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Lessons from the pragmatic randomized trials of high-dose vs. standard-dose influenza vaccine against severe clinical outcomes (FLUNITY-HD)

Joshua Nealon
Sanofi Vaccines Medical

Presentation outline

1. FlunityHD study: rationale
2. FlunityHD study: methods and main results
3. Conclusions and discussion

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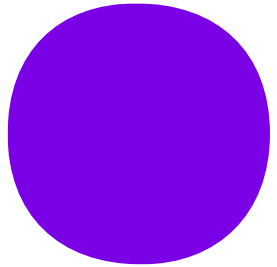
01 FlunityHD study: rationale



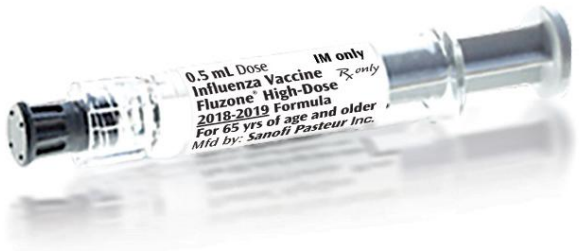
High-dose (HD) influenza vaccine

HD vaccine is a split inactivated influenza vaccine containing 60 µg of hemagglutinin (HA) per strain[1,2]

- It contains 4× the amount of HA compared with standard-dose influenza vaccines
- It was first developed in a trivalent formulation (US license in 2009)
- It was then developed into a quadrivalent formulation (US license in 2019: Fluzone HD quadrivalent® and EU license in 2020: Efluelda®[3–5])

HD vaccine is indicated for the prevention of influenza in people 60[7] or 65[2] years of age and older depending on the country

281 M doses of HD vaccine (including 142 M doses of QIV-HD) have been distributed, as of October 2023[6]



EU: European Union; HA: hemagglutinin; HD: high-dose; M: million; QIV-HD: high-dose quadrivalent influenza vaccine; TIV-HD: high-dose trivalent influenza vaccine; US: United States.
References in slide notes.

Randomized phase 3 immunogenicity study demonstrated improved immune response with HD compared with standard dose (SD)

MAJOR ARTICLE

Randomized, Double-Blind Controlled Phase 3 Trial Comparing the Immunogenicity of High-Dose and Standard-Dose Influenza Vaccine in Adults 65 Years of Age and Older

Ann R. Falsey,[1,2] John J. Treanor,[3] Nadia Tornieporth,[4] Jose Capellan,[5] and Geoffrey J. Gorse[6]

(See the editorial commentary by Poland and Mulligan, on pages 161–3.)

Background. Influenza-associated morbidity and mortality has not decreased in the last decade, despite increased receipt of vaccine. To improve the immunogenicity of influenza vaccine, a high-dose (HD) trivalent, inactivated influenza vaccine was developed.

Methods. A multicenter, randomized, double-blind controlled study was conducted to compare HD vaccine (which contains 60 μg of hemagglutinin per strain) with the licensed standard-dose (SD) vaccine (which contains 15 μg of hemagglutinin per strain) in adults ≥65 years of age. HD vaccine was administered to 2575 subjects, and SD vaccine was administered to 1262 subjects.

Results. There was a statistically significant increase in the rates of seroconversion and mean hemagglutination inhibition titers at day 28 after vaccination among those who received HD vaccine, compared with those who received SD vaccine. Mean postvaccination titers for individuals who received HD vaccine were 116 for H1N1, 609 for H3N2, and 69 for B strain; for those who received SD vaccine, mean postvaccination titers were as 67 for H1N1, 333 for H3N2, and 52 for B strain. The HD vaccine met superiority criteria for both A strains, and the responses for B strain met noninferiority criteria. Seroprotection rates were also higher for those who received HD vaccine, for all strains. Local reactions were more frequent in individuals who received SD vaccine vaccine, but the reactions were mild to moderate.

Conclusions. There was a statistically significant increase in the level of antibody response induced by HD influenza vaccine, compared with that induced by SD vaccine, without an attendant increase in the rate or severity of clinically relevant adverse reactions. These results suggest that the high-dose vaccine may provide improved protective benefits for older adults.

Trial registration. ClinicalTrials.gov identifier: NCT00391053.

Although vaccination is an effective method for reducing influenza-associated morbidity and mortality, the rates of hospitalization and death due to seasonal influenza in elderly individuals have increased substantially in the past 2 decades despite increasing influenza vaccine coverage [1–3]. The protective efficacy of inactivated influenza vaccine is estimated to be 70%–90% in young adults, whereas serologic response rates and vaccine effectiveness are generally lower in older adults [1, 4–6]. Thus, efforts are needed to improve the im-

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Reprints or correspondence: Ann R. Falsey, MD, Infectious Diseases Unit, Rochester General Hospital, 1425 Portland Ave., Rochester, NY 14621 (arfa@uhealth.org).

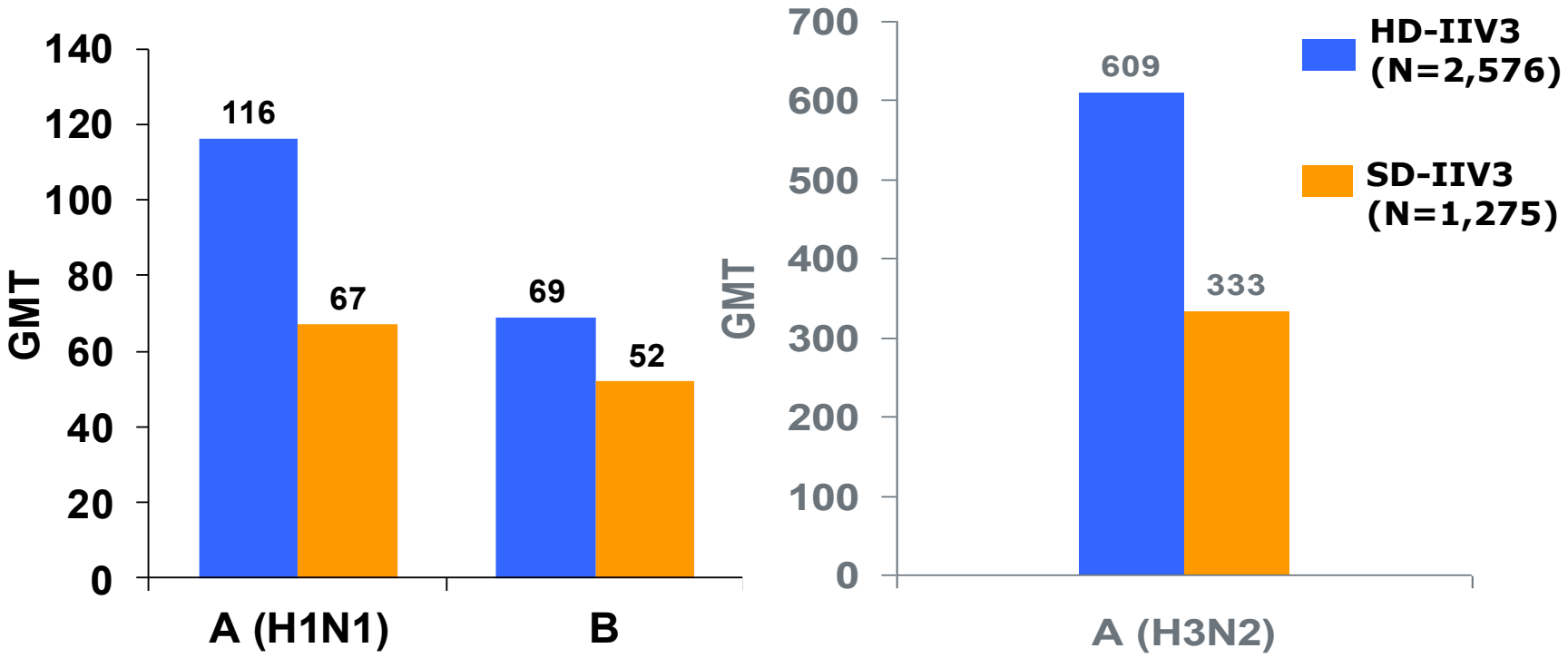
The Journal of Infectious Diseases 2009;200:172–80

0022-1899/2000/20002-0004$15.00
DOI: 10.1086/599790

Potential conflicts of interest: A.R.F. has consulted for Merck, Wyeth, and GlaxoSmithKline and is on the advisory board for Gilead. J.J.T. has received research support from Protein Sciences, Merck, Wyeth, GlaxoSmithKline, Antigen Express, Merck-Pharma, Vaxtrovir, Ligocyte, sanofi pasteur, and CSL Biotherapies; has served as a consultant and/or scientific advisory board member for Alphavax, Epimmune, Dynavax, Immune Targeting Systems, Palmetto, Powderject, Paxilus, and Tripep; and has served on a data safety monitoring board member for Medimmune and Novavax. N.T. and J.C. are employees of sanofi pasteur. G.J.G. reports no relevant conflicts.

