ORIGINAL ARTICLE

Recombinant or Standard-Dose Influenza Vaccine in Adults under 65 Years of Age

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ABSTRACT

BACKGROUND

Quadrivalent recombinant influenza vaccines contain three times the amount of hemagglutinin protein as standard-dose egg-based vaccines, and the recombinant formulation is not susceptible to antigenic drift during manufacturing. Data are needed on the relative effectiveness of recombinant vaccines as compared with standard-dose vaccines against influenza-related outcomes in adults under the age of 65 years.

METHODS

In this cluster-randomized observational study, Kaiser Permanente Northern California facilities routinely administered either a high-dose recombinant influenza vaccine (Flublok Quadrivalent) or one of two standard-dose influenza vaccines during the 2018–2019 and 2019–2020 influenza seasons to adults 50 to 64 years of age (primary age group) and 18 to 49 years of age. Each facility alternated weekly between the two vaccine formulations. The primary outcome was influenza (A or B) confirmed by polymerase-chain-reaction (PCR) testing. Secondary outcomes included influenza A, influenza B, and influenza-related hospitalization outcomes. We used Cox regression analysis to estimate the hazard ratio of the recombinant vaccine as compared with the standard-dose vaccines against each outcome. We calculated the relative vaccine effectiveness as 1 minus the hazard ratio.

RESULTS

The study population included 1,630,328 vaccinees between the ages of 18 and 64 years (632,962 in the recombinant-vaccine group and 997,366 in the standard-dose group). During this study period, 1386 cases of PCR-confirmed influenza were diagnosed in the recombinant-vaccine group and 2435 cases in the standard-dose group. Among the participants who were 50 to 64 years of age, 559 participants (2.00 cases per 1000) tested positive for influenza in the recombinant-vaccine group as compared with 925 participants (2.34 cases per 1000) in the standard-dose group (relative vaccine effectiveness, 15.3%; 95% confidence interval [CI], 5.9 to 23.8; P=0.002). In the same age group, the relative vaccine effectiveness against influenza A was 15.7% (95% CI, 6.0 to 24.5; P=0.002). The recombinant vaccine was not significantly more protective against influenza-related hospitalization than were the standard-dose vaccines.

CONCLUSIONS

The high-dose recombinant vaccine conferred more protection against PCR-confirmed influenza than an egg-based standard-dose vaccine among adults between the ages of 50 and 64 years. (Funded by Sanofi; ClinicalTrials.gov number, NCT03694392.)

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Every year in the United States, influenza causes mild-to-severe illness in a wide range of persons (9 million to 41 million).[1] Influenza vaccination is the primary method for preventing influenza-related illnesses,[2] although the vaccine effectiveness ranges from 20% in years in which the vaccine is antigenically mismatched to the circulating viral strain to 40 to 60% in years in which the vaccine is antigenically well matched.[2,3] This large variation in effectiveness between years suggests that more effective vaccines are needed.

In traditional quadrivalent standard-dose inactivated influenza vaccines (SD-IIV4), chicken eggs are used to manufacture the influenza virus. Mutations in the hemagglutinin protein during egg-based manufacturing can result in mismatch between the selected strain and the vaccine strain.[4] The Flublok Quadrivalent influenza vaccine (RIV4, Sanofi) is manufactured without chicken eggs, resulting in a recombinant hemagglutinin protein that is genetically identical to that in the selected strain.[5] The vaccine also contains three times the amount of hemagglutinin protein as standard-dose vaccines, an increased level that has been correlated with increased protective hemagglutinin antibodies.[6]

To estimate the relative effectiveness of the recombinant vaccine as compared with standard-dose vaccines against laboratory-confirmed influenza and influenza-related outcomes, we compared the two formulations of vaccines among members of the Kaiser Permanente Northern California (KPNC) health care system who were between 18 and 64 years of age during the two influenza seasons of 2018–2019 and 2019–2020.

METHODS

STUDY POPULATION AND OVERSIGHT

KPNC is an integrated health care delivery system with 4.6 million members, nearly 65% of whom are adults between the ages of 18 and 64 years. Members receive nearly all their care at system-owned facilities, which includes 259 medical clinics and 21 hospitals. The members' electronic medical records capture all medical services, including inpatient and outpatient diagnoses, laboratory tests, and vaccinations. The KPNC members include approximately a third of the population in Northern California and broadly represent adults in California regarding racial, ethnic, and socioeconomic characteristics, although the proportions of Hispanic, Asian, and multiracial residents are higher than those in other U.S. regions (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[7] Approximately 10% of the members are covered by Medicaid.[8] The KPNC institutional review board approved the study with a waiver of informed consent.

