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MAJOR ARTICLE

Effectiveness of Messenger RNA-1273 Vaccine Booster Against Coronavirus Disease 2019 (COVID-19) in Immunocompetent Adults

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Background. We conducted a prospective cohort study at Kaiser Permanente Southern California to evaluate the relative vaccine effectiveness (rVE) of a booster dose vs 2-dose primary series of messenger RNA (mRNA)-1273 in immunocompetent individuals.

Methods. Immunocompetent adults who received a booster dose of mRNA-1273 from October 2021 through December 2021 were matched 1:1 to randomly selected 2-dose mRNA-1273 recipients by age, sex, race/ethnicity, and second-dose date and followed up through January 2022. Cox proportional hazards models were used to estimate adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs), comparing outcomes (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] infection and coronavirus disease 2019 [COVID-19] hospitalization and hospital death) in the booster-dose and 2-dose groups. Adjusted rVE (%) was calculated as $(1 - \text{aHR}) \times 100$. aHRs and rVE were also estimated by subgroup and month of follow-up.

Results. The study included 431 328 booster-dose vaccinated adults matched to 431 328 2-dose vaccinated adults. rVE was 61.3% (95% CI: 60.5%–62.2%) against SARS-CoV-2 infection, 89.0% (86.2%–91.2%) against COVID-19 hospitalization, and 96.0% (68.0%–99.5%) against COVID-19 hospital death. rVE against SARS-CoV-2 infection ranged from 55.6% to 66.7% across all subgroups. rVE against SARS-CoV-2 infection decreased from 67.1% (0 to <1 month of follow-up) to 30.5% (2 to <3 months). For COVID-19 hospitalization, rVE decreased from 91.2% (0 to <1 month) to 78.7% (2 to <3 months).

Conclusions. Among immunocompetent adults, the mRNA-1273 booster conferred additional protection against SARS-CoV-2 infection and severe COVID-19 disease compared with the 2-dose mRNA-1273 primary series during periods of Delta and Omicron predominance.

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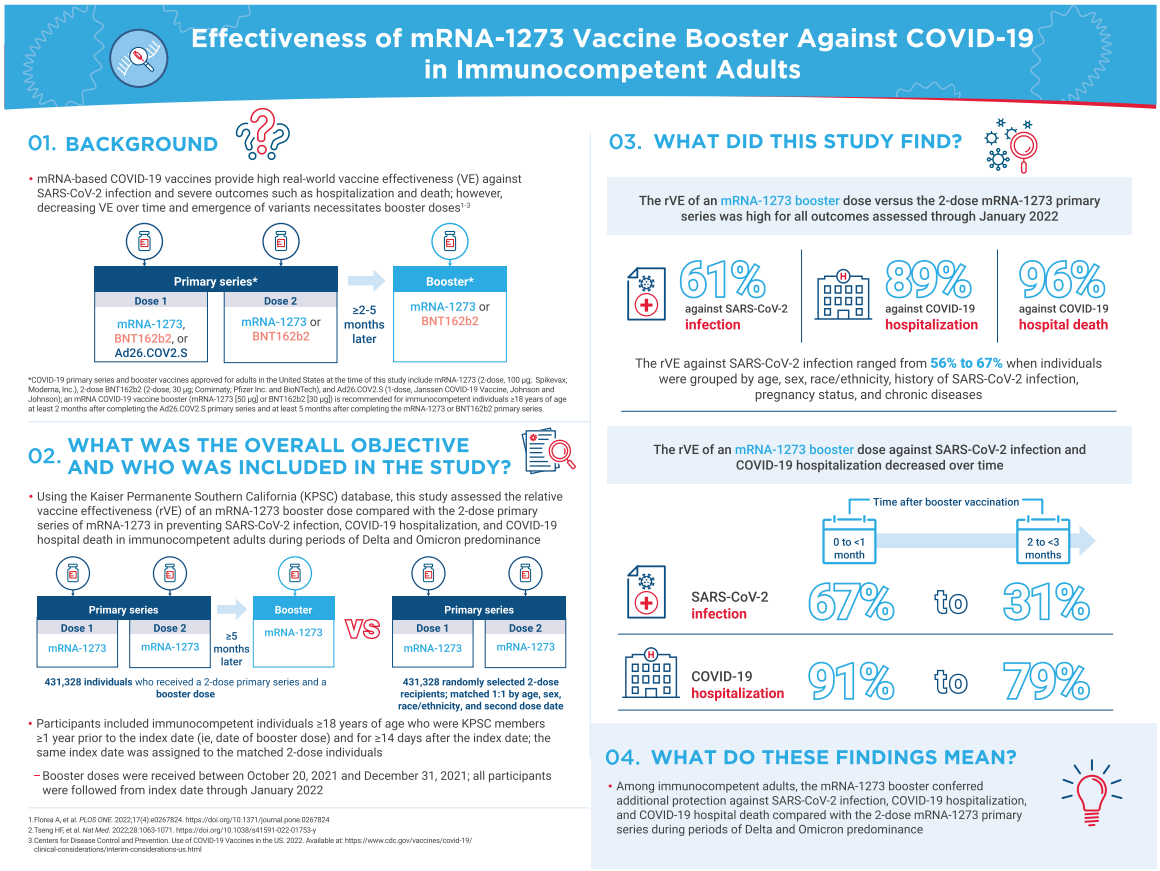
Graphical Abstract



Keywords. COVID-19; immunocompetent; mRNA-1273; booster; vaccine effectiveness.

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to more than 85 million infections and more than 1 million deaths in the United States [1]. To mitigate the spread of SARS-CoV-2 and reduce the global burden of COVID-19, several vaccines were rapidly developed and deployed. Among the COVID-19 vaccines authorized for use in the United States, messenger RNA (mRNA)-1273 (COVID-19 vaccine, SPIKEVAX; Moderna, Inc, Cambridge, MA) is a 2-dose primary series (100 µg/dose) initially authorized for individuals aged ≥18 years [2, 3]. Since the rollout of COVID-19 vaccines, real-world studies have shown the mRNA-based vaccines to have high vaccine effectiveness (VE) against SARS-CoV-2 infection and severe outcomes in adults, including COVID-19 hospitalization and death [4, 5]. However, emerging evidence suggests that the protection afforded by vaccination may decrease over time [6–9] due to both declining vaccine-induced immunity and lower VE against SARS-CoV-2 variants including Delta and Omicron [5, 7, 10–13]. Consequently, health agencies, such as the US Food and Drug Administration, have authorized the expansion of existing COVID-19 vaccination regimens to include booster doses for continued protection against COVID-19 [14–17].

