Effectiveness of mRNA-1273 against SARS-CoV-2 omicron and delta variants

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Abstract

Background

The recently emerged SARS-CoV-2 omicron variant raised concerns around potential escape from vaccine-elicited immunity. Limited data are available on real-world vaccine effectiveness (VE) of mRNA-1273 against omicron. Here, we report VE of 2 or 3 mRNA-1273 doses against infection and hospitalization with omicron and delta, including among immunocompromised individuals.

Methods

This test negative study was conducted at Kaiser Permanente Southern California. Cases were individuals aged ≥18 years testing positive by RT-PCR with specimens collected between 12/6/2021 and 12/23/2021 with variant determined by spike gene status. Randomly sampled test negative controls were 5:1 matched to cases by age, sex, race/ethnicity, and specimen collection date. Conditional logistic regression models were used to evaluate adjusted odds ratio (aOR) of vaccination with mRNA-1273 doses between cases and controls. VE(%) was calculated as (1-aOR)x100.

Results

6657 test positive cases (44% delta, 56% omicron) were included. The 2-dose VE against omicron infection was 30.4% (95% CI, 5.0%-49.0%) at 14-90 days after vaccination and declined quickly thereafter. The 3-dose VE was 95.2% (93.4%-96.4%) against delta infection and 62.5% (56.2%-67.9%) against omicron infection. The 3-dose VE against omicron infection was low among immunocompromised individuals (11.5%;

0.0%-66.5%). None of the cases (delta or omicron) vaccinated with 3 doses were hospitalized compared to 53 delta and 2 omicron unvaccinated cases.

Conclusions

VE of 3 mRNA-1273 doses against infection with delta was high and durable, but VE against omicron infection was lower. VE against omicron infection was particularly low among immunocompromised individuals. No 3-dose recipients were hospitalized for COVID-19.

Introduction

The recently emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) omicron (B.1.1.529) variant contains multiple novel spike (S) protein mutations, raising concerns about escape from naturally acquired or vaccine-elicited immunity.[1] Several *in vitro* studies reported reduced vaccine-induced neutralization activity against omicron.[2,3] Specifically, sera from individuals vaccinated with 2 doses of mRNA coronavirus disease 2019 (COVID-19) vaccines, including mRNA-1273 (Moderna COVID-19 vaccine), showed substantial reductions in neutralization activity against omicron compared with wild-type SARS-CoV-2.[2,4,5] However, an mRNA-1273 booster increased neutralization activity against omicron, albeit lower than wild-type.[2,3] We previously reported high and durable vaccine effectiveness (VE) of mRNA-1273 against infection and hospitalization from COVID-19 caused by other emerging SARS-CoV-2 variants, including delta (B.1.617.2).[6] Limited data are available on real-world VE of mRNA-1273 against omicron.

As omicron has a deletion at positions 69-70, omicron-positive specimens exhibit S-gene target failure (SGTF). To provide timely results, we used SGTF as a marker for omicron in specimens collected during December 2021 for these analyses. The US Food and Drug Administration (FDA) and World Health Organization advised that SGTF from select COVID-19 RT-PCR assays, including the Thermo Fisher TaqPath™ COVID-19 Combo kits, can be used as a screening method for omicron;[7,8] SGTF has served as a proxy in the United Kingdom for identifying omicron.[9,10] In Southern California where delta was the dominant strain before omicron,[11] and the proportion of SGTF among

SARS-CoV-2 positive specimens increased from 2.7% to 83.9% from 12/06/2021 to 12/23/2021, SGTF can be used as a proxy for omicron, while positive specimens negative for SGTF can be considered delta. Herein, we report VE of mRNA-1273 against infection and hospitalization with omicron and delta within the Kaiser Permanente Southern California (KPSC) healthcare system in the United States.

Methods

Study setting

KPSC is an integrated healthcare system that provides care to over 4.6 million sociodemographically diverse health plan members at 15 hospitals and associated medical offices across Southern California. Comprehensive electronic health records (EHRs) included information on demographics, immunizations, diagnoses, laboratory tests, procedures, and pharmacy records. KPSC began administering mRNA-1273 on 12/18/2020. Outside COVID-19 vaccinations were imported into members' EHR daily from external sources, including the California Immunization Registry, Care Everywhere (system on the Epic EHR platform that allows healthcare systems to exchange patients' medical information), claims (e.g., retail pharmacies), and self-report by members (with valid documentation).

Laboratory methods

Molecular diagnostic testing for SARS-CoV-2 is available to members who request it for any reason, before procedures and hospital admissions, with and without symptoms. Specimens were primarily collected using nasopharyngeal/oropharyngeal swabs (for symptomatic individuals) or saliva (for asymptomatic individuals). Specimens were

tested using RT-PCR TaqPath COVID-19 High-Throughput Combo Kit (Thermo Fisher Scientific). SGTF is defined as a RT-PCR test in which N and ORF1ab genes were detected (Ct values < 37), but S gene was not detected. Specimens with SGTF were considered to be omicron, whereas positive specimens without SGTF were considered to be delta.

Study design

This study employed a test negative design. Test positive cases included individuals who tested positive by the RT-PCR TaqPath COVID-19 kit, with specimens taken between 12/6/2021 and 12/23/2021, were aged ≥18 years, and had ≥12 months of KPSC membership before the specimen collection date (needed to ascertain exposure status and covariates accurately). Individuals were excluded if they received a COVID-19 vaccine other than mRNA-1273, any dose of mRNA-1273 <14 days before the specimen collection date, 2 or 3 doses of mRNA-1273 <24 days apart from previous dose, or >3 doses of mRNA-1273 prior to the specimen collection date. Additional exclusions included a positive SARS-CoV-2 test or COVID-19 diagnosis code ≤90 days before the specimen collection date. COVID-19 hospitalization included hospitalization with a SARS-CoV-2 positive test or hospitalization ≤7 days after a SARS-CoV-2 positive test. COVID-19 hospitalization was confirmed by manual chart review conducted by a physician investigator [BKA] to verify the presence of severe COVID-19 symptoms. Test negative controls included all individuals who tested negative with specimens taken between 12/6/2021 and 12/23/2021 and with the same age and membership requirement as cases. Randomly sampled test negative controls were 5:1 matched to

cases by age (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 specimen collection date. Matching was conducted separately for the 1-, 2-, and 3-dose VE analysis. To accommodate variation in real-world practice, analyses did not require dose 3 to be ≥6 months from dose 2, as some members received dose 3 at a shorter interval in this study.

Exposure

The exposure of interest was 1, 2, or 3 doses of mRNA-1273. Dose 3 in this analysis included both the 100-µg additional primary dose in immunocompromised persons, as well as the 50-µg and 100-ug booster dose in adults.

Covariates

Demographic and clinical covariates were extracted from EHRs.[12] Variables assessed included socioeconomic status (Medicaid, neighborhood median household income), medical center area, pregnancy status, KPSC physician/employee status, smoking, body mass index, Charlson comorbidity score, autoimmune conditions, healthcare utilization (virtual, outpatient, emergency department, and inpatient encounters), preventive care (other vaccinations, screenings, and wellness visits), chronic diseases (kidney, heart, lung, and liver disease, and diabetes), and frailty index. Other variables included history of SARS-CoV-2 molecular test performed from 3/1/2020 to specimen collection date (irrespective of result), history of COVID-19 (positive SARS-CoV-2

molecular test or a COVID-19 diagnosis code) from 3/1/2020 to specimen collection date, and immunocompromised status.

Statistical analyses

Characteristics of cases and controls for each analysis were compared by using the χ^2 test or Fisher's exact test for categorical variables and two-sample *t* test or Wilcoxon rank sum test for continuous variables. The distribution of variant type by vaccination status was tabulated. Conditional logistic regression was used to estimate the adjusted odds ratios (OR) and 95% confidence intervals (CI) for vaccination against infection with delta or omicron. Analyses were adjusted for potential confounders, determined by scientific relevance, or by absolute standardized differences (ASD) >0.1 and P value <0.1. VE(%) was calculated as (1–adjusted OR)×100.