Representatives of the study sponsor, Sanofi, did not have a role in the design or conduct of the study or in the analyses of the data. The Flublok Quadrivalent influenza vaccine was donated by Sanofi, and the two standard-dose vaccines used during the study seasons were purchased by KPNC. The first author wrote the first draft of the manuscript. The authors vouch for the accuracy and completeness of the data presented and for the fidelity of the study to the protocol (available at NEJM.org).

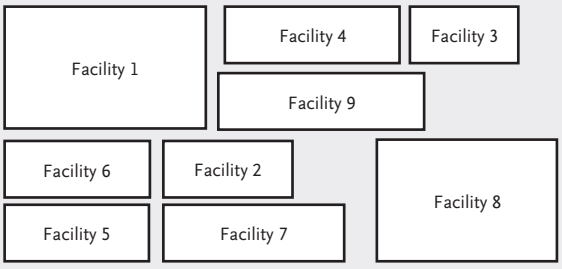
STUDY DESIGN

This was a cluster-randomized observational study that was designed to include all KPNC members between the ages of 18 and 64 years who had received a licensed recombinant or standard-dose vaccine as part of routine clinical care during the three influenza seasons from 2018 to 2021.[9] The 2019–2020 season was truncated in March 2020 because of the outbreak of the coronavirus disease 2019 pandemic; data from the 2020–2021 season were subsequently excluded from the analyses because there were too few cases of influenza during the pandemic to be informative. During the study period, influenza vaccination coverage was similar to national coverage (Table S1). The study excluded unvaccinated patients.

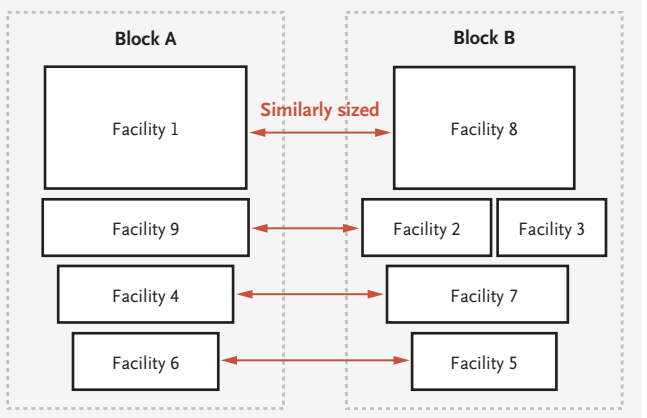
The KPNC system includes seven geographic regions, each containing 8 to 12 medical facilities. In each region, the facilities were assigned to either Block A or Block B to optimize the balance between blocks with respect to facility size (Fig. 1). We randomly assigned Block A to start with administration of a standard-dose vaccine and Block B to start with administration of the recombinant vaccine. Thereafter, each facility alternated the administration of the two vaccines weekly.

Key features of the study design were that

1. A KPNC service area contains facilities of various sizes.



2. KPNC facilities of similar size within a service area area were randomly assigned to Block A or Block B.



3. After Block A and Block B were assigned to SD-IIV4 or RIV4 for the first week of the influenza vaccination season, every facility alternated formulations weekly until the end of the season. For illustrative purposes, only 4 weeks of the schedule are shown.

Facilities within a service area	Week 1	Week 2	Week 3	Week 4
Facility 1: Block A	SD-IIV4	RIV4	SD-IIV4	RIV4
Facility 2: Block B	RIV4	SD-IIV4	RIV4	SD-IIV4
Facility 3: Block B	RIV4	SD-IIV4	RIV4	SD-IIV4
Facility 4: Block A	SD-IIV4	RIV4	SD-IIV4	RIV4
Facility 5: Block B	RIV4	SD-IIV4	RIV4	SD-IIV4
Facility 6: Block A	SD-IIV4	RIV4	SD-IIV4	RIV4
Facility 7: Block B	RIV4	SD-IIV4	RIV4	SD-IIV4
Facility 8: Block B	RIV4	SD-IIV4	RIV4	SD-IIV4
Facility 9: Block A	SD-IIV4	RIV4	SD-IIV4	RIV4

Figure 1. Study Cluster Randomization, According to Service Area and Facility Size.

The size of each facility in the Kaiser Permanente Northern California (KPNC) health care system refers to the number of influenza vaccines that were administered during the 2017–2018 influenza season immediately preceding the current study period. RIV4 denotes quadrivalent recombinant influenza vaccine, and SD-IIV4 quadrivalent standard-dose inactivated influenza vaccines.

formulations alternated in weekly intervals of time and that during each weekly interval, approximately half the facilities administered the recombinant vaccine while the other half administered a standard-dose vaccine. The format of having alternating formulations each week at each facility was intended to emulate a randomized trial in which the vaccine formulations would be randomly assigned within each facility. This design was intended to achieve balance between the two vaccine groups, which would have similar distribution with respect to observed and unobserved risk factors at every facility and in the overall study population during

the weeks when influenza was circulating. Patients were unaware of which vaccine was available at any facility. During the study period, the facilities administered primarily high-dose vaccines to adults who were 65 years of age or older, which made it infeasible to include those members in the study randomization.

