NEJM Evidence

Published January 23, 2023
NEJM Evid 2023; 2 (2)
DOI: 10.1056/EVIDoa2200206

ORIGINAL ARTICLE

A Pragmatic Randomized Feasibility Trial of Influenza Vaccines

Niklas Dyrby Johansen, M.D.,[1,2] Daniel Modin, M.B.,[1,2] Joshua Nealon, Ph.D.,[3] Sandrine Samson, Ph.D.,[4] Camille Salamand, M.Sc.,[4] Matthew M. Loiacono, Ph.D.,[5] Carsten Schade Larsen, M.D., D.M.Sc.,[6] Anne Marie Reimer Jensen, M.D.,[1,2] Nino Emanuel Landler, M.D.,[1,2] Brian L. Claggett, Ph.D.,[7] Scott D. Solomon, M.D.,[7] Martin J. Landray, Ph.D.,[8,9] Gunnar H. Gislason, M.D., Ph.D.,[1,10,11,12] Lars Køber, M.D., D.M.Sc.,[10,13] Jens Ulrik Stæhr Jensen, M.D., Ph.D.,[14] Pradeesh Sivapalan, M.D., Ph.D.,[14] Lasse Skafte Vestergaard, M.D., Ph.D.,[15] Palle Valentiner-Branth, M.D., Ph.D.,[15] Tyra Grove Krause, M.D., Ph.D.,[15] and Tor Biering-Sørensen, M.D., Ph.D., M.P.H.[1,2]

Abstract

BACKGROUND The relative vaccine effectiveness (rVE) of high-dose quadrivalent influenza vaccines (QIV-HD) versus standard-dose quadrivalent influenza vaccines (QIV-SD) against hospitalizations and mortality in the general older population has not been evaluated in an individually randomized trial. Because of the large sample size required, such a trial will need to incorporate innovative, pragmatic elements.

METHODS We conducted a pragmatic, open-label, active-controlled, randomized feasibility trial in Danish citizens aged 65 to 79 years during the 2021–2022 influenza season. Participants were randomly assigned 1:1 to receive QIV-HD or QIV-SD. Randomization was integrated into routine vaccination practice, and the trial relied solely on nationwide administrative health registries for data collection. Outcomes consisted of a feasibility assessment and descriptive rVE estimates.

RESULTS We invited 34,000 persons to participate. A total of 12,477 randomly assigned participants were included in the final analyses. Mean (±SD) age was 71.7±3.9 years, and 5877 (47.1%) were women. Registry-based data collection was feasible, with complete follow-up data for 99.9% of participants. Baseline characteristics were comparable to those of the overall Danish population aged 65 to 79 years. The incidence of hospitalization for influenza or pneumonia was 10 (0.2%) of 6245 in the QIV-HD group and 28 (0.4%) of 6232 in the QIV-SD group (rVE, 64.4%; 95% confidence interval, 24.4 to 84.6). All-cause death occurred in 21 (0.3%) and 41 (0.7%) participants in the QIV-HD and QIV-SD groups, respectively (rVE, 48.9%; 95% confidence interval, 11.5 to 71.3).

CONCLUSIONS Conducting a pragmatic randomized trial of QIV-HD versus QIV-SD using existing infrastructure and registry-based data collection was feasible. The findings of lower incidence of hospitalization for influenza or pneumonia and all-cause mortality in

The author affiliations are listed at the end of the article.

Dr. Biering-Sørensen can be contacted at tor.biering@gmail.com or at Department of Cardiology, Copenhagen University Hospital–Herlev and Gentofte, Gentofte Hospitalsvej 8, 3.th., 2900 Hellerup, Denmark.

the QIV-HD group compared with the QIV-SD group require replication in a future, fully powered trial. (Funded by Sanofi; ClinicalTrials.gov number, NCT05048589.)

Introduction

Influenza vaccination effectively reduces the incidence of influenza infection and influenza-related morbidity and mortality,[1-3] and annual vaccination of persons aged 65 years and older as well as other high-risk groups is widely recommended.[4,5] In a prior randomized trial, high-dose (HD) trivalent influenza vaccine reduced the incidence of laboratory-confirmed influenza illness by an additional 24.2% compared with standard-dose trivalent influenza vaccine,[6] and recent meta-analyses have similarly suggested consistent benefits in the relative effectiveness (rVE) of HD influenza vaccines compared with standard-dose vaccines.[7,8] HD quadrivalent influenza vaccines (QIV-HD) are approved for use in persons 60 or 65 years of age and older, depending on the country, but are not yet widely implemented. Currently, there is no clinically directive evidence from an individually randomized trial that has evaluated the rVE of QIV-HD versus standard-dose quadrivalent influenza vaccine (QIV-SD) against severe clinical outcomes such as hospitalizations and mortality in the general older population; such evidence would allow for an assessment of the full public health value of QIV-HD. Because such a trial would potentially require a sample size of more than 200,000 participants,[9] we designed the DANFLU-1 (Feasibility of Randomizing Danish Citizens Aged 65–79 Years to High-Dose Quadrivalent Influenza Vaccine vs. Standard-Dose Quadrivalent Influenza Vaccine in a Pragmatic Registry-Based Setting) trial to evaluate the feasibility of integrating an individually randomized study into routine seasonal influenza vaccination practice and using administrative health registries for data collection.

Methods

STUDY DESIGN

The trial design and organization have previously been described in detail.[10] In brief, the trial was conducted during the 2021–2022 influenza season as a pragmatic, open-label, active-controlled, randomized feasibility trial organized with a central trial site located at a public university hospital (Copenhagen University Hospital–Herlev and Gentofte). The central site was responsible for overall study conduct, registry data collection, and safety monitoring/reporting. The trial was integrated into daily routine vaccination practice at more than 1000 decentralized vaccination sessions across Denmark organized by a private vaccination provider (Danske Lægers Vaccinations Service, part of European LifeCare Group). The private vaccination provider was responsible for recruitment, inclusion, randomization, and vaccination. The study was conducted during the 2021–2022 Northern Hemisphere influenza season.