Currently, for immunocompetent individuals aged ≥18 years, a first 50-µg booster mRNA COVID-19 dose (50 µg mRNA-1273 or 30 µg BNT162b2 [Comirnaty; Pfizer Inc, New York, NY and BioNTech Manufacturing GmbH, Mainz, Germany]) is recommended ≥5 months after completing the 2-dose mRNA primary series [18, 19]. Real-world studies have shown that booster doses of mRNA COVID-19 vaccines after a 2-dose mRNA primary series reduced the risk of SARS-CoV-2 infection and associated severe outcomes [11, 20–26]. More specifically, immunocompetent adults who received a 3-dose homologous or heterologous vaccination with mRNA-1273 or BNT162b2 were less likely to experience symptomatic SARS-CoV-2 infection compared with unvaccinated individuals and those who received a 2-dose primary mRNA series only [27], and VE against COVID-19 hospitalization increased post-mRNA booster [21]. The high VE of

mRNA vaccine boosters also extends to circulating variants [28]. These results have been replicated in our earlier studies in this population, where mRNA-1273 VE against infection and hospitalization during the Omicron period was higher among those who received 3 doses vs a 2-dose mRNA-1273 primary series [11].

Nevertheless, large observational studies assessing VE of the mRNA-1273 booster dose in individuals who received a homologous 2-dose mRNA-1273 primary series are currently lacking, as much of the available evidence combines both mRNA COVID-19 vaccines as the exposure and does not evaluate the relative VE (rVE) stratified by chronic condition, pregnancy status, or prior history of SARS-CoV-2 infection. Therefore, in this study, among immunocompetent adults, we assessed the rVE of the mRNA-1273 booster dose against SARS-CoV-2 infection and severe COVID-19 disease compared with the 2-dose mRNA-1273 primary series.

METHODS

Study Setting

Kaiser Permanente Southern California (KPSC) is an integrated healthcare system that serves a diverse population of more than 4.6 million members [29]. KPSC's comprehensive electronic health record (EHR) captures details of care received across inpatient, outpatient, emergency, and virtual care settings; claims also capture care received outside of the KPSC system. The KPSC Institutional Review Board reviewed and approved the study with waivers of informed consent and written Health Insurance Portability and Accountability Act authorization.

Study Objectives

This was a planned interim analysis of a 5-year cohort study at KPSC to evaluate the VE of mRNA-1273 in preventing SARS-CoV-2 infection and severe COVID-19 disease [5, 30]. The primary objective was to assess the rVE of a booster dose vs the 2-dose primary series of mRNA-1273 in preventing SARS-CoV-2 infection and severe COVID-19 disease in immunocompetent adults. Secondary objectives included assessing rVE of a booster dose of mRNA-1273 in preventing SARS-CoV-2 infection by age, sex, race/ethnicity, history of SARS-CoV-2 infection, pregnancy status, and chronic disease subgroups as well as assessing rVE of a booster dose of mRNA-1273 in preventing SARS-CoV-2 infection and severe COVID-19 disease by month of follow-up.

Study Population

For the study cohort, the index date was defined as the date of receipt of the booster dose of mRNA-1273 for the booster-dose individuals; their matched 2-dose vaccinated counterparts were assigned the same index date. Eligible individuals were immunocompetent and aged ≥18 years at index date and were KPSC members for ≥1 year prior to the index date (allowing a 31-day membership gap) and for ≥14 days after the index date. Individuals were considered immunocompetent if they did not have a documented history of immunocompromising conditions (human immunodeficiency virus, leukemia/lymphoma, congenital and other immunodeficiencies, asplenia/hyposplenia, hematopoietic stem cell/solid organ transplant, receipt of immunosuppressive medications) as of the index date. Individuals who received a COVID-19 vaccine other than mRNA-1273 on or before the index date and individuals who died, had a COVID-19 outcome, or received any COVID-19 vaccine <14 days after the index date were excluded.

The booster-dose mRNA-1273 vaccinated group was composed of immunocompetent adults who received a booster dose (ie, third dose received ≥150 days after completion of their initial 2-dose mRNA-1273 primary series) from 20 October 2021 (when the booster dose of mRNA-1273 was authorized) through 31 December 2021. The 2-dose mRNA-1273 vaccinated group was composed of immunocompetent adults who completed their mRNA-1273 primary series by the index date. These comparators were randomly selected and matched 1:1 to the booster-dose vaccinated individuals by age group (18–44 years, 45–64 years, 65–74 years, and ≥75 years), sex, race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, non-Hispanic Asian, and other/unknown), and date of the second dose. Index dates were also balanced through matching since matched booster-dose and 2-dose vaccinated individuals shared the same index date.

Exposures and Outcomes

Information on the mRNA-1273 exposure was ascertained from KPSC's EHR. The EHR included vaccines administered within KPSC as well as COVID-19 vaccines imported daily into the KPSC EHR from the California Immunization Registry (CAIR), Care Everywhere (Epic EHR feature that allows healthcare systems to exchange medical information), claims (eg, pharmacies), and member self-report with documentation. All providers of COVID-19 vaccines were required by law to provide COVID-19 vaccine administration data daily to CAIR [31].

The first primary outcome was SARS-CoV-2 infection, defined as a positive molecular test or a COVID-19 diagnosis code for both symptomatic and asymptomatic infections. SARS-CoV-2 infections with a COVID-19 diagnosis code or a SARS-CoV-2–positive molecular test in the 90 days prior were not considered incident cases. The second primary outcome was severe COVID-19 disease, which included COVID-19 hospitalization (hospitalization with a SARS-CoV-2–positive test or a COVID-19 diagnosis code, or a hospitalization ≤7 days after a SARS-CoV-2–positive test)

and COVID-19 hospital death (death that occurred during COVID-19 hospitalization). COVID-19 hospitalization was confirmed by at least 1 documented, oxygen saturation, SpO_2, level < 90% during hospital stay for all patients *and* a labor and delivery stay >2 days for pregnant patients, or by chart review, as needed; manual chart review was completed by a physician investigator (B. K. A.) and trained chart abstractors to verify the presence of severe COVID-19 symptoms.

