The Relative Vaccine Effectiveness of High-Dose vs Standard-Dose Influenza Vaccines in Preventing Hospitalization and Mortality: A Meta-Analysis of **Evidence From Randomized Trials**

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KEY TAKEAWAYS

- First meta-analysis to incorporate all randomized trials of High-Dose Influenza Vaccine (HD-IV) vs Standard Dose Influenza Vaccine (SD-IV), beginning December 31, 2009
- HD-IV vs SD-IV reduced Pneumonia and Influenza (P&I) hospitalizations (rVE: 23.5 %, [95 % CI: 12.3 to 33.2]) and all-cause hospitalizations (rVE: 7.3 %, [95 % CI: 4.5 to 10.0]). No significant difference observed on all-cause death
- While the pooled rVE estimates provided in the study by Lee et al.² are not directly comparable to these findings, both studies found that HD-IV prevented more P&I hospitalizations and all-cause hospitalizations compared to standard dose in adults 65 years and older



BACKGROUND

- Older adults (aged \geq 65 years) are more susceptible to suffering severe complications from influenza infection, including hospitalizations, loss of independence and death^{3,4}
- Conventional SD-IV presents a suboptimal protection due to the attenuated immune response in older adults than younger adults⁵
- To address this, the HD-IV was developed, containing 4x the amount of hemagglutinin (HA) compared with SD-IV^{6,7} The HD influenza vaccine has demonstrated superior protection compared with the SD influenza vaccine among adults aged ≥65 years in an RCT against laboratory-confirmed influenza infection (rVE: 24.2%, [95% CI: 9.7%-36.5%])⁶
 - **OBJECTIVES** (T
- A prespecified meta-analysis was in order to estimate the pooled rVE of HD-IV vs SD-IV for preventing hospitalization for P&I, all-cause hospitalization, and all-cause death in randomized trials of older adults ≥65 years followed over at least one influenza season

Primary analysis



The primary analysis was conducted in adults aged \geq 65 years from trials that compared HD-IV to SD-IV in the same age group

adults \geq 65 years since December 31,2009 (after 1st

licensure of HD-IV) and trials with adults of all ages

Secondary analysis

Secondary analyses were performed in subgroups with and without cardiovascular disease, and different age categories (65-79 and ≥80 years)

STUDY CONDUCT

Data search process (Systematic review and meta-analysis)

Two investigators independently searched, identified and evaluated randomized studies assessing rVE of HD-IV vs SD-IV regarding P&I hospitalization, all-cause hospitalization, and all-cause death in adults over at least one season via PubMed and Embase databases. Search period: beginning December 31, 2009)

Inclusion criteria



Exclusion criteria

- Studies conducted in animals
- Studies conducted in 2009/10 H1N1 pandemic season



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Five RCTs encompassing 105,685 participants met the pre-defined inclusion criteria for the meta-analysis:



 Three were individually randomized trials: Johansen (2023) Vardeny (2021) DiazGranados (2015)



Two were cluster-randomized trials: Gravenstein (2018) Gravenstein (2017)

Mean age: 66 to 85 years

rVE of HD-IV vs. SD-IV based on P&I hospitalization, all-cause hospitalization and all-cause death

P&I hospitalization

Primary analysis (conducted across 4 studies, excluding the Gravenstein 2018 study*):

 A reduction in P&I hospitalizations was observed as overall rVE of 23.5% (95% CI: 12.3 to 33.2) with HD-IV vs SD-IV (Figure 1)

Additional analysis:

- Similar estimates were obtained in random-effects model (rVE=26.1% [95% CI: -5.6 to 48.3]), and were consistent across various subgroup analyses, including all adults
- *Excluded as P&I endpoint was not assessed/investigated

All-cause hospitalization

Primary analysis (excluded the INVESTED trial*):

 A reduction in all-cause hospitalizations was observed as overall rVE was 7.3% [95% CI: 4.5 to 10.0] with HD-IV vs SD-IV (Figure 2)

Secondary analysis (INVESTED trial was considered**):

 Subgroup analysis in individuals without CV disease and in individuals ages 65-79 demonstrated comparable results. However, among those 80 years of age and older and those with CV disease, there was no evidence that HD-IV was more effective than SD-IV

*Excluded as all-cause hospitalization endpoint was not reported; ** Cardiopulmonary hospitalization endpoint was meta-analyzed in place of all-cause hospitalization in this secondary analysis

All-cause death -

Primary analysis (included all the 5 trials):

- All trials reported deaths and death rates were similar between the HD-IV and SD-IV groups among adults aged ≥65 years (9.7% vs 9.9%)
- There was no difference in overall treatment effect between HD-IV and SD-IV regarding all-cause death (rVE = 1.6% [95% CI: -2.0 to 5.0]) (Figure 3)

Secondary analysis:

- There was no difference in the effect of HD-IV vs SD-IV in studies conducted in secondary analyses of all adults
- However, statistically significant positive effects were observed in those aged 65 to 79 years