OUTCOMES

The primary outcome was influenza as confirmed by polymerase-chain-reaction (PCR) testing (Cepheid GeneXpert PCR assay, a test that also identifies respiratory syncytial virus [RSV]). Physicians at each facility ordered influenza PCR tests at their discretion on the basis of clinical presentation; rapid influenza antigen testing was not performed.

Secondary outcomes were PCR-confirmed influenza A, PCR-confirmed influenza B, and hospitalization for PCR-confirmed influenza, for community-acquired pneumonia, and for cardiorespiratory events including community-acquired pneumonia. We identified community-acquired pneumonia and other cardiorespiratory events using primary discharge diagnosis codes as listed in the *International Classification of Diseases, 10th Revision* (ICD-10) (Table S2).

Exploratory outcomes were an influenza diagnosis (PCR-confirmed or clinically diagnosed influenza on the basis of ICD-10 codes), nonelective hospitalization for any cause, and death from any cause. For each outcome except death from any cause, we counted only the first event during each season that occurred more than 14 days after vaccination. All deaths after vaccination within the study period were considered to be a safety outcome and were counted even if they had occurred within 14 days after vaccination.

OBJECTIVES

The primary objective was to estimate the relative vaccine effectiveness of the recombinant vaccine as compared with a standard-dose vaccine against PCR-confirmed influenza in patients between the ages of 50 and 64 years, the primary age group (Table S3). The secondary objectives were to estimate the relative vaccine effectiveness of the recombinant vaccine against secondary outcomes in patients in the primary age group and against secondary outcomes in five prespecified subgroups of patients with preexisting conditions (cardiovascular disease, respiratory disease, cardiorespiratory disease, obesity, and diabetes) in the primary age group. Other estimates of relative vaccine effectiveness were considered to be exploratory.

STATISTICAL ANALYSIS

We tested the null hypotheses that the recombinant vaccine would not be any more or any less effective than a standard-dose vaccine against influenza, using a two-sided test with a P value of less than 0.05 indicating statistical significance. We estimated that the administration of 400,000 doses each of the two vaccine formulations to patients between the ages of 18 and 64 years each influenza season would provide the study with 86% power to detect a relative vaccine effectiveness of 10.0% against PCR-confirmed influenza. On the basis of previous data, we estimated the occurrence of 2.18 PCR-confirmed influenza cases per 1000 participants in the standard-dose group.

We used Cox regression analysis to estimate the adjusted hazard ratio and 95% confidence intervals for the recombinant vaccine as compared with a standard-dose vaccine for each outcome. The model specified a calendar time scale and included adjustments for sex, race or ethnic group, and age and an age-squared factor (in case age and risk had either a linear or curvilinear association). Risk sets were formed on each date on which at least one outcome event occurred in either study group. Each risk set contained every participant in follow-up on that calendar date. Most of the participants had been vaccinated before the beginning of the influenza season and were included in every risk set throughout the season.

The Cox model also used stabilized weights that were based on propensity scores. The statistical analysis plan prespecified the use of propensity scores if imbalances were found in any study variables. We observed modest imbalances at some facilities in one or both seasons, although not overall (Tables S4 and S5). Thus, we created propensity scores that were specific for each facility and season. The propensity scores were derived by logistic regression to estimate the probability of the receipt of a recombinant vaccine rather than a standard-dose vaccine with respect to sex, race, age, coexisting illnesses,

indicators of health care–seeking behavior (e.g., previous influenza vaccination), 2-month intervals of calendar time, and other factors. Missing data were not imputed.

The relative vaccine effectiveness was based on the hazard ratio (1 minus the hazard ratio, expressed as a percentage). This calculation estimated the percent reduction in the incidence of the outcome in the recombinant-vaccine group as compared with that in the standard-dose group. The proportional-hazards assumption of the Cox regression was evaluated, and no violation was found (Fig. S1).

For secondary objectives in participants between the ages of 50 and 64 years, we adjusted for multiplicity by Holm's method.[10] Subgroup analyses involving participants with preexisting conditions were not adjusted for multiplicity. We conducted sensitivity analyses in which we used propensity scores in alternative ways, used a robust variance estimator, stratified risk sets according to facility and vaccination week, and specified age as a spline (see the Supplementary Methods section).