Approvals were obtained from the Regional Danish Committee on Biomedical Research Ethics (H-21035316) and the Danish Medicines Agency (EudraCT no. 2021-003170-31). The trial was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. The protocol is available with the statistical analysis plan as supplementary material. Individual author contributions are listed in the Supplementary Appendix (p. 2). The trial was registered at ClinicalTrials.gov (NCT05048589) on September 17, 2021.

PARTICIPANTS

The trial included persons between 65 and 79 years of age, with the only exclusion criterion being allergy to the vaccines used in the study. The upper age limit was set at 79 years to avoid ethical concerns because, at the time the study was designed, Danish citizens aged 80 years and older were expected to be routinely offered QIV-HD in the official Danish vaccination program. Vaccination personnel evaluated potential contraindications (e.g., concurrent infection) as part of routine practice at the vaccination visit. All participants provided written informed consent.

Participants were recruited through the vaccination provider's database of prior vaccinees and web-based advertising. The trial aimed to recruit 40,000 participants. The projected sample size was chosen to stress the study infrastructure sufficiently to assess the feasibility of the design for a potential definitive trial. The trial was not powered for the evaluation of clinical outcomes.

RANDOMIZATION

Participants were randomly assigned 1:1 to receive QIV-HD or QIV-SD using centralized computerized blocked randomization. The trial was open-label; clinical outcomes were assessed using prespecified registry-based definitions to minimize the risk of ascertainment bias.

TRIAL PROCEDURES

QIV-HD (Fluzone High-Dose Quadrivalent [United States and Canada]/Efluelda [Europe]; Sanofi) contained 60 μg of hemagglutinin antigen for each strain. QIV-SD contained 15 μg of hemagglutinin antigen for each strain. QIV-HD and QIV-SD contained the same four strains as recommended by the World Health Organization for the 2021–2022 Northern Hemisphere influenza season. For pragmatic reasons, the study protocol allowed for any QIV-SD to be used as a comparator in the study. Due to vaccine purchase decisions made by the Danish health authorities, all administered QIV-SD were Influvac Tetra (Viatris).

Initial data collection was performed by the vaccination provider, who subsequently transferred identifying information, signed informed consent, randomization group, and details of the administered vaccine to the central trial site. Through upload of the participants' social security numbers to the Danish Health Data Authority, participants were linked to the Danish nationwide administrative health registries containing data on all contacts and procedures in the Danish public health system.[11] The registries are described in detail in the Supplementary Appendix (p. 3 and 4).

International Classification of Diseases, 10th Edition, and Anatomical Therapeutic Chemical codes were used to define baseline conditions, medication use, and outcomes. All definitions were prespecified and are reported in Tables S1 to S3. A look-back period of 10 years was used for baseline conditions. Participants were observed for clinical outcomes from 14 days after vaccination until May 31, 2022. The 14-day period was in place to allow for a sufficient immune response to the vaccines.

OUTCOMES

The primary outcome was feasibility. Feasibility was evaluated on the basis of an overall assessment of obtainment of approvals, recruitment rate, randomization agreement, comparability of the trial population to the overall Danish population aged 65 to 79 years, and reliability with regard to the registry-based obtainment of baseline characteristics, safety events, and clinical end points.

The end points of hospitalization for pneumonia or influenza, hospitalization for respiratory disease, and hospitalization for cardiorespiratory disease were only to be reported in the case of adequate influenza circulation during the 2021–2022 influenza season, a feature introduced as a result of uncertainty regarding influenza circulation during the Covid-19 pandemic. For this purpose, an influenza circulation threshold was prespecified in the statistical analysis plan at 4 or more weeks (consecutive or nonconsecutive) of 10% or more influenza test positivity in national Danish surveillance data. The remaining end points (hospitalization for cardiovascular disease, hospitalization for any cause, all-cause mortality, and hospitalization for Covid-19) were to be assessed regardless of influenza circulation.

For safety assessment, only serious adverse events (SAEs), defined in this pragmatic trial as deaths and hospitalizations, were recorded. There is a large body of evidence regarding nonserious adverse events with HD versus standard-dose influenza vaccines,[12-14] and such events were not registered in this trial. All participants were screened for the occurrence of any SAEs once at approximately 3 months after vaccination. Participants who died or had at least one hospital contact of any type, including in the inpatient, emergency, or outpatient settings, were identified using the administrative health registries and subsequently evaluated through electronic medical record review by investigators at the central trial site, including causality assessment.

STATISTICAL ANALYSIS

Baseline characteristics were summarized according to randomization group. October 1, 2021, was used as the index date for the assessment of characteristics for the overall Danish population aged 65 to 79 years. For the comparison of baseline characteristics between the trial population and the overall Danish population, absolute differences in proportions were calculated and presented along with 95% confidence intervals (CIs). For the comparison of event rates between the trial population and the overall Danish population, events in the overall Danish population were counted from October 15, 2021 (corresponding to the first day of the vaccination period plus 14 days), to May 31, 2022 (corresponding to the end of follow-up). Analyses of clinical outcomes were conducted using the intention-to-treat principle. For the primary analyses, only first events were counted. The total number of events was also assessed. rVE was calculated as 1 minus the relative risk of the specified outcome among those receiving QIV-HD versus QIV-SD and expressed as a percentage. CIs for rVE estimates were calculated using the Clopper–Pearson method.[15]

In a sensitivity analysis, all clinical outcomes, other than all-cause death, were analyzed using competing risk regression with death as competing risk. An additional

sensitivity analysis was performed considering all events from the time of randomization, rather than from 14 days after randomization.

No adjustments for multiplicity were prespecified, and CIs have not been adjusted for multiple comparisons. For the comparison of SAEs across groups, the threshold for statistical significance was set at 5%. Statistical analysis was performed with the use of SAS software version 9.4 (SAS Institute, Inc.) and Stata MP version 17.0 (StataCorp).