Individuals were followed for COVID-19 outcomes ≥14 days after the index date through 31 January 2022 (end of follow-up) or until occurrence of a censoring event (termination of KPSC membership allowing for a 31-day gap, death, or receipt of a COVID-19 vaccine). The 2-dose vaccinated individuals stopped contributing 2-dose vaccinated person-time if they received a booster dose of mRNA-1273 during follow-up and started contributing booster-dose person-time 14 days after they received an eligible booster dose of mRNA-1273.

Other Variables

Prespecified potential confounders were identified a priori based on the literature. Baseline characteristics were extracted from the EHR. Variables assessed at index date included age, sex, race/ethnicity, socioeconomic status (Medicaid coverage, neighborhood median household income), medical center area, pregnancy status, and KPSC physician/employee status. Variables assessed in the year prior to the index date included Charlson comorbidity score, frailty index [32], chronic diseases (kidney disease, heart disease, lung disease, liver disease, diabetes), autoimmune conditions (rheumatoid arthritis, inflammatory bowel disease, psoriasis and psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus), healthcare utilization (virtual, outpatient, emergency department, inpatient encounters), and preventive care (other vaccinations, screenings, well visits). Variables assessed in the 2 years prior to index date included body mass index (BMI) and smoking. Other variables included history of SARS-CoV-2 infection and molecular test performed from 1 March 2020 to index date (irrespective of result) and receipt of concomitant vaccine with the booster dose.

Statistical Analyses

Baseline characteristics of the booster-dose and 2-dose vaccinated groups were described. Continuous variables were compared using the 2-sample *t* test or Wilcoxon rank sum test, as appropriate, and categorical variables were compared using the χ^2 test or Fisher exact test, as appropriate. To assess the balance of covariates across groups, absolute standardized differences (ASDs) were used. Covariates with ASD >0.1, as well as age, sex, race/ethnicity, month of index date, and time between second dose and index date, were included in the multivariable models. The missing indicator method was used for covariates with missing data [33].

Incidence rates (IRs) per 1000 person-years of SARS-CoV-2 infection, COVID-19 hospitalization, and COVID-19 hospital death for both booster-dose and 2-dose vaccinated groups were calculated by dividing the number of incident events by person-years. Cumulative incidences of SARS-CoV-2 infection, COVID-19 hospitalization, and COVID-19 hospital death for both groups were estimated through Kaplan–Meier curves and compared using the log-rank test.

Unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) comparing SARS-CoV-2 infection, COVID-19 hospitalization, and COVID-19 hospital death in the booster-dose and 2-dose vaccinated groups overall were estimated using Cox proportional hazards regression models. rVE (%) was calculated as $(1 - \text{HR}) \times 100$. rVE (%) can be considered to be 1 − ratio of HRs ($\text{HR}_{3\text{-dose}}/\text{HR}_{2\text{-dose}}$), while $\text{VE}_{3\text{-dose}} = 1 - \text{HR}_{3\text{-dose}}$ and $\text{VE}_{2\text{-dose}} = 1 - \text{HR}_{2\text{-dose}}$ using the unvaccinated as the referent group. HRs and rVE were also estimated comparing SARS-CoV-2 infection in booster-dose and 2-dose vaccinated individuals by age, sex, race/ethnicity, history of SARS-CoV-2 infection, pregnancy status, and chronic diseases. rVE against SARS-CoV-2 infection, COVID-19 hospitalization, and COVID-19 hospital death was also estimated by month of follow-up (0 to <1, 1 to <2, and 2 to <3 months) using time-varying Cox regression models. All analyses were conducted using SAS software version 9.4 (Cary, NC).

RESULTS

Baseline Characteristics

The study cohort consisted of 431 328 booster-dose vaccinated individuals and 431 328 matched 2-dose vaccinated individuals (Figure 1). Overall, 61.4% of individuals were aged 18–64 years (median, 59); there were more females than males (55.1%), and 37.1% were non-Hispanic White, 33.2% were Hispanic, 15.6% were non-Hispanic Asian, and 7.6% were non-Hispanic Black (Table 1). The proportions of booster-dose and 2-dose groups were similar (ASD ≤0.1) in terms of BMI, smoking, Charlson comorbidity score, frailty index, chronic diseases, autoimmune conditions, pregnancy status, history of SARS-CoV-2 infection and molecular test, emergency department visits, hospitalizations, Medicaid enrollment, median household income, and KPSC physician/employee status. Compared with the 2-dose group, the booster-dose group had more outpatient and virtual visits and more preventive care visits in the year prior to the index date (ASD >0.1). Among the booster-dose individuals, 52.5% received their booster dose 150 to <240 days after their second dose, with 44.5% receiving the booster in November 2021 and 41.8% in December 2021.

rVE Against SARS-CoV-2 Infection, COVID-19 Hospitalization, and COVID-19 Hospital Death

There were 17 591 cases of SARS-CoV-2 infection in the booster-dose group and 19 750 cases in the 2-dose group (Table 2). IRs per 1000 person-years for SARS-CoV-2 infection,

