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Efficacy and Effectiveness of High-Dose versus Standard-Dose Influenza Vaccination for Older Adults:

A Systematic Review and Meta-analysis

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Disclosure Statement

- I am an employee of Sanofi Pasteur, the vaccines division of Sanofi and a manufacturer of influenza vaccines.

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ORIGINAL RESEARCH

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Efficacy and effectiveness of high-dose versus standard-dose influenza vaccination for older adults: a systematic review and meta-analysis

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ABSTRACT

Background: Influenza is responsible for a significant disease burden annually, especially in older adults. This study reviews the relative vaccine efficacy or effectiveness (rVE) of high-dose inactivated trivalent influenza vaccine (HD-IIV3) compared to standard-dose influenza vaccines (SD-IIV3) in adults ≥65 against influenza-associated outcomes to inform evidence-based decision-making to shift clinical practice and standard of care in this population.

Methods: A systematic review was conducted for studies assessing the rVE of HD-IIV3 against probable/laboratory-confirmed influenza-like illness (ILI), hospital admissions, and death in adults ≥65. Results from individual seasons were meta-analyzed and a random-effects model was used to estimate pooled rVEs.

Results: After screening 992 studies, seven studies were meta-analyzed. HD-IIV3 demonstrated better protection against ILI compared to SD-IIV3 (rVE = 19.5%; 95% CI: 8.6–29.0%). HD-IIV3 was also more effective at preventing hospital admissions from all-causes (rVE = 9.1%; 95% CI: 2.4–15.3%), as well as from influenza (rVE = 17.8%; 95% CI: 8.1–26.5%), pneumonia (rVE = 24.3%, 95% CI: 13.9–33.4%), and cardiorespiratory events (rVE = 18.2%; 95% CI: 6.8–28.1%). rVE against post-influenza mortality was 22.2% (95% CI: -18.2–48.8%) and 2.5% (95% CI: -5.2–9.5%) against all-cause mortality.

Conclusions: Available evidence suggests HD-IIV3 is more effective than SD-IIV3 at reducing the clinical outcomes associated with influenza infection in older adults and should be considered for routine use in the 65+ population.

ARTICLE HISTORY
Received 1 March 2018
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KEYWORDS
High dose influenza vaccine; influenza; seniors; elderly; efficacy; effectiveness; hospitalization; death; systematic review; meta-analysis

Background

- Seasonal influenza epidemics continue to represent a substantial public health burden, especially in older adults due to the presence of medical co-morbidities and weakened immune systems

- While influenza vaccines are recommended for older adults, only recently have there been vaccines that are indicated specifically for individuals 65 years of age and older

- One of these vaccines, the high-dose inactivated trivalent influenza vaccine (HD-IIV3; Fluzone® High-Dose), has seen widespread use in the US, and incorporation into some publicly-funded programs in Canada

- A number of recent studies have compared the efficacy and effectiveness of HD-IIV3 to standard-dose influenza vaccine (SD-IIV3) in preventing influenza-related illness, hospitalizations and deaths

Study Rationale and Objectives

Rationale:

- Understanding the efficacy and effectiveness of influenza vaccines in preventing influenza-related 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 decision making by providing the best available data on influenza vaccine effectiveness

Objective:

