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
- (DerSimionian and Laird) for each clinical outcome
- Study heterogeneity was assessed using I²
- Publication bias was assessed using funnel plots • Quality of individual studies assessed by Downs and Black critical appraisal tool



Results

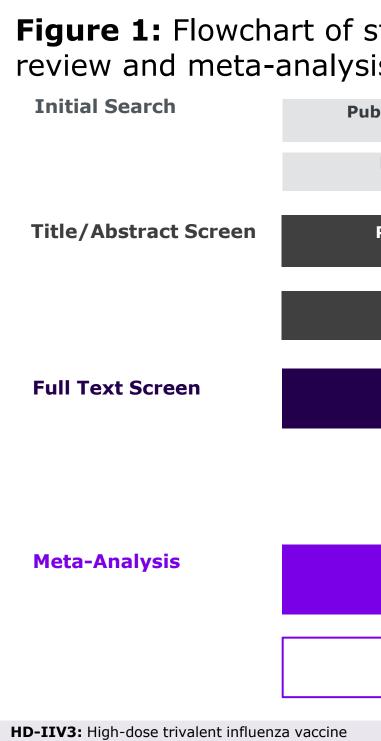


Table 1: Summary of HD-IIV Efficacy/Effectiveness Publications

| (NCT01815268)effectiveness, cluster RCT0.52013-14+HD: 26,639; SD: 26,369- Hospital admission by any causeObservational StudiesIzurieta, 2015Retrospective Cohort StudyUS2012-13 2012-13 toMedicare beneficiaries ≥65 4HD: 2929,730; SD: 1,615,545- Probable influenza infection - Post-influenza death, hospitalization /ED visits - Post-influenza death, hospitalization/ED visitsShay, 2017Retrospective Cohort StudyUS2017-18 2013-14Medicare beneficiaries ≥65 4HD: 2,547,821; SD: 3,560,591- Influenza-related hospital encounters / inpatient stays / office visitsIzurieta, 2018Retrospective cohort studyUS2012-13 to 2017-18Medicare beneficiaries ≥65 4HD: 13,770,207; SD: 6,151,913- Influenza-related hospital encounters / inpatient stays / office visitsIzurieta, 2020Retrospective Cohort StudyUS2018-19 2018-19Medicare beneficiaries ≥65 4HD: 13,770,207; SD: 6,151,913- Influenza-related hospital encounters / inpatient stays / office visitsPaudel, 2020Retrospective Cohort StudyUS2011-12 to 2014-152011-12 to 2014-15- Medicare beneficiaries ≥65 4HD: 2,976,984; SD: 2,976,984- Probable Influenza (Inpatient Hospitalization or Outpatient medical encounter followed by antiviral Rx within 7 days) 4HD: 2,976,882; SD: 2,760,882; SD: 2,760,882- Pneumonia/influenza, cardiorespiratory hospitalizations | Author (Year) | | Study Location | Influenza Seasons | Study Population | Study Outcomes |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|----------------------------------|-------------------|---------------------------------------|----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Diaz Granados, 2013 (NCT00976027)Phase IIIb, multi-center, double- bind, RCTUS2009-10Healthy adults 265 + HD: 6,117; SD: 3,055- Laboratory-confirmed influenza Hospital admission for pumonaibDiaz Granados, 2014, 2015 (NCT012427309)Phase IIIb-TV, multi-center, double-bind RCTUS + | Randomized Studies ^a | | | S S S S S S S S S S S S S S S S S S S | | |
| (NCT01427309)double-blind RCTCanada2012-13• HD: 15,991; SD: 15,998- Influenza-related SAE*Gravenstein, 2017 (NCT01720277)Pilot study for cluster RCTUS2012-13Residents 265 in NHs • HD: 1,461; SD: 1,496- All-cause hospitalizations • HM mortality • Functional declineGravenstein, 2017 (NCT01515268) Observational StudiesSingle-blind, pragmatic, comparative effectiveness, cluster RCTUS2013-14Residents 265 in NHs • HD: 26,639; SD: 26,369- Hospital admissions related to pulmonary and influenza-like condition • Hospital admission brance clusterObservational StudiesUS2012-13Medicare beneficiaries 265 • HD: 929,730; SD: 1,615,545- Probable influenza infection • Post-influenza death, hospitalization or ED visitShay, 2017Retrospective Cohort StudyUS2017-18Medicare beneficiaries 265 • HD: 2,747,821; SD: 1,863,654- Influenza-related physicial encounters / inpatient stays / office visitsLu, 2019Retrospective cohort studyUS2012-13 to 2017-18Medicare beneficiaries 265 • HD: 13,770,207; SD: 6,151,913- Influenza-related hospital encounters / inpatient stays / office visitsLu, 2019Retrospective cohort studyUS2018-14Medicare beneficiaries 265 • HD: 13,770,207; SD: 6,151,913- Influenza-related hospital encounters / inpatient stays / office visitsPaudel, 2020Retrospective Cohort StudyUS2018-14Medicare beneficiaries 265 • HD: 7,976,9821; SD: 1,455,254- Influenza-related hospital encounters / inpatient stays / office visitsHow is the main transpective Cohort Study | DiazGranados, 2013 | | US | 2009-10 | | |