To assess possible residual confounding, we examined PCR-confirmed RSV infection as a negative control outcome because we would not expect influenza vaccination to be associated with a reduction in this infection. A nontrivial association between receipt of the recombinant vaccine and RSV infection would suggest bias in our estimate of the relative vaccine effectiveness against influenza. Conversely, a finding of no association between receipt of the recombinant vaccine and RSV infection would be reassuring that our estimates of relative vaccine effectiveness were not biased by unmeasured factors that might affect the risk of both laboratory-confirmed RSV infection and influenza. All data analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

STUDY PARTICIPANTS

The study population included 1,630,328 participants during influenza seasons in 2018–2019 and 2019–2020. Of these participants, 632,962 (38.8%) received the recombinant vaccine and 997,366 (61.2%) received a standard-dose vaccine (Fig. 2 and Table S6). In both seasons, delays in shipments of the recombinant vaccine occasionally left some clinics temporarily without enough recombinant vaccine to comply with the weekly schedule, so standard-dose vaccines were then administered to prevent interruptions in patient care.

Among the 675,252 patients between 50 and 64 years of age, 279,400 (41.4%) received the recombinant vaccine and 395,852 (58.6%) received a standard-dose vaccine (Table 1). Among the 955,076 patients between 18 and 49 years of age, 353,562 (37.0%) received the recombinant vaccine and 601,514 (63.0%) received a standard-dose vaccine (Table S6).

Of the 16,340 influenza PCR tests performed in the study population, 3821 (23.4%) were influenza positive. Of the PCR-confirmed influenza cases, 1484 (38.8%) were diagnosed in patients between the ages of 50 and 64 years and 2337 (61.2%) in patients between the ages of 18 and 49 years. Among the participants with PCR-confirmed influenza, hospitalization occurred in 248 of 1484 participants (16.7%) among those between the ages of 50 and 64 years and in 136 of 2337 (5.8%) of those between the ages of 18 and 49 years.

The demographic characteristics of the participants at baseline were similar in the two vaccine groups and in the two age groups (Table 1 and Table S6). There was some variation in the timing of the administration of the two vaccines according to geographic region, although during the two influenza seasons, most vaccinations in the two groups had occurred by mid-to-late November (Tables S4 and S5).

PRIMARY AND SECONDARY ANALYSES

In patients between the ages of 50 and 64 years, 559 (2.00 cases per 1000) tested positive for influenza in the recombinant-vaccine group as compared with 925 (2.34 per 1000) in the standard-dose group (Table 2). For the primary objective, the relative vaccine effectiveness of the recombinant vaccine as compared with standard-dose vaccines against all PCR-confirmed influenza was 15.3% (95% CI, 5.9 to 23.8; P=0.002).

The estimate of relative vaccine effectiveness for the secondary objective of PCR-confirmed influenza A was 15.7% (95% CI, 6.0 to 24.5; P=0.002; the P value was below Holm's multiplicity-adjusted threshold of an alpha level of

