

High-Dose Influenza Vaccine Effectiveness against Hospitalization in Older Adults

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ABSTRACT

BACKGROUND

High-dose inactivated influenza vaccine has been shown to provide protection against influenza that is superior to that with the standard dose. However, data from individually randomized trials on the effectiveness of the high-dose vaccine against severe outcomes are limited.

METHODS

In this pragmatic, open-label, randomized, controlled trial conducted in Denmark during the 2022–2023, 2023–2024, and 2024–2025 influenza seasons, we assigned older adults (≥ 65 years of age) to receive the high dose of the inactivated influenza vaccine or the standard dose. Data collection relied on nationwide administrative health registries. The primary end point was hospitalization for influenza or pneumonia that occurred from 14 days after vaccination through May 31 of the following year.

RESULTS

Of the 332,438 participants who underwent randomization, 166,218 were assigned to receive the high-dose vaccine and 166,220 to receive the standard-dose vaccine. The mean ($\pm$ SD) age of the participants was 73.7 ± 5.8 years, and 161,538 participants (48.6%) were women. A primary end-point event occurred in 1138 participants (0.68%) in the high-dose group and in 1210 (0.73%) in the standard-dose group (relative vaccine effectiveness, 5.9%; 95.2% confidence interval [CI], -2.1 to 13.4 ; $P=0.14$). Hospitalization for influenza occurred in 0.06% of the participants in the high-dose group and in 0.11% of those in the standard-dose group (relative vaccine effectiveness, 43.6%; 95.2% CI, 27.5 to 56.3); hospitalization for pneumonia occurred in 0.63% and 0.63%, respectively (relative effectiveness, 0.5%; 95.2% CI, -8.6 to 8.8); hospitalization for cardiorespiratory disease in 2.25% and 2.38% (relative effectiveness, 5.7%; 95.2% CI, 1.4 to 9.9); hospitalization for any cause in 9.38% and 9.58% (relative effectiveness, 2.1%; 95.2% CI, -0.1 to 4.3), and death from any cause in 0.67% and 0.66% (relative effectiveness, -2.5 %; 95.2% CI, -11.6 to 5.9). The incidence of serious adverse events was similar in the two groups.

CONCLUSIONS

In this trial, a high-dose inactivated influenza vaccine did not result in a significantly lower incidence of hospitalization for influenza or pneumonia than a standard dose among older adults. (Funded by Sanofi; DANFLU-2 ClinicalTrials.gov number, NCT05517174; EU Clinical Trials Register number, 2022-500657-17-00.)

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SEASONAL INFLUENZA IS ESTIMATED TO cause 290,000 to 650,000 deaths from respiratory causes per year worldwide¹ and is also associated with an increased risk of cardiovascular events, including atherosclerotic events and heart failure.² Influenza vaccination effectively reduces the risk of influenza infection and associated complications³⁻⁵; however, conventional vaccines typically prevent 30 to 50% of influenza cases, with lower effectiveness in vulnerable populations, such as older adults.^{6,7} Newer influenza vaccines have been developed to provide increased protection in older adults, including the high-dose inactivated influenza vaccine, which contains four times the amount of hemagglutinin contained in standard-dose inactivated influenza vaccines. In a previous double-blind trial involving adults 65 years of age or older, the relative efficacy of the high-dose vaccine as compared with a standard-dose vaccine was 24.2% (95% confidence interval [CI], 9.7 to 36.5) against laboratory-confirmed influenza, which met the criterion for superiority.⁸ However, owing to very large sample-size requirements, data are limited from individually randomized trials to evaluate the relative effectiveness of a high-dose vaccine as compared with a standard-dose vaccine against severe clinical outcomes, such as hospitalization, among older adults in the general population. We took advantage of the features inherent in the Danish health system, including nationwide administrative health databases and a governmental electronic letter system,⁹ to conduct a trial assessing the relative effectiveness of a high-dose vaccine as compared with a standard-dose vaccine against severe outcomes in older adults.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted DANFLU-2 (A Pragmatic Randomized Trial to Evaluate the Effectiveness of High-Dose Quadrivalent Influenza Vaccine versus Standard-Dose Quadrivalent Influenza Vaccine in Older Adults), a pragmatic, registry-based, open-label, randomized, controlled trial comparing the high-dose inactivated influenza vaccine with a standard-dose vaccine, in Denmark during the 2022–2023, 2023–2024, and 2024–2025 influenza seasons. The trial design was based on a pilot trial conducted during the 2021–2022 influenza

season.⁹ A detailed description of the trial design has been published previously.¹⁰ Only one trial visit was required for randomization and vaccine administration, equivalent to a vaccination visit in a standard governmental vaccination program. We used nationwide administrative health registries to obtain baseline and end-point data and to screen for safety events. The trial was designed to minimize the burden on participants in order to ensure the feasibility of large-scale, individual randomization.

