



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

Niklas Dyrby Johansen, Daniel Modin, Jacobo Pardo-Seco, Carmen Rodriguez-Tenreiro-Sánchez, Matthew M Loiacono, Rebecca C Harris, Marine Dufournet, Robertus van Aalst, Ayman Chit, Carsten Schade Larsen, Lykke Larsen, Lothar Wiese, Michael Dalager-Pedersen, Brian L Claggett, Kira Hyldekær Janstrup, Carmen Duran-Parrondo, Marta Piñeiro-Sotelo, Martín Criebeiro-González, Mónica Conde-Pájaro, Susana Mirás-Carballal, Juan-Manuel González-Pérez, Scott D Solomon, Pradeesh Sivapalan, Cyril Jean-Marie Martel, Jens Ulrik Stæhr Jensen, Federico Martínón-Torres, Tor Biering-Sørensen, for the DANFLU-2 Study Group* and the GALFLU Trial Team*

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

Department of Cardiology (N D Johansen MD, D Modin MD, K H Janstrup PhD, Prof T Biering-Sørensen MD), Respiratory Medicine Section, Department of Medicine (P Sivapalan MD, Prof J U S Jensen), Copenhagen University Hospital-Herlev and Gentofte, Copenhagen, Denmark; Center for Translational Cardiology and Pragmatic Randomized Trials, Department of Biomedical Sciences (N D Johansen, D Modin, K H Janstrup, Prof T Biering-Sørensen), Department of Clinical Medicine (P Sivapalan, Prof J U S Jensen MD), Faculty of Health and Medical Sciences, University of Copenhagen, Denmark; Genetics, Vaccines and Infectious Diseases Research Group (GENVIP), Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS), Santiago de Compostela, Spain (J Pardo-Seco PhD, C Rodriguez-Tenreiro-Sánchez PhD, Prof F Martínón-Torres MD); WHO Collaborating Centre for Vaccine Safety, Santiago de Compostela, Spain (J Pardo-Seco, C Rodriguez-Tenreiro-Sánchez, Prof F Martínón-Torres); Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain (J Pardo-Seco, C Rodriguez-Tenreiro-Sánchez, Prof F Martínón-Torres); GenPoB Research Group,

Instituto de Investigación Sanitaria (IDIS) (J Pardo-Seco), Translational Pediatrics and Infectious Diseases (C Rodríguez-Tenreiro-Sánchez, Prof F Martínón-Torres), Hospital Clínico Universitario de Santiago (SERGAS) and University of Santiago de Compostela (USC), Santiago de Compostela, Galicia, Spain; Sanofi, Morristown, NJ, USA (M M Loiacono PhD, R van Aalst PhD, A Chit PhD); Leslie Dan Faculty of Pharmacy, University of Toronto, ON, Toronto, Canada (A Chit); Department of Epidemiology, University of Delaware, Newark, DE, USA (M M Loiacono); Sanofi, Singapore (R C Harris PhD); Sanofi, Lyon, France (M Dufournet PhD); Department of Clinical Medicine – Department of Infectious Diseases, Aarhus University Hospital, Aarhus, Denmark (C S Larsen MD); Danske Lægers Vaccinations Service/European LifeCare Group, Søborg, Denmark (C S Larsen); Department of Infectious Diseases, Odense University Hospital, Odense, Denmark (L Larsen MD); Department of Infectious Diseases, Zealand University Hospital, Roskilde, Denmark (L Wiese MD); Department of Infectious Diseases (M Dalager-Pedersen MD), Department of Clinical Medicine (M Dalager-Pedersen), Aalborg University Hospital, Aalborg, Denmark; Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA (B L Claggett PhD, Prof S D Solomon MD); Dirección Xeral de Saúde Pública, Consellería de Sanidade, Xunta de Galicia, Santiago de Compostela, Spain (C Duran-Parrondo PharmD, M Piñeiro-Sotelo MHA, M Conde-Pájaro MHA, S Mirás-Carballal MHA); Dirección Xeral de Recursos Económicos, Servizo Galego de Saúde, Santiago de Compostela, Galicia, Spain (M Cribeiro-González MHA); Subdirección de Sistemas y Tecnologías de la Información, Consellería de Sanidade, Xunta de Galicia, Santiago de Compostela, Spain (J-M González-Pérez BS); Statens

Research in context

Evidence before this study

Older adults (aged ≥ 65 years) are at increased risk of severe influenza-related complications compared with younger adults. Although vaccination remains the most effective means of reducing burden, traditional standard-dose inactivated influenza vaccines (SD-IIV) confer suboptimal protection in this vulnerable population. High-dose inactivated influenza vaccine (HD-IIV) was developed to improve protection in older adults and has demonstrated superior efficacy compared with SD-IIV against laboratory-confirmed influenza infection. Previous data have suggested benefits of HD-IIV over SD-IIV against severe clinical outcomes, but limited evidence exists from adequately powered individually randomised studies. As part of a previous meta-analysis (Skaarup et al, 2024), we reviewed existing literature on HD-IIV's relative vaccine effectiveness (rVE) versus SD-IIV via a PubMed and Embase search on May 22, 2023, combining groups of search terms for influenza, vaccine, high-dose and trial/randomised using the Boolean "OR" within groups and "AND" between groups (no date or language restrictions; excluded studies conducted during the 2009–10 influenza pandemic). The five smaller randomised trials included were meta-analysed ($n=105\,685$), showing significantly lower incidence of hospitalisation-based outcomes with HD-IIV than with SD-IIV; however, a need remained for high-quality, adequately powered individually randomised studies to confirm these findings.

Added value of this study

FLUNITY-HD is a large influenza vaccine effectiveness analysis conducted among individually randomised older adults, assessing the rVE of HD-IIV versus SD-IIV against severe clinical outcomes, including hospitalisations, across 466 320 older adults over two geographical areas and three seasons.

