Poster #102

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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Introduction

- Seasonal influenza epidemics continue to represent a substantial public health burden, especially in older adults.
- High-dose inactivated influenza vaccine (HD-IIV) has been used in older adults in 31 countries since its initial approval in 2009.
- Studies comparing HD-IIV to standard-dose influenza vaccines (SD-IIV) have demonstrated continued protection against influenza-associated respiratory illness, cardio-vascular disease, and all-cause hospitalizations.
- Understanding the efficacy and effectiveness of influenza vaccines in preventing clinical outcomes is critical to designing optimal vaccination programs that control the burden of influenza in older adults
- Systematic reviews and meta-analyses can help guide evidence-based decisions by providing the best available data on influenza vaccine effectiveness

Objective

Synthesize evidence update of previously-conducted reviews of the relative vaccine efficacy/effectiveness (rVE) of HD-IIV compared to SD-IIV in adults ≥65 years, with additional sub-analyses by both seasonal and recipient characteristics.

Methods

Search Objective:

- Randomized or observational studies that evaluate the efficacy or effectiveness of HD-IIV3 against clinical outcomes in adults aged 65 and older

Inclusion Criteria:

- Studies of HD-IIV3-
- Population aged 65+
- English, human studies

Exclusion Criteria:

- Pandemic/avian/swine influenza vaccines
- Experimental vaccines (monovalent/bivalent seasonal vaccines)
- Immunogenicity studies
- Studies of specialized populations (e.g. HIV, immunocompromised, transplant patients, etc.)

Analysis:

- Odds ratios (OR) of each clinical outcome were collected for individual influenza seasons from identified studies
- Meta-analyses performed using random effects models (DerSimonian and Laird) for each clinical outcome
- Study heterogeneity was assessed using I^2
- Publication bias was assessed using funnel plots
- Quality of individual studies assessed by Downs and Black critical appraisal tool

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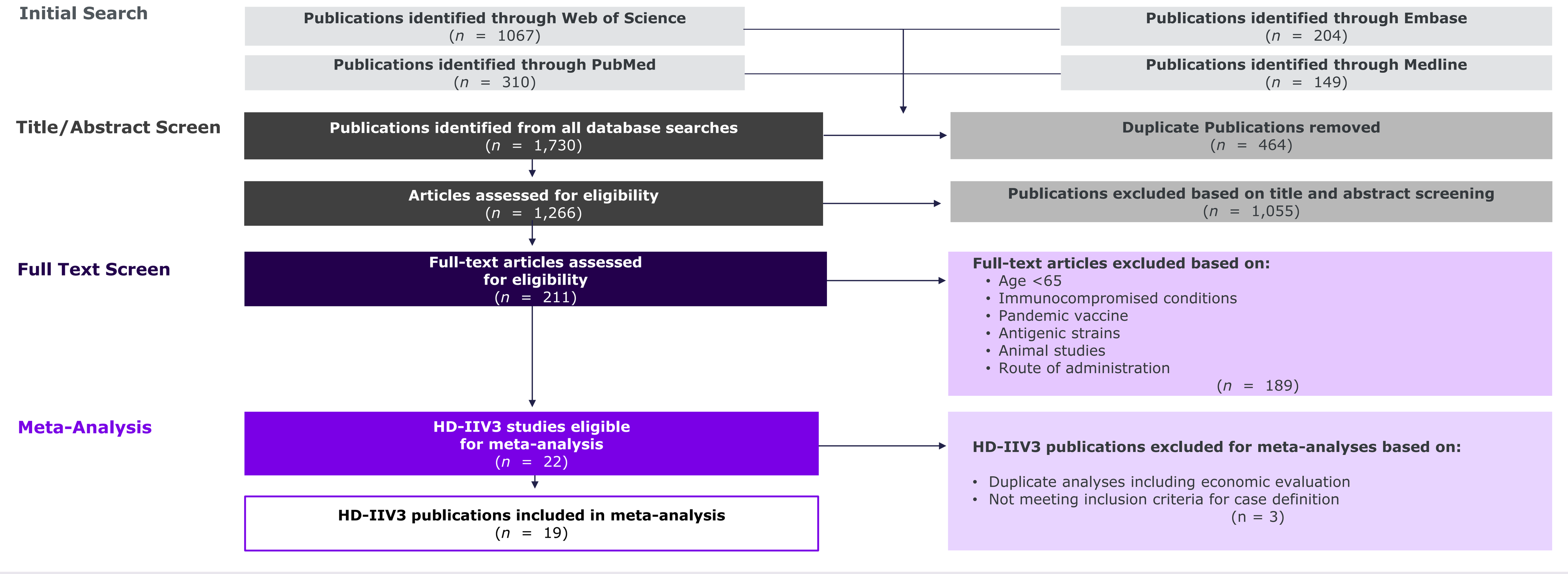
Results