VE against hospitalization with delta or omicron by number of vaccine doses was also estimated using conditional logistic regression. Due to sample size, some variables were removed from the model due to lack of model convergence.

We also assessed 2-dose and 3-dose VE against infection with delta or omicron by time since receipt of mRNA-1273 dose 2 or 3 (for 2-dose VE: 14-90 days, 91-180 days, 181-270 days, and >270 days; for 3-dose VE: on or before 10/20/2021 versus on or after 10/21/2021). 10/21/2021 was chosen since it was the date the Centers for Disease Control and Prevention's (CDCs) Advisory Committee on Immunization Practices (ACIP) recommended a 50-µg booster of mRNA-1273 for individuals who completed

their primary series ≥6 months prior.[13,14] As more immunocompromised persons might have received dose 3 before the October 2021 recommendation, we conducted a separate analysis that excluded immunocompromised individuals to assess durability of protection of 3 doses in immunocompetent individuals. We also evaluated 3-dose VE in select subgroups, including by age (<65, ≥65 years), sex, race/ethnicity (Hispanic, Non-Hispanic, and others), and immunocompromised status (yes, no). Conditional logistic regression was used for the age, sex, and race/ethnicity subgroup. Unconditional logistic regression with additional adjustment of matching factors in the model was used for the immunocompromised status subgroup and time since vaccination analyses because matched sets needed to be broken for analyses in these subgroups. SAS 9.4 was used for analyses. The study was approved by KPSC Institutional Review Board.

Results

The study included 6657 test positive cases with SGTF status available; 3513 (52.8%) individuals were unvaccinated (2040 delta, 1473 omicron), and 3144 (47.2%) were vaccinated (886 delta, 2258 omicron; 100 vaccinated with 1 dose, 2648 vaccinated with 2 doses, 396 vaccinated with 3 doses). The flow chart depicting selection steps is provided in Supplementary Figure 1. The distribution of covariates by test outcomes, separated by variant type, is summarized in Table 1 (2-dose and 3-dose analyses) and Supplementary Table 1 (1-dose analysis).

Omicron cases appeared to be younger and more frequently had a history of COVID-19 than delta cases. In the 2-dose and 3-dose analyses, 73.9% and 73.2% of omicron cases, respectively, were among 18-44 year-olds compared to 59.2% and 61.4% of

delta cases (Table 1). 13.0% and 14.9% of omicron cases in the 2-dose and 3-dose analyses, respectively, had a history of COVID-19 versus 1.7% and 2.2% of delta cases.

Table 2 shows VE against delta and omicron infection or hospitalization. Overall, the 1-dose VE was 60.2% (95% CI, 42.6%-72.3%) and 20.3% (0.0%-39.8%), the 2-dose VE was 60.7% (56.5%-64.5%) and 0.0% (0.0%-3.1%), and the 3-dose VE was 95.2% (93.4%-96.4%) and 62.5% (56.2%-67.9%) against delta and omicron infection, respectively.

In analyses of 2-dose VE against delta infection by time since receipt of dose 2, VE at 14-90 days was 82.8% (69.6%-90.3%) and subsequently declined, with VE of 63.6% (51.8%-72.5%) at 91-180 days, 61.4% (56.8%-65.5%) at 181-270 days, and 52.9% (43.7%-60.5%) at >270 days (Table 2, Figure 1). The 2-dose VE against omicron infection was 30.4% (5.0%-49.0%) at 14-90 days and declined quickly to 15.2% (0.0%-30.7%) at 91-180 days and 0.0% after 180 days. The 3-dose VE against delta infection was >90%, regardless of whether the third dose was received before or after 10/20/2021. For vaccinated cases, the median number of days from vaccination to positive test date was 35 and 112 days if dose 3 was received after 10/20/2021 or on and before that day, respectively. However, the VE against omicron infection was 63.6% (57.4%-68.9%) if dose 3 was received after 10/20/2021 (for vaccinated cases, median number of days from vaccination to positive test date was 36 days) and 39.1% (3.8%-61.5%) if received on or before 10/20/2021 (for vaccinated cases, median number of days from vaccination to positive test date was 103 days; Table 2). These estimates were similar in analyses excluding immunocompromised individuals, except

that the VE against omicron infection increased to 49.0% (12.6%-70.2%) among immunocompetent individuals who received dose 3 before or on 10/20/21 (Table 2, Figure 2).

Only 4 vaccinated delta cases were hospitalized, of whom one received 1 dose and 3 received 2 doses (Table 2). Only 2 vaccinated omicron cases were hospitalized; both received 2 doses. None of the delta or omicron cases vaccinated with 3 doses were hospitalized. In comparison, 53 delta and 2 omicron unvaccinated cases were hospitalized (Table 2).

Table 3 presents the 3-dose VE against infection by subgroups. The 3-dose VE against delta was >95% across age, sex, and race/ethnicity groups but lower in the immunocompromised population (72.2% [12.2%-91.2%]). The 3-dose VE against omicron was 63.1% (56.6%-68.6%) in those <65 years and 57.1% (14.2%-78.6%) in those ≥65 years and only 11.5% (0.0%-66.5%) in the immunocompromised population compared to 63.6% (57.4%-68.9%) in the immunocompetent population.

Discussion

We evaluated the effectiveness of mRNA-1273 against the highly mutated omicron variant in a sociodemographically diverse population in a real-world setting. Between 12/6/2021 and 12/23/2021, the rapidly increasing proportion of omicron positive specimens indicated unprecedented transmissibility and raised concerns over protection conferred by currently authorized or licensed COVID-19 vaccines. Our study demonstrates that while VE of 2 doses of mRNA-1273 against infection with delta is high and wanes slowly, consistent with our previous findings,[6,12] the 2-dose VE against

omicron infection is poor and wanes quickly, providing minimal protection of 30% within 3 months of vaccination and virtually none thereafter. In addition, while the 3-dose VE against infection with delta is high and durable, that against omicron is lower. Nevertheless, the point estimate (>50%) and lower bound of the 95% CI (>30%) still meet the US FDA criteria for emergency use authorization for 2 doses of COVID-19 vaccines.[15] Also, this VE is similar to that against asymptomatic infection observed in the trial (63.0% [56.6%-68.5%]).[16] The VE of 3 doses of mRNA-1273 against infection with omicron is negligible among immunocompromised persons. Taken together, these data suggest that third (booster) doses may be needed <6 months after dose 2 in immunocompetent individuals and that 3 doses can be inadequate to protect against omicron infection in immunocompromised individuals. Furthermore, the data highlight the potential need for periodic adjustment of vaccines to target circulating variants, including omicron, that have evolved to escape current vaccine-induced immunity. While there are limited prior data on VE of 2 or 3 doses of mRNA-1273 vaccine against infection or hospitalization with omicron, a preliminary analysis from Denmark found an initial VE of 2 doses of mRNA-1273 against omicron infection of 36.7% that waned quickly, similar to our findings.[17] An early report by Andrews et al found waning of 2-dose protection with an initial VE of 2 doses of BNT162b2 against symptomatic infection with omicron of 88% (65.9%-95.8%) 2-9 weeks after dose 2 that declined to 34%-37% (95% CIs ranging from -5 to 59.6%) after 15 weeks post-dose 2, but increased to 75.5% (56.1%-86.3%) a median of 41 days (range 14-72 days) after a BNT162b2 booster.[18] Collie et al found that the VE of 2 doses of BNT162b2 against hospitalization during a proxy omicron period was 70% at least 14 days after receipt of dose 2.[19] In England,

after a primary course of BNT162b2 vaccine, VE against omicron infection was initially 70% after a BNT162b2 booster, dropping to 45% after ≥10 weeks, but stayed around 70%-75% for up to 9 weeks after an mRNA-1273 booster.[10]

A growing number of reports indicate that omicron disease is less severe than delta disease, resulting in a lower risk of hospitalization.[1,20] This may reflect greater replication of omicron in the upper versus lower respiratory tract, which may also contribute to more efficient transmission, resulting in increased absolute[21] numbers of hospitalizations. Booster vaccination has the potential to decrease hospital burden and improve outcomes.[22] While the number of cases and follow-up period were not sufficient in our study or other studies to assess potential waning VE against hospitalization with omicron, our results of waning VE against infection with omicron after dose 3 of mRNA-1273 underscores the importance of monitoring VE against hospitalization with omicron.