ROLE OF THE FUNDING SOURCE

Sanofi funded the study and provided the QIV-HD doses along with a financial contribution covering remaining expenses. The protocol was codeveloped with the funder. The legal sponsor of the trial was Copenhagen University Hospital–Herlev and Gentofte. Sanofi had no access to raw data but was involved in the interpretation of the summarized results and the preparation and review of the manuscript.

Results

ENROLLMENT, RANDOMIZATION, AND VACCINATION

Participants were included from October 1, 2021, to November 20, 2021. In total, 34,000 persons aged 65 to 79 years were invited to participate, 12,551 of whom were included and randomly assigned, corresponding to a participation rate of 36.9%. At nine vaccination sessions (of a total 1102 sessions), trial personnel mistakenly attempted to recruit participants who had no prior knowledge of the trial. This was a violation of the protocol's recruitment procedure and, therefore, the information given to participants included at these sessions before consent was subsequently judged as insufficient by the regional ethics committee. These participants were given an explicit option to withdraw from the trial, and 72 of 342 such participants chose to do so. In addition, two randomly assigned participants did not meet the age inclusion criterion and were excluded, leaving 12,477 participants for analysis: 6245 in the QIV-HD group and 6232 in the QIV-SD group (Fig. 1). Agreement between randomized assignment and administered vaccine was 99.95% in the QIV-HD group (three received QIV-SD) and 99.90% in the QIV-SD group (six received QIV-HD). All QIV-SD administered in the trial were Influvac Tetra (Viatris). The final study database was assembled on June 15, 2022.

BASELINE CHARACTERISTICS

Registry linkage was successful for all but four participants. Baseline characteristics were balanced across randomization groups (Table 1). In the entire trial population, mean (±SD) age was 71.7±3.9 years; 5877 participants (47.1%) were women; and 850 (6.8%) had chronic lung disease, 1363 (10.9%) cancer, 962 (7.7%) ischemic heart disease, 275 (2.2%) heart failure, 1162 (9.3%) diabetes, and 6469 (51.9%) hypertension.

The representativeness of the trial population compared with the overall Danish general population aged 65 to 79 years is presented in Table 2 and Table S4. Most comorbidities and medication use were more frequent in the general population; however, the prevalence of cancer and chronic lung disease and the use of inhaled glucocorticoids were similar between groups.

CLINICAL OUTCOMES

Four participants, two from each randomization group, emigrated during the follow-up period; any hospitalizations or deaths occurring in these participants, as well as in the four participants with unsuccessful registry linkage, would therefore not be expected to be recorded in the Danish registries. Complete follow-up data were available for more than 99.9% of participants.

The influenza circulation threshold was met with 6 weeks of 10% or more influenza test positivity in national Danish surveillance data during the 2021–2022 influenza season,[16] allowing for analysis of all clinical outcomes (Table 3). The incidence of hospitalization for influenza or pneumonia was 10 (0.2%) of 6245 in the QIV-HD group and 28 (0.4%) of 6232 in the QIV-SD group (rVE, 64.4%; 95% CI, 24.4 to 84.6). The incidence of all-cause mortality was 21 (0.3%) of 6245 in the QIV-HD group and 41 (0.7%) of 6232 in the QIV-SD group (rVE, 48.9%; 95% CI, 11.5 to 71.3). The incidence of the remaining end points was similar between groups. The numerical difference in the incidence of hospitalization for cardiorespiratory disease was driven solely by respiratory hospitalizations. The total number of events for each end point is presented in Table S5. The results were similar when accounting for death as a competing risk (Table S6) and when considering all events occurring from the time of randomization rather than from 14 days after randomization (Table S7).

A comparison of event rates between the trial population and the overall Danish population is given in Table 2.

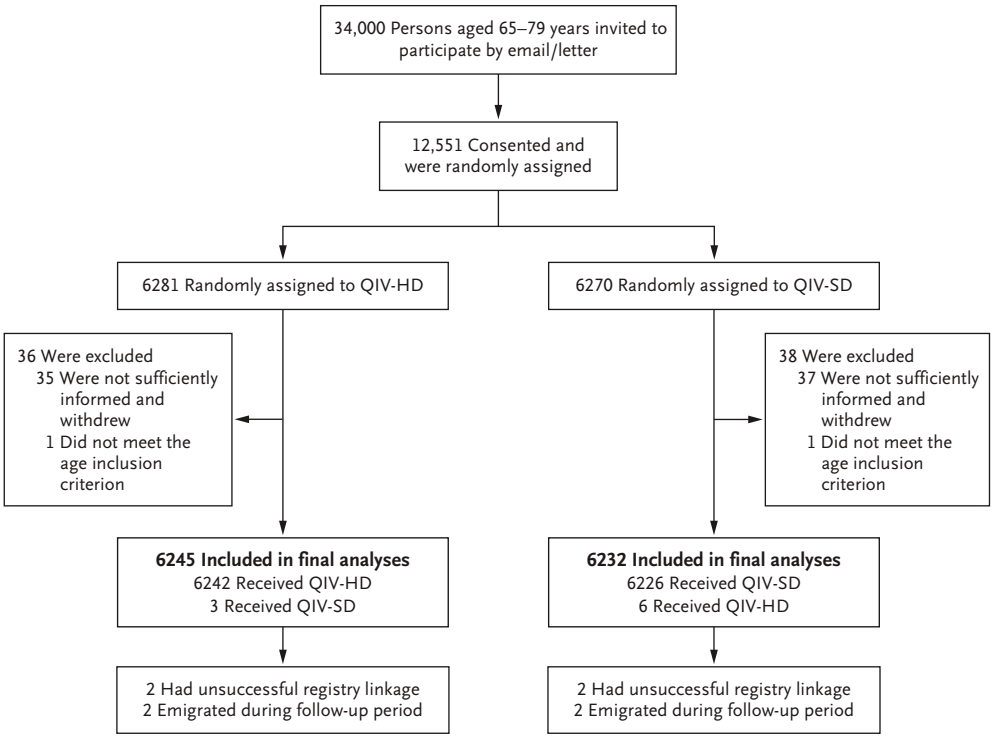

Figure 1. Flowchart of Trial Enrollment.