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



HD-IIV3: High-dose trivalent influenza vaccine

Table 1: Summary of HD-IIV Efficacy/Effectiveness Publications

Author (Year)	Study Design	Study Location	Influenza Seasons	Study Population	Study Outcomes
Randomized Studies[a]					
DiazGranados, 2013 (NCT00976027)	Phase IIIb, multi-center, double-blind, RCT	US	2009-10	Healthy adults ≥65 • HD: 6,117; SD: 3,055	- Laboratory-confirmed influenza - Hospital admission for pneumonia[b]
DiazGranados, 2014, 2015 (NCT01427309)	Phase IIIb–IV, multi-center, double-blind RCT	US + Canada	2011-12 to 2012-13	Healthy adults ≥65 • HD: 15,991; SD: 15,998	- Laboratory-confirmed influenza - Influenza-related SAE[c]
Gravenstein, 2017 (NCT01720277)	Pilot study for cluster RCT	US	2012-13	Residents ≥65 in NHs • HD: 1,461; SD: 1,496	- All-cause hospitalizations - NH mortality - Functional decline
Gravenstein, 2017 (NCT01815268)	Single-blind, pragmatic, comparative effectiveness, cluster RCT	US	2013-14	Residents ≥65 in NHs • HD: 26,639; SD: 26,369	- Hospital admissions related to pulmonary and influenza-like conditions - Hospital admission by any cause
Observational Studies					
Izurieta, 2015	Retrospective Cohort Study	US	2012-13	Medicare beneficiaries ≥65 • HD: 929,730; SD: 1,615,545	- Probable influenza infection - Post-influenza hospitalization or ED visit
Shay, 2017	Retrospective Cohort Study	US	2012-13 to 2013-14	Medicare beneficiaries ≥65 • HD: 2,547,821; SD: 3,560,591	- Post-influenza death, hospitalization/ED visits - Influenza-related physician visits
Izurieta, 2018	Retrospective cohort study	US	2017-18	Medicare beneficiaries ≥65 • HD: 8,489,159; SD: 1,863,654	- Influenza-related hospital encounters / inpatient stays / office visits
Lu, 2019	Retrospective cohort study	US	2012-13 to 2017-18	Medicare beneficiaries ≥65 • HD: 13,770,207; SD: 6,151,913	- Influenza-related hospital encounters / inpatient stays
Izurieta, 2020	Retrospective Cohort Study	US	2018-19	Medicare beneficiaries ≥65 • HD: 7,904,821; SD: 1,455,254	- Influenza-related hospital encounters / inpatient stays / office visits