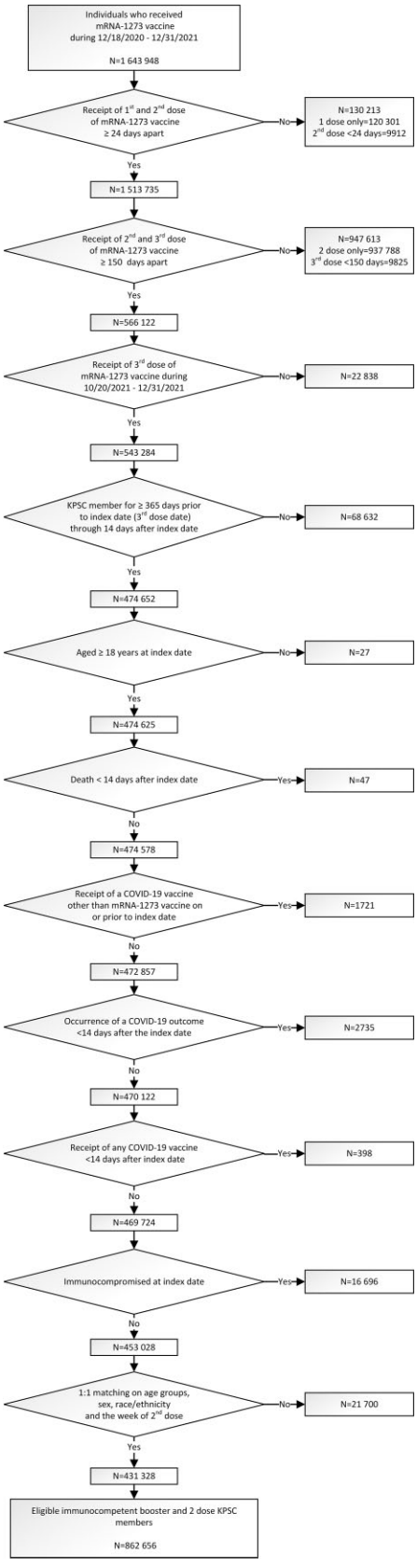


Figure 1. Flowchart for booster-dose and 2-dose messenger RNA-1273 vaccine cohorts. Abbreviations: COVID-19, coronavirus disease 2019; KPSC, Kaiser Permanente Southern California; mRNA, messenger RNA.

Table 1. Baseline Characteristics of Booster-Dose and 2-Dose Messenger RNA-1273 Vaccinated Immunocompetent Cohorts

Characteristic	Booster-Dose Vaccinated N = 431 328	2-Dose Vaccinated N = 431 328	Absolute Standardized Difference
	N (%)		
Age at index date, median (interquartile range), y	60 (45–70)	59 (45–70)	0.03
Age at index date, y			N/A
18–44	106 353 (24.7)	106 353 (24.7)	…
45–64	158 315 (36.7)	158 315 (36.7)	…
65–74	98 132 (22.8)	98 132 (22.8)	…
≥75	68 528 (15.9)	68 528 (15.9)	…
Sex			N/A
Female	237 784 (55.1)	237 784 (55.1)	…
Male	193 544 (44.9)	193 544 (44.9)	…
Race/Ethnicity			N/A
Non-Hispanic White	160 182 (37.1)	160 182 (37.1)	…
Non-Hispanic Black	32 911 (7.6)	32 911 (7.6)	…
Hispanic	143 085 (33.2)	143 085 (33.2)	…
Non-Hispanic Asian	67 190 (15.6)	67 190 (15.6)	…
Other/unknown	27 960 (6.5)	27 960 (6.5)	…
Body mass index,[a] kg/m^2			0.09
<18.5	4787 (1.1)	4887 (1.1)	…
18.5 to <25	101 387 (23.5)	97 705 (22.7)	…
25 to <30	132 089 (30.6)	128 120 (29.7)	…
30 to <35	82 367 (19.1)	80 975 (18.8)	…
35 to <40	38 631 (9.0)	36 770 (8.5)	…
40 to <45	16 222 (3.8)	15 339 (3.6)	…
≥45	10 146 (2.4)	9724 (2.3)	…
Unknown	45 699 (10.6)	57 808 (13.4)	…
Smoking[a]			0.09
No	315 447 (73.1)	304 716 (70.6)	…
Yes	81 898 (19.0)	81 383 (18.9)	…
Unknown	33 983 (7.9)	45 229 (10.5)	…
Charlson comorbidity score[b]			0.05
0	260 075 (60.3)	270 499 (62.7)	…
1	73 724 (17.1)	67 838 (15.7)	…
≥2	97 529 (22.6)	92 991 (21.6)	…
Frailty index[b]			0.06
Quartile 1	94 601 (21.9)	92 173 (21.4)	…
Quartile 2	116 087 (26.9)	128 496 (29.8)	…
Quartile 3	110 463 (25.6)	105 194 (24.4)	…
Quartile 4, most frail	110 177 (25.5)	105 465 (24.5)	…
Chronic diseases[b]			
Kidney disease	35 298 (8.2)	34 619 (8.0)	0.01
Heart disease	18 554 (4.3)	19 546 (4.5)	0.01
Lung disease	43 447 (10.1)	40 308 (9.3)	0.02
Liver disease	15 417 (3.6)	14 252 (3.3)	0.01
Diabetes	85 967 (19.9)	80 984 (18.8)	0.03
Autoimmune conditions[b]	11 674 (2.7)	10 964 (2.5)	0.01
Rheumatoid arthritis	4049 (0.9)	4055 (0.9)	…
Inflammatory bowel disease	2104 (0.5)	1883 (0.4)	…
Psoriasis and psoriatic arthritis	5052 (1.2)	4595 (1.1)	…
Multiple sclerosis	707 (0.2)	651 (0.2)	…
Systemic lupus erythematosus	723 (0.2)	643 (0.1)	…