This study provides novel data complementing recent reports of the effectiveness of other COVID-19 vaccines against omicron and has several strengths and limitations. Testing for SARS-CoV-2 infection was readily available among KPSC members, including drive-through testing and self-scheduled test appointments. Furthermore, we used a highly specific and sensitive RT-PCR test and monitored variant proportions at KPSC, allowing us to quickly assess VE of mRNA-1273 against omicron. Second, we considered all SGTF specimens as omicron, rather than specifying a Ct value threshold, although this may have overestimated omicron detection. Our rate of SGTF closely mirrored regional trends in omicron emergence from the CDC.[11] Furthermore, based on whole genome sequencing results received for a subset of 227 positive specimens, we confirmed that all 6 omicron cases exhibited SGTF, and the remaining 221 delta cases

were all negative for SGTF. Third, this study was representative of a large, diverse racial, ethnic, and socioeconomic population in Southern California, but may be less representative of other populations. However, analysis of the effectiveness of mRNA-1273 against delta and omicron in parallel provided an internal comparator that put results in context.[12] Fourth, some immunocompetent members who received a third dose before the 10/21/2021 ACIP recommendation may have received a 100-µg dose rather than a 50-µg booster dose of mRNA-1273. However, we were not able to clearly assess the difference, as dosage information was not available from external vaccination records. Finally, the number of hospitalized patients included was too small to draw definitive conclusions regarding VE and durability of 3 doses in preventing hospitalization. Long-term follow-up is needed to evaluate the durability of both 100-µg and 50-µg booster doses in preventing infection and hospitalization.

In conclusion, this study of mRNA-1273 found waning 2-dose VE against delta infection, high VE 3-dose VE against delta infection, and low 2-dose and 3-dose VE against omicron infection. Protection against omicron infection wanes within 3 months after dose 2, suggesting a need for a shorter interval between second and booster doses. Lack of protection against omicron infection in the immunocompromised population underscores the importance of the recommended fourth dose (booster) for this population. Continued monitoring of VE against omicron infection and hospitalization in immunocompetent and immunocompromised individuals and surveillance for the emergence of newer SARS-CoV-2 variants are warranted to inform future vaccination strategies.

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List of Tables

Table 1. Characteristics of SARS-CoV-2 test positive cases and test negative controls, by variant

	2-dose						3-dose					
	Delta			Omicron			Delta			Omicron		
	Test Positive N=2833	Test Negative N=14165	p-value/ASD	Test Positive N=3328	Test Negative N=16640	p-value/ASD	Test Positive N=2097	Test Negative N=10485	p-value/ASD	Test Positive N=1812	Test Negative N=9060	p-value/ASD
Age at specimen collection date, years			0.67 / 0.01			<0.01 / 0.13			0.04 / 0.05			<0.01 / 0.14
mean (sd)	42.46 (14.57)	42.64 (14.64)		36.64 (12.76)	38.32 (12.81)		41.64 (14.49)	42.40 (14.55)		37.27 (13.62)	39.19 (13.54)	
median	41	41		34	36		40	40		35	37	
Q1, Q3	32, 53	31, 53		26, 45	29, 45		31, 52	31, 53		26, 45	30, 46	
min, max	18, 92	18, 98		18, 93	18, 93		18, 89	18, 103		18, 93	18, 97	
Age at specimen collection date, years, n (%)			N/A			N/A			N/A			N/A
18-44	1676 (59.2%)	8380 (59.2%)		2458 (73.9%)	12290 (73.9%)		1288 (61.4%)	6440 (61.4%)		1327 (73.2%)	6635 (73.2%)	
45-64	946 (33.4%)	4730 (33.4%)		778 (23.4%)	3890 (23.4%)		659 (31.4%)	3295 (31.4%)		399 (22.0%)	1995 (22.0%)	
65-74	156 (5.5%)	780 (5.5%)		75 (2.3%)	375 (2.3%)		114 (5.4%)	570 (5.4%)		64 (3.5%)	320 (3.5%)	
≥75	55 (1.9%)	275 (1.9%)		17 (0.5%)	85 (0.5%)		36 (1.7%)	180 (1.7%)		22 (1.2%)	110 (1.2%)	
Sex, n (%)			N/A			N/A			N/A			N/A
Female	1536 (54.2%)	7680 (54.2%)		1912 (57.5%)	9560 (57.5%)		1110 (52.9%)	5550 (52.9%)		1015 (56.0%)	5075 (56.0%)	
Male	1297 (45.8%)	6485 (45.8%)		1416 (42.5%)	7080 (42.5%)		987 (47.1%)	4935 (47.1%)		797 (44.0%)	3985 (44.0%)	
Race/Ethnicity, n (%)			N/A			N/A			N/A			N/A
Non-Hispanic White	1120 (39.5%)	5600 (39.5%)		969 (29.1%)	4845 (29.1%)		846 (40.3%)	4230 (40.3%)		603 (33.3%)	3015 (33.3%)	
Non-Hispanic Black	153 (5.4%)	765 (5.4%)		384 (11.5%)	1920 (11.5%)		124 (5.9%)	620 (5.9%)		211 (11.6%)	1055 (11.6%)	
Hispanic	1242 (43.8%)	6210 (43.8%)		1401 (42.1%)	7005 (42.1%)		890 (42.4%)	4450 (42.4%)		709 (39.1%)	3545 (39.1%)	
Non-Hispanic Asian	111 (3.9%)	555 (3.9%)		238 (7.2%)	1190 (7.2%)		71 (3.4%)	355 (3.4%)		115 (6.3%)	575 (6.3%)	
Other/Unknown	207 (7.3%)	1035 (7.3%)		336 (10.1%)	1680 (10.1%)		166 (7.9%)	830 (7.9%)		174 (9.6%)	870 (9.6%)	
BMI[b], n (%)			<0.01 / 0.17			<0.01 / 0.14			<0.01 / 0.20			<0.01 / 0.17
<18.5	19 (0.7%)	131 (0.9%)		38 (1.1%)	186 (1.1%)		13 (0.6%)	99 (0.9%)		25 (1.4%)	101 (1.1%)	
18.5 - <25	484 (17.1%)	2925 (20.6%)		839 (25.2%)	3598 (21.6%)		362 (17.3%)	2232 (21.3%)		456 (25.2%)	2074 (22.9%)	
25 - <30	756 (26.7%)	3964 (28.0%)		903 (27.1%)	4423 (26.6%)		550 (26.2%)	3055 (29.1%)		524 (28.9%)	2430 (26.8%)	
30 - <35	593 (20.9%)	2780 (19.6%)		563 (16.9%)	3192 (19.2%)		423 (20.2%)	1987 (19.0%)		296 (16.3%)	1631 (18.0%)	
35 - <40	278 (9.8%)	1493 (10.5%)		283 (8.5%)	1692 (10.2%)		209 (10.0%)	1020 (9.7%)		136 (7.5%)	909 (10.0%)	
40 - <45	114 (4.0%)	652 (4.6%)		127 (3.8%)	781 (4.7%)		87 (4.1%)	441 (4.2%)		56 (3.1%)	437 (4.8%)	
≥45	76 (2.7%)	424 (3.0%)		77 (2.3%)	576 (3.5%)		47 (2.2%)	274 (2.6%)		38 (2.1%)	282 (3.1%)	
Unknown	513 (18.1%)	1796 (12.7%)		498 (15.0%)	2192 (13.2%)		406 (19.4%)	1377 (13.1%)		281 (15.5%)	1196 (13.2%)	