Presented in part: American Geriatric Society, Washington, DC, 2 May 2008 (abstract 0120).

Financial support: sanofi pasteur (to A.R.F.).



Superiority of immune responses achieved for A (H1N1) and A (H3N2); non-inferiority for B. All comparisons, *P* <0.0001

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Reference: Falsey AR, et al. J Infect Dis. 2009;200(2):172-180.

FDA discussions on the definition of superiority

Designation of “superiority” would be granted if, in a fully-powered RCT, rVE of TIV-HD vs TIV-SD had lower bound of the 95% confidence >9.1% (to give confidence of at least 10% higher efficacy).

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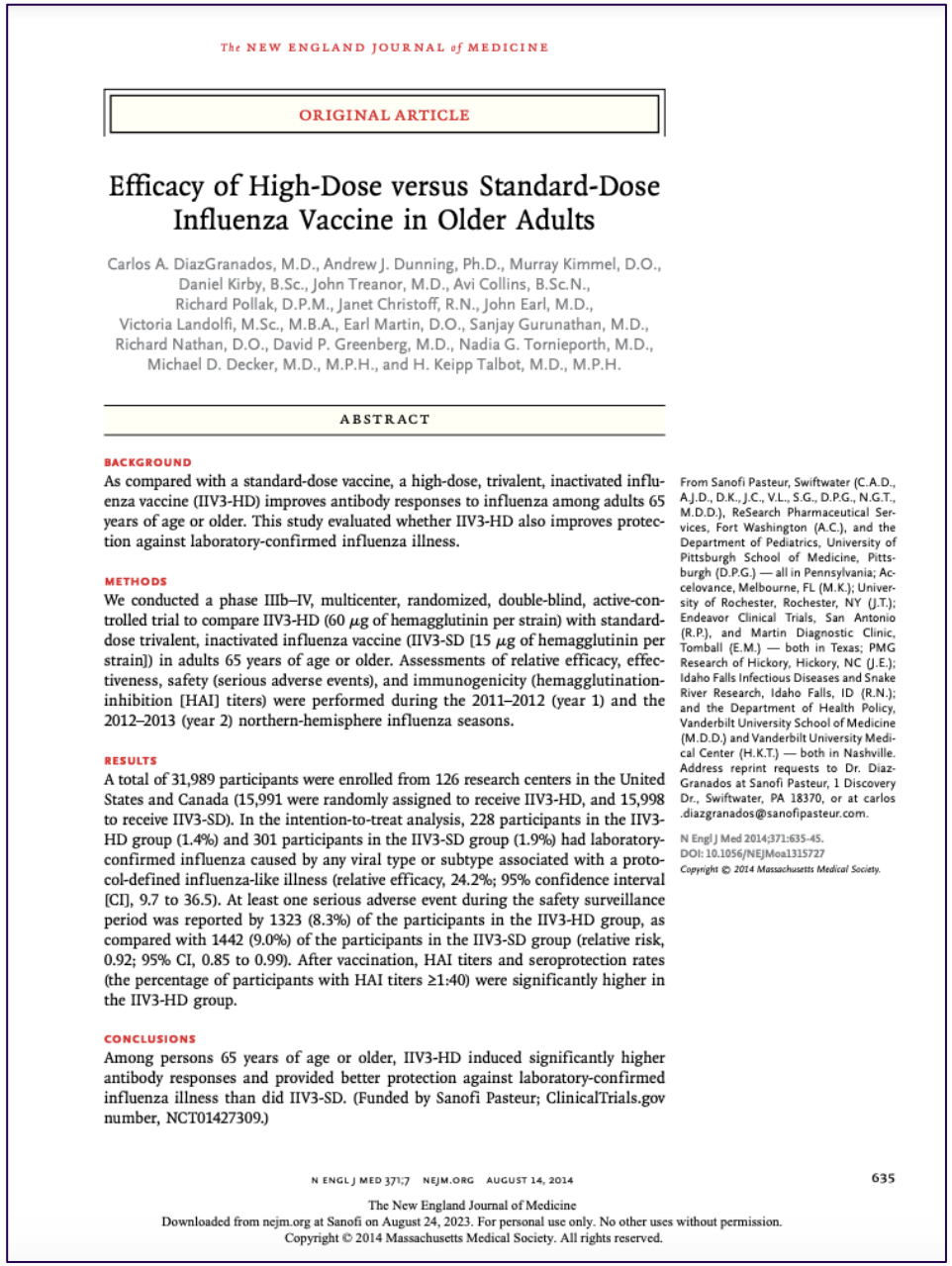
DiazGranados C a, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. *NEJM*. 2014;371(7):635-645.

FIM12 study



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults

Carlos A. DiazGranados, M.D., Andrew J. Dunning, Ph.D., Murray Kimmel, D.O., Daniel Kirby, B.Sc., John Treanor, M.D., Avi Collins, B.Sc.N., Richard Pollak, D.P.M., Janet Christoff, R.N., John Earl, M.D., Victoria Landolfi, M.Sc., M.B.A., Earl Martin, D.O., Sanjay Gurunathan, M.D., Richard Nathan, D.O., David P. Greenberg, M.D., Nadia G. Tornieporth, M.D., Michael D. Decker, M.D., M.P.H., and H. Keipp Talbot, M.D., M.P.H.

ABSTRACT

BACKGROUND

As compared with a standard-dose vaccine, a high-dose, trivalent, inactivated influenza vaccine (IIV3-HD) improves antibody responses to influenza among adults 65 years of age or older. This study evaluated whether IIV3-HD also improves protection against laboratory-confirmed influenza illness.

METHODS

We conducted a phase IIIb–IV, multicenter, randomized, double-blind, active-controlled trial to compare IIV3-HD (60 μg of hemagglutinin per strain) with standard-dose trivalent, inactivated influenza vaccine (IIV3-SD [15 μg of hemagglutinin per strain]) in adults 65 years of age or older. Assessments of relative efficacy, effectiveness, safety (serious adverse events), and immunogenicity (hemagglutination-inhibition [HAI] titers) were performed during the 2011–2012 (year 1) and the 2012–2013 (year 2) northern-hemisphere influenza seasons.

RESULTS

A total of 31,989 participants were enrolled from 126 research centers in the United States and Canada (15,991 were randomly assigned to receive IIV3-HD, and 15,998 to receive IIV3-SD). In the intention-to-treat analysis, 228 participants in the IIV3-HD group (1.4%) and 301 participants in the IIV3-SD group (1.9%) had laboratory-confirmed influenza caused by any viral type or subtype associated with a protocol-defined influenza-like illness (relative efficacy, 24.2%; 95% confidence interval [CI], 9.7 to 36.5). At least one serious adverse event during the safety surveillance period was reported by 1323 (8.3%) of the participants in the IIV3-HD group, as compared with 1442 (9.0%) of the participants in the IIV3-SD group (relative risk, 0.92; 95% CI, 0.85 to 0.99). After vaccination, HAI titers and seroprotection rates (the percentage of participants with HAI titers ≥1:40) were significantly higher in the IIV3-HD group.

CONCLUSIONS

Among persons 65 years of age or older, IIV3-HD induced significantly higher antibody responses and provided better protection against laboratory-confirmed influenza illness than did IIV3-SD. (Funded by Sanofi Pasteur; ClinicalTrials.gov number, NCT01427309.)

From Sanofi Pasteur, Swiftwater (C.A.D., A.J.D., D.K., J.C., V.L., S.G., D.P.G., N.G.T., M.D.D.), ReSearch Pharmaceutical Services, Fort Washington (A.C.), and the Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh (D.P.G.) — all in Pennsylvania; Accelovance, Melbourne, FL (M.K.); University of Rochester, Rochester, NY (J.T.); Endeavor Clinical Trials, San Antonio (R.P.), and Martin Diagnostic Clinic, Tomball (E.M.) — both in Texas; PMG Research of Hickory, Hickory, NC (J.E.); Idaho Falls Infectious Diseases and Snake River Research, Idaho Falls, ID (R.N.); and the Department of Health Policy, Vanderbilt University School of Medicine (M.D.D.) and Vanderbilt University Medical Center (H.K.T.) — both in Nashville. Address reprint requests to Dr. Diaz-Granados at Sanofi Pasteur, 1 Discovery Dr., Swiftwater, PA 18370, or at carlos.diazgranados@sanofipasteur.com.