The academic research group at the Center for Translational Cardiology and Pragmatic Randomized Trials (CTCPR) at the Department of Cardiology, Copenhagen University Hospital in Herlev and Gentofte, Copenhagen, oversaw the trial and assumed full responsibility for trial conduct. The trial funder (Sanofi) participated in the trial design and development of the protocol (available with the full text of this article at NEJM.org) but had no role in the trial conduct or in the collection or analysis of the data. The trial was conducted in collaboration with the private vaccination provider Danske Lægers Vaccinations Service, part of European LifeCare Group, which organized vaccination sessions at more than 500 locations in Denmark, obtained consent from the participants, performed randomization, and administered the trial vaccines. Various locations were used for the vaccination sessions, including vaccination clinics, primary care facilities, community centers, and retirement homes. CTCPR served as the central trial site, and the CTCPR staff oversaw trial conduct, ensured linkage to registry data, and performed safety monitoring.

The trial was approved as a low-intervention clinical trial under the European Union Clinical Trials Regulation 536/2014 by the Medical Research Ethics Committees in Denmark and the Danish Medicines Agency and received approval from the data authority in the Capital Region of Denmark (approval number, P-2021-841).

The first and last authors had unrestricted access to the data and vouch for the accuracy and completeness of the data. The first author wrote the first draft of the manuscript. All the authors provided critical review of the manuscript, approved the manuscript for submission for publication, and vouch for the adherence of the trial to the protocol and the statistical analysis plan (available with the protocol).

PARTICIPANTS AND GROUP ASSIGNMENTS

We enrolled adults 65 years of age or older regardless of coexisting conditions. No formal exclusion criteria were specified; the protocol required only that vaccines be administered according to routine vaccine administration procedures, which included assessment of allergies and contraindications. Each season, invitations to participate were sent to up to 1 million randomly selected Danish citizens 65 years of age or older by means of electronic invitation letters that were delivered through the Danish governmental electronic letter system (Digital Post), a secure email system established in Denmark for delivery of official correspondence from institutions such as government authorities, banks, and hospitals.¹¹ The inbox is accessible through Web portals and smartphone apps, and the system is available for use by researchers for purposes such as trial recruitment. Further information on the trial was available on a sign-up website in written and video form. After booking a trial visit, participants could provide informed consent online without any requirement for real-time contact with trial staff. The trial staff were available by phone or email in case of questions. Alternatively, participants could provide written informed consent in person at the trial visit.

At the trial visit, participants were randomly assigned in a 1:1 ratio to receive the high-dose inactivated influenza vaccine or the standard-dose vaccine. Randomization was performed with the use of a tablet application linked to a centralized randomization algorithm. Separate unstratified randomization lists with random permuted blocks were generated for each trial season. Participants who reenrolled in subsequent seasons underwent randomization again and were treated as individual observations for the primary analyses because the effect of correlation on statistical inference in such trial designs has been shown to be negligible.¹²

The participants and trial staff were aware of the treatment groups. However, randomization occurred at the trial visit with no alternative access to the high-dose vaccine in Denmark, the investigators were not involved in subsequent treatment of the participants, and the end points were severe events (hospitalizations or death) that were assessed with the use of passively collected registry data; therefore, the risk of bias related

to knowledge of treatment assignment was expected to be low.

VACCINES

Each season, participants received a single dose of either the quadrivalent high-dose vaccine (Fluzone High-Dose Quadrivalent/Efluelda/Efluelda Tetra, Sanofi) or the quadrivalent standard-dose vaccine (VaxigripTetra, Sanofi). The high-dose vaccine contained 60 μ g of hemagglutinin antigen for each strain, and the standard-dose vaccine contained 15 μ g. The high-dose vaccine was not offered in the standard Danish governmental vaccination program in any of the trial seasons. The trial allowed for coadministration with other seasonal vaccines according to local recommendations, including those for coronavirus disease 2019 (Covid-19).

DATA COLLECTION AND SAFETY SURVEILLANCE

Minimal data were collected at the trial visit (identifying information, consent, and information on randomization and vaccine administration). Additional data were sourced primarily from nationwide administrative health registries, which contain routinely collected data from all inpatient and outpatient hospital contacts within the universal Danish health care system.¹³ Baseline characteristics and end points were ascertained with the use of prespecified definitions (Tables S1 through S4 and Annex 1 in the Supplementary Appendix, available at NEJM.org). Safety surveillance involved the use of the registries to screen for hospitalizations and deaths at approximately 3 months after vaccination. Manual review of electronic medical records was subsequently performed for each hospitalization or death by investigators who were unaware of the trial-group assignment. In accordance with an agreement with the Danish Medicines Agency, only serious adverse events, defined in this trial as hospitalization or death, were recorded. No other data on adverse events were obtained.

