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

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ABSTRACT

This updated systematic review and *meta*-analysis of randomized and observational studies published up to April 2023 assessed the relative performance of high-dose inactivated influenza vaccine (HD-IIV) and standard-dose influenza vaccines (SD-IIV) against influenza-associated outcomes in older adults (≥65 years).

The analysis included studies conducted over 12 influenza seasons (2009/2010 to 2019/2020, 2021/2022), including over 45 million individuals aged ≥ 65 years, and showed that HD-IIV provided significantly better protection than SD-IIV against influenza-like illness and influenza-related hospitalizations, as well as cardiovascular, cardiorespiratory, and all-cause hospitalizations. Subgroup analyses showed HD-IIV consistently provided better protection than SD-IIV against influenza outcomes across the age range (65+, 75+ 85+ years), and regardless of the predominantly circulating influenza strain and vaccine antigenic match/mismatch.

Randomized studies continue to drive high-quality evidence on the effectiveness of high-dose inactivated influenza vaccine relative to SD-IIV against severe influenza outcomes in adults aged ≥ 65 years, supported by observational data.

Introduction

The burden of influenza and influenza-related complications is much higher in older adults (≥65 years) than in other age groups [1], yet little is known about how the burden changes with advanced age beyond 65 years. A systematic review and *meta*-analysis covering the period 1967 to 2011 highlighted the non-optimal protection against seasonal influenza in older people [2].

Among seasonal influenza vaccines administered to people aged ≥ 65 years during the 2018/19 influenza season in the US, nearly two-thirds received high-dose (HD), inactivated vaccine (Fluzone High-Dose, Sanofi Pasteur Inc) [3]. The trivalent version of the HD vaccine (HD-IIV3) was first approved in the US in 2009, and was available until the end of the 2019/20 influenza season, after which it was replaced by the quadrivalent (HD-IIV4) version which was approved in 2019 [3]. A systematic review and *meta*-analysis of HD-IIV3 based on 15 studies conducted during influenza seasons between 2009/10 and 2018/19 in the US showed that the relative vaccine effectiveness (rVE) for HD-IIV3 versus standard-dose (SD) IIV was 15.9% (95% CI 4.1%, 26.3%) against ILI and was 8.4% (5.7%; 11.0%) against all-cause hospital admissions [4]. The analysis showed that HD-IIV3 provided significantly better protection than SD-IIV at reducing influenza infections and associated complications regardless of dominant circulating strain and antigenic match.

For the 2022/23 influenza season, the Advisory Committee on Immunization Practices (ACIP) recommended that adults aged ≥ 65 years preferentially receive quadrivalent high-dose inactivated influenza vaccine (HD-IIV4), quadrivalent recombinant influenza vaccine (RIV4), or quadrivalent adjuvanted inactivated influenza vaccine (aIIV4) [5,6]. This recommendation, based on a Grading of Recommendations Assessment, Development and Evaluation (GRADE) review performed by ACIP in June 2022, stated that 'the most data, for the most outcomes, are available to support the high dose vaccine.' [1,5].

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In this updated *meta*-analysis, we build upon the existing evidence for HD-IIV3/4 [7] with newly published studies, additional outcomes, and age subgroup analyses.

Methods

Systematic review

The methods of this systematic review and *meta*-analysis have been previously published [7]. This report provides an update including studies published up to 30 April 2023. A PRISMA framework was used to identify randomized and observational studies evaluating the rVE of HD-IIV versus SD-IIV against influenza-related outcomes in adults aged ≥ 65 years.

The primary objective was to estimate the pooled rVEs across influenza seasons against: laboratory-confirmed or probable ILI (visits with a rapid influenza diagnostic test followed by prescription of antiviral medication); hospitalizations due to influenza, pneumonia, cardiorespiratory, cardiovascular, and all-cause admissions; and hospitalizations/ER visits due to influenza or pneumonia. To improve specificity of the non-influenza outcomes, studies using administrative databases were included only if admission or discharge diagnostic codes of interest were used for the principal or secondary diagnosis.