Flowchart of invitation, enrollment, and randomization. At nine vaccination sessions, the information given to participants before consent was subsequently judged as insufficient by the regional ethics committee. Participants included at these sessions were given an explicit option to withdraw from the trial and, subsequently, 72 of 342 such participants chose to do so. QIV-HD denotes high-dose quadrivalent influenza vaccine; and QIV-SD, standard-dose quadrivalent influenza vaccine.

Incidence rates were between 12% and 68% lower in the trial population, with the largest difference found in all-cause death.

SAFETY

During the 3-month safety surveillance period, a total of 945 SAEs were observed: 452 in the QIV-HD group and 493 in the QIV-SD group (Table 4). More cardiovascular SAEs were observed in the QIV-SD group. Five SAEs were considered related to study treatment, one in the QIV-HD group and four in the QIV-SD group. Twenty-one fatal SAEs were observed, none of which was deemed related to study treatment (most frequent causes of death: cardiovascular [n=10], cancer [n=3], Covid-19 [n=3], and pneumonia [n=3]).

Discussion

In this pragmatic randomized feasibility trial, we enrolled more than 12,000 patients in 7 weeks. The number of enrolled participants was lower than the planned sample size of 40,000, one possible reason being delays in the obtainment of regulatory approvals, which meant that recruitment was initiated only 7 days before the start of the influenza vaccination period. The participation rate of approximately 37% was encouraging when considering that approximately 17% of the Danish population aged 65 years and older (200,000 of 1.2 million) would have to be enrolled in a potential fully powered trial to meet the sample size requirement.[9] Registry-based data collection and linkage were feasible, and they allowed for the accurate and timely assessment of baseline characteristics, outcomes, and safety during the conduct of the trial with complete follow-up data available for more than 99.9% of participants. The trial design enabled successful randomization between treatment groups, as well as assessment of the representativeness of the trial population compared with the general population on the basis of both baseline characteristics and outcome incidence rates. This trial was not powered to assess clinical outcomes. Our findings of a

Table 1. Baseline Characteristics According to Randomization Group.*

Characteristic	QIV-HD (n=6245)	QIV-SD (n=6232)
Age (yr)	71.8±3.9	71.7±3.9
Female sex	2956 (47.3)	2921 (46.9)
Inclusion week (during 2021)		
October 1–October 7	3864 (61.9)	3847 (61.7)
October 8–October 14	1708 (27.4)	1703 (27.3)
October 15–October 21	471 (7.5)	475 (7.6)
October 22–October 28	99 (1.6)	103 (1.7)
October 29–November 4	63 (1.0)	67 (1.1)
November 5–November 11	25 (0.4)	23 (0.4)
November 11–November 18	14 (0.2)	13 (0.2)
November 19–November 25	1 (0.0)	1 (0.0)
Chronic cardiovascular disease	1227 (19.7)	1313 (21.1)
Ischemic heart disease	450 (7.2)	512 (8.2)
Heart failure	137 (2.2)	138 (2.2)
Atrial fibrillation	458 (7.3)	420 (6.7)
Cerebrovascular disease	219 (3.5)	237 (3.8)
Hypertension	3254 (52.1)	3215 (51.6)
Diabetes	574 (9.2)	588 (9.4)
Chronic lung disease	435 (7.0)	415 (6.7)
Chronic obstructive pulmonary disease	227 (3.6)	190 (3.0)
Cancer	695 (11.1)	668 (10.7)
Immunodeficiency	244 (3.9)	239 (3.8)

* Values are presented as the mean (±SD) or no. (%). Four participants, two in each arm, had unsuccessful registry linkage and therefore only have available data for age, sex, and inclusion week. These participants do not count toward the denominator for the remaining baseline variables. Chronic cardiovascular disease is a composite of several cardiovascular diseases, including, but not limited to, ischemic heart disease, heart failure, atrial fibrillation, and cerebrovascular disease. The full list of International Classification of Diseases, 10th Edition, and Anatomical Therapeutic Chemical codes used for the definition of baseline characteristics is presented in Table S1. QIV-HD denotes high-dose quadrivalent influenza vaccine; and QIV-SD, standard-dose quadrivalent influenza vaccine.

lower incidence of hospitalization for influenza or pneumonia and all-cause mortality in the QIV-HD group compared with the QIV-SD group require confirmation in a fully powered trial.

This individually randomized trial was conducted relying solely on the nationwide Danish administrative health registries for the collection of baseline, outcome, and safety data. By integrating the gold standard of randomization into routine vaccination practice, it was possible to efficiently conduct a large-scale randomized trial in a real-world setting. Given the high costs and regulatory requirements of conducting traditional randomized trials,[17,18] pragmatic approaches are important to consider. In addition, such approaches may increase external validity by potentially improving the representativeness of trial populations relative to traditional clinical trials.

The use of health data routinely obtained in a universal public health care system and captured in administrative registries as the primary data source in randomized trials has several advantages: it increases the feasibility of conducting large-scale trials by reducing the administrative burden placed on investigators, minimizes loss to follow-up, and facilitates streamlined trial design.[19,20] Using prespecified definitions that are based on administrative coding may improve consistency and reduce ascertainment bias in the assessment of baseline characteristics and outcomes, and allows for a comparison of the trial population with the corresponding real-world population using the same definitions, facilitating the process of assessing the external validity of a trial. Although the use of routine health data can also pose substantial risks, including misclassification and underreporting, these risks would be expected to be equally distributed across randomized arms.[19] The Danish administrative health registries have been widely used for observational studies and are generally well validated, in particular within the cardiovascular domain where most incident events have positive predictive values of more than 90%[21]; however, even within the cardiovascular domain, the heart failure diagnosis has previously been shown to be underreported.[22] Additional validation work is warranted to examine how the registries perform as the primary data source in a randomized trial setting.