Table 1. Continued

Characteristic	Booster-Dose Vaccinated N = 431 328	2-Dose Vaccinated N = 431 328	Absolute Standardized Difference
	N (%)		
Pregnancy status	2305 (0.5)	2546 (0.6)	0.01
First trimester	560 (0.1)	707 (0.2)	…
Second trimester	864 (0.2)	1008 (0.2)	…
Third trimester	881 (0.2)	831 (0.2)	…
History of SARS-CoV-2 infection[c]	38 443 (8.9)	44 963 (10.4)	0.05
History of SARS-CoV-2 molecular test[c]	229 444 (53.2)	219 536 (50.9)	0.05
Number of outpatient and virtual visits[b]			0.15
0	15 473 (3.6)	25 554 (5.9)	…
1–4	103 865 (24.1)	118 498 (27.5)	…
5–10	143 858 (33.4)	140 160 (32.5)	…
≥11	168 132 (39.0)	147 116 (34.1)	…
Number of emergency department visits[b]			0.03
0	369 771 (85.7)	365 743 (84.8)	…
1	44 902 (10.4)	46 662 (10.8)	…
≥2	16 655 (3.9)	18 923 (4.4)	…
Number of hospitalizations[b]			0.02
0	413 341 (95.8)	411 904 (95.5)	…
1	14 425 (3.3)	15 059 (3.5)	…
≥2	3562 (0.8)	4365 (1.0)	…
Preventive care[b]	363 352 (84.2)	330 079 (76.5)	0.20
Medicaid	25 106 (5.8)	28 167 (6.5)	0.03
Neighborhood median household income			0.05
<$40 000	17 112 (4.0)	19 029 (4.4)	…
$40 000–$59 999	77 194 (17.9)	81 900 (19.0)	…
$60 000–$79 999	100 337 (23.3)	103 033 (23.9)	…
$80 000+	236 422 (54.8)	227 048 (52.6)	…
Unknown	263 (0.1)	318 (0.1)	…
Kaiser Permanente Southern California physician/ employee	17 333 (4.0)	14 561 (3.4)	0.03
Concomitant vaccination[d]	19 290 (4.5)	N/A	N/A
Time between second dose and index date, d			<0.01
150–<240	226 302 (52.5)	226 402 (52.5)	…
≥240	205 026 (47.5)	204 926 (47.5)	…
Index date			N/A
October 2021	58 767 (13.6)	58 767 (13.6)	…
November 2021	192 139 (44.5)	192 139 (44.5)	…
December 2021	180 422 (41.8)	180 422 (41.8)	…

Medical center area not shown ($P \leq 0.01$ and absolute standardized difference = 0.11). There were differences in the distribution of the booster-dose vaccinated and 2-dose vaccinated individuals across the 19 medical center areas.

Abbreviations: N/A, not applicable; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Defined in the 2 years prior to index date.

[b]Defined in the 1 year prior to index date.

[c]Defined based on all available medical records from 1 March 2020 to index date.

[d]Among patients with concomitant vaccines received with the booster dose: influenza vaccine (90.4%), pneumococcal conjugate vaccine/pneumococcal polysaccharide vaccine (PCV13/PPSV23) (1.9%), tetanus, diphtheria, and pertussis (Tdap) (6.7%), and other vaccine (4.2%).

COVID-19 hospitalization, and COVID-19 hospital death were 279.15 (95% CI: 275.06–283.31), 1.67 (1.38–2.02), and 0.02 (.00–.11), respectively, among the booster-dose group and 701.84 (692.12–711.69), 11.76 (10.58–13.07), and 0.34

Table 2. Incidence Rate, Hazard Ratio, and Relative Vaccine Effectiveness of Booster Dose of Messenger RNA-1273 Vaccine in Preventing Severe Acute Respiratory Syndrome Coronavirus 2 Infection, Coronavirus Disease 2019 (COVID-19) Hospitalization, and COVID-19 Hospital Death Among Immunocompetent Individuals

Outcome	Booster-Dose Vaccinated (N = 431 328)		2-Dose Vaccinated (N = 431 328)		Hazard Ratio (95% CI)		Relative Vaccine Effectiveness (95% CI)	
	Number of Cases	Incidence Per 1000 Person-Years (95% CI)	Number of Cases	Incidence Per 1000 Person-Years (95% CI)	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Severe acute respiratory syndrome coronavirus 2 infection	17 591	279.15 (275.06–283.31)	19 750	701.84 (692.12–711.69)	0.37 (.37–.38)	0.39 (.38–.40)	62.6 (61.8–63.4)	61.3 (60.5–62.2)
COVID-19 hospitalization	107	1.67 (1.38–2.02)	345	11.76 (10.58–13.07)	0.11 (.09–.14)	0.11 (.09–.14)[b]	88.5 (85.7–90.8)	89.0 (86.2–91.2)[b]
COVID-19 hospital death	1	0.02 (.00–.11)	10	0.34 (.18–.63)	0.05 (.01–.36)	0.04 (.01–.32)[c]	95.4 (64.2–99.4)	96.0 (68.0–99.5)[c]

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019.

[a]Adjusted for covariates age, sex, race/ethnicity, index date (in months), time between second dose and index date, number of outpatient and virtual visits, preventive care, and medical center area.

[b]Adjusted for covariates age, sex, race/ethnicity, index date (in months), time between second dose and index date, number of outpatient and virtual visits, and preventive care.

[c]Adjusted for covariates age, sex, time between second dose and index date, and number of outpatient and virtual visits.

(.18–.63), respectively, among the 2-dose group. The cumulative incidences of SARS-CoV-2 infection, COVID-19 hospitalization, and COVID-19 hospital death were all significantly higher in the 2-dose group than in the booster-dose group (log-rank test $P < .02$; Figure 2*A*–*C*). The adjusted rVE (Table 2) was 61.3% (95% CI: 60.5%–62.2%) against SARS-CoV-2 infection, 89.0% (86.2%–91.2%) against COVID-19 hospitalization, and 96.0% (68.0%–99.5%) against COVID-19 hospital death.

rVE Against SARS-CoV-2 Infection by Subgroups

Among the booster-dose and 2-dose groups, the IR of SARS-CoV-2 infection was higher in those aged <65 years than in those aged ≥65 years, in females than in males, and among Hispanic individuals than among other racial/ethnic groups (Table 3). Pregnant women also had an elevated IR of SARS-CoV-2 infection in both the booster-dose (647.21 [561.84–745.54]) and 2-dose (1795.54 [1607.53–2005.54]) groups. Among the chronic disease subgroups, those with liver disease had the highest IR of SARS-CoV-2 infection in both the booster-dose (321.16 [299.00–344.95]) and 2-dose (788.75 [732.20–849.67]) groups.