Introduction

Influenza remains a major public health issue,¹ with seasonal influenza causing an estimated 290 000–650 000 respiratory deaths globally each year.² Effectiveness of standard-dose vaccines for prevention of influenza typically ranges from 30% to 50%,³ but it is often even lower in older adults (aged ≥ 65 years).⁴ The high-dose inactivated influenza vaccine (HD-IIV) was developed to improve protection against influenza infection and its associated complications among older adults,⁵ and the superior efficacy of HD-IIV in preventing laboratory-confirmed influenza compared with standard-dose inactivated influenza vaccine (SD-IIV) has previously been demonstrated.⁶ However, individually randomised evidence regarding the effectiveness in preventing severe outcomes such as hospitalisations and mortality has been limited. To evaluate the relative vaccine effectiveness (rVE) of HD-IIV versus SD-IIV against severe clinical outcomes, two methodologically harmonised pragmatic, individually randomised trials were recently conducted. This report presents the results of

As a prespecified pooled analysis of two a priori methodologically harmonised individually randomised trials, this study included more than four times the number of randomised older adults as the post-hoc meta-analysis of non-harmonised RCTs (Skaarup et al, 2024). Designed to assess the rVE of HD-IIV versus SD-IIV against severe outcomes beyond influenza infection, the study provides the first definitive evidence of the superior protection of HD-IIV versus SD-IIV against hospitalisation outcomes including due to influenza or pneumonia. HD-IIV also reduced the incidence of the secondary endpoints of cardiorespiratory hospitalisation, laboratory-confirmed influenza hospitalisation, and all-cause hospitalisation—severe outcomes of great importance to patients, clinicians, and decision makers. To our knowledge, no influenza vaccine tailored for older adults has previously demonstrated superior rVE against hospitalisations versus SD-IIV in a powered, individually randomised study to date. These findings confirm the full breadth of protection conferred by HD-IIV beyond influenza infection, from specific laboratory-confirmed influenza hospitalisations to broader all-cause hospitalisations, consistently across seasons.

Implications of all the available evidence

This critical and timely evidence will inform evidence-based decision making by health-care providers, policy makers, and immunisation technical advisory groups, contributing to potential optimisation of influenza vaccination strategies in the vulnerable older adult population globally. At an estimated 515 older adults needed to be vaccinated with HD-IIV instead of SD-IIV to prevent one all-cause hospitalisation, a simple switch from SD-IIV to HD-IIV could substantially reduce the burden of influenza on health systems.

the prespecified, individual-level pooled analysis of 466 320 older adults from the two harmonised trials (FLUNITY-HD), assessing the rVE of HD-IIV versus SD-IIV against severe clinical outcomes.

Methods

Study design and oversight

FLUNITY-HD was a prespecified, individual-level pooled analysis of the DANFLU-2 (NCT05517174) and GALFLU (NCT06141655) trials. Both DANFLU-2 and GALFLU were methodologically harmonised pragmatic, registry-based, open-label, active-controlled, individually randomised trials of HD-IIV versus SD-IIV. GALFLU was designed based on the DANFLU-2 protocol, with a priori intention of pooling with DANFLU-2 to enhance statistical power, external validity, and thereby generalisability of the results. 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. Both trials only required participants to appear at one physical trial visit

for randomisation and vaccination and relied on administrative health-care databases for data collection: nationwide administrative health registries in Denmark and regional health registries in Galicia. Separate descriptions of the study designs have been published previously,^{7,8} and the primary results of each individual trial are published separately.^{9,10}

The academic research group at the Center for Translational Cardiology and Pragmatic Randomized Trials (CTCPR) at the Department of Cardiology, Copenhagen University Hospital–Herlev and Gentofte, Copenhagen, Denmark, acted as the sponsor and central trial site of the DANFLU-2 trial, which utilised the infrastructure of the private vaccination provider Danske Lægers Vaccinations Service/European LifeCare Group for vaccine administration. GALFLU was sponsored by Dr Federico Martínón-Torres and conducted in collaboration with the Galician Health Service through the General Public Health Directorate and the Regional Vaccination Programme of Galicia. Each trial was approved by the local ethics committee and competent authority (EU CT numbers: 2022–500657–17–00[DANFLU-2] and 2023–506977–36–00[GALFLU]). CTCPR sponsored the FLUNITY-HD pooled analysis in regulatory and legal terms. Protocols and statistical analysis plans for both individual trials as well as for the pooled analysis are available in the appendix (pp 40–618). The pooled analysis is registered with ClinicalTrials.gov, NCT06506812.

Participants

Both trials enrolled older adults regardless of comorbidity. DANFLU-2 enrolled any adults aged 65 years and older, whereas GALFLU enrolled community-dwelling older adults aged 65–79 years, as individuals aged 80 years or older and those older than 60 years in nursing homes were eligible to receive HD-IIV via the Galician public vaccination programme. The trials had no additional exclusion criteria.

In DANFLU-2, participants were primarily recruited through electronic invitation letters sent by the sponsor to approximately 1 000 000 randomly selected Danish citizens aged 65 years and older each season via the Danish governmental electronic letter system (Digital Post). Participants could then sign up on a website, where they could also provide informed consent online without any requirement of real-time contact with study staff. Traditional sign-up and consent processes were also available. In GALFLU, participants were invited through the Regional Vaccination Programme of Galicia using a text message system and social media with approximately 450 000 individuals invited each season; written informed consent was obtained in person.

Randomisation and masking

In both trials, participants were individually randomised (1:1) to receive either HD-IIV or SD-IIV. Randomisation

was implemented using centralised unstratified randomisation algorithms. Participants who participated in multiple seasons were re-randomised and treated as unique observations for statistical purposes.¹¹ Both trials were open-label with neither participants nor study staff blinded to treatment allocation. However, the primary and secondary endpoints were severe clinical outcomes, which were not expected to be affected by knowledge of treatment assignment, outcomes were ascertained using passively collected routine health data, and study staff were not involved in the clinical treatment of participants. In both trials, HD-IIV was not available outside of the trial for the targeted populations.