N Engl J Med 2014;371:635-45.
DOI: 10.1056/NEJMoa1315727

DiazGranados CA, *et al. N Engl J Med*. 2014;371(7):635-645

Proven superior efficacy versus standard dose influenza vaccine in preventing ILI in a RCT in adults aged 65 years and older

31,989
Adults ≥65 years old

126
sites

2
Influenza seasons
2011–12
2012–13

Randomized 1:1

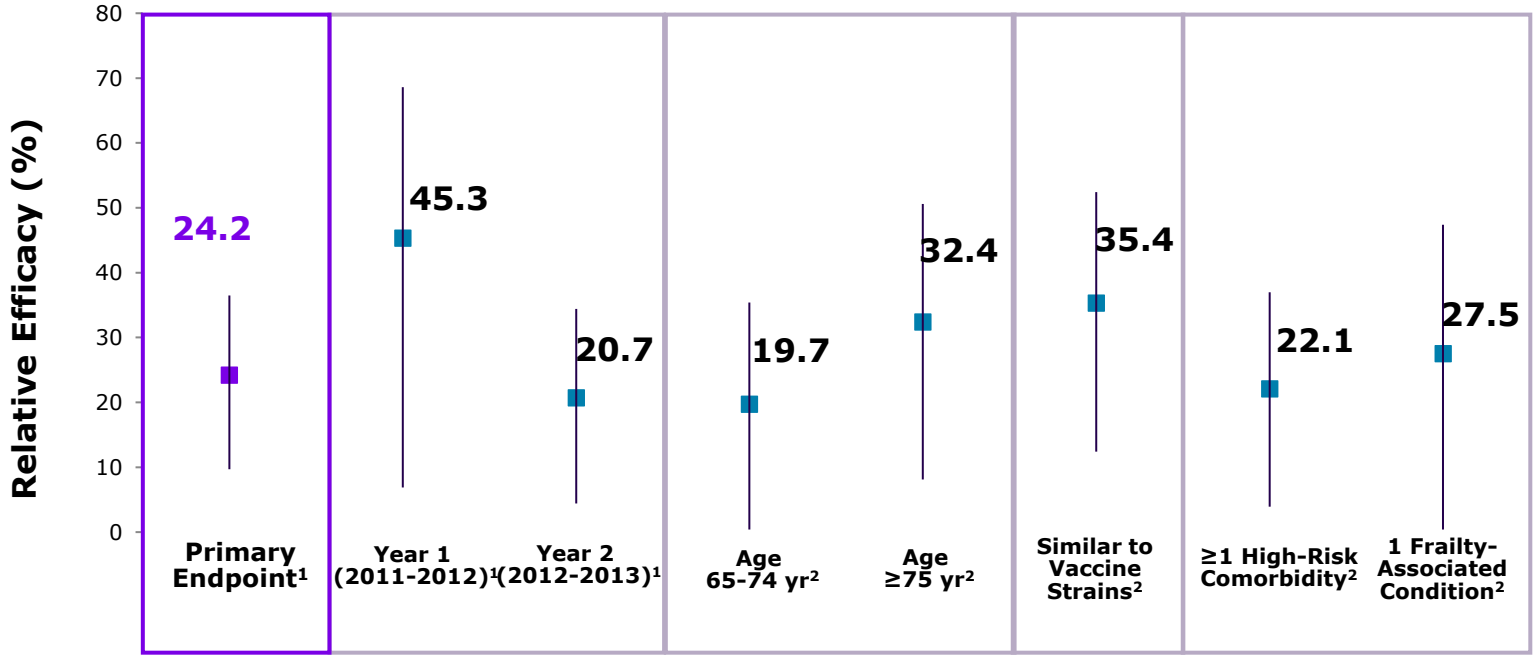
High-dose trivalent influenza vaccine (TIV-HD)

or

Standard-dose trivalent influenza vaccine (TIV-SD)

Primary endpoint

Laboratory-confirmed influenza associated with protocol defined influenza-like illness

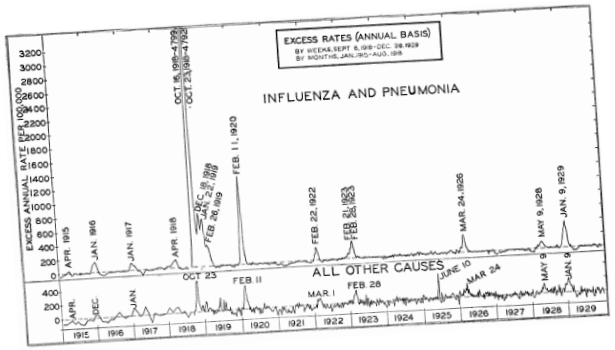


Compared with SD influenza vaccine, the benefit of HD vaccine was demonstrated across age groups, comorbidities/frailty conditions in community-dwelling seniors over 2 influenza seasons

HD: high-dose; SD: standard-dose; TIV-HD: high-dose trivalent influenza vaccine; TIV-SD: standard-dose trivalent influenza vaccine.

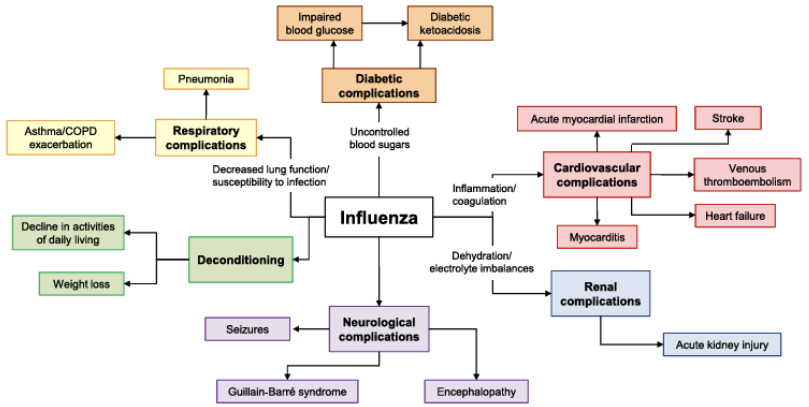
References: 1. DiazGranados CA et al. *N Engl J Med* 2014;371:635-45. doi: 10.1056/nejmoa1315727. 2. DiazGranados CA et al. 2015 *Vaccine*;33:4565-71. doi: 10.1016/j.vaccine.2015.07.003.

Prior evidence indicated possible cardiovascular benefit of influenza vaccination

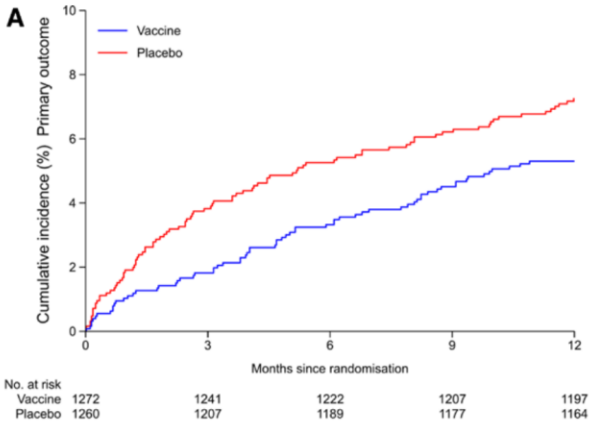


Observational time series from nearly a century ago[1]

Excess modeling studies of increasing complexity[3,4,5]



Literature reviews identified a range of extra-pulmonary sequelae of influenza infection[2]



RCT of SD flu vaccine prevents CV events[6]

1. Collins, S. D. (1932). Public Health Reports (1896-1970), 47(46), 2159–2179.
2. Macias AE, et al. Vaccine. 2021;39 Suppl 1:A6-A14.
3. Warren-Gash C, et al. J Infect Dis. 2011;203(12):1710-1718.
4. López-Cuadrado T, et al., Gac Sanit. 2012;26(4):325-329.
5. Zucs P, et al., Emerg Themes Epidemiol. 2005;2(1):6.
6. Fröbert O, Götberg M, Erlinge D, et al. Circulation. 2021;144(18):1476-1484.