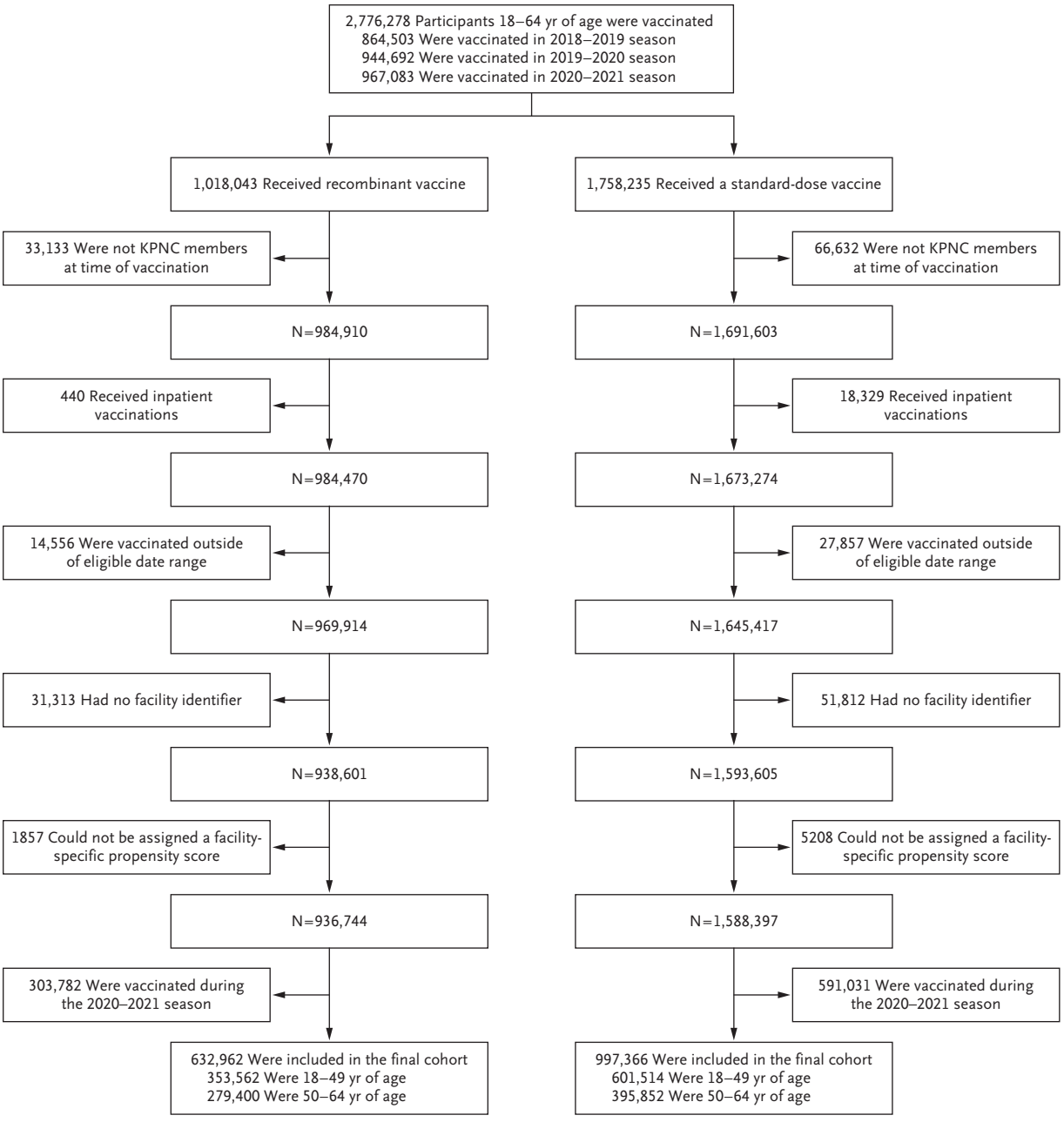


Figure 2. Vaccinated Adults in the Study Population (2018–2021).

Shown is the final cohort of study participants between 18 and 64 years of age after the application of exclusion criteria. Patients who were vaccinated as inpatients were excluded from the study because such influenza vaccinations could not be included in the randomization. The eligible date ranges for influenza vaccinations were September 17, 2018, to April 21, 2019; September 3, 2019, to February 25, 2020; and August 31, 2020, to April 8, 2021. In some cases, data were excluded from the analyses because records did not indicate the location of the facility where the vaccine had been administered. Propensity scores were derived by logistic regression to estimate the probability of the receipt of a recombinant vaccine rather than a standard-dose vaccine with respect to sex, race, age, coexisting illnesses, indicators of health care–seeking behavior, 2-month intervals of calendar time, and other factors. Some patients were vaccinated at facilities where the data were too sparse to generate a facility-specific propensity score. Data for the third influenza season (2020–2021) were not included in the study because of virtually no circulation of influenza virus during the first year of the coronavirus disease 2019 pandemic.

Table 1. Characteristics of the Participants at Baseline (50 to 64 Years of Age).*

Characteristic	Recombinant Vaccine (N = 279,400)	Standard-Dose Vaccine (N = 395,852)	All Vaccinees (N = 675,252)
		no. of participants (%)	
Sex — no. (%)			
Male	124,540 (45)	175,600 (44)	300,140 (44)
Female	154,860 (55)	220,252 (56)	375,112 (56)
Race or ethnic group — no. (%)†			
White	142,757 (51)	198,434 (50)	341,191 (51)
Black	13,693 (5)	20,814 (5)	34,507 (5)
Asian	58,416 (21)	84,154 (21)	142,570 (21)
Pacific Islander	1,686 (1)	2,363 (1)	4,049 (1)
Native American	1,268 (<1)	1,836 (<1)	3,104 (<1)
Multiracial	7,299 (3)	10,908 (3)	18,207 (3)
Unknown or other	54,281 (19)	77,343 (20)	131,624 (19)
Hispanic ethnic group — no. (%)†			
Yes	46,318 (17)	65,868 (17)	112,186 (17)
No or unknown	233,082 (83)	329,984 (83)	563,066 (83)
Coexisting illness — no. (%)			
Asthma	39,909 (14)	56,398 (14)	96,307 (14)
Diabetes	49,506 (18)	69,924 (18)	119,430 (18)
Chronic obstructive pulmonary disease	5,628 (2)	7,729 (2)	13,357 (2)
Coronary heart disease	10,613 (4)	14,883 (4)	25,496 (4)
Receipt of influenza vaccine in previous year			
Yes	207,236 (74)	290,370 (73)	497,606 (74)
No	72,164 (26)	105,482 (27)	177,646 (26)

* Additional details regarding the demographic and clinical characteristics of the participants in this age group, for those in the younger age group (18 to 49 years), and for the entire study population (18 to 64 years of age) are provided in Table S6 in the Supplementary Appendix.
† Race or ethnic group was reported by the participants.