Procedures

In each study season, participants received a single intramuscular dose of either quadrivalent HD-IIV (Fluzone High-Dose Quadrivalent/Efluelda/Efluelda Tetra [Sanofi, Swiftwater, PA, USA]) or quadrivalent SD-IIV (Vaxigrip Tetra [Sanofi, Val-de-Reuil, France] in DANFLU-2; Influvac Tetra [Viatris, Olst, Netherlands] in GALFLU). HD-IIV contained 60 µg of haemagglutinin (HA) antigen per strain whereas SD-IIV contained 15 µg of HA antigen per strain. Co-administration with other seasonal vaccines, including COVID-19 vaccines, was permitted in accordance with local guidelines. Vaccines were administered over 3–4-week periods in each season, which started in alignment with governmental programmes, in early October in Denmark and late October in Galicia.

In both trials, only basic data were collected at the trial visit including identifying information, consent, and information on randomisation and vaccine administration. All additional data were obtained from Danish and Galician administrative health registries. In both trials, additional information on potential safety events were obtained from medical records. Both DANFLU-2 and GALFLU used harmonised, pre-specified definitions for ascertainment of baseline characteristics and endpoints (appendix pp 5–22, 32–39). Participants were treated in real-world health systems and study staff had no influence on decision to admit to hospital, decision to perform respiratory testing, or coding of hospitalisations.

Outcomes

In each season, participants were followed up for the occurrence of endpoints from 14 days after vaccination to May 31 the following year. Only first events were considered for each endpoint. Primary, secondary, and exploratory endpoints were identical across the trials. The primary endpoint in both trials was hospitalisation (admission to hospital) for influenza or pneumonia. Secondary endpoints were hospitalisation for any cardiorespiratory disease, laboratory-confirmed influenza hospitalisation, all-cause hospitalisation, all-cause mortality, hospitalisation for influenza (ICD-10), and hospitalisation for pneumonia. There were no specific prespecified safety outcomes

Serum Institut, Copenhagen, Denmark (C-J-M Martel PhD); Department of Cardiology, Copenhagen University Hospital–Rigshospitalet, Copenhagen, Denmark (Prof T Biering-Sørensen); Steno Diabetes Center Copenhagen, Herlev, Denmark (Prof T Biering-Sørensen)

Correspondence to: Prof Tor Biering-Sørensen, Center for Translational Cardiology and Pragmatic Randomized Trials, Department of Cardiology, Copenhagen University Hospital–Herlev and Gentofte, 2900 Hellerup, Denmark tor.biering@gmail.com

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in the pooled analysis, but safety was assessed in the individual trials. Both trials used identical hierarchical testing procedures. As the European Centre for Disease Prevention and Control and other recommending bodies updated their evidence grading for influenza vaccines with a focus on laboratory-confirmed influenza, the hierarchy for the pooled analysis was changed compared with the individual trials, promoting the endpoint of laboratory-confirmed influenza hospitalisation from exploratory to the second secondary endpoint. No other changes were made to the primary or secondary endpoints or to the testing procedure for the pooled analysis. Both trials did not consider hospitalisation-based events with an associated COVID-19 ICD-10 discharge diagnosis code (B34.2, B97.2) as eligible endpoints to increase endpoint specificity.

Statistical analysis

Each trial was independently powered for the primary endpoint of hospitalisation for influenza or pneumonia. This pooled analysis was prespecified to secure sufficient statistical power to assess the rVE of HD-IIV versus SD-IIV against hospitalisation for influenza or pneumonia, particularly in case of lower-than-expected event rates in the individual trials. Additionally, the pooled analysis was intended to provide increased power for secondary analyses and to increase generalisability by integrating data from two countries with different health systems, populations of different descent, and possible local variability in influenza epidemiology.

In this pooled analysis, baseline characteristics are presented for each individual trial and for the pooled dataset. The primary effectiveness analyses consisted of crude rVE calculations in the pooled dataset, performed according to the intention-to-treat principle with rVE calculated as 1 minus the relative risk of the outcome and expressed as a percentage. No accounting for censoring was prespecified for the rVE calculation as censoring was expected to occur very rarely. Corresponding CIs were calculated using the Clopper–Pearson method¹² and one-sided p values were generated from binomial tests. Superiority was predefined as lower bound of the 95% CI greater than zero. As a supportive analysis, rVE estimates adjusted for trial and for season were generated using fixed-effects log-binomial regression models. The primary analysis used a one-sided alpha-level of 0.025 with primary and key secondary endpoints tested using a pre-specified hierarchical testing sequence where testing only continued down the hierarchy as long as the endpoint tested met statistical significance (appendix p 23).^{13,14} Number needed to vaccinate was calculated as the inverse of the absolute effect size. Subgroup analyses were performed to assess heterogeneity of treatment effect with rVE estimates calculated for each subgroup stratum, and p values for interaction were estimated by including interaction terms in log-binomial regression models adjusted for trial and for season. A prespecified sensitivity

analysis was performed for the primary endpoint and its components, where both primary and secondary discharge diagnoses were considered as opposed to the main analyses, which only considered primary discharge diagnoses. Although not the main analytical approach due to the prespecified nature of the individual-level data pooling, a two-stage random-effects meta-analysis was performed as a sensitivity analysis.

Role of the funding source

The funder participated in the study design, protocol development, and manuscript review phases, but had no responsibilities in trial conduct, data collection, nor data analysis.

Results

A total of 466 320 individually randomised older adults were included in this analysis (332 438 from DANFLU-2 and 133 882 from GALFLU), of these, 233 311 were randomly assigned to HD-IIV and 233 009 to SD-IIV (figure 1). By season, 19 699 participants were randomised in the 2022–23 season (DANFLU-2 only), 219 786 in 2023–24, and 226 835 in 2024–25. A total of 330 045 unique individuals were randomised in the trials, of which 128 001 (38.8%) were enrolled in more than one season. The final pooled dataset was assembled on July 11, 2025. Varied influenza epidemiology was observed across seasons, with all three major types and subtypes, and different durations, intensity, and severity represented (appendix p 24). Vaccine match to circulating strains was generally good, although moderate in some seasons for A(H3N2). In total, 232 515 (99.7%) participants assigned to HD-IIV and 232 067 (99.6%) participants assigned to SD-IIV received the assigned study vaccine. Baseline characteristics were balanced across the HD-IIV and SD-IIV groups in the pooled dataset (table 1). Mean age was 73.3 years (SD 5.4) and 223 681 (48.0%) were female. 228 125 (48.9%) participants had at least one chronic condition. A history of cardiovascular disease was present in 107 700 (23.1%) participants, while 31 976 (6.9%) had chronic lung disease and 64 981 (13.9%) had diabetes. Compared with the GALFLU population, DANFLU-2 participants were slightly older and had a higher prevalence of comorbidities including cardiovascular disease (27.4% vs 12.5%), cancer (13.8% vs 8.3%), and chronic lung disease (8.2% vs 3.6%).