Secondary objectives were to estimate stratified rVE estimates, including: by age (65–74 years, 74–85 years, ≥ 75 years, and ≥ 85 years); during A/H3N2– or A/H1N1-predominant seasons; during antigenically-matched or mismatched seasons. Data on the predominant circulating strain and antigenic match/mismatch of the vaccine was evaluated using US CDC viral surveillance data [1]. Additional sensitivity analyses were performed using only randomized and observational studies to estimate the pooled rVE.

Data abstraction and meta-analysis

Articles were included if they were primary research studies (randomized controlled trials [RCTs] and observational studies) conducted in adults aged ≥ 65 years where the interventions included HD-IIV and SD-IIV and reported on the rVE against clinical (not immunogenicity) outcomes. A modified Downs and Black critical appraisal tool for randomized and non-randomized studies was used to assess study quality: excellent (25–27), good (19–24), fair (14–18), and poor (≤ 13) [8]. Data abstraction was performed as previously described [7], and the odds ratios (ORs) and standard error (SE) were calculated. Egger's test was used to quantify potential asymmetry between the ORs of effect measures and the SEs [9]. Higgins' I^2 statistic was used to assess study heterogeneity [10].

Results from individual seasons were stratified based on clinical outcomes, characteristics of study subjects, and influenza season. Meta-analyses were then performed to estimate pooled rVEs of HD-IIV versus SD-IIV. Pooled ORs across multiple studies and influenza seasons were calculated using a random-effects model with DerSimonian–Laird estimators, and rVE was calculated for the pooled estimates with 95% confidence intervals (CI).

Results

Characteristics of identified studies

A flowchart of the publications included in the analysis is shown in Supplement 1. This updated analysis included six new studies (Table 1), beyond the 15 included in the 2020 analysis (Supplement 2)[11–16]. No evidence of publication bias was detected with funnel plots/Egger's test (Supplement 3).

Table 1
Overview of new studies identified for inclusion in the 2022 systematic review.

Citation, year	Design, country	Influenza seasons	Dominant strain (% of all circulating strains); antigenic match of dominant strain with the vaccine	Size of population aged ≥ 65 years	Influenza-related outcomes	Study quality (Downs and Black Score)
VanAalst, 2021 [16]	Retrospective cohort study, US	2010–11 2011–12 2012–13 2013–14 2014–15	A/H3N2 (84.0%); 96.8% match A/H3N2 (87.0%); 82.0% match A/H3N2 (86.4%); 99.6% mismatch A/H1N1 (57.2%); 99.9% match A/H3N2 (90.6%); 18.6% mismatch	VHA adults HD: 158,636 SD: 3,480,288	Cardiovascular, respiratory, cardiorespiratory hospitalization	**Good (19)**
Machado, 2021 [14]	Retrospective cohort study, US	2012–13 2013–14 2014–15 2015–16 2016–17 2017–18	A/H3N2 (86.4%); 99.6% mismatch A/H1N1 (57.2%); 99.9% match A/H3N2 (90.6%); 18.6% mismatch A/H1N1 (48.4%); 99.9% match A/H3N2 (79.0%); 96.6% mismatch A/H3N2 (69.4%); 93.4% mismatch	Adults from MarketScan® databases HD: 728,223 SD: 1,633,093	Influenza / pneumonia hospital/ER visit	**Good (20)**
Balasubramani, 2020 [11]	Test-negative case control study, US	2015–16 2016–17 2017–18 2018–19	A/H1N1 (48.4%); 99.9% match A/H3N2 (79.0%); 96.6% mismatch A/H3N2 (69.4%); 93.4% mismatch A/H3N2 (53.3%) 11.0% mismatch	HAIVEN patients HD: 3,861 SD: 2,993	Influenza-confirmed acute respiratory illness	**Good (21)**
Izurieta, 2021 [12]	Retrospective cohort study, US	2019–20	A/H1N1 (71.0%); 96.0% match	Medicare beneficiaries HD: 7,173,433 SD: 1,584,451	Influenza-related hospital encounters / inpatient stays	**Good (19)**
Saade, 2022 [15] (NCT01815268)	Single-blind, pragmatic, comparative effectiveness, cluster RCT	2013–14	A/H1N1 (57.2%); 99.9% match	*Residents ≥ 65 in NHs* • HD: 26,639 • SD: 26,369	- Hospital admissions related to cardiovascular, pulmonary and influenza-like conditions - Major acute cardiovascular events or respiratory admissions - Hospital admission by any cause	**Good (24)**
Johansen, 2023 [13] (NCT05048589)	Pragmatic, open-label, active-controlled, randomized feasibility trial	2021–22	A/H3N2 (78.7%); 21.0% mismatch	Danish adults 65–79 • HD: 6,245 • SD: 6,232	- Hospitalization for pneumonia or influenza, respiratory or cardiorespiratory disease - All-cause mortality	**Good (24)**