Smoking[b], n (%)			<0.01 / 0.13			<0.01 / 0.08			<0.01 / 0.17			<0.01 / 0.09
No	1913 (67.5%)	10162 (71.7%)		2484 (74.6%)	12328 (74.1%)		1389 (66.2%)	7595 (72.4%)		1332 (73.5%)	6673 (73.7%)	
Yes	500 (17.6%)	2526 (17.8%)		445 (13.4%)	2586 (15.5%)		365 (17.4%)	1771 (16.9%)		243 (13.4%)	1416 (15.6%)	
Unknown	420 (14.8%)	1477 (10.4%)		399 (12.0%)	1726 (10.4%)		343 (16.4%)	1119 (10.7%)		237 (13.1%)	971 (10.7%)	
Charlson comorbidity score[a], n (%)			<0.01 / 0.11			<0.01 / 0.15			<0.01 / 0.15			<0.01 / 0.18
0	2274 (80.3%)	10860 (76.7%)		2836 (85.2%)	13522 (81.3%)		1719 (82.0%)	8067 (76.9%)		1539 (84.9%)	7132 (78.7%)	
1	348 (12.3%)	1815 (12.8%)		365 (11.0%)	1948 (11.7%)		241 (11.5%)	1328 (12.7%)		189 (10.4%)	1167 (12.9%)	
≥2	211 (7.4%)	1490 (10.5%)		127 (3.8%)	1170 (7.0%)		137 (6.5%)	1090 (10.4%)		84 (4.6%)	761 (8.4%)	
Frailty index[a], n (%)			<0.01 / 0.18			<0.01 / 0.12			<0.01 / 0.20			<0.01 / 0.15
Quartile 1	667 (23.5%)	3228 (22.8%)		888 (26.7%)	4104 (24.7%)		480 (22.9%)	2492 (23.8%)		463 (25.6%)	2249 (24.8%)	
Quartile 2	922 (32.5%)	3610 (25.5%)		905 (27.2%)	4075 (24.5%)		692 (33.0%)	2627 (25.1%)		503 (27.8%)	2221 (24.5%)	
Quartile 3	667 (23.5%)	3658 (25.8%)		833 (25.0%)	4172 (25.1%)		511 (24.4%)	2634 (25.1%)		483 (26.7%)	2236 (24.7%)	
Quartile 4 (most frail)	577 (20.4%)	3669 (25.9%)		702 (21.1%)	4289 (25.8%)		414 (19.7%)	2732 (26.1%)		363 (20.0%)	2354 (26.0%)	
Chronic diseases[a], n (%)												
Kidney disease	49 (1.7%)	449 (3.2%)	<0.01 / 0.09	17 (0.5%)	308 (1.9%)	<0.01 / 0.12	33 (1.6%)	286 (2.7%)	<0.01 / 0.08	15 (0.8%)	203 (2.2%)	<0.01 / 0.12
Heart disease	31 (1.1%)	335 (2.4%)	<0.01 / 0.10	15 (0.5%)	212 (1.3%)	<0.01 / 0.09	24 (1.1%)	197 (1.9%)	0.02 / 0.06	19 (1.0%)	148 (1.6%)	0.06 / 0.05
Lung disease	209 (7.4%)	1246 (8.8%)	0.01 / 0.05	235 (7.1%)	1327 (8.0%)	0.07 / 0.03	142 (6.8%)	898 (8.6%)	0.01 / 0.07	122 (6.7%)	802 (8.9%)	<0.01 / 0.08
Liver disease	86 (3.0%)	494 (3.5%)	0.23 / 0.03	57 (1.7%)	455 (2.7%)	<0.01 / 0.07	56 (2.7%)	340 (3.2%)	0.17 / 0.03	30 (1.7%)	271 (3.0%)	<0.01 / 0.09
Diabetes	213 (7.5%)	1300 (9.2%)	<0.01 / 0.06	157 (4.7%)	1128 (6.8%)	<0.01 / 0.09	128 (6.1%)	870 (8.3%)	<0.01 / 0.08	76 (4.2%)	697 (7.7%)	<0.01 / 0.15
Immunocompromised status, n (%)			<0.01 / 0.10			<0.01 / 0.09			<0.01 / 0.16			<0.01 / 0.12
No	2787 (98.4%)	13721 (96.9%)		3278 (98.5%)	16180 (97.2%)		2072 (98.8%)	10095 (96.3%)		1782 (98.3%)	8742 (96.5%)	
Yes	46 (1.6%)	444 (3.1%)		50 (1.5%)	460 (2.8%)		25 (1.2%)	390 (3.7%)		30 (1.7%)	318 (3.5%)	
HIV/AIDS	2 (4.3%)	34 (7.7%)		8 (16.0%)	30 (6.5%)		1 (4.0%)	48 (12.3%)		4 (13.3%)	34 (10.7%)	
Leukemia/lymphoma, congenital and other immunodeficiencies, asplenia/hyposplenia	21 (45.7%)	145 (32.7%)		18 (36.0%)	141 (30.7%)		10 (40.0%)	128 (32.8%)		10 (33.3%)	105 (33.0%)	
Organ transplant	3 (6.5%)	28 (6.3%)		2 (4.0%)	28 (6.1%)		2 (8.0%)	24 (6.2%)		1 (3.3%)	23 (7.2%)	
Immunosuppressant medications	25 (54.3%)	291 (65.5%)		27 (54.0%)	321 (69.8%)		16 (64.0%)	239 (61.3%)		18 (60.0%)	215 (67.6%)	
Autoimmune conditions[a], n (%)			0.24 / 0.02			0.05 / 0.04			0.02 / 0.06			0.01 / 0.07
No	2768 (97.7%)	13785 (97.3%)		3274 (98.4%)	16280 (97.8%)		2055 (98.0%)	10182 (97.1%)		1781 (98.3%)	8809 (97.2%)	
Yes	65 (2.3%)	380 (2.7%)		54 (1.6%)	360 (2.2%)		42 (2.0%)	303 (2.9%)		31 (1.7%)	251 (2.8%)	
Rheumatoid arthritis	19 (29.2%)	158 (41.6%)		25 (46.3%)	134 (37.2%)		10 (23.8%)	101 (33.3%)		16 (51.6%)	82 (32.7%)	
Inflammatory bowel disease	18 (27.7%)	83 (21.8%)		11 (20.4%)	105 (29.2%)		14 (33.3%)	80 (26.4%)		5 (16.1%)	72 (28.7%)	
Psoriasis and psoriatic arthritis	24 (36.9%)	125 (32.9%)		13 (24.1%)	102 (28.3%)		15 (35.7%)	107 (35.3%)		7 (22.6%)	89 (35.5%)	