Baseline characteristics were similar between the trial population and the overall Danish population, supporting the generalizability of the findings. End point incidence rates were between 12% and 68% lower in the trial population, which may be explained, in part, by a 100% vaccination rate in the trial population compared with 77.8% in the general Danish population aged 65 to 81 years.[23] In addition, recruiting individuals already seeking vaccination may have introduced a healthy user effect, as individuals accepting vaccination may be healthier and exhibit different patterns of health care–seeking behavior (e.g., increased use of preventive care) than nonvaccinees[24]; however, these data provide an estimate for the generalizability of the findings and may be used to adjust expected event rates calculated from registry data for future trials. Other studies have made similar comparisons to registry populations and excluded patients[25-27]; however, their results are not directly comparable to ours because of very different trial populations and designs.

Table 2. Comparison of Baseline Characteristics and Event Rates between Trial Population and Overall Danish Population Aged 65 to 79 Years.*

Demographic, Comorbidity, and Outcome	DANFLU-1 Population (n=12,477)	Overall Danish Population Aged 65–79 Years (n=889,689)	Absolute Difference — Percentage Points (95% CI)
Demographic characteristics			
Female sex	5877 (47.1)	463,645 (52.1)	−5.0 (−5.9 to −4.1)
Age (yr)	71.7±3.9	72.2±4.2	−0.4 (−0.3 to −0.5)
Comorbidity			
Chronic cardiovascular disease	2540 (20.4)	203,488 (22.9)	−2.5 (−3.2 to −1.8)
Ischemic heart disease	962 (7.7)	75,251 (8.5)	−0.7 (−1.2 to −0.3)
Myocardial infarction	306 (2.5)	25,299 (2.8)	−0.4 (−0.7 to −0.1)
Heart failure	275 (2.2)	26,632 (3.0)	−0.8 (−1.0 to −0.5)
Atrial fibrillation	878 (7.0)	68,663 (7.7)	−0.7 (−1.1 to −0.2)
Valvular disease	358 (2.9)	29,276 (3.3)	−0.4 (−0.7 to −0.1)
Cerebrovascular disease	456 (3.7)	51,402 (5.8)	−2.1 (−2.5 to −1.8)
Peripheral vascular disease	101 (0.8)	11,532 (1.3)	−0.5 (−0.6 to −0.3)
Hypertension	6469 (51.9)	497,413 (55.9)	−4.0 (−4.9 to −3.2)
Diabetes	1,162 (9.3)	117,852 (13.2)	−3.9 (−4.4 to −3.4)
Dyslipidemia	4528 (36.3)	340,286 (38.2)	−1.9 (−2.8 to −1.1)
Chronic lung disease	850 (6.8)	64,158 (7.2)	−0.4 (−0.8 to 0.0)
Chronic obstructive pulmonary disease	417 (3.3)	41,301 (4.6)	−1.3 (−1.6 to −1.0)
Asthma	442 (3.5)	24,322 (2.7)	0.8 (0.5 to 1.1)
Cancer	1363 (10.9)	96,498 (10.8)	0.1 (−0.5 to 0.6)
Chronic kidney disease	275 (2.2)	24,315 (2.7)	−0.5 (−0.8 to −0.3)
Liver disease	140 (1.1)	13,185 (1.5)	−0.4 (−0.5 to −0.2)
Immunodeficiency	483 (3.9)	41,293 (4.6)	−0.8 (−1.1 to −0.4)
Neurologic/neuromuscular disease	225 (1.8)	32,956 (3.7)	−1.9 (−2.1 to −1.7)
Dementia	35 (0.3)	12,294 (1.4)	−1.1 (−1.2 to −1.0)
Rheumatic disease	213 (1.7)	18,482 (2.1)	−0.4 (−0.6 to −0.1)

	DANFLU-1 Population (n=12,477)		Overall Danish Population Aged 65–79 Years (n=889,689)		
	Events	Incidence Rate per 1000 Person-Years (95% CI)	Events	Incidence Rate per 1000 Person-Years (95% CI)	Incidence Rate Ratio (95% CI)
Outcome					
Hospitalization for influenza or pneumonia	38 (0.3)	5.0 (3.7 to 6.9)	6327 (0.7)	11.4 (11.2 to 11.7)	0.44 (0.31 to 0.61)
Hospitalization for respiratory disease	64 (0.5)	8.5 (6.7 to 10.9)	10,711 (1.2)	19.4 (19.0 to 19.8)	0.44 (0.34 to 0.56)
Hospitalization for cardiorespiratory disease	220 (1.8)	29.3 (25.7 to 33.5)	23,421 (2.6)	42.7 (42.2 to 43.3)	0.69 (0.60 to 0.78)
Hospitalization for cardiovascular disease	163 (1.3)	21.6 (18.5 to 25.2)	13,520 (1.5)	24.5 (24.1 to 25.0)	0.88 (0.75 to 1.03)
Hospitalization for Covid-19	27 (0.2)	3.6 (2.5 to 5.2)	3465 (0.4)	6.3 (6.1 to 6.5)	0.57 (0.38 to 0.83)
Hospitalization for any cause	1063 (8.5)	146.3 (137.7 to 155.4)	98,201 (11.0)	186.8 (185.7 to 188.0)	0.78 (0.74 to 0.83)
All-cause death	62 (0.5)	7.7 (6.0 to 9.9)	13,263 (1.5)	24.0 (23.5 to 24.4)	0.32 (0.24 to 0.41)

* Values are presented as the mean (±SD) or no. (%). Four DANFLU-1 (Standard-Dose Quadrivalent Influenza Vaccine in a Pragmatic Registry-Based Setting) participants had unsuccessful registry linkage and therefore only have available data for age and sex. These participants do not count toward the denominator for the remaining variables. For event rate calculations, only first events were counted. The widths of the confidence intervals (CIs) have not been adjusted for multiplicity; therefore, the CIs should not be used to reject or not reject effects. Covid-19 denotes coronavirus disease 2019; QIV-HD, high-dose quadrivalent influenza vaccine; and QIV-SD, standard-dose quadrivalent influenza vaccine.

