (3 - 8%); n=6; I ² = 16%	5% (1 - 8%); n=4; I ² = 32%	7% (4 - 11%); n=2; I ² = 0%	5% (1 - 9%); n=3; I ² = 56%	6% (3 - 9%); n=3; I ² = 0%
Hospitalisation					
Influenza (ICD coded)^c	16% (11 - 21%); n=21; I ² = 75%	16% (9 - 23%); n=10; I ² = 81%	18% (9 - 26%); n=10; I ² = 70%	19% (11 - 25%); n=14; I ² = 72%	14% (6 - 21%); n=6; I ² = 83%
Influenza (lab confirmed)	29% (20 - 37%); n=11; I ² = 0%	25% (11 - 38%); n=4; I ² = 89%	31% (20 - 41%); n=7; I ² = 0%	29% (20 - 37%); n=3; I ² = 0%	-
Pneumonia^d	7% (-2 - 16%); n=13; I ² = 90%	-1% (-9 - 7%); n=6; I ² = 70%	10% (-2 - 20%); n=7; I ² = 71%	7% (-5 - 17%); n=10; I ² = 92%	18% (-18 - 43%); n=3; I ² = 0%
Pneumonia or Influenza^a	9% (4 - 14%); n=18; I ² = 45%	7% (2 - 13%); n=9; I ² = 50%	12% (5 - 18%); n=8; I ² = 11%	9% (4 - 14%); n=13; I ² = 24%	12% (-3 - 24%); n=4; I ² = 76%
Respiratory	12% (6 - 18%); n=13; I ² = 90%	13% (5 - 20%); n=9; I ² = 85%	16% (14 - 17%); n=4; I ² = 0%	9% (1 - 17%); n=8; I ² = 90%	20% (5 - 33%); n=5; I ² = 90%
Cardiovascular	8% (2 - 13%); n=12; I ² = 87%	7% (1 - 12%); n=9; I ² = 89%	13% (7 - 18%); n=3; I ² = 0%	9% (0 - 16%); n=7; I ² = 86%	7% (-5 - 16%); n=5; I ² = 90%
Cardiorespiratory	8% (5 - 11%); n=23; I ² = 93%	7% (3 - 10%); n=14; I ² = 89%	10% (6 - 13%); n=8; I ² = 51%	8% (4 - 12%); n=15; I ² = 94%	9% (3 - 14%); n=7; I ² = 90%
All-cause	6% (3 - 8%); n=18; I ² = 66%	8% (5 - 11%); n=10; I ² = 54%	4% (1 - 7%); n=8; I ² = 57%	4% (2 - 6%); n=13; I ² = 35%	11% (8 - 15%); n=5; I ² = 38%

Table 2 (B): Sub-analyses by subject age

Outcome rVE (95% CI); n; p-value	Subject Age			
	65-74	75-84 (incl. 75+)	75+	85+
Probable or laboratory confirmed ILI	21% (13 - 29%); n=2; I ² = 0%	18% (5 - 29%); n=1; I ² = NA	25% (12 - 36%); n=3; I ² = 23%	36% (12 - 53%); n=1; I ² = NA
Influenza ER Visit or Hospitalisation^a	7% (0 - 13%); n=7; I ² = 35%	11% (5 - 18%); n=7; I ² = 84%	11% (5 - 18%); n=7; I ² = 82%	16% (11 - 21%); n=7; I ² = 76%
Influenza Hospitalisation (ICD coded)^a	13% (5 - 20%); n=9; I ² = 34%	12% (5 - 19%); n=9; I ² = 74%	-	19% (12 - 25%); n=8; I ² = 75%
Influenza Hospitalisation (lab confirmed)	36% (22 - 48%); n=4; I ² = 0%	-	22% (-5 - 42%); n=2; I ² = 0%	-
Pneumonia or Influenza Hospitalisation^c	7% (-9 - 17%); n=3; I ² = 0%	9% (-19 - 30%); n=3; I ² = 64%	6% (-5 - 15%); n=2; I ² = 0%	24% (-41 - 59%); n=2; I ² = 76%
Pneumonia Hospitalisation^b	5% (-16 - 22%); n=2; I ² = 24%	4% (-8 - 14%); n=2; I ² = 0%	1% (-11 - 11%); n=2; I ² = 0%	24% (-41 - 59%); n=2; I ² = NA
Respiratory Hospitalisation	8% (-1 - 16%); n=3; I ² = 0%	7% (-10 - 22%); n=2; I ² = 64%	2% (-7 - 10%); n=3; I ² = 0%	32% (-52 - 69%); n=2; I ² = 67%
Cardiovascular Hospitalisation	10% (3 - 17%); n=3; I ² = 7%	2% (-6 - 10%); n=2; I ² = 0%	2% (-8 - 12%); n=3; I ² = 20%	-3% (-64 - 35%); n=2; I ² = 56%
Cardiorespiratory Hospitalisation	9% (3 - 14%); n=3; I ² = 0%	4% (-2 - 10%); n=2; I ² = 0%	3% (-4 - 9%); n=3; I ² = 6%	8% (-6 - 20%); n=2; I ² = 0%
All-cause Hospitalisation	3% (1 - 6%); n=2; I ² = 0%	0% (-3 - 3%); n=2; I ² = 0%	0% (-3 - 3%); n=2; I ² = 0%	4% (-4 - 11%); n=1; I ² = NA

^aBased on US CDC national surveillance data (2009-10 to 2019-20) and based on FLUNET (sentinel only, norther hemisphere; 2021-22 to 2024-25) data on viral antigenic characterisation comparing reference vaccine strains with circulating viruses; ^bICD-9-CM 487, 488; ICD-10 J09 to J11 coded hospitalisations; ^cICD-9-CM 480-486; ICD-10 J12-J18 coded hospitalisations; CI, confidence interval; ER, Emergency Room; I², Heterogeneity; ILI, Influenza like illness rVE, relative vaccine efficacy/effectiveness

Figure 2: Forest plot of the pooled odds ratio of HD-IIIV versus SD-IIIV against influenza-like illness



A random-effects model with DerSimonian-Laird estimators was used to calculate the pooled OR across multiple studies and influenza seasons.

DISCUSSION & CONCLUSIONS

- HD-IIIV consistently showed greater protection versus SD-IIIV against influenza infection and severe outcomes, including hospitalisations ranging from influenza to all-causes across 15 seasons
- Sub-analyses showed consistent benefit regardless of circulating strains, vaccine match or mismatch, or study type (randomised or observational designs). Age-stratified analyses suggested consistent relative benefit by age
- I² values were indicative of high heterogeneity for ILI, influenza hospitalisation, and cardiorespiratory hospitalisation endpoints; however, heterogeneity dropped in the stratum of randomised studies, demonstrating the importance of randomization and indicating this stratum may be the most robust



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