Multiple sclerosis	4 (6.2%)	20 (5.3%)		5 (9.3%)	25 (6.9%)		3 (7.1%)	24 (7.9%)		3 (9.7%)	17 (6.8%)	
Systemic lupus erythematosus	2 (3.1%)	48 (12.6%)		12 (22.2%)	37 (10.3%)		1 (2.4%)	27 (8.9%)		7 (22.6%)	30 (12.0%)	
Pregnancy status at specimen collection date, n (%)			<0.01 / 0.08			<0.01 / 0.13			0.01 / 0.07			<0.01 / 0.15
No	2786 (98.3%)	13765 (97.2%)		3277 (98.5%)	16043 (96.4%)		2058 (98.1%)	10180 (97.1%)		1781 (98.3%)	8671 (95.7%)	
Yes	47 (1.7%)	400 (2.8%)		51 (1.5%)	597 (3.6%)		39 (1.9%)	305 (2.9%)		31 (1.7%)	389 (4.3%)	
1st trimester	15 (31.9%)	41 (10.3%)		7 (13.7%)	61 (10.2%)		11 (28.2%)	25 (8.2%)		5 (16.1%)	50 (12.9%)	
2nd trimester	18 (38.3%)	102 (25.5%)		18 (35.3%)	148 (24.8%)		15 (38.5%)	83 (27.2%)		11 (35.5%)	92 (23.7%)	
3rd trimester	14 (29.8%)	257 (64.3%)		26 (51.0%)	388 (65.0%)		13 (33.3%)	197 (64.6%)		15 (48.4%)	247 (63.5%)	
History of COVID-19[c], n (%)			<0.01 / 0.62			<0.01 / 0.18			<0.01 / 0.58			<0.01 / 0.10
No	2786 (98.3%)	11328 (80.0%)		2896 (87.0%)	13387 (80.5%)		2050 (97.8%)	8425 (80.4%)		1542 (85.1%)	7366 (81.3%)	
Yes	47 (1.7%)	2837 (20.0%)		432 (13.0%)	3253 (19.5%)		47 (2.2%)	2060 (19.6%)		270 (14.9%)	1694 (18.7%)	
History of SARS-CoV-2 molecular test[c], n (%)			<0.01 / 0.31			0.04 / 0.04			<0.01 / 0.36			0.16 / 0.04
No	978 (34.5%)	2933 (20.7%)		831 (25.0%)	3880 (23.3%)		748 (35.7%)	2067 (19.7%)		426 (23.5%)	1993 (22.0%)	
Yes	1855 (65.5%)	11232 (79.3%)		2497 (75.0%)	12760 (76.7%)		1349 (64.3%)	8418 (80.3%)		1386 (76.5%)	7067 (78.0%)	
Number of outpatient and virtual visits[a], n (%)			<0.01 / 0.32			<0.01 / 0.16			<0.01 / 0.41			<0.01 / 0.23
0	353 (12.5%)	984 (6.9%)		234 (7.0%)	1117 (6.7%)		326 (15.5%)	819 (7.8%)		173 (9.5%)	707 (7.8%)	
1-4	1004 (35.4%)	3863 (27.3%)		1113 (33.4%)	4801 (28.9%)		777 (37.1%)	2858 (27.3%)		653 (36.0%)	2514 (27.7%)	
5-10	756 (26.7%)	4052 (28.6%)		1047 (31.5%)	4810 (28.9%)		511 (24.4%)	2797 (26.7%)		491 (27.1%)	2491 (27.5%)	
≥11	720 (25.4%)	5266 (37.2%)		934 (28.1%)	5912 (35.5%)		483 (23.0%)	4011 (38.3%)		495 (27.3%)	3348 (37.0%)	
Number of ED visits[a], n (%)			<0.01 / 0.17			<0.01 / 0.14			<0.01 / 0.14			<0.01 / 0.12
0	2414 (85.2%)	11205 (79.1%)		2820 (84.7%)	13359 (80.3%)		1796 (85.6%)	8467 (80.8%)		1511 (83.4%)	7216 (79.6%)	
1	302 (10.7%)	1952 (13.8%)		386 (11.6%)	2235 (13.4%)		216 (10.3%)	1354 (12.9%)		228 (12.6%)	1262 (13.9%)	
≥2	117 (4.1%)	1008 (7.1%)		122 (3.7%)	1046 (6.3%)		85 (4.1%)	664 (6.3%)		73 (4.0%)	582 (6.4%)	
Number of hospitalizations[a], n (%)			<0.01 / 0.09			<0.01 / 0.16			0.04 / 0.07			<0.01 / 0.12
0	2700 (95.3%)	13271 (93.7%)		3230 (97.1%)	15649 (94.0%)		1994 (95.1%)	9856 (94.0%)		1739 (96.0%)	8521 (94.1%)	
1	112 (4.0%)	670 (4.7%)		90 (2.7%)	769 (4.6%)		86 (4.1%)	476 (4.5%)		67 (3.7%)	414 (4.6%)	
≥2	21 (0.7%)	224 (1.6%)		8 (0.2%)	222 (1.3%)		17 (0.8%)	153 (1.5%)		6 (0.3%)	125 (1.4%)	
Preventive care[a], n(%)			<0.01 / 0.15			<0.01 / 0.08			<0.01 / 0.26			<0.01 / 0.17
No	1360 (48.0%)	5778 (40.8%)		1538 (46.2%)	6991 (42.0%)		1119 (53.4%)	4229 (40.3%)		885 (48.8%)	3684 (40.7%)	
Yes	1473 (52.0%)	8387 (59.2%)		1790 (53.8%)	9649 (58.0%)		978 (46.6%)	6256 (59.7%)		927 (51.2%)	5376 (59.3%)	
Medicaid, n (%)			0.70 / 0.01			0.05 / 0.04			0.03 / 0.05			0.87 / <0.01
No	2547 (89.9%)	12768 (90.1%)		2983 (89.6%)	14715 (88.4%)		1861 (88.7%)	9471 (90.3%)		1606 (88.6%)	8018 (88.5%)	
Yes	286 (10.1%)	1397 (9.9%)		345 (10.4%)	1925 (11.6%)		236 (11.3%)	1014 (9.7%)		206 (11.4%)	1042 (11.5%)	

Neighborhood median household income, n(%)			0.19 / 0.05			<0.01 / 0.08			0.07 / 0.07			0.55 / 0.05
< $40,000	115 (4.1%)	646 (4.6%)		131 (3.9%)	775 (4.7%)		87 (4.1%)	436 (4.2%)		78 (4.3%)	412 (4.5%)	
$40,000-$59,999	520 (18.4%)	2753 (19.4%)		622 (18.7%)	3513 (21.1%)		354 (16.9%)	2028 (19.3%)		339 (18.7%)	1836 (20.3%)	
$60,000-$79,999	760 (26.8%)	3579 (25.3%)		857 (25.8%)	4253 (25.6%)		569 (27.1%)	2659 (25.4%)		450 (24.8%)	2159 (23.8%)	
$80,000+	1437 (50.7%)	7173 (50.6%)		1715 (51.5%)	8077 (48.5%)		1086 (51.8%)	5351 (51.0%)		942 (52.0%)	4642 (51.2%)	
Unknown	1 (0.0%)	14 (0.1%)		3 (0.1%)	22 (0.1%)		1 (0.0%)	11 (0.1%)		3 (0.2%)	11 (0.1%)	
KPSC physician/employee status, n (%)			<0.01 / 0.25			<0.01 / 0.06			<0.01 / 0.33			0.01 / 0.07
No	2763 (97.5%)	13029 (92.0%)		3185 (95.7%)	15710 (94.4%)		2053 (97.9%)	9473 (90.3%)		1731 (95.5%)	8510 (93.9%)	
Yes	70 (2.5%)	1136 (8.0%)		143 (4.3%)	930 (5.6%)		44 (2.1%)	1012 (9.7%)		81 (4.5%)	550 (6.1%)	
Specimen type, n (%)			<0.01 / 0.46			<0.01 / 0.32			<0.01 / 0.51			<0.01 / 0.29
Nasopharyngeal/oropharyngeal Swab	2535 (89.5%)	10187 (71.9%)		2992 (89.9%)	13015 (78.2%)		1848 (88.1%)	7081 (67.5%)		1556 (85.9%)	6724 (74.2%)	
Saliva	298 (10.5%)	3978 (28.1%)		336 (10.1%)	3625 (21.8%)		249 (11.9%)	3404 (32.5%)		256 (14.1%)	2336 (25.8%)	

[a] Defined in the 1 year prior to specimen collection date.
[b] Defined in the 2 years prior to specimen collection date.
[c] Defined based on all available medical records from March 1, 2020 to specimen collection date.
Medical center area not shown. There were differences in the distribution of the vaccinated and unvaccinated individuals across the 19 medical center areas.
N/A = not applicable

Table 2. Vaccine effectiveness of test positive SARS-CoV-2 cases among mRNA-1273 vaccinated vs. unvaccinated individuals