In our trial, the observed rVE point estimates for QIV-HD compared with QIV-SD against hospitalization for influenza or pneumonia and all-cause mortality were large; however, the relatively wide CIs around the point estimates reflect the fact that the study was not powered for these outcomes. These findings were comparable to others found in the literature, however. In an article examining SAE rates in the 2015 trial by

Table 3. Relative Vaccine Effectiveness for QIV-HD versus QIV-SD across Clinical Outcomes.*

Outcome	Events		rVE
	QIV-HD (n=6245)	QIV-SD (n=6232)	
Hospitalization for influenza or pneumonia	10 (0.2)	28 (0.4)	64.4 (24.4 to 84.6)
Hospitalization for respiratory disease	24 (0.4)	40 (0.6)	40.1 (−1.8 to 65.5)
Hospitalization for cardiorespiratory disease	103 (1.6)	117 (1.9)	12.1 (−15.5 to 33.3)
Hospitalization for cardiovascular disease	82 (1.3)	81 (1.3)	−1.0 (−39.1 to 26.6)
Hospitalization for Covid-19	15 (0.2)	12 (0.2)	−24.7 (−191.9 to 45.5)
Hospitalization for any cause	513 (8.2)	550 (8.8)	6.9 (−5.2 to 17.6)
All-cause death	21 (0.3)	41 (0.7)	48.9 (11.5 to 71.3)

* Values are presented as no. (%) or % (95% confidence interval). Only first events were counted. Relative vaccine effectiveness (rVE) was calculated as 1 minus the relative risk of the specified outcome in the high-dose quadrivalent influenza vaccine (QIV-HD) group versus the standard-dose quadrivalent influenza vaccine (QIV-SD) group. Confidence intervals for rVE estimates were calculated by using the Clopper–Pearson method. The widths of the confidence intervals have not been adjusted for multiplicity; therefore, the confidence intervals should not be used to reject or not reject effects. Covid-19 denotes coronavirus disease 2019.

DiazGranados et al.,[12] a trivalent HD vaccine reduced serious pneumonia by 39.8% (95% CI, 19.3 to 55.1) and all-cause hospitalization by 6.9% (95% CI, 0.5 to 12.8) compared with a trivalent standard-dose vaccine. These effect sizes are comparable to those observed in our study, with the previously reported 39.8% reduction in serious pneumonia contained in the 95% CI for hospitalization for influenza or pneumonia and the 6.9% reduction in all-cause hospitalization matching the trend observed in our trial. A recent meta-analysis of predominantly observational studies showed consistently superior protection of HD versus standard-dose vaccines over 10 seasons and in more than 34 million people.[8]

Table 4. SAEs during the 3-Month Safety Surveillance Period According to Vaccine Received.*

Event	Participants		*P*
	QIV-HD (n=6248)	QIV-SD (n=6229)	
Any SAE	373 (6.0)	405 (6.5)	0.22
Any cardiovascular SAE	63 (1.0)	87 (1.4)	0.047
Any respiratory SAE	24 (0.4)	26 (0.4)	0.77
Any gastrointestinal SAE	23 (0.4)	24 (0.4)	0.88
Any infection-related SAE	22 (0.4)	19 (0.3)	0.65
Any injury-related SAE	94 (1.5)	98 (1.6)	0.75
Fatal SAE	8 (0.1)	13 (0.2)	0.27
Any serious adverse reaction	1 (0.0)	4 (0.1)	0.18

* Values are presented as no. (%) of participants experiencing at least one event. Comparisons between groups were performed by using Pearson's χ^2 test. QIV-HD denotes high-dose quadrivalent influenza vaccine; QIV-SD, standard-dose quadrivalent influenza vaccine; and SAE, serious adverse event.

Another individually randomized trial that compared the rVE of HD versus standard-dose vaccines against hospitalizations and mortality was the INVESTED (Influenza Vaccine to Effectively Stop Cardio Thoracic Events and Decompensated Heart Failure) trial.[28] This trial investigated the effect of a trivalent HD vaccine compared with QIV-SD on a primary composite end point of all-cause death or cardiopulmonary hospitalization in high-risk patients with cardiovascular disease. No significant difference was found in the incidence of the primary end point in a study population that differed substantially from our general population sample. The IAMI (Influenza Vaccination After Myocardial Infarction) trial reported a 28% reduction in the composite primary end point of all-cause death, myocardial infarction, or stent thrombosis with influenza vaccination versus placebo in a population of mostly post–myocardial infarction patients.[29] This conflicts with our findings with regard to cardiovascular end points, but our study was not powered for clinical outcomes and compared two different vaccine types — a very different comparison than evaluating vaccination against placebo.

Of interest, Danish influenza surveillance data for the 2021–2022 influenza season indicated no observable vaccine effectiveness against the circulating influenza A (H3N2) strain with quadrivalent influenza vaccines in adults older than age 45 years.[30] Despite this trial not being powered to assess clinical end points, our data still suggest a possible benefit with QIV-HD compared with QIV-SD during this influenza season, potentially supporting the previously proposed idea of nonspecific immunomodulatory effects of influenza vaccination independent of the prevention of influenza infection.[31,32]

The current study has several potential limitations. First, it was a feasibility study, which was not powered to assess clinical outcomes and, therefore, the rVE estimates are based on relatively few events. The observed reductions in the incidence of hospitalization for influenza or pneumonia and all-cause mortality among those vaccinated with QIV-HD require confirmation in a larger, fully powered trial with adequate control of type I error. Second, as a result of the pragmatic nature of the trial, no systematic laboratory testing for influenza was performed. Nonetheless, despite the absence of laboratory confirmation, by virtue of randomization, any differences observed between groups can effectively be attributed to treatment. Third, the trial was open-label; however, the outcomes of hospitalizations and deaths may be less affected by knowledge of treatment group assignment than more subjective outcomes. Fourth, there was no adjudication of clinical outcomes, which were based solely on administrative health data; however, data from several large-scale cardiovascular trials and reviews indicate that adjudication might not alter effect estimates from randomized trials,[33-37] and using routine health data might increase the generalizability of the results. Fifth, no data on race and/or ethnicity were available. Because the study was conducted in Denmark, the study sample would be expected to be predominantly White. Sixth, the trial was conducted during only one influenza season, precluding comparisons across multiple influenza seasons with different circulating strains or accounting for the possible differential impact of Covid-19 restrictions. Seventh, the vaccination provider's database of prior vaccinees was based on email addresses only and, therefore, no identifier was available for us to distinguish the invitees in the registries and compare these with the recruited trial population. We were able, however, to show the comparability of the trial population to the overall Danish population in the same age group.