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 (unadjusted rVE 8.8%, 95% CI 1.7–15.5; $p=0.0082$; table 2). HD-IIV also reduced the incidence of the secondary hospitalisation endpoints: hospitalisation for any cardiorespiratory disease (4720 [2.02%] participants in the HD-IIV group vs 5033 [2.16%] participants in the SD-IIV group; rVE 6.3%, 2.5–10.0; $p=0.0006$); laboratory-confirmed

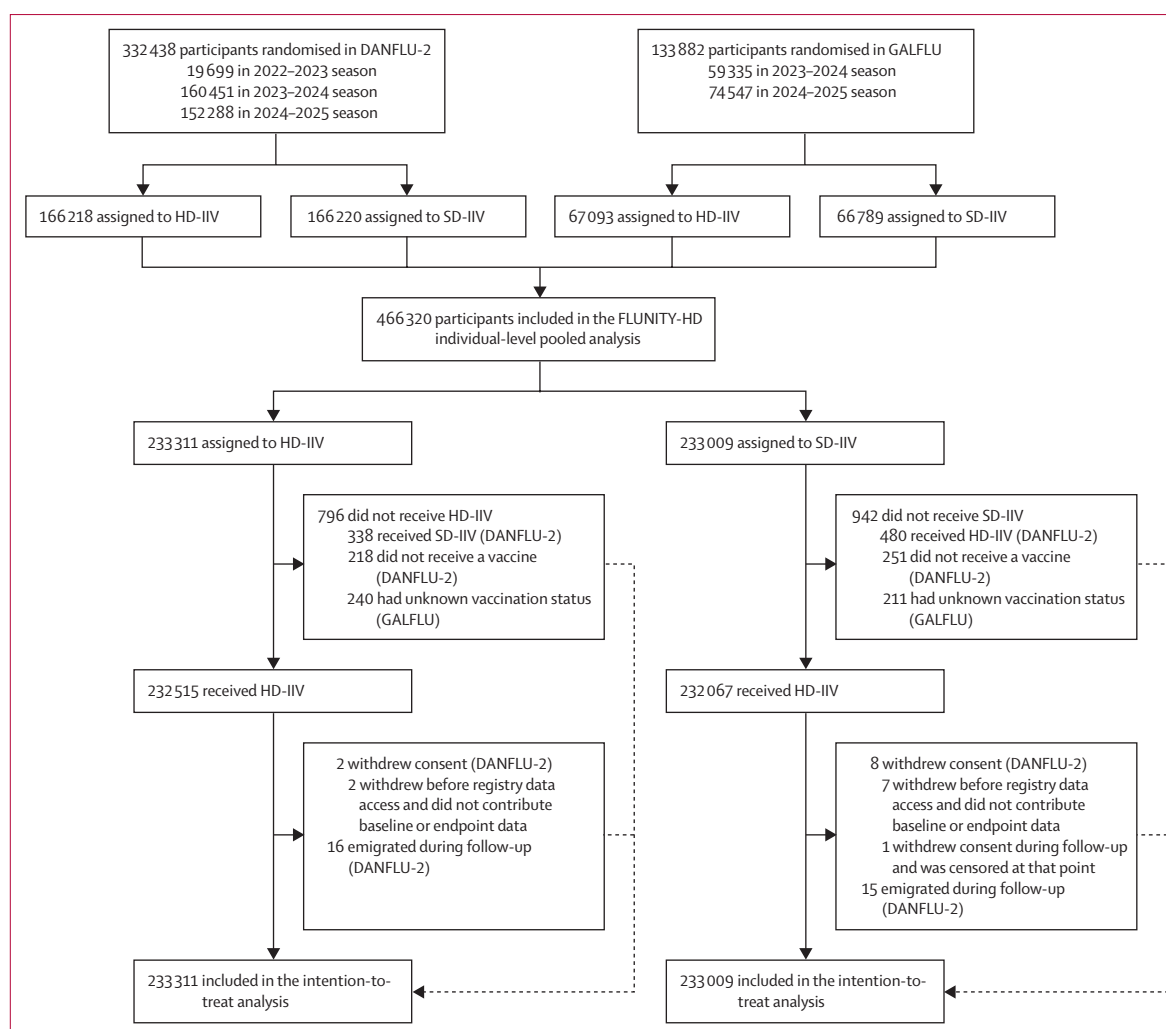


Figure 1: Study profile

The individual trials allowed participants to enrol in subsequent seasons, in which case they were randomly assigned to groups again. In DANFLU-2, participants withdrawing consent before registry data access for that particular season did not contribute registry data to the study database, but only contributed data on age, sex, randomisation, and vaccination. HD-IIV=high-dose inactivated influenza vaccine. SD-IIV=standard-dose inactivated influenza vaccine.

influenza hospitalisation (249 [0·11%] participants in the HD-IIV group vs 365 [0·16%] participants in the SD-IIV group; rVE 31·9%, 19·7–42·2; $p<0\cdot0001$), and all-cause hospitalisation (19921 [8·54%] participants in the HD-IIV group vs 20348 [8·73%] participants in the SD-IIV group; rVE 2·2%, 0·3–4·1; $p=0\cdot012$). No difference in all-cause mortality was found. The observed reduction in the primary endpoint with HD-IIV was driven by a decrease in hospitalisations for influenza. rVE estimates adjusted for trial and for season were similar to those of the crude analyses (table 2). Number needed to vaccinate with HD-IIV instead of SD-IIV to prevent one additional event was 1839 (95% CI 1049–9756) for hospitalisation for influenza or pneumonia, 730 (463–1832) for hospitalisation for any cardiorespiratory disease, 2003 (1511–3233) for laboratory-confirmed influenza hospitalisation, and 515 (278–3929) for all-cause hospitalisation (table 2).