HD, high-dose; IIV, inactivated influenza vaccine; SD, standard dose, VHA, veteran health administration.

Table 2
Pooled relative vaccine efficacy/effectiveness of HD-IIV3 versus SD-IIV against influenza-related outcomes.

Outcome	All seasons HD vs SD rVE (95% CI)	Predominant circulating strain[a] HD vs SD rVE (95% CI)		Antigenic similarity with predominant circulating strain[b] HD vs SD rVE (95% CI)		Study design[c] HD vs SD rVE (95% CI)	
		A/H3N2-dominant	A/H1N1- dominant	Matched seasons	Mismatched seasons	RCTs	Observational studies
Influenza-like illness[d]	n = 11 14.3% (4.2%, 23.3%) p = 0.007	n = 7 16.3% (2.5%, 28.2%) p = 0.022	n = 4 8.0% (−3.7%, 18.4%) p = 0.170	n = 4 20.4% (−10.7%, 42.7%) p = 0.175	n = 7 13.7% (0.0%, 25.5%) p = 0.050	n = 3 24.1% (10.0%, 36.1%) p = 0.002	n = 8 11.1% (−0.1%, 21.0%) p = 0.051
Hospitalization/ER							
Influenza[e]	n = 13 10.4% (6.8%, 13.9%) p < 0.001	n = 8 10.3% (5.4%, 15.0%) p < 0.001	n = 5 11.0% (3.8%, 17.6%) p = 0.003	n = 5 11.0% (3.8%, 17.6%) p = 0.003	n = 8 10.3% (5.4%, 15.0%) p < 0.001	–	n = 13 10.4% (6.8%, 13.9%) p < 0.001
Pneumonia[f]	n = 5 4.4% (−0.1%, 8.6%) p = 0.053	n = 3 2.2% (−2.8%, 6.9%) p = 0.384	n = 2 8.4% (−0.7%, 16.7%) p = 0.069	n = 2 8.4% (−0.7%, 16.7%) p = 0.069	n = 3 2.2% (−2.8%, 6.9%) p = 0.384	–	n = 5 4.4% (−0.1%, 8.6%) p = 0.053
Hospitalization							
Influenza[e]	n = 11 11.2% (7.4%, 14.8%) p < 0.001	n = 7 13.7% (7.0%, 20.0%) p < 0.001	n = 4 7.2% (3.3%, 11.0%) p < 0.001	n = 4 7.2% (3.3%, 11.0%) p < 0.001	n = 7 13.7% (7.0%, 20.0%) p < 0.001	–	n = 11 11.2% (7.4%, 14.8%) p < 0.001