Conclusions

Conducting a pragmatic randomized trial of QIV-HD versus QIV-SD using existing infrastructure for recruitment, inclusion, randomization, and vaccination and relying solely on registry-based data collection was feasible. The findings of a lower incidence of hospitalization for influenza or pneumonia and all-cause mortality in the QIV-HD group compared with QIV-SD require confirmation in a future fully powered trial.

Disclosures

Supported by Sanofi, which provided the QIV-HD doses along with a financial contribution covering remaining expenses. The protocol was codeveloped with the funder.

Author disclosures and other supplementary materials are available at evidence.nejm.org.

Data from the nationwide Danish administrative health registries are subject to Danish legislation and can only be made available to a third party under certain conditions. The corresponding author can be contacted in case of any inquiries. A data sharing statement provided by the authors is available with the full text of this article at evidence.nejm.org.

We thank all personnel at Danske Lægers Vaccinations Service, part of European LifeCare Group, for collaborating and assisting with study procedures.

Author Affiliations

[1] Department of Cardiology, Copenhagen University Hospital–Herlev and Gentofte, Copenhagen

[2] Center for Translational Cardiology and Pragmatic Randomized Trials, Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen

[3] School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong

[4] Sanofi, Lyon, France

[5] Sanofi, Swiftwater, PA

[6] Department of Clinical Medicine, Department of Infectious Diseases, Aarhus University Hospital, Aarhus, Denmark

[7] Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston

[8] Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Public Health, University of Oxford, Oxford, United Kingdom

[9] Big Data Institute, University of Oxford, Oxford, United Kingdom

[10] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen

[11] The Danish Heart Foundation, Copenhagen

[12] The National Institute of Public Health, University of Southern Denmark, Copenhagen

[13] Department of Cardiology, Copenhagen University Hospital–Rigshospitalet, Copenhagen

[14] Respiratory Medicine Section, Department of Medicine, Copenhagen University Hospital–Herlev and Gentofte, Copenhagen

[15] Epidemiological Infectious Disease Preparedness, Statens Serum Institut, Copenhagen

References

1. Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. The efficacy of influenza vaccine in elderly persons. A meta-analysis and review of the literature. Ann Intern Med 1995;123:518-527. DOI: 10.7326/0003-4819-123-7-199510010-00008.

2. Ohmit SE, Thompson MG, Petrie JG, et al. Influenza vaccine effectiveness in the 2011–2012 season: protection against each

circulating virus and the effect of prior vaccination on estimates. Clin Infect Dis 2014;58:319-327. DOI: 10.1093/cid/cit736.

3. Jackson ML, Chung JR, Jackson LA, et al. Influenza vaccine effectiveness in the United States during the 2015–2016 season. N Engl J Med 2017;377:534-543. DOI: 10.1056/NEJMoa1700153.

4. Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases (NCIRD). Influenza (Flu). People at higher risk of flu complications. Centers for Disease Control and Prevention. October 21, 2021 (https://www.cdc.gov/flu/highrisk/index.htm).

5. European Centre for Disease Prevention and Control (ECDC). Seasonal Influenza Vaccines. Risk groups for severe influenza. European Centre for Disease Prevention and Control. October 21, 2021 (https://www.ecdc.europa.eu/en/seasonal-influenza/prevention-and-control/vaccines/risk-groups).

6. DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. N Engl J Med 2014;371:635-645. DOI: 10.1056/NEJMoa1315727.

7. Lee JKH, Lam GKL, Shin T, et al. Efficacy and effectiveness of high-dose versus standard-dose influenza vaccination for older adults: a systematic review and meta-analysis. Expert Rev Vaccines 2018;17:435-443. DOI: 10.1080/14760584.2018.1471989.

8. Lee JKH, Lam GKL, Shin T, Samson SI, Greenberg DP, Chit A. Efficacy and effectiveness of high-dose influenza vaccine in older adults by circulating strain and antigenic match: an updated systematic review and meta-analysis. Vaccine 2021;39:A24-A35. DOI: 10.1016/j.vaccine.2020.09.004.

9. Nealon J, Modin D, Ghosh RE, et al. The feasibility of pragmatic influenza vaccine randomized controlled real-world trials in Denmark and England. NPJ Vaccines 2022;7:25. DOI: 10.1038/s41541-022-00444-6.

10. Johansen ND, Modin D, Nealon J, et al. Feasibility of randomizing Danish citizens aged 65–79 years to high-dose quadrivalent influenza vaccine vs. standard-dose quadrivalent influenza vaccine in a pragmatic registry-based setting: rationale and design of the DANFLU-1 trial. Pilot Feasibility Stud 2022;8:87. DOI: 10.1186/s40814-022-01044-w.

11. Thygesen LC, Daasnes C, Thaulow I, Brønnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. Scand J Public Health 2011;39:12-16. DOI: 10.1177/1403494811399956.

12. DiazGranados CA, Robertson CA, Talbot HK, Landolfi V, Dunning AJ, Greenberg DP. Prevention of serious events in adults 65 years of age or older: a comparison between high-dose and standard-dose inactivated influenza vaccines. Vaccine 2015;33:4988-4993. DOI: 10.1016/j.vaccine.2015.07.006.

13. Chang L-J, Meng Y, Janosczyk H, Landolfi V, Talbot HK. Safety and immunogenicity of high-dose quadrivalent influenza vaccine in adults ≥65 years of age: a phase 3 randomized clinical trial. Vaccine 2019;37:5825-5834. DOI: 10.1016/j.vaccine.2019.08.016.