- Post-hoc reanalysis of FIM12 study
- Explored safety data to assess event rates in each arm
- Randomization remains intact: possible to infer causality

Vaccine 33 (2015) 4988–4993

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Prevention of serious events in adults 65 years of age or older: A comparison between high-dose and standard-dose inactivated influenza vaccines☆

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Aged, 80 and over

ABSTRACT

Background: A recent study showed that a high-dose inactivated influenza vaccine (IIV-HD) was 24.2% more efficacious than a standard-dose inactivated influenza vaccine (IIV-SD) in preventing laboratory-confirmed symptomatic influenza in adults ≥65 years. Here we evaluate the effectiveness of IIV-HD compared to IIV-SD in preventing serious illnesses considered potential sequelae or complications of influenza infection.

Methods: The original study was a double-blind, randomized, active-controlled, multicenter trial. Participants were adults ≥65 years randomized to receive IIV-HD or IIV-SD, and followed for 6–8 months post-vaccination for the occurrence of influenza and serious adverse events (SAEs). SAEs were events: leading to death or hospitalization (or its prolongation); considered life-threatening or medically important; or resulting in disability. For the present analysis, reported SAEs were classified as possibly related to influenza by three blinded physicians and rates per 1000 participant-seasons were calculated. Relative vaccine effectiveness (rVE) was estimated as (1 − Rate Ratio) × 100.

Results: 31,989 participants were enrolled, with 15,991 and 15,998 randomized to receive IIV-HD and IIV-SD, respectively. IIV-HD was significantly more effective than IIV-SD in preventing SAEs possibly related to influenza overall (rVE, 17.7%; 95% confidence interval [CI], 6.6–27.4%) and serious pneumonia (rVE, 39.8%; 95% CI, 19.3–55.1%). Borderline significance was observed for the efficacy of IIV-HD relative to IIV-SD for the prevention of all-cause hospitalizations (rVE, 6.9%; 95% CI, 0.5–12.8%).

Conclusions: Compared to IIV-SD, IIV-HD reduced the risk of SAEs possibly related to influenza. The observed relative effectiveness against serious pneumonia is particularly noteworthy considering the burden of influenza and pneumonia in older adults.

1. Introduction

Adults 65 years of age and older are particularly vulnerable to complications from influenza infection, accounting for most seasonal influenza-related hospitalizations and deaths [1,2]. The high burden of influenza in this population persists despite documented improvements in vaccination rates [3]. Accordingly, the availability of improved influenza vaccines for older adults had been considered an unmet medical need [4,5]. A recently completed double-blind, randomized, controlled trial (NCT01427309) demonstrated that a high-dose inactivated influenza vaccine (IIV-HD) was 24.2% (95% confidence interval [CI], 9.7%–36.5%) more efficacious than a standard-dose inactivated influenza vaccine (IIV-SD) in preventing laboratory-confirmed symptomatic influenza in adults 65 years of age and older [6].

In addition to the observed improvement in efficacy, 119 fewer study participants developed at least one serious adverse event (SAE) of any cause in the IIV-HD group compared to the IIV-SD group. The risk of developing at least one SAE during the study was

Abbreviations: IIV-HD, high-dose inactivated influenza vaccine; CI, confidence interval; IIV-SD, standard-dose inactivated influenza vaccine; SAE, serious adverse event; COPD, chronic obstructive pulmonary disease; RR, rate ratios; rVE, relative vaccine effectiveness; FAS, Full Analysis Set; ITT, intent-to-treat; CAP, community-acquired pneumonia.

☆ Presented in part at AMDA Long Term Care Medicine – 2014, Nashville, TN, 27 February–2 March 2014. Abstract available at: JAMDA 2014; 15(3): Page B28 (DOI: http://dx.doi.org/10.1016/j.jamda.2013.12.076).

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http://dx.doi.org/10.1016/j.vaccine.2015.07.006
0264-410X/

DiazGranados, C. A., et al., 2015. *Vaccine*, *33*(38), 4988–4993.

Effectiveness of HD vs SD at preventing serious cardio-respiratory events: FIM12 reanalysis

	Year 1 *N* = 14,497, rVE% (95% CI)	Year 2 *N* = 17,486, rVE% (95% CI)	Combined *N* = 31,983, rVE% (95% CI)
All-cause hospitalization	−0.4 (−10.1; 8.5)	13.6 (5.1; 21.4)	6.9 (0.5; 12.8)
Serious cardio-respiratory events	13.7 (−3.8; 28.2)	21.0 (6.1; 33.5)	17.7 (6.6; 27.4)
Pneumonia events	46.4 (15.9; 65.8)	34.3 (3.1; 55.4)	39.8 (19.3; 55.1)
Asthma/COPD/bronchial events	−90.2 (−222.3; −12.3)	37.0 (3.3; 58.9)	1.3 (−36.0; 28.4)
Influenza events[a]	NE	49.9 (−100.1; 87.5)	33.3 (−136.2; 81.2)
Coronary artery events	21.5 (−11.5; 44.8)	−22.4 (−75.1; 14.5)	2.4 (−25.3; 24.0)
Congestive heart failure	14.4 (−47.5; 50.3)	29.7 (−9.6; 54.9)	24.0 (−7.2; 46.1)
Cerebrovascular events	−10.1 (−69.7; 28.5)	23.6 (−23.8; 52.8)	6.5 (−28.9; 32.1)
Other respiratory events	45.9 (−6.2; 72.4)	21.6 (−45.1; 57.7)	34.0 (−3.8; 58.1)

Abbreviations: rVE, relative vaccine effectiveness; CI, confidence interval; COPD, chronic obstructive pulmonary disease; NE, non-evaluable.

[a] Corresponding to serious laboratory-confirmed influenza diagnosed outside study procedures by a participant's health-care provider.

DiazGranados, C. A., Robertson, C. A., Talbot, H. K., Landolfi, V., Dunning, A. J., & Greenberg, D. P. (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), 4988–4993.

Observational studies provided evidence for HD rVE against hospitalized events, including non-respiratory events

Vaccine: X 14 (2023) 100327

Contents lists available at ScienceDirect

Vaccine: X

journal homepage: www.elsevier.com/locate/jvacx

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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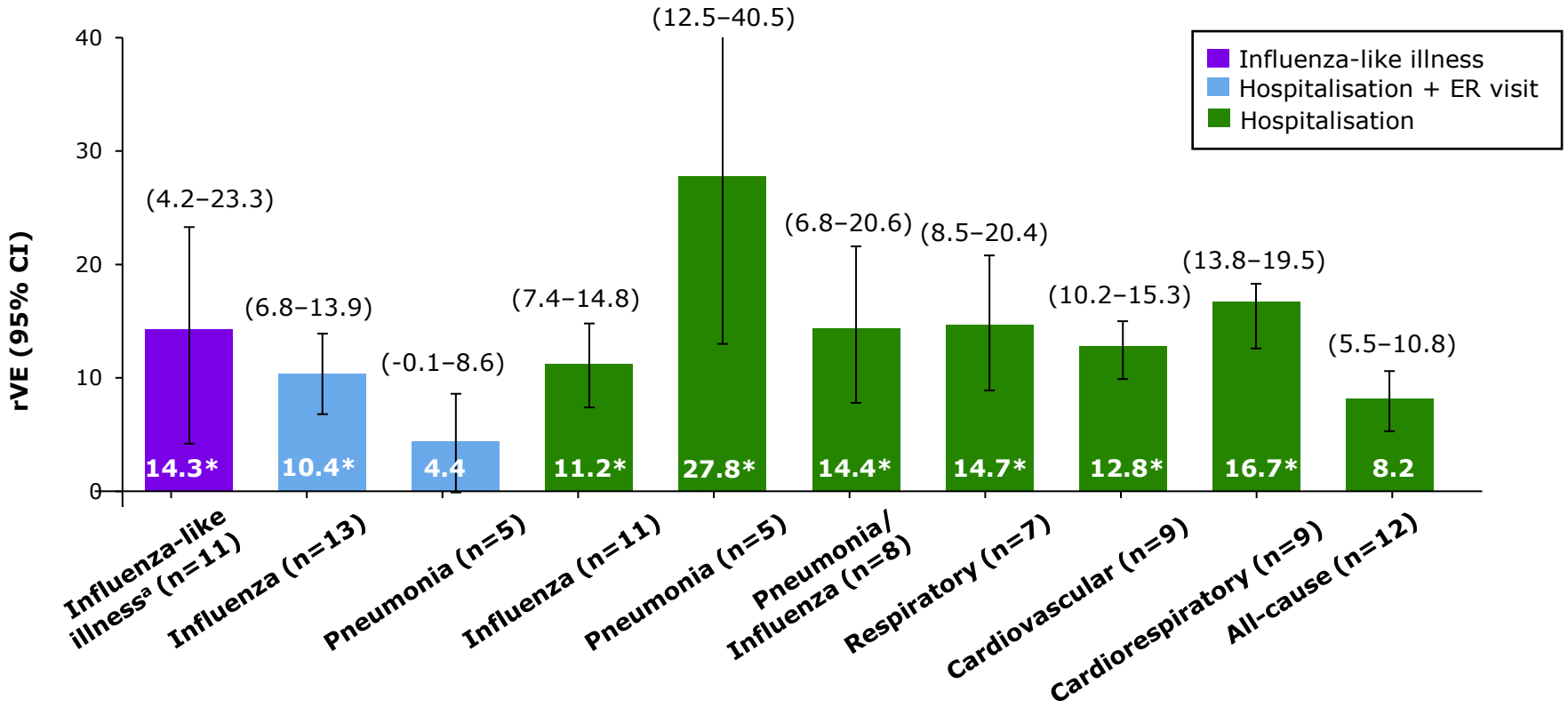
HD more effective than SD influenza vaccines irrespective across outcome, season, circulating strain, antigenic match, study type, study setting and age subgroup[1]