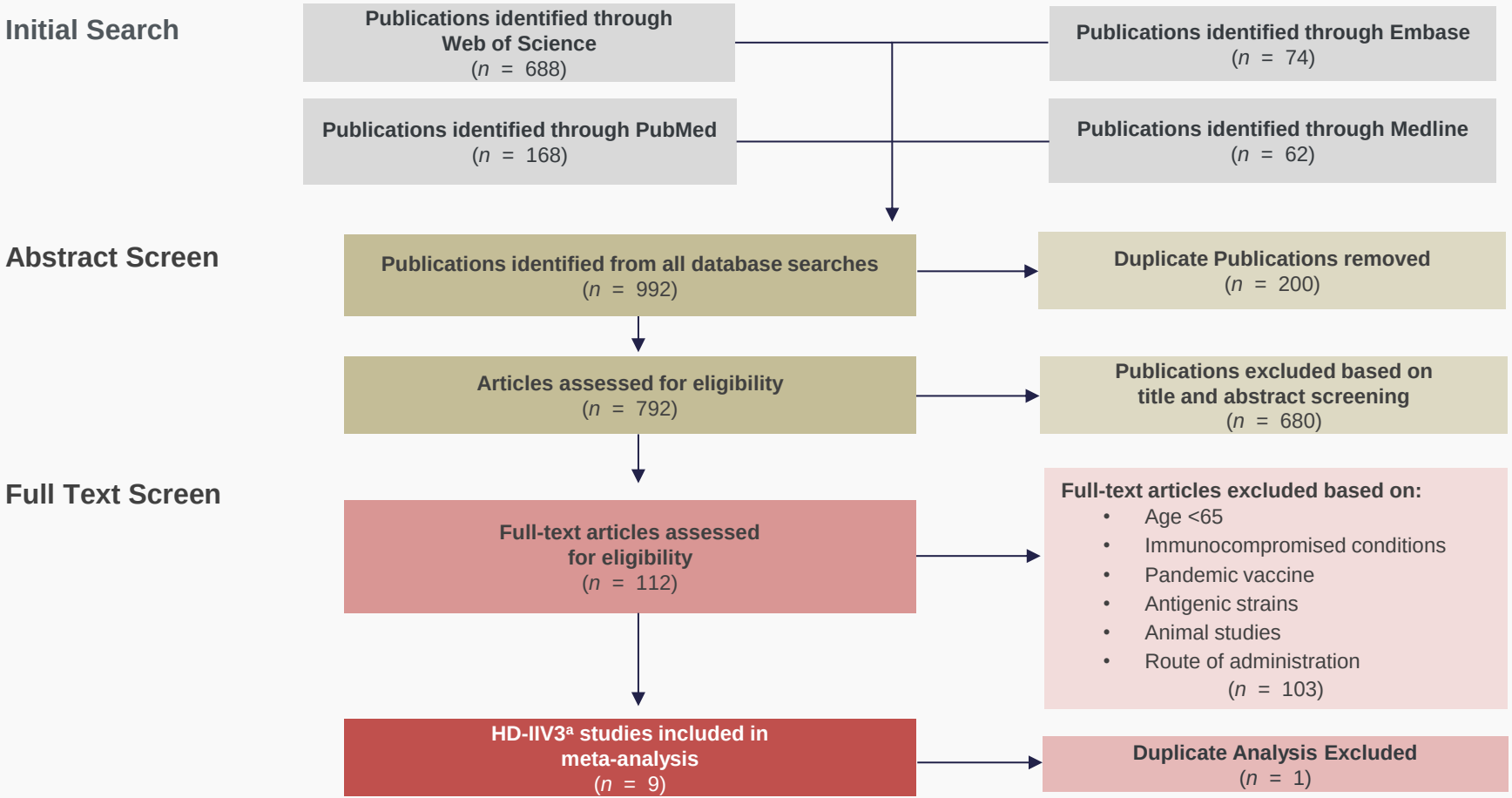
- Synthesize evidence on the efficacy/effectiveness of HD-IIV3 compared to SD-IIV3 in preventing clinical outcomes typically associated with influenza

Methods: Search Criteria

Search Objective: Randomized or observational studies that evaluate high dose influenza vaccine efficacy/effectiveness against clinical outcomes in adults aged 65 and older

- **Inclusion Criteria:**
  - English, human studies
  - Population aged 65+
  - Studies on high-dose influenza vaccine

- **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.)