Across all subgroups, the adjusted rVE against SARS-CoV-2 infection ranged from 55.6% to 66.7%. Within the age subgroup, those aged ≥75 years had the highest adjusted rVE of 66.7% (63.9%–69.3%). Adjusted rVE against SARS-CoV-2 infection in females and in males was 61.7% (60.6%–62.8%) and 60.6% (59.3%–61.9%), respectively. Within the race/ethnicity subgroups, adjusted rVE was highest in non-Hispanic Whites (65.7% [64.3%–67.1%]). Adjusted rVE for those with no history of SARS-CoV-2 infection was 62.1% (61.2%–63.0%); for pregnant women, the adjusted rVE was 63.0% (55.3%–69.3%); and among chronic diseases, those with heart disease had the highest adjusted point estimate of rVE of 66.3% (62.0%–70.0%).

rVE Against SARS-CoV-2 Infection, COVID-19 Hospitalization, and COVID-19 Hospital Death by Month of Follow-up

Adjusted rVE against SARS-CoV-2 infection decreased from 67.1% at 0 to <1 month to 30.5% at 2 to <3 months (Table 4). Adjusted rVE against COVID-19 hospitalization also decreased from 91.2% at 0 to <1 month to 78.7% at 2 to <3 months. Adjusted rVE against COVID-19 hospital death was 93.1% at 0 to <1 month.

DISCUSSION

In this large cohort study, we examined the real-world effectiveness of a homologous booster dose of mRNA-1273 compared with the 2-dose mRNA-1273 primary series in immunocompetent adults. The immunocompetent individuals

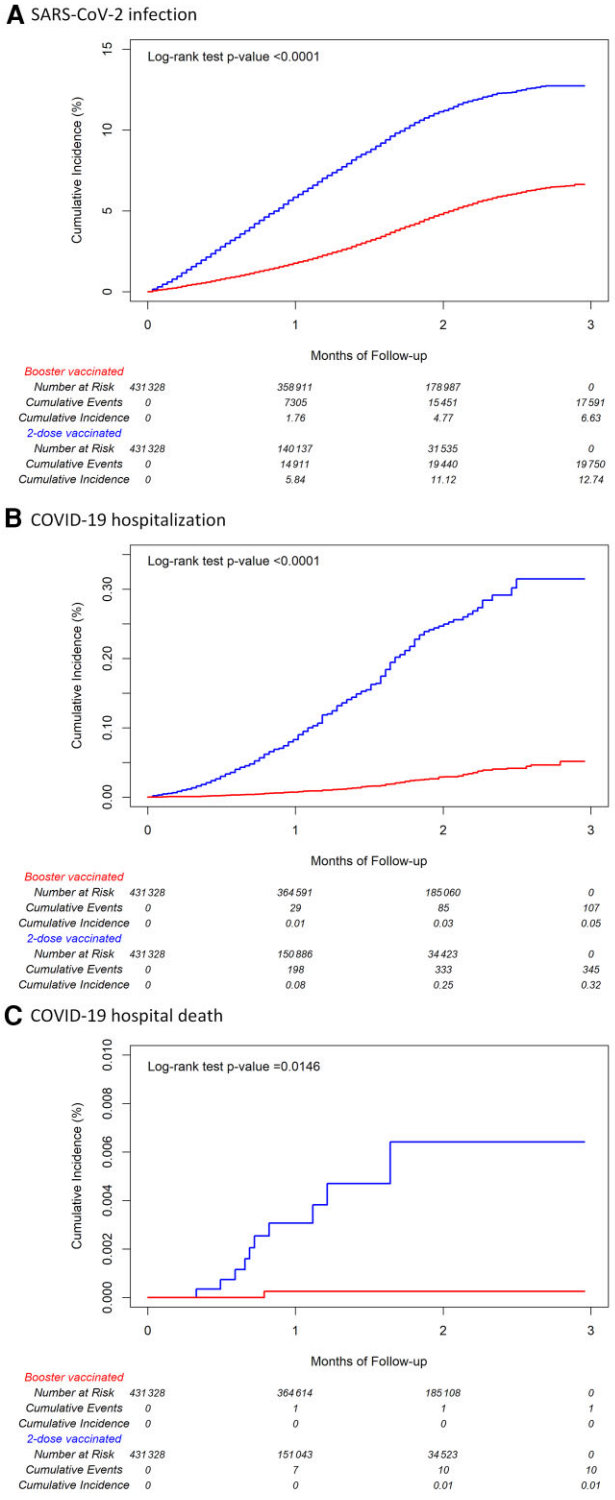


Figure 2. Cumulative incidence estimates of SARS-CoV-2 infection, COVID-19 hospitalization, and COVID-19 hospital death in booster-dose and 2-dose messenger RNA-1273 immunocompetent vaccine cohorts. *A,* SARS-CoV-2 infection. *B,* COVID-19 hospitalization. *C,* COVID-19 hospital death. Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 3. Incidence Rate, Hazard Ratio, and Relative Vaccine Effectiveness of Booster Dose of Messenger RNA-1273 Vaccine in Preventing Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection Among an Immunocompetent Population by Age, Sex, Race/Ethnicity, History of SARS-CoV-2 Infection, Pregnancy Status, and Chronic Disease Subgroups