LIMITATIONS

- Studies were not powered to determine effect on severe clinical outcomes (i.e. mortality)
- Data on P&I hospitalization and all-cause hospitalization from two trials was not recorded & subgroup data from Gravenstein trials was unavailable
- With only 5 studies addressing the research question, the power to detect small-study bias and ability to assess heterogeneity
 was limited

CONCLUSIONS

- − HD-IV reduced the incidence of P&I and all-cause hospitalization vs SD-IV in adults ≥65 years in this meta-analysis that included randomized trials, and no significant difference was observed in all-cause death rates
- The primary analyses findings were consistent across most subgroups and in sensitivity analyses
- The findings of this analysis complement the growing evidence that HD-IV provides better protection against influenza-related complications than SD-IV in older adults

Abbreviations: CI: confidence interval; CV, cardiovascular; HA: hemagglutinin; HD-IV: high dose – inactivated vaccine; P&I: pneumonia & influenza; rVE: relative vaccine efficacy/effectiveness; RCT: randomized controlled trial; SD-IV: standard dose – inactivated vaccine

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Study (Influenza season)	Number with events/ HD-IV	number of participants (% SD-IV	%)	rVE (95% CI)	Weight (%)
DiazGranados 2015 (2011-2013)	70/15,990 (0.4%)	114/15,993 (0.7%)		38.6% (17.4 to 54.3)	21.2
Gravenstein 2017 (2013-2014)	247/19,127 (1.3%)	309/19,129 (1.6%)	 =	20.1% (5.6 to 32.3)	67.6
Vardeny 2021 (2016-2019)	36/2,010 (1.8%)	27/2,077 (1.3%) —	•	-37.8% (-126.1 to 16.	0) 7.6
Johansen 2023 (2021-2022)	10/6,245 (0.2%)	28/6,204 (0.4%)		- 64.4% (26.7 to 82.7)) 3.6
Overall Summary estimate (DerSimonian and Laird model)			$\diamond \diamond$	23.5% (12.3 to 33 26.1% (-5.6 to 48.3)	.2)
Cochran's Q Statist Test for overall trea Fixed-effects invers	tics=12.11, p=0.007 atment effect: p<0.003 se-variance model	Favors SD-IV	► Fa 0 63 rVE (%)	vors HD-IV	

Figure 1: P&I hospitalizations in individuals aged ≥65 years

Figure 2: All-cause hospitalizations in individuals aged ≥65 years

Study	Number with events/number of participants (%))	rVE	Weight
(Influenza season)	HD-IV	SD-IV	/	(95% CI)	(%)
DiazGranados 2015 (2011-2013)	1,149/15,990 (7.2%)	1,264/15,993 (7.9%)		9.1% (1.8 to 15.8)	14.6
Gravenstein 2018 (2012 - 2013)) 197/1,461 (13.5%)	301/1,496 (20.1%)	-	33.0% (21.0 to 43.2)	3.2
Gravenstein 2017 (2013-2014)	5,251/26,639 (19.7%)	5,513/26,369 (20.9%)	•	5.7% (2.5 to 8.9)	75.7
Johansen 2023 (2021-2022)	513/6,245 (8.2%)	550/6,232 (8.8%)	+	6.9% (-4.4 to 17.0)	6.5
Overall			l 🔷	7.3% (4.5 to 10.0)	
Summary estimate (DerSimonian and Laird model $I^2=81\%$			\diamond	12.2% (0.3 to 20.4)	
Cochran's Q Statist Test for overall trea	ics=16.16, <i>p</i> =0.001 atment effect: <i>p</i> <0.001	Favors SD-IV 🗲 -	╞╺┣	Favors HD-IV	
Fixed-effects invers	se-variance model	rV	0 18 ′E(%)	33 45	

Figure 3: All-cause death in individuals aged ≥65 years

Study (Influenza season)	Number with events/n HD-IV	umber of participants SD-IV	(%)	rVE (95% CI)	Weight (%)
DiazGranados 2015 (2011-2013)	74/15,990 (0.5%)	80/15,993 (7.9%)		7.5% (-26.8 to 32.5)	1.3
Gravenstein 2018 (2012 - 2013)	249/1,461 (17.0%)	274/1,496 (18.3%)	+	6.9% (-8.7 to 20.4)	5.2
Gravenstein 2017 (2013-2014)	4,542/26,639 (17.1%)	4,531/26,369 (17.2%)	0.8% (-3.0 to 4.4)	90.0
Vardeny 2021 (2016-2019)	158/1,467 (10.8%)	169/1,520 (11.1%)	+	3.1% (-18.9 to 21.1)	3.0
Johansen 2023 (2021-2022)	21/6,245 (0.3%)	41/6,232 (0.7%)		48.9% (13.6 to 69.8)	0.5
Overall			k	1.6% (-2.0 to 5.0)	
Summary estimate (DerSimonian and Laird model) 1 ² =4.2%				5.4% (-4.6 to 14.4)	
Cochran's Q Statistics=6.84, p=0.14 Favors SD- Test for overall treatment effect: p=0.38		Favors SD-IV		vors HD-IV	
Fixed-effects inverse-variance model		-65 0 39 63 rVE(%)			