Initial Search
Publications identified through Web of Science (n = 688)
Publications identified through Embase (n = 74)
Publications identified through PubMed (n = 168)
Publications identified through Medline (n = 62)
Abstract Screen
Publications identified from all database searches (n = 992)
Duplicate Publications removed (n = 200)
Articles assessed for eligibility (n = 792)
Publications excluded based on title and abstract screening (n = 680)
Full Text Screen
Full-text articles assessed for eligibility (n = 112)
Full-text articles excluded based on:
Age <65
Immunocompromised conditions
Pandemic vaccine
Antigenic strains
Animal studies
Route of administration
(n = 103)
HD-IIV3[a] studies included in meta-analysis (n = 9)
Duplicate Analysis Excluded (n = 1)

Data Analysis

Meta Analyses

- Odds ratios of each clinical outcome were collected for individual influenza seasons from identified studies
- Meta-analyses for each clinical outcome was performed using a random effects model (DerSimionian and Laird) for all studies
  - **Influenza-like illness** (laboratory-confirmed/probable)
  - **Hospitalization** (influenza, pneumonia, cardiorespiratory events, all-cause)
  - **Mortality** (post-influenza, all-cause)
- Additional sensitivity analyses performed using subset of studies
  - **Randomized studies, observational studies, community-dwelling seniors, long-term care residents**

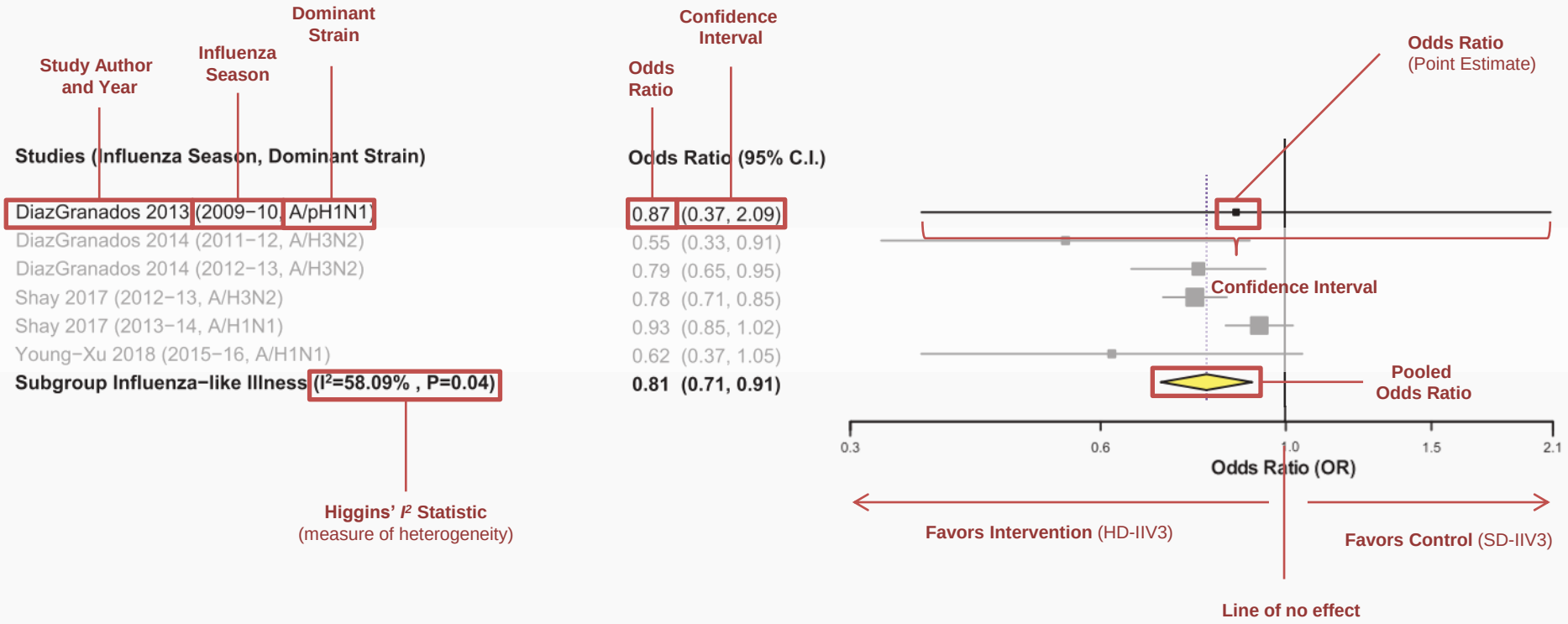
Quality Assessment

- Quality of individual studies assessed by Downs and Black critical appraisal tool
- Publication bias assessed using funnel plots
- Study heterogeneity assessed using the Higgins' I^2 statistic.