END POINTS

The primary end point was hospitalization for influenza or pneumonia, an end point that was selected on the basis of previous evidence^{14,15} and biologic plausibility that influenza vaccination can reduce the incidence of pneumonia hospitalizations because viral respiratory infections can

confer a predisposition to secondary bacterial pneumonia.¹⁶ The trial was also powered to assess the first secondary end point of hospitalization for cardiorespiratory disease, which included hospitalization for influenza, pneumonia, other upper or lower respiratory tract infections, chronic obstructive pulmonary disease, asthma, atherosclerotic cardiovascular disease, heart failure, arrhythmia, and pericarditis, myocarditis, or endocarditis. The remaining secondary end points were hospitalization for any cause, death from any cause, and the individual components of the primary end point. The primary and secondary end points related to hospitalization were ascertained according to *International Classification of Diseases, 10th Revision* (ICD-10), diagnosis codes.

We also report relative vaccine effectiveness against hospitalization for laboratory-confirmed influenza, a prespecified exploratory end point, to assess whether it was consistent with effectiveness against hospitalization for influenza according to ICD-10 codes. Hospitalization for laboratory-confirmed influenza was defined by an overnight hospitalization associated with a positive test for influenza that was performed from 14 days before hospital admission through 3 days after admission, in accordance with the Centers for Disease Control and Prevention definition,¹⁷ regardless of the ICD-10 code for hospitalization (a list of the prespecified end points is available in Table S5). The primary ICD-10 codes assigned to the laboratory-confirmed hospitalizations are listed in Table S6. To improve specificity given the context of the Covid-19 pandemic, any hospitalizations with an ICD-10 discharge diagnosis code for Covid-19 (B34.2 or B97.2) were not considered to be eligible for assessment. Each season, trial vaccinations occurred from late September through December, with 99.8% of the vaccinations completed by the end of October. The follow-up period was defined in each season as occurring from 14 days after vaccination through May 31 of the following year; only first events were considered for each end point.

STATISTICAL ANALYSIS

On the basis of data from a previous meta-analysis,¹⁸ we estimated that 2340 primary end-point events would be required to provide the trial with 90% power to detect a 12.5% relative

vaccine effectiveness with the high-dose vaccine as compared with the standard-dose vaccine, at a one-sided alpha level of 0.025. The sample size was initially estimated at 208,000 participants, under the assumption of an incidence of 1.2% for the primary end point in the standard-dose group¹⁹; however, the sample size was expanded to 286,900 participants after the first season and to 339,700 participants after the second season owing to lower-than-expected event rates. This final sample-size calculation assumed an incidence of 0.74% in the standard-dose group. In addition, the final intended sample size would also provide the trial with 90% power to detect a 7.5% relative vaccine effectiveness against hospitalization for cardiorespiratory disease, the first secondary end point, under the assumption of an incidence of 2.1% in the standard-dose group.¹⁹

Given the fact that we conducted the trial during the Covid-19 pandemic, full data analysis was contingent on an influenza circulation threshold being reached in each season to avoid false negative conclusions driven by low influenza circulation levels; the designated threshold was that at least 10% of performed influenza tests should be positive in national surveillance data for at least 4 weeks. The primary analysis was conducted in the intention-to-treat population, which included all the participants who underwent randomization, regardless of whether they received the intended treatment. A hierarchical testing sequence was used to test the primary end point and the first three secondary end points at a one-sided alpha level of 0.02416 (after adjustment for two prespecified interim analyses), which corresponded to a two-sided P value of 0.04832. If a null hypothesis could not be rejected, subsequent end points would be analyzed descriptively only. Relative vaccine effectiveness was calculated as 1 minus the relative risk of the outcome and is presented as a percentage. To account for the interim analyses, 95.2% confidence intervals ($1 - 0.02416 \times 2 = 95.168\% \approx 95.2\%$) are reported, calculated with the Clopper-Pearson method.²⁰ P values were estimated with the use of binomial tests. The consistency of the treatment effect on the primary end point was assessed across prespecified subgroups. The safety population included all the participants according to the treatment received (as-treated

population), and adverse events were reported with P values without adjustment for multiple testing. In three sensitivity analyses, we accounted for within-participant correlation in those who enrolled in more than one season, using a log-binomial regression model with participant-level clustered standard errors; we included end-point events occurring within 14 days after vaccination; and we adjusted for season.