The incidence of serious adverse events has previously been reported in the individual trials as similar between groups.^{9,10} In the pooled dataset, there were a total of 16032 serious adverse events with HD-IIV compared with 15857 with SD-IIV (appendix p 25).

Results for the primary endpoint consistently favoured HD-IIV in subgroup analyses including across age, sex, and comorbidities (figure 2). Primary and secondary endpoint results by trial and season are shown in the appendix (pp 26–29). While estimates were broadly consistent across trial and season, moderate between-trial heterogeneity was suggested for the primary endpoint (rVE 5·9%, 95% CI –2·1 to 13·3, in DANFLU-2; rVE 23·7%, 6·6 to 37·7, in GALFLU; $p_{\text{interaction}}=0\cdot055$). A sensitivity analysis in which the definitions of the primary endpoint and its components were expanded to also include secondary discharge diagnoses yielded

	Overall		DANFLU-2		GALFLU	
	HD-IIV group (n=233 311)	SD-IIV group (n=233 009)	HD-IIV group (n=166 218)	SD-IIV group (n=166 220)	HD-IIV group (n=67 093)	SD-IIV group (n=66 789)
Mean age, years (SD)	73.3 (5.4)	73.3 (5.4)	73.7 (5.8)	73.7 (5.8)	72.3 (4.2)	72.3 (4.3)
Female sex	111 809 (47.9%)	111 872 (48.0%)	80 781 (48.6%)	80 757 (48.6%)	31 028 (46.2%)	31 115 (46.6%)
Male sex	121 502 (52.1%)	121 137 (52.0%)	85 437 (51.4%)	85 463 (51.4%)	36 065 (53.8%)	35 674 (53.4%)
Presence of at least one chronic disease	114 073 (48.9%)	114 052 (48.9%)	81 997 (49.3%)	82 166 (49.4%)	25 238 (37.6%)	25 118 (37.6%)
Cardiovascular disease	54 061 (23.2%)	53 639 (23.0%)	45 688 (27.5%)	45 338 (27.3%)	8373 (12.5%)	8301 (12.4%)
Diabetes	32 489 (13.9%)	32 492 (13.9%)	21 929 (13.2%)	21 952 (13.2%)	10 560 (15.7%)	10 540 (15.8%)
Cancer	28 548 (12.2%)	28 455 (12.2%)	22 922 (13.8%)	22 996 (13.8%)	5626 (8.4%)	5459 (8.2%)
Chronic kidney disease	24 062 (10.3%)	24 195 (10.4%)	23 302 (14.0%)	23 486 (14.1%)	760 (1.1%)	709 (1.1%)
Atrial fibrillation	19 179 (8.2%)	19 043 (8.2%)	17 076 (10.3%)	17 009 (10.2%)	2103 (3.1%)	2034 (3.0%)
Ischaemic heart disease	19 033 (8.2%)	18 809 (8.1%)	15 666 (9.4%)	15 446 (9.3%)	3367 (5.0%)	3363 (5.0%)
Chronic lung disease	16 022 (6.9%)	15 954 (6.8%)	13 575 (8.2%)	13 577 (8.2%)	2447 (3.6%)	2377 (3.6%)
Chronic obstructive pulmonary disease	8252 (3.5%)	8100 (3.5%)	6799 (4.1%)	6689 (4.0%)	1453 (2.2%)	1411 (2.1%)
Heart failure	6497 (2.8%)	6536 (2.8%)	5201 (3.1%)	5209 (3.1%)	1296 (1.9%)	1327 (2.0%)
Immunosuppression	12 308 (5.3%)	12 308 (5.2%)	7187 (4.3%)	7128 (4.3%)	5121 (7.6%)	5180 (7.8%)
Co-administration with COVID-19 vaccine	165 412 (70.9%)	165 424 (71.0%)	102 242 (61.5%)	102 481 (61.7%)	63 170 (94.2%)	62 943 (94.2%)
COVID-19 vaccine during same season	224 353 (96.2%)	224 055 (96.2%)	160 436 (96.5%)	160 432 (96.5%)	63 917 (95.3%)	63 623 (95.3%)
Pneumococcal vaccination after age 65 years	184 946 (79.3%)	185 170 (79.5%)	140 432 (84.5%)	140 414 (84.5%)	44 514 (66.3%)	44 756 (67.0%)

Data are n (%), unless otherwise indicated. Baseline characteristics were sourced from nationwide administrative health registries using prespecified definitions (appendix pp 5–14,32–39). In DANFLU-2, nine participants withdrew consent before registry data linkage; therefore, these participants did not contribute baseline data other than age and sex. Due to data availability, DANFLU-2 and GALFLU used different definitions for chronic kidney disease and immunosuppression. COVID-19 co-administration was defined as receiving COVID-19 vaccination on the same day as the study vaccine. HD-IIV=high-dose inactivated influenza vaccine. SD-IIV=standard-dose inactivated influenza vaccine.

Table 1: Baseline characteristics of participants

	HD-IIV (n=233 311)	SD-IIV (n=233 009)	Crude relative vaccine effectiveness (95% CI)	Adjusted relative vaccine effectiveness (95% CI)	One-sided p value	Number needed to vaccinate (95% CI)
Primary endpoint						
Hospitalisation for influenza or pneumonia	1312 (0.56%)	1437 (0.62%)	8.8% (1.7 to 15.5)	8.7% (1.7 to 15.3)	0.0082	1839 (1049 to 9756)
Secondary endpoints						
Hospitalisation for any cardiorespiratory disease	4720 (2.02%)	5033 (2.16%)	6.3% (2.5 to 10.0)	6.3% (2.5 to 9.9)	0.0006	730 (463 to 1832)
Laboratory-confirmed influenza hospitalisation	249 (0.11%)	365 (0.16%)	31.9% (19.7 to 42.2)	31.9% (20.0 to 42.0)	<0.0001	2003 (1511 to 3233)
All-cause hospitalisation	19 921 (8.54%)	20 348 (8.73%)	2.2% (0.3 to 4.1)	2.2% (0.3 to 4.0)	0.012	515 (278 to 3929)
All-cause mortality	1421 (0.61%)	1437 (0.62%)	1.2% (−6.3 to 8.3)	1.2% (−6.3 to 8.2)	0.38	..
Hospitalisation for influenza (ICD-10)	164 (0.07%)	271 (0.12%)	39.6% (26.4 to 50.5)	39.6% (26.7 to 50.2)	NA	..
Hospitalisation for pneumonia	1161 (0.50%)	1187 (0.51%)	2.3% (−6.0 to 10.0)	2.2% (−6.0 to 9.8)	NA	..