Summary of Published Fluzone HD Efficacy & Effectiveness Studies

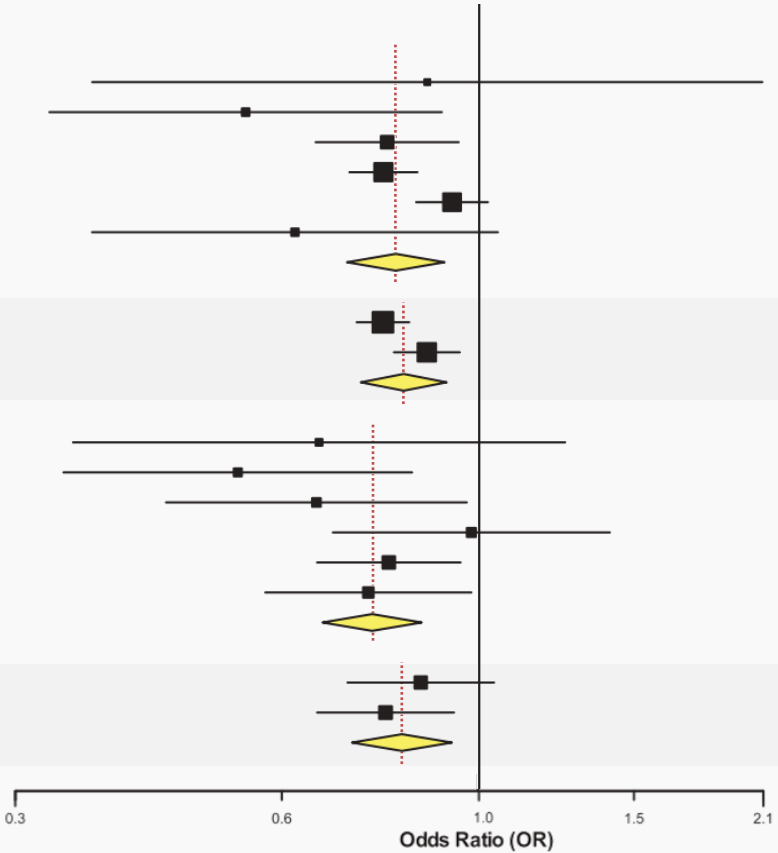
Author (Year)	Study Design	Study Location	Influenza Seasons	Study Population	Study Outcomes	Study Quality (D&B Score)
Randomized Studies						
DiazGranados, 2014, 2015 (NCT01427309)	Phase IIIb–IV, multi-center, double-blind RCT	US and Canada	2011 – 12 2012 – 13	Healthy adults ≥65 • HD: 15,991 • SD: 15,998	- Lab-confirmed influenza (any viral strain) - Influenza-related SAE	Good (24)
DiazGranados, 2013 (NCT00976027)	Phase IIIb, multi-center, double-blind, RCT	US	2009 – 10	Healthy adults ≥65 • HD: 6,117 • SD: 3,055	- Lab-confirmed influenza (viral strains similar to vaccine) - Lab-confirmed influenza (any viral strain) - Hospital admission for pneumonia[b]	Good (24)
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	Good (24)
Gravenstein, 2017 (NCT01720277)	Pilot study for cluster RCT	US	2012 – 13	Residents ≥65 in NHs • HD: 1,461 • SD: 1,496	- All-cause hospitalizations - Nursing home mortality - Functional decline	Good (23)
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	Good (19)
Shay, 2017	Retrospective Cohort Study	US	2012 – 13 2013 – 14	Medicare beneficiaries ≥65 • HD: 2,547,821 • SD: 3,560,591	- Post-influenza death - Post-influenza hospitalization or ED visits - Influenza-related physician visits	Good (20)
Richardson, 2015	Retrospective Cohort Study	US	2010 – 11	VHA adults ≥65 • HD: 1,461 • SD: 1,496	- Hospitalization for influenza or pneumonia - All-cause hospitalization and mortality	Good (21)
Young-Xu, 2018	Retrospective Cohort Study	US	2015-16	*VHA adults ≥65* • HD: 125,776 • SD: 104,965	- Pneumonia/influenza or all-cause hospitalization - Pneumonia/influenza or all-cause outpatient visits - Laboratory-confirmed influenza	Good (19)