RESULTS

PARTICIPANTS

We randomly assigned a total of 332,438 participants: 19,699 in the 2022–2023 season, 160,451 in the 2023–2024 season, and 152,288 in the 2024–2025 season (Fig. 1). A total of 226,876 unique participants underwent randomization in at least one season, with 87,826 participants

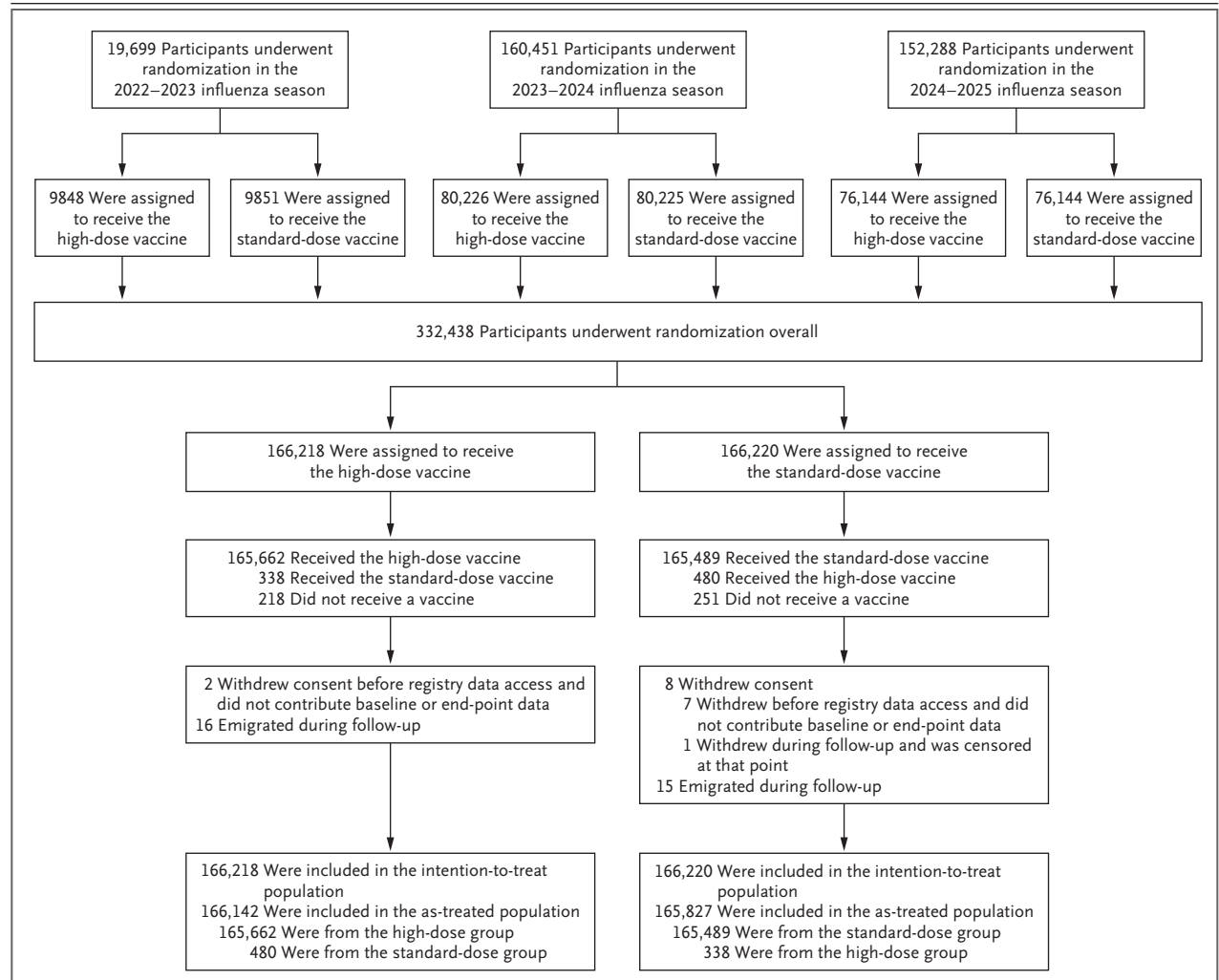


Figure 1. Randomization and Follow-up.

Participants underwent randomization over the course of three consecutive influenza seasons and were randomly assigned in a 1:1 ratio to receive the high-dose inactivated influenza vaccine or the standard-dose vaccine. Participants were allowed to reenroll in subsequent seasons, at which point they underwent randomization again. Participants who withdrew consent before registry data were accessed for that particular season did not contribute registry data to the trial database; only data on age, sex, group assignment, and vaccination status were collected for these participants. The primary analysis was conducted in the intention-to-treat population, which included all the participants who underwent randomization, regardless of whether they received the intended treatment. The safety population included all the participants according to the treatment received (as-treated population).