0.01) (Table 2). For outcomes involving hospitalization, the recombinant vaccine was not significantly more effective than the standard-dose vaccines, although the point estimate was 15.9% for hospitalization for PCR-confirmed influenza and 16.7% for hospitalization for community-acquired pneumonia (Table 2). Post hoc analysis of these two hospitalization outcomes combined yielded an estimate for relative vaccine effectiveness of 19.7% (95% CI, 2.8 to 33.7).

SUBGROUP AND EXPLORATORY ANALYSES

In subgroup analyses among participants in the older age group (50 to 64 years) with any of the five prespecified preexisting conditions, the only measure of relative vaccine effectiveness that significantly differed from zero was against PCR-confirmed influenza B in the subgroup with respiratory conditions (relative vaccine effectiveness, 78.2%; 95% CI, 3.1 to 95.1) (Table S7). In post hoc analyses among participants in the same age subgroup with any of the prespecified preexisting conditions, measures of relative vaccine effectiveness were 14.3% (95% CI, 2.4 to 24.8) for PCR-confirmed influenza and 14.9% (95% CI, 2.6 to 25.7) for influenza A infection (Fig. 3 and Table S7).

Among participants in the younger age group (18 to 49 years), 827 (2.34 cases per 1000) tested positive for influenza in the recombinant-vac-

Table 2. Primary and Secondary Outcomes and Relative Vaccine Effectiveness among Participants 50 to 64 Years of Age.*

Outcome	Recombinant Vaccine (N=279,400)	Standard-Dose Vaccine (N=395,852)	Unadjusted Rate Ratio	Adjusted Hazard Ratio (95% CI)†	Relative Vaccine Effectiveness (95% CI)	P Value‡
	no. of cases per 1000				%	
Primary outcome						
PCR-confirmed influenza	559 (2.00)	925 (2.34)	0.86	0.85 (0.76 to 0.94)	15.3 (5.9 to 23.8)	0.002
Secondary outcomes						
PCR-confirmed influenza A	522 (1.87)	862 (2.18)	0.86	0.84 (0.76 to 0.94)	15.7 (6.0 to 24.5)	0.002
PCR-confirmed influenza B	37 (0.13)	64 (0.16)	0.82	0.90 (0.60 to 1.34)	10.3 (–33.9 to 39.9)	0.59
Hospitalization for PCR-confirmed influenza	95 (0.34)	153 (0.39)	0.88	0.84 (0.65 to 1.09)	15.9 (–9.2 to 35.2)	0.19
Hospitalization for community-acquired pneumonia	106 (0.38)	183 (0.46)	0.82	0.83 (0.66 to 1.06)	16.7 (–5.6 to 34.4)	0.13
Hospitalization for cardiorespiratory event	631 (2.26)	890 (2.25)	1.004	0.98 (0.88 to 1.08)	2.4 (–8.1 to 11.9)	0.64

* PCR denotes polymerase chain reaction.
† Models were adjusted for age, age squared, sex, and race or ethnic group after weighting with stabilized facility-specific propensity scores. In post hoc sensitivity analyses, models were further adjusted for potential clustering according to facility and yielded results similar to those listed here. Details are provided in Table S13.
‡ Adjustment for multiplicity for the secondary outcomes was performed with the use of Holm's adjustment method. The P values that were obtained for the five secondary outcomes were rank-ordered and compared with corresponding adjusted nominal alpha values of 0.01, 0.0125, 0.0167, 0.025, and 0.05.

cine group as compared with 1510 participants (2.51 cases per 1000) in the standard-dose group (Table S8). For three exploratory objectives in this age group, the relative vaccine effectiveness was 10.2% (95% CI, 1.4 to 18.2) against influenza A, 10.8% (95% CI, 6.6 to 14.7) against diagnosed influenza, and 19.5% (95% CI, 5.4 to 31.5) against influenza A in the subgroup with obesity (Tables S7 and S8).