	Booster-Dose Vaccinated (N = 431 328)		2-Dose Vaccinated (N = 431 328)		Hazard Ratio (95% CI)		Relative Vaccine Effectiveness (95% CI)	
Characteristics	Number of Cases	Incidence Per 1000 Person-Years (95% CI)	Number of Cases	Incidence Per 1000 Person-Years (95% CI)	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Age at index date, y								
18–44	6238	474.67 (463.04–486.60)	7828	1100.95 (1076.83–1125.61)	0.41 (.40–.43)	0.41 (.40–.43)	58.8 (57.4–60.2)	58.9 (57.4–60.3)
45–64	6862	325.98 (318.36–333.79)	8204	860.01 (841.60–878.82)	0.35 (.34–.36)	0.36 (.35–.37)	65.1 (64.0–66.3)	64.1 (62.8–65.3)
65–74	3025	179.74 (173.45–186.26)	2336	338.17 (324.73–352.16)	0.43 (.41–.46)	0.44 (.42–.47)	56.5 (54.1–58.9)	55.6 (52.9–58.1)
≥75	1466	122.23 (116.13–128.65)	1382	301.56 (286.07–317.89)	0.32 (.30–.35)	0.33 (.31–.36)	67.9 (65.3–70.2)	66.7 (63.9–69.3)
Sex								
Female	10 183	291.93 (286.31–297.65)	11 525	745.83 (732.34–759.57)	0.37 (.36–.38)	0.38 (.37–.39)	63.1 (62.1–64.1)	61.7 (60.6–62.8)
Male	7408	263.32 (257.39–269.38)	8225	648.26 (634.40–662.42)	0.38 (.37–.39)	0.39 (.38–.41)	62.0 (60.7–63.2)	60.6 (59.3–61.9)
Race/ethnicity								
Non-Hispanic White	4704	191.37 (185.98–196.92)	5683	533.41 (519.72–547.46)	0.34 (.32–.35)	0.34 (.33–.36)	66.4 (65.1–67.7)	65.7 (64.3–67.1)
Non-Hispanic Black	1209	251.04 (237.28–265.60)	1403	734.99 (697.52–774.47)	0.32 (.30–.35)	0.35 (.32–.38)	67.7 (65.0–70.2)	65.1 (62.1–67.9)
Hispanic	7891	399.49 (390.78–408.41)	8889	949.97 (930.43–969.93)	0.39 (.38–.40)	0.41 (.39–.42)	61.3 (60.1–62.5)	59.4 (58.0–60.7)
Non-Hispanic Asian	2708	270.25 (260.26–280.63)	2543	608.34 (585.15–632.45)	0.41 (.39–.44)	0.42 (.40–.45)	58.8 (56.4–61.0)	57.5 (55.0–59.9)
History of severe acute respiratory syndrome coronavirus 2 infection								
No	16 193	279.71 (275.44–284.05)	17 888	712.01 (701.65–722.52)	0.37 (.36–.38)	0.38 (.37–.39)	63.1 (62.2–63.9)	62.1 (61.2–63.0)
Yes	1398	272.86 (258.93–287.55)	1862	617.12 (589.72–645.80)	0.41 (.38–.44)	0.42 (.39–.46)	58.7 (55.6–61.5)	57.7 (54.5–60.7)
Pregnant								
Yes	192	647.21 (561.84–745.54)	314	1795.54 (1607.53–2005.54)	0.34 (.28–.41)	0.37 (.31–.45)	66.3 (59.5–72.0)	63.0 (55.3–69.3)
Chronic diseases								
Kidney disease	1049	176.88 (166.49–187.91)	985	437.83 (411.32–466.04)	0.33 (.31–.37)	0.35 (.31–.38)	66.6 (63.5–69.5)	65.4 (62.1–68.5)
Heart disease	595	196.20 (181.05–212.62)	667	512.73 (475.26–553.15)	0.33 (.29–.37)	0.34 (.30–.38)	67.3 (63.3–70.8)	66.3 (62.0–70.0)
Lung disease	1873	273.14 (261.05–285.80)	1818	718.52 (686.23–752.31)	0.34 (.31–.36)	0.35 (.33–.38)	66.4 (64.0–68.5)	64.7 (62.2–67.1)
Liver disease	752	321.16 (299.00–344.95)	694	788.75 (732.20–849.67)	0.36 (.33–.40)	0.38 (.34–.43)	63.8 (59.7–67.5)	61.9 (57.5–65.9)
Diabetes	3481	258.26 (249.82–266.98)	3226	636.81 (615.21–659.17)	0.35 (.33–.37)	0.36 (.34–.37)	65.1 (63.3–66.8)	64.4 (62.6–66.2)

Abbreviation: CI, confidence interval.

[a]Adjusted for covariates age, sex, race/ethnicity, index date (in months), time between second dose and index date, number of outpatient and virtual visits, and preventive care.

started receiving their boosters in mid-October 2021 through December 2021 with follow-up through January 2022; Omicron began spreading throughout the United States in late 2021 as one of the more infectious SARS-CoV-2 variants [34]. At KPSC, at the start of our study period (mid-October), Delta was the dominant variant; the proportion attributed to Omicron increased from 1.7% on 1 December 2021 to 99.2% on 31 January 2022, with Omicron surpassing Delta around mid-December [11]. We found that the rVE of the booster dose vs 2 doses tended to increase with disease severity; the rVE was 61.3%, 89.0%, and 96.0% against SARS-CoV-2 infection, COVID-19 hospitalization, and COVID-19 hospital death, respectively. Furthermore, while rVE against SARS-CoV-2 infection decreased from 67.1% to 30.5% in the first 3 months after booster vaccination, rVE against COVID-19 hospitalization remained high at 78.7% up to 3 months after booster vaccination.

The use of COVID-19 vaccine boosters has expanded as more studies have found waning VE of COVID-19 vaccinations over time [5–7, 9] and as newer, more infectious SARS-CoV-2 variants have spread [35]. Our results add to a growing body of evidence evaluating the VE of COVID-19 vaccine boosters. A matched cohort study in Qatar of mRNA-1273 recipients from January 2021 to January 2022 found an rVE of a booster dose vs the 2-dose mRNA-1273 series against symptomatic infection of 47.3% (40.7%–53.3%) [22]. Further, a retrospective cohort study conducted across the Department of Veterans Affairs (VA) healthcare system with booster vaccinations from September 2021 to December 2021 found an rVE against SARS-CoV-2 infection of 27% (24%–30%) when a booster vs 2-dose mRNA-1273 primary series was compared [36]. Conversely, our study results showed a higher rVE against SARS-CoV-2 infection (61.3% [60.5%–62.2%]) during a period when Omicron was on the rise. This may be due to our study population focusing on immunocompetent individuals, whereas the previous studies also included immunocompromised individuals. Similar to our findings, another national study, also among an immunocompetent population reported, during Omicron, found an adjusted odds ratio of 0.31 (or an adjusted rVE of 69%) against SARS-CoV-2 infection when 3 vs 2 doses of mRNA-1273 was compared [27]. Our study also found a high IR of SARS-CoV-2 infection in individuals with liver disease, a subgroup severely impacted by COVID-19 [37]; however, our results still showed an rVE of 61.9% in this subgroup. Last, of the subgroups included in our study, pregnant women had the highest IRs of SARS-CoV-2 infection in both the booster-dose and 2-dose groups with an rVE of 63.0%. The rVE is encouraging as pregnant women are at a 2- to 3-times increased risk of COVID-19–related complications [38, 39] and would thus benefit from an mRNA-1273 booster dose.

mRNA COVID-19 boosters have been shown to have a high VE against severe disease. The study conducted at the VA