Paudel, 2020	Retrospective Cohort Study	US	2011-12 to 2014-15	Medicare beneficiaries ≥65 (Outpatient) • HD: 2,976,994; SD: 2,976,994 (Pharmacy) • HD: 2,760,882; SD: 2,760,882	- Probable Influenza (Inpatient Hospitalization or Outpatient medical encounter followed by antiviral Rx within 7 days) - Pneumonia/influenza, cardiorespiratory hospitalizations
Izurieta, 2021	Retrospective cohort study	US	2019-20	Medicare beneficiaries ≥65 • HD: 7,173,433; SD: 1,584,451	- Influenza-related hospital encounters / inpatient stays
Richardson, 2015	Retrospective Cohort Study	US	2010-11	VHA adults ≥65 • HD: 25,714; SD: 139,511	- Hospitalization for influenza or pneumonia - All-cause hospitalization and mortality
Young-Xu, 2018	Retrospective Cohort Study	US	2015-16	VHA adults ≥65 • HD: 125,776; SD: 104,965	- Pneumonia/influenza or all-cause hospitalization / outpatient visits - Laboratory-confirmed influenza
Young-Xu, 2019; Van Aalst, 2019	Retrospective cohort study	US	2010-11 to 2014-15	VHA adults ≥65 • HD: 158,636; SD: 3,480,288	- Pneumonia/influenza, cardiorespiratory, all-cause hospitalizations - Urinary tract infection
Young-Xu, 2020	Retrospective Cohort Study	US	2012-13 to 2014-15	VHA adults ≥65 • HD: 361,978; SD: 207,574	- Influenza/pneumonia, cardiorespiratory mortality - All-cause hospitalization
Van Aalst, 2021	Retrospective cohort study	US	2010-11 to 2014-15	VHA adults ≥65 • HD: 158,636; SD: 3,480,288	- Cardiovascular, respiratory, cardiorespiratory hospitalization
Machado, 2021	Retrospective cohort study	US	2012-13 to 2017-18	Adults ≥65 from MarketScan® databases • HD: 728,223; SD: 1,633,093	- Influenza / Pneumonia hospital/ED visit
Doyle, 2020	Test-negative Case Control Study	US	2015-16 to 2016-17	HAIVEN patients ≥65 • HD: 622; SD: 485	- Laboratory-confirmed influenza hospitalization
Robison, 2018	Retrospective cohort study	US	2016-17	Portland, OR adults ≥65 (ALERT IIS) • HD: 78,602; SD: 65,705	- Laboratory-confirmed influenza hospitalization
Balasubramani, 2020	Test-negative Case Control Study	US	2015-16 to 2018-19	HAIVEN patients ≥65 • HD: 3,861; SD: 2,993	- influenza-confirmed acute respiratory illness