	Variant	SARS-CoV-2 Test Positive		SARS-CoV-2 Test Negative		Odds Ratio (95% CI)		VE (95% CI)	
		Vaccinated (%)	Unvaccinated (%)	Vaccinated (%)	Unvaccinated (%)	Unadjusted[a]	Adjusted[b]	Unadjusted[a]	Adjusted[b]
Infection									
1-dose	Delta	36 (1.8%)	2017 (98.2%)	365 (3.6%)	9900 (96.4%)	0.482 (0.341, 0.681)	0.398 (0.277, 0.574)	51.8% (31.9%, 65.9%)	60.2% (42.6%, 72.3%)
	Omicron	64 (4.2%)	1451 (95.8%)	337 (4.4%)	7238 (95.6%)	0.947 (0.721, 1.245)	0.797 (0.602, 1.056)	5.3% (0.0%, 27.9%)	20.3% (0.0%, 39.8%)
2-dose	Delta	793 (28.0%)	2040 (72.0%)	6374 (45.0%)	7791 (55.0%)	0.463 (0.424, 0.507)	0.393 (0.355, 0.435)	53.7% (49.3%, 57.6%)	60.7% (56.5%, 64.5%)
	14-90 days	13 (0.6%)	2040 (99.4%)	245 (3.0%)	7791 (97.0%)	0.203 (0.116, 0.355)	0.172 (0.097, 0.304)	79.7% (64.5%, 88.4%)	82.8% (69.6%, 90.3%)
	91-180 days	60 (2.9%)	2040 (97.1%)	542 (6.5%)	7791 (93.5%)	0.423 (0.322, 0.554)	0.364 (0.275, 0.482)	57.7% (44.6%, 67.8%)	63.6% (51.8%, 72.5%)
	181-270 days	541 (21.0%)	2040 (79.0%)	4361 (35.9%)	7791 (64.1%)	0.474 (0.428, 0.525)	0.386 (0.345, 0.432)	52.6% (47.5%, 57.2%)	61.4% (56.8%, 65.5%)
	>270 days	179 (8.1%)	2040 (91.9%)	1226 (13.6%)	7791 (86.4%)	0.558 (0.473, 0.657)	0.471 (0.395, 0.563)	44.2% (34.3%, 52.7%)	52.9% (43.7%, 60.5%)
	Omicron	1855 (55.7%)	1473 (44.3%)	8326 (50.0%)	8314 (50.0%)	1.268 (1.175, 1.368)	1.051 (0.969, 1.141)	0.0% (0.0%, 0.0%)	0.0% (0.0%, 3.1%)
	14-90 days	48 (3.2%)	1473 (96.8%)	370 (4.3%)	8314 (95.7%)	0.733 (0.540, 0.995)	0.696 (0.510, 0.950)	26.7% (0.5%, 46.0%)	30.4% (5.0%, 49.0%)
	91-180 days	126 (7.9%)	1473 (92.1%)	732 (8.1%)	8314 (91.9%)	0.972 (0.798, 1.183)	0.848 (0.693, 1.037)	2.8% (0.0%, 20.2%)	15.2% (0.0%, 30.7%)
	181-270 days	1265 (46.2%)	1473 (53.8%)	5489 (39.8%)	8314 (60.2%)	1.301 (1.198, 1.413)	1.080 (0.988, 1.181)	0.0% (0.0%, 0.0%)	0.0% (0.0%, 1.2%)
	>270 days	416 (22.0%)	1473 (78.0%)	1735 (17.3%)	8314 (82.7%)	1.353 (1.200, 1.527)	1.116 (0.983, 1.267)	0.0% (0.0%, 0.0%)	0.0% (0.0%, 1.7%)
3-dose	Delta	57 (2.7%)	2040 (97.3%)	2946 (28.1%)	7539 (71.9%)	0.047 (0.035, 0.063)	0.048 (0.036, 0.066)	95.3% (93.7%, 96.5%)	95.2% (93.4%, 96.4%)
	3rd dose on or after 10/21/2021	48 (2.3%)	2040 (97.7%)	2680 (26.2%)	7539 (73.8%)	0.066 (0.050, 0.088)	0.043 (0.031, 0.058)	93.4% (91.2%, 95.0%)	95.7% (94.2%, 96.9%)
	3rd dose on or prior to 10/20/2021	9 (0.4%)	2040 (99.6%)	266 (3.4%)	7539 (96.6%)	0.125 (0.064, 0.243)	0.093 (0.047, 0.186)	87.5% (75.7%, 93.6%)	90.7% (81.4%, 95.3%)
	Omicron	339 (18.7%)	1473 (81.3%)	2914 (32.2%)	6146 (67.8%)	0.416 (0.362, 0.479)	0.375 (0.321, 0.438)	58.4% (52.1%, 63.8%)	62.5% (56.2%, 67.9%)
	3rd dose on or after 10/21/2021	314 (17.6%)	1473 (82.4%)	2751 (30.9%)	6146 (69.1%)	0.476 (0.418, 0.542)	0.364 (0.311, 0.426)	52.4% (45.8%, 58.2%)	63.6% (57.4%, 68.9%)
	3rd dose on or prior to 10/20/2021	25 (1.7%)	1473 (98.3%)	163 (2.6%)	6146 (97.4%)	0.640 (0.418, 0.979)	0.609 (0.385, 0.962)	36.0% (2.1%, 58.2%)	39.1% (3.8%, 61.5%)
3-dose excluding immunocompromised patients	Delta	52 (2.5%)	2020 (97.5%)	2756 (27.3%)	7339 (72.7%)	0.069 (0.052, 0.091)	0.043 (0.032, 0.058)	93.1% (90.9%, 94.8%)	95.7% (94.2%, 96.8%)
	3rd dose on or after 10/21/2021	46 (2.2%)	2020 (97.8%)	2574 (26.0%)	7339 (74.0%)	0.065 (0.048, 0.087)	0.041 (0.030, 0.056)	93.5% (91.3%, 95.2%)	95.9% (94.4%, 97.0%)
	3rd dose on or prior to 10/20/2021	6 (0.3%)	2020 (99.7%)	182 (2.4%)	7339 (97.6%)	0.120 (0.053, 0.271)	0.069 (0.030, 0.161)	88.0% (72.9%, 94.7%)	93.1% (83.9%, 97.0%)
	Omicron	323 (18.1%)	1459 (81.9%)	2747 (31.4%)	5995 (68.6%)	0.483 (0.425, 0.550)	0.364 (0.311, 0.426)	51.7% (45.0%, 57.5%)	63.6% (57.4%, 68.9%)
	3rd dose on or after 10/21/2021	306 (17.3%)	1459 (82.7%)	2643 (30.6%)	5995 (69.4%)	0.476 (0.417, 0.543)	0.359 (0.306, 0.421)	52.4% (45.7%, 58.3%)	64.1% (57.9%, 69.4%)
	3rd dose on or prior to 10/20/2021	17 (1.2%)	1459 (98.8%)	104 (1.7%)	5995 (98.3%)	0.672 (0.401, 1.125)	0.510 (0.298, 0.874)	32.8% (0.0%, 59.9%)	49.0% (12.6%, 70.2%)
Hospitalization									

1-dose	Delta	1 (1.9%)	53 (98.1%)	10 (3.7%)	260 (96.3%)	0.490 (0.061, 3.914)	0.311 (0.006, 17.49)	51.0% (0.0%, 93.9%)	68.9% (0.0%, 99.4%)
	Omicron	0 (0.0%)	2 (100.0%)	2 (20.0%)	8 (80.0%)	0.000 (N/A)	N/A	100.0% (N/A)	N/A
2-dose	Delta[c]	3 (5.4%)	53 (94.6%)	146 (52.1%)	134 (47.9%)	0.034 (0.008, 0.143)	0.020 (0.003, 0.128)	96.6% (85.7%, 99.2%)	98.0% (87.2%, 99.7%)
	Omicron	2 (50.0%)	2 (50.0%)	11 (55.0%)	9 (45.0%)	0.835 (0.109, 6.410)	N/A	16.5% (0.0%, 89.1%)	N/A
3-dose	Delta	0 (0.0%)	53 (100.0%)	106 (40.0%)	159 (60.0%)	0.000 (N/A)	N/A	100.0% (N/A)	N/A
	Omicron	0 (0.0%)	2 (100.0%)	6 (60.0%)	4 (40.0%)	0.000 (N/A)	N/A	100.0% (N/A)	N/A

[a] Models for time since vaccination analyses are unconditional logistic models, and the rest are conditional logistic models conditioned on matched pairs.

[b] Model adjustment:

Model for 1-dose delta variant adjusted for covariates: BMI, smoking, frailty index, immunocompromised status, history of COVID-19, history of SARS-CoV-2 molecular test, number of outpatient and virtual visits, number of ED visits, KPSC physician/employee status, medical center area, specimen type.

Model for 2-dose delta variant adjusted for covariates: BMI, smoking, Charlson comorbidity score, frailty index, history of COVID-19, history of SARS-CoV-2 molecular test, number of outpatient and virtual visits, number of ED visits, preventive care, KPSC physician/employee status, medical center area, specimen type.