Endpoints occurring between 14 days after vaccination and May 31 the following year were defined as eligible for analysis. Only first events were considered for each endpoint. Median follow-up was 232 days (IQR 211–239). Endpoints were ascertained using data from Danish and Galician administrative health registries. Prespecified endpoint definitions are shown in the appendix pp 15–22. The endpoint of hospitalisation for influenza required an ICD-10 code for influenza but did not require a positive influenza test, whereas the endpoint of laboratory-confirmed influenza hospitalisation required a positive influenza test between 14 days before and 3 days after hospital admission but no specific ICD-10 code. Relative vaccine effectiveness was calculated as 1 minus the relative risk of the outcome. p values were estimated using binomial tests, corresponding to the crude relative vaccine effectiveness estimates. The adjusted relative vaccine effectiveness estimates are adjusted for trial and for season and generated using log-binomial regression models. NA denotes not applicable since p values are reported only for endpoints formally tested in the hierarchical testing procedure. Number needed to vaccinate describes the number of individuals needed to be vaccinated with HD-IIV instead of SD-IIV to prevent one additional event and is calculated only for endpoints with significant relative vaccine effectiveness estimates. HD-IIV=high-dose inactivated influenza vaccine. NA=not applicable. SD-IIV=standard-dose inactivated influenza vaccine.

Table 2: Effectiveness endpoints

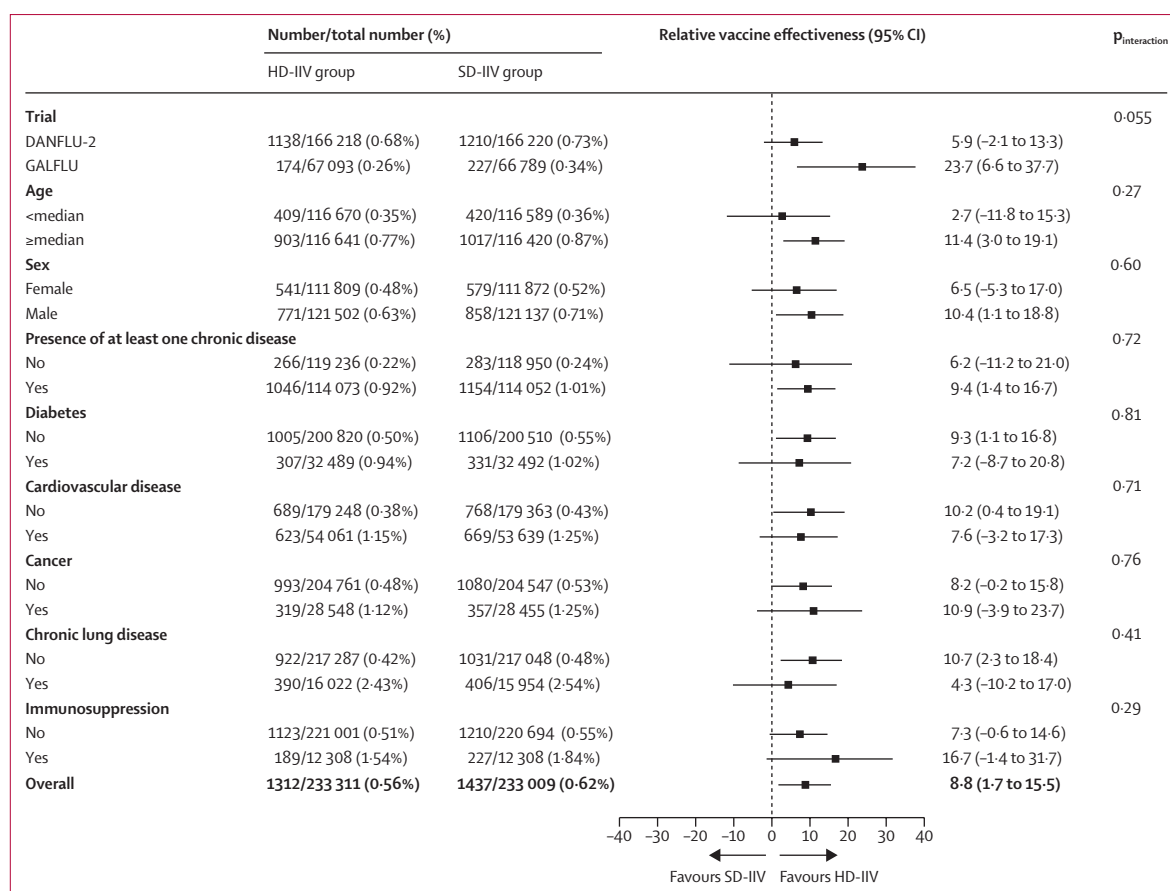


Figure 2: Primary endpoint in major prespecified subgroups

The primary endpoint was hospitalisation for influenza or pneumonia. Relative vaccine effectiveness was calculated as 1 minus the relative risk. Median age was 72.7 years. *p* values for interaction were estimated by including interaction terms in log-binomial regression models adjusted for trial and season. HD-IIV=high-dose inactivated influenza vaccine. SD-IIV=standard-dose inactivated influenza vaccine.

results consistent with the main analysis (appendix p 30). The results from a two-stage random-effects meta-analysis conducted as a post-hoc sensitivity analysis are presented in the appendix (p 31). The findings of this analysis were consistent with the main pooled analysis, also suggesting the presence of moderate heterogeneity across trials for the primary endpoint, and they were potentially suggestive of the main analytical approach delivering a more conservative estimate.