Pneumonia[f]	n = 5 27.8% (12.5%, 40.5%) p < 0.001	n = 2 39.9% (19.3%, 55.3%) p < 0.001	n = 2 19.1% (5.0%, 31.2%) p = 0.010	n = 3 28.7% (6.0%, 45.9%) p = 0.016	–	n = 4 27.8% (12.5%, 40.5%) p < 0.001	
Pneumonia/ Influenza[g]	n = 8 14.4% (6.8%, 20.6%) p < 0.001	n = 6 13.7% (5.3%, 21.4%) p = 0.002	n = 2 19.6% (3.0%, 33.4%) p = 0.023	n = 5 13.5% (5.0%, 21.3%) p = 0.002	n = 3 19.3% (−0.3%, 35.1%) p = 0.053	–	n = 7 13.4% (7.3%, 19.2%) p < 0.001
Respiratory	n = 7 14.7% (8.5%, 20.4%) p < 0.001	n = 5 16.6% (8.4%, 24.1%) p < 0.001	n = 2 10.3% (1.9%, 17.9%) p = 0.018	n = 5 9.9% (4.5%, 14.9%) p < 0.001	n = 3 21.3% (15.6%, 26.7%) p < 0.001	n = 2 19.6% (−12.8%, 42.8%) p = 0.207	n = 5 14.8% (7.6%, 21.5%) p < 0.001
Cardiovascular	n = 9 12.8% (10.2%, 15.3%) p < 0.001	n = 7 12.8% (10.0%, 15.6%) p < 0.001	n = 2 12.6% (5.8%, 18.9%) p < 0.001	n = 5 12.5% (8.4%, 16.4%) p < 0.001	n = 4 12.6% (8.6%, 16.4%) p < 0.001	n = 4 7.8% (−2.5, 17.0%) p = 0.132	n = 5 13.2% (10.5%, 15.8%) p < 0.001
Cardiorespiratory	n = 9 16.7% (13.8%, 19.5%) p < 0.001	n = 7 17.6% (14.2%, 20.9%) p < 0.001	n = 2 14.1% (3.7%, 23.4%) p = 0.009	n = 5 15.6% (11.8%, 19.2%) p < 0.001	n = 4 18.4% (13.8%, 22.9%) p < 0.001	n = 4 12.2% (5.6%, 18.3%) p < 0.001	n = 5 17.9% (14.7%, 21.0%) p < 0.001
All-cause	n = 12 8.2% (5.5%, 10.8%) p < 0.001	n = 9 8.0% (4.4%, 11.6%) p < 0.001	n = 3 8.9% (5.4%, 12.2%) p < 0.001	n = 7 6.1% (3.6%, 8.4%) p < 0.001	n = 5 12.6% (7.8%, 17.2%) p < 0.001	n = 5 10.6% (2.7%, 17.8%) p = 0.009	n = 7 7.8% (5.3%, 10.3%) p < 0.001