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	High-Dose Vaccine (N = 166,218)	Standard-Dose Vaccine (N = 166,220)
Age — yr	73.7±5.8	73.7±5.8
Female sex — no. (%)	80,781 (48.6)	80,757 (48.6)
Presence of ≥1 chronic disease — no. (%)	88,835 (53.4)	88,934 (53.5)
Diabetes — no. (%)	21,929 (13.2)	21,952 (13.2)
History of cardiovascular disease — no. (%)	45,688 (27.5)	45,338 (27.3)
Ischemic heart disease — no. (%)	15,666 (9.4)	15,446 (9.3)
Atrial fibrillation — no. (%)	17,076 (10.3)	17,009 (10.2)
Heart failure — no. (%)	5,201 (3.1)	5,209 (3.1)
History of cancer — no. (%)	22,922 (13.8)	22,996 (13.8)
Chronic lung disease — no. (%)	13,575 (8.2)	13,577 (8.2)
Chronic obstructive pulmonary disease — no. (%)	6,799 (4.1)	6,689 (4.0)
Chronic kidney disease — no. (%)	23,302 (14.0)	23,486 (14.1)
Immunosuppression — no. (%)	7,187 (4.3)	7,128 (4.3)
Influenza vaccination completed during preceding season — no. (%)	160,958 (96.8)	161,099 (96.9)
Coadministration with Covid-19 vaccine — no. (%)†	102,242 (61.5)	102,481 (61.7)
Covid-19 vaccine completed during same season — no. (%)	160,436 (96.5)	160,432 (96.5)

* Plus-minus values are means ±SD. Baseline characteristics were obtained from nationwide administrative health registries according to prespecified definitions (see the Supplementary Appendix). A total of nine participants withdrew consent before registry data linkage; therefore, the data for these participants, except for age and sex, are not included in the baseline data.

† Participants in this category received coronavirus disease 2019 (Covid-19) vaccination on the same day as the trial vaccine.

enrolled in two seasons and 8868 participating in all three seasons. In total, 231,345 participants (69.6%) provided informed consent online before their trial visit, and 101,093 participants (30.4%) provided consent in person at the trial visit. Of the 166,218 participants assigned to receive the high-dose vaccine, 165,662 (99.7%) received the assigned vaccine; of the 166,220 participants assigned to receive the standard-dose vaccine, 165,489 (99.6%) received the assigned vaccine. A total of 320,868 participants (96.5%) received the Covid-19 vaccine during their trial season, and 204,446 (61.5%) had the Covid-19 vaccine administered on the same day as the trial vaccine.

The characteristics of the participants at baseline were balanced in the two groups overall and according to season (Table 1 and Table S7, respectively). The mean age of the participants was 73.7±5.8 years, 161,538 (48.6%) were women, and 177,769 (53.5%) had at least one chronic condition. A total of 91,026 participants (27.4%) had a history of cardiovascular disease, 43,881 (13.2%) had

diabetes, 27,152 (8.2%) had chronic lung disease, and 45,918 (13.8%) had a history of cancer. The trial population appeared to be representative of persons 65 years of age or older in the overall Danish population (Table S8).

The three trial seasons showed distinct epidemiologic patterns, characterized by variability in the timing, duration, and intensity of influenza activity (Table S9).²¹⁻²³ National surveillance data indicated that influenza A predominated across all seasons, with a circulating H1N1:H3N2 ratio of approximately 2:1 among adults 65 years or older, whereas some circulation of influenza B was observed in the 2022–2023 and 2024–2025 seasons. Overall, vaccine strains appeared to be a good antigenic match with circulating viruses, although a moderate match was reported during the 2022–2023 season.

EFFECTIVENESS END POINTS

The influenza circulation threshold was reached in all three seasons, which allowed for analysis

Table 2. Primary and Secondary End Points and Relative Vaccine Effectiveness.*

End Point	High-Dose Vaccine (N = 166,218) no. of participants (%)	Standard-Dose Vaccine (N = 166,220) no. of participants (%)	Relative Vaccine Effectiveness† %	P Value‡
Primary end point				
Hospitalization for influenza or pneumonia	1,138 (0.68)	1,210 (0.73)	5.9 (–2.1 to 13.4)	0.14
Secondary end points				
Hospitalization for cardiorespiratory disease	3,735 (2.25)	3,962 (2.38)	5.7 (1.4 to 9.9)	
Hospitalization for any cause	15,585 (9.38)	15,921 (9.58)	2.1 (–0.1 to 4.3)	
Death from any cause	1,116 (0.67)	1,089 (0.66)	–2.5 (–11.6 to 5.9)	
Hospitalization for influenza§	101 (0.06)	179 (0.11)	43.6 (27.5 to 56.3)	
Hospitalization for pneumonia	1,045 (0.63)	1,050 (0.63)	0.5 (–8.6 to 8.8)	
Exploratory end point				
Hospitalization for laboratory-confirmed influenza¶	177 (0.11)	276 (0.17)	35.9 (22.2 to 47.3)	

* End-point events that occurred from 14 days after vaccination through May 31 of the following year were eligible for analysis. Only first events were considered for each end point. End points were ascertained with the use of data from nationwide administrative health registries; the primary and secondary hospitalization end points were assessed according to the *International Classification of Diseases, 10th Revision* (ICD-10), diagnosis codes (see the Supplementary Appendix).

† The relative vaccine effectiveness was calculated as 1 minus the relative risk of the outcome and is shown as a percentage.