Discussion

The prespecified FLUNITY-HD pooled vaccine effectiveness analysis in older adults encompassed 466 320 participants over three seasons and two regions, allowing for fully powered randomised assessment of highly meaningful severe outcomes that are typically not evaluable in traditional vaccine trials. The study demonstrates the superior benefit of HD-IIV, specifically developed for older adults, compared with SD-IIV against a wide range of hospitalisation outcomes in a prespecified and powered analysis, providing crucial evidence for informing public health and vaccination strategies globally.

Our findings demonstrated superior protection with HD-IIV versus SD-IIV against both influenza-specific outcomes as well as several less specific hospitalisation outcomes, demonstrating benefits of HD-IIV beyond preventing influenza infection. Nearly 9% of hospitalisations for influenza or pneumonia were prevented with HD-IIV compared with SD-IIV. Importantly, similar rVE estimates were observed in patients with comorbidities with higher baseline risk of the primary endpoint, suggesting that the number needed to vaccinate per case averted in these populations would be lower. When considering influenza-specific hospitalisations, both ICD-coded and laboratory-confirmed, rVE was even more pronounced, with point estimates ranging roughly from 32% to 40%, which exceed those reported previously.^{15,16} Beyond respiratory complications, influenza infection poses substantial risk among older adults with regard to cardiovascular-related complications.^{17,18} Such complications often occur without the confirmation of an associated influenza diagnosis; therefore, the outcome of hospitalisation for cardiorespiratory disease reported

here was not dependent on an influenza diagnostic code or test. The 6·3% reduction in hospitalisations for cardiorespiratory disease with HD-IIV compared with SD-IIV represents a clinically meaningful finding with important implications for cardiovascular preventive care, warranting consideration in clinical practice guidelines. Moreover, we observed a significant 2·2% reduction in all-cause hospitalisation among those receiving HD-IIV compared with those receiving SD-IIV, meaning that vaccinating just 515 older adults with HD-IIV instead of SD-IIV could prevent one additional hospitalisation from all causes.

While the absolute differences in outcomes may seem small, it should be noted that the effect sizes observed with vaccines, which are implemented to prevent disease from occurring, cannot be compared with those of standard drug therapies for specific pre-existing diseases—particularly in this trial, in which the added benefit of HD-IIV was demonstrated on top of the well known benefits conferred by SD-IIV. An influenza vaccine is only administered once per year, imposes no daily burden on the individual, and can be obtained at a much lower cost than many medical therapies. In addition, influenza vaccination is recommended for a very broad range of individuals, resulting in lower baseline outcome risk in the target population than with most drug therapies, and thereby lower absolute effect sizes. An estimated 765 million standard-dose influenza vaccines are administered worldwide each year,¹⁹ assuming that 500 million of these are administered in older adults and at an estimated 515 individuals needed to be vaccinated with HD-IIV instead of SD-IIV to prevent one all-cause hospitalisation, administering HD-IIV instead could potentially prevent up to almost 1 000 000 additional all-cause hospitalisations annually in the older adult population, further showcasing the potential of HD-IIV to substantially reduce health-care system burden and improve public health.

This study provides high-quality evidence on the benefit of HD-IIV versus SD-IIV against severe clinical outcomes, with findings mostly consistent with previous meta-analyses of observational data and smaller randomised trials. In a meta-analysis of studies conducted across 12 seasons, HD-IIV was shown to significantly reduce hospitalisation for influenza, cardiorespiratory disease, and various other causes compared with SD-IIV.¹⁵ A previous meta-analysis of randomised trials only similarly showed significant reductions in hospitalisation for influenza or pneumonia and for all causes among approximately 105 000 older adults.¹⁶ Our prespecified pooled analysis was conducted across over 466 000 individually randomised older adults—a sample more than four times larger than this previous meta-analysis, which included all evidence from randomised trials conducted before DANFLU-2 and GALFLU. In addition, our study included a population of almost 49% with at least one chronic condition, reflecting

appropriate inclusion of important risk groups and generalisability to the older adult population.

Although no significant heterogeneity was observed between trials, potential effectiveness differences were suggested for the primary endpoint. Both trials showed similar rVE against influenza hospitalisation, but rVE differed for pneumonia hospitalisation (15·7% reduction in GALFLU vs 0·5% in DANFLU-2). Notably, although influenza hospitalisation rates were similar across the two trials, influenza hospitalisations constituted a third of primary endpoint events in GALFLU compared with less than 15% of events in DANFLU-2, where pneumonia-coded hospitalisations were three times more frequent than in GALFLU. Regardless of the slightly older population in DANFLU-2, the incidence of pneumonia would not be expected to truly be tripled in Denmark compared with Galicia, and this could therefore suggest that pneumonia ICD-10 codes in Denmark may be used for additional conditions non-modifiable by influenza vaccination. The stronger rVE against influenza-specific outcomes in DANFLU-2 indicates differences in testing and coding rather than lack of HD-IIV benefit. In addition, the reductions observed with HD-IIV in the broader hospitalisation endpoints were consistent across the two trials including all-cause hospitalisation, which would be expected to be unaffected by differences in coding or testing practices. These findings reinforce the overall benefits with HD-IIV and strengthen the argument that the moderate heterogeneity observed in relation to the primary endpoint could be explained by differences in coding and respiratory testing patterns.

Moreover, lower influenza testing rates in Galicia (1·7% vs 3·1% of participants tested at least once) and less laboratory-confirmation of ICD-10-coded influenza hospitalisations (66·5% vs 98·6%) likely contributed to miscoding influenza as pneumonia. This hypothesis is further strengthened by the fact that the study's influenza seasons in Galicia were classified as more severe than the study's influenza seasons in Denmark, which could potentially also suggest that more pneumonia events might have been driven by influenza rather than by other pathogens. Furthermore, post-COVID-19 changes in testing practices and circulation of other pathogens (eg, mycoplasma, pneumococcal, adenovirus outbreaks) might have impacted pneumonia-related events,^{20–22} warranting further investigation of regional differences.

The main strength of this pooled analysis is that it offers a distinct methodological advantage as opposed to other individual-level meta-analyses: both DANFLU-2 and GALFLU were prospectively co-developed using the same protocol, eligibility criteria, outcome definitions, and statistical analysis plans, with a priori intention to pool the individual-level data. This degree of alignment and harmonisation minimises heterogeneity across trials and regions, maximising external validity and generalisability while simultaneously increasing statistical power.