CDC, Centers for Disease Control and prevention; CI, confidence interval; ER, emergency room; HD, high-dose; IIV, inactivated influenza vaccine; RCT, randomized controlled trial; rVE, relative vaccine efficacy/effectiveness; SD, standard dose.

[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] Individual-level randomized and cluster-randomized studies.
[d] Probable/laboratory confirmed influenza-like illness.
[e] ICD-9-CM 487 coded hospitalizations.
[f] ICD-9-CM 480–486 coded hospitalizations.
[g] ICD-9-CM 480–488 coded hospitalizations.

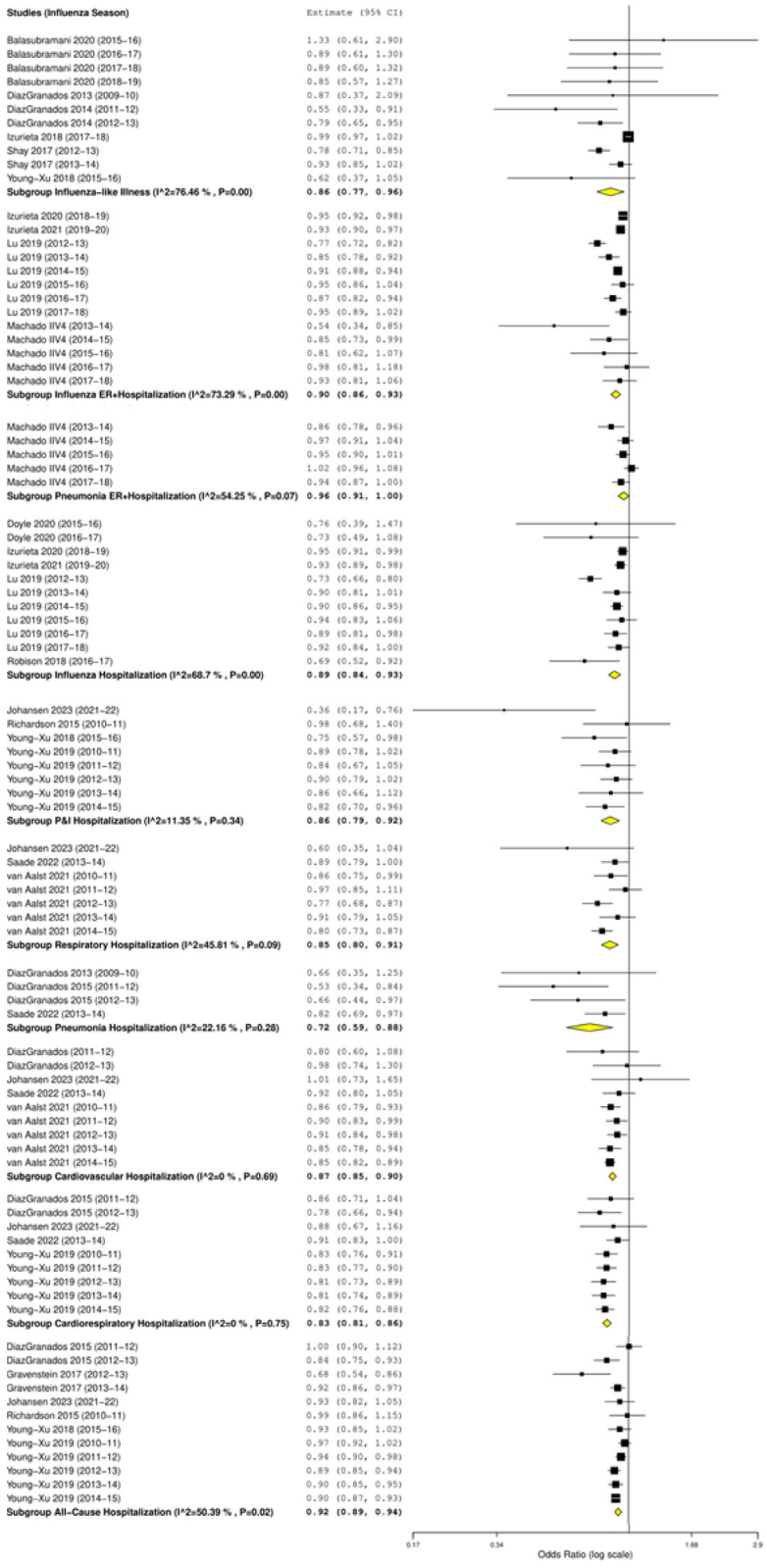

Fig. 1. Forest plots of the pooled OR of HD-IIV3 versus SD-IIV against influenza-related outcomes.

Probable or laboratory-confirmed ILI

Based on 11 studies the rVE of HD-IIV3 versus SD-IIV against ILI was 14.3% (95% CI 4.2%, 23.3%; p = 0.007) across all seasons. For A/H3N2-dominant seasons, the rVE was 16.3% (95% CI 2.5%, 28.2%; p = 0.022), and for A/H1N1-dominant seasons the rVE was 8.0% (95% CI −3.7%, 18.4%; p = 0.170) (Table 2; Fig. 1).

In eight of the 12 seasons, there was a mismatch between vaccine and circulating strains, including during 2018/19, when half of the circulating strains were A/H3N2, of which 11.0%

Table 3
Pooled relative vaccine efficacy/effectiveness of HD-IIV3 versus SD-IIV against influenza-related outcomes according to age.