Model for 3-dose delta variant adjusted for covariates: BMI, smoking, Charlson comorbidity score, frailty index, immunocompromised status, history of COVID-19, history of SARS-CoV-2 molecular test, number of outpatient and virtual visits, number of ED visits, preventive care, KPSC physician/employee status, medical center area, specimen type.

Model for 1-dose omicron variant adjusted for covariates: BMI, smoking, Charlson comorbidity score, frailty index, kidney disease, diabetes, immunocompromised status, pregnancy status at index date, history of COVID-19, number of outpatient and virtual visits, number of ED visits, number of hospitalizations, medical center area, specimen type.

Model for 2-dose omicron variant adjusted for covariates: BMI, Charlson comorbidity score, frailty index, kidney disease, pregnancy status at index date, history of COVID-19, number of outpatient and virtual visits, number of ED visits, number of hospitalizations, medical center area, specimen type.

Model for 3-dose omicron variant adjusted for covariates: BMI, Charlson comorbidity score, frailty index, kidney disease, diabetes, immunocompromised status, pregnancy status at index date, history of COVID-19, number of outpatient and virtual visits, number of ED visits, number of hospitalizations, preventive care, medical center area, specimen type.

Models for time since vaccination analyses are unconditional logistic models, and are adjusted for matching variables age groups, sex, and race/ethnicity in addition to the covariates adjusted in conditional models.

[c] Adjusted model for 2-dose delta variant did not adjust for medical center area due to lack of model convergence.

N/A = not applicable

Table 3. Vaccine effectiveness of test positive SARS-CoV-2 cases by subgroups among mRNA-1273 (3 doses) vaccinated vs. unvaccinated individuals

Variant[a]	SARS-CoV-2 Test Positive		SARS-CoV-2 Test Negative		Odds Ratio (95% CI)		VE (95% CI)	
	Vaccinated (%)	Unvaccinated (%)	Vaccinated (%)	Unvaccinated (%)	Unadjusted[a]	Adjusted[b]	Unadjusted[a]	Adjusted[b]
Delta								
Age at specimen collection date								
<65	33 (1.7%)	1914 (98.3%)	2356 (24.2%)	7379 (75.8%)	0.046 (0.033, 0.066)	0.048 (0.033, 0.069)	95.4% (93.4%, 96.7%)	95.2% (93.1%, 96.7%)
≥65	24 (16.0%)	126 (84.0%)	590 (78.7%)	160 (21.3%)	0.049 (0.029, 0.084)	0.028 (0.013, 0.059)	95.1% (91.6%, 97.1%)	97.2% (94.1%, 98.7%)
Sex								
Female	28 (2.5%)	1082 (97.5%)	1517 (27.3%)	4033 (72.7%)	0.050 (0.033, 0.074)	0.048 (0.032, 0.072)	95.0% (92.6%, 96.7%)	95.2% (92.8%, 96.8%)
Male	29 (2.9%)	958 (97.1%)	1429 (29.0%)	3506 (71.0%)	0.045 (0.029, 0.069)	0.045 (0.029, 0.071)	95.5% (93.1%, 97.1%)	95.5% (92.9%, 97.1%)
Race/ethnicity								
Hispanic	17 (1.9%)	873 (98.1%)	969 (21.8%)	3481 (78.2%)	0.042 (0.024, 0.072)	0.040 (0.022, 0.071)	95.8% (92.8%, 97.6%)	96.0% (92.9%, 97.8%)
Non-Hispanic and Others	40 (3.3%)	1167 (96.7%)	1977 (32.8%)	4058 (67.2%)	0.050 (0.035, 0.071)	0.052 (0.036, 0.074)	95.0% (92.9%, 96.5%)	94.8% (92.6%, 96.4%)
Immunocompromised status								
Yes[c]	5 (20.0%)	20 (80.0%)	190 (48.7%)	200 (51.3%)	0.263 (0.097, 0.715)	0.278 (0.088, 0.878)	73.7% (28.5%, 90.3%)	72.2% (12.2%, 91.2%)
No	52 (2.5%)	2020 (97.5%)	2756 (27.3%)	7339 (72.7%)	0.069 (0.052, 0.091)	0.043 (0.032, 0.058)	93.1% (90.9%, 94.8%)	95.7% (94.2%, 96.8%)
Omicron								
Age at specimen collection date								
<65	279 (16.2%)	1447 (83.8%)	2555 (29.6%)	6075 (70.4%)	0.414 (0.358, 0.478)	0.369 (0.314, 0.434)	58.6% (52.2%, 64.2%)	63.1% (56.6%, 68.6%)
≥65[d]	60 (69.8%)	26 (30.2%)	359 (83.5%)	71 (16.5%)	0.452 (0.266, 0.770)	0.429 (0.214, 0.858)	54.8% (23.0%, 73.4%)	57.1% (14.2%, 78.6%)
Sex								
Female	191 (18.8%)	824 (81.2%)	1613 (31.8%)	3462 (68.2%)	0.433 (0.360, 0.521)	0.346 (0.282, 0.424)	56.7% (47.9%, 64.0%)	65.4% (57.6%, 71.8%)
Male	148 (18.6%)	649 (81.4%)	1301 (32.6%)	2684 (67.4%)	0.396 (0.320, 0.490)	0.429 (0.336, 0.548)	60.4% (51.0%, 68.0%)	57.1% (45.2%, 66.4%)
Race/ethnicity								
Hispanic	98 (13.8%)	611 (86.2%)	890 (25.1%)	2655 (74.9%)	0.425 (0.333, 0.543)	0.369 (0.282, 0.484)	57.5% (45.7%, 66.7%)	63.1% (51.6%, 71.8%)
Non-Hispanic and Others	241 (21.8%)	862 (78.2%)	2024 (36.7%)	3491 (63.3%)	0.412 (0.348, 0.488)	0.381 (0.315, 0.462)	58.8% (51.2%, 65.2%)	61.9% (53.8%, 68.5%)
Immunocompromised status								
Yes[e]	16 (53.3%)	14 (46.7%)	167 (52.5%)	151 (47.5%)	1.033 (0.488, 2.188)	0.885 (0.335, 2.333)	0.0% (0.0%, 51.2%)	11.5% (0.0%, 66.5%)
No	323 (18.1%)	1459 (81.9%)	2747 (31.4%)	5995 (68.6%)	0.483 (0.425, 0.550)	0.364 (0.311, 0.426)	51.7% (45.0%, 57.5%)	63.6% (57.4%, 68.9%)

[a] Models for immunocompromised status subgroup analyses are unconditional logistic models, and the rest are conditional logistic models conditioned on matched pairs.
[b] Model adjustment:

Model for delta variant adjusted for covariates: BMI, smoking, Charlson comorbidity score, frailty index, immunocompromised status, history of COVID-19, history of SARS-CoV-2 molecular test, number of outpatient and virtual visits, number of ED visits, preventive care, KPSC physician/employee status, medical center area, specimen type.

Model for omicron variant adjusted for covariates: BMI, Charlson comorbidity score, frailty index, kidney disease, diabetes, immunocompromised status, pregnancy status at index date, history of COVID-19, number of outpatient and virtual visits, number of ED visits, number of hospitalizations, preventive care, medical center area, specimen type.

Models for immunocompromised status analyses are unconditional logistic models, and are adjusted for matching variables age groups, sex, and race/ethnicity in addition to the covariates adjusted in conditional models.

[c] Adjusted OR and adjusted VE adjusted age group with 65-74 year old and 75 years and older groups combined, and did not adjust for BMI, pregnancy status at index date, history of COVID-19, number of outpatient and virtual visits, number of hospitalizations, specimen type, medical center area due to lack of model convergence.

[d] Adjusted OR and adjusted VE did not adjust for BMI, number of hospitalizations due to lack of model convergence.

[e] Adjusted OR and adjusted VE did not adjust for BMI, number of outpatient and virtual visits, medical center area due to lack of model convergence.