[a]Includes both individual-level randomized and cluster-randomized studies; [b]Data from personal communication from study authors
RCT, Randomized controlled trial; **HD,** High-dose trivalent influenza vaccine; **SD,** Standard-dose trivalent/quadrivalent influenza vaccine; **SAE,** Serious adverse event; **NH,** Nursing home; **ED,** Emergency department; **HAIVEN,** US Hospitalized Adult Influenza Vaccine Effectiveness Network; **VHA,** Veterans Health Administration.

Figure 2: Forest plots of the pooled OR of HD-IIV3 vs. SD-IIV against influenza-related outcomes

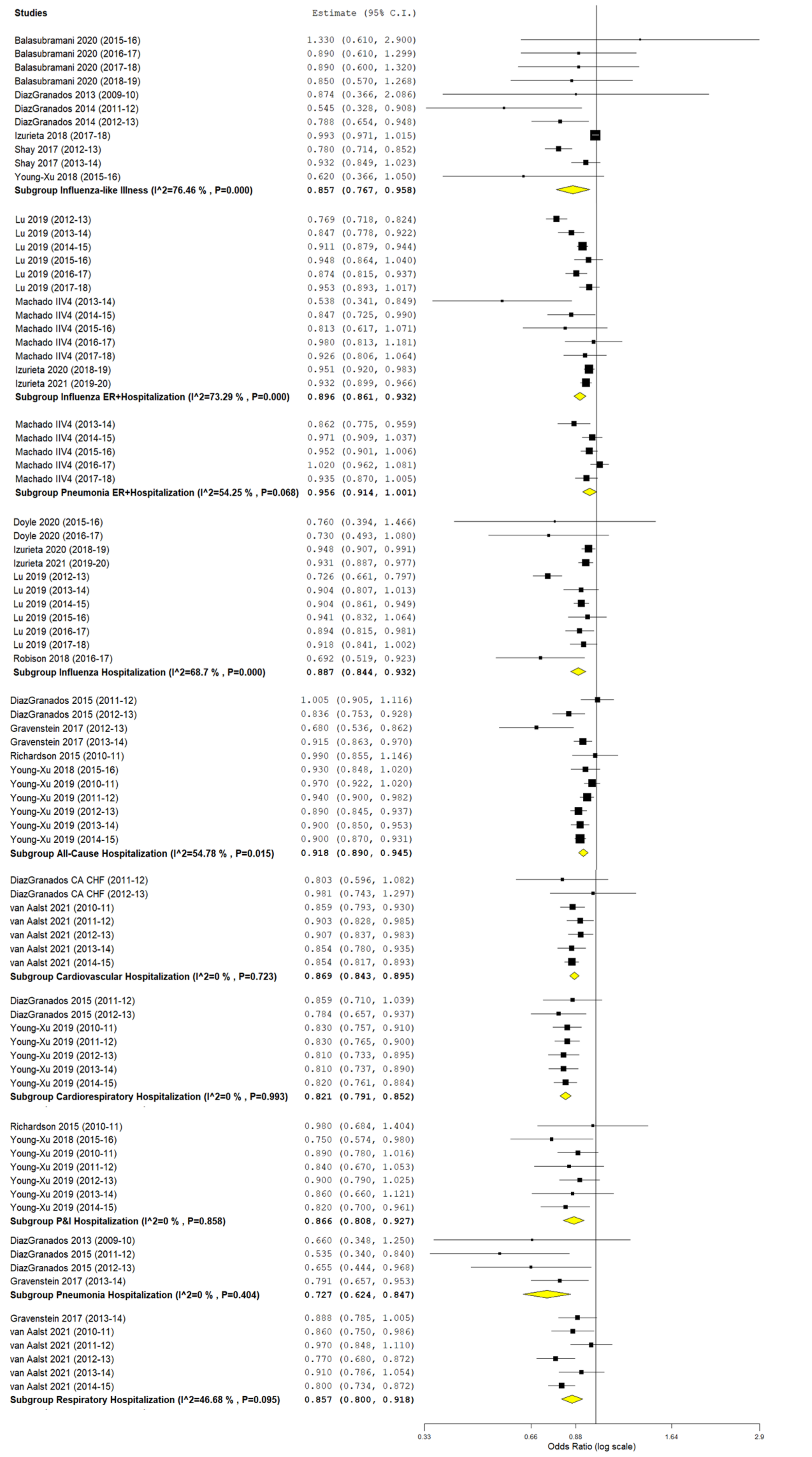


Table 2: Pooled relative vaccine efficacy/effectiveness of HD-IIV3 vs. SD-IIV against influenza-related outcomes