| Gravenstein, 2017Pilot study for cluster RCTUS2012-13Residents 263 in Mis of HD: 1,461 SD: 1,496- NH mortalityGravenstein, 2017Single-blind, pragmatic, comparative effectiveness, cluster RCTUS2013-14Residents 265 in NHs of HD: 1,461 SD: 1,496- NH mortalityIzurieta, 2015Retrospective Cohort StudyUS2012-13Medicare beneficiaries 265 • HD: 22,5639; SD: 26,369- Probable influenza infection • Post-influenza death, hospitalization rED visitShay, 2017Retrospective Cohort StudyUS2012-13 2013-14Medicare beneficiaries 265 • HD: 22,547,821; SD: 3,560,591- Influenza infection • Post-influenza death, hospitalization rED visitsIzurieta, 2018Retrospective cohort studyUS2017-18Medicare beneficiaries 265 • HD: 2,976,981- Influenza-related hospital encounters / inpatient stays / office visitsLu, 2019Retrospective cohort studyUS2018-19Medicare beneficiaries 265 • HD: 13,770,207; SD: 6,151,913- Influenza-related hospital encounters / inpatient stays / office visitsIzurieta, 2020Retrospective Cohort StudyUS2018-19Medicare beneficiaries 265 • HD: 13,770,207; SD: 6,151,913- Influenza-related hospital encounters / inpatient stays / office visitsPaudel, 2020Retrospective Cohort StudyUS2011-12 to • 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 | | | | | • | |
| (NCT01815268)effectiveness, cluster RCT0.32013-14• HD: 26,639; SD: 26,369- Hospital admission by any causeObservational StudiesIzurieta, 2015Retrospective Cohort StudyUS2012-13Medicare beneficiaries ≥65 • HD: 929,730; SD: 1,615,545- Probable influenza infection • Post-influenza hospitalization or ED visit • Post-influenza death, hospitalization/FD visits • Influenza-related physician visitsShay, 2017Retrospective Cohort StudyUS2017-18 2017-18Medicare beneficiaries ≥65 • HD: 8,489,159; SD: 1,863,654- Post-influenza death, hospitalization/FD visits • Post-influenza-related physician visitsIzurieta, 2018Retrospective cohort studyUS2017-18 2012-13 toMedicare beneficiaries ≥65 • HD: 8,489,159; SD: 1,863,654- Influenza-related hospital encounters / inpatient stays / office visits • Influenza-related hospital encounters / inpatient staysIzurieta, 2020Retrospective Cohort StudyUS2018-19 2018-19Medicare beneficiaries ≥65 • HD: 7,904,821; SD: 3,760,984; • HD: 2,976,984; SD: 2,976,984; • HD: 2,976,984; SD: 2,976,984; • HD: 2,976,984; SD: 2,976,984; • Pneumonia/influenza, cardiorespiratory hospitalization s • Pneumonia/influenza, cardiorespiratory hospitalization s • Pneumonia/influenza, cardiorespiratory hospitalization s • Pneumonia/influenza, cardiorespiratory hospitalizations | - | Pilot study for cluster RCT | US | 2012-13 | • HD: 1 461: SD: 1 496 | - NH mortality |