Table 4. Incidence Rate, Hazard Ratio, and Relative Vaccine Effectiveness of Booster Dose of Messenger RNA-1273 Vaccine in Preventing Severe Acute Respiratory Syndrome Coronavirus 2 Infection, Coronavirus Disease 2019 (COVID-19) Hospitalization, and COVID-19 Hospital Death Among an Immunocompetent Population by Month of Follow-Up

	Booster-Dose Vaccinated (N = 431 328)		2-Dose Vaccinated (N = 431 328)		Hazard Ratio (95% CI)		Relative Vaccine Effectiveness (95% CI)	
Outcome	Number of Cases	Incidence Per 1000 Person-Years (95% CI)	Number of Cases	Incidence Per 1000 Person-Years (95% CI)	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Severe acute respiratory syndrome coronavirus 2 infection								
0–<1 mo	7305	212.12 (207.31–217.04)	14 911	704.55 (693.33–715.95)	0.29 (.28–.30)	0.33 (.32–.34)	70.7 (69.9–71.5)	67.1 (66.1–68.0)
1–<2 mo	8146	368.84 (360.92–376.94)	4529	731.81 (710.81–753.44)	0.50 (.48–.52)	0.46 (.44–.48)	49.7 (47.9–51.6)	53.8 (52.0–55.6)
2–<3 mo	2140	329.68 (316.00–343.94)	310	393.54 (352.08–439.88)	0.93 (.83–1.05)	0.70 (.61–.79)[b]	6.9 (4.7–17.4)	30.5 (21.3–38.6)[b]
COVID-19 hospitalization								
0–<1 mo	29	0.84 (.58–1.20)	198	9.10 (7.91–10.46)	0.08 (.06–.13)	0.09 (.06–.13)[b]	91.5 (87.5–94.3)	91.2 (86.9–94.0)[b]
1–<2 mo	56	2.48 (1.91–3.22)	135	20.09 (16.97–23.78)	0.12 (.09–.17)	0.11 (.08–.15)[b]	87.8 (83.3–91.1)	89.1 (84.9–92.1)[b]
2–<3 mo	22	3.26 (2.15–4.96)	12	13.98 (7.94–24.61)	0.25 (.12–.50)	0.21 (.10–.45)[b]	75.5 (50.1–88.0)	78.7 (54.5–90.0)[b]
COVID-19 hospital death								
0–<1 mo	1	0.03 (.00–.20)	7	0.32 (.15–.67)	0.08 (.01–.63)	0.07 (.01–.57)[c]	92.3 (37.2–99.1)	93.1 (43.1–99.2)[c]
1–<2 mo	0	NE	3	0.45 (.14–1.38)	NE	NE	NE	NE

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; NE, not estimable.

[a]Adjusted for covariates age, sex, race/ethnicity, index date (in months), time between second dose and index date, number of outpatient and virtual visits, preventive care, and medical center area.

[b]Adjusted for covariates age, sex, race/ethnicity, index date (in months), time between second dose and index date, number of outpatient and virtual visits, and preventive care.

[c]Adjusted for covariates age, sex, time between second dose and index date, and number of outpatient and virtual visits.

found an rVE against COVID-19 hospitalization of 55% (46%–61%) and an rVE against COVID-19 intensive care unit admission and death of 72% (24%–90%) when a booster dose vs 2-dose mRNA-1273 series was compared [36]. Although we also found that rVE increased with COVID-19 severity (rVE of 89.0% and 96.0% for COVID-19 hospitalization and COVID-19 hospital death, respectively), our study's rVEs were higher than in the VA study. This may be due to the fact that the VA study cohort consisted of an older, primarily male population that also included immunocompromised individuals, while our study population was younger, had more females, and excluded immunocompromised individuals. Moreover, a study across 21 hospitals in 18 US states from August 2021 to December 2021 reported an effectiveness of an mRNA vaccine among immunocompetent patients of 82% (2-dose vaccinated vs unvaccinated) and 97% (3-dose vaccinated vs unvaccinated) against COVID-19 hospitalizations [25]. This translates to an unadjusted rVE against COVID-19 hospitalization, in 3-dose vs 2-dose vaccinated, of 87% in immunocompetent patients, similar to the unadjusted rVE against COVID-19 hospitalization found in our study (88.5% [85.7%–90.8%]).

Our study's strengths include KPSC's large, demographically and racially/ethnically diverse member population that allowed us to examine the effectiveness of a homologous booster among immunocompetent individuals only. This allowed for high generalizability to the underlying population. Furthermore, we used KPSC's comprehensive EHR to collect data on variables such as COVID-19 vaccine information, healthcare utilization, and potential demographic and clinical conditions. Nevertheless, residual confounding might still be present. The EHR does not capture health-seeking behaviors such as adequate masking and occupation; these may lead to differences between the booster-dose and 2-dose groups in COVID-19 risk and likelihood of receiving a booster. Nondifferential misclassification of SARS-CoV-2 infection due to inaccurate diagnosis codes from outside claims or due to false-positive or false-negative results may have underestimated the rVE, though we expect this misclassification would be minimal. The rVE estimates should also be interpreted with caution as the booster-dose group was compared against a 2-dose vaccinated group rather than against an unvaccinated group; however, rVE estimation minimized potential confounders and differences between unvaccinated and vaccinated individuals. Last, although our study occurred during the emergence of Omicron, we did not differentiate SARS-CoV-2 variants in our analyses.

Overall, we evaluated the effectiveness of a homologous booster in an mRNA-1273–vaccinated immunocompetent population. We observed that receipt of a booster dose following completion of the 2-dose mRNA-1273 primary series increased protection against both SARS-CoV-2 infection and severe COVID-19 disease. However, as of 29 March 2022, a second mRNA booster dose was recommended in the United States for immunocompetent adults aged ≥50 years, ≥4 months after the first booster dose [18]. Thus, future studies are needed to evaluate the effectiveness of a second booster in this population, as well as to evaluate continued long-term follow-up of a single booster in the immunocompetent population.

Notes

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Data sharing. Individual-level data reported in this study are not publicly shared. Upon request and subject to review, Kaiser Permanente Southern California may provide the deidentified aggregate-level data that support the findings of this study. Deidentified data (including participant data as applicable) may be shared upon approval of an analysis proposal and a signed data access agreement.

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