Interpretation of Forest Plots



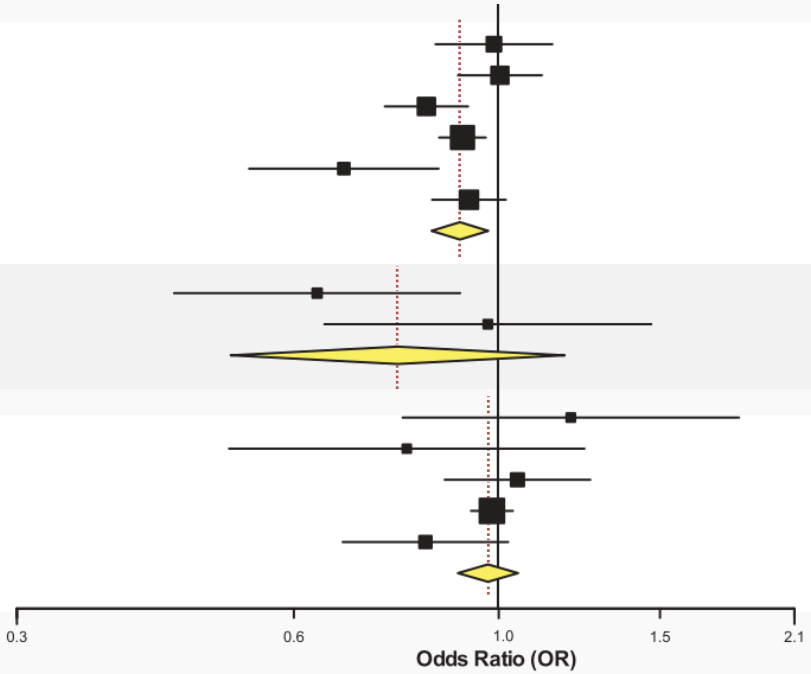
Forest Plots: ILI + Hospitalizations

Studies (Influenza Season, Dominant Strain)	Odds Ratio (95% C.I.)
DiazGranados 2013 (2009−10, A/pH1N1)	0.87 (0.37, 2.09)
DiazGranados 2014 (2011−12, A/H3N2)	0.55 (0.33, 0.91)
DiazGranados 2014 (2012−13, A/H3N2)	0.79 (0.65, 0.95)
Shay 2017 (2012−13, A/H3N2)	0.78 (0.71, 0.85)
Shay 2017 (2013−14, A/H1N1)	0.93 (0.85, 1.02)
Young−Xu 2018 (2015−16, A/H1N1)	0.62 (0.37, 1.05)
Subgroup Influenza−like Illness (I^2=58.09% , P=0.04)	**0.81 (0.71, 0.91)**
Shay 2017 (2012−13, A/H3N2)	0.78 (0.73, 0.83)
Shay 2017 (2013−14, A/H1N1)	0.87 (0.80, 0.95)
Subgroup Influenza Hospitalization (I^2=75.98% , P=0.04)	**0.82 (0.74, 0.92)**
DiazGranados 2013 (2009−10, A/pH1N1)	0.66 (0.35, 1.25)
DiazGranados 2015 (2011−12, A/H3N2)	0.53 (0.34, 0.84)
DiazGranados 2015 (2012−13, A/H3N2)	0.66 (0.44, 0.97)
Richardson 2015 (2010−11, A/H3N2)	0.98 (0.68, 1.40)
Gravenstein 2017a (2013−14, A/H1N1)	0.79 (0.66, 0.95)
Young−Xu 2018 (2015−16, A/H1N1)	0.75 (0.57, 0.98)
Subgroup Pneumonia Hospitalization (I^2=3.3% , P=0.40)	**0.76 (0.67, 0.86)**
DiazGranados 2015 (2011−12, A/H3N2)	0.86 (0.71, 1.04)
DiazGranados 2015 (2012−13, A/H3N2)	0.78 (0.66, 0.94)
Subgroup Cardiorespiratory Hospitalization (I^2=0% , P=0.49)	**0.82 (0.72, 0.93)**