14. Pepin S, Nicolas J-F, Szymanski H, et al. Immunogenicity and safety of a quadrivalent high-dose inactivated influenza vaccine compared with a standard-dose quadrivalent influenza vaccine in healthy people aged 60 years or older: a randomized phase III trial. Hum Vaccin Immunother 2021;17:5475-5486. DOI: 10.1080/21645515.2021.1983387.

15. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med 1998;17:857-872. DOI: 10.1002/(SICI)1097-0258(19980430)17:8<857::AID-SIM777>3.0.CO;2-E.

16. World Health Organization. WHO Flumart outputs. June 22, 2022 (https://apps.who.int/flumart/Default?ReportNo=12).

17. Reith C, Landray M, Devereaux PJ, et al. Randomized clinical trials — removing unnecessary obstacles. N Engl J Med 2013;369:1061-1065. DOI: 10.1056/NEJMsb1300760.

18. James S, Rao SV, Granger CB. Registry-based randomized clinical trials — a new clinical trial paradigm. Nat Rev Cardiol 2015;12:312-316. DOI: 10.1038/nrcardio.2015.33.

19. Mc Cord KA, Al-Shahi Salman R, Treweek S, et al. Routinely collected data for randomized trials: promises, barriers, and implications. Trials 2018;19:29. DOI: 10.1186/s13063-017-2394-5.

20. Hemkens LG. How routinely collected data for randomized trials provide long-term randomized real-world evidence. JAMA Netw Open 2018;1:e186014. DOI: 10.1001/jamanetworkopen.2018.6014.

21. Sundbøll J, Adelborg K, Munch T, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. BMJ Open 2016;6:e012832. DOI: 10.1136/bmjopen-2016-012832.

22. Kümler T, Gislason GH, Kirk V, et al. Accuracy of a heart failure diagnosis in administrative registers. Eur J Heart Fail 2008;10:658-660. DOI: 10.1016/j.ejheart.2008.05.006.

23. Statens Serum Institut. Influenza — ugens opgørelse. July 6, 2022 (https://www.ssi.dk/sygdomme-beredskab-og-forskning/sygdomsovervaagning/i/influenza-ugens-opgoerelse).

24. Remschmidt C, Wichmann O, Harder T. Frequency and impact of confounding by indication and healthy vaccinee bias in observational studies assessing influenza vaccine effectiveness: a systematic review. BMC Infect Dis 2015;15:429. DOI: 10.1186/s12879-015-1154-y.

25. Steg PG, López-Sendón J, Lopez de Sa E, et al. External validity of clinical trials in acute myocardial infarction. Arch Intern Med 2007;167:68-73. DOI: 10.1001/archinte.167.1.68.

26. Paul M, Bronstein E, Yahav D, Goldberg E, Bishara J, Leibovici L. External validity of a randomised controlled trial on the treatment of severe infections caused by MRSA. BMJ Open 2015;5:e008838. DOI: 10.1136/bmjopen-2015-008838.

27. Grønhøj MH, Gerke O, Mickley H, et al. External validity of a cardiovascular screening including a coronary artery calcium examination in middle-aged individuals from the general population. Eur J Prev Cardiol 2018;25:1156-1166. DOI: 10.1177/2047487318774850.

28. Vardeny O, Kim K, Udell JA, et al. Effect of high-dose trivalent vs standard-dose quadrivalent influenza vaccine on mortality or cardiopulmonary hospitalization in patients with high-risk cardiovascular disease: a randomized clinical trial. JAMA 2021;325:39-49. DOI: 10.1001/jama.2020.23649.

29. Fröbert O, Götberg M, Erlinge D, et al. Influenza vaccination after myocardial infarction: a randomized, double-blind, placebo-controlled, multicenter trial. Circulation 2021;144:1476-1484. DOI: 10.1161/CIRCULATIONAHA.121.057042.

30. Emborg H-D, Vestergaard LS, Botnen AB, Nielsen J, Krause TG, Trebbien R. A late sharp increase in influenza detections and low interim vaccine effectiveness against the circulating A(H3N2) strain, Denmark, 2021/22 influenza season up to 25 March 2022. Euro Surveill 2022;27:2200278. DOI: 10.2807/1560-7917.ES.2022.27.15.2200278.

31. Bucasas KL, Franco LM, Shaw CA, et al. Early patterns of gene expression correlate with the humoral immune response to influenza vaccination in humans. J Infect Dis 2011;203:921-929. DOI: 10.1093/infdis/jiq156.

32. Atoui R, Ebrahim F, Saroka K, Mireau J, McElhaney JE, Hare GMT. Influenza vaccination blunts the inflammatory response in patients undergoing cardiopulmonary bypass. Ann Thorac Surg 2021;111:1923-1930. DOI: 10.1016/j.athoracsur.2020.07.052.

33. Pfeffer MA, Claggett B, Lewis EF, et al. Impact of sacubitril/valsartan versus ramipril on total heart failure events in the PARADISE-MI trial. Circulation 2022;145:87-89. DOI: 10.1161/CIRCULATIONAHA.121.057429.

34. Harper C, Mafham M, Herrington W, et al. Comparison of the accuracy and completeness of records of serious vascular events in routinely collected data vs clinical trial-adjudicated direct follow-up data in the UK: secondary analysis of the ASCEND randomized clinical trial. JAMA Netw Open 2021;4:e2139748. DOI: 10.1001/jamanetworkopen.2021.39748.

35. Gaba P, Bhatt DL, Dagenais GR, et al. Comparison of investigator-reported vs centrally adjudicated major adverse cardiac events: a secondary analysis of the COMPASS trial. JAMA Netw Open 2022;5:e2243201. DOI: 10.1001/jamanetworkopen.2022.43201.

36. Ndounga Diakou LA, Trinquart L, Hróbjartsson A, et al. Comparison of central adjudication of outcomes and onsite outcome assessment on treatment effect estimates. Cochrane Database Syst Rev 2016;3:MR000043. DOI: 10.1002/14651858.MR000043.pub2.

37. Granger CB, Vogel V, Cummings SR, et al. Do we need to adjudicate major clinical events? Clin Trials 2008;5:56-60. DOI: 10.1177/1740774507087972.