‡ P values are reported only for end points formally tested in the hierarchical testing procedure. P values were estimated with the use of binomial tests; 95.2% confidence intervals are reported to account for alpha spent at interim analyses.

§ The end point of hospitalization for influenza required an ICD-10 code for influenza but did not require a positive influenza test.

¶ Hospitalization for laboratory-confirmed influenza required a positive influenza test from 14 days before through 3 days after hospital admission but did not require a specific ICD-10 code.

of the full dataset. Hospitalization for influenza or pneumonia (the primary end point) occurred in 1138 of 166,218 participants (0.68%) in the high-dose group and in 1210 of 166,220 participants (0.73%) in the standard-dose group (relative vaccine effectiveness, 5.9%; 95.2% CI, –2.1 to 13.4; $P=0.14$) (Table 2). Results for the primary and secondary end points according to season are shown in Table S10. Hospitalization for cardiorespiratory disease (secondary end point) occurred in 3735 participants (2.25%) in the high-dose group and in 3962 participants (2.38%) in the standard-dose group (relative vaccine effectiveness, 5.7%; 95.2% CI, 1.4 to 9.9). Hospitalization for influenza, the first component of the primary end point, occurred in 101 participants (0.06%) in the high-dose group and in 179 participants (0.11%) in the standard-dose group (relative vaccine effectiveness, 43.6%; 95.2% CI, 27.5 to 56.3), whereas hospitalization for pneumonia, the

second component of the primary end point, occurred in 1045 participants (0.63%) in the high-dose group and in 1050 participants (0.63%) in the standard-dose group (relative vaccine effectiveness, 0.5%; 95.2% CI, –8.6 to 8.8). Hospitalization for laboratory-confirmed influenza, an exploratory end point, occurred in 177 participants (0.11%) in the high-dose group and in 276 participants (0.17%) in the standard-dose group (relative vaccine effectiveness, 35.9%; 95.2% CI, 22.2 to 47.3).

The results of the analysis conducted in the as-treated population yielded results similar to those of the primary analysis (Table S11), as did the results of sensitivity analyses that accounted for potential correlation in participants enrolled in more than one season, that included events occurring within 14 days after vaccination, and that were adjusted for the season in which vaccination occurred (Tables S12 through S14). The re-

sults for the primary end point were largely consistent across prespecified subgroups (Fig. 2 and Fig. S1).

SAFETY

During the 3-month post-vaccination safety surveillance period, 25,953 serious adverse events (hospitalizations or deaths) were recorded in the safety population. At least one serious adverse event occurred in 9814 participants (5.91%) in the high-dose group and in 9804 participants

(5.91%) in the standard-dose group ($P=0.95$) (Table 3). After blinded review of each serious adverse event, a total of 132 events were deemed to be related to the trial treatment (75 in the high-dose group and 57 in the standard-dose group). Two events categorized as suspected unexpected serious adverse reactions occurred, both in the high-dose group: antisynthetase syndrome developed in one participant 3 days after vaccination, and pericarditis developed in one participant 1 day after vaccination. Both participants had also re-

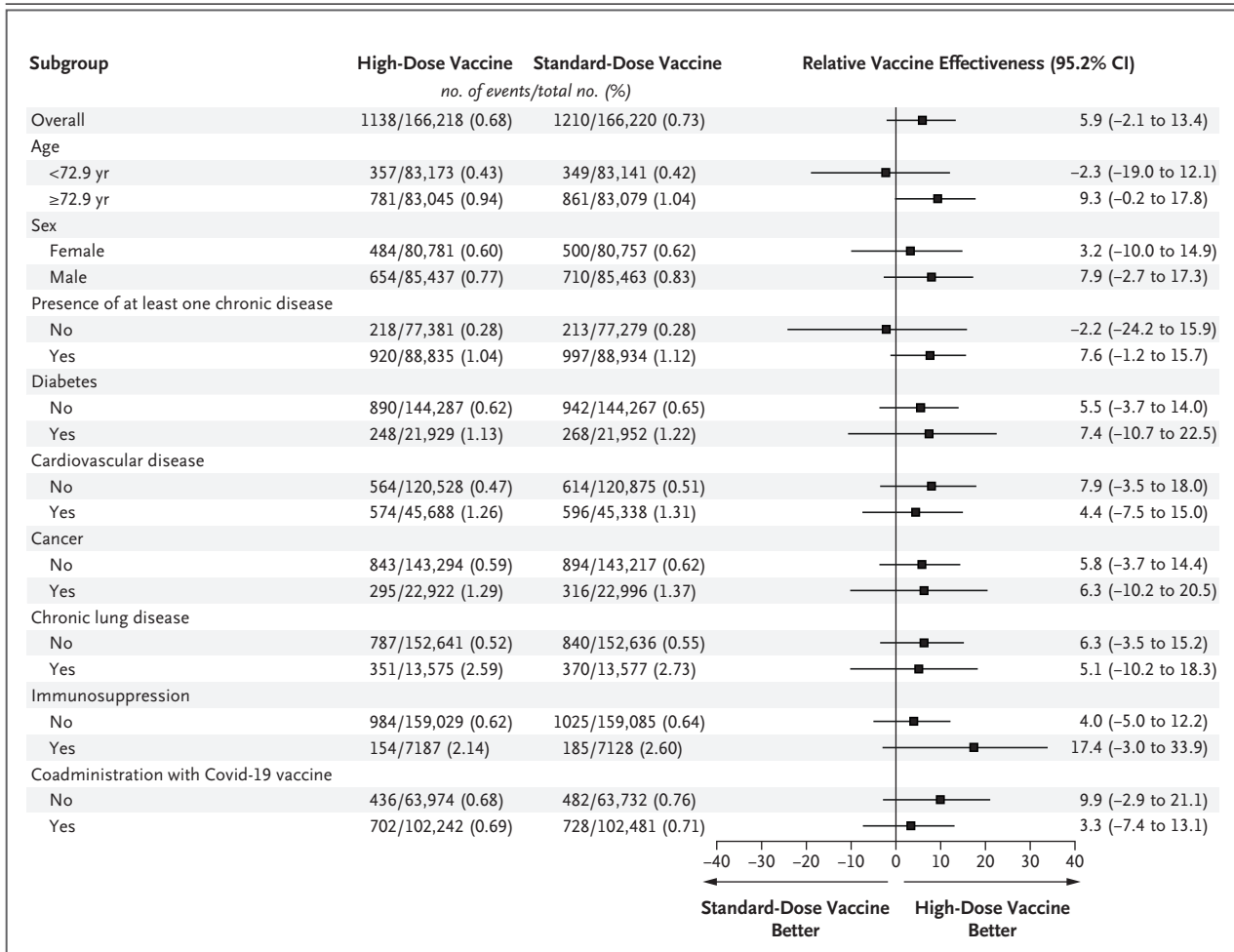


Figure 2. Subgroup Analysis of the Primary End Point.

Shown are the results of a subgroup analysis of the relative vaccine effectiveness of the high-dose vaccine as compared with the standard-dose vaccine in preventing hospitalization for influenza or pneumonia (the primary end point). Subgroups were defined according to prespecified definitions (a list of the definitions and details regarding additional analyses are available in the Supplementary Appendix). Relative vaccine effectiveness was calculated as 1 minus the relative risk and presented as a percentage. The 95.2% confidence intervals are reported to account for alpha spent at interim analyses. The median age of the participants was 72.9 years. Coadministration with the coronavirus disease 2019 (Covid-19) vaccine indicates that the participant received Covid-19 vaccination on the same day as the trial vaccine.

Table 3. Serious Adverse Events within 3 Months after Vaccination.*

Serious Event	High-Dose Vaccine (N = 166,142)	Standard-Dose Vaccine (N = 165,827)	P Value
	no. of participants (%)		
Any	9814 (5.91)	9804 (5.91)	0.95
Considered to be related to trial treatment	73 (<0.1)	57 (<0.1)	0.16
Cardiovascular-related	1747 (1.05)	1755 (1.06)	0.85
Respiratory-related	853 (0.51)	816 (0.49)	0.38
Gastrointestinal-related	996 (0.60)	953 (0.57)	0.35
Infection-related	421 (0.25)	436 (0.26)	0.59
Injury-related	1347 (0.81)	1317 (0.79)	0.59
Death	352 (0.21)	330 (0.20)	0.41

* Safety events were assessed approximately 3 months after vaccination through registry-based screening for hospitalizations and deaths occurring among the participants. Only serious adverse events, defined in this trial as hospitalizations or deaths, were recorded. No other data on adverse events were obtained. Comparisons between groups were performed with Pearson's chi-square test.

ceived the Covid-19 vaccine on the same day as the influenza vaccine. A total of 682 deaths occurred during the safety period; none of the deaths were deemed to be related to the trial treatment.

DISCUSSION

DANFLU-2 was a large trial with adequate statistical power to assess the relative effectiveness of high-dose inactivated influenza vaccine as compared with the standard-dose vaccine against severe clinical outcomes in older adults. The trial had a pragmatic design that leveraged routinely collected health data and digital enrollment solutions to perform individual randomization of 332,438 participants. As a large-scale trial, with a severe condition as the clinical primary end point, in the field of vaccine effectiveness research, in which most evidence has previously been based on observational data, the methods used in this trial provide a blueprint for future evidence generation. Data from DANFLU-2 contributed to a prespecified pooled analysis with the methodologically harmonized GALFLU trial,²⁴ encompassing a total of 466,320 individually randomized older adults. Results from this pooled analysis showed significant reductions in the primary end point of influenza or pneumonia hospitalizations, as well as hierarchically tested cardiorespiratory hospitalizations, laboratory-confirmed

influenza hospitalizations, and hospitalizations from any cause.²⁵ In line with previous literature, these data support the clinical benefit of the high-dose vaccine over the standard-dose vaccine against severe outcomes.

This trial did not provide evidence of significant effectiveness of the high-dose vaccine as compared with the standard dose against hospitalization for influenza or pneumonia (the primary end point). Considering this nonsignificant finding, we conducted no hypothesis testing for the secondary end points, and, therefore, no conclusions can be drawn. However, the observed differences between the high-dose and standard-dose groups in the incidence of ICD-10-coded influenza hospitalizations (0.06% vs. 0.11%; relative vaccine effectiveness, 43.6%; 95.2% CI, 27.5 to 56.3) and laboratory-confirmed influenza (0.11% vs. 0.17%; relative effectiveness, 35.9%; 95.2% CI, 22.2 to 47.3) were in line with previously reported data.^{8,15} The observed difference between the two groups in the incidence of hospitalization for cardiorespiratory disease (2.25% vs. 2.38%; relative vaccine effectiveness, 5.7%; 95.2% CI, 1.4 to 9.9) suggests a possible benefit with the high-dose vaccine over the standard-dose vaccine, a finding that is aligned with and provides further support of previous research.^{8,15} The results in our trial were consistent across three epidemiologically diverse trial seasons, despite vary-

ing circulating strains and peak season timing. The incidence of serious adverse events that were observed during the 3-month post-vaccination safety surveillance period was similar in the two groups.

The fact that the high-dose vaccine did not result in a significantly lower incidence of hospitalization for influenza or pneumonia or the individual component of hospitalization for pneumonia is inconsistent with previous data; in recent meta-analyses of randomized data, the high-dose vaccine was associated with a 23.5% lower incidence of hospitalization for influenza or pneumonia²⁶ and a 27.8% lower incidence of hospitalization for pneumonia than a standard dose.¹⁵ Changes since the Covid-19 pandemic in respiratory testing, coding practices, and disease epidemiology may provide an explanation for this inconsistency. An increase in respiratory testing has improved influenza detection and coding accuracy,²⁷ as evidenced by influenza hospitalization rates that nearly doubled during the trial as compared with prepandemic seasons.¹⁹ Although this would explain some decrease in the number of influenza-related events (and therefore events potentially modifiable by the high-dose vaccine) included in the pneumonia component of the end point, the decrease in the incidence of pneumonia exceeded the increase in influenza events. This finding suggests a potential post-pandemic shift in the etiologic factors of pneumonia but may also reflect temporal or geographic changes in coding practices, increased use of testing that permits more specific nonpneumonia coding of other microorganisms, or both.^{28,29} Unlike previous trials with adjudicated end points, this trial used routine health data coded by practicing physicians, which resulted in the pneumonia end-point component potentially capturing disease processes that differ from those in other trials.

The strengths of the trial include the use of individual-level randomization, which provides a stronger foundation for causal inference than previous analyses of the relative vaccine effectiveness of the high-dose vaccine as compared with the standard-dose vaccine against severe outcomes, which have been based primarily on observational data.¹⁵ The pragmatic trial design enabled individual-level randomization on a large

scale, which allowed for evaluation of severe outcomes beyond infection in a sufficiently powered, randomized trial. Broad eligibility criteria and a low burden of participation increased the representativeness of recruitment and enhanced generalizability of the results. Although we used quadrivalent vaccines exclusively, previous research has shown noninferiority of quadrivalent to trivalent high-dose vaccines,³⁰ which ensures that the results will remain applicable, considering the return to trivalent influenza vaccine formulations worldwide.³¹

Potential limitations include the open-label nature of the trial, which theoretically might have led to differences between the two groups in health care-seeking behavior. However, the risk of bias was considered to be low because the end points were severe clinical outcomes that are unlikely to be influenced by knowledge of the group assignment, the investigators were not involved in clinical treatment of participants, and the end-point data were obtained passively through administrative databases. The use of routine health data may have introduced imprecision in the trial data, but this would not be expected to be distributed differentially between the groups. Testing for influenza as part of the trial was performed in only a subgroup of approximately 12,000 participants¹⁰ (results not reported here); however, linkage to national testing data obtained from routine practice reinforced the results for hospitalization for influenza identified on the basis of ICD-10 codes.

In this trial, the high-dose vaccine did not result in a significantly lower incidence of hospitalization for influenza or pneumonia (the composite primary end point) among adults 65 of age or older than the standard-dose vaccine. Although no definitive conclusions can be drawn regarding the secondary end points, the results are consistent with possible benefits of the high-dose vaccine over the standard-dose vaccine for prevention of hospitalization for influenza and cardiorespiratory disease.

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