Outcome	Age subgroup rVE (95% CI)			
	65–74 years	**75–84 years**	**≥75 years**	**≥85 years**
Influenza-like illness	n = 2 21.1% (12.4%, 28.9%) p < 0.001	n = 2 21.9% (7.8%, 33.9%) p = 0.004	n = 3 24.8% (12.3%, 35.6%) p < 0.001	–
Influenza-related				
Hospitalization/ER visit	n = 6 4.6% (-1.7%, 10.5%) p = 0.146	n = 6 9.0% (3.1%, 14.5%) p = 0.003	n = 12 12.0% (7.8%, 16.0%) p < 0.001	n = 6 14.9% (9.4%, 20.1%) p < 0.001
Hospitalization	n = 7 8.7% (1.5%, 15.2%) p = 0.018	n = 7 8.3% (1.4%, 14.7%) p = 0.019	n = 13 12.2% (7.3%, 16.9%) p < 0.001	n = 6 16% (9.8%, 21.8%) p < 0.001

CI, confidence interval; ER, emergency room; HD, high-dose; IIV, inactivated influenza vaccine; rVE, relative vaccine efficacy/effectiveness; SD, standard dose.

were mismatched with the vaccine strain[1]. Sub-analyses showed that the rVE of HD versus SD against ILI was 20.4% (95% CI −10.7%, 42.7%; p=0.175) in matched seasons and 13.7% (95% CI 0.0%, 25.5%; p = 0.050) in mismatched seasons. Apart from the antigenic mismatch of pandemic A/H1N1 virus with the seasonal vaccine in 2009/10, all of the other mismatched seasons were dominated by A/H3N2 viruses that had mutated.

Hospitalizations and ER visits

HD-IIV was more effective than SD-IIV for the prevention of influenza-related hospitalizations, with an rVE of 11.2% (7.4%, 14.8%; p<0.001) for all seasons and 13.7% (7.0%, 20.0%; p<0.001) for A/H3N2-dominant seasons. Included in this updated analysis were respiratory-related hospitalizations and cardiovascular-related hospitalizations, where pooled rVEs across seasons were 14.7% (8.5%, 20.4%; p < 0.001) and 12.8% (10.2%, 15.3%; p<0.001), respectively.

Further outcomes reported in this update were influenza- or pneumonia-related hospitalizations/ER visits. Based on 13 observational studies of HD-IIV3 versus SD-IIV, rVE against influenza-related hospitalizations/ER visits was 10.4% (6.8%, 13.9%; p=0.001) across all seasons (Table 2**;** Fig. 1). HD-IIV3 was more effective than SD-IIV for protection against influenza-related hospitalizations/ER visits during matched and mismatched season, and during A/H3N2– and A/H1N1-dominant seasons (Table 2).

Subgroup analysis by age

The rVE was consistent across all age ranges. Among 65–74 year-olds, the rVE for HD-IIV3 versus SD-IIV against ILI was 21.1% (12.4%, 28.9%; p<0.001); among those aged ≥75 years, the rVE was 24.8% (12.3%, 35.6%; p<0.001) (Table 3). For influenza-related hospitalizations, HD-IIV3 was more effective than SD-IIV with a rVE of 8.7% (1.5%, 15.2%; p=0.018) in those aged 65–74 years; however, rVE increased with age to 12.2% (7.3%, 16.9%; p<0.001) in those aged ≥75 years, and to 16.0% (9.8%, 21.8%; p<0.001) in those aged ≥85 years. A similar trend was observed for rVE against influenza-related hospitalization/ER visit.

Subgroup analysis by study type

In RCTs, the rVE for HD-IIV3 versus SD-IIV against ILI was 24.1% (10.0%, 36.1%; p=0.002; three studies); in observational studies, the rVE was 11.1% (-0.1%, 21.0%; p=0.051; eight studies) (Table 1). The largest RCT of HD-IIV3 versus SD-IIV against laboratory-confirmed influenza, which included 32,000 participants in the USA and Canada over the 2011/12 and 2012/13 influenza seasons and met the pre-defined criteria for superiority, demonstrated an rVE of 24.2% (9.7%, 36.5%) [17].