Forest Plots: Hospitalizations + Deaths

Studies (Influenza Season, Dominant Strain)	Odds Ratio (95% C.I.)
Richardson 2015 (2010−11, A/H3N2)	0.99 (0.86, 1.15)
DiazGranados 2015 (2011−12, A/H3N2)	1.00 (0.90, 1.12)
DiazGranados 2015 (2012−13, A/H3N2)	0.84 (0.75, 0.93)
Gravenstein 2017a (2013−14, A/H1N1)	0.92 (0.86, 0.97)
Gravenstein 2017b (2012−13, A/H3N2)	0.68 (0.54, 0.86)
Young−Xu 2018 (2015−16, A/H1N1)	0.93 (0.85, 1.02)
Subgroup All−Cause Hospitalization (I^2=62.11% , P=0.02)	**0.91 (0.85, 0.98)**
Shay 2017 (2012−13, A/H3N2)	0.64 (0.44, 0.91)
Shay 2017 (2013−14A/H1N1)	0.97 (0.65, 1.47)
Subgroup Post−Influenza Mortality (I^2=57.81% , P=0.12)	**0.78 (0.51, 1.18)**
DiazGranados 2015 (2011−12, A/H3N2)	1.20 (0.79, 1.83)
DiazGranados 2015 (2012−13, A/H3N2)	0.80 (0.51, 1.24)
Richardson 2015 (2010−11, A/H3N2)	1.05 (0.88, 1.26)
Gravenstein 2017a (2013−14, A/H1N1)	0.99 (0.93, 1.04)
Gravenstein 2017b (2012−13, A/H3N2)	0.83 (0.68, 1.03)
Subgroup All−Cause Mortality (I^2=13.85% , P=0.33)	**0.98 (0.90, 1.05)**



Meta-Analysis of Fluzone HD Efficacy/Effectiveness

Clinical Outcome	Pooled Relative VE (95% CI)	P-value
All Studies (Observational + Randomized Studies)		
Influenza-like Illness	**19.5%** (8.6%, 29.0%)	<0.001
Influenza Hospitalization	**17.8%** (8.1%, 26.5%)	<0.001
Pneumonia Hospitalization	**24.3%** (13.9%, 33.4%)	<0.001
Cardiorespiratory Hospitalization	**18.2%** (6.8%, 28.1%)	0.002
All-cause Hospitalization	**9.1%** (2.4%, 15.3%)	0.009
Post-Influenza Mortality	**22.2%** (-18.2%, 48.8%)	0.240
All-cause Mortality	**2.5%** (-5.2%, 9.5%)	0.514
Randomized Studies Only		
Influenza-like Illness	**24.1%** (10.0%, 36.1%)	0.002
Pneumonia Hospitalization	**27.3%** (15.3%, 37.6%)	<0.001
All-cause Hospitalization	**11.9%** (2.0%, 20.7%)	0.019
All-cause Mortality	**4.9%** (-6.5%, 15.1%)	0.381