A: All seasons and sub-analyses by season type

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]
Influenza-like Illness[d]	**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[e]	**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[f]	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[e]	**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[f]	**27.3%** (15.3 - 37.6%) n=4; p<0.001	**39.9%** (19.3 - 55.3%) n=2; p<0.001	**22.0%** (6.7 - 34.8%) n=2; p<0.001	**28.9%** (10.1 - 43.8%) n=3; p=0.004	-
Pneumonia/Influenza[g]	**13.4%** (7.3 - 19.2%) n=7; p<0.001	**12.4%** (5.7 - 18.7%) n=5; p<0.001	**19.6%** (3.0 - 33.4%) n=2; p=0.023	**13.5%** (5.0 - 21.3%) n=5; p=0.002	**13.3%** (4.1 - 21.6%) n=2; p=0.005
Respiratory	**14.3%** (8.2 – 20.0%) n=6; p<0.001	**15.9%** (7.6 – 23.4%) n=5; p<0.001	**10.3%** (1.4 – 18.4%) n=2; p=0.027	**9.4%** (3.1 – 15.3%) n=4; p=0.004	**21.0%** (15.2 – 26.4%) n=2; p=0.004
Cardiovascular	**13.1%** (10.5 – 15.7%) n=7; p<0.001	**12.9%** (10.1 – 15.7%) n=6; p<0.001	-	**13.0%** (8.7 – 17.2%) n=4; p<0.001	**12.7%** (8.3 – 16.9%) n=3; p<0.001
Cardiorespiratory	**17.9%** (15.0 - 20.8%) n=7; p<0.001	**17.7%** (14.5 - 20.8%) n=6; p<0.001	-	**17.4%** (13.5 - 21.1%) n=4; p<0.001	**18.6%** (14.1 - 22.9%) n=3; p<0.001
All-cause	**8.4%** (5.7 - 11.0%) n=11; p<0.001	**8.3%** (4.5 - 12.0%) n=8; p<0.001	**8.9%** (5.4 - 12.2%) n=3; p<0.001	**6.4%** (4.1 - 8.6%) n=7; p<0.001	**12.6%** (7.8 - 17.2%) n=4; p<0.001

B: Sub-analyses by study type

Outcome	Randomized Studies[h]			Observational Studies		
	n	rVE[c] (95% CI)	p-value	n	rVE[c] (95% CI)	p-value
Influenza-like Illness	3	**24.1%** (10.0 – 36.1%)	0.002	8	11.1% (-0.1 – 21.0%)	0.051
Hospitalization+ER Visit						
Influenza	-	-	-	13	**10.4%** (6.8 – 13.9%)	<0.001
Pneumonia	-	-	-	5	4.4% (-0.1 - 8.6%)	0.053
Hospitalization						
Influenza	-	-	-	11	**11.2%** (7.4 – 14.8%)	<0.001
Pneumonia	4	**27.3%** (15.3 - 37.6%)	<0.001			
Pneumonia/Influenza	-	-	-	7	**13.4%** (7.3 - 19.2%)	<0.001
Respiratory	-	-	-	5	**14.8%** (7.6 – 21.5%)	<0.001
Cardiovascular	2	10.6% (-9.6 – 27.1%)	0.279	5	**13.2%** (10.5 – 15.8%)	<0.001
Cardiorespiratory	2	**18.2%** (6.8 – 28.1%)	0.002	5	**17.9%** (14.7 – 21.0%)	<0.001
All-cause	4	**11.9%** (2.0 – 20.7%)	0.019	7	**7.8%** (5.3 – 10.3%)	<0.001

C: Sub-analyses by subject age

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

[a] Determined using national CDC viral surveillance data of circulating strains in adults 65 years of age and older; [B] Based on CDC data on viral antigenic characterization comparing reference vaccine strains to circulating viruses; mismatched seasons includes seasons of antigenic mismatch (2009–10, 2014–15, 2018–19) as well as seasons where egg-adapted vaccine strains may have affected vaccine effectiveness (2012–13, 2016–17, 2017–18); [c] A random-effects model with DerSimonian-Laird estimators was used to calculate the pooled OR across multiple studies and influenza seasons; [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; [h] Includes both individual-level randomized and cluster-randomized studies.
CI, confidence interval; **ER,** emergency room; **rVE,** relative vaccine efficacy/effectiveness

Discussion

Study continues to highlight breadth of published literature on HD-IIV efficacy/effectiveness

- Studies in 11 consecutive influenza seasons
- Diversity in study design and outcomes
- Large sample size (>29 million HD recipients, >45 million total)

Use of clinical outcomes that are relevant to clinicians and decision makers

Conclusions

Study results suggest that irrespective of study type, study setting, age of vaccine recipients, circulating strains or antigenic match, HD-IIV is expected to be more effective than SD-IIV in preventing clinical outcomes associated with influenza

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