Observational studies susceptible to critical biases.[2] RCTs powered for rare, hospitalized outcomes are infeasibly large.[3]

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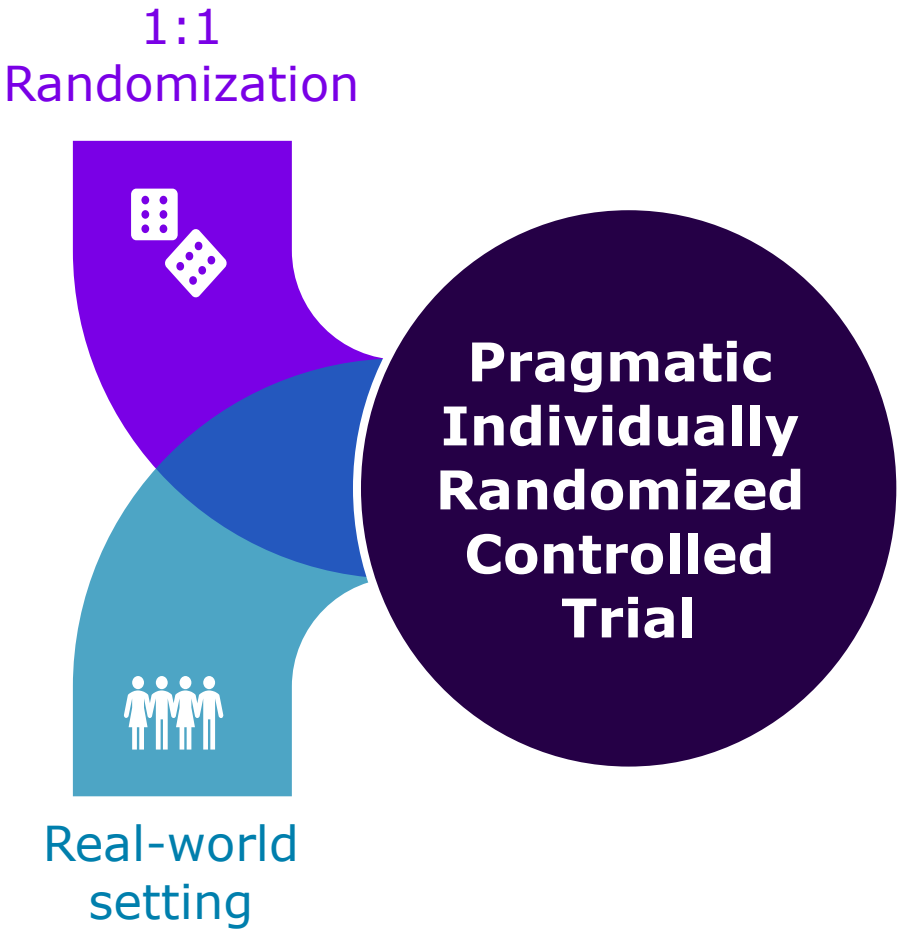
1. Lee J, et al. *Vaccine: X*. 2023;14:100327
2. Ioannidis JPA. JAMA. 2005;294(2):218-228.
3. Nealon J, et al. npj Vaccines. 2022;7(1):1-9.

Pragmatic individually RCT: an innovative approach to assess influenza vaccine performance[1]



Digital trial invitation (e.g. email, SMS) and option for online e-consent

Only one in-person trial visit – attend appointment at vaccination site

All baseline, outcomes and safety data collected through national or regional registries

Data analyzed centrally at External Sponsor site

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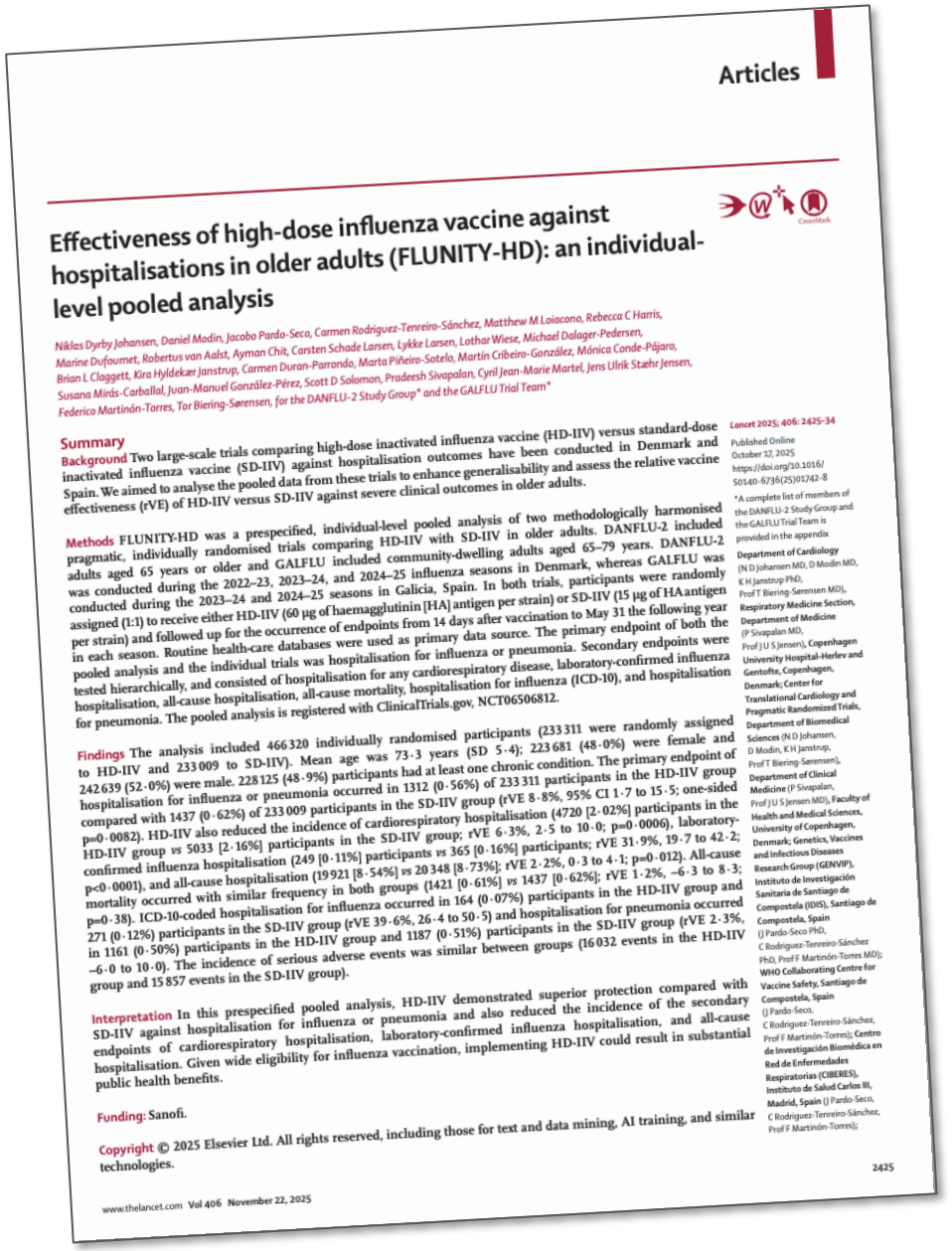
1. Hollingsworth R, Palmu A, et al. Effectiveness of the quadrivalent high-dose influenza vaccine for prevention of cardiovascular and respiratory events in people aged 65 years and above: Rationale and design of a real-world pragmatic randomized clinical trial. American Heart Journal. 2021;237:54-61.