Discussion

This *meta*-analysis of studies conducted over 12 influenza seasons, including over 45 million individuals aged ≥65 years, showed that HD-IIV provided significantly better protection than SD-IIV against ILI and influenza-related hospitalizations, as well as pneumonia-related hospitalizations, and cardiovascular, cardiorespiratory, and all-cause hospitalizations. New outcomes in the updated analysis were hospitalizations/ER visits and CV hospitalizations, against which HD-IIV provided better protection than SD-IIV. Furthermore, HD-IIV was more effective than SD-IIV against ILI during A/H3N2-dominant seasons and during seasons with vaccine mismatches.

This updated analysis included a subgroup analysis by age. HD-IIV provided better protection than SD-IIV against ILI in those aged 65–74 years and ≥75 years, and provided better protection against hospitalization/ER visits among those aged ≥75 years and ≥85 years, but not among those aged 65–74 years. Overall, the trend of protection for HD-IIV over SD-IIV against severe influenza outcomes across the age groups is consistent with and well supported by prior research [18,19].

A recent study assessing the rVE of HD-IIV versus SD-IIV against cardiopulmonary outcomes was not included in this analysis [20]. This RCT, assessing rVE against all-cause death or cardiopulmonary hospitalization over three seasons (2016/17–2019/20) among 5,373 high-risk patients aged 18+ years with recent acute myocardial infarction or heart failure hospitalization and ≥1 additional risk factor, reported no significant difference between the two groups [20]. This study was excluded as the population was not exclusively aged ≥65 years, results were not stratified by age and, moreover, these findings were not generalizable to the general population, given the high-risk status of all enrolled participants.

A key difficulty in developing improved vaccines for adults aged ≥65 years is recruiting large enough populations in RCTs to establish causal relationships with the clinical benefits, as exemplified by two adjuvanted vaccine trials that failed to meet their prespecified endpoints [21,22]. To overcome these challenges, new studies of HD-IIV4 versus SD-IIV4 aim to integrate individual randomization into routine vaccination practice while simultaneously leveraging real-world registry-based data collection for all follow-up [23]. Conducted in Denmark during the 2021/22 season, the DANFLU-1 trial (NCT05048589), which was included in this systematic review and *meta*-analysis, established the feasibility of this approach, randomizing >12,000 participants aged ≥65 years and showing reduced rates of hospitalization for influenza or pneumonia (rVE 64.4% [24.2%, 84.6%]) and all-cause mortality (48.9%

[24.2%, 84.6%]) among those receiving HD-IIV4 [23]. The ongoing DANFLU-2 trial (NCT05517174) aims to build upon DANFLU-1, assessing the rVE of HD-IIV4 versus SD-IIV4 against severe influenza outcomes in a fully-powered, multi-season study among >200,000 adults aged ≥65 years in Denmark [24].

Limitations

There are several limitations to the data in the study, including the high degree of statistical heterogeneity observed in several of the pooled rVE estimates and the inclusion of unmeasured confounders, such as health-seeking behaviour or selection bias, that could affect the findings of the observational studies, as previously detailed [4].

Conclusions

Evidence from 12 influenza seasons from randomized and real-world studies in >45 million study participants (including >29 million HD-IIV recipients) continues to show that HD-IIV was more effective than SD-IIV at reducing influenza and associated serious outcomes in people aged ≥65 years, irrespective of age or characteristics of the influenza season. This is consistent with GRADE analyses performed by several health authorities, including the US (CDC/ACIP), Europe (ECDC), Germany (STIKO), Australia (NCIRS/ATAGI), and Canada (NACI), each highlighting greater quality and volume of data supporting the improved protection conferred by HD-IIV over SD-IIV against influenza among those aged ≥65 years [5,25–28].

Studies are ongoing to strengthen the estimate of the efficacy and effectiveness of HD-IIV relative to SD-IIV against severe outcomes, including hospitalisation as primary endpoints in older adults, thanks to large-scale randomized pragmatic trials, integrating randomization into routine clinical practice while leveraging registry-based data collection for follow-up.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and were derived from manuscripts available in the public domain.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JKHL, GKLL, JKY, MML, and SIS are employees of Sanofi, the manufacturer of the high-dose influenza vaccine, and may hold shares and/or stock options in the company.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvacx.2023.100327.

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