Study Strengths

- **Comprehensive literature review on efficacy and effectiveness studies of HD-IIV3**
- **Study highlights breadth of published literature on HD-IIV3 efficacy or effectiveness**
  - Diversity in study design and study outcomes
  - Studies in 5 influenza seasons
  - Large sample size (97,126 in randomized studies, 6,336,110 in observational studies)
- **Use of clinical outcomes that are relevant for public health decision makers**
  - Influenza illness, hospitalizations, deaths

Study Limitations

- **High heterogeneity in treatment effect estimates between studies**
  - Variability likely due to differences between influenza seasons, circulating strains and disease severity
  - Larger treatment effect for HD-IIV3 generally observed in A/H3N2 dominant seasons

- **Data not available in all studies to perform additional subgroup meta-analyses**
  - Specific age groups (e.g. 75+, 85+)
  - Specific medical co-morbidities (e.g. cardiovascular diseases, diabetes)
  - Impact of circulating strains or vaccine strain match

Conclusions

- **9 publications that evaluated HD-IIV3 vs. SD-IIV3 in preventing influenza-related clinical outcomes were identified following the screening of 992 studies.**

- **HD-IIV3 was found to have a statistically significant pooled rVE against:**

  - **Influenza-like Illness** **19.5%** (8.6%, 29.0%)
  - **Influenza Hospitalization** **17.8%** (8.1%, 26.5%)
  - **Pneumonia Hospitalization** **24.3%** (13.9%, 33.4%)
  - **Cardiorespiratory Hospitalization** **18.2%** (6.8%, 28.1%)
  - **All-cause Hospitalization** **9.1%** (2.4%, 15.3%)

- **Available evidence suggests that HD-IIV3 is more effective than SD-IIV3 at reducing the clinical outcomes typically associated with influenza infection in older adults.**

List of Articles in Systematic Review

1. DiazGranados CA, Dunning AJ, Jordanov E, Landolfi V, Denis M, Talbot HK. (2013). High-dose trivalent influenza vaccine compared to standard dose vaccine in elderly adults: safety, immunogenicity and relative efficacy during the 2009-2010 season. Vaccine. 31(6): 861-6.

2. DiazGranados CA, Dunning AJ, Kimmel M, Kirby D, Treanor J, Collins A, et al. (2014). Efficacy of high-dose versus standard-dose influenza vaccine in older adults. The New England journal of medicine. 371(7): 635-45.

3. DiazGranados CA, Robertson CA, Talbot HK, Landolfi V, Dunning AJ, Greenberg DP. (2015). Prevention of serious events in adults 65 years of age or older: A comparison between high-dose and standard-dose inactivated influenza vaccines. Vaccine. 33(38): 4988-93.

4. Gravenstein S, Davidson HE, Han LF, Ogarek JA, Dahal R, Gozalo PL, Taljaard M, Mor V. Feasibility of a cluster-randomized influenza vaccination trial in US nursing homes: Lessons learned. Human vaccines & immunotherapeutics. 2018 Mar 4;14(3):736-43.

5. Gravenstein S, Davidson HE, Taljaard M, Ogarek J, Gozalo P, Han L, Mor V. Comparative effectiveness of high-dose versus standard-dose influenza vaccination on numbers of US nursing home residents admitted to hospital: a cluster-randomised trial. The Lancet Respiratory Medicine. 2017 Sep 1;5(9):738-46.

6. Izurieta HS, Thadani N, Shay DK, Lu Y, Maurer A, Foppa IM, et al. (2015). Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis. The Lancet Infectious diseases. 15(3): 293-300.

7. Richardson DM, Medvedeva EL, Roberts CB, Linkin DR. (2015). Comparative effectiveness of high-dose versus standard-dose influenza vaccination in community-dwelling veterans. Clinical infectious diseases. 61(2):171-6.

8. Shay D.K., et al. (2017). Comparative Effectiveness of High-Dose Versus Standard-Dose Influenza Vaccines Among US Medicare Beneficiaries in Preventing Postinfluenza Deaths During 2012-2013 and 2013-2014. The Journal of infectious diseases. 215(4): 510-517.