03 FlunityHD study: methods and main results

Effectiveness of high-dose influenza vaccine against hospitalisations in older adults (FLUNITY-HD): an individual-level pooled analysis

Johansen, Niklas DyrbyBartholdy, Katja VuSenin, Ana Maria Abal et al.
The Lancet, Volume 406, Issue 10518, 2425 - 2434



Articles

Effectiveness of high-dose influenza vaccine against hospitalisations in older adults (FLUNITY-HD): an individual-level pooled analysis

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Summary

Background Two large-scale trials comparing high-dose inactivated influenza vaccine (HD-IIV) versus standard-dose inactivated influenza vaccine (SD-IIV) against hospitalisation outcomes have been conducted in Denmark and Spain. We aimed to analyse the pooled data from these trials to enhance generalisability and assess the relative vaccine effectiveness (rVE) of HD-IIV versus SD-IIV against severe clinical outcomes in older adults.

Methods FLUNITY-HD was a prespecified, individual-level pooled analysis of two methodologically harmonised pragmatic, individually randomised trials comparing HD-IIV with SD-IIV in older adults. DANFLU-2 included adults aged 65 years or older and GALFLU included community-dwelling adults aged 65–79 years. DANFLU-2 was conducted during the 2022–23, 2023–24, and 2024–25 influenza seasons in Denmark, whereas GALFLU was conducted during the 2023–24 and 2024–25 seasons in Galicia, Spain. In both trials, participants were randomly assigned (1:1) to receive either HD-IIV (60 µg of haemagglutinin [HA] antigen per strain) or SD-IIV (15 µg of HA antigen per strain) and followed up for the occurrence of endpoints from 14 days after vaccination to May 31 the following year in each season. Routine health-care databases were used as primary data source. The primary endpoint of both the pooled analysis and the individual trials was hospitalisation for influenza or pneumonia. Secondary endpoints were tested hierarchically, and consisted of hospitalisation for any cardiorespiratory disease, laboratory-confirmed influenza hospitalisation, all-cause hospitalisation, all-cause mortality, hospitalisation for influenza (ICD-10), and hospitalisation for pneumonia. The pooled analysis is registered with ClinicalTrials.gov, NCT06506812.

Findings The analysis included 466 320 individually randomised participants (233 311 were randomly assigned to HD-IIV and 233 009 to SD-IIV). Mean age was 73·3 years (SD 5·4); 223 681 (48·0%) were female and 242 639 (52·0%) were male. 228 125 (48·9%) participants had at least one chronic condition. The primary endpoint of hospitalisation for influenza or pneumonia occurred in 1312 (0·56%) of 233 311 participants in the HD-IIV group compared with 1437 (0·62%) of 233 009 participants in the SD-IIV group (rVE 8·8%, 95% CI 1·7 to 15·5; one-sided p=0·0082). HD-IIV also reduced the incidence of cardiorespiratory hospitalisation (4720 [2·02%] participants in the HD-IIV group *vs* 5033 [2·16%] participants in the SD-IIV group; rVE 6·3%, 2·5 to 10·0; p=0·0006), laboratory-confirmed influenza hospitalisation (249 [0·11%] participants *vs* 365 [0·16%] participants; rVE 31·9%, 19·7 to 42·2; p<0·0001), and all-cause hospitalisation (19 921 [8·54%] *vs* 20 348 [8·73%]; rVE 2·2%, 0·3 to 4·1; p=0·012). All-cause mortality occurred with similar frequency in both groups (1421 [0·61%] *vs* 1437 [0·62%]; rVE 1·2%, −6·3 to 8·3; p=0·38). ICD-10-coded hospitalisation for influenza occurred in 164 (0·07%) participants in the HD-IIV group and 271 (0·12%) participants in the SD-IIV group (rVE 39·6%, 26·4 to 50·5) and hospitalisation for pneumonia occurred in 1161 (0·50%) participants in the HD-IIV group and 1187 (0·51%) participants in the SD-IIV group (rVE 2·3%, −6·0 to 10·0). The incidence of serious adverse events was similar between groups (16 032 events in the HD-IIV group and 15 857 events in the SD-IIV group).

Interpretation In this prespecified pooled analysis, HD-IIV demonstrated superior protection compared with SD-IIV against hospitalisation for influenza or pneumonia and also reduced the incidence of the secondary endpoints of cardiorespiratory hospitalisation, laboratory-confirmed influenza hospitalisation, and all-cause hospitalisation. Given wide eligibility for influenza vaccination, implementing HD-IIV could result in substantial public health benefits.

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*A complete list of members of the DANFLU-2 Study Group and the GALFLU Trial Team is provided in the appendix
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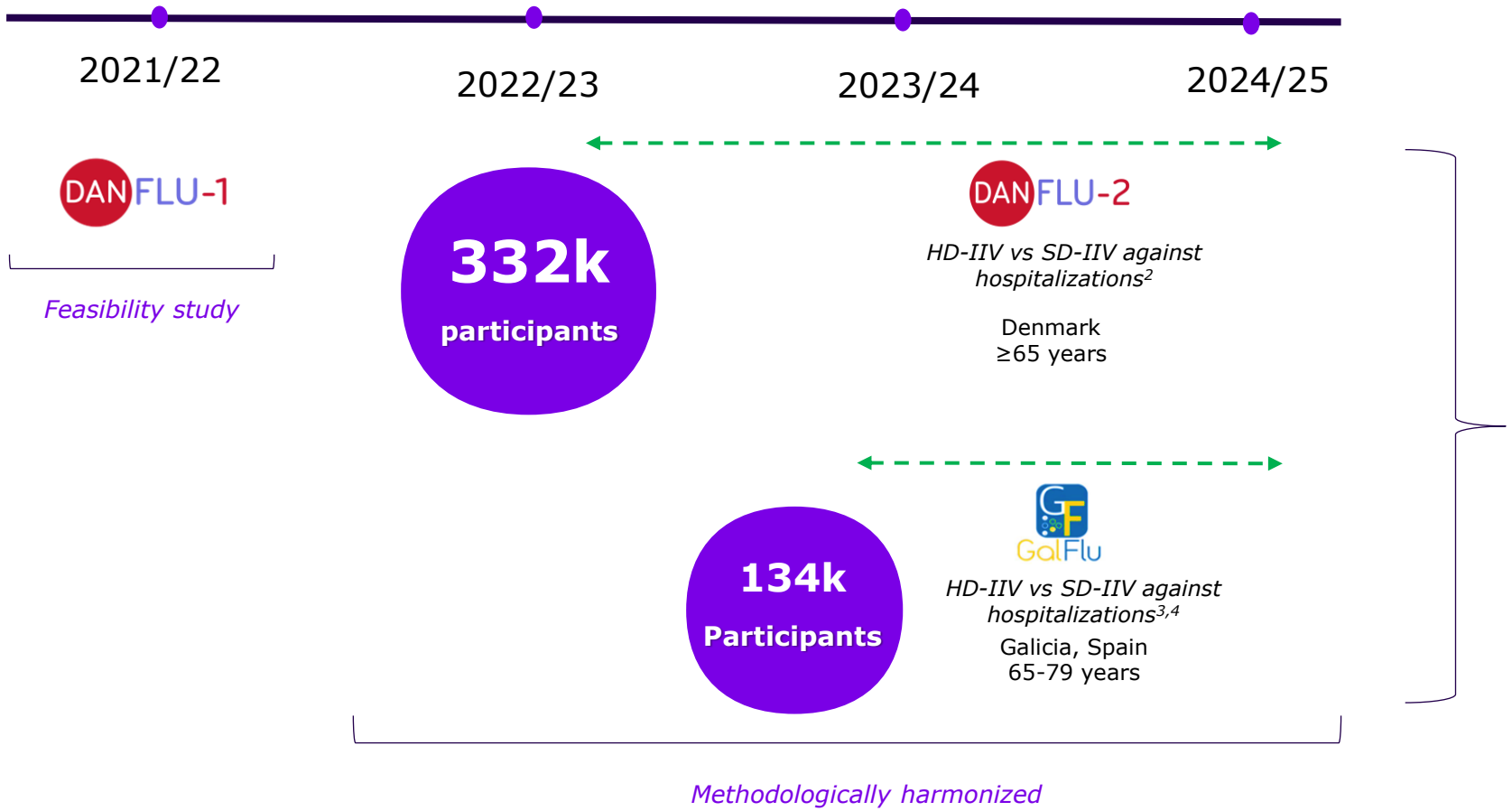
Flunity-HD: from feasibility to fully powered