This study also has limitations. In the individual trials, potential limitations included the open-label nature of the trials, lack of systematic influenza testing, and lack of data on race or ethnicity. Reliance on routine health-care data might have introduced imprecision into the trial data. Reflecting current clinical practice, COVID-19 vaccine co-administration rates were very high in both trials, which might have complicated judgement of relatedness for individual adverse events. However, as COVID-19 vaccine co-administration rates were similar across the HD-IIV and SD-IIV groups, any differences observed would be expected to be caused by the difference in study vaccine—no significant differences in serious adverse events were observed in either trial.^{9,10} Event rates were lower than expected; in DANFLU-2, the incidence of the primary endpoint was 0.73% in the SD-IIV group compared with an initially expected incidence of 1.2% based on historical data,²³ whereas in GALFLU, the observed incidence was 0.34% compared with an expected incidence of 0.8%. Although these differences are likely due to post-COVID-19 changes, an alternative hypothesis could be that the trial populations were not representative of the target populations. However, the DANFLU-2 population was comparable with the overall Danish population aged 65 years and older, as reported in a recent randomised implementation trial that included all Danish citizens of that age²⁴ (eg, mean age 73.7 years in DANFLU-2 vs 73.8 years in Danish study, 48.6% vs 51.5% female, 27.4% with cardiovascular disease in both studies, and 13.2% vs 12.9% with diabetes). In GALFLU, the trial population was comparable with the overall Galician population aged 65–79 years in terms of mean age (72.3 years in GALFLU vs 72.4 years) and sex distribution (46.4% vs 52.0% female; data from internal registry extract). In addition, no evidence of substantial heterogeneity in effectiveness was observed across subgroups in the pooled analysis or the individual trials, indicating that relative effect sizes remained consistent across different baseline risk strata.

For the pooled analysis, despite harmonisation of study protocols and endpoint definitions across trials, there was potential for heterogeneity between the trials, considering differences in regions, local epidemiology, enrolment ages, and local health-care practices (medical documentation, testing, diagnosis, coding, etc); however, while the results revealed some variability between DANFLU-2 and GALFLU, especially for the primary endpoint, no significant heterogeneity was detected. The harmonisation of study protocols with pre-specified, identical endpoint definitions across trials, coupled with the absence of significant heterogeneity in our analyses, suggests that bias was minimised despite variations in study settings. Rather, consistency in results across seasons, regions, health systems, and subgroups provides compelling evidence as to the reliability and generalisability of our findings. Although the nature of the data pooling process did not allow for an analysis

accounting for within-participant correlation in the pooled dataset, such analyses were indeed conducted in each individual trial and yielded results consistent with the primary analyses.^{9,10}

In conclusion, in this prespecified pooled analysis of more than 466 000 individually randomised older adults aged 65 years and older across two regions (Denmark and Galicia) and three influenza seasons, HD-IIV demonstrated superior protection against hospitalisations for influenza or pneumonia compared with SD-IIV and also reduced the incidence of the secondary endpoints of cardiorespiratory hospitalisation, laboratory-confirmed influenza hospitalisation, and all-cause hospitalisation. These results provide further evidence that widespread adoption of HD-IIV could substantially reduce the burden of influenza on both older adults and health-care systems globally.

Contributors

NDJ, DM, JP-S, CR-T-S, MML, RCH, MD, RvA, AC, CSL, LL, LW, MD-P, BLC, KHJ, CD-P, MP-S, MC-G, MC-P, SM-C, SDS, PS, CJ-MM, JUSJ, FM-T, and TB-S made substantial contributions to the conceptualisation and design of the study. NDJ, CSL, J-MG-P, and TB-S collected the data. NDJ, DM, KHJ, and TB-S had access to and analysed the raw data. NDJ and TB-S had full access to individual-level data from both trials and vouch for the data and the data analyses. NDJ wrote the first draft of this manuscript. All authors reviewed the manuscript draft, approved the final manuscript, and had final responsibility for the decision to submit for publication.

Declaration of interests

MML, RCH, MD, RvA, and AC are full-time employees of Sanofi and may own shares and/or stock options in the company. CSL has received speaker fees and served on advisory boards for GlaxoSmithKline, MSD, Pfizer, Takeda, and Valneva. BLC has received consulting fees from Amgen, Cardurion, Corvia, Myokardia, and Novartis. SDS has received research grants from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, BMS, Celladon, Cytokinetics, Eidos, Gilead, GlaxoSmithKline, Ionis, Lilly, Mesoblast, MyoKardia, National Institute for Health and Care Research/National Heart, Lung, and Blood Institute, Neurotronik, Novartis, Novo Nordisk, Respicardia, Sanofi, Theracos, US2, AI, and consulted for Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GlaxoSmithKline, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi, Dinaqor, Trembeau, CellProThera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros, and Puretech Health. FM-T has acted as principal investigator for other studies sponsored by AstraZeneca, GlaxoSmithKline, Janssen, Medimmune, Moderna, MSD, Novavax, Novartis, Pfizer, Regeneron, Roche, Sanofi Pasteur, and Seqirus, with honoraria paid to his institution; and has consulting or advisory relationships with GlaxoSmithKline, Janssen, Medimmune, Moderna, MSD, Pfizer, Sanofi Pasteur, and Seqirus. TB-S has received research grants from Bayer, Novartis, Pfizer, Sanofi Pasteur, GlaxoSmithKline, Novo Nordisk, AstraZeneca, Boston Scientific, and GE Healthcare, consulting fees from Novo Nordisk, IQVIA, Parexel, Amgen, CSL Seqirus, GlaxoSmithKline, and Sanofi Pasteur, and lecture fees from AstraZeneca, Bayer, Novartis, Sanofi Pasteur, GE Healthcare, and GlaxoSmithKline. All other authors declare no competing interests.

Data sharing

Individual-level participant data stemming from the Danish and Galician health registries cannot be shared according to Danish and Galician law, respectively, outside of prespecified approved protocols. Summarised data can be made available upon reasonable request.

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