Figure Legend

Figure 1. Vaccine effectiveness of 2-dose mRNA-1273 against omicron and delta variants by time since vaccination

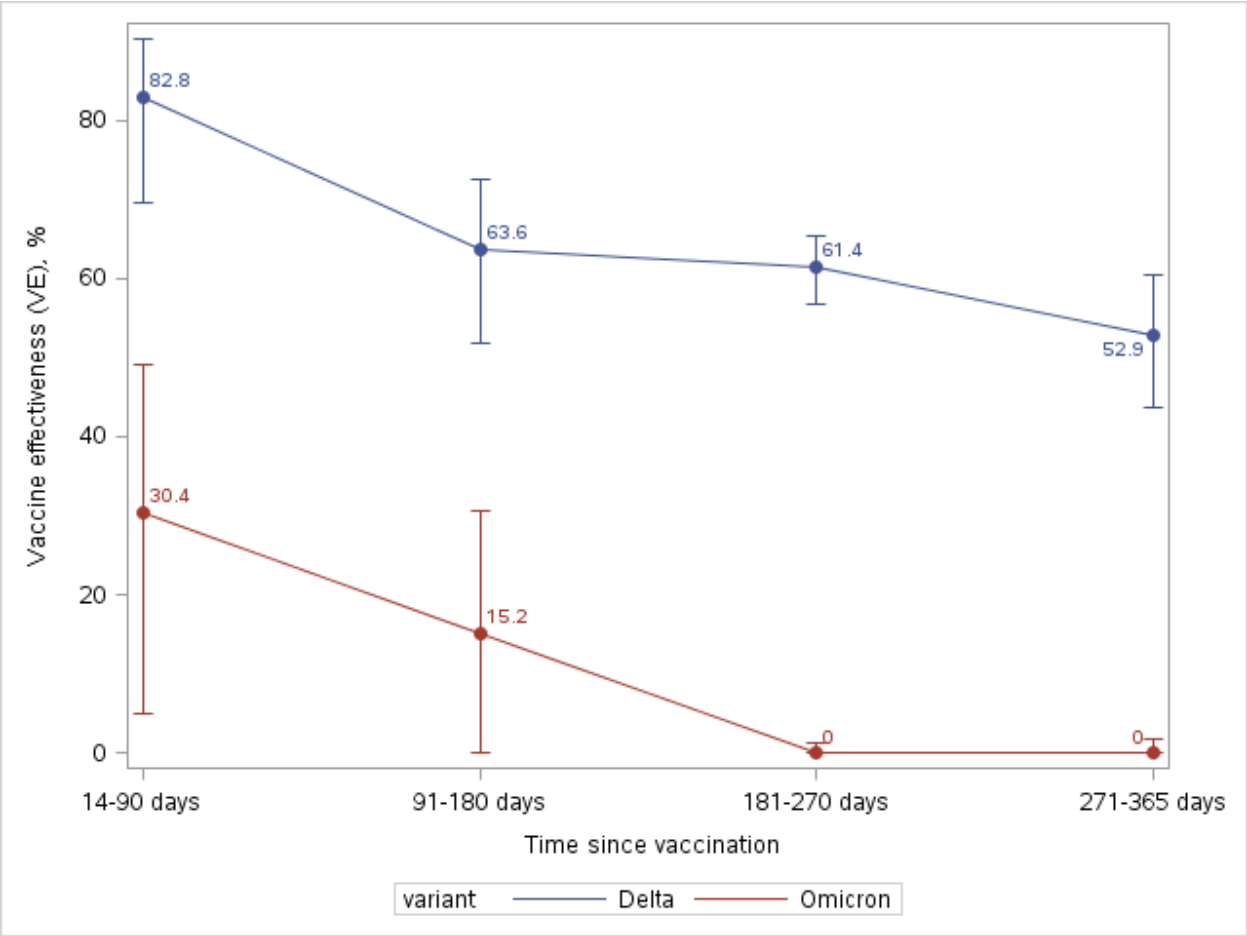
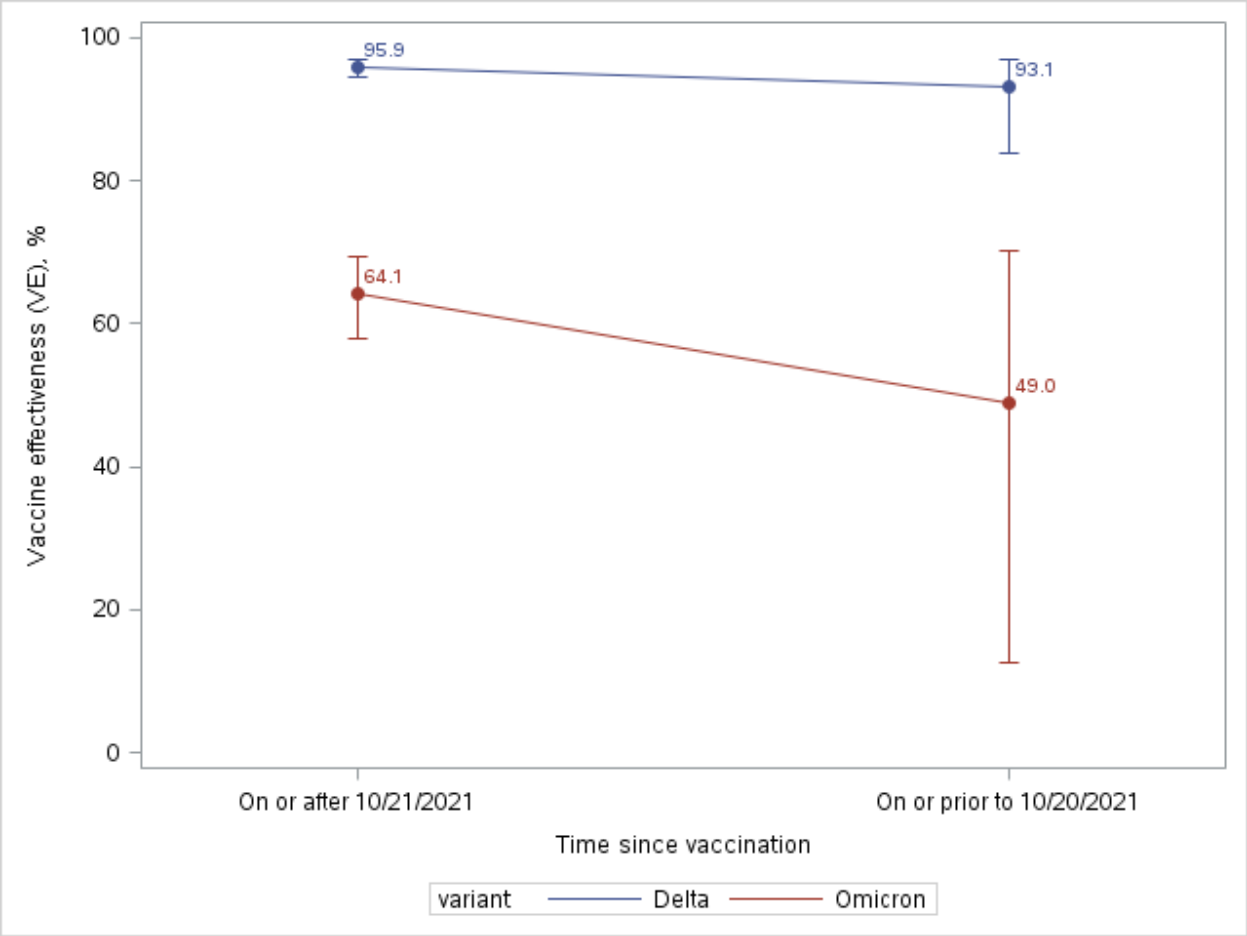


Figure 2. Vaccine effectiveness of 3-dose mRNA-1273 against omicron and delta variants by time since vaccination among immunocompetent population



Author Contributions

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Acquisition, analysis, or interpretation of data	HFT, LSS, LQ, KJB, BKA, CAT
Drafting of the manuscript	HFT, BKA
Critical revision of the manuscript for important intellectual content	YL, LSS, CAT, YT, KJB, JET, AF, JHK, GSL, SKC, HST, MA, LQ
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Data Sharing

Individual-level data reported in this study are not publicly shared. Upon request, and subject to review, KPSC 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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Disclosures

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