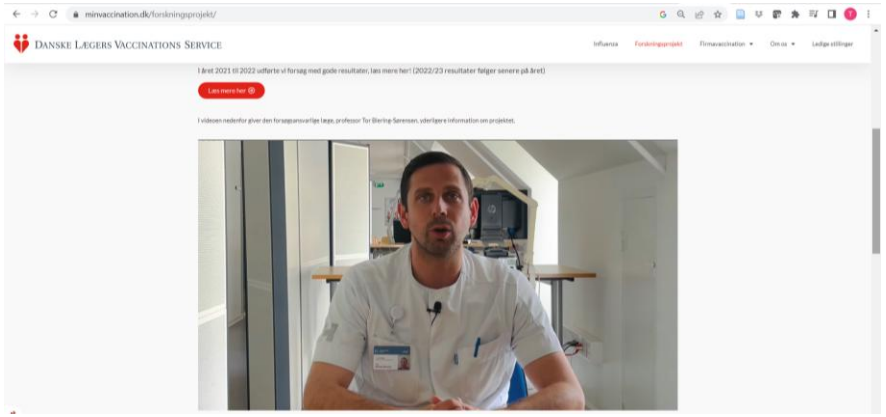
FLUNITY-HD

466k participants

Designed and powered to demonstrate the benefit of HD-IIV vs SD-IIV against severe clinical outcomes

Trial organization and data flow

~ 1,000,000 invites each season



Initial participant data

UNIVERSITY OF COPENHAGEN

REGION H Gentofte Hospital

Center for Pragmatic Randomized Trials

Participant SSN

Baseline characteristics and outcomes

Vaccination clinic network:

- Open year-round: not just for flu vaccination
- Vaccinates > 200,000 persons/year and rapidly upscaling
- Inclusion and randomization
- Administration of study drug

- Central trial site
- Study oversight
- Database management
- Nationwide access to all medical records and lab results

Registry data:

- Nationwide tax-funded public health system
- Nationwide registries can be crosslinked using social security numbers (SSN)
- Every hospital contact, death, redeemed prescription is captured in the registries

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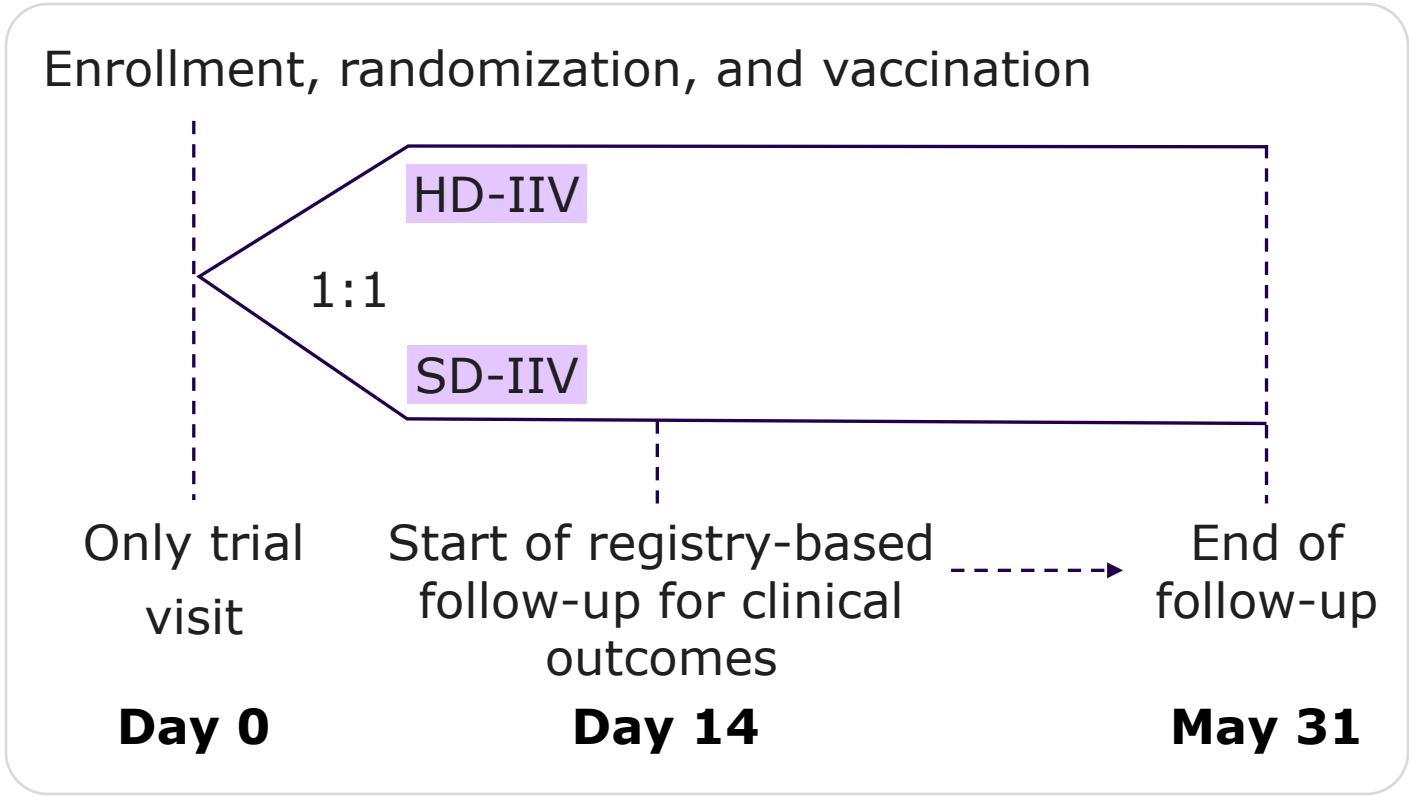
Reference: Johansen ND, et al. *Am Heart J. 2025*:S0002-8703(25)00287-X.

Methods pragmatic, registry-based, open-label, active-controlled, individually randomized trials

Inclusion criteria:
Age ≥ 65 years or 65 – 79 yrs old
Signed informed consent

Exclusion criterion:
Allergy/hypersensitivity towards the vaccines used in the study



Reference: Johansen ND, et al. *Am Heart J*. *2025*:S0002-8703(25)00287-X.

Epidemiology and vaccine match by trial/country and season

Influenza Season	Trial *Click on each link for details*	Circulating Strains	Season Duration	Activity Peak	Season Severity	Vaccine Match
2022/23	***DANFLU-2***	A:B 50:50 (A mostly H1N1)[3]	Long, 3 peaks with late 2nd & 3rd peak[1]	Comparable positivity%, but late[1]	Low[2]	Well matched A(H1) & B, moderate for A(H3)[4]
2023/24	***DANFLU-2***	A(H1N1) predominant[5]	Short[1]	Early, lower than average[1]	Low[2]	Well matched[6]
	GALFLU	A(H1N1) predominant[9]	Short[8]	Very high[10]	Moderate[8,9]	Well matched A(H1N1) & B, moderate for A(H3N2)[11]
2024/25	***DANFLU-2***	Mixed H3/H1. Increased B late in season[7]	Average[1]	High peak, moderately late[1]	Low[2]	Well matched[12]
	GALFLU	A(H3N2) predominant, with B peak early season[9]	Extended[8]	Moderate[10]	Moderate[8,9]	Not yet published

Flunity-HD: pre-specified and powered endpoints

Primary

- **Hospitalization for influenza or pneumonia** (composite endpoint based on primary ICD10 code)

Secondary

- **Hospitalization for cardio-respiratory disease** (composite endpoint, statistically powered)
- **Laboratory-confirmed influenza hospitalization**
- **All-cause hospitalization**
- **All-cause mortality**
- Hospitalization for influenza (ICD10 coded)
- Hospitalization for pneumonia (ICD 10 coded)

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Clinicaltrials.gov: NCT06506812; Johansen ND, et al. LANCET. 2025

Balanced baseline characteristics across HD and SD groups

	HD-IIV (n = 233,311)*	SD-IIV (n = 233,009)*
Age, years, mean±SD	73.3±5.4	73.3±5.4
Female	111,809 (47.9)	111,872 (48.0)
Presence of at least one chronic disease	114,073 (48.9)	114,052 (48.9)
Diabetes	32,489 (13.9)	32,492 (13.9)
Cardiovascular disease	54,061 (23.2)	53,639 (23.0)
Ischemic heart disease	19,033 (8.2)	18,809 (8.1)
Atrial fibrillation	19,179 (8.2)	19,043 (8.2)
Heart failure	6497 (2.8)	6536 (2.8)
Cancer	28,548 (12.2)	28,455 (12.2)
Chronic lung disease	16,022 (6.9)	15,954 (6.8)
Chronic obstructive pulmonary disease	8252 (3.5)	8100 (3.5)
Chronic kidney disease	24,062 (10.3)	24,195 (10.4)
Immunosuppression	12,308 (5.3)	12,308 (5.2)
Co-administration with COVID-19 vaccine	165,412 (70.9)	165,424 (71.0)
COVID-19 vaccine during same season	224,353 (96.2)	224,055 (96.2)
Pneumococcal vaccination after the age of 65	184,946 (79.3)	185,170 (79.5)