| Izurieta, 2015Retrospective Cohort StudyUS2012-13Medicare beneficiaries ≥65 (HD: 929,730; SD: 1,615,545Probable influenza infection - Post-influenza hospitalization or ED visitShay, 2017Retrospective Cohort StudyUS2012-13 to 2013-14Medicare beneficiaries ≥65 2013-14Post-influenza death, hospitalization/ED visits - Influenza death, hospitalization visitsIzurieta, 2018Retrospective cohort studyUS2017-18 2017-18Medicare beneficiaries ≥65 (HD: 8,489,159; SD: 1,863,654Influenza-related hospital encounters / inpatient stays / office visits - Influenza-related hospital encounters / inpatient stays / office visitsLu, 2019Retrospective cohort studyUS2018-19 2017-18Medicare beneficiaries ≥65 (HD: 7,904,821; SD: 1,455,254Influenza-related hospital encounters / inpatient staysInfluenza-related hospital encounters / inpatient staysIzurieta, 2020Retrospective Cohort StudyUS2011-12 to 2014-15Medicare beneficiaries ≥65 (Outpatient) (HD: 2,976,994; SD: 2,976,994 (Pharmacy) - HD: 2,760,882; SD: 2,760,882- Influenza-related hospital encounters / inpatient stays / office visits - Influenza-related hospital encounters / inpatient stays / office visitsPaudel, 2020Retrospective Cohort StudyUS2011-12 to 2014-15Medicare beneficiaries ≥65 (Outpatient) - HD: 2,760,882; SD: 2,760,882- Influenza (Inpatient Hospitalization or Outpatient medical encounter followed by antiviral Rx within 7 days) - Pneumonia/influenza, cardiorespiratory hospitalizations | (NCT01815268) | | US | 2013-14 | | Hospital admissions related to pulmonary and influenza-like conditions Hospital admission by any cause |
| Izurieta, 2015Retrospective Conort StudyUS2012-13• HD: 929,730; SD: 1,615,545• Post-influenza hospitalization or ED visitShay, 2017Retrospective Cohort StudyUS2012-13 to 2013-14Medicare beneficiaries ≥65 • HD: 2,547,821; SD: 3,560,591• Post-influenza death, hospitalization/ED visits • Influenza-related physician visitsIzurieta, 2018Retrospective cohort studyUS2017-18 2017-18Medicare beneficiaries ≥65 • HD: 8,489,159; SD: 1,863,654• Influenza-related hospital encounters / inpatient stays / office visitsIzurieta, 2020Retrospective Cohort StudyUS2018-19 2018-19Medicare beneficiaries ≥65 • HD: 7,904,821; SD: 1,455,254• Influenza-related hospital encounters / inpatient stays / office visits • Influenza-related hospital encounters / inpatient stays / office visits • HD: 13,770,207; SD: 6,151,913• Influenza-related hospital encounters / inpatient stays • Influenza-related hospital encounters / inpatient staysPaudel, 2020Retrospective Cohort StudyUS2011-12 to 2014-15Medicare beneficiaries ≥65 (Outpatient) • HD: 2,976,994; SD: 2,976,994 • HD: 2,976,984; SD: 2,976,984 • Probable Influenza (Inpatient Hospitalization or Outpatient medical encounter followed by antiviral Rx within 7 days) • Pneumonia/influenza, cardiorespiratory hospitalizations | Observational Studies | | | | Modionno homoficiaria NGE | Droboble influenze infection |
| Shay, 2017Retrospective Cohort StudyUS2013-14• HD: 2,547,821; SD: 3,560,591- Influenza-related physician visitsIzurieta, 2018Retrospective cohort studyUS2017-18Medicare beneficiaries ≥65 • HD: 13,770,207; SD: 6,151,913- Influenza-related hospital encounters / inpatient stays / office visitsLu, 2019Retrospective cohort studyUS2012-13 to 2017-18Medicare beneficiaries ≥65 • HD: 13,770,207; SD: 6,151,913- Influenza-related hospital encounters / inpatient staysIzurieta, 2020Retrospective Cohort StudyUS2018-19Medicare beneficiaries ≥65 • HD: 7,904,821; SD: 1,455,254- Influenza-related hospital encounters / inpatient stays / office visitsPaudel, 2020Retrospective Cohort StudyUS2011-12 to 2014-15Medicare beneficiaries ≥65 (Outpatient) • HD: 2,976,994; SD: 2,976,994; • HD: 2,760,882; SD: 2,760,882- Influenza (Inpatient Hospitalization or Outpatient medical encounter followed by antiviral Rx within 7 days) • Pneumonia/influenza, cardiorespiratory hospitalizations | Izurieta, 2015 | Retrospective Cohort Study | US | | • HD: 929,730; SD: 1,615,545 | - Post-influenza hospitalization or ED visit |