9. Young-Xu Y, Van Aalst R, Mahmud SM, Rothman KJ, Thornton Snider J, Westreich D, Mor V, Gravenstein S, Lee JK, Thommes EW, Decker MD. Relative Vaccine Effectiveness of High-Dose versus Standard-Dose Influenza Vaccines among Veterans Health Administration Patients. The Journal of infectious diseases. 2018 Feb 14.

Thank You

Supplemental Slides

Search Methodology

Database	Database-Specific Search Algorithm
Medline	• SET[1]: exp Aging/ or exp "Aged, 80 and over"/ or exp Aged/[a] or senior* or geriatric* or old* adult.mp. • SET[2]: influenza vaccine.mp. or exp Influenza Vaccines/ • SET[3]: (high-dose trivalent or high dose trivalent or high dose influenza or fluzone high dose or fluzone high-dose or fluzone hd or high-dose tiv or high dose tiv or high-dose iiv3 or high dose iiv3 or iiv3-hd or high dose or high-dose or HD).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] • SET[4]: 1 and 2 and 3 • SET[5]: limit 4 to (english language and humans)
Embase	• SET[1]: (influenza vaccine or flu vaccine).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading] • SET[2]: (high-dose trivalent or high dose trivalent or high dose influenza or fluzone high dose or fluzone high-dose or fluzone hd or high-dose tiv or high dose tiv or high-dose iiv3 or high dose iiv3 or iiv3-hd or high dose or high-dose or HD).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] • SET[3]: 1 and 2 • SET[4]: limit 3 to (humans and English language and aged <65+ years>
Web of Science	• SET[1]: (influenza vaccine); DocType=All document types; Language=All languages; • SET[2]: Refined by: TOPIC (high dose OR high-dose OR HD) • SET[3]: Refined by: TOPIC (elder* OR old* adult OR senior* OR age* OR geriatric*) • SET[4]: Refined by: LANGUAGES: (English)
Pubmed	• SET[1]: (influenza vaccin*) • SET[2]: ("high-dose trivalent" or "high dose trivalent" or "high dose influenza" or "Fluzone high dose" or "Fluzone high-dose" or "Fluzone HD" or "high-dose TIV" or "high dose TIV" or "high-dose IIV3" or "high dose IIV3" or "IIV3-HD" or “high dose” or “high-dose” or “HD”) • SET[3]: ((aged[a] OR (aged, 80 and over) OR senior* OR geriatric* OR old* adult OR 65)) • SET[4]: 1 and 2 and 3

Additional Sensitivity Analyses

Clinical Outcome	Pooled Relative Vaccine Efficacy/Effectiveness[a] (95% CI)	P-value
Observational Studies Only		
Influenza-like Illness	**17.1%** (1.9%, 29.9%)	0.029
Pneumonia Hospitalization	**16.6%** (-7.7%, 35.5%)	0.164
All-cause Hospitalization	**5.3%** (-2.4%, 12.4%)	0.169
Post-Influenza Mortality	**22.2%** (-18.2%, 48.8%)	0.240
Community-dwelling Adults 65+		
Influenza-like Illness	**19.5%** (8.6%, 29.0%)	<0.001
Influenza Hospitalization	**17.8%** (8.1%, 26.5%)	<0.001
Pneumonia Hospitalization	**27.1%** (11.9%, 39.7%)	0.001
Cardiorespiratory Hospitalization	**18.2%** (6.8%, 28.1%)	0.002
All-cause Hospitalization	**6.6%** (-1.4%, 14.0%)	0.103
Post-Influenza Mortality	**22.2%** (-18.2%, 48.8%)	0.240
All-cause Mortality	**-3.4%** (-20.9%, 11.6%)	0.680
Long-term Care Residents 65+		
All-cause Hospitalization	**19.3%** (-7.6%, 39.4%)	0.147
All-cause Mortality	**6.5%** (-8.8%, 19.6%)	0.077

Funnel Plots