Superior protection versus SD against hospitalizations

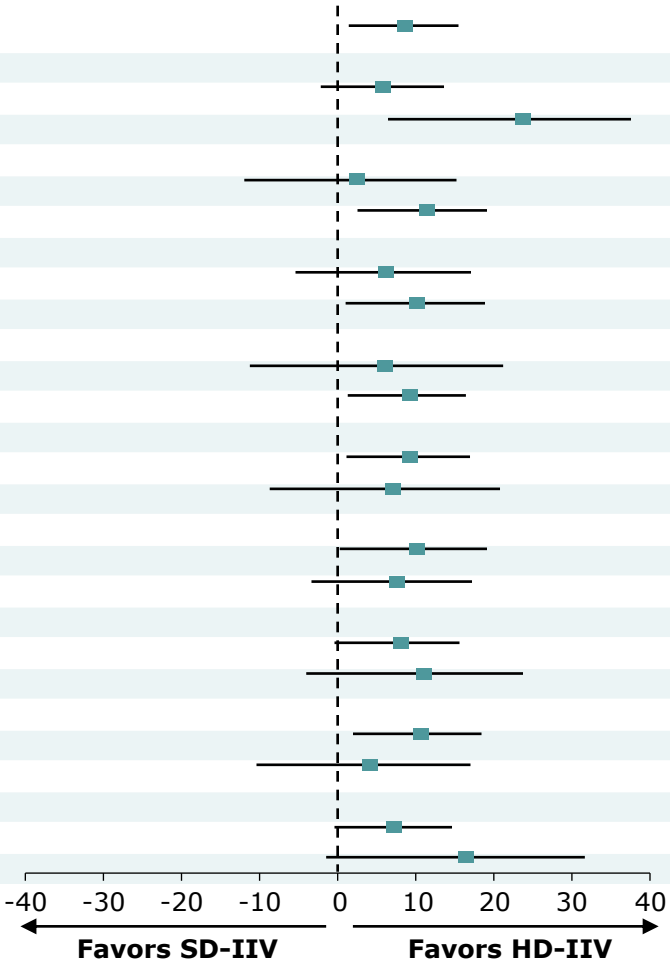
n (%)	HD-IIV (n = 233,311)	SD-IIV (n = 233,009)	Crude rVE (95% CI)	One-sided P value
Primary endpoint				
Hospitalization for "pneumonia or influenza"	1312 (0.56)	1437 (0.62)	**8.8 (1.7 to 15.5)**	**0.0082**
Secondary endpoints				
Hospitalization for any cardio-respiratory disease	4720 (2.02)	5033 (2.16)	**6.3 (2.5 to 10.0)**	**0.0006**
Laboratory-confirmed influenza hospitalization	249 (0.11)	365 (0.16)	**31.9 (19.7 to 42.2)**	**<0.0001**
All-cause hospitalization	19,921 (8.54)	20,348 (8.73)	**2.2 (0.3 to 4.1)**	**0.012**
All-cause mortality	1421 (0.61)	1437 (0.62)	1.2 (-6.3 to 8.3)	0.38
Hospitalization for influenza	*164 (0.07)*	*271 (0.12)*	*39.6 (26.4 to 50.5)*	*NA*
Hospitalization for pneumonia	*1161 (0.50)*	*1187 (0.51)*	*2.3 (-6.0 to 10.0)*	*NA*

Reference: Johansen ND, et al. *LANCET*. 2025

Consistent rVE outcomes across subgroups

Subgroup analyses

		HID-IIV	SD-IIV	Relative Vaccine Effectiveness (95% CI)	P value
		no./total no. (%)			
Overall		1,312/233,311 (0.56)	1,437/233,009 (0.62)	8.8 (1.7 to 15.5)	
Trial					0.055
	DANFLU-2	1,138/166,22 (0.68)	1,210/166,220 (0.73)	5.9 (-2.1 to 13.3)	
	GALFLU	174/67,093 (0.26)	227/66,789 (0.34)	23.7 (6.6 to 37.7)	
Age (median 73.3 years)					0.27
	<median	409/116,670 (0.35)	420/116,589 (0.36)	2.7 (-11.8 to 15.3)	
	≥median	903/116.641 (0.77)	1,017/116,420 (0.87)	11.4 (3.0 to 19.1)	
Sex					0.60
	Female	541/111,809 (0.48)	579/111,872 (0.52)	6.5 (-5.3 to 17.0)	
	Male	771/121.502 (0.63)	858/121,137 (0.71)	10.4 (1.1 to 18.8)	
Presence of at least one chronic disease					0.72
	No	266/119,236 (0.22)	283/118,950 (0.24)	6.2 (-11.2 to 21.0)	
	Yes	1,046/114,073 (0.92)	1,154/114,052 (1.01)	9.4 (1.4 to 16.7)	
Diabetes					0.81
	No	1,005/200,820 (0.50)	1,106/200,510 (0.55)	9.3 (1.1 to 16.8)	
	Yes	307/32,489 (0.94)	331/32,492 (1.02)	7.2 (-8.7 to 20.8)	
Cardiovascular disease					0.71
	No	689/179,248 (0.38)	768/179,363 (0.43)	10.2 (0.4 to 19.1)	
	Yes	623/54,061 (1.15)	669/53,639 (1.25)	7.6 (-3.2 to 17.3)	
Cancer					0.76
	No	993/204,761 (0.48)	1,080/204,547 (0.53)	8.2 (-0.2 to 15.8)	
	Yes	319/28,548 (1.12)	357/28,455 (1.25)	10.9 (-3.9 to 23.7)	
Chronic lung disease					0.41
	No	922/217,287 (0.42)	1,031/217,048 (0.48)	10.7 (2.3 to 18.4)	
	Yes	390/16,022 (2.43)	406/15,954 (2.54)	4.3 (-10.2 to 17.0)	
Immunosuppression					0.29
	No	1,123/221,001 (0.51)	1,210/220,694 (0.55)	7.3 (-0.6 to 14.6)	
	Yes	189/12,308 (1.54)	227/12,308 (1.84)	16.7 (-1.4 to 31.7)	



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Reference: Johansen ND, et al. *LANCET*. 2025

Notable pre-specified exploratory endpoints from FLUNITY-HD

Pre-specified exploratory endpoint	rVE against hospitalization vs SD
Heart failure	21.3 (7.4 to 33.2)
Any cardio-vascular disease	6.6 (1.6 to 11.5)

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Johansen ND, Modin D, Pardo-Seco J, et al. High-Dose vs. Standard-Dose Influenza Vaccine and Cardiovascular Outcomes in Older Adults: The FLUNITY-HD Prespecified Pooled Analysis. Circulation. 0(0). doi:10.1161/CIRCULATIONAHA.125.077801

Potential weaknesses to using these data for regulatory purposes

Combination of two studies is not equivalent to one, fully-powered trial	Pre-specified individual analysis; analogous to >1 clinical trial site
No double-blinding (open label study)	Healthcare seeking bias unlikely for severe outcomes. No "better" vaccine available elsewhere
Lab confirmation not routine	Consistent coding and outcome ascertainment; clinically-indicated lab testing was captured
Multiple endpoints give rise to risk of type 1 errors	Pre-specified, hierachal testing
Different age inclusion criteria in different countries reduces comparability	Pragmatic trials demand flexibility according to routine healthcare practices

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Conclusions

Lessons from the pragmatic randomized trials of high-dose vs. standard-dose influenza vaccine against severe clinical outcomes (FLUNITY-HD)

Large pragmatic designs using approved vaccines are feasible and accepted in certain environments after prior demonstration of efficacy

Flunity-HD has **proven superiority of HD vs SD** in protecting against influenza hospitalizations and complications in a individually randomized trial

The **“magic of randomization”** can be applied to understanding rare but important outcomes in an unbiased environment

What might be the scope these designs in pre-licensure phase or for other regulatory purposes?

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FLUNITY DAN GAL HD
Over 466,000 individually
randomized older adults

Thank you