In the younger age group, the only exploratory objective for which the relative vaccine effectiveness was significantly below zero was death from any cause (–45.5; 95% CI, –100.2 to –5.8) (Table S8). During the two influenza seasons, there were 145 deaths: 66 in the recombinant-vaccine group and 79 in the standard-dose group; most of these deaths occurred at least 61 days after vaccination. The most common causes of death in both study groups were cancer, accidents, homicide, suicide, and cardiovascular events (Table S9). Causes of death as assessed by chart review were not considered by the investigators to be related to either influenza or influenza vaccination.

Single-season estimates of relative vaccine effectiveness were generally consistent with the combined two-season estimates (Tables S10 and S11). For the outcome of PCR-confirmed influenza among patients in the older age group, relative vaccine effectiveness was 14.4% (95% CI, –1.1 to 27.5) during 2018–2019 and 16.1% (95% CI, 3.7 to 26.9) during 2019–2020.

For both the PCR-confirmed influenza and hospitalization outcomes, the results of sensitivity analyses were consistent with findings in the primary analyses (Tables S12 and S13). The estimates of relative vaccine effectiveness from the RSV-negative control analyses did not differ from zero (Table S14).

DISCUSSION

In this real-world study, we evaluated the effectiveness of a high-dose recombinant vaccine as compared with an egg-based standard-dose vaccine among more than 1.6 million adults during two influenza seasons. In our analysis of the primary outcome in older patients between 50 and 64 years of age, the incidence of PCR-confirmed influenza was 15.3% lower among those who received the recombinant vaccine than among those who received a standard-dose vaccine, a finding that rejected the null hypothesis. The evidence that the recombinant vaccine con-

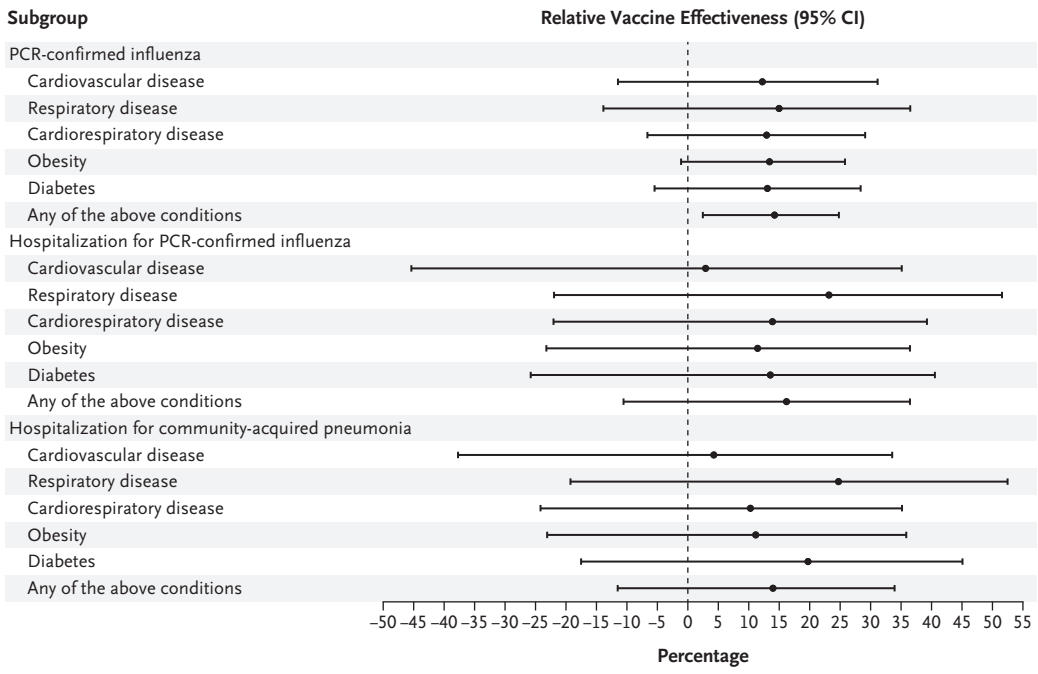


Figure 3. Subgroup Analysis of Relative Vaccine Effectiveness against Influenza among Participants between 50 and 64 Years of Age, According to Preexisting Conditions.

Shown is a forest plot of the relative effectiveness of the recombinant vaccine as compared with a standard-dose vaccine against influenza as confirmed by polymerase-chain-reaction (PCR) assay, hospitalization for PCR-confirmed influenza, and hospitalization for community-acquired pneumonia among study participants in the older age group, according to the presence of five prespecified preexisting conditions.

ferred more protection against influenza than standard-dose vaccines was strengthened by our cluster-randomized study design.

In secondary analyses involving the same older age group, the incidence of PCR-confirmed influenza A was 15.7% lower in the recombinant-vaccine group than in the standard-dose group (P=0.002). Our analyses of the three additional secondary outcomes in this age group suggested that the recombinant vaccine may confer more protection than standard-dose vaccines against hospitalization outcomes. Although these findings were not significant, a post hoc analysis combining hospitalization for PCR-confirmed influenza and hospitalization for community-acquired pneumonia yielded a relative vaccine effectiveness of 19.7% (95% CI, 2.8 to 33.7).