| Izurieta, 2018Retrospective cohort studyUS2017-18• HD: 8,489,159; SD: 1,863,654- Influenza-related hospital encounters / inpatient stays / office visitsLu, 2019Retrospective cohort studyUS2012-13 to 2017-18Medicare beneficiaries ≥65 • HD: 13,770,207; SD: 6,151,913- Influenza-related hospital encounters / inpatient staysIzurieta, 2020Retrospective Cohort StudyUS2018-19Medicare beneficiaries ≥65 • HD: 7,904,821; SD: 1,455,254- Influenza-related hospital encounters / inpatient stays / office visitsPaudel, 2020Retrospective Cohort StudyUS2011-12 to 2011-12 to 2014-15Medicare beneficiaries ≥65 (Outpatient) • HD: 2,976,994; SD: 2,976,994 • HD: 2,760,882; SD: 2,760,882- Influenza (Inpatient Hospitalization or Outpatient medical encounter followed by antiviral Rx within 7 days) • Pneumonia/influenza, cardiorespiratory hospitalizations | Shay, 2017 | Retrospective Cohort Study | US | | • HD: 2,547,821; SD: 3,560,591 | |
| Lu, 2019Retrospective conort studyUS2017-18• HD: 13,770,207; SD: 6,151,913• Influenza-related hospital encounters / inpatient staysIzurieta, 2020Retrospective Cohort StudyUS2018-19Medicare beneficiaries ≥65 • HD: 7,904,821; SD: 1,455,254• Influenza-related hospital encounters / inpatient stays / office visitsPaudel, 2020Retrospective Cohort StudyUS2011-12 to 2014-15Medicare 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, 2018 | Retrospective cohort study | US | | • HD: 8,489,159; SD: 1,863,654 | - Influenza-related hospital encounters / inpatient stays / office visits |
| Izurieta, 2020Retrospective Cohort StudyUS2018-19• HD: 7,904,821; SD: 1,455,254- Influenza-related hospital encounters / inpatient stays / office visitsPaudel, 2020Retrospective Cohort StudyUS2011-12 to 2014-15Medicare beneficiaries ≥65 (Outpatient) • HD: 2,976,994; SD: 2,976,994; SD: 2,976,994 • HD: 2,760,882; SD: 2,760,882 • HD: 2,760,882; SD: 2,760,882- Influenza-related hospital encounters / inpatient stays / office visits • Probable Influenza (Inpatient Hospitalization or Outpatient medical encounter followed by antiviral Rx within 7 days) • Pneumonia/influenza, cardiorespiratory hospitalizations | Lu, 2019 | Retrospective cohort study | US | | • HD: 13,770,207; SD: 6,151,913 | - Influenza-related hospital encounters / inpatient stays |
| Paudel, 2020Retrospective Cohort StudyUS2011-12 to 2014-15• 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, 2020 | Retrospective Cohort Study | US | 2018-19 | | - Influenza-related hospital encounters / inpatient stays / office visits |
| Medicare beneficiaries >65 | Paudel, 2020 | Retrospective Cohort Study | US | | • HD: 2,976,994; SD: 2,976,994 (Pharmacy) | |
| Izurieta, 2021 Retrospective cohort study US 2019-20 - Influenza-related hospital encounters / inpatient stays • HD: 7,173,433; SD: 1,584,451 - Influenza-related hospital encounters / inpatient stays | Izurieta, 2021 | Retrospective cohort study | US | 2019-20 | • HD: 7,173,433; SD: 1,584,451 | - Influenza-related hospital encounters / inpatient stays |
| Richardson, 2015Retrospective Cohort StudyUS2010-11VHA adults ≥65 • HD: 25,714; SD: 139,511- Hospitalization for influenza or pneumonia - All-cause hospitalization and mortality | Richardson, 2015 | Retrospective Cohort Study | US | 2010-11 | • HD: 25,714; SD: 139,511 | - All-cause hospitalization and mortality |
| Young-Xu, 2018Retrospective Cohort StudyUS2015-16VHA adults ≥65 • HD: 125,776; SD: 104,965- Pneumonia/influenza or all-cause hospitalization / outpatient visits • Laboratory-confirmed influenza | Young-Xu, 2018 | Retrospective Cohort Study | US | 2015-16 | | |
| Young-Xu, 2019; Van Aalst, 2019Retrospective cohort studyUS2010-11 to 2014-15VHA adults ≥65 • HD: 158,636; SD: 3,480,288- Pneumonia/influenza, cardiorespiratory, all-cause hospitalizations • Urinary tract infection | | Retrospective cohort study | US | | | |
| Young-Xu, 2020Retrospective Cohort StudyUS2012-13 to 2014-15VHA adults ≥65 +HD: 361,978; SD: 207,574- Influenza/pneumonia, cardiorespiratory mortality - All-cause hospitalization | Young-Xu, 2020 | Retrospective Cohort Study | US | | | |
| Van Aalst, 2021Retrospective cohort studyUS2010-11 to 2014-15VHA adults ≥65 • HD: 158,636; SD: 3,480,288- Cardiovascular, respiratory, cardiorespiratory hospitalization | Van Aalst, 2021 | Retrospective cohort study | US | | | - Cardiovascular, respiratory, cardiorespiratory hospitalization |
| Machado, 2021Retrospective cohort studyUS2012-13 to 2017-18Adults ≥65 from MarketScan® databases • HD: 728,223; SD: 1,633,093- Influenza / Pneumonia hospital/ED visit | Machado, 2021 | Retrospective cohort study | US | | Adults \geq 65 from MarketScan® databases | - Influenza / Pneumonia hospital/ED visit |
| Doyle, 2020Test-negative Case Control StudyUS2015-16 to 2016-17HAIVEN patients ≥65 • HD: 622; SD: 485- Laboratory-confirmed influenza hospitalization | Doyle, 2020 | Test-negative Case Control Study | US | | | - Laboratory-confirmed influenza hospitalization |
| Robison, 2018Retrospective cohort studyUS2016-17Portland, OR adults ≥65 (ALERT IIS) • HD: 78,602; SD: 65,705- Laboratory-confirmed influenza hospitalization | Robison, 2018 | Retrospective cohort study | US | 2016-17 | | - Laboratory-confirmed influenza hospitalization |
| Balasubramani, 2020Test-negative Case Control StudyUS2015-16 to 2018-19HAIVEN patients ≥65 • HD: 3,861; SD: 2,993- influenza-confirmed acute respiratory illness | Balasubramani, 2020 | Test-negative Case Control Study | US | | HAIVEN patients ≥65 | - influenza-confirmed acute respiratory illness |

^aIncludes both individual-level randomized and cluster-randomized studies; ^bData 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.

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| tudies included in the systematic s | |
|-------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| lications identified through Web of Science (n = 1067) | Publications identified through Embase(n = 204) |
| Publications identified through PubMed (n = 310) | Publications identified through Medline(n = 149) |
| Publications identified from all database searches $(n = 1,730)$ | Duplicate Publications removed (n = 464) |
| | |
| Articles assessed for eligibility (n = 1,266) | Publications excluded based on title and abstract screening (<i>n</i> = 1,055) |
| | |
| Full-text articles assessed for eligibility (n = 211) | Full-text articles excluded based on: Age <65 Immunocompromised conditions Pandemic vaccine Antigenic strains Animal studies Route of administration (n = 189) |
| | |
| HD-IIV3 studies eligible for meta-analysis (n = 22) | HD-IIV3 publications excluded for meta-analyses based on: Duplicate analyses including economic evaluation |
| ▼ | Not meeting inclusion criteria for case definition |
| HD-IIV3 publications included in meta-analysis (n = 19) | (n = 3) |

DISCLOSURES: JKL, GKL, RV, JKY, BTS, MML, and SIS are employees of Sanofi at the conduct of this study and may hold shares and/or stock options in the company.

| | influenza- | related outcom | es | related outcomes | | | | | | |
|---------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|--------------------------------------|----|---------------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------|-------------------------|---------------------------------------------|-----------------------------------------|
| ies | Estimate (95% C.I.) | | | | | | | | | |
| subramani 2020 (2015-16) | 1.330 (0.610, 2.900) | · · · · · · | | A: All seasons and sub- | analyses by season type | | | | | |
| subramani 2020 (2016-17) subramani 2020 (2017-18) | 0.890 (0.610, 1.299) 0.890 (0.600, 1.320) | | | Outcome <i>rVE (95% CI); n; p-value</i> | All Seasons | A/H3N2-dominant Seasons ^a | A/H1N1-domina | nt Seasons ^a | Matched Seasons ^b | Mismatched Seaso |
| subramani 2020 (2018-19) Granados 2013 (2009-10) | 0.850 (0.570, 1.268) 0.874 (0.366, 2.086) | • | | | | | 0.00/ (2.7 | 10.40() | | |
| Granados 2014 (2011-12) Granados 2014 (2012-13) | 0.545 (0.328, 0.908) 0.788 (0.654, 0.948) | | | 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 - n=4; p=0 | - | 20.4% (-10.7 – 42.7%) n=4; p=0.175 | 13.7% (0.0 – 25.5 n=7; p=0.050 |
| eta 2018 (2017-18) | 0.993 (0.971, 1.015) | | | | n=11, p=0.007 | n=7, p=0.022 | Π- 4 , β-0 | .170 | Π=4, β=0.175 | Π=7, p=0.050 |
| 2017 (2012-13) 2017 (2013-14) | 0.780 (0.714, 0.852) 0.932 (0.849, 1.023) | - - | | Hospitalization+ER Visit | | | | | | |
| I-Xu 2018 (2015-16) roup Influenza-like Illness (I^2=76.46 % , P=0.000) 19 (2012-13) | 0.620 (0.366, 1.050) 0.857 (0.767, 0.958) 0.769 (0.718, 0.824) | - | | 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 · n=5; p=0 | , | 11.0% (3.8 - 17.6%) n=5; p=0.003 | 10.3% (5.4 - 15. n=8; p<0.001 |
| 9 (2013-14) 9 (2014-15) 9 (2015-16) | 0.847 (0.778, 0.922) 0.911 (0.879, 0.944) 0.948 (0.864, 1.040) | | | 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 - n=2; p=0 | - | 8.4% (-0.7 - 16.7%) n=2; p=0.069 | 2.2% (-2.8 – 6.9 n=3; p=0.384 |
| (2016-17) (2017-18) | 0.874 (0.815, 0.937) 0.953 (0.893, 1.017) | -=- | | Hospitalization | | | | | | |
| o IIV4 (2013-14) o IIV4 (2014-15) | 0.538 (0.341, 0.849) — 0.847 (0.725, 0.990) | _ | | | 11.2% (7.4 – 14.8%) | 13.7% (7.0 – 20.0%) | 7.2% (3.3 – | 11 00%) | 7.2% (3.3 – 11.0%) | 13.7% (7.0 – 20. |
| do IIV4 (2015-16) | 0.813 (0.617, 1.071) | | | Influenza ^e | n=11; p<0.001 | n=7; p<0.001 | n=4; p<0 | - | n=4; p<0.001 | n=7; p<0.001 |
| do IIV4 (2016-17) do IIV4 (2017-18) | 0.980 (0.813, 1.181) 0.926 (0.806, 1.064) | | | | | | | | | 11 77 p (0100) |
| ta 2020 (2018-19) ta 2021 (2019-20) roup Influenza ER+Hospitalization (I^2=73.29 %,P=0.000) | 0.951 (0.920, 0.983) 0.932 (0.899, 0.966) 0.896 (0.861, 0.932) | ₩ ₩ ◆ | | 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 n=2; p<0 | - | 28.9% (10.1 - 43.8%) n=3; p=0.004 | - |
| do IIV4 (2013-14) do IIV4 (2014-15) do IIV4 (2015-16) | 0.862 (0.775, 0.959) 0.971 (0.909, 1.037) 0.952 (0.901, 1.006) | e - e - e | | 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 - n=2; p=0 | • | 13.5% (5.0 - 21.3%) n=5; p=0.002 | 13.3% (4.1 - 21. n=2; p=0.005 |
| do IIV4 (2016-17) do IIV4 (2017-18) oup Pneumonia ER+Hospitalization (I^2=54.25 % , P=0.06 | 1.020 (0.962, 1.081) 0.935 (0.870, 1.005) 3) 0.956 (0.914, 1.001) | | | 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 - n=2; p=0 | - | 9.4% (3.1 - 15.3%) n=4; p=0.004 | 21.0% (15.2 – 26 n=2; p=0.004 |
| 020 (2015-16) 020 (2016-17) 2020 (2018-19) 2021 (2019-20) | 0.760 (0.394, 1.466) 0.730 (0.493, 1.080) 0.948 (0.907, 0.991) 0.931 (0.887, 0.977) | | | 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 n=3; p<0.00 |
| 2012-13) 2013-14) | 0.726 (0.661, 0.797) | _ —_ _ | | | 17.9% (15.0 - 20.8%) | 1770 / (1/ E 20.00/) | | | 17 /0/ (12 5 01 10/) | |
| 014-15) | 0.904 (0.807, 1.013) 0.904 (0.861, 0.949) | | | Cardiorespiratory | 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 n=3; p<0.00 |
| 15-16) 16-17) | 0.941 (0.832, 1.064) 0.894 (0.815, 0.981) | | | | | | | | | |
| 17-18) 18 (2016-17) nfluenza Hospitalization (I^2=68.7 % , P=0.000) | 0.918 (0.841, 1.002) 0.692 (0.519, 0.923) 0.887 (0.844, 0.932) | | | 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 - n=3; p<0 | • | 6.4% (4.1 - 8.6%) n=7; p<0.001 | 12.6% (7.8 - 17 n=4; p<0.003 |
| nados 2015 (2011-12) nados 2015 (2012-13) stein 2017 (2012-13) | 1.005 (0.905, 1.116) 0.836 (0.753, 0.928) 0.680 (0.536, 0.862) | | | B: Sub-analyses by stud | dy type | | | | | |
| ein 2017 (2013-14) | 0.915 (0.863, 0.970) | - | | Outcome | | Randomized Studies ^h | | | Observational Stud | es |
| m 2015 (2010-11) 2018 (2015-16) | 0.990 (0.855, 1.146) 0.930 (0.848, 1.020) | | | | n | rVEº (95% CI) | p-value | n | rVE ^c (95% CI) | p-val |
| ı 2019 (2010-11) ı 2019 (2011-12) | 0.970 (0.922, 1.020) 0.940 (0.900, 0.982) | -# | | Influenza-like Illness | 3 2 | 24.1% (10.0 – 36.1%) | 0.002 | 8 | 11.1% (-0.1 - 21.0%) | 0.05 |
| u 2019 (2012-13) u 2019 (2013-14) | 0.890 (0.845, 0.937) 0.900 (0.850, 0.953) | -#- | | Hospitalization+ER Visit | | | | | | |
| 2019 (2014-15) | 0.900 (0.870, 0.931) | | | Influenza | - | - | - | 13 | 10.4% (6.8 - 13.9%) | <0.00 |
| o All-Cause Hospitalization (I^2=54.78 % , P=0.015) | 0.918 (0.890, 0.945) | ◆ | | Pneumonia | - | - | - | 5 | 4.4% (-0.1 - 8.6%) | 0.05 |
| ados CA CHF (2011-12) ados CA CHF (2012-13) | 0.803 (0.596, 1.082) 0.981 (0.743, 1.297) | _ | | Hospitalization | | | | | | |
| 021 (2010-11) 021 (2011-12) | 0.859 (0.793, 0.930) 0.903 (0.828, 0.985) | - e - - e - | | Influenza | - | - | - | 11 | 11.2% (7.4 - 14.8%) | <0.00 |
| 021 (2012-13) | 0.907 (0.837, 0.983) | | | Pneumonia | 4 2 | 27.3% (15.3 - 37.6%) | <0.001 | | | |
| 021 (2013-14) 021 (2014-15) | 0.854 (0.780, 0.935) 0.854 (0.817, 0.893) | | | Pneumonia/Influenza | - | - | - | 7 | 13.4% (7.3 - 19.2%) | <0.00 |
| Cardiovascular Hospitalization (I^2=0 % , P=0.723) | 0.869 (0.843, 0.895) | ◆ | | Respiratory | - | - | - | 5 | 14.8% (7.6 - 21.5%) | <0.00 |
| os 2015 (2011-12) os 2015 (2012-13) | 0.859 (0.710, 1.039) 0.784 (0.657, 0.937) | | | Cardiovascular | | 10.6% (-9.6 – 27.1%) | 0.279 | 5 | 13.2% (10.5 - 15.8%) | <0.00 |
| 19 (2010-11) 19 (2011-12) | 0.830 (0.757, 0.910) 0.830 (0.765, 0.900) | - e | | Cardiorespiratory | | 18.2% (6.8 – 28.1%) | 0.002 | 5 | 17.9% (14.7 - 21.0%) | <0.00 |
| 19 (2012-13) | 0.810 (0.733, 0.895) | _ _ | | All-cause | 4 | 11.9% (2.0 – 20.7%) | 0.019 | 7 | 7.8% (5.3 – 10.3%) | <0.00 |
| 9 (2013-14) 9 (2014-15) irdiorespiratory Hospitalization (I^2=0 % , P=0.993) | 0.810 (0.737, 0.890) 0.820 (0.761, 0.884) 0.821 (0.791, 0.852) | | | C: Sub-analyses by sub | oject age | | | | | |
| 5 (2010-11) | 0.980 (0.684, 1.404) | | | Outcome | | | Subject Age | | | |
| (2015-16) (2010-11) | 0.750 (0.574, 0.980) 0.890 (0.780, 1.016) | _ | | rVE (95% CI); n; p-value | 65-74 | 75-84 (incl. 75 | +) | 75+ | | 85+ |
| 9 (2011-12) | 0.840 (0.670, 1.013) 0.900 (0.790, 1.025) | _ | | Influenza-like Illness | 21.1% (12.4 – 28.9% | | - | 24.8% (12.3 | - | _ |
| 9 (2012-13) 9 (2013-14) | 0.860 (0.660, 1.121) | | | | n=2; p < 0.001 | n=2; p=0.004 | 4 | n=3; p < | 0.001 | |
| 9 (2014-15) I Hospitalization (I^2=0 % , P=0.858) | 0.820 (0.700, 0.961) 0.866 (0.808, 0.927) | ↓ | | Hospitalization+ER Visit | | | | | | |
| \$ 2013 (2009-10) | 0.660 (0.348, 1.250) — | | | | 4.6% (-1.7 – 10.5%) | 9.0% (3.1 – 14. | 5%) | 12.0% (7.8 | - 16.0%) 14 | 9% (9.4 – 20.1%) |
| 2015 (2011-12) 2015 (2012-13) | 0.535 (0.340, 0.840) — 0.655 (0.444, 0.968) | | | Influenza | n=6; p=0.146 | n=6; p=0.003 | , | n=12; p< | - | n=6; p<0.001 |
| 017 (2013-14) eumonia Hospitalization (I^2=0 % , P=0.404) | 0.791 (0.657, 0.953) 0.727 (0.624, 0.847) | | | Hospitalization | | | | - - | | |
| neumonia Hospitalization (1^2=0 % , P=0.404) 2017 (2013-14) | 0.727 (0.624, 0.847) | | | | | | 70/) | | 16.00() | |
| 021 (2010-11) | 0.860 (0.750, 0.986) | _ | | Influenza | 8.7% (1.5 – 15.2%) | 8.3% (1.4 – 14. n=7; p=0.019 | • | 12.2% (7.3 | - | (9.8 - 21.8%) |
| 4 (0044 40) | 0.970 (0.848, 1.110) 0.770 (0.680, 0.872) | 8 | | | n=7; p=0.018 | n=7; p=0.01 | 2 | n=13; p< | 0.001 | n=6; p<0.001 |
| 21 (2011-12) 21 (2012-13) | 0.770 (0.000, 0.072) | | | | | | | | | |

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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