The 12 exploratory analyses yielded somewhat inconsistent results. For influenza diagnoses overall (including unconfirmed diagnoses) among patients between the ages of 18 and 49 years, the incidence was lower in the recombinant-vaccine group than in the standard-dose group (relative vaccine effectiveness, 10.8%; 95% CI, 6.6 to 14.7). For PCR-confirmed influenza A, the incidence was similarly lower in the recombinant-vaccine group (relative vaccine effectiveness, 10.2; 95% CI, 1.4 to 18.2). For 5 of the other 10 exploratory analyses (2 of which were performed in participants between 50 and 64 years of age), the estimated relative vaccine effectiveness was in the range of 1 to 10% with 95% confidence intervals overlapping 0%. The remaining 5 exploratory analyses (1 of which was performed in participants between 50 and 64 years of age) yielded negative estimates for relative vaccine effectiveness, including the analysis of death from any cause among participants between 18 and 49 years of age (relative vaccine effectiveness, −45.5; 95% CI, −100.2 to −5.8). Chart reviews of all 145 deaths in this age group did not suggest that the recombinant vaccine caused any deaths or that standard-dose vaccines prevented more deaths than the recombinant

vaccine. Mortality in both groups of vaccinees was substantially lower than population-wide mortality at KPNC and nationwide in a similar age group.[11,12]

If standard-dose vaccines were already preventing most cases of influenza and breakthrough cases were uncommon, preventing 15% of breakthrough cases would be of modest public health benefit. However, since standard-dose vaccines prevent at most 40 to 60% of influenza cases annually,[13] reducing the incidence of breakthrough influenza by 15% would provide a substantial public health benefit, especially during more severe influenza seasons.

Several studies have shown benefit for the recombinant vaccine and other high-dose influenza vaccines as compared with standard-dose vaccines in adults who are 65 years of age or older, findings that have been attributed to an improved immune response.[5,14-17] In the current study, we compared the effectiveness of the high-dose recombinant vaccine with that of standard-dose vaccines in patients between the ages of 18 and 64 years. The effectiveness of standard-dose vaccines — especially against the influenza A H3N2 subtype — may be attenuated by antigenic drift during egg-based manufacturing, whereas the recombinant vaccine is not susceptible to such drift. However, data from the California Department of Public Health showed that the H3N2 strain circulated only during the second half of the 2018–2019 season,[18] and even then, the circulating strain had drifted such that it was poorly matched to both the recombinant vaccine and the standard-dose vaccines.[19,20] During our study period, the observed benefit of the recombinant vaccine as compared with a standard-dose vaccine seems less likely due to higher relative vaccine effectiveness against H3N2 than to higher effectiveness against influenza A overall associated with its higher dose of hemagglutinin antigen.

A strength of our study is that the two study vaccine formulations were alternated in weekly intervals of time at each facility, which allowed us to balance covariates of interest as designed. In every KPNC geographic area, when influenza arrived, there were already participants who had received one of the two formulations of vaccine and who were similar with respect to demographic characteristics, coexisting illnesses, health care–seeking behavior, and the number of weeks since vaccination. To our knowledge, this design has not been previously used, and its handling of potential confounding bias has not been formally studied. Our intent was to minimize imbalances between the participants who received each vaccine, both within and between facilities. We also included several sensitivity analyses to address potential biases from clustering according to facility. Sensitivity analyses that were stratified either according to facility (to compare within facilities) or according to week (to compare between facilities) showed a relative vaccine effectiveness of approximately 15%, similar to the findings of our primary analysis.

Our study also has several limitations. First, in our real-world setting, compliance with the weekly assigned vaccine schedule occasionally varied because of logistic constraints, including supply-chain issues for the recombinant vaccine, which led to different numbers of participants in the two groups. Second, our data were limited to two influenza seasons; relative vaccine effectiveness may vary across seasons, depending on the vaccine match with circulating strains. Third, our primary outcome did not include infections in persons who did not undergo PCR testing, which limits its generalizability. Fourth, the study had limited power to detect a clinically meaningful benefit of the recombinant vaccine as compared with a standard-dose vaccine with respect to less frequent outcomes, such as hospitalization for PCR-confirmed influenza. Finally, although KPNC has a diverse population, it may not be representative of other populations in the United States.

In this study performed during two influenza seasons, participants between the ages of 50 and 64 years who received the recombinant vaccine had more protection against confirmed influenza than those who received a